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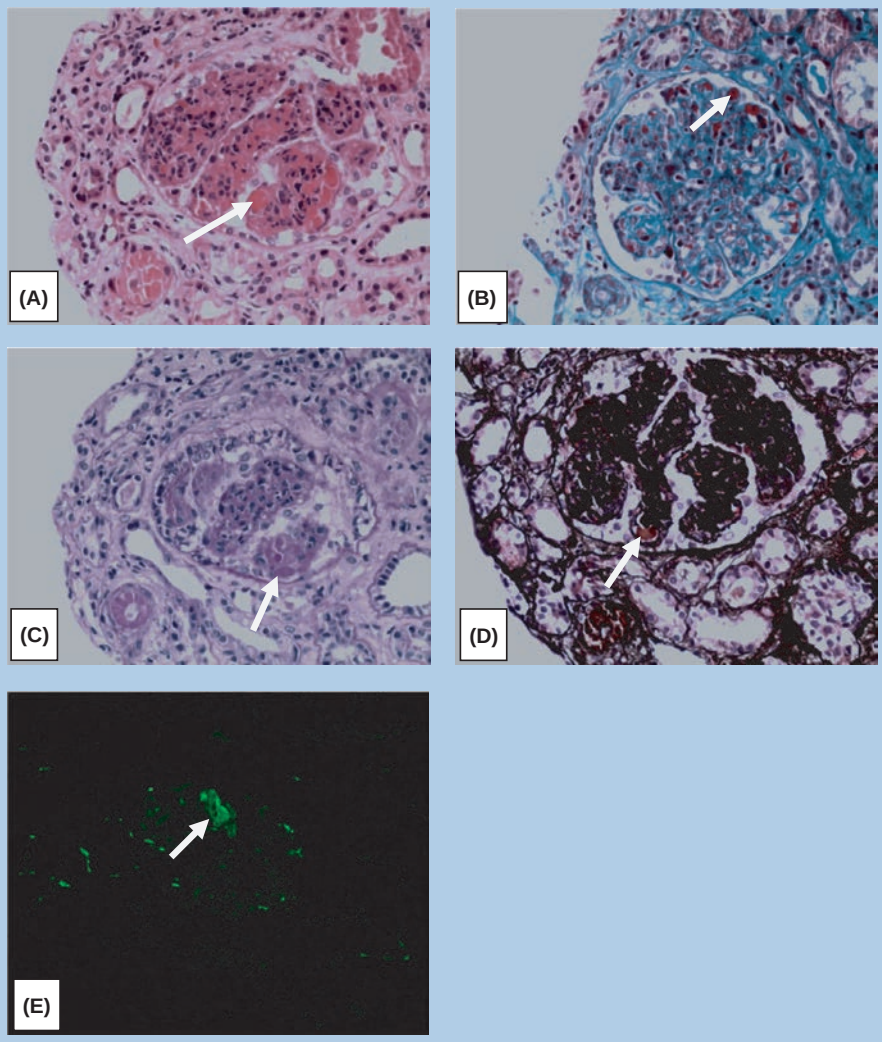

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EDITORIAL

Management of systemic sclerosis-associated interstitial lung disease in the current era

Interstitial lung disease (ILD) is a group of diseases describing thickening of the interstitium surrounding pulmonary alveolar walls due to underlying inflammation. ILD is often associated with connective tissue diseases. Among connective tissue disease-related ILDs, 80% of systemic sclerosis (SSc) patients develop ILD[1] with associated morbidity and mortality,[2] although a large proportion may not develop clinically significant disease. Screening, early diagnosis and treatment of SSc-associated ILD (SSc-ILD) is important as up to 33% of SSc-related deaths are attributed to ILD[3] and initiating treatment early in the course of the disease has been shown to slow disease progression.[4,5] This article summarizes the risk factors for SSc-ILD and best practices for diagnosis and treatment of SSc-ILD.

1 | RISK FACTORS AND SCREENING

The goal of treatment in SSc-ILD is prevention of progression where progression is defined as new or worsening symptoms, increase in the extent of pulmonary fibrosis on high-resolution computed tomography (HRCT) and/or by a decline in pulmonary function tests (PFTs).[6,7] This highlights the need for identifying patients at risk of disease progression before worsening occurs. The risk factors for progressive ILD are shown in Table 1. Although no absolute risk factors have been identified, these risk factors have been reported to be associated with progressive ILD in patients with SSc.

The risk of developing ILD is greatest early in the course of the disease and the most rapid decline in lung function (forced vital capacity [FVC]) occurs within the initial 3-5 years of disease onset.[5] In addition, the extent of lung involvement on HRCT at baseline combined with reduced or declining FVC and diffusing capacity of the lung for carbon monoxide (DLCO) is predictive of mortality.[6,8-10] Currently, the diagnosis of SSc-ILD is based on characteristic findings of increase reticulations with or without ground glass opacity on HRCT of the chest, irrespective of PFT results. Therefore, it is recommended that all patients with SSc receive HRCT at baseline.[11,12] Additionally, all patients should be evaluated for evidence of cardiac involvement including assessment for pulmonary hypertension at the initial visit.[13]

Due to concern for radiation exposure with repeated HRCT, evaluation of lung function via spirometry and DLCO is recommended every 4-6 months in the first 3-5 years of the disease onset as this has been shown to provide valuable information about disease trajectory.[6,14,15]

2 | TREATMENT

The concepts for management of autoimmune ILD, including SSc-ILD, is shown in Figure 1. Not every patient with SSc-ILD requires treatment. Since early SSc-ILD is driven by immune activation and inflammation, the current approach involves the use of immunosuppressive therapy with the goal of initiation early in the disease to prevent advanced fibrotic disease.[16] Our group has recently published single-center recommendations on the management of SSc-ILD.[17] One strategy is to stratify patients by their lung disease severity (subclinical [defined as minimal ILD on HRCT, normal or near normal FVC and DLCO with no symptoms attributable to ILD] vs clinical ILD). For those with subclinical ILD, one may initiate therapy for ILD, especially with high-risk features or monitor closely for progressing symptoms, PFTs, and with repeat HRCT if necessary.[17] Current practice involves treating patients on a case by case basis and only after careful review of risks vs benefits, as there is significant toxicity associated with some of the available medications.

The treatment for SSc-ILD has included the use of immunosuppressive therapies, in particular cyclophosphamide (CYC) and mycophenolate mofetil (MMF). MMF is largely used in North America and the UK for the management of SSc-ILD and it is generally given as 3000 mg/d in divided doses. This is based on the Scleroderma Lung Study II which showed that treatment with MMF offers comparable efficacy as oral CYC and has a better safety profile.[18]

Recent data from a Phase 3 trial showed that the treatment of early ILD (mean FVC% of 82% with mild ILD on HRCT) in high-risk populations (early diffuse cutaneous SSc and elevated C-reactive protein [CRP] with 50% having positive anti-SCL-70 antibodies) with tocilizumab led to stabilization of FVC% vs a decline of 6.5% in the placebo group at 48 weeks.[19] Similarly, an open-label trial of patients with early diffuse cutaneous SSc and positive anti-SCL-70 found improvement in FVC% at 24 weeks with the use of two courses of rituximab (1000 mg × 2 doses) vs monthly pulse CYC.[20] We offer treatment to patients with subclinical ILD and elevated CRP and/or positive anti-SCL-70.

Other therapy includes autologous hematopoietic stem cell transplantation (HSCT). Several trials have shown that HSCT following immunosuppressives has a beneficial effect in some patients with diffuse cutaneous SSc with multi-organ involvement.[21] The appropriate patient has early disease with progressive ILD and is not responding to immunosuppressive therapy. The goal is to target aggressive and reversible disease.

TABLE 1 Risk factors for progressive interstitial lung disease in systemic sclerosis[a]

Demographics
Male gender
African-American ethnicity
Disease type
Diffuse cutaneous SSc
Biomarkers
Anti-SCL-70/anti-topoisomerase Ab
Anti-nucleolar Ab (representing AntiTh/To, U3RNP)
C-reactive protein/interleukin-6
Chemokine (C-C motif) ligand (CCL-18)
Krebs von den Lungen protein (KL6)[b]
Surfactant protein D (SP-D)[b]

Abbreviations: Anti-SCL 70, anti-scleroderma-70 antibody; SSc, systemic sclerosis.

[a]Recently reviewed in Khanna et al.[1]

[b]CCL-18, KL6 and SP-D are serum markers for endothelial injury.

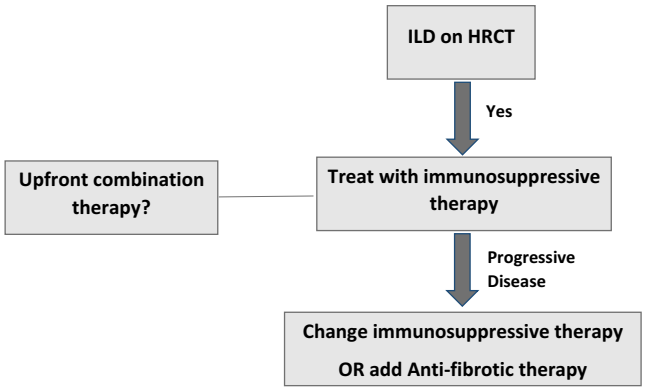

FIGURE 1 Overview of management of systemic sclerosis-associated interstitial lung disease. HRCT, high-resolution computed tomography; ILD, interstitial lung disease

As shown in Figure 1, a clinician may consider anti-fibrotic therapies in patients with progressive ILD or those intolerant of immuno-modulatory therapy (eg, due to recurrent infections). The SENSCIS trial, a large Phase 3 trial, demonstrated a smaller decline in FVC with the addition of nintedanib (an intracellular multiple tyrosine kinase inhibitor) to background MMF or no therapy vs placebo.[22] Based on published data, sequential combination therapy could be considered for patients with high risk of progression (not addressed in the SENSCIS trail), where progression has occurred under monotherapy, or contraindication to the immunosuppressive therapy.

In addition to the above, comorbid conditions including infections and gastrointestinal disease/gastro-esophageal reflux disease (GERD) leading to chronic aspiration should be considered in patient with SSc-ILD. In addition to treatment of GERD, appropriate immunization, supplemental oxygen to keep saturations above 88%, and education on tobacco cessation should be part of every patient's ongoing care. Lastly, pulmonary rehabilitation may be effective for some patients.[23]

3 | CONCLUSION/SUMMARY

Aside from autologous hematopoietic stem cell transplant, there is limited evidence to support a mortality benefit among SSc-ILD treatments and the benefits of all treatment strategies including combination therapies will need to be weighed against their side effects. Current management includes immunosuppressive therapy in those with subclinical ILD with high-risk features or those with clinical ILD. Anti-fibrotics should be considered in those with progressive ILD despite being on immunosuppressive therapy or if there is contraindication to immunosuppressive therapy. The ongoing trial Scleroderma Lung Study III is assessing if upfront combination of MMF and pirfenidone (anti-fibrotic) is more efficacious than MMF alone in early SSc-ILD (https://medicine.umich.edu/sites/default/files/content/downloads/SclerodermaLungStudies-August2019-Final.pdf). Future research in SSc-ILD should aim at developing tools to identify patients at risk of progressive SSc-ILD and assess appropriate timing and treatment sequences in patients with SSc.

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ORIGINAL ARTICLE

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Singapore Chapter of Rheumatologists updated consensus statement on the eligibility for government subsidization of biologic and targeted-synthetic therapy for the treatment of rheumatoid arthritis

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Abstract

Introduction: Approximately 30% of patients with rheumatoid arthritis (RA) respond inadequately to conventional-synthetic disease-modifying anti-rheumatic drugs (cs-DMARDs). However, widespread use of biologic DMARDs (bDMARDs) and targeted-synthetic (tsDMARDs) is limited by cost. We formulated updated recommendations for eligibility criteria for government-assisted funding of bDMARDs/tsDMARDs for RA patients in Singapore.

Materials and Methods: Published guidelines regarding use of bDMARD and tsDMARDs were reviewed. We excluded those without a systematic literature review, formal consensus process or evidence grading. Separately, unpublished national reimbursement guidelines were included.

Results: Eleven recommendations regarding choice of disease activity measure, initiation, order of selection and continuation of bDMARD/tsDMARDs were formulated. A bDMARD/tsDMARD is indicated if a patient has: (a) at least moderately active RA with a Disease Activity Score in 28 joints/erythrocyte sedimentation rate (DAS28-ESR) score of ≥3.2; (b) failed ≥2 csDMARD strategies, 1 of which must be a combination; (c) received an adequate dose regimen of ≥3 months for each strategy. For the first-line bDMARD/tsDMARD, either tumor necrosis factor inhibitors (TNFi), non-TNFi (abatacept, tocilizumab, rituximab), or tsDMARDs, may be considered. If a first-line TNFi fails, options include another TNFi, non-TNFi biologic or tsDMARDs. If a first-line non-TNFi biologic or tsDMARD fails, options include TNFi or another non-TNF biologic or tsDMARD. For continued bDMARD/tsDMARD subsidization, a patient must have a documented DAS28-ESR every 3 months and at least a moderate European League Against Rheumatism response by 6 months.

Conclusion: These recommendations are useful for guiding funding decisions, making bDMARD/tsDMARDs usage accessible and equitable in RA patients who fail csDMARDs.

KEYWORDS
biologic, consensus, reimbursement, rheumatoid arthritis, subsidy, targeted-synthetic

1 | INTRODUCTION

Rheumatoid arthritis (RA) affects 0.3% to 0.7% of the global population.[1] Inadequately treated RA may result in joint damage, serious extra-articular manifestations, and complications including osteoporosis and cardiovascular disease.[2-4]

Approximately 30% of patients respond inadequately to conventional-synthetic disease-modifying anti-rheumatic drugs (csDMARDs).[5] Cost limits treatment with biologic bDMARDs (bDMARDs) and targeted-synthetic DMARDs (tsDMARDs) in spite of eligibility for treatment. In Singapore, government subsidies only apply to a standard drug list. In order to qualify for subsidies for biologic therapy for RA classified under "non-standard drugs", an additional application via the Medication Assistance Fund (MAF) is needed. The MAF was set up in 2010, to help needy patients pay for expensive drugs used for selected medical conditions meeting specific clinical indicators. In many countries, the financial sustainability of high-cost therapies is a pressing issue. Evidence-based guidelines provide a framework for escalation and continuation of expensive treatments, thereby prioritizing limited resources for eligible patients. In 2013 the Singapore Chapter of Rheumatologists, College of Physicians, Academy of Medicine published a consensus guideline to guide eligibility criteria for funding bDMARDs. Since then multiple studies regarding the efficacy, safety and cost-effectiveness of newer drugs have emerged.[6-9] Several established rheumatology societies have published their recommendations after reviewing the literature. We conducted an up-to-date synthesis of evidence and applied a consensus building process to develop a set of eligibility criteria for funding of bDMARDs/tsDMARDs for treatment of Singaporean RA patients who failed csDMARDs.

The list of biologic DMARDs available in Singapore includes tumor necrosis factor inhibitors (TNFi), adalimumab (ADA), etanercept (ETA), golimumab (GOL), infliximab (INF); B cell depleting agent rituximab (RTX); T cell costimulation modulator, abatacept (ABT); and interleukin-6 inhibitor, tocilizumab (TCZ). Tofacitinib and baracitinib are 2 oral synthetic small molecule tsDMARD that have recently become available. Please see Appendix for the grouping and abbreviations of treatments for rheumatoid arthritis used in the following text and tables.

2 | METHODS

Modified Delphi methodology was used to obtain consensus, similar to the American College of Rheumatology (ACR) procedures for formulation of clinical practice guidelines and the European League Against Rheumatism (EULAR) standardized operating procedures.[10,11] This was developed in parallel with an update of the Chapter's recommendations for biologic therapy in psoriatic arthritis and axial spondyloarthritis. We formed the core workgroup (CWG: ML, GGT, PC, JL, SD), and invited a representative group of rheumatologists from restructured government hospitals and the private sector to form the taskforce panel (TFP: WWSF, KHL, YYL, AL, NLL, MM, MS, AS, ES, TTC). We aimed to update eligibility criteria for funding treatments in adult RA patients.

2.1 | Defining questions for systematic literature review of established guidelines

The CWG emailed the TFP to propose clinical questions relevant to the use of bDMARD/tsDMARDs, in addition to those addressed in the earlier guideline.[12] These focused on: (a) choice of disease activity measure; (b) disease activity threshold that warrants escalation of therapy; (c) definition of failure of csDMARD (number of strategies, combination and duration); and (d) choice of bDMARD/tsDMARD options in order of preference. Factors pertaining to continuation of bDMARD/tsDMARD therapy including frequency of documentation of disease activity and response and definition of adequate response were addressed.

2.2 | Review of established guidelines

A literature search was performed by CWG members, JL and SD. In lieu of a systematic review of the primary literature, international best practice guidelines and recommendations of rheumatology societies on bDMARD/tsDMARDs were reviewed. We searched PubMed for publications from 1 January 2011 to 22 August 2018 to identify relevant articles using the Medical Subject Headings (MeSH) terms; ("Consensus"[MeSH] OR "Consensus Development Conference, NIH" [Publication Type] OR "Consensus Development Conference" [Publication Type] OR "Consensus Development Conferences, NIH as Topic"[MeSH] OR "Consensus Development Conferences as Topic"[MeSH]) OR ("Guidelines as Topic" [MeSH] OR "Practice Guidelines as Topic" [MeSH] OR "Guideline" [Publication Type] OR "Health Planning Guidelines" [MeSH] OR "Standard of Care" [MeSH] OR "Practice Guideline" [Publication Type] OR "Clinical Protocols" [MeSH] OR "Health Systems Plans" [MeSH]) AND "Arthritis, Rheumatoid" [MeSH]. We applied the filters "English" and "Human subjects". We separately searched for unpublished guidelines governing subsidization of bDMARD/ tsDMARDs.

This search yielded 284 citations. One CWG member (JL) reviewed titles of the 284 citations and excluded those that were irrelevant, leaving 42 citations. JL reviewed abstracts of the 42 citations and excluded 13 commentaries or audits of practice, leaving 29 guidelines. Of the 29 full texts, 3 organizations had updated their guidelines once during the period of 2011 to 2018; hence, we chose

TABLE 1 Guidelines on management of rheumatoid arthritis included in the evidence synthesis for consensus development

Guideline	First author	Year of publication	Purpose	Systematic literature review	Consensus method	Evidence grading/Strength of recommendation
BSR/BHPR rheumatoid arthritis guidelines on eligibility criteria for the first biological therapy[16]	Deighton, C.	2010	Best practice	Yes	Not specified	Yes/ Yes
BSR/ BHPR guidelines on the use of rituximab in rheumatoid arthritis[30]	Bukhari, M.	2011	Best practice	Yes	Not specified	Yes/ Yes
German Society of Rheumatology[14]	Albrecht, K.	2012	Best practice	Yes	Yes	Yes/ Yes
Canadian Rheumatology Association[15]	Bykerk, V. P.	2012	Best practice	Yes	Yes	Yes/ Yes
Mexican College of Rheumatology[21]	Cardiel, M. H.	2012	Best practice	Yes	Yes	Yes/ Yes
Spanish Society of Rheumatology[24]	Sanmarti, R.	2014	Best practice	Yes	Yes	Yes/ Yes
Asia-Pacific League of Associations for Rheumatology (APLAR)[23]	Lau, C. S.	2015	Best practice	Yes	Yes	Yes/ Yes
American College of Rheumatology[25]	Singh, J. A.	2015	Best practice	Yes	Yes	Yes/Yes
Thai Rheumatism Association[22]	Louthrenoo, W.	2016	Best practice	Yes	Yes	Yes/ Yes
European League Against Rheumatism (EULAR)[26]	Smolen, J. S.	2016	Best practice	Yes	Yes	Yes/Yes
National Institute for Health and Care Excellence, NICE (TA 195): Adalimumab, etanercept, infliximab, rituximab and abatacept for the treatment of rheumatoid arthritis after the failure of a TNF inhibitor[18]	-	2010	Reimbursement	Yes	Not specified	Yes/ No
National Institute for Health and Care Excellence, NICE (TA 375): Adalimumab, etanercept, infliximab, certolizumab pegol, golimumab, tocilizumab and abatacept for rheumatoid arthritis not previously treated with DMARDs or after conventional DMARDs only have failed[17]	-	2016	Reimbursement	Yes	Not specified	Yes/ No
National Institute for Health and Care Excellence, NICE (TA 480): Tofacitinib for moderate to severe rheumatoid arthritis[19]	-	2017	Reimbursement	Yes	Not specified	Yes/ No
National Institute for Health and Care Excellence, NICE (TA 466): Baricitinib for moderate to severe rheumatoid arthritis[20]	-	2017	Reimbursement	Yes	Not specified	Yes/ No
Australia Medicare Pharmaceutical Benefits Scheme (PBS)[27]	-	2018	Reimbursement	Yes	Not specified	No/ No

the later versions. Three were not directly relevant to the clinical questions. We excluded best practice guidelines that did not undertake a systematic literature review, consensus method and evidence grading or strength of recommendations.[13] Of the remaining 23, 10 were excluded. Of the 13 guidelines, 11 were best practice and 2 (NICE and Australia's Medicare) were reimbursement guidelines (Table 1). The Australia reimbursement guidelines did not employ an evidence grading system or strength of recommendation.

In summary, the CWG reviewed guidelines published from the following: German Society of Rheumatology, Canadian Rheumatology Association, British Society of Rheumatology/ British Health Professionals for Rheumatology (BSR/ BHPR), NICE, Mexican College of Rheumatology, Thai Rheumatism Association, Asia-Pacific League against Rheumatism (APLAR), Spanish Society of Rheumatology, ACR,[11] EULAR and Australia's Medicare.[14-27] Recommendations are summarized in Table 2.

2.3 | Rating of consensus statements and assessing level of agreement with recommendations by the TFP

Voting was carried out by the TFP on the 12 draft consensus statements drawn up by the CWG.

In the first round of ratings, the TFP received an email with evidence synthesized from recent guidelines. Based on the literature synthesis and their clinical judgment, the TFP individually rated the 12 statements using a 5-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree, 5 = strongly agree). Consensus was reached if there was ≥70% agreement or disagreement. For statements that did not meet consensus after the first rating, a face-to-face meeting moderated by a CWG member (TGG) was convened, with clarification of statements and review of evidence tables. The first round of rating comprised 11 panelists. Subsequent rating was completed by 10 panelists as 1 member withdrew due to unavailability.

3 | RESULTS

Table 3 presents the final consensus statements and median level of agreement by the TFP.

3.1 | Consensus 1: A uniform disease activity measure, the DAS28-ESR should be the disease activity measure used to assess RA activity

Validated measures of RA disease activity include Clinical Disease Activity Index (CDAI), Simplified Disease Activity Index (SDAI), Routine Assessment of Patient Index Data 3 (RAPID3) and Disease Activity Score of 28 joints (DAS28) scores. The DAS28 is a composite measure, combining information on swollen and tender joints, acute phase reactants as an objective measurement of inflammation and patient global assessment on a visual analog scale.[28]

The ACR recommends a "treat-to-target approach" but did not specify a particular disease activity measure.[25] All remaining 8 best practice and both reimbursement guidelines which addressed the choice of disease activity measure included DAS28-ESR (erythrocyte sedimentation rate), among other disease activity measures. Two society guidelines, BSR/ BHPR and German Society of Rheumatology, recommended DAS28 as the disease activity measure of choice. The TFP concluded that it is preferable to have 1 uniform scale to ensure consistency in determining eligibility for subsidies. The DAS28 is widely used in clinical trials, guidelines and clinical practice.[29] It is embedded in the assessment for EULAR response criteria, commonly used to determine continuation of bDMARD/tsDMARDs. However, the swollen and tender joint count of the DAS28-ESR does not capture active synovitis in the ankle or joints of the foot and ESR may be elevated in other inflammatory conditions.

3.2 | Consensus 2: The patient must have at least moderate disease activity, defined as a DAS28-ESR ≥ 3.2

In our previous guidelines, besides a DAS28-ESR ≥ 3.2, a criterion of ≥6 swollen and tender joints was required. In the first rating, there was no agreement regarding inclusion of a swollen and tender joint count. At the meeting, it was highlighted that this requirement was meant to distinguish patients with active synovitis from patients with high patient global assessment scores leading to an erroneous reflection of active disease. Many TFP members opined that it is the responsibility of the treating rheumatologist, to identify these cases and decide against treatment escalation.

An ESR in the range of 10 to 15, a reasonable patient global assessment score of 15 or more, and less than 6 swollen or tender joints would often qualify for a DAS28-ESR ≥ 3.2. Patients with moderately active disease by DAS28-ESR but not ≥6 swollen and tender joints might never meet the threshold for treatment escalation. This may lead to denial of effective treatment in deserving patients.

In the second round of rating, TFP members agreed unanimously that there was no need for a criterion of swollen and tender joints.

The TFP's decision was consistent with the literature. All established guidelines advocated escalation to bDMARD/tsDMARDs as long as DAS28-ESR was ≥3.2, except 2: (a) NICE, which has a threshold of DAS28-ESR of ≥5.1; and (b) Australia's Medicare which has a threshold of >20 tender and swollen joints, or ≥4 major active joints including the elbow, wrist, knee, shoulder, ankle and/or hip.[17-20,27]

3.3 | Consensus 3: The patient must have failed 2 csDMARD strategies, including methotrexate (MTX) unless contraindicated, at optimal dose. At least ONE strategy must be a combination

In our previous guideline, a patient would have to fail 2 combination csDMARDs, each combination at optimal doses for ≥3 months, due

TABLE 2 Summary of recommendations for use of biologic and targeted-synthetic disease modifying anti-rheumatic drugs for rheumatoid arthritis

Guidelines	Disease Activity Measure	Definition of active disease	Definition of non-biologic treatment failure
BSR/BHPR: first biological therapy[16]	DAS28 > 3.2 & ≥3 SJ+TJ	DAS28 > 3.2	At least 2 csDMARDs, incl. MTX unless contraindicated, concurrently over 6 mo, 2 mo at target dose
BSR/BHPR on RTX[30]	DAS28 > 3.2 & ≥3 SJ+TJ	DAS28 > 3.2	At least 2 csDMARDs, incl. MTX unless contraindicated, concurrently over 6 mo, 2 mo at target dose
German Society of Rheumatology[14]	DAS28	Moderate to severe disease	At least 2 csDMARDs monotherapy or combination -by 3 mo
Canadian Rheumatology Association[15]	ACR/EULAR Boolean-based, SDAI, DAS, DAS28, RADAI, RAPID3	Moderate to high disease activity	At least 2 csDMARDs incl MTX unless contraindicated in monotherapy or combination by 3 mo at target dose csDMARD monotherapy failure if poor prognostic factors
Mexican College of Rheumatology[21]	NA	Moderate to severe disease	NA
Spanish Society of Rheumatology[24]	Any "Objective validated indices": DAS28, SDAI, ACR/EULAR	NA	csDMARD monotherapy or in combined; duration not specified Earlier bDMARD if poor prognostic factors - high disease activity, positive for CCP or RF, radiographic erosions
Asia-Pacific League of Associations for Rheumatology (APLAR)[23]	Any "clinical activity measurement"	Inadequate response by 6 mo	At least 2 csDMARDs in combination at optimal doses for 6 mo; earlier bDMARD if poor prognostic factors
American College of Rheumatology[25]	Treat-to-target strategy, not specified	Moderate or high disease activity	Early & established RA: csDMARD monotherapy or in combination, of which 1 should include MTX; duration not specified
Thai Rheumatism Association[22]	Any "Validated composite measure": DAS 28, CDAI, SDAI etc	Moderate to severe disease activity	At least 2 csDMARDs as monotherapy or combination - improvement by 3 mo; remission or low disease by 6 mo
European League Against Rheumatism (EULAR)[26]	Any validated "Composite disease activity measure"	Moderate or high disease activity	MTX monotherapy (first-line) or if MTX intolerant, LEF or SSZ; any of the 3 as monotherapy or in combination; improvement by 3 mo; remission or low disease by 6 mo
NICE (TA 195): ADA, ETA,INF, RTX and ABT for the treatment of RA after the failure of a TNFi[18]	DAS28	DAS28 > 5.1	DAS28>5.1; inadequate response to combination csDMARD; and at least one TNFi
NICE (TA 375): ADA, ETA, INF, CER,GOL, TCZ for RA not previously treated with DMARDs or after csD-MARDs only have failed[17]	DAS28	DAS28 > 5.1	DAS28>5.1; inadequate response to combination csDMARD
NICE (TA 480): Tofacitinib[19]	DAS28	DAS28 > 5.1	DAS28>5.1; inadequate response to combination csDMARD
NICE (TA 466): Baricitinib[20]	DAS28	DAS28 > 5.1	DAS28>5.1; inadequate response to combination csDMARD
Australia Medicare Pharmaceutical Benefits Scheme27	Swollen and tender joint count & ESR/CRP	Active joint count of ≥20 joints OR ≥4 major joints (defined as elbows, wrists, knees, ankles, shoulders, hips) & ESR > 25 mm/h or CRP > 15 mg/L	At least 2 csDMARD (MTX,SSZ, LEF, Azathioprine, CyA, Sodium aurothiomalate at standard doses) for≥3 mo each

Abbreviations: ABT, abatacept; ADA, adalimumab; bDMARD, biologic disease-modifying anti-rheumatic agent; BSR/BHPR, British Society of Rheumatology/ British Health Professionals for Rheumatology; CDAI, Clinical Disease Activity Index; CER, certolizumab; CRP, C-reactive protein; csDMARD, conventional-synthetic disease-modifying anti-rheumatic agent; CyA, cyclosporine A; DAS28, Disease Activity Score – 28 joints; ESR, erythrocyte sedimentation rate; ETA, etanercept; GOL, golimumab; HCQ, hydroxychloroquine; INF, infliximab; LEF, leflunomide; MTX, methotrexate; NA, not available; NICE, National Institute for Health and Care Excellence; non-TNFi, non-tumor necrosis factor inhibitor; RADAI, Rheumatoid Arthritis Disease Activity Index; RAPID3, Routine Assessment of Patient Index Data; RTX, rituximab; SDAI, simplified disease activity index; SSZ, sulphasalazine; TCZ, tocilizumab; TNFi, tumor necrosis factor inhibitor; tsDMARD, targeted-synthetic disease-modifying anti-rheumatic agent.

Choice of 1st line biologic after failure of 2 csDMARD strategies	Stand on RTX based on serology	Stand on biosimilar	Definition of response	Choice of 2nd line biologic
TNFi, ABT, TCZ	NA	NA	Good or moderate EULAR response	NA
RTX; especially if TNFi contraindicated	Seropositive patients are more likely to respond	NA	Good or moderate EULAR response	NA
TNFi, ABT, TCZ	NA	NA	Remission or low disease activity by 6 mo	Another TNFi, ABT, RTX, or TCZ
TNFi or RTX if seropositive	RTX after failure of DMARDs or TNFi if RF positive	NA	Remission or low disease activity by 3 mo	RTX if RF positive or ABT,TCZ or another TNFi after TNFi failure of TNFi
TNFi, CER, GOL; use RTX if contraindication to TNFi	Seropositive patients are more likely to respond	NA	Remission or low disease activity by 6 mo	CER, GOL, ABT, RTX or TCZ
TNFi+MTX, TCZ, ABT or "in certain cases" RTX	Seropositive patients are more likely to respond	NA	Assess at 1-3 mo intervals if active disease, new treatment initiated or therapeutic goal not reached	TNFi+MTX, TCZ, ABT or in certain cases RTX
TNFi, ABT, TCZ, RTX	NA	NA	Remission or low disease activity by 6 mo	TNFi, ABT, TCZ, RTX or tofacitinib
Early RA: TNFi or non-TNFi Established RA: TNFi or non-TNFI or tofacitinib	NA	NA	Low disease activity; duration not specified	Fail TNFi first-line: use non-TNFi biologic over tofacitinib Fail non-TNFi: use another non-TNFi over tofacitinib
Any bDMARD or tsDMARD	NA	NA	Achieve improvement by 3 mo, remission or low disease activity by 6 mo	Switch to any bDMARD or tsDMARD
bDMARD over tsDMARD	NA	Use interchangeably	Achieve improvement by 3 mo, remission or low disease activity by 6 mo	Switch to any bDMARD or tsDMARD
ADA,ETA, INF, CER, GOL, TCZ, ABT	NA	NA	Moderate EULAR response by 6 mo	ADA, ETA,INF, RTX and ABT
ADA,ETA, INF, CER, GOL, TCZ, ABT	NA	NA	Moderate EULAR response by 6 mo	RTX+MTX
Tofacitinib may be used	NA	NA	Moderate EULAR response by 6 mo	NA
Baricitinib may be used	NA	NA	Moderate EULAR response by 6 mo	NA
ABT, ADA, ETA, GOL, TCZ, CER, INF, RTX, tofacitinib, baricitinib	NA	NA	20% decrease in no. of active joints, ESR and/or CRP, by 3 mo	NA

to lack of efficacy or desired response or side effects, before qualifying for bDMARDs.[12]

In this current systematic review, 8 major best practice guidelines, including ACR and EULAR, recommend ≥2 csDMARDs as monotherapy or in combination.[14-16,22-26,30] Only the Mexican College of Rheumatology guidelines did not address this.[21] Australia's Medicare requires a patient to have received ≥2 csDMARD for ≥3 months each at standard doses, in monotherapy or combination therapy.[27] Methotrexate (MTX) should be included unless contraindicated by significant toxicity,[31] consistent with evidence that a third of patients respond to MTX monotherapy and combination therapy is efficacious.[32,33] NICE requires patients to have received combination csDMARDs before escalation (17-20). All TFP members agreed with this updated statement, allowing earlier escalation to bDMARD/tsDMARDs.

3.4 | Consensus 4: An optimal duration of a csDMARD strategy should be ≥3 months

The optimal duration of csDMARDs was not specified in the ACR, Mexican and Spanish guidelines. The Spanish guidelines recommend earlier bDMARDs/tsDMARDs if there are poor prognostic factors such as seropositivity, erosions or high disease activity.[21,24,25]

The EULAR, APLAR and Thai Rheumatism Association recommend treatment escalation if there is no improvement by 3 months or inadequate response by 6 months with csDMARDs.[22,23,26] The German and Canadian guidelines recommend escalation after 3 months of ≥2 csDMARD strategies at optimal doses.[14,15] The BSR/BHPR guidelines were less stringent with recommended 2-month duration of ≥2 csDMARDs strategies at target doses.[16,30]

NICE recommends treatment escalation in inadequate response to csDMARDs but does not state the duration. Australia's Medicare recommends escalation after ≥2 csDMARDs in monotherapy or combination therapy for ≥3 months each.

The TFP agreed that each optimally dosed csDMARD strategy should be used for at least 3 months to allow adequate duration for demonstrable efficacy and desired response due to the slow onset of action of most csDMARDs.

3.5 | Consensus 5: An optimal trial of csDMARDs should include MTX at 15-20 mg/wk, unless contraindicated

EULAR recommends a dose of MTX at 25-30 mg/wk. Special mention was made that maximally tolerated doses are lower in Asians, specifically, 20 mg/wk in China and 16 mg/wk in Japan.[26] German guidelines advocate a minimum of 15 mg/wk. In renal or hepatic impairment, or advanced age, lower doses of 7.5-10 mg/wk are considered adequate.[14] The Canadian and Mexican guidelines recommend titrating MTX up to 25 mg/wk.[15,21] APLAR advocates titrating MTX up to a "maximally tolerated dose".[23] Australia's Medicare reimbursement guidelines suggest MTX ≥ 20 mg/wk.[27]

Four best practice guidelines including the ACR and BSR/BHPR, and the NICE reimbursement guidelines did not specify the optimal dose.[16-20,22,24,25,30]

In keeping with the above-mentioned international guidelines, and tailored to an Asian population, MTX 15-20 mg/wk is considered adequate to assess its efficacy.

3.6 | Consensus 6: For the first-line biologic, either TNFi, non-TNFi (ABT, TCZ, RTX), or tsDMARD may be considered, in no order of preference

The above recommendations reflect the evidence that the addition of a bDMARD in patients who fail csDMARDs is effective in controlling inflammation, retarding radiological progression and improving function in RA.[6,7,10,34-37] In the first round of voting, all TFP members voted that TNFi could be considered as first-line, but no consensus was reached regarding non-TNFi, RTX or tsDMARDs. It was clarified during the meeting that choice of the above options as first-line was not mutually exclusive; TFP members could agree to more than 1 option as a first-line bDMARD/tsDMARD. With this clarification, all TFP members voted in support of any bDMARD or tsDMARD as first-line options after failure of csDMARDs.

Pertaining to the use of TNFi and non-TNFi (ABT, TCZ) as first-line, all best practice guidelines except the Canadian, and both NICE and Australia's Medicare reimbursement guidelines, included all as first-line biologic options in no order of preference.[14,15,17,22-27,30]

With regard to RTX as a first-line biologic, older guidelines published before 2015 and NICE did not recommend RTX as a first-line biologic (Table 1). In contrast, more recent publications from major societies including ACR and EULAR and the BSR recommended that RTX can be used as a first-line biologic after csDMARD failure, as did Thai, APLAR and Australia's national reimbursement guideline.[22,23,25-27,30] To our knowledge, head-to-head studies of biologics in csDMARD inadequate responders are lacking, and no trials compare the efficacy of RTX versus ABT or TCZ in csDMARD failure. One recent study showed that RTX is non-inferior to TNFi in seropositive RA patients who were biologic-naïve.[38]

There were conflicting recommendations on using tsDMARDs as a first-line biologic. ACR recommends a bDMARD (TNFi or ABT, TCZ, and RTX) over tofacitinib for early RA (defined as 6 months or less) after MTX monotherapy failure.[25] This was a conditional recommendation; quality of evidence relating to the superiority of 1 option over another was low. Similarly, EULAR and APLAR recommended any bDMARD over a tsDMARD. In contrast, for established RA (defined as ≥6 months), ACR recommended tsDMARD on par with any bDMARD. The Thai guidelines suggested that any bDMARD or tsDMARD may be used based on a high level of evidence and agreement.[22]

In summary, the advent of newer biologics/tsDMARD has expanded our armamentarium for RA refractory to csDMARD. These

TABLE 3 Updated consensus statement on initiation and continuation of bDMARD/tsDMARD for treatment of rheumatoid arthritis

	Agreement score (1st voting round: 11 respondents; 2nd voting round: 10 respondents)	Median agreement scores of clinical scenarios on a Likert scale of 5	Voting round
Recommendations relating to initiation of bDMARD/tsDMARD therapy			
1. A uniform disease activity measure, the DAS28-ESR, should be used as the disease activity measure to assess RA activity	100% (4 agree, 7 strongly agree)	5	1
2. The patient must have at least moderate disease activity, defined as a DAS28-ESR of ≥3.2	100% (5 agree, 6 strongly agree)	5	1
3. The patient must have failed 2 csDMARD strategies, including methotrexate (MTX) unless contraindicated, at optimal dose. At least 1 strategy must be a combination.	100% (2 agree, 8 strongly agree)	5	2
4. An optimal duration of a csDMARD strategy should be ≥3 mo	100% (2 agree, 8 strongly agree)	5	2
5. An optimal trial of therapy should include MTX at target dose of 15-20 mg/wk, unless contraindicated	90.91% (2 agree, 8 strongly agree)	5	1
Recommendations relating to options of bDMARD/tsDMARD therapy			
6. For the first-line biologic, either TNFi, non-TNFi (ABT, TCZ or RTX) or tsDMARD may be considered, in no particular order of preference A For choice of first-line biologic, TNFi may be considered B For choice of first-line biologic, ABT or TCZ may be considered C For choice of first-line biologic, RTX may be considered D For choice of first-line biologic, a tsDMARD may be considered	100% (10 strongly agree) 100% (1 agree, 9 strongly agree) 100% (2 agree, 8 strongly agree) 100% (1 agree, 9 strongly agree)	5 5 5 5	2
7. Choice of second-line bDMARD/tsDMARD after failing TNFi: If first-line TNFi fails, second-line treatment may be another TNFi, non-TNF biologic (ABT, TCZ or RTX) or tsDMARD, in no particular order of preference A second-line treatment may be another TNFi B second-line treatment may be ABT or TCZ C second-line treatment may be RTX D second-line treatment may be a tsDMARD	100% (3 agree, 7 strongly agree) 100% (10 strongly agree) 100% (2 agree, 8 strongly agree) 100%(10 strongly agree)	5 5 5 5	2
8. Choice of second-line bDMARD/tsDMARD after failing non-TNFi or tsDMARD: If a first-line non-TNFi (ABT, TCZ, or RTX) or tsDMARD fails, second-line treatment may be a TNFi, another non-TNF biologic (ABT, TCZ or RTX) or tsDMARD A second-line treatment may be a TNFi B second-line treatment may be ABT or TCZ C second-line treatment may be RTX D second-line treatment may be a tsDMARD	100% (10 strongly agree) 100% (10 strongly agree) 100% (10 strongly agree) 100% (10 strongly agree)	5 5 5 5	2
9. Co-morbidities, pregnancy/lactation and drug safety should be considered when determining treatment strategies and selecting a bDMARD/tsDMARD	100% (2 agree, 9 strongly agree)	5	1
10. A biosimilar may be substituted for the originator drug for better cost-effectiveness	90.91% (5 agree, 5 strongly agree)	4	1
Recommendations relating to continuation of bDMARD/tsDMARD therapy			
11. All patients on bDMARD or tsDMARD must have DAS28-ESR documented every 3 mo; bDMARD/tsDMARD therapy may be continued if the patient has at least a EULAR moderate response by 6 mo from commencement	100% (5 agree, 6 strongly agree)	5	1

are being included in newer guidelines as evidence of clinical efficacy and long-term safety data accrue.

In real-world practice, the choice among the non-TNFi biologics is often based on specific patient characteristics, safety considerations, patient preference and experience of the prescribing physician. It is well recognized that seropositivity confers a better response to RTX. A B-cell depleting agent may also be preferred in a RA patient with lymphoma or systemic lupus erythematosus-RA overlap. ABT may be preferred in patients with multiple serious co-morbidities, as a network meta-analysis suggested it to be associated with a significantly lower risk of serious adverse events compared to other bDMARDs.[39] Concurrent treatment with MTX is known to improve the efficacy of most biologics and many clinical trials examine the efficacy of biologics when used in combination with MTX.[40-45] However, observational registry data show that approximately 10%-30% of patients are on biologic monotherapy for various reasons

such as MTX intolerance, suggesting that MTX-biologic combination occurs less frequently in practice than in clinical trials.[46-49] In a setting where patients are unable to take concomitant csDMARDs, TCZ or tofacitinib may be preferred as non-inferiority of monotherapy versus combination with MTX has been demonstrated in RA.[50-52]

3.7 | Consensus 7: Choice of second-line bDMARD/tsDMARD after failing TNFi: If first-line TNFi fails, second-line treatment may be another TNFi, non-TNF biologic (ABT, TCZ or RTX) or tsDMARD, in no order of preference

All 9 best practice guidelines and reimbursement guidelines allow any bDMARD to be used after failure of a TNFi as first-line.[14-27,30]

Five best practice guidelines did not include tsDMARDs, as they were not available or new at the time of formulating the recommendations.[14-16,21,24,30] Two recent best practice guidelines, the EULAR and Thai Rheumatism Association and both reimbursement guidelines allow any bDMARD or tsDMARD after failure of a TNFi.[17-20,22,26,27] APLAR conditionally recommends any bDMARD over a tsDMARD due to less long-term safety data in the latter.[23]

The ACR conditionally recommends a non-TNFi over another TNFi, with tofacitinib being a consideration after a non-TNFi.[25] This was based on evidence of better efficacy for non-TNFi (ABA, TCZ and RTX) in patients who have already received TNFi therapy.[53]

The TFP appraised in consensus any bDMARD or tsDMARD as appropriate second-line agent after failure of a TNFi due to lack of efficacy or side effects. Theoretically, where there is primary failure of the first biologic, a biologic of a different class with a different mode of action may be preferred; whereas, in secondary failure where patients lose the initial good response due to purported anti-drug antibodies, cycling to another biologic of the same class (ie another TNFi) may still produce a good clinical response.[54] There are no interventional trials examining the efficacy of various bDMARDs in primary versus secondary failure. Nonetheless, studies have shown that approximately half of TNFi failures do respond to a second TNFi, regardless of reasons for discontinuation of the previous drug, justifying this as a reasonable option.[55,56]

3.8 | Consensus 8: Choice of second-line bDMARD/tsDMARD after failing non-TNFi or RTX or tsDMARD

If a first-line non-TNFi (ABT, TCZ, RTX) biologic or tsDMARD fails, second-line treatment may be a TNFi or another non-TNF biologic (TCZ, ABT, RTX) or tsDMARD.

Switching to any bDMARD due to moderate or high disease activity despite a non-TNFi is supported by 6 best practice guidelines including ACR and EULAR, and both reimbursement guidelines.[14,16,22,24-26,30] The ACR conditionally recommended non-TNFi agents over tofacitinib because of the longer-term safety data and clinical experience with non-TNF biologics compared to tofacitinib at time of the guideline development.[25] Also, other non-TNFi with different mechanisms of action may be efficacious.[25]

However, use of any bDMARD or tsDMARD in the instance of failing a first-line non-TNFi is supported by the two most recently published best practice guidelines in 2016 (EULAR and Thai Rheumatism Association) and Australia's Medicare and NICE reimbursement guidelines.[17-20,22,25,27,57]

In keeping with recommendations from major rheumatology societies and reimbursement guidelines, with recent studies of tsDMARD efficacy and safety,[58,59] all TFP members voted for the use of all other options (bDMARD/ tsDMARD) as second-line after failure of non-TNFi. This leaves the treating rheumatologist with significant discretion in deciding on a second-line agent.

3.9 | Consensus 9: Co-morbidities, pregnancy/lactation and drug safety should be considered when determining treatment strategies and selecting a bDMARD/tsDMARD

The TFP emphasized that the benefits and risks of prescribing a bDMARD/tsDMARD need to be discussed with the individual. The choice of biologics should be individualized to each patient, based on their comorbidity profile and special circumstances, for which specific guidance is beyond the scope and intent of this consensus guideline. This statement provides a safeguard against expectations and demands to indiscriminately escalate biologics. Limitations of the available evidence should be discussed with the patient to arrive at a shared decision.[60-62]

3.10 | Consensus 10: A biosimilar may be substituted for the originator drug for cost-effectiveness

Most major guidelines did not address this, as there was insufficient evidence regarding the safety and efficacy of biosimilars at time of publication. EULAR and NICE were of the opinion that biosimilars can be used interchangeably with the originator drug.[26,57] Healthcare being a shared resource, the most cost-effective treatment should be prioritized if safety and efficacy are similar.

3.11 | Consensus 11: All patients on bDMARD/tsDMARDs must have DAS28-ESR documented every 3 months; bDMARD/tsDMARD therapy may be continued if the patient has at least a EULAR moderate response by 6 months

Response to treatment should be determined by 6 months, with 6 major best practice guidelines including EULAR and APLAR; and the NICE reimbursement guideline in agreement, stating that an improvement would be expected by 3 months and a response by 6 months.[14,17-23,26] There were varying definitions of "response".

Many defined it as remission or low disease activity, without specifying the measure used. Most used DAS28-ESR as the disease activity measure of choice. The NICE guidelines defined response as at least a moderate EULAR response.[17-20]

Two best practice guidelines (Canadian and Spanish) and Australia's Medicare require treatment response to be determined by 3 months.[15,24,27] The ACR and BSR/BHPR guidelines do not specify the duration after initiation of bDMARD/tsDMARDs to assess response. ACR defines response as remission or low disease activity.[25] BSR/BHPR defines response as a moderate-good EULAR response.

All TFP members agreed that to standardize disease monitoring during bDMARD/ tsDMARD treatment, DAS28-ESR should be documented at least every 3 months, and response defined as at least a moderate EULAR response by 6 months. The EULAR response criterion was selected as it embeds the DAS28-ESR.

4 | DISCUSSION

An updated set of recommendations on the use of bDMARDs and tsDMARDs was derived for RA patients with refractory disease despite csDMARDs. An eligible patient should have active RA with moderate to severe disease activity with a DAS28-ESR ≥ 3.2. There is no minimum swollen and/or tender joint count. They must have failed ≥2 csDMARD strategies, ≥1 strategy must be a combination, lasting ≥3 months each. This should include MTX, unless contraindicated, at a minimum of 15-20 mg/wk.

Eligible patients may be given any bDMARD/tsDMARD as first-line. For continued therapy, all patients on bDMARD/tsDMARDs must have a DAS28-ESR documented 3 monthly and demonstrate at least a EULAR moderate response after 6 months. Switching to another bDMARD/tsDMARD may be done at the rheumatologist's discretion if DAS28-ESR remains ≥3.2. If a TNFi as first-line has failed, the patient may be switched to either a TNFi, non-TNFi (ABT, TOC, RTX), or tsDMARD. Similarly, if a non-TNFi as first-line has failed, the patients may be switched to any bDMARD/tsDMARD. This reflects the growing evidence of TNFi, non-TNFi and tsDMARDs' efficacies in improving disease activity, radiographic outcomes and safety. Flexibility in the updated consensus statements allows significant discretion by the treating rheumatologist based on each patient's characteristics. The choice of bDMARD/tsDMARD should factor in patients' co-morbidities. Where safety data is limited, this should be discussed to come to a shared decision.

There are several limitations to our study. Not all clinically relevant questions were addressed as they were not specifically raised by the TFP and thus not included in our systematic literature review. For example, we did not specifically examine the scenario of use of subsequent biologics in primary versus secondary biologic failure. Primary literature that is pertinent to these may not have been included but we believe various caveats were incorporated in the TFP discussions by expert opinion. As only 1 person (JL) performed the review, excluded citations and reviewed abstracts, this could create some bias in the selection of the literature search. Of note, we did not perform a review of the primary literature of clinical trials; we could not assign an evidence level or grading to each recommendation.

The consensus methodology used is rigorous and is a systematic approach to reaching agreement through evidence-based literature and expert opinion. Funding decisions for expensive therapies such as the biologics in RA should not be left to the treating physician's prerogative and discretion of each institution's authority in countries where there is no universal healthcare coverage. Consensus criteria at a national level will provide consistency and guide best practice. Our evidence-based recommendations are not only useful in the local context but applicable to the Asia-Pacific and wider regions where there is a need to prioritize limited healthcare budget resources for eligible patients. It provides a framework for escalation of treatment and continuation of expensive treatments like biologics. The consensus can be revised as future evidence on treatment strategies emerge.

5 | CONCLUSION

We developed a set of eligibility criteria to aid subsidization of bDMARD/tsDMARDs for patients with active RA who have failed csDMARDs in Singapore. This is an important step toward ensuring equitable access to effective therapy in similarly resource-constrained countries, where government schemes help fund expensive treatments.

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CONFLICT OF INTEREST

The authors have disclosed the following conflicts of interest. JL has received conference support from Johnson & Johnson, AbbVie, Sanofi. PPC has received research support from Novartis and conference support from Sanofi. WWSF has served on advisory boards for AbbVie and received speaker honorarium from Novartis. YYL has participated on advisory boards for Pfizer and Boehringer Ingelheim, received research support from Pfizer and conference support from AbbVie. NLL has participated on advisory boards for Pfizer. MM has been involved in educational activities supported by Novartis, Pfizer, AbbVie, Roche, Johnson & Johnson, Astellas, Sanofi, Amgen, Celltrion, Euroimmun. AS has been involved in educational activities supported by Novartis; received research support from Novartis and conference support from Pfizer. MKS has received conference support from Pfizer, Amgen, AbbVie. TTC has received conference support from Pfizer. GGT has received conference support from AbbVie. ML has participated on advisory boards for Pfizer, Eli Lilly, Gilead;

speaking honorarium from Johnson & Johnson; conference support from Pfizer, Novartis and Sanofi and is the site-PI for a pharmaceutical-funded registry. All other authors declare no conflict of interest.

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APPENDIX

Grouping and Abbreviations of Treatment for Rheumatoid Arthritis

csDMARD	MTX, SSZ, LEF, HCQ, CyA
bDMARD	TNFi, ABT, RTX, TCZ
tsDMARD	Tofacitinib, Baricitinib
TNFi	ADA, CER, ETA, GOL, INF
non-TNFi	ABT, TCZ, RTX

Abbreviations: ABT, Abatacept; ADA, adalimumab; bDMARD, biologic disease-modifying anti-rheumatic agent; CER, certolizumab; csDMARD, conventional synthetic disease-modifying anti-rheumatic agent; CyA, Cyclosporine A; ETA, etanercept; GOL, golimumab; HCQ, Hydroxychloroquine; INF, infliximab; LEF, Leflunomide; MTX, Methotrexate; non-TNFi, non- Tumour Necrosis Factor inhibitor; RTX, rituximab; SSZ, Sulphasalazine; TCZ, tocilizumab; TNFi, Tumor Necrosis factor inhibitor; tsDMARD, targeted synthetic disease-modifying anti-rheumatic agent.

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Singapore chapter of rheumatologists' updated consensus statement on the eligibility for government subsidization of biologic and targeted therapy for the treatment of psoriatic arthritis

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Abstract

Aim: There have been major advances in biologic treatment options for psoriatic arthritis (PsA) since the publication of the 2015 consensus recommendations by the Chapter of Rheumatologists, College of Physicians, Academy of Medicine, Singapore, for government-assisted funding, thus warranting a revision of this guideline.

Methods: Recent trials and nine published guidelines on the use of biologic therapy for PsA were reviewed. Based on the synthesized evidence, a task force panel (TFP), consisting of 10 practicing rheumatologists in Singapore, rated the statements pertaining to the use of biologic therapy, using a modified Delphi approach. Consensus was obtained if >70% agreed on a statement.

Results: The TFP agreed on 10 recommendations pertaining to the initiation, choice and continuation of biologic therapy. A biologic is indicated in patients with PsA: (a) with at least three swollen and tender joints, digits or entheses; and (b) who have failed at least two conventional synthetic disease-modifying anti-rheumatic drug (csDMARD) strategies for a minimum of 3 months each. Any approved drug class including tumor necrosis factor inhibitors, interleukin-17 inhibitors (IL-17i), IL-12/23i or targeted synthetic DMARDs may be considered as first-line treatment, and continued only if a response is achieved by 6 months.

Conclusion: These recommendations developed through a formal consensus method may be useful to guide funding considerations for appropriate and equitable use of biologic therapy for eligible patients with PsA.

KEYWORDS

biologic therapy, consensus, psoriatic arthritis, recommendations

1 | INTRODUCTION

Psoriatic arthritis (PsA) is a heterogeneous, chronic inflammatory disease characterized by inflammatory arthritis involving peripheral and axial joints, enthesitis and dactylitis, skin psoriasis and nail dystrophy. It affects 0.02%-0.25% of people globally. Although only limited epidemiological data are available from Asia, prevalence rates are believed to be low (0.02% in China).[1] In Singapore, PsA patients constituted 4% of outpatients with rheumatologic conditions at a tertiary hospital.[2]

Disease severity may range from mild to severe and erosive, deforming arthritis. PsA is also associated with metabolic syndrome and a higher risk of cardiovascular death.[3,4] Uncontrolled disease is associated with progressive joint damage, poor health-related quality of life (HRQoL), functional and work impairment, all of which are worse in patients with PsA than in those with skin psoriasis alone.[5-7] The psychosocial burden in PsA further affects the HRQoL, and is much worse than in patients with rheumatoid arthritis (RA).[7-9] It is evident that this disease is associated with substantial clinical burden and cost to both the patient and society.

Current treatment options include nonsteroidal anti-inflammatory drugs (NSAIDs), conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs), biological DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs). Although csDMARDs remain first-line options along with NSAIDs and local glucocorticoid injections, there are only limited data from randomized controlled trials (RCT). Most trials done to date are either underpowered or show conflicting results.[10,11] Widely used csDMARDs include sulfasalazine, leflunomide, methotrexate (MTX) and cyclosporine.[11,12]

By contrast, there is growing evidence for bDMARDs, with several RCTs demonstrating improved clinical and radiological outcomes in patients naïve to csDMARD as well as in those with failure of csDMARD or tumor necrosis factor inhibitors (TNFi).[12-21] However, the high cost prohibits the widespread use of these drugs. In Singapore, expensive medications including bDMARDs are funded through a complex mix of personal out-of-pocket payment, hospitalization-focused personal and government-aided medical insurance schemes and limited government subsidies provided only to patients in lower income classes. The Medication Assistance Fund (MAF) was established in 2013 to support prescription of costly drugs for specific clinical indications. These drugs are selected based on guideline recommendations and cost-effective analyses by the newly set up Agency for Care Effectiveness (ACE) established by the Singapore Ministry of Health. We published a consensus statement in 2015 providing recommendations on eligibility for bDMARDs to guide such government funding decisions.[22] Our consensus statement was reviewed and adopted by ACE, which led to the inclusion of TNFi in the MAF approved list. This guidance has largely determined the pattern of biologic use for subsidized patients in the public sector hospitals. At the time of the literature review for the previous consensus (up to 2013), TNFi were the only licensed bDMARDs for use in PsA. Since then, treatment options have widened with the availability of interleukin-17 inhibitor (IL17i) secukinumab, IL-12/23 inhibitor (IL12/23i) ustekinumab, the oral Janus kinase inhibitor tofacitinib and the phosphodiesterase-4 inhibitor (PDE4i) apremilast.[12-21]

The Chapter of Rheumatologists, College of Physicians, Academy of Medicine, Singapore (henceforth called 'the Chapter') thus saw importance in updating the recommendations for the appropriate use of biologic agents for PsA. Our guideline seeks to outline an eligibility framework to guide government funding decisions to facilitate equitable access to biologic therapy.

2 | METHODS

The guidelines were developed in parallel with an update of the Chapter's recommendations for biologic therapy in RA and axial spondyloarthritis (axSpA). A Core Working Group (CWG) was formed (CC, ML, GGT, PC). Two members of the CWG (ML, CC) reviewed the primary clinical trials, and performed a systematic literature review of established practice guidelines and recommendations on biologic therapy in PsA published after 2011. The CWG developed draft recommendations for rating by an invited task force panel (TFP). A modified Delphi approach was used, which is similar to that followed by the American College of Rheumatology (ACR) and the European League Against Rheumatism (EULAR).[23,24] The TFP (MM, YYL, TCT, SMK, AL, AS, NLL, KHL, ES, WF) comprised of 10 locally recognized rheumatologists from all government restructured hospitals in Singapore, with additional representation from rheumatologists in the private sector.

2.1 | Review of literature and established guidelines

The CWG first reviewed six primary clinical trials on non-TNFi biologic therapy, namely secukinumab, ustekinumab and tofacitinib (Table 1). We excluded trials on TNFi as they were reviewed in our previous Chapter guidelines.[22]

A systematic search in MEDLINE was also conducted to identify relevant practice guidelines from 1 January 2011 to 22 August 2018 using the following Medical Subject Headings (MeSH) terms: (("Consensus"[MeSH] OR "Consensus Development Conference, NIH" [Publication Type] OR "Consensus Development Conference" [Publication Type] OR "Consensus Development Conferences, NIH as Topic"[MeSH] OR "Consensus Development Conferences as Topic"[MeSH]) OR ("Guidelines as Topic"[MeSH] OR "Practice Guidelines as Topic"[MeSH] OR "Guideline" [Publication Type] OR "Health Planning Guidelines"[MeSH] OR "Standard of Care"[MeSH] OR "Practice Guideline" [Publication Type] OR "Clinical Protocols"[MeSH] OR "Health Systems Plans"[MeSH])) AND "Arthritis, Psoriatic"[MeSH]. The filters "English" and "Human subjects" were then applied. This search yielded 137 citations. Two CWG members (CC, ML) independently screened through the titles and/or abstracts of the 137 citations and excluded those that were not relevant (eg subject matter was not PsA or not pertaining to treatment of PsA). We then selected only English guidelines

TABLE 1 Summary of non-TNFi biologic trials in psoriatic arthritis published up to August 2018[a]

Drug	Study, (y)	Dose	N	Population	Entry criteria	Mean/ median SJC, TJC at entry	ACR20[b] % (time of assessment)	Improvement in					
								Arthritis	Enthesitis	Dactylitis	Skin	Nails	Axial disease
Secukinumab (SEC) IL-17i	FUTURE1 (2015)[17]	IV 150 mg q 4 wk	606	NSAID, csD-MARD &/or TNFi IR	≥3 SJC + ≥3 TJC	12.5, 23.8[c]	50% (wk 24)[c]	Y	Y	Y	Y	NA	NA
		IV 75 mg q 4 wk				12.7, 23.4[c]	50.5% (wk 24)[c]	Y			Y	NA	NA
Secukinumab (SEC) IL-17i	FUTURE2 (2015)[18]	SC 300 mg q 4 wk	397	NSAID, csD-MARD &/or TNFi IR	≥3 SJC + ≥3 TJC	11.2/20.2	54% (wk 24)[c]	Y	NS	NS	Y	NA	NA
		SC 150 mg q 4 wk				11.9, 24.1	51% (wk 24)[c]	Y			Y	NA	NA
		SC 75 mg q 4 wk				10.8, 22.2	29% (wk 24)[c]	±			NS	NA	NA
Ustekinumab (UST) IL-12/23i	PSUMMIT1 (2013)[15]	45 mg q 12 wk	615	NSAID &/or csDMARD IR	≥5 SJC + ≥5 TJC CRP ≥ 3.0 mg/L Active PsO	10/18	42.4% (wk 24)	Y	Y	Y	Y	NA	Y
		90 mg q 12 wk				10, 20	49.5% (wk 24)	Y	Y	Y	Y	NA	Y
Ustekinumab (UST) IL-12/23i	PSUMMIT2 (2014)[14]	45 mg q 12 wk	312	NSAID, csD-MARD &/or TNFi IR	≥5 SJC + ≥5 TJC CRP ≥ 3.0 mg/L	12, 22	43.7% (wk 24)	Y	NS	NS	Y	NA	NS
		90 mg q 12 wk				11, 22	43.8% (wk 24)	Y	Y	NS	Y	NA	NS
Tofacitinib (TOF) Oral JAKi	OPAL Beyond (2017)[19]	5 mg twice daily	395	TNFi IR	≥3 SJC + ≥3 TJC Active PsO	12.1, 20.5	50% (3 mo)	Y	NS	NS	NS	NA	NA
		10 mg twice daily				12.8, 25.5	47% (3 mo)	Y	NS	NS	Y	NA	NA
Tofacitinib (TOF) Oral JAKi	OPAL Broaden (2017)[20]	5 mg twice daily	422	csDMARD IR, TNFi naïve	≥3 SJC +≥3 TJC Active PsO	12.9, 20.5	50% (3 mo)	Y	NS	NA	Y	NA	NA
		10 mg twice daily				11.7, 20.3	61% (3 mo)	Y	Y	NA	Y	NA	NA

Abbreviations: ACR20, American College of Rheumatology 20% improvement criteria; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; IL-12/23i, interleukin-12/23 inhibitors; IL-17i, interleukin-17 inhibitors; IR, inadequate responders; JAKi, Janus kinase inhibitor; NA, not assessed; NS, not significant; PsO, psoriasis; q, every; SJC, swollen joint count; TJC, tender joint count; TNFi, tumor necrosis factor inhibitors; Y, yes.

[a]Excluded studies on certolizumab pegol, Ixekizumab and Apremilast as these are not available in Singapore.

[b]Primary endpoint of all studies was ACR 20 (or modified ACR 20 using 76/78 SJC/TJC).

[c]Denotes use of the 76/78 SJC/TJC. All other joint counts based on 66/68 SJS/TJC.

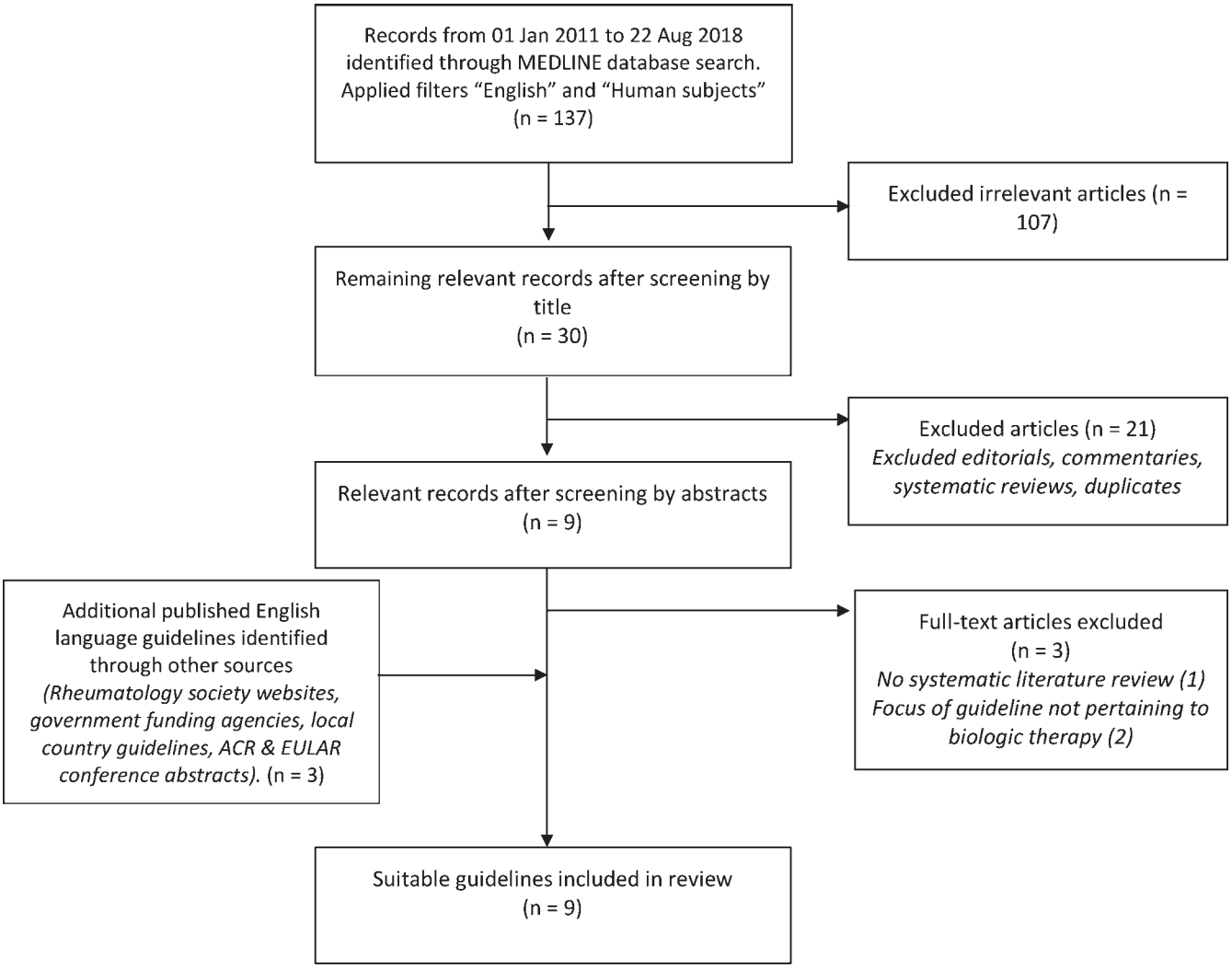

FIGURE 1 Flow diagram on study selection process

that included a systematic literature review with appropriate quality assessment of evidence and a consensus process. We additionally searched websites for guidelines of rheumatology societies or agencies governing subsidization of biologic therapy that were not published in MEDLINE, ACR and EULAR conference abstracts for unpublished updated guidelines and contacted practicing clinicians from other countries for their country guidelines. This process finally yielded nine guidelines (Figure 1, Table 2).

We excluded trials on apremilast as it is currently not available in Singapore and other South-East Asian countries, and its efficacy is modest with limited guideline recommendations for its use. Abatacept was not considered as it is not recommended by any of the reviewed guidelines.

2.2 | Creation of preliminary statements

To draft statements relevant for discussion, the CWG sent out preselected topics to the TFP and solicited their opinions on further clinically important topics. Considering the TFP's input, the CWG then selected topics relevant to clinical decision-making in the eligibility for biologic therapy and where evidence-based guidance was available. Statements for TFP voting were finalized in a CWG meeting.

2.3 | Rating the appropriateness of preliminary statements by the TFP

Ratings were conducted via an online survey platform. In the first round, the TFP was provided with summarized evidence synthesized from the reviewed trials and guidelines, rating instructions and a link to an online rating form. Based on the presented literature and their expert opinion, each TFP member independently rated each statement on a five-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree, 5 = strongly agree). An agreement was defined as Likert score of 4 or 5. A consensus was obtained if there was ≥70% agreement. The CWG and the TFP convened a face-to-face

TABLE 2 Summary of recommendations reviewed for biologic disease-modifying anti-rheumatic drug use in psoriatic arthritis

Organization (y of publication)	Type	Criteria for active disease	Treatments to have failed	1st line biologic	2nd line if 1st line fails/ contraindicated	Combination with csDMARDs?	Assessment of response
National Institute For Health and Care Excellence (NICE) (2015-2018)[26,27,30]	Reimbursement	≥3 SJC & ≥3 TJC	2 csDMARD mono or combination therapy	TNFi	TNFi, IL17i, IL12/23i	May use CZP, SEC, UST, IXE alone or with MTX	PsARC1 at 12-24 wk (TNFi: 12 wk SEC, IXE: 16 wk UST: 24 wk)
Singapore Chapter of Rheumatologists (2015)[22]	Reimbursement	≥5 swollen & 5 tender joints/ digits/entheses	2 csDMARDs including 1 combination for 3 mo each	TNFi	Another TNFi, up to 2 or 3 sequential trials for primary or secondary failure/intolerance respectively	Yes for IFX	PsARC every 3 mo
Medicare Australia (2018)[31,32]	Reimbursement	ESR > 25 or CRP > 15 AND Active joints (TJC + SJC) ≥20 or ≥4 active major joints[a]	1 combination csDMARD for 3 mo	TNFi, IL17i, IL12/23i	TNFi, IL17i, IL12/23i	Nil	ESR/CRP, TJC & SJC
Department of Indigenous Services Canada Non-Insured Health Benefits (NIHB) program (2018)[60]	Reimbursement	≥5 SJC or ≥1 proximal joint[b] ≥2 dactylitis digits Refractory enthesitis or tenosynovitis	2 different NSAIDs for 4 wk + 2 csDMARDs for 8-12 wk (MTX: 8 wk, LEF: 10 wk, SSZ: 3 mo) For enthesitis/tenosynovitis: NSAIDs & steroid injection	TNFi, IL17i	TNFi, IL17i	Nil	PsARC
British Society for Rheumatology, British Health Professionals in Rheumatology (BSR, BHPR) (2012)[28]	Best practice	3 TJC + 3 SJC	2 csDMARDs for 12 wk (1 if adverse prognostic factor)	TNFi	Partial response: trial TNFi 12 more wk. No response: another TNFi[c]	Nil	PsARC at 3 mo
French Society for Rheumatology (2014)[29]	Best practice	≥3 SJC + TJC at 2 visits 1 mo apart	1 csDMARD	TNFi	Another TNFi[c]	No	DAS-based EULAR response at ≥3 mo
Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada (2014)[66]	Best practice	Nil	1 csDMARD	TNFi	Another TNFi	IE (MTX + TNFi may affect drug persistence but not clinical efficacy)	Joint count (≥30% reduction) at 16 wk
European League Against Rheumatism (EULAR) (2015)[35]	Best practice	Beyond MDA	1 csDMARD for 3-6 mo	TNFi	Another bDMARD including alternative TNFi	IE	Nil
Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) (2015)[36]	Best practice	Nil	csDMARD	TNFi, IL-12/23i (strong) IL17i[d] (conditional)	Another TNFi or tsDMARD	Nil	Nil

Abbreviations: ACR20, American College of Rheumatology 20% improvement criteria; bDMARD, biological disease-modifying anti-rheumatic drug; CRP, C-reactive protein; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; CZP, certolizumab pegol; ESR, erythrocyte sedimentation rate; IE, insufficient evidence to make recommendation; IFX, infliximab; IL-12/23i, interleukin-12/23 inhibitors; IL-17i, interleukin-17 inhibitors; IR, inadequate responders; JAKi, Janus kinase inhibitor; MDA, minimal disease activity; MTX, methotrexate; Nil, no recommendation made; NS, not significant; NSAIDs, nonsteroidal anti-inflammatory drugs; PsARC, Psoriatic Arthritis Response Criteria; SEC, secukinumab; SJC, swollen joint count; TJC, tender joint count; TNFi, tumor necrosis factor inhibitors; tsDMARD, targeted synthetic disease-modifying anti-rheumatic drug; UST, ustekinumab.

[a]Major joints defined as: (elbow, wrist, knee, ankle, shoulder, hip).

[b]Proximal joints: proximal to or including wrist/ankle.

[c]SEC, UST studies ongoing at time of guideline.

[d]Only abstract data available at time of guideline.

TABLE 3 Consensus statement on initiation and continuation of a biologic disease-modifying anti-rheumatic drug for psoriatic arthritis with peripheral joint involvement requiring government subsidization[a]

	Median agreement score of clinical scenarios on a Likert scale of 5[b]	n (%) with agreement[c]	Voting round
Counts of swollen joints/digits (SJC) and tender joints/digits/entheses (TJC) should be used as the disease activity measure to assess PsA.	5	11/11 (100%)	1
Patient should have a minimum of 3 swollen AND tender joints/digits/entheses to be considered for biologic therapy	NA	8/11 (73%)	1
Unless contraindicated, patient should have failed 2 csDMARD strategies at optimal doses for a minimum of 3 mo each to be considered for biologic therapy	5	10/10 (100%)	2
For dactylitis/enthesitis, failure of NSAIDs and/or local injection should be documented, if appropriate	4	10/11 (91%)	1
For choice of first biologic, TNFi, IL-17i, IL-12/13i, tsDMARD may be considered	5 (TNFi, IL-17i, tsDMARD) 4 (IL-12/23i)	10/10 (100%) for all	2
If first-line treatment with TNFi fails, second line may be another TNFi, IL-17i, IL-12/23i or tsDMARD	5 (for all)	10/10 (100%) (for TNFi, IL17i, tsDMARD) 9/10 (90%) for IL12/23i)	2
If a first-line treatment with a non-TNFi (IL-17i, IL-12/23i, tsDMARDs) fails, second-line treatment may be a TNFi or another non-TNFi	5	10/10 (100%)	2
All patients on bDMARD/tsDMARD must have response to therapy measured and documented every 3 mo	5	8/11 (73%)	1
For continuation of therapy with bDMARD/tsDMARD, patient must achieve an adequate response by 6 mo[d]	5	11/11 (100%)	1
Infliximab should be used in combination with methotrexate unless contraindicated	5	9/10 (90%)	1
Co-morbidities, pregnancy/lactation and drug safety should be considered when determining treatment strategies and selecting a bDMARD/tsDMARD	5	11/11 (100%)	1
A biosimilar may be substituted for the originator drug for better cost-effectiveness	4	10/11 (91%)	1

Abbreviations: bDMARD, biological disease-modifying anti-rheumatic drug; csDMARD, conventional synthetic disease-modifying anti-rheumatic drug; IL-12/23i, interleukin-12/23 inhibitors; IL-17i, interleukin-17 inhibitors; NSAID, nonsteroidal anti-inflammatory drug; PsARC, Psoriatic Arthritis Response Criteria; SJC, swollen joint count; TJC, tender joint count; TNFi, Tumor necrosis factor inhibitors; tsDMARDs, targeted synthetic disease-modifying anti-rheumatic drug.

[a]For predominantly axial involvement, please refer to the AS/SpA recommendations. These recommendations are not intended to refer to children with PsA or patients with skin psoriasis alone.

[b]Likert scale of 5 unless otherwise stated, where 1 = strongly disagree, 5 = strongly agree.

[c]Agreement defined as score of 4-5 on the Likert scale. Disagreement as score of 1-2.

[d]As there was no consensus on choice of response criteria (PsARC vs 20% SJC & TJC improvement vs either), recommendations from the previous Chapter guidelines to use PsARC as the response measure will be retained.[22]

meeting after the first round of rating. Aggregated results from the rating were presented and a discussion moderated by a CWG member (ML) was carried out for statements that did not meet consensus. Definitions were clarified and the statements were reworded if needed. This was followed by further rounds of independent rating by the TFP for statements without agreement.

2.4 | Finalizing the consensus statements

The final consensus statements were written after completion of rating by the TFP. If consensus was not reached, the statement was not included. Only positive statements were included in our recommendations (eg when to implement biologic therapy rather than when to avoid it).

3 | RESULTS

Altogether three rounds of rating were carried out by the TFP. The first round of voting comprised 11 panelists; in subsequent rounds, one member dropped out due to unavailability and voting was completed by the remaining 10 panelists. The final consensus statements are summarized in Table 3.

3.1 | Consensus 1. Counts of swollen joints/digits (SJC) and tender joints/digits/entheses (TJC) should be used as the disease activity measure to assess PsA

The evaluation of disease activity in PsA has traditionally been challenging due to its heterogeneity. Physician-assessed domains such as peripheral arthritis, axial disease, dactylitis, enthesitis, skin and nail disease as well as patient-reported outcomes such as patient global assessment, quality of life, fatigue, functional or work impairment need to be considered for holistic evaluation.[25]

In our previous consensus process, we recognized that there was no single composite measure that reflected all components of PsA activity that was practical for routine clinical use. We discussed the use of Disease Activity Score in 28 joints (DAS28) and Disease Activity for Psoriatic Arthritis (DAPSA).[22] Both the composite measures were deemed inappropriate due to lack of both distal interphalangeal joint assessment (DAS28) and skin assessment. The DAS28 was developed for RA and has not been validated for use on PsA. DAPSA was developed from the disease activity in reactive arthritis scale, only evaluated in patients with polyarticular disease and not a widely used measure. We hence agreed to use the swollen and tender joint count, which is used in several international guidelines and is the entry criterion for most PsA trials. As counts of dactylitis and inflamed entheses are key outcome measures in PsA, we suggest to incorporate these counts into overall joint count assessment. Likewise, in our current consensus process, we agreed to continue using the number of swollen and tender joints, digits or entheses as the disease activity measure of choice.

3.2 | Consensus 2. Patients should have a minimum of 3 swollen AND tender joints/digits/entheses to be considered for biologic therapy

The number of swollen and tender joints required for initiation of biologic therapy was much debated in our previous consensus process and was finally agreed to be five swollen and tender joints (with a swollen enthesis or dactylitis site counted as a swollen joint for the purpose of calculation), largely due to Australia's Medicare criteria for 20 or more swollen and tender joints for active disease.[22]

In our current process, the consensus was to use three swollen and three tender joints as the threshold disease activity measure. This is in line with several other funding guidelines such as the National Institute for Health and Care Excellence (NICE), the British Society for Rheumatology (BSR) and the British Health Professionals in Rheumatology (BHPR) and the French Society for Rheumatology, as well as most clinical trials of biologic therapy in PsA.[17-20,22,26-30] Baseline swollen and tender joint count, as well as patient and physician global assessment on a Likert scale of 1-5, should be documented prior to initiation of biologic therapy to enable subsequent response evaluation.

3.3 | Consensus 3. Patients should have failed 2 csDMARD strategies at optimal doses unless contraindicated, for a minimum of 3 months each, to be considered for biologic therapy.

From the previous Chapter guideline, the requirement for one strategy to include a csDMARD combination and specifications on the choice of csDMARDs were removed. Apart from Australia's Medicare, no other guideline specified the requirement to fail a csDMARD combination.[31,32] Indeed, unlike RA, the evidence in favor of combination csDMARD therapy for PsA is weak.[10,33] We also left the choice of specific csDMARDs to the discretion of the treating rheumatologist.

3.4 | Consensus 4. For dactylitis/enthesitis, failure of NSAIDs and/or local injection should be documented, if appropriate

Studies on the treatment of enthesitis and dactylitis are limited. In current practice, NSAIDs and local corticosteroid injections remain the first-line options, although largely based on expert opinion and limited studies.[34] By contrast, biologic therapies, in particular TNFi and ustekinumab have consistently been demonstrated to be effective for enthesitis and dactylitis.[14,15] Nonetheless, given their easy availability, most guidelines still recommend NSAIDs and local corticosteroid injections as first-line treatment options for active enthesitis and dactylitis, failing which biologic therapy may be considered.[29,35,36]

3.5 | Consensus 5. For choice of first biologic, TNFi, IL-17i, IL-12/23i, tsDMARD may be considered

The previous Chapter guidelines only recommended TNFi as first-choice biologics, as they were the only approved class of drugs available at that time. In patients with contraindications to TNFi, options were limited. Clinical trials for IL-17i (secukinumab), IL-12/23i (ustekinumab) and tsDMARDs (tofacitinib) have now been published in the spectrum of patients with PsA including those TNFi-naïve, csDMARD inadequate responders and those TNFi-experienced, and these therapies are now approved by the US Food and Drug Administration (FDA), European Medicines Agency (EMA) and the Singapore Health Sciences Authority (HSA).[14,15,17-20,37-44] The CWG and TFP agreed that, given the evidence for efficacy of all drug classes in PsA, increasing the repertoire of approved drugs would allow the treating physician to individualize treatment in accordance with patient characteristics and preferences.[14,15,17-20]

Other guidelines published between 2011 and 2018 tend to favor TNFi as first-choice biologic (Table 2), primarily due to longer experience with this class and their established safety. However, we decided to include all the approved drug classes, as no unusual

safety signals have emerged thus far and clinicians have increasing experience with their use.[14,15,45-50]

3.6 | Consensus 6. If first-line treatment with TNFi fails, second line may be another TNFi, IL-17i, IL-12/23i or tsDMARD

The most common reason for switching TNFi is the lack of efficacy, followed by adverse effects.[51-54] In our previous guideline, we allowed up to a maximum of two TNFi for primary or secondary treatment failures, or three for TNFi intolerance. In the current guideline, given the availability of non-TNFi alternatives, we did not make recommendations on the maximum number of TNFi to subsidize. Studies on the use of adalimumab, certolizumab, secukinumab, ustekinumab and tofacitinib in PsA have demonstrated good response in the subgroup of patients who were TNFi-experienced.[14,17-19,54-58] While there is evidence that switching to a drug of a different mechanism may be more effective after primary TNFi failure in RA, no such direct evidence exists in PsA.[57,59]

3.7 | Consensus 7. If first-line treatment with a non-TNFi (IL-17i, IL-12/23i, tsDMARD) fails, second-line treatment may be a TNFi or another non-TNFi

No RCT or registry data are available on switching after failure of a non-TNFi. However, consistent with other guidelines, we agreed that any of TNFi, IL-17i, IL-12/23i or tsDMARDs could be used as second-line options following inefficacy or intolerability of the first drug.[31,32,36,60]

3.8 | Consensus 8. All patients on bDMARD/tsDMARD must have response to therapy measured and documented every 3 months

Regular evaluation of treatment response is recommended as part of a treat-to-target strategy, with a change in treatment considered in case of inadequate response.[61] Evaluated guidelines have recommended an evaluation within 3 months after initiation of treatment. Similar to our previous recommendation, we agreed that 3 months is a reasonable timeframe to evaluate progress and treatment response.

3.9 | Consensus 9. For continuation of therapy with bDMARD/tsDMARD, patient must achieve an adequate response by 6 months

In most clinical trials, primary outcomes were measured at week 24 of intervention suggesting that 6 months was a reasonable and acceptable timeframe to assess the response of biologic therapy. While our previous consensus was that continuation of therapy requires a response at 3 months, we agreed that some patients may continue to improve up until 6 months after initiation of therapy, and agreed on this timeframe for approval of continuation of therapy.

3.9.1 | Response measure

Our previous guideline recommended the use of Psoriatic Arthritis Response Criteria (PsARC) as the treatment response indicator. A PsARC response is defined as: (a) an improvement in any two of the following four elements, with at least one being a joint score; and (b) worsening in none of the four elements: (a) patient global assessment (on a 1-5 Likert scale, improvement defined as decrease of one point, worsening defined as increase of one point); (b) physician global assessment (on a 1-5 Likert scale, improvement defined as decrease of one point, worsening defined as increase of one point); (c) 68 tender joint count (improvement defined as reduction in at least 30%, worsening defined as increase of at least 30%); (d) 66 swollen joint count (improvement defined as reduction in at least 30%, worsening defined as increase of at least 30%). In the current consensus exercise, TFP members debated the use of PsARC or a 20% improvement in TJC and SJC or either as the response measure of choice. However, an agreement could not be reached in spite of discussion and three rounds of voting with 2/10 agreeing on PsARC, 2/10 on 20% TJC and SJC improvement and 6/10 on the use of either, thus not reaching the required 70% for consensus. The CWG collectively agreed that PsARC should be retained as the response measure of choice from our previous guideline.[22]

3.10 | Consensus 10. Infliximab should be used in combination with MTX unless contraindicated

The co-administration of a csDMARD with TNFi has been shown to reduce anti-drug antibody (ADAb) formation.[62,63] This is mainly seen in the use of MTX with infliximab and adalimumab and has been more widely studied in RA cohorts or a mixed cohort of patients with RA, spondyloarthritis (SpA), psoriasis and inflammatory bowel disease.[62] Specifically in PsA, co-administration of MTX with TNFi did not result in significant differences in clinical response but was found to improve drug survival especially in patients receiving infliximab.[64,65] The majority of guidelines reviewed did not comment on the combination of a biologic with csDMARDs but when stated, there was insufficient evidence to provide a firm recommendation.[35,66] The Canadian Rheumatology Association/Spondyloarthritis Research Consortium of Canada found that TNFi persistence may improve with MTX but improvement in clinical efficacy has not been convincingly demonstrated.[66] Given the evidence that ADAb may potentially reduce the response to TNFi, the TFP agreed that a combination with MTX should be used with infliximab.[62]

3.11 | Consensus 11: Co-morbidities, pregnancy/lactation and drug safety should be considered when determining treatment strategies and selecting a bDMARD/tsDMARD

The TFP unanimously agreed on the above statement in the RA consensus process and to extend the consensus to this PsA guidance.

3.12 | Consensus 12: A biosimilar may be substituted for the originator drug for better cost-effectiveness

According to the EULAR guideline, a biosimilar is regarded to be similar and equally applicable to the biological originator drug.[35] The Department of Indigenous Services Canada Non-insured Health Benefits program for government subsidization also provides the infliximab biosimilar Inflectra for all infliximab requests.[60] While there are no head-to-head trials in PsA comparing the originator drug with the biosimilar, 2 cohort studies (Danish biologic registry [DANBIO] and NOR-SWITCH trial) on switching in inflammatory arthritis showed no negative effect in terms of efficacy and safety with the biosimilar Remsima (the only biosimilar currently available in Singapore) as compared to the originator drug Remicade.[67-69] The use of an approved biosimilar in the same way as an originator drug has been endorsed by an international task force.[70] The TFP unanimously agreed to allowing initiation of treatment with, or substitution of a biosimilar in place of the bio-originator. Multiple switching was not addressed due to lack of evidence in this area.

4 | DISCUSSION

We developed this consensus statement to guide the use of biologic therapy for PsA in patients requiring government subsidization in Singapore. Patients with PsA may be considered for initiation of a biologic if they have a minimum of three swollen and three tender joints/digits/entheses despite treatment with two csDMARD strategies and NSAIDs and/or local injection for any dactylitis/enthesitis. The csDMARDs should have been used at optimal doses for at least 3 months each in the absence of contraindications. The choice of a first-line biologic may include any of approved TNFi, IL-17i, IL-12/23i or tsDMARD. If the first-line biologic fails, a second drug from the same or a different class may be used. Treatment response should be assessed and documented every 3 months after commencement of biologic therapy and patients must achieve adequate response by 6 months in order to be eligible for continuation of therapy.

We previously recommended with 100% agreement that patients had to either fulfill the Classification for Psoriatic Arthritis (CASPAR) criteria for PsA or have a physician diagnosis of PsA for consideration of biologic therapy.[22] We felt that this statement was redundant and hence dropped it from the current version.

Consensus was obtained from a second round of voting on all but one statement. We could not achieve a consensus on the choice of response criteria, with opinions divided between PsARC and improvement in tender joint count and swollen joint count. There is a similar lack of consensus globally in the PsA literature on the assessment of disease activity and treatment response, likely due to the heterogeneity of the disease.[71,72] There is no consensus on the best outcome measure that should be used in PsA. Composite measures which include assessment of peripheral joints, scores for skin and nail psoriasis, enthesitis, dactylitis, spinal disease, quality of life, and patient global assessments are ideal but remain unsuitable for routine clinical practice. The tender and swollen joint count is used most frequently in PsA clinical trials, with the PsARC response used as a secondary measure. The Disease Activity in Psoriatic Arthritis (DAPSA) and the Composite Psoriatic Disease Activity Index are specific for PsA but are not widely used.[71] Existing Chapter guidelines recommend the PsARC based on previous consensus and we propose that this remains unchanged until more data are available to prompt a revision.[22]

These statements were formulated and agreed upon by experts comprising of rheumatologists in both the public and private healthcare sectors in Singapore. We adopted a rigorous protocol that adapted key procedures used by the ACR and EULAR for the development of guidelines. Recent evidence from RCTs as well as established best practice guidelines from various rheumatology associations and national guidelines published since our last consensus process were comprehensively reviewed, synthesized and presented to the TFP to ensure that our recommendations were evidence-based. Most statements had a median score of five on the Likert scale reflecting strong agreement.

The main limitation was that our literature search was only as up-to-date as the latest published guidelines which were in 2015 (GRAPPA and EULAR). Most guidelines that we reviewed were written while the studies on secukinumab and ustekinumab were still ongoing and prior to the approval of tofacitinib for PsA. We thus opted to present data from IL-17i, IL-12/23i and tsDMARD primary trials and believe that the TFP considered this latest evidence in their rating of the statements. The most recent 2018 ACR guideline was not published at the time of our review and consensus process. The focus of this guideline was on evidence-based treatment in PsA with all biologic drug classes endorsed for use as first and alternate lines of therapy and recommended based on specific disease characteristics.[73]

With the growing number of studies and the increasing number of approved agents in the treatment of PsA, this update to our consensus guideline is timely. There is growing evidence of better outcomes in PsA with early treatment and a treat-to-target approach to achieve remission.[61,74,75] We believe that these updated guidelines will allow earlier initiation of biologic therapy in a wider group of patients and provide more equitable access to these expensive drugs. Following the development of these guidelines, the Chapter is working to engage pharmaceutical companies to try pricing their drugs competitively for the government tender. The Chapter has

also engaged the ACE. It is envisioned that the list of drugs and criteria for eligibility for MAF funding will be expanded sometime next year, taking into account this guidance.

We recognize as a limitation that other stakeholders such as patients and government agencies were not directly engaged in the consensus process. We hope to consider this in future iterations of this guideline. While direct applicability of this consensus statement to other countries may be limited by the national funding structure and healthcare budget, we believe that this can be a useful reference framework for nations facing similar resource limitations. We also recognize that periodic reviews to update the Chapter's recommendations may be required as newer data, drug classes or treatment strategies in PsA continue to emerge and intend to do so every 5 years.

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CONFLICT OF INTEREST

The authors have disclosed the following conflicts of interest. GGT has received conference support from AbbVie. PPC has received research support from Novartis and conference support from Sanofi. WWSF has served on advisory boards for AbbVie and received speaker honorarium from Novartis. YYKL has participated on advisory boards for Pfizer and Boehringer Ingelheim, received research support from Pfizer and conference support from AbbVie. NLL has participated on advisory boards for Pfizer. MM has been involved in educational activities supported by Novartis, Pfizer, AbbVie, Roche, Johnson & Johnson, Astellas, Sanofi, Amgen, Celltrion, Euroimmun. AS has been involved in educational activities supported by Novartis; received research support from Novartis and conference support from Pfizer. MKS has received conference support from Pfizer, Amgen, AbbVie. TTC has received conference support from Pfizer. ML has participated on advisory boards for Pfizer, Eli Lilly, Gilead; speaking honorarium from Johnson & Johnson; conference support from Pfizer, Novartis and Sanofi and is the site-PI for a pharmaceutical funded registry. All other authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

All designated as authors have met the criteria for authorship recommended by the International Committee of Medical Journal Editors (ICMJE).

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ORIGINAL ARTICLE

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Update on recommendations for eligibility of government subsidization of biologic disease-modifying antirheumatic drugs for the treatment of axial spondyloarthritis in Singapore

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Abstract

Aims: The field of axial spondyloarthritis (axSpA) has undergone significant changes recently in particular with disease classification, assessment of disease activity and increased treatment options for biologics. In order to reflect these developments, we aimed to update the local consensus recommendations for subsidization of biologics.

Methods: A modified Delphi approach was used. Six published guidelines from major rheumatology societies and healthcare authorities on axSpA were reviewed. Findings were synthesized and used in formulating updated recommendation statements. Recommendations were rated by 10 practicing rheumatologists in Singapore. Consensus was reached if there was more than 70% agreement or disagreement.

Results: Ten statements achieved consensus. Patients may be considered for subsidization of biologic therapy if they fulfill the Assessment of Spondyloarthritis International Society or modified New York criteria, with persistently active disease (defined either by Ankylosing Spondylitis Disease Activity Score ≥ 2.1 or Bath Spondylitis Disease Activity Index ≥ 4), despite 4 weeks of full-dose non-steroidal anti-inflammatory drugs and regular exercise. Either tumor necrosis factor inhibitors or interleukin 17 inhibitors may be used as first-line therapy, and should be continued if adequate response is achieved at 6 months.

Conclusion: Recommendation statements were formulated through a formal consensus process by local experts with a view to assist relevant authorities in funding considerations and for use in clinical practice.

KEYWORDS

ankylosing spondylitis, anti-TNF, axial spondyloarthritis, biologics, consensus, government, IL17 inhibitors, recommendation, spondyloarthritis, subsidy

1 | INTRODUCTION

Axial spondyloarthritis (axSpA) is part of a heterogenous group of inflammatory arthritides that share a number of specific clinical features, with a preponderance toward the axial skeleton. Patients typically present with inflammatory back pain, sacroiliiitis, and possibly peripheral arthritis and enthesitis with extra-articular features such as uveitis and psoriasis.[1]

Historically, radiographic sacroiliitis was a key feature in diagnosis, with ankylosing spondylitis (AS) as the prototype for this group of conditions.[1] The modified New York criteria for AS remains widely used as inclusion criteria for clinical trials and for qualification for subsidized biologic treatment in axSpA patients in many countries.[2-4] However, there has been increasing recognition that radiographic sacroiliitis is a late finding and signs of inflammation may be detected by magnetic resonance imaging (MRI) far earlier than conventional radiographs. As a result, definitions have broadened beyond the modified New York criteria, and have incorporated non-radiographic axSpA in their treatment recommendations.[5,6]

Treatment of axSpA has also advanced. Traditionally, non-steroidal anti-inflammatory drugs (NSAIDs) have been the mainstay of treatment, but cardiovascular and gastrointestinal toxicity limit their therapeutic use.[5,7] Conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) like sulphasalazine (SSZ) are useful for peripheral arthritis but are less effective in axial disease.[8] For patients who continue to have active disease despite conventional treatment, tumor necrosis factor inhibitors (TNFi) have been shown to be effective for controlling disease activity and improving quality of life. Recently, a new class of biologic DMARD (bDMARD), interleukin-17 inhibitors (IL-17i) has emerged, with evidence showing it is effective in patients who failed with or could not tolerate TNFi.[9]

This increase in armamentarium is welcomed as axSpA remains a debilitating condition. The disease affects up to 1% of the general population[8] and patients suffer from significant pain, reduced quality of life[1] and reduced economic productivity.[10] In a cross-sectional study performed in Singapore, up to 20.5% of patients with axSpA were unemployed.[11]

However, treatment of axSpA with bDMARDs remains expensive in Singapore and often requires financial subsidization by government agencies. Previously, clinical eligibility was not standardized and was decided on a case-by-case basis, which prompted the development of the 2013 consensus statements for pragmatic recommendation of biologic subsidization in AS patients.[12]

Given the recent advancements such as the recognition of non-radiographic axSpA and the addition of IL17i as an entirely new class of bDMARD, clinical practice in management of axSpA has significantly changed. Thus, the objective of this endeavor is to update existing consensus statements in order to reflect these changes.

2 | METHODS

A core working group (CWG) (KFP, GGT, ML, PPC) was formed to steer the consensus process. A modified Delphi technique was used to obtain consensus. The CWG invited 11 locally recognized rheumatologists from public restructured hospitals and private practice in Singapore to serve in an expert Task Force Panel (TFP). Specific clinical questions and concerns that needed to be addressed were solicited from members of the TFP via email. These included definitions of axSpA, measures of disease activity, and newer therapeutic options that were previously not available in Singapore. Consideration was given to biologics accessible in Singapore, namely adalimumab, etanercept, golimumab, infliximab, and secukinumab.

The CWG subsequently performed a systematic literature review of the latest guidelines and recommendations from major rheumatology societies and health authorities. Results collected from the systematic review were summarized and proposed updates were drafted. Based on the evidence provided and their expert clinical experiences, the TFP evaluated and voted on the consensus statements.

This consensus process was held in parallel with two other similar exercises for rheumatoid arthritis and psoriatic arthritis.

2.1 | Review of international guidelines and recommendations

One member of the CWG (PKF), performed a literature search in MEDLINE for guidelines published after 1 January 2011, which was the cut-off date for the previous chapter guideline. Specified search terms used were consensus, guideline, health planning guidelines, practice guideline, standard of care, clinical protocols OR health system plans, AND ankylosing spondylitis, ankylosing spondyloarthritides, ankylosing spondylarthritis, ankylosing, spondyloarthritis, spondyloarthritis, axial spondyloarthritis OR non-radiographic spondyloarthritis.

English guidelines published that included systematic reviews and consensus processes were selected. In addition, the Australia Medicare's Schedule of Pharmaceutical Benefits[13] and National Institute for Healthcare and Clinical Excellence (NICE) guidelines[6,14,15] were retrieved from their respective websites. In total, six articles from 155 search results were selected, including Australia Medicare and NICE guidelines (Table 1).[3-6,13-17]

2.2 | Rating of consensus statements by the TFP

The first round of voting was performed by an electronic survey sent over email. Members of the TFP were provided with a summary of the above literature and the draft consensus statements. Members rated each statement using a 5-point Likert scale (1 = strongly disagree, 2 = disagree, 3 = neutral, 4 = agree, 5 = strongly agree). Consensus was defined as at least 70% of panelists either agreeing or strongly agreeing to the specified statement (agreement), or an equal proportion disagreeing or strongly disagreeing with a statement (disagreement). Subsequently, 10 members of the TFP and the CWG held a 1-day meeting on 4 November 2018 under the auspices of The Singapore Chapter of Rheumatologists, College of Physicians, Academy of Medicine, Singapore. One member of the CWG (PPC) moderated the

proceedings. Results from the first round of voting were discussed and areas of uncertainties clarified. Statements that did not reach consensus were reworded and a second round of voting was carried out by email after the meeting.

3 | RESULTS

Table 2 presents the final consensus statements along with median level of agreement by the TFP.

3.1 | Relating to the initiation of bDMARD, patients should fulfill either ASAS criteria for spondyloarthritis or modified New York criteria for ankylosing spondylitis

This recommendation remained unchanged from the 2013 consensus statements.[12] The modified New York criteria remains the most frequently used criteria in many axSpA trials involving biologic therapy.[2] However, one disadvantage of the modified New York criteria is the need for presence of radiographic sacroiliiitis, which may manifest late in the course of the disease. The Assessment of Spondyloarthritis International Society (ASAS) criteria allows diagnosis of axSpA using supportive clinical features and MRI, which can detect inflammatory changes in patients without radiographic sacroiliiitis.[5] This is now recognized as non-radiographic axSpA. The recent years have seen increasing use of the ASAS criteria and newer trials have showed that TNFi achieve similar clinical outcomes in patients with non-radiographic axSpA when compared to AS.[18-23] Hence, the TFP agreed that patients with or without radiographic sacroiliiitis benefit from biologic therapy, hence both criteria should be kept.

One important change was the inclusion of non-radiographic disease into the current recommendations. While the ASAS criteria were included in 1 of the 2013 consensus statements, its previous scope as a whole pertained only to AS. The current recommendations used the term "axSpA" instead for a more accurate coverage over this disease spectrum.

3.2 | Patients with active disease may be defined by either BASDAI score of 4 or more or ASDAS score of 2.1 or more

Traditionally, the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) is the clinical index used to monitor disease activity.[24] It is a composite index comprising of patient-reported symptoms severity for spinal pain, peripheral pain, stiffness, fatigue and enthesitis. A score of 4 or more indicates active disease. Recently the Ankylosing Spondylitis Disease Activity Score (ASDAS) was developed, which incorporates patient-reported symptoms similar to BASDAI and additional laboratory acute phase reactants (C-reactive protein or erythrocyte sedimentation rate).[25] ASDAS has been validated in an Asian population and was shown to be more discriminatory than BASDAI for patient global score, inflammatory markers and MRI changes.[26] In addition, for measuring responsiveness to treatment with TNFi, ASDAS showed good correlation with clinical response, MRI inflammation score, and inflammatory biomarkers.[27,28] ASDAS also has prognostic significance, with higher ASDAS scores associated with worse clinical and radiological outcomes, and reduced quality of life. The previous 2013 statement recommended using BASDAI only.[12] Given the robust evidence for ASDAS, there was agreement to include ASDAS in the updated statement.

3.3 | Patients should have failed two sequential NSAIDs at maximum tolerated doses for a total duration of at least 4 weeks and should be participants in an appropriate physiotherapy and exercise program

This statement remained mostly unchanged from before. The TFP acknowledged that NSAIDs are useful in providing symptomatic relief; however, there is great variation in response between patients and the widely recognized cardiovascular and gastrointestinal side effects limit continuous use. Most guidelines recommended a trial of at least 2 NSAIDs between 4 weeks to 3 months.[3-5] The TFP continued to agree that a 4-week trial is reasonable before consideration of alternative therapy. Physiotherapy has been a mainstay of treatment for axSpA[1] and the previous statement reflected this by recommending compliance to "ongoing, concomitant, appropriate physiotherapy of at least 3 months duration". However, the TFP acknowledged that consistent accessibility to physiotherapy is difficult to achieve for many patients. Reasons include cost, transportation issues, and work commitments. The TFP agreed that while physiotherapy should be emphasized to every patient, they should not be excluded from bDMARD if disease activity is high and debilitating.

3.4 | For patients with peripheral arthritis, sulphasalazine at optimal dose should have been used for at least 12 weeks unless contraindicated

There has been no new evidence for csDMARD, hence the current statement remained unchanged from 2013. Some evidence for SSZ in peripheral arthritis exists and there are conflicting results for methotrexate (MTX).[5,29,30] While there is lack of robust evidence, members of the TFP agreed that patients with peripheral arthritis should receive at least 3 months trial of SSZ.

3.5 | Symptomatic enthesitis should have failed appropriate local treatment

Local treatment is defined as local glucocorticoid injections at inflamed sites if appropriate. The latest American, ASAS/EULAR (European League Against Rheumatism) and Canadian guidelines continue to recommend consideration of local glucocorticoid injections at sites of musculoskeletal inflammation, although all acknowledged evidence for this remain low.[3,5,17] Our statement also remained unchanged from 2013.[12] To date, there are only two

TABLE 1 Summary of guidelines used for Task Force Panel discussion

Organization, (y)	Type	Diagnostic criteria	Disease activity measure	Definition of active disease
Canadian Rheumatology Association (2014)[16,17]	Best practice	Clinician's judgement	BASDAI, acute phase reactants, imaging changes	2 of following: BASDAI ≥ 4, acute phase reactants, imaging changes
ACR/SPARTAN (2015)[3]	Best practice	mNY	Use validated measure, none specified	Symptoms at an unacceptably bothersome level as per patient and judged by clinician to be due to SpA
ASAS-EULAR (2016)[5]	Best practice	Clinician's judgement	ASDAS preferred over BASDAI	BASDAI ≥ 4 or ASDAS ≥ 2.1
BSR/BHRP (2017)[4]	Best practice	mNY or positive MRI ± raised CRP	BASDAI, spinal pain VAS	BASDAI ≥ 4 on two occasions at least 4 wk apart, spinal pain VAS ≥ 4
NICE (2017)[6,14,15]	Reimbursement	Consider validated criteria: ASAS, Berlin, Rome, mNY	BASDAI, spinal pain VAS	Not discussed
Australia Medicare PBS (2018)[13]	Reimbursement	mNY	BASDAI	BASDAI ≥ 4, ESR > 25, CRP > 10
APLAR[a] (2018)[52]	Best practice	mNY ASAS	BASDAI ASDAS	BASDAI ≥ 4 or ASDAS ≥ 2.1

Abbreviations: ACR/SPARTAN, American College of Rheumatology/ Spondyloarthritis Research and Treatment Network; APLAR, Asia-Pacific League of Associations for Rheumatology; ASAS, Assessment of Spondyloarthritis; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI, Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biologic disease-modifying antirheumatic drug; BSR/BHRP, British Society for Rheumatology/ British Health Professionals in Rheumatology Standards; CRP, C-reactive protein; ESR, erythrocyte sedimentation rate; EULAR, European League Against Rheumatism; ICER, incremental cost-effectiveness ratio; IL17i, interleukin 17 inhibitors; mNY, modified New York criteria; MRI, magnetic resonance imaging; NICE, National Institute for Health and Care Excellence; NSAIDs, nonsteroidal anti-inflammatory drug; PBS, Pharmaceutical Benefits Scheme; TNFi, tumor necrosis factor inhibitors; VAS, visual analog scale.

[a]This recommendation was not included during the consensus process as it was not published at the time of the consensus-seeking exercise with the Task Force Panel.

randomized controlled trials supporting use of glucocorticoid injections in sacroiliac joints; however, both trials have small patient numbers and one trial was not blinded.[31,32] In spite of this, there is longstanding anecdotal evidence that local glucocorticoid injections provide pain relief and reduction of inflammation, and therefore remain widely used.

3.6 | If bDMARD is considered, either TNFi or IL17i may be considered as first-line therapy

Previously, the only class of bDMARD available for treatment of AS was TNFi. TNFi are effective, with up to 60% of patients achieving good response on this therapy.[33-35] However, a significant proportion of patients does not achieve adequate response or may develop adverse side effects. Secukinumab, an IL17i is a new class of bDMARD that has been shown to be effective in AS patients.[9] It was recently approved for use in Singapore in April 2016 and is indicated for treatment of active AS in patients who have inadequate response to conventional therapy. While trial data for secukinumab showed comparable response (60%) to TNFi, there is less experience with the use of secukinumab at this point, hence ASAS/EULAR recommended TNFi as the only first-line bDMARD treatment.[5] However, members of the TFP felt that specific clinical considerations in the local context need to be acknowledged, such as higher exposure to tuberculosis. A recent review of pool safety data from trials involving secukinumab did not show an increased risk of tuberculosis infection.[36] Alongside growing experience of the use of secukinumab in Singapore, having an additional first-line option available is

Definition of non-biologic treatment failure	First-line bDMARD	Second-line bDMARD	Definition of response	Recommendations on biosimilars
Failed 2 NSAIDs each given at least 2 wk at maximum dose, unless contraindicated	Shared decision between patient and physician	Switch to another TNFi	BASDAI improvement 50% or ≥2.0 and spinal pain VAS reduction ≥2.0 Assess response every 16 wk	Not discussed
Failed 2 NSAIDs over 1 mo OR Incomplete response with 2 NSAIDs over 2 mo	TNFi	Switch to another TNFi	Recommend monitoring disease activity (measure not specified)	Not discussed
Failed at least 2 NSAIDs over 4 wk. One local steroid injection if appropriate	TNFi first as less experience with IL17i	Switch to another TNFi if secondary failure, switch to IL17i if primary failure	ASDAS improvement ≥1.1 or BASDAI improvement ≥2.0 Assess response after 12 wk	Similar outcomes expected. Consider costs and local context
Failed 2 NSAIDs for at least 2 wk each unless contraindicated	TNFi	Switch to another TNFi	BASDAI improvement ≥2.0 and spinal pain VAS reduction ≥2.0. If unable to do BASDAI: clinician's assessment. Assess response 3-6 mo, then 6-monthly	Decisions made should be clinical and not on cost grounds
Failed NSAIDs	TNFi	Switch to another TNFi Use IL17i if conventional therapy (NSAIDs and TNFi) inadequate	BASDAI improvement 50% or ≥2.0 and spinal pain VAS reduction ≥2.0 Assess response: 12 wk for TNFi, 16 wk for IL17i	Infliximab and its biosimilar has higher ICER than other TNFi
Failed at least 2 NSAIDs over 3 mo. Completed appropriate concomitant exercise program	Not discussed	Not discussed	BASDAI ≥ 2.0 AND 1 of: ESR < 25, CRP < 10, ESR/CRP < 10 Assess response after 12 wk	Not discussed
Failed 2 different NSAIDs	TNFi	Another TNFi or secukinumab	Not stated	High cost of biosimilars makes them inaccessible in the region

important. The TFP believed that treatment strategies should be individualized according to each patient's clinical characteristics and the option between TNFi or IL17i should be open.

3.7 | If first-line bDMARD fails, switch to either another TNFi or IL17i (if not used previously)

Inadequate response to bDMARD therapy may be divided into primary failure or secondary failure.[37] Primary failure is defined as lacking clinical improvement during induction therapy, normally within 3 months, while secondary failure is loss of treatment response after initial good response. Secondary failure is thought to be due to formation of anti-drug antibodies against TNFi.[38] Most guidelines recommend switching to another TNFi[3,4,17] and previous experience has shown that patients who failed 1 TNFi may respond to another. However, in primary failure with TNFi, there is a theoretical benefit in switching to a treatment with a different mechanism of action. This is consistent with the ASAS/EULAR guidelines, which recommend switching to IL17i if there is primary failure with TNFi.[5]

3.8 | The choice of bDMARD should take into consideration patients' unique characteristics and the extra-articular manifestations of SpA such as uveitis and inflammatory bowel disease

To date, there is are still no head-to-head trials comparing different TNFi, or between TNFi and IL17i. Choice of therapy should take into

TABLE 2 Consensus statement on initiation and continuation of a biologic disease-modifying anti-rheumatic drugs for axial spondyloarthritis

Recommendations relating to initiating biologic therapy	Median agreement scores on a Likert scale of 5	N (%) with agreement	Voting round
1. Patients should fulfill either ASAS criteria for spondyloarthritis or modified New York criteria for ankylosing spondylitis.	5	10/11 (91%)	1
2. Patients with active disease may be defined by either BASDAI ≥ 4 or ASDAS ≥ 2.1	4	9/11 (82%)	1
3. Patients should have failed 2 sequential NSAIDs at maximum tolerated doses for a total duration of at least 4 wk and should be participants in an appropriate physiotherapy and exercise program.	5	9/11 (82%)	1
4. For patients with peripheral arthritis, SSZ at optimal dose should have been used for at least 12 wk unless contraindicated.	5	10/11 (91%)	1
5. Symptomatic enthesitis should have failed appropriate local treatment.	4	8/11 (73%)	1
6. If bDMARD is considered, either TNFi or IL17i may be considered as first-line therapy.			
(A) No. voted for TNFi as first-line therapy	5[a]	10/10 (100%)	2
(B) No. voted IL17i as first-line therapy.	5[a]	7/10 (70%)	2
7. If first-line bDMARD fails, switch to either another TNFi or IL17i.			2
(A) No. voted for TNFi as second-line therapy	5[a]	8/10 (80%)	2
(B) No. voted for IL17i as second-line therapy.	5	11/11 (100%)	1
8. The choice of bDMARD therapy should take into consideration patients' unique characteristics and the extra-articular manifestations of SpA such as uveitis and inflammatory bowel disease.	5	9/11 (82%)	1
9. All patients on bDMARD therapy should have response to therapy measured and documented every 3 mo. For continuation of therapy with bDMARD, patients should achieve an adequate response at 6 mo.	5	11/11 (100%)	1
10. Response should be monitored by the disease activity measure used to initiate biologic therapy, and is defined by ASDAS improvement ≥ 1.1 or BASDAI improvement ≥ 2.0.	5	11/11 (100%)	1
11. A biosimilar may be substituted for the originator drug for better cost-effectiveness.	4	10/11 (91%)	1

Abbreviations: ASAS, Assessment of Spondyloarthritis; ASDAS, Ankylosing Spondylitis Disease Activity Score; BASDAI: Bath Ankylosing Spondylitis Disease Activity Index; bDMARD, biologic disease-modifying antirheumatic drug; IL17i, interleukin 17 inhibitor; NSAIDs, non-steroidal anti-inflammatory drugs; SSZ, sulphasalazine; TNFi, tumor necrosis factor inhibitor.
[a]Denotes statements entering the second round of voting with 10 members of the TFP.

consideration factors such as extra-articular manifestations of SpA like uveitis, inflammatory bowel disease and skin psoriasis, and social factors including financial cost, convenience and insurance coverage. For instance, etanercept is associated with higher risk of anterior uveitis and inflammatory bowel disease and thus should be avoided in patients with these concurrent conditions.[39,40] Similarly, there is no evidence to show that IL17i is effective in inflammatory bowel disease and other bDMARDs may be preferred in these patients.[41] Skin psoriasis is also another important extra-articular manifestation to consider. There are patients with axSpA and skin psoriasis who may not fit into the classical description of psoriatic arthritis[42] where targeting both the axial and skin components would be necessary. Hence, the introduction of IL17i is a welcome addition in our armamentarium of bDMARDs as secukinumab has also been shown to be efficacious in skin psoriasis.[43] Separate guidelines on recommendations for biologics in psoriatic arthritis have been drafted.

3.9 | All patients on bDMARD therapy should have response to therapy measured and documented every 3 months. For continuation of therapy with bDMARD, patient should achieve an adequate response at 6 months

Almost all guidelines suggest assessing response 12-16 weeks after biologic initiation.[4-6,13,17] The previous 2013 consensus statement recommended assessment after 3 months.[12] The current TFP agreed that 3 months continues to be an appropriate time interval to evaluate treatment response. In addition, the panel recommended that continuation of funding for bDMARDs should be reviewed every 6 months. Some patients may take longer than 3 months to achieve adequate response and 6 months was deemed an appropriate time to give a specific therapy enough opportunity to exert its effect.

3.10 | Response should be monitored by the disease activity measure used to initiate biologic therapy, and adequate response is defined by ASDAS improvement ≥1.1 or BASDAI improvement ≥2.0

The use of BASDAI for monitoring treatment response continues to feature in many guidelines, including ASAS/EULAR, Canadian and NICE guidelines.[5,6,17] The majority recommend an improvement of more than 2.0 points as adequate response. In addition, with the introduction of ASDAS as a new tool for monitoring disease activity, ASAS/EULAR has suggested using ASDAS to evaluate treatment response too, with cut-off set at 1.1.,[5] the TFP recommended consistency in disease monitoring: if either BASDAI or ASDAS is used to initiate therapy, the same disease measure should be used to monitor treatment response. The previous 2013 statement required spinal pain be evaluated as an additional component. After discussion, the TFP recommended removing this component as spinal pain is evaluated within both BASDAI and ASDAS.

3.11 | A biosimilar may be substituted for the originator drug for better cost-effectiveness

Lastly, there is now an increasing trend to use biosimilars over bio-originators in view of cost reduction. For AS, there is evidence that biosimilars achieve comparable pharmacokinetics and clinical outcomes.[44,45] In Singapore, institution subsidization has started a preference for the use of biosimilar, Remsima, over its bio-originator Remicade, a trend we believe is only to increase in the future. The TFP unanimously agreed that biosimilars may be substituted for the bio-originator as per the discretion of the treating physician.

4 | DISCUSSION

In summary, this is an update of the 2013 consensus statements recommending use of bDMARD therapy for patients with axSpA in Singapore. All 10 previous clinical important decision points were preserved, although several statements underwent changes to reflect recent advancements in disease monitoring, treatment options and clinical definitions. However, they are not meant to be prescriptive. Clinical management needs to be contextualized to a patient's individual needs and preferences by the treating rheumatologist.

These recommendations address the reality that healthcare resources are not limitless. There is government subsidization for expensive therapies such as bDMARDs; however, eligibility requires patients to meet specified clinical indications and undergo financial assessment that considers various factors like household income, with the aim of higher subsidies for lower-income groups. Our consensus statements aim to provide guidance on such government funding decisions and create more equitable access to bDMARDs for patients who most need them. Subsequent steps would include engaging both government funding agencies and pharmaceutical companies that would compete for government tenders. We believe our framework is also applicable to other countries with similar resource limitations. Nations could perform their own therapeutics appraisals and formulate guidelines that suit their particular landscapes, and be used by central bodies with aggravated purchasing powers to negotiate for fairer prices.

With regard to the recent developments in axSpA, members of the TFP were unanimous in including the ASAS criteria as well as the New York criteria, and the inclusion of ASDAS as a disease activity score in current guidelines. This reflects the recognition of non-radiographic axSpA as a disease entity, and agreement for using bDMARD for this condition. There was some debate regarding choice of first-line therapy. As stated earlier, there are no head-to-head trials between TNFi. While members of the TFP had good outcomes with use of IL17i, more clinical experience with this new class of drug is warranted. Furthermore, no trial has directly compared TNFi with IL17i.

There are strengths in our method for developing these consensus statements. The CWG performed a rigorous literature search and selected only guidelines which included a systematic literature search and a formal consensus process. We additionally supplemented this with guidelines from governmental funding organizations. Members of the TFP were all practicing rheumatologists from a diverse range of clinical environments, both in the public and private setting. Discussions during the meeting were based on evidence, supplemented by expert opinion derived from the local Singapore context. There were some limitations in this exercise. Cost-effectiveness analysis was not performed, although cost was taken into consideration during discussions. There was no patient representative in the TFP, a feature that is now increasingly prevalent in development of clinical guidelines.

Tapering of bDMARD was not specifically discussed in our consensus process, as this was not among the scenarios brought up for voting by the CWG or TFP. The literature around tapering is mostly limited to studies of RA[46,47] and the most recent American College of Rheumatology/ Spondyloarthritis Research and Treatment Network guidelines do not recommend bDMARD tapering as a routine.[3] However, in recent years there is evolving evidence supporting tapering in patients with axSpA with low disease activity, including two small randomized controlled trials.[48-51] Regimens described include either dose reduction or lengthening intervals between doses. As access to biologics improves and are used earlier in the disease course, it is hoped that evidence-based tapering regimens will be incorporated into future iterations of our guideline.

In conclusion, axSpA is an inflammatory condition that contributes to chronic pain, disability and loss of societal involvement. Treatment with biologic therapy is effective but costly. The updated consensus statements were crafted to take account of recent understanding of the disease and newer therapeutic options. Similar to the recently published Asia-Pacific League of Associations for Rheumatology recommendations, the goal is to provide guidance relevant to the Asia-Pacific region.[52] As newer evidence will continue

to emerge, exercises to update the consensus statements will continue to be periodically performed.

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REVIEW

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WILEY

Primary hyperparathyroidism is associated with a higher level of serum uric acid: A systematic review and meta-analysis

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Abstract

Objectives: Studies have suggested that primary hyperparathyroidism could be a risk factor for hyperuricemia although the results were not consistent across the studies. This systematic review and meta-analysis was performed in order to identify all available studies and summarize their results together.

Methods: A systematic review was performed using EMBASE and MEDLINE from inception to August 2018 to identify all cohort studies that consisted of 2 cohorts, a cohort of patients with primary hyperparathyroidism and a cohort of individuals without hyperparathyroidism. Eligible studies had to provide data on mean serum uric acid level and standard deviation of both cohorts, which would be extracted to calculate mean difference (MD). Pooled MD was then calculated by combining MDs of each study using a random-effects model. Funnel plot was used for evaluation for publication bias.

Results: A total of 9 cohort studies met the inclusion criteria and were included into the meta-analysis. The pooled analysis found that patients with primary hyperparathyroidism had a significantly higher level of serum uric acid than individuals without hyperparathyroidism with the pooled MD of 65.00 μmol/L (95% CI 37.74-92.25). The statistical heterogeneity was high with I^2 of 90%. The funnel plot was relatively symmetric and did not provide evidence for publication bias.

Conclusion: Patients with primary hyperparathyroidism had a significantly higher level of serum uric acid compared to individuals without hyperparathyroidism.

KEYWORDS

hyperuricemia, meta-analysis, parathyroid hormone, primary hyperparathyroidism, uric acid

1 | INTRODUCTION

Primary hyperparathyroidism (PHPT) is a pathological condition characterized by excessive production and secretion of parathyroid hormone (PTH) by at least 1 of the 4 parathyroid glands without an appropriate stimulus. It is the 3rd most common endocrine disorder with the reported global prevalence of 1-21 per 1000 individuals. Skeletal abnormality, including decreased bone mineral density, bone pain, pathologic fracture and the classic osteitis fibrosa cystica, is the most common manifestation of PHPT. Common extra-skeletal manifestations include nephrolithiasis and hypercalcemia. Remarkably, up to 70%-80% of PHPT patients are asymptomatic at the time of diagnosis.[1] More recent studies also found an association between PHPT and an increased risk of hypertension, diabetes mellitus and obesity[1,2] as well as an increased mortality from cardiovascular diseases (ie stroke, myocardial infarction and heart failure).[3]

Uric acid is the end product of purine metabolism derived exogenously from dietary ingestion and endogenously from cellular

metabolism.[4] The persistently high level of serum uric acid can cause several adverse health consequences such as gout, nephrolithiasis and urate nephropathy. It is also closely associated with metabolic syndrome and cardiovascular diseases via the interaction with its associated conditions, such as insulin resistance, hypertension, dyslipidemia and central obesity.[5,6] The prevalence of hyperuricemia varies in regions of the world, and is as high as 18% in some populations.[7]

Several epidemiological studies have suggested the relationship between PHPT and hyperuricemia although the results were not consistent across all studies. In fact, some studies even reported a significant reduction of levels of serum uric acid in patients with PHPT whose PTH was normalized after parathyroidectomy.[8-10] This systematic review and meta-analysis was performed in order to identify all studies that compared the level of serum uric acid between patients with PHPT and individuals without PHPT and summarize their results together.

2 | METHODS

2.1 | Search strategy

Three investigators (PU, BP, NC) independently searched published studies indexed in EMBASE and MEDLINE from inception to August 2018. No language limitation was applied. Search terms comprised those related to primary hyperparathyroidism and uric acid, including words representing its serum levels. The detailed search strategy is provided in Appendix S1.

2.2 | Inclusion criteria

Studies that were eligible for the meta-analysis had to be cohort studies that consisted of 2 groups of adult participants (age ≥18 years), with 1 group being patients with PHPT, either biochemically, surgically or histopathologically proven, and the other group being individuals without PHPT. The eligible studies also had to report mean and standard deviation (SD) of serum uric acid levels of participants in both groups.

Two investigators (BP and NC) independently determined the study eligibility. Disagreement between investigators were resolved by conference with the senior investigator (PU). Two investigators (NC and PU) evaluated the quality of the studies using the Newcastle-Ottawa quality assessment scale for non-randomized studies.[11]

2.3 | Data extraction

A standardized data collection form was used to extract the following information: 1st author's last name, the country in which the study was performed, type of study design, year of publication, number of participants who were cases with PHPT and comparators without PHPT, recruitment of participants, average age of participants of each group, percentage of females in each group, comorbidities, mean and SD of serum uric acid levels in each group.

2.4 | Statistical analysis

Review Manager 5.3 software from the Cochrane Collaboration (London, UK) was used to perform the data analysis. Mean serum uric acid levels and SD of participants in both groups were extracted from each study to calculate mean difference (MD). Pooled MD was then calculated by combining MDs of each study using random-effects model. The heterogeneity of the MDs of the different studies was quantified using the Q-statistic, which is complimented with I^2 statistics. A value of I^2 of 0%-25% indicates insignificant heterogeneity, 26%-50% low heterogeneity, 51%-75% moderate heterogeneity and 76%-100% high heterogeneity.[12] Visual inspection of the funnel plot was used to assess for the presence of publication bias.

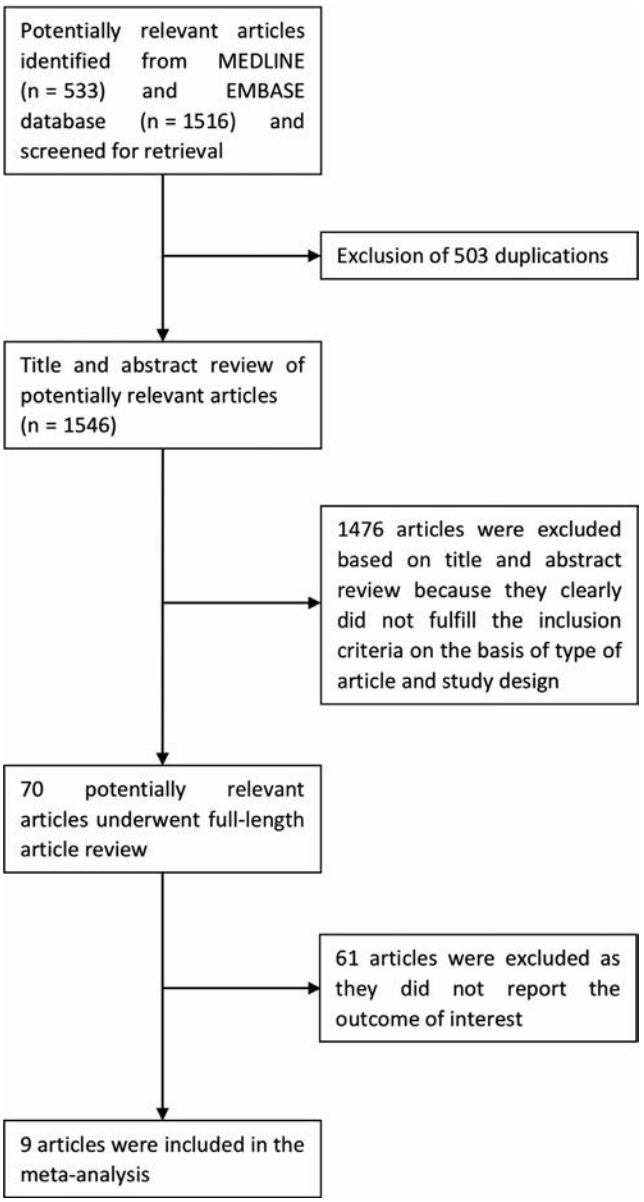

FIGURE 1 Study identification and literature review process

TABLE 1 Main characteristics of the studies included in the meta-analysis

	Broulik et al[13]	Yamamoto et al[14]	Pepersack et al[15]
Country	Czechoslovakia	Japan	Belgium
Year of publication	1987	1987	1989
Type of study	Cohort	Cohort	Cohort
Total number of participants	Cases: 53 Controls: 40	Cases: 29 Controls: 20	Cases: 37 Controls: 37
Recruitment of participants	Cases: Cases were patients with biochemically, surgically, and histologically proven PHPT with age 20-65 y with available urate measurements, normal renal function and no previous medical treatment known to affect serum urate levels who were identified from the database of Charles University Faculty of Medicine, Prague, Czechoslovakia. Controls: Controls were age- and sex-matched subjects without PHPT who were identified from the health screening register of the same institute.	Cases: Cases were patients with PHPT proven by histopathology after surgery who were recruited from University School of Medicine, Tokushima, Japan. Controls: Controls were patients without PHPT who underwent other urological operations at the same institute.	Cases: Cases were patients with surgically proven PHPT with no previous medical treatment known to affect serum urate levels who were recruited from Brugmann University Hospital, Brussels, Belgium. Controls: Controls were age- and sex-matched subjects without PHPT.
Average age of participants, y	N/A	Cases: 42.4 Controls: N/A	Cases: 57.0 Controls: N/A
Percentage of females	Cases: 83.0% Controls: 78.8%	Cases: 55.2 Controls: N/A	Cases: 56.8 Controls: N/A
Comorbidities	N/A	Urolithiasis: 100%	Renal stone: 56.8% Nephrocalcinosis: 16.2%
Serum creatinine level, mg/dL	Cases: 0.93 ± 0.12 Controls: 0.95 ± 0.11	N/A	N/A
Creatinine clearance, mL/min	N/A	N/A	Cases: 91 ± 27 Controls: 98 ± 28
UA level in PHPT patients, μmol/L	371.90 ± 95.70	347.06 ± 59.48	370.59 ± 86.85
UA level in normal subjects, μmol/L	242.20 ± 42.30	327.17 ± 59.48	276.01 ± 73.76
Newcastle-Ottawa score	Selection: 3 Comparability: 2 Outcome: 3	Selection: 3 Comparability: 0 Outcome: 3	Selection: 3 Comparability: 2 Outcome: 3

	Lind et al[16]	Delfini et al[17]	Erem et al[18]
Country	Sweden	Italy	Turkey
Year of publication	1992	2007	2008
Type of study	Cohort	Cohort	Cohort
Total number of participants	Cases: 86 Controls: 106	Cases: 67 Controls: 46	Cases: 23 Controls: 20
Recruitment of participants	Cases: Cases were patients with surgically proven PHPT who were identified from the database of Gavle County Hospital, Uppsala, Sweden. Controls: Controls were subjects without PHPT and hypercalcemia who were identified from the inpatient database of the same institute.	Cases: Cases were patients with PHPT who were diagnosed based on biochemical tests and imaging studies. Cases were recruited from University of Rome, Italy between December 2002 and July 2005. Controls: Controls were subjects without PHPT who were recruited from the same institute.	Cases: Cases were patients with symptomatic PHPT which was diagnosed based on biochemical tests and clinical assessment. Cases were recruited from Karadeniz Technical University Medical Faculty, Turkey between May 2005 and December 2006. Controls: Controls were age- and sex-matched subjects without PHPT who were recruited from the same institute.

(Continues)

TABLE 1 (Continued)

	Lind et al[16]	Delfini et al[17]	Erem et al[18]
Average age of participants, y	Cases: 64.0 Controls: 67.0	Cases: 57.9 Controls: 58.1	Cases: 52.9 Controls: 49.4
Percentage of females	Cases: 83.0 Controls: 58.0	Cases: 83.6 Controls: 65.2	Cases: 82.6 Controls: 85.0
Comorbidities	N/A	Patients with comorbid conditions and criticality were excluded, otherwise not reported.	N/A
Serum creatinine level, mg/dL	Cases: 0.98 ± 0.25 Controls: 1.02 ± 0.38	Cases: 0.96 ± 0.41 Controls: 0.94 ± 0.34	N/A
Creatinine clearance, mL/min	N/A	N/A	N/A
UA level in PHPT patients, μmol/L	356 ± 98	303.37 ± 83.28	315.27 ± 113.02
UA level in normal subjects, μmol/L	336 ± 110	214.15 ± 65.43	261.73 ± 53.54
Newcastle-Ottawa score	Selection: 3 Comparability: 0 Outcome: 3	Selection: 3 Comparability: 0 Outcome: 3	Selection: 3 Comparability: 2 Outcome: 3

	Broulik et al[19]	Ishay et al[20]	Kahal et al[21]
Country	Czech Republic	Israel	UK
Year of publication	2011	2011	2012
Type of study	Cohort	Cohort	Cohort
Total number of participants	Cases: 1020 Controls: 1020	Cases: 34 Controls: 42	Cases: 23 Controls: 22
Recruitment of participants	Cases: Cases were patients with biochemically, surgically, and histologically proven PHPT who were identified from the database of the Third Internal Clinic Medical School of Charles University of Prague between 1998 and 2007. Controls: Controls were age-, sex-, smoking status- and BMI-matched subjects without PHPT. Controls were identified from database of patients receiving periodic health examinations at the outpatient ward between January 2004 and December 2005.	Cases: Cases were patients with PHPT proven by histopathology after surgery who were recruited from the Endocrine Institute, Haemek Medical Center, Afula, Israel. Controls: Controls were age- and BMI-matched subjects without PHPT who were recruited from community-based health centers of the same geographic area.	Cases: Cases were patients with PHPT proven by histopathology after surgery who were recruited from a University Teaching Hospital in the UK. Controls: Controls without PHPT were consecutive euthyroid patients who underwent diagnostic hemithyroidectomy for a cold thyroid nodule in the same center. Controls were recruited at the same time period as cases.
Average age of participants, y	Cases: 58.0 Controls: 60.0	Cases: 51.0 Controls: 49.9	Cases: 60.0 Control: 43.0
Percentage of females	Cases: 83.0 Controls: 83.0	Cases: 67.6 Controls: 81.0	Cases: 93.1 Controls: 70.4
Comorbidities	HT (71% of cases vs 48% of controls) Smoking (17% of cases vs 18% of controls) Nephrolithiasis/nephrocalcinosis (31% of cases vs 6% of controls)	Individuals with known DM, thyroid dysfunction, coronary artery disease, a history of stroke, and serum 25-hydroxyvitamin D <20 ng/mL were excluded, otherwise not reported.	Individuals undergoing surgery for thyroid cancer were excluded, otherwise not reported.
Serum creatinine level, mg/dL	Cases: 0.84 ± 0.06 Controls: 0.80 ± 0.10	Cases: 0.93 ± 0.16 Controls: 0.89 ± 0.13	N/A

(Continues)

TABLE 1 (Continued)

	Broulik et al[19]	Ishay et al[20]	Kahal et al[21]
Creatinine clearance, mL/min	N/A	N/A	N/A
UA level in PHPT patients, μmol/L	368 ± 45	315.27 ± 89.23	300 ± 100
UA level in normal subjects, μmol/L	266 ± 42	267.68 ± 53.54	300 ± 100
Newcastle-Ottawa score	Selection: 3 Comparability: 2 Outcome: 3	Selection: 4 Comparability: 2 Outcome: 3	Selection: 3 Comparability: 0 Outcome: 3

Abbreviations: BMI, body mass index; DM, diabetes mellitus; HT, hypertension; MI, myocardial infarction; PHPT, primary hyperparathyroidism; UA, uric acid.

3 | RESULTS

3.1 | Search results

The search strategy yielded 2049 potentially relevant articles (1516 from EMBASE and 533 from MEDLINE database). After removing 503 duplicated articles, 1546 articles were left for title and abstract review. After title and abstract review, 1476 articles were excluded as they obviously did not fulfill the inclusion criteria based on type of article and study design, leaving 70 articles for full-length article review. A total of 61 articles were excluded at this stage as they did not report the outcomes of interest. Finally, nine cohort studies were included into the meta-analysis.[13-21] The study review and selection process are described in Figure 1. The basic characteristics of all included studies are summarized in Table 1.

3.2 | Serum uric acid levels between patients with primary hyperparathyroidism versus individuals without primary hyperparathyroidism

The meta-analysis found that patients with primary hyperparathyroidism had significantly higher serum uric acid levels than individuals without primary hyperparathyroidism with the pooled MD of 65.00 μmol/L (95% CI 37.74-92.25). The statistical heterogeneity of this meta-analysis was high with I^2 of 90% (Figure 2).

3.3 | Evaluation for publication bias

Funnel plot was used for the assessment of publication bias. The plot result was relatively symmetric and did not provide evidence for publication bias (Figure 3).

4 | DISCUSSION

This study is the first systematic review and meta-analysis to compare the level of serum uric acid between patients with PHPT and individuals without PHPT by summarizing data from all available studies. The pooled analysis found that, on average, the level of serum uric acid among patients with PHPT was 65.00 μmol/L higher than individuals without PHPT. This observation may have some clinical implications for the management of hyperuricemia. For instance, similar to other causes of secondary hyperuricemia, PHPT may be considered as a treatable/modifiable cause of hyperuricemia. In fact, a number of studies have demonstrated a reduction in levels of serum uric acid in patients with PHPT after parathyroidectomy.[8-10,13-15,19-21]

The exact pathophysiology as to why PHPT could lead to hyperuricemia is not completely understood. Reduced urinary excretion of urate in the presence of high levels of PTH is one of the possible explanations[22,23] as PTH is known to directly decrease renal tubular secretion of uric acid by down-regulating a renal urate exporter, ABCG2.[22] Another possible mechanism is related to hypercalcemia as a high level of calcium is known to cause extracellular volume depletion due to osmotic diuresis and/or partial or complete nephrogenic diabetes insipidus.[24] Although overt hypercalcemia-related extracellular volume contraction is unusual for patients with PHPT, mild-to-moderate degree of extravascular volume contraction can be seen which could enhance renal tubular reabsorption of uric acid.[23]

It is important to note that this systematic review and meta-analysis had some limitations so that the results need to be carefully interpreted. First, statistical heterogeneity in this study was high which is likely due to the difference in background populations of the included studies. Second, the number of eligible studies was relatively low which may jeopardize the reliability of the interpretation of the funnel plot. Therefore, it is still possible that publication bias in favor of positive studies may have been present. Finally, this is a meta-analysis of observational studies that did not adjust their results for potential confounders. Thus, confounders, such as comorbidities, could indeed be the major players that were responsible for the high level of serum uric, not PHPT itself.

5 | CONCLUSION

In summary, this study found that patients with primary hyperparathyroidism had a significantly higher level of serum uric acid compared to individuals without hyperparathyroidism.

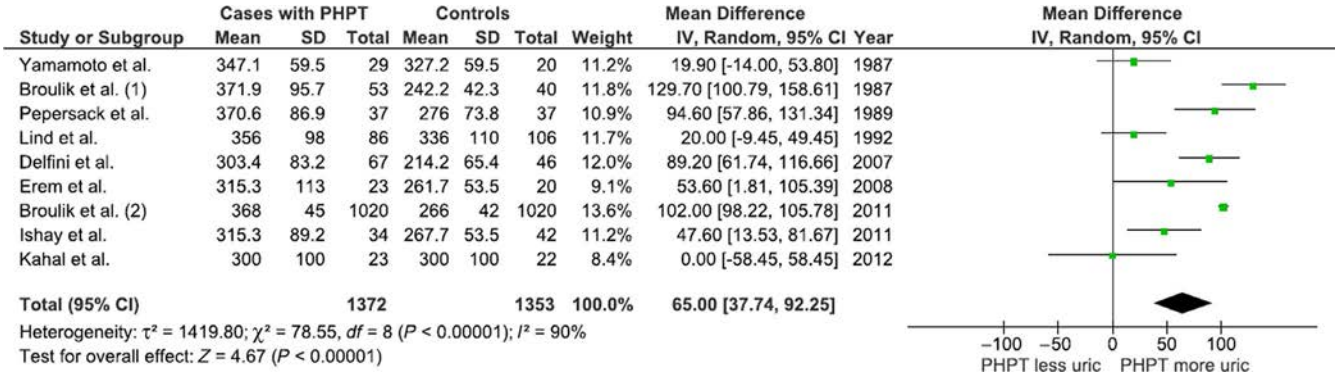

FIGURE 2 Forest plot of the meta-analysis of primary hyperparathyroidism cases versus controls

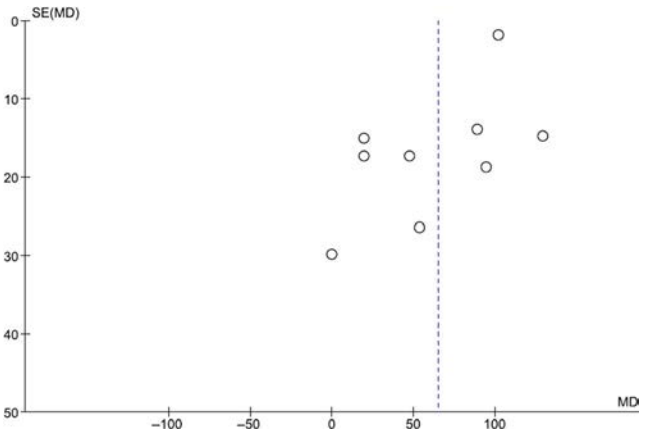

FIGURE 3 Funnel plot of the meta-analysis of primary hyperparathyroidism cases versus controls

CONFLICT OF INTEREST

We do not have any financial or non-financial potential conflicts of interest.

AUTHORS' CONTRIBUTIONS

All authors had access to the data and a role in writing the manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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ORIGINAL ARTICLE

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The risk of herpes zoster among patients with ankylosing spondylitis: A population-based cohort study in Taiwan

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Abstract

Objectives: The incident rate of herpes zoster (HZ) is higher in some autoimmune diseases; however the relationship of HZ and ankylosing spondylitis (AS) is still unclear. This research aims to determine the incidence of HZ in Taiwan AS patients.

Methods: This study included 2819 AS patients and 11 276 non-AS controls between 2003 and 2013. All participants were selected from the Longitudinal Health Insurance Database 2000 Taiwan. The endpoint was diagnosis of HZ by International Classification of Diseases, Ninth Revision, Clinical Modification coding for at least 3 outpatient visits or one admission until the end of 2013. We used Chi-square test, Cox proportional hazard models and a Kaplan-Meier analysis to calculate the hazards ratio (HR), disease-free survival and incidental density of HZ. Subgroup analysis and sensitivity tests were also done.

Results: Comorbidities such as chronic urticaria, inflammatory bowel disease, thyroid disorders, hypertension, diabetes mellitus, hyperlipidemia, coronary artery disease, cerebrovascular accident, were higher in patients with AS than that in controls. Patients age ≥60 or comorbid disease such as thyroid disorders or cancer had a higher HR of HZ; the adjusted HRs were 2.273 (95% CI 1.314-3.931), 1.577 (95% CI 1.008-2.466) and 1.855 (95% CI 1.248-2.758) respectively, on multivariable modeling. The crude HR for HZ among AS patient was 1.178 (95% CI 0.953-1.455, $P > 0.05$), and the adjust HZ was 1.070 (95% CI 0.835-1.371, $P > 0.05$), compared to non-AS controls.

Conclusions: There is no difference in incidence rate of HZ between Taiwan AS patients and non-AS controls. Among AS patients, age and cancer were major risk factors for incidental HZ.

KEYWORDS

ankylosing spondylitis, hazards ratio, herpes zoster

1 | INTRODUCTION

Herpes zoster (HZ), is a painful skin eruption, which is caused by reactivation of latent varicella zoster virus (VZV). The reactivation of VZV can cause neuronal damage. The risk of HZ is 25%-30% over a lifetime, and the risk of developing HZ is rising to 50% in individuals aged over 80 years.[1-3] There are three phases of HZ pain: acute pain phase, subacute pain and post-herpetic neuralgia phase. HZ and its complications constitute a significant burden on patients.[4,5] It was reported that patients' immune systems play an

Shuya Wang and James Cheng-Chung Wei made equal contributions to this work.

important role in the reactivation of VZV.[6] Studies have shown that HZ events are several times higher among systemic lupus erythematosus (SLE) and rheumatoid arthritis patients as compared to healthy individuals.[7] This higher incidence may be due to the usage of disease-modifying anti-rheumatic drugs (DMARDs) or the dysregulation of the immune system by the disease itself. Ankylosing spondylitis (AS) is a kind of chronic autoimmune-related disease, the etiology of which is still unknown. It usually occurs in young men and affects the axial skeleton and extra-articular structures. Immunomodulatory and immune-suppressive drugs are frequently used in AS patients.[8] It was reported that the incidence rate of HZ in AS patients is a bit higher than in the general population in the USA, but without statistical significance.[9] The incidence rate of HZ in South Korean AS patients was comparable with the general population.[10] However, those studies were either cross-sectional or had small sample sizes. Hence, we aimed to determine whether AS increases the risk of HZ in a long-term population-based cohort database.

2 | MATERIALS AND METHODS

2.1 | Data source

In this population-based retrospective cohort study, patients' data were obtained from the Longitudinal Health Insurance Database 2000 (LHID2000), which contained 1 million randomly sampled beneficiaries from the National Health Institutes Research Database (NHIRD) in 2000. NHIRD is a population-based database, which was created in 1995, and it enrolls more than 99% of the Taiwan population. This database contains all the registrations and claims data, including diagnoses, drug prescriptions, inpatient care, outpatient visits and International Classification of diseases, Ninth Revision, Clinical Modification (ICD-9-CM) diagnostic codes of patients in Taiwan. NHIRD is a peer-reviewed database with a punishment system to ensure the accuracy of data input and has been used to published more than 3000 articles in international journals.

2.2 | Study cohort and controls

We identified 4922 patients who were newly diagnosed as having AS between 1 January, 1997 and 31 December, 2013, from the LHID2000. Patients with the first record of the ICD-9-CM code 720.0 in at least 1 inpatient claim or had three or more outpatient services were considered to be newly diagnosed as having AS. We excluded 1890 patients diagnosed with AS before 1997 and 121 patients with HZ diagnosis before the index date.

A total of 917 202 individuals who were never diagnosed as having AS were randomly selected during the period from 1997 to 2013; they were included in the control cohort. We matched 11 276 controls to AS patients as a ratio of 1:4 by age and sex.

2.3 | Outcome assessment

Follow-up started on the index date and ended on the HZ diagnosis date or 31 December, 2013. The index date was defined as the date when patients were first diagnosed as having AS. The date of patient withdrawal from the NHI program was defined as the end date. New cases of HZ were identified from the database by the presence of records of ICD-9-CM code 053. Patients were considered to be newly diagnosed as HZ only if they had ICD-9-CM code 053 and whose clinical history included at least 2 outpatient visits or 1 hospital admission.

2.4 | Statistical analysis

We used the Chi-square test to compare the demographic data of the AS and non-AS groups. Cox proportional hazard models were used to estimate the hazard ratios (HRs) and to adjust for covariates that were associated with HZ. A Kaplan-Meier analysis was done to discriminate the impact on developing HZ as the time gone by between the AS and non-AS group. Sensitivity tests were done using 3 different adjusted models. Subgroup analysis was also performed by age and gender. All the statistical analyses were performed by utilizing SPSS 18 (SPSS Inc). Statistical significance was defined as a P value of less than 0.05.

3 | RESULTS

3.1 | Study population

The selection of participants is shown in Figure 1. After we excluded those participants missing demographic data and who died before 2003, 4803 AS patients were identified with at least three outpatient visits or one admission for AS. We further exclude those AS cases diagnosed before 2003 and HZ cases diagnosed before the index date. A total of 14 095 patients were recruited from the claims database, where 2819 of the subjects were AS patients and 11 276 were non-AS patients.

3.2 | Baseline characteristics of patients with AS

Of the sampled AS patients, 38.77% were women and 61.23% were men. After matching for sex, age and index date, there was no difference in urbanization level, little difference in monthly income. Compared to the control group, AS patients were more likely to have comorbid chronic urticaria ($P = 0.0101$), inflammatory bowel disease ($P < 0.0001$), thyroid disorders ($P < 0.0001$), hypertension ($P < 0.0001$), diabetes mellitus ($P = 0.0100$), hyperlipidemia ($P < 0.0001$), coronary artery disease ($P < 0.0001$), cerebrovascular accident ($P < 0.0001$), chronic kidney disease ($P < 0.0001$), asthma ($P < 0.0001$), chronic obstructive pulmonary disease ($P < 0.0001$), esophageal disease ($P < 0.0001$), and peptic ulcer ($P < 0.0001$; Table 1).

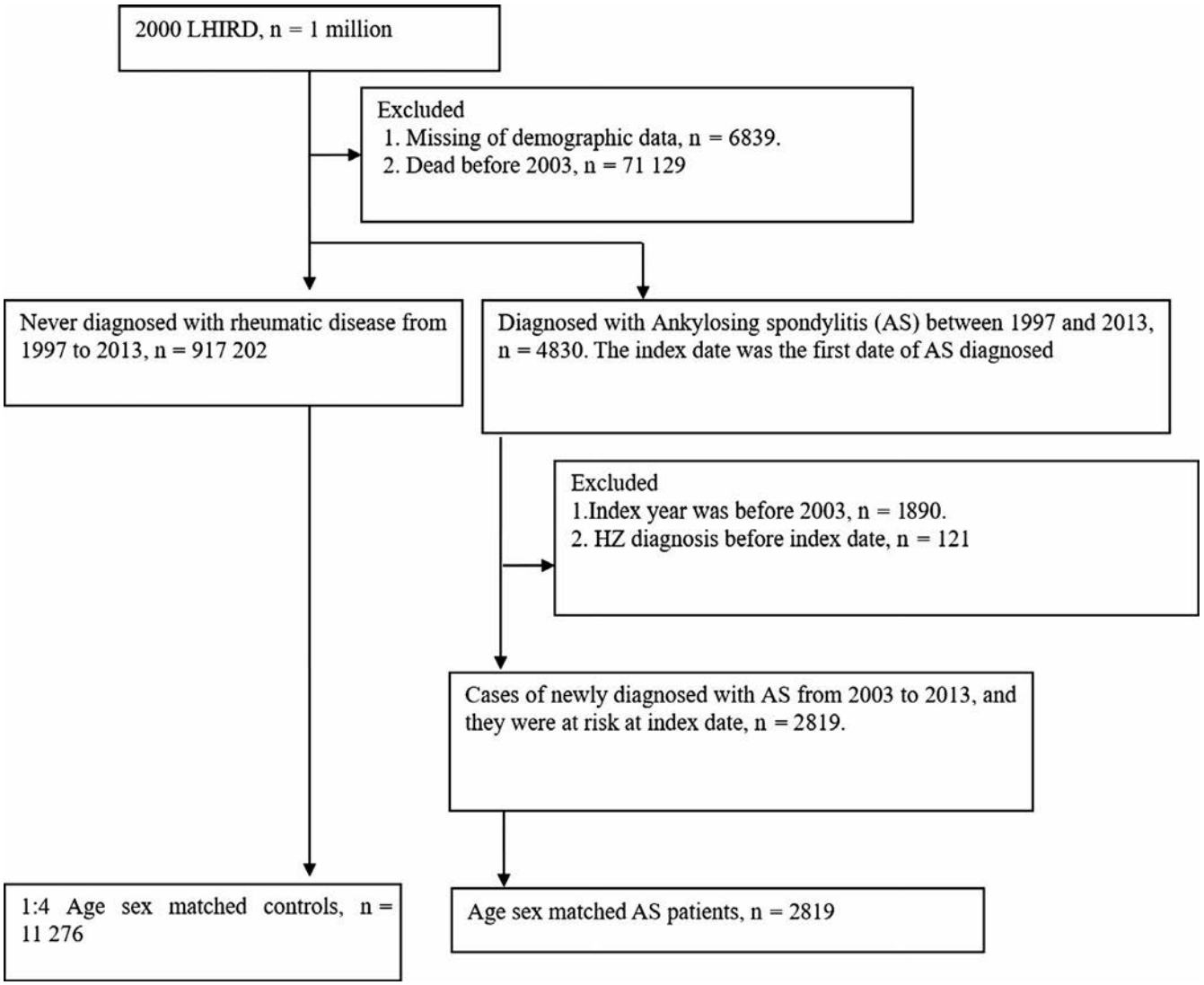

FIGURE 1 Flowchart of the patients' selection. LHIRD, Longitudinal Health Insurance Research Dataset

3.3 | HRs of HZ infection

Cox proportional hazard regression shown that on multivariable modeling, patients ≥60 years or with comorbid disease such as thyroid disorders or cancer have a higher HR of HZ infection ($P < 0.05$); the adjusted HRs (aHRs) were 2.273 (95% CI 1.314-3.931), 1.577 (95% CI 1.008-2.466) and 1.855 (95% CI 1.248-2.758) respectively, but compared with the control group AS patients had no significant difference in HZ infection (adjusted HR 1.070, 95% CI 0.835-1.371) (Table 2).

3.4 | Time-to-event analysis and subgroup analysis

Table 3 showed incidence rates (per 1000 persons a year) of HZ of 6.52 (95% CI 5.42-7.86) and 5.54 (95% CI 5.01-6.13) in the AS and control groups, respectively, from 2003 to 2013 in Taiwan. The Kaplan-Meier curves of cumulative incidence proportion of HZ are shown in Figure 2; there was no difference in incidence risk between AS and control groups (log-rank, $P = 0.1285$). The crude HR for HZ among subjects with AS was 1.178 (95% CI 0.953-1.455, $P = 0.1298$). The aHR for HZ among subjects with AS was 1.180 (95% CI 0.955-1.458, $P = 0.1260$, model 2) after adjustment of age, sex, and urbanization. Then, we added the lengths of hospital stays and comorbidities into the multivariate analysis, and the aHR was 1.103 (95% CI 0.888-1.369, $P = 0.3752$). After we put the medication into the model, the aHR was still non-significant (aHR = 1.071, 95% CI 0.836-1.372, $P = 0.5857$). For the subgroup analysis, we found no difference in aHR between AS and control groups (Table 4).

4 | DISCUSSION

We found the incidence rate of HZ was 5.54 per 1000 person-years in Taiwan non-AS patients, and 6.52 per 1000 person-years in Taiwan AS patients, in this large population-based study. There was no difference in HR for HZ infection between AS and

TABLE 1 Characteristics among groups

	Controls N = 11 276	Ankylosing spondylitis patients N = 2819	*P* value
Age at index date			
<20	584 (5.18%)	146 (5.18%)	1.0000
20-39	4520 (40.09%)	1130 (40.09%)	
40-59	3848 (34.13%)	962 (34.13%)	
≥=60	2324 (20.61%)	581 (20.61%)	
Sex			
Female	4372 (38.77%)	1093 (38.77%)	1.0000
Male	6904 (61.23%)	1726 (61.23%)	
Urbanization			
Urban	6754 (59.9%)	1648 (58.46%)	0.2702
Suburban	3404 (30.19%)	895 (31.75%)	
Rural	1118 (9.91%)	276 (9.79%)	
Low income	61 (0.54%)	7 (0.25%)	0.0449
Length of hospital stay			
0	9857 (87.42%)	2281 (80.92%)	<0.0001
1-6	867 (7.69%)	293 (10.39%)	
7-13	264 (2.34%)	129 (4.58%)	
≥14	288 (2.55%)	116 (4.11%)	
Comorbidities (within 2 y before index date)			
Chronic urticaria	66 (0.59%)	29 (1.03%)	0.0101
Inflammatory bowel disease	9 (0.08%)	11 (0.39%)	<0.0001
Thyroid disorders	248 (2.20%)	103 (3.65%)	<0.0001
Hypertension	1901 (16.86%)	591 (20.96%)	<0.0001
Diabetes mellitus	966 (8.57%)	285 (10.11%)	0.0100
Hyperlipidemia	122 7(10.88%)	431 (15.29%)	<0.0001
Coronary artery disease	708 (6.28%)	259 (9.19%)	<0.0001
Cerebrovascular accident	406 (3.6%)	147 (5.21%)	<0.0001
Chronic kidney disease	287 (2.55%)	123 (4.36%)	<0.0001
Asthma	459 (4.07%)	193 (6.85%)	<0.0001
Chronic obstructive pulmonary disease	801 (7.10%)	286 (10.15%)	<0.0001
Esophageal disease	507 (4.50%)	270 (9.58%)	<0.0001
Peptic ulcer	1075 (9.53%)	499 (17.70%)	<0.0001
Cancer	284 (2.52%)	85 (3.02%)	0.1397

non-AS control groups. Using Cox proportional hazard analysis, the HR of HZ was higher in patients aged ≥60 or comorbid disease such as thyroid disorders or cancer; the aHRs were 2.273 (95% CI 1.314-3.931), 1.577 (95% CI 1.008-2.466) and 1.855 (95% CI 1.248-2.758), respectively.

It was reported that the HZ incidence in Taiwan was 4.04 to 6.24 per 1000 person-years,[11-13] which was higher than that in the USA (3.2-3.7 per 1000 person-years)[14] or Europe (3.7 per 1000 person-years).[15] The reason for regional differences in HZ morbidity are still unclear; this may be because of the ethnic distinction and the cultural differences.[16] Many studies have shown that the incidence of HZ is higher in some autoimmune diseases, for example RA[17] and SLE,[7,18] but few studies have shown the incidence of HZ in AS patients. In the USA, the incidence rate of HZ in AS patients is higher than in the general population, but the results showed no statistical significance.[9] It was reported that the incidence rate of HZ in South Korean AS patients was comparable with the general population: the incidence rate was 11.0 per 1000 person-years[10] and 10.04 per 1000 person-years.[19] Our study presented similar result to these researches.

TABLE 2 Estimation the hazard ratio (HR) of herpes zoster infection by using Cox proportional hazard regression

	Univariate modeling		Multivariate modeling	
	HR	95% CI	Adjusted HR	95% CI
Exposure of AS (ref: non-AS)				
AS patient	1.178	0.953-1.455	1.070	0.835-1.371
Age at index date (ref: <20)				
20-39	0.696	0.403-1.202	0.685	0.396-1.184
40-59	1.665	0.983-2.820	1.480	0.870-2.518
≥60	2.843	1.682-4.806	2.273	1.314-3.931*
Sex (ref: female)				
Male	0.703	0.588-0.840	0.963	0.799-1.161
Urbanization (ref: urban)				
Suburban	0.974	0.797-1.189	0.940	0.768-1.150
Rural	1.176	0.885-1.563	0.974	0.729-1.300
Length of hospital stay (ref:0)				
1-6	1.344	1.006-1.795	1.011	0.750-1.364
7-13	1.850	1.215-2.818	1.183	0.759-1.844
≥14	1.725	1.133-2.627	0.915	0.575-1.456
Comorbidities				
Chronic urticaria	2.665	1.191-5.961	2.056	0.898-4.707
Inflammatory bowel disease	1.159	0.163-8.248	0.680	0.095-4.895
Thyroid disorders	2.153	1.404-3.302	1.577	1.008-2.466*
Hypertension	2.141	1.767-2.594	1.090	0.811-1.465
Diabetes mellitus	1.746	1.363-2.236	1.040	0.711-1.521
Hyperlipidemia	1.976	1.575-2.479	1.097	0.825-1.461
Coronary artery disease	2.123	1.655-2.723	1.094	0.813-1.474
Cerebrovascular accident	1.483	1.025-2.146	0.738	0.495-1.100
Chronic kidney disease	1.717	1.179-2.499	1.015	0.685-1.504
Asthma	1.859	1.359-2.542	1.254	0.89-1.765
Chronic obstructive pulmonary disease	1.859	1.447-2.388	1.057	0.795-1.404
Esophageal disease	1.927	1.353-2.744	1.333	0.908-1.955
Peptic ulcer	1.784	1.419-2.242	1.103	0.847-1.435
Cancer	2.872	1.973-4.181	1.855	1.248-2.758*
Medications (at baseline)				
Corticosteroids	1.763	1.127-2.758	1.134	0.702-1.832
Diclofenac	1.245	0.874-1.772	0.972	0.670-1.410
Naproxen	1.201	0.718-2.009	1.359	0.632-2.923
Celecoxib	1.591	0.791-3.200	0.815	0.476-1.397
Meloxicam	1.689	0.801-3.562	1.192	0.743-1.911
Methotrexate	0.643	0.091-4.562	0.617	0.084-4.549
Sulfasalazine	0.915	0.547-1.530	1.008	0.576-1.767
Statin	2.634	1.849-3.751	1.518	0.992-2.321

Note: Medications were identified within 180 days before or after index date.
*$P < 0.05$.

Age is an important risk factor for HZ infection. Many studies show that HR increases in the elderly, especially in patients over 60 years.[11,13,20-24] It was reported that there was an age-specific decrease in VZV memory CD4 cells, so immunosenescence may be the key cause which leads to the increase of VZV infection and re-activation in the elderly.[25] Previous studies showed that in Taiwan age is also a major risk factor for HZ.[17] We obtained a similar result. Cox proportional hazard regression showed that on multivariable

TABLE 3 Time-to-event analysis

	Control N = 11 276	AS patients N = 2819	*P* value
Follow-up person months	816 752	204 188	
Event of HZ	377	111	
Incidence rate[a] (95% CI)	5.54 (5.01-6.13)	6.52 (5.42-7.86)	
Model 1: Crude HR (95% CI)	Reference	1.178 (0.953-1.455)	0.1298
Model 2: aHR (95% CI)[b]	Reference	1.180 (0.955-1.458)	0.1260
Model 3: aHR (95% CI)[c]	Reference	1.103 (0.888-1.369)	0.3752
Model 4: aHR (95% CI)[d]	Reference	1.071 (0.836-1.372)	0.5857

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; AS, ankylosing spondylitis; HZ, herpes zoster.
[a]Per 1000 person-years.
[b]Model 2: adjusted demographic variables at baseline including age, sex and urbanization.
[c]Model 3: adjusted demographics, length of hospital stay and comorbidities at baseline.
[d]Model 4: adjusted demographics, length of hospital stay, comorbidities and medication at baseline.

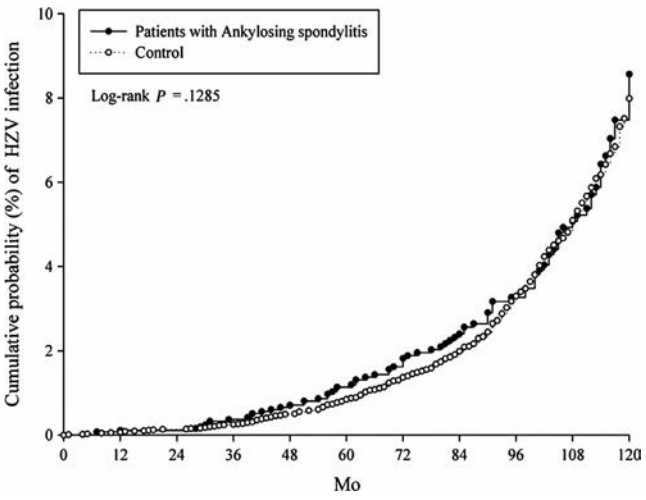

FIGURE 2 Kaplan-Meier curve of cumulative incidence proportion of herpes zoster (HZ) in the ankylosing spondylitis (AS) and the control population. HZV, herpes zoster virus

modeling, patients ≥60 have a higher HR of HZ infection (aHR 2.273, 95% CI 1.314-3.931, $P < 0.05$).

Due to the compromised immune system, Rusthoven[26] and Dunst et al[27] reported that the incidence rate of HZ in their cancer patient cohort was 2-3 times and 3-5 times higher than that in the general population, respectively. These results have been affirmed again by the following research.[28] In our study, the aHR of HZ infection in cancer patients was 1.855 (95% CI 1.248-2.758, $P < 0.05$), which was similar to the previous report.

In accordance with previous studies, corticosteroids and some other potent immunosuppressive drugs may be associated with a higher risk of HZ infection but drug-related HZ in patients is still controversial. Some studies showed that conventional DMARDs (cDMARDS) and biological DMARDs increased rates of HZ in patients.[10,29,30] However, some researches showed no relationship between DMARDs usage and HZ infection.[31-33] Our result showed that the crude HR and aHR of HZ in patients using methotrexate were 0.643 (95% CI 0.091-4.562) and 0.617 (95% CI 0.084-4.549), and the crude HR and aHR of HZ in patients using sulfasalazine were 0.915 (95% CI 0.547-1.530) and 1.008 (95% CI 0.576-1.767), respectively ($P > 0.05$). This is similar to Zisman's

TABLE 4 Subgroup analysis

	Non-AS		AS		
Subgroup	n	Incidence rate (95% CI)	n	Incidence rate[a] (95% CI)	aHR[b] (95% CI)
Female	4372	6.60 (5.68-7.67)	1093	7.87 (5.98-10.36)	1.100 (0.796-1.519)
Male	6904	4.89 (4.26-5.60)	1726	5.69 (4.42-7.33)	1.053 (0.782-1.417)
Age < 20	584	3.23 (1.79-5.83)	146	4.69 (1.76-12.51)	1.372 (0.376-5.007)
Age 20-39	4520	2.30 (1.80-2.94)	1130	3.74 (2.55-5.50)	1.539 (0.965-2.455)
Age 40-59	3848	6.04 (5.11-7.13)	962	7.52 (5.58-10.15)	1.145 (0.806-1.628)
Age ≥ 60	2324	11.71 (10.05-13.65)	581	10.85 (7.90-14.91)	0.883 (0.613-1.273)

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; AS, ankylosing spondylitis; HZ, herpes zoster.
[a]Per 1000 person-years.
[b]Adjustment for age, sex, urbanization, length of hospital stay and comorbidities at baseline.

results that the risk of HZ was significantly increased with combination of anti-tumor necrosis factor-α agents and cDMARDs, but not with cDMARDs therapy alone.[34] While the present study does not adequately corroborate the study by Zisman et al, as only methotrexate and sulfasalazine were reported here, we make the conclusion that HZ infection is not associated with AS per se, but might be associated with medications such as glucocorticoid and DMARDs.

A major strength of our study is that NHIRD is a peer-reviewed long-term population-based database which covers about 99% of 23 million Taiwan inhabitants. Further, we calculate the aHRs for HZ among subjects with AS by conventional risk factors, such as age, sex, urbanization, the length of hospital stays and comorbidities. However, there are some limitations in our study. First, this study used ICD-9-CM diagnostic codes, instead of any medical records to confirm of diagnose of AS and HZ. This may cause the including of cases misdiagnosed or over-diagnosed. Second, some other confounding factors, such as disease activity, patients' smoking habits, alcohol consumption, exercise habits, body mass index values were not collected in our study. Another limitation is that the LHID2000 database collects information up to 2013. Data concerning the newly introduced biologics for AS may be unavailable.

In conclusion, this is the first large epidemiological study to demonstrate that there is no difference in incidence rates of HZ between AS and non-AS patients in Taiwan.

4.1 | Key messages

The incidence rate of HZ in Taiwan AS patients was comparable with the non-AS controls.

Age and cancer were major risk factors for incidental HZ in Taiwan AS patients.

CONFLICT OF INTEREST

No conflicts of interest are declared.

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ORIGINAL ARTICLE

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Risk of cutaneous herpes zoster in patients with spondyloarthritis treated with conventional and biologic disease-modifying antirheumatic drugs

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Abstract

Objectives: To investigate the risk of cutaneous herpes zoster (HZ) in spondyloarthritis (SpA) compared with that in rheumatoid arthritis (RA), and in disease-modifying antirheumatic drugs (DMARDs) used in SpA.

Method: A total of 727 patients with an expert diagnosis of SpA were identified retrospectively from four rheumatology centers in Hong Kong. Electronic medical records from 1995 to 2018 were reviewed for incidence of cutaneous HZ and demographic data including age, sex, comorbidities, smoking and drinking status. DMARDs used included sulphasalazine, methotrexate, leflunomide, steroids, etanercept, infliximab, adalimumab, golimumab, secukinumab and ustekinumab. Cox regression models were used to evaluate hazard ratios (HRs) of different DMARDs in patients with SpA. Propensity score was used for matching and comparison with 857 patients with RA.

Results: There were 23 cases of cutaneous HZ in patients with SpA and 59 cases in patients with RA. Among patients with SpA, 7 cases of cutaneous HZ may be attributed to sulfasalazine treatment, 7 to methotrexate, 2 to leflunomide, 2 to infliximab, 1 to etanercept, 2 to adalimumab, and 1 to secukinumab. Risks of cutaneous HZ were the same in SpA (stratified HR 0.97; 95% CI 0.58; 1.61; $P = .89$) and RA. Methotrexate (adjusted HR 3.47; 95% CI 1.25; 9.63; $P = .02$) and infliximab (adjusted HR 10.67; 95% CI 1.37; 82.88; $P = .02$) were found to be associated with HZ after adjustments for traditional risk factors.

Conclusion: Risk of cutaneous HZ in SpA was not lower than in RA. Methotrexate and infliximab were associated with cutaneous HZ in SpA.

KEYWORDS

DMARD, herpes zoster, infliximab, methotrexate, rheumatoid arthritis, spondyloarthritis

1 | INTRODUCTION

The field of spondyloarthritis (SpA) has experienced major progress in the last decade, especially with regard to earlier diagnosis and new treatments. Although the first-line agent recommended for SpA is non-steroidal anti-inflammatory drugs (NSAIDs), many patients show inadequate response to NSAID monotherapy and require concomitant use of disease-modifying antirheumatic drugs (DMARDs). The introduction of biological DMARDs (bDMARDs) has

Wong and Li contributed equally to the study.

transformed the management of inflammatory arthritis with disease remission becoming an increasingly achievable goal, but it is not without potential risks.

Herpes zoster (HZ) is one of the most common adverse events reported in clinical trials of bDMARDs. It is caused by the reactivation of latent varicella zoster virus (VZV) when specific cell-mediated immunity is compromised. Cutaneous HZ, one of the most common manifestations, is associated with pain and disability.[1] Complications such as post-herpetic neuralgia[2] may result in significant morbidity of pain, depression, and long-term disability. The incidence of HZ increases with age and compromised immune status.[3] Among those with autoimmune diseases, risks in rheumatoid arthritis (RA) patients have been most extensively proven.[4-6] In a population-based case-control study of electronic healthcare records in the UK,[7] Forbes et al found that risk of HZ was increased by more than 30% among patients with RA (adjusted odds ratio 1.46, 1.38-1.55). In contrast, data in SpA is lacking. There were also limited reports on risks of HZ in DMARDs and in SpA.[6,8]

Retrospective data from 727 patients with SpA from 4 rheumatology centers in Hong Kong were collected from the centralized computer medical record system, the Hospital Authority Clinical Management System (CMS). The system was established in 1995 and serves as a detailed electronic record on all patients attending public hospitals in Hong Kong. Since cutaneous HZ is the most common and researched form of HZ,[9] we analyzed the data to determine the contribution of various DMARDs to the risk of cutaneous HZ in patients with SpA. We also compared the risk of cutaneous HZ in SpA with RA, the commonest inflammatory arthritis.

2 | METHODS

All electronic medical records of patients following up in rheumatology clinics were manually searched. Patients with expert-diagnosed SpA, ankylosing spondylitis (AS), psoriatic arthritis (PsA), inflammatory bowel disease (IBD)-associated arthritis, reactive arthritis (ReA), and RA were identified from 4 rheumatology centers (Queen Mary Hospital, Grantham Hospital, Tung Wah Hospital and Caritas Medical Centre) in Hong Kong. Detailed records of the identified patients were retrieved from the CMS. Data were collected from December 1995 to December 2018. Clinical data retrieved were age, sex, smoking and drinking status, dates of first and last follow-up, history of psoriasis, history of IBD, comorbidities (including diabetes, chronic kidney disease, thyroid disease, asthma or chronic obstructive airway disease [COAD], congestive heart failure, and depression), use of DMARDs and steroid medications. Conventional DMARDs (cDMARDs) included sulfasalazine, methotrexate (MTX), leflunomide; biological DMARDs (bDMARDs) included infliximab, etanercept, adalimumab, golimumab, tocilizumab, abatacept, rituximab, ustekinumab, and secukinumab; and tissue-specific DMARD (tsDMARD) included tofacitinib.

The clinical outcome assessed was the first occurrence of cutaneous HZ, either diagnosed or self-reported. Individual DMARDs were independently analyzed for risks of cutaneous HZ. Zoster sine herpete was not included in the study.

2.1 | Duration of follow-up

Duration of follow-up was defined as the time between initial assessment at the rheumatology clinic and one of the following endpoints: first cutaneous HZ, discontinuation of DMARD, death, or end of study.

2.2 | Duration of DMARD use

Duration of DMARD use was defined as the time between initial use of DMARD and one of the following endpoints: first cutaneous HZ, discontinuation of DMARD, death, or end of study.

2.3 | Statistical analyses

Independent *t* tests and Chi-square tests were used to compare continuous variables and categorial variables between patients with RA and patients with SpA. Crude incidence rates were reported as the number of first HZ infections per 1000 patient-years in patients with SpA and RA. Risks of HZ in patients with SpA and RA were compared by propensity score matching method.[10] The propensity score was calculated by means of logistic regression using known or potential risk factors[7,11-14] for HZ as covariates. These included: age, sex, diabetes, chronic renal impairment, asthma or COAD, congestive heart failure, depression, and use of steroid, sulfasalazine, MTX, leflunomide, infliximab, etanercept, adalimumab, and golimumab. The score was grouped into quintiles with non-overlapping parts trimmed. Cox proportional hazard model stratified according to propensity score was used to determine the hazard ratio (HR) of HZ in patients with SpA with reference to patients with RA.

As each type of DMARD had different study durations, we individually analyzed them. Univariate Cox proportional hazard models with time-dependent covariates were used to screen the risks of HZ for each individual DMARD. Duration of follow-up and duration of each DMARD used were considered in individual analyses. The time-dependent covariates tested included: duration of use of sulfasalazine, MTX, leflunomide, infliximab, etanercept, adalimumab, golimumab, secukinumab, and ustekinumab. Other time-independent covariates tested included: age, female gender, smoking and drinking status, diabetes, chronic kidney disease (stage 3 or above), asthma or COAD, congestive heart failure, depression, thyroid disease, and concomitant use of individual cDMARDs and bDMARDs. Covariates with P values < .1 were selected for multivariate regression analyses. Results were reported as HR and 95% confidence intervals (CI). P values < .05 were considered statistically significant. All statistics were performed using the IBM SPSS package 25.0.

2.4 | Ethics approval

The study was approved by the Institutional Review Boards of the study centers involved (the University of Hong Kong UW 18-263;

TABLE 1 Baseline characteristics

	Spondyloarthritis	Rheumatoid arthritis	*P* value
Age	50.0 ± 14.2	60.1 ± 13.7	<.001
Female gender	249/727 (34.3%)	734/857 (85.6%)	<.001
Smoker	206/692 (29.8%)	98/736 (13.3%)	<.001
Drinker	55/689 (8.0%)	29/721 (4.0%)	.002
Study duration, y	8.6 ± 5.9	11.5 ± 5.6	<.001
Study duration, patient-y	6220.7	9855.5	
Herpes zoster during the period	23/727 (3.2%)	59/856 (6.9%)	.001
DMARDs			
Sulfasalazine	222/727 (30.5%)	386/857 (45.0%)	<.001
Methotrexate	180/727 (24.8%)	553/857 (64.5%)	<.001
Leflunomide	31/727 (4.3%)	169/857 (19.7%)	<.001
Steroid	58/727 (8.0%)	275/857 (32.1%)	<.001
Infliximab	10/727 (1.4%)	14/857 (1.6%)	.67
Etanercept	53/727 (7.3%)	40/857 (4.7%)	.03
Adalimumab	61/727 (8.4%)	19/857 (2.2%)	<.001
Golimumab	39/727 (5.4%)	17/857 (2.0%)	<.001
Tocilizumab	NA	39/857 (4.6%)	
Rituximab	NA	10/857 (1.2%)	
Tofacitiub	NA	10/857 (1.2%)	
Secukinumab	16/727 (2.2%)	NA	
Ustekinumab	8/727 (1.1%)	NA	
Comorbidities			
Diabetes	74/727 (10.2%)	87/857 (10.2%)	.99
Chronic renal impairment (Stage 3 or above)	35/727 (4.8%)	106/857 (12.4%)	<.001
Stage 1	510/727 (70.2%)	427/857 (49.8%)	
Stage 2	182/727 (25.0%)	324/857 (37.8%)	
Stage 3	29/727 (4.0%)	96/857 (11.2%)	
Stage 4	5/727 (0.7%)	6/857 (0.7%)	
Stage 5	1/727 (0.1%)	4/857 (0.5%)	
Asthma or COAD	20/726 (2.8%)	64/857 (7.5%)	<.001
Congestive heart failure	30/727 (4.1%)	62/857 (7.2%)	.01
Thyroid disease	19/727 (2.6%)	70/857 (8.2%)	<.001
Depression	21/727 (2.9%)	48/857 (5.6%)	.01

Abbreviations: COAD, chronic obstructive airway disease; DMARDs, disease-modifying antirheumatic drugs.

the Kowloon West Cluster KW/EX-18-113[127-09]), and conducted in accordance with the Declaration of Helsinki and the guidance for good clinical practice, 30 November 2006.

3 | RESULTS

3.1 | Baseline characteristics

A total of 727 SpA and 857 RA patients were included in the study. Baseline characteristics are shown in Table 1. Most patients were middle-aged.[15] Patients with SpA differed significantly from RA with regard to age, male gender, smoking and drinking habit. In addition, patients with SpA had fewer comorbidities and had fewer cDMARDs, bDMARDs and steroids prescribed. The study duration of patients with RA was also longer than patients with SpA. In patients with SpA, 147 (20.2%) had a history of psoriasis and 10 (1.4%) had a history of IBD. Average duration of biologics used in SpA were: infliximab, 4.5 ± 3.8 years; etanercept, 3.4 ± 2.7 years; adalimumab, 2.5 ± 2.3 years; golimumab, 2.3 ± 1.9 years; secukinumab, 0.6 ± 0.6 years; and ustekinumab, 1.6 ± 1.7 years.

3.2 | Crude incidence and HR of cutaneous HZ in the SpA group when compared to the RA group

There were 23 events of cutaneous HZ in the SpA group and 59 in the RA group. The crude incidence rate of cutaneous HZ in SpA was lower than that in RA (3.7 per 1000 patient-years vs 6.0 per 1000 patient-years). However, upon group-to-group matching using the propensity score method, the HR of cutaneous HZ in the SpA group was similar to that in the RA group (Table 2).

3.3 | Choices of cDMARDs in SpA

In patients with non-psoriatic form of SpA, there was an increased usage of sulfasalazine (196/580 [33.8%] in non-psoriatic form of SpA vs 26/147 [17.7%] in psoriatic form of SpA; $P < .001$). In contrast, use of MTX (80/580 [13.8%] in non-psoriatic form of SpA vs 100/147 [68.0%] in psoriatic form of SpA; $P < .001$) and leflunomide (16/580 [2.8%] in non-psoriatic form of SpA vs 15/147 [10.2%] in psoriatic form of SpA; $P < .001$) were increased in the psoriatic form of SpA. There was no difference in steroid usage between the two forms of SpA (44/580 [7.6%] in non-psoriatic form of SpA vs 14/147 [9.5%] in psoriatic form of SpA; $P = .44$).

TABLE 2 Crude incidences and risks of cutaneous HZ in SpA and RA patients

	Spondyloarthritis	RA
Number of herpes zoster	23	59
Patient-y	6220.7	9855.5
Incidence per 1000 patient-y	3.7	6.0
Risk of herpes zoster after matching by propensity score		
	HR (95% CI)	***P* value**
RA	1 (reference)	
Spondyloarthritis (22/76)	0.92 (0.55-1.56)	.76

Note: Propensity score variables included: age, sex, diabetes, chronic renal impairment, chronic obstructive airway disease, chronic heart disease, depression, thyroid disease, steroid usage, sulfasalazine, methotrexate, leflunomide, infliximab, etanercept, adalimumab, and golimumab.
Abbreviations: CI, confidence interval; HR, hazard ratio; HZ, herpes zoster; RA, rheumatoid arthritis; SpA, spondyloarthritis.

3.4 | Univariate and multivariate Cox proportional hazard models

In the SpA group, sulphalazine and MTX were the two cDMARDs and etanercept and adalimumab were the two bDMARDs most commonly used. Overall, lower dosages of cDMARDs were used when compared with the Caucasian population with inflammatory arthritis.[16,17] Details are shown in Table 3. Univariate regression analyses showed that the use of MTX, leflunomide, infliximab and certolizumab were associated with cutaneous HZ in patients with SpA.

Univariate and multivariate Cox proportional hazard models with time-dependent covariates were built independently for MTX, leflunomide, infliximab, and certolizumab. In univariate analyses, the associated risk factors were similar in the four drug models which included age, chronic kidney disease, thyroid disease, and depression (in the infliximab univariate model only). In the MTX analyses, multivariate regression models showed that MTX, thyroid disease, and concomitant use of golimumab were independently associated with cutaneous HZ (Table 4). In the leflunomide analyses, multivariate regression models showed that thyroid disease and concomitance use of golimumab were independently associated with cutaneous HZ (Table 5). No association was found between leflunomide and cutaneous HZ. Since no patient had concomitant use of leflunomide and infliximab, this combination was not included in the analyses. In the infliximab analyses, multivariate regression showed that thyroid disease and infliximab were independently associated with cutaneous HZ (Table 6). No association was found between steroid use and cutaneous HZ in any of the drug models.

TABLE 3 Dosage of cDMARDs and bDMARDs and patient-years of use in patients with SpA

	Drug information		Univariate Cox regression	
DMARD used	**Average dosage**	**Patient-y**	**HR (95% CI)**	***P* value**
Sulfasalazine	1728.2 ± 628.1 mg/d	1362.7	1.87 (0.62-5.70)	.27
Methotrexate	11.7 ± 4.9 mg/wk	1004.8	3.61 (1.33-9.77)	.01
Leflunomide	16.1 ± 4.3 mg/d	85.0	4.44 (1.04-18.98)	.04
Infliximab	243.3 ± 105.1 mg once every 6 wk	44.8	9.60 (1.25-73.51)	.03
Etanercept	48.1 ± 6.6 mg/wk	176.9	0.05 (0.00-337.05)	.50
Adalimumab	40.0 ± 0.00 mg/2 wk	156.92	0.74 (0.10-5.56)	.77
Golimumab	52.4 ± 10.8 mg/mo	95.1	1.45 (0.20-10.80)	.72
Secukinumab	215.6 ± 76.9 mg/mo	10.0	1.49 (0.20-11.08)	.70
Ustekinumab	50.6 mg/3 mo	12.6	0.05 (0.00->999)	.75

Abbreviations: bDMARD, biological disease-modifying antirheumatic drug; cDMARD, conventional disease-modifying antirheumatic drug; SpA, spondyloarthritis.

TABLE 4 Univariate and multivariate Cox proportional hazard models of methotrexate

Characteristics	Patients with HZ	Univariate Cox regression		Multivariate Cox regression	
		HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Age		1.03 (1.00-1.06)	.07	1.02 (0.99-1.05)	.25
Female	11/24	1.57 (0.70-3.50)	.27		
Smoker	6/23	0.90 (0.36-2.29)	.83		
Drinker	0/23	0.04 (0.00-40.69)	.37		
Diabetes	3/24	1.07 (0.32-3.60)	.91		
Chronic kidney disease	4/24	2.75 (0.93-8.14)	.07	2.03 (0.61-6.70)	.25
Asthma or COAD	0/24	0.05 (0.00-859.55)	.54		
Congestive heart failure	1/24	0.64 (0.09-4.73)	.66		
Depression	2/24	1.55 (0.36-6.67)	.56		
Thyroid disease	2/24	6.30 (1.45-27.39)	.01	6.88 (1.50-31.53)	.01
Methotrexate	7/24	3.61 (1.33-9.77)	.01	3.47 (1.25-9.63)	.02
Concomitant use of cDMARD					
Sulfasalazine	0/24	0.05 (0.00->999)	.80		
Leflunomide	2/24	3.86 (0.91-16.43)	.07	3.56 (0.80-15.93)	.10
Steroid	3/24	1.60 (0.48-5.38)	.45		
Concomitant use of bDMARD					
Infliximab	0/24	0.05 (0.00->999)	.76		
Etanercept	1/24	2.24 (0.30-16.64)	.43		
Adalimumab	1/24	1.75 (0.24-13.02)	.59		
Golimumab	1/24	38.41 (4.60-320.52)	.001	26.57 (2.86-247.24)	.004
Secukinumab	1/24	2.57 (0.35-19.15)	.36		

Abbreviations: bDMARD, biological disease-modifying antirheumatic drug; cDMARD, conventional disease-modifying antirheumatic drug; CI, confidence interval; COAD, chronic obstructive airway disease; HR, hazard ratio; HZ, herpes zoster.

4 | DISCUSSION

In contrast to RA, there is a dearth of data on the risks and incidence of cutaneous HZ in SpA. This study investigated the risks of HZ in SpA and in DMARDs used in SpA. Our study showed that the risk of cutaneous HZ in SpA was not less than in RA, although its crude incidence was lower. Patients taking MTX and infliximab were more prone to developing cutaneous HZ. Combination of cDMARDs and bDMARDs could also increase the risk of cutaneous HZ.

The lower crude incidence rate of HZ in SpA than in RA was consistent with previous studies. Observational reports on the incidence of HZ in patients with SpA are scarce. Most were derived from randomized controlled trials in selected patients with short durations of follow-up. Among the few real-life reports appertaining to SpA, most were confined to AS, thereby under-recognizing SpA as a family of inflammatory back diseases. In a study using the USAs' Multipayer Claims Database, the age- and sex-standardized incidence rate per 1000 person-years of HZ were 12.5 in patients with RA and 9.3 for patients with AS.[18] In this study, the incidence rate per 1000 person-years were 6.5 in patients with RA and 3.8 in patients with SpA, consistent with previous epidemiological data of lower rates in Hong Kong compared with other Asian countries.[19] Our incidence rate in patients with SpA was also lower than that reported in Taiwan.[20] The inclusion of only cutaneous forms of HZ may have been another factor.

Comparison of crude incidence rates may result in an erroneous difference in outcome. A major confounder is the diverse combination of therapies. A wide range of combinations of DMARDs are commonly used in the treatment of RA, whereas only a limited choice of DMARDs are available for SpA.[21] Because certain DMARDs may be independent risk factors for HZ[22] and are more commonly used in patients with RA, propensity score matching was done to control for this treatment effect. The result of this method showed that the risk of HZ in SpA was not less than in RA (HR = 0.93, *P* = .77) despite a lower crude incidence. RA is a well-established risk factor for HZ in several population-based case-control studies. Data from the UK Clinical Practice Research Datalink reported a 30% increased risk of HZ in RA,[7] and a Japanese health insurance database found an odds ratio of 1.43.[23] This was the first study to demonstrate that the risk of HZ in SpA, irrespective of DMARD treatment, was not less than that in RA.

An increased risk of cutaneous HZ in SpA patients on MTX therapy (adjusted HR [aHR] = 3.24, *P* < .02) was largely consistent with previous studies. A large retrospective cohort study in Korea[8] found an aHR of 3.70 for HZ in cDMARD (SSZ or MTX) users. Other studies have found that MTX was associated with HR of 3.02 for HZ in

TABLE 5 Univariate and multivariate Cox proportional hazard models of leflunomide

Characteristics	Patients with HZ	Univariate Cox regression		Multivariate Cox regression	
		HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Age		1.03 (1.00-1.06)	.05	1.02 (0.99-1.05)	.30
Female	11/24	1.59 (0.71-3.56)	.26		
Smoker	6/23	0.92 (0.36-2.34)	.86		
Drinker	0/23	0.04 (0.00-45.19)	.38		
Diabetes	3/24	1.16 (0.35-3.88)	.81		
Chronic kidney disease	4/24	2.96 (1.01-8.70)	.05	2.15 (0.66-7.05)	.21
Asthma or COAD	0/24	0.05 (0.00-334.264)	.50		
Congestive heart failure	1/24	0.69 (0.09-5.09)	.71		
Depression	2/24	1.82 (0.43-7.80)	.42		
Thyroid disease	2/24	6.59 (1.51-28.72)	.01	6.93 (1.51-31.81)	.01
Leflunomide	2/24	4.44 (1.04-18.98)	.04	1.51 (0.19-12.30)	.70
Concomitant use of cDMARD					
Sulfasalazine	0/24	0.05 (0.00->999)	.77		
Methotrexate	2/24	5.23 (1.22-22.53)	.03	2.94 (0.24-35.58)	.40
Steroid	3/24	1.32 (0.39-4.44)	.66		
Concomitant use of bDMARD					
Etanercept	1/24	8.77 (1.17-65.43)	.03	1.48 (0.04-55.07)	.83
Adalimumab	1/24	10.30 (1.38-77.07)	.02	2.44 (0.05-119.34)	.65
Golimumab	1/24	54.73 (6.69-447.64)	<.001	26.95 (2.60-279.33)	.01
Secukinumab	0/24	0.05 (0.00->999)	.83		

Abbreviations: bDMARD, biological disease-modifying antirheumatic drug; cDMARD, conventional disease-modifying antirheumatic drug; CI, confidence interval; COAD, chronic obstructive airway disease; HR, hazard ratio; HZ, herpes zoster.

RA patients[24] and HR of 3 in SpA patients.[8,24] The use of DMARDs in general was associated with increased risk of HZ, as shown in a meta-analysis by Marra et al,[22] and with adjusted odds ratio of 1.27 and 1.37 in RA patients from two retrospective studies.[4,5] Nonetheless, a recent population-based cohort in Taiwan failed to show the increased risk of HZ in patients with SpA.[20] The unique role of MTX in triggering HZ, in contrast to other commonly used cDMARDs, remains speculative.

This study also found a higher risk of HZ in patients taking infliximab, a tumor necrosis factor (TNF) inhibitor (aHR = 10.67, *P* = .02). The result should be interpreted with caution as the patient-pool on biologics was small. Infection rates were generally reported to be higher in users of TNF inhibitors compared with non-users in many studies.[25,26] A large prospective cohort study in Germany was the first to report increased risk of HZ in TNF inhibitors.[25] Comparative risks of different TNF inhibitors were largely done in patients with RA. In a large sample of RA patients in the Veteran's Affairs healthcare system, McDonald et al[27] found that the risk of HZ associated with infliximab exceeded that of other TNF inhibitors. A review article[28] also noted that infliximab had the highest risk of HZ within TNF inhibitor class in most cohort studies.

Differential risks of HZ among the various TNF inhibitors would have implications for clinicians managing SpA. A gene array study by Haider et al[29] demonstrated that infliximab and etanercept had distinct pharmacodynamic properties. Infliximab downregulated interferon (IFN)-γ activation by 5.9-fold but none were evident for etanercept. Since IFN-γ is a critical factor for enhancement of natural killer activity and inhibition of VZV replication,[30] it was postulated that defective IFN-γ production may be related to VZV reactivation.[31,32] Pharmacokinetic differences also play a role. According to the therapeutic window concept,[33] the steady-state range of serum or tissue drug concentrations should be adequate to neutralize surplus TNF, yet not so high as to threaten host defense. Thus, a low peak–trough ratio ensures safety within the therapeutic window. However, infliximab had wide fluctuations in serum concentration,[34] with a peak drug concentration 50-fold greater[35] than median trough concentrations. This contrasted with the relatively constant concentrations of etanercept or adalimumab, and may perhaps offer an explanation for its higher HR for HZ.

Steroids have been shown to be an independent risk factor for HZ in various autoimmune diseases[36,37]; however, this was not found in our analyses. A possible explanation was the low percentage (8%) of patients being treated with steroids. Although we had no data, the average steroid dosage used in our cohort was unlikely to be high as the drug is not recommended in treating SpA.[38] The low dosage could further decrease the effect of steroids on HZ.

TABLE 6 Univariate and multivariate Cox proportional hazard models of infliximab

Characteristic	Patients with HZ	Univariate Cox regression		Multivariate Cox regression	
		HR (95% CI)	*P* value	Adjusted HR (95% CI)	*P* value
Age		1.03 (1.00-1.07)	.04	1.02 (0.99-1.06)	.17
Female	10/23	1.42 (0.62-3.23)	.41		
Smoker	6/22	0.97 (0.38-2.47)	.94		
Drinker	0/22	0.04 (0.00-57.01)	.39		
Diabetes	3/23	1.22 (0.36-4.11)	.75		
Chronic kidney disease	4/23	2.86 (0.96-8.51)	.06	2.53 (0.81-7.92)	.11
Asthma or COAD	0/24	0.05 (0.00-576.29)	.52		
Congestive heart failure	1/24	0.71 (0.10-5.31)	.74		
Depression	2/23	1.87 (0.44-8.05)	.40	2.31 (0.52-10.18)	.27
Thyroid disease	2/23	7.05 (1.61-30.92)	.01	6.52 (1.42-29.94)	.02
Infliximab	2/23	9.60 (1.25-73.51)	.03	10.67 (1.37-82.88)	.02
Concomitant use of cDMARD					
Sulfasalazine	0/23	0.05 (0.00->999)	.87		
Methotrexate	0/23	0.05 (0.00->999)	.82		
Steroid	3/23	1.34 (0.40-4.56)	.64		

Abbreviations: cDMARD, conventional disease-modifying antirheumatic drug; CI, confidence interval; COAD, chronic obstructive airway disease; HR, hazard ratio; HZ, herpes zoster.

Combination therapy of MTX and golimumab was found to increase the risk of cutaneous HZ in SpA, consistent with a previous study of elevated risk with MTX and anti-TNF combinations.[39] Cumulative blockade of multiple immune pathways is a possible explanation; however, this may be less of a concern in SpA as combination therapy is less common in SpA as in RA. The small patient-pool on bDMARDs warrants cautious interpretation. Further studies with larger sample sizes of bDMARD users will be needed.

Finally, we reported an increased risk of cutaneous HZ in patients with SpA and thyroid disease. Thyroid hormone has been suggested to control herpes virus gene expression and replication in neurons via epigenetics through its nuclear receptors.[40] The proposed mechanism is supported by various observation cohorts which showed thyroid disease as an independent risk factor for HZ.[12,20,40] Our data are consistent with the international cohorts.

4.1 | Limitation

Although we included 727 patients with SpA in the analyses, the number of patients on bDMARDs was small and may have contributed to potential bias. A larger number of bDMARDs user should be studied in the future for a more robust result on the risk of HZ in patients with SpA.

5 | CONCLUSION AND VACCINE RECOMMENDATIONS

The risk of cutaneous HZ in SpA was not less than in RA. Among patients with SpA, MTX and infliximab were independently associated with cutaneous HZ, and combinations of c- and bDMARDs may further increase the risk. Rheumatologists may consider preventive HZ vaccination prior to treatment with these drugs.

CONFLICT OF INTEREST

The authors declare no conflict of interest.

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Risk factors for herpes zoster infection among Filipinos with systemic lupus erythematosus

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Abstract

Aim: To identify clinical risk factors associated with herpes zoster (HZ) infections in systemic lupus erythematosus (SLE).

Methods: A case-control study of HZ infection was performed in SLE patients seen at the University of Santo Tomas Lupus Clinics from 2009-2014. Cases were matched 1:2 to SLE controls without HZ infection for age, sex, and disease duration. Clinical characteristics, SLE disease activity, and immunosuppressive use were compared.

Results: Sixty-five SLE patients (61, 93.8% female) who developed HZ were matched with 130 SLE patients without HZ. Mean age was 36.75 years (±1.35; P = 1.00) for the case group; mean SLE disease duration at first HZ infection was 6.1 years (±3.3; P = .919). Four patients had more than 1 episode of HZ. There was localized HZ in 63/65 (97%), and 2 (3%) disseminated HZ infections. The case group received higher doses of prednisone 64/65 (P = .012), mean prednisone dose 18.62 mg/d (±1.48, P < .001) and more were exposed to cyclophosphamide (Cyc) (19/65; P < .001) compared to the control group's mean prednisone dose of 11.73 mg/d (±1.16); there was Cyc use in 7/130 patients. Cyc in addition to mycophenolate mofetil (MMF) use among lupus nephritis patients conferred the highest risk for HZ infection occurrence. Hydroxychloroquine (HCQ) use reduced the risk for HZ by 87% (adjusted odds ratio 0.13, P = .003).

Conclusion: Immunosuppressives and corticosteroid use are risk factors associated with the development of HZ in SLE. The risk for HZ increases among patients given intravenous Cyc and MMF for lupus nephritis. SLE disease activity did not show a direct association with HZ occurrence. HCQ use appeared to have a protective role against HZ infection.

KEYWORDS

Filipino, herpes zoster, lupus, risk factors, systemic lupus erythematosus

1 | INTRODUCTION

Varicella-zoster virus (VZV) is a member of the family *Herpesviridae* which commonly infects young individuals via the respiratory route. It causes 2 distinct clinical entities: varicella (chickenpox) and herpes zoster (HZ).[1] Following primary infection clinically presenting as chicken pox, the latent virus persists in the sensory dorsal root ganglia and may reactivate at a later date to cause HZ. Reactivation occurs most frequently in the immunocompromised and elderly and places the affected patient at risk for developing painful sequelae of post-herpetic neuralgia.[2]

The incidence of HZ in the general population is 1.2 to 4.9 cases per 1000 person-years, depending on the ethnic group.[3,4] On the other hand, previous retrospective studies reported more than

6-fold increase of HZ among systemic lupus erythematosus (SLE) patients with an incidence rate of 6.4-37.7 cases per 1000 person-years.[5,6] Moreover, a recent prospective study by Chakravarty et al reported more HZ occurrence among SLE patients at all age groups, with an age-adjusted incidence rate at 12 per 1000 patient-years.[7]

Increasing age and reduced functional status were independent predictors of HZ. In SLE, prednisone and mycophenolate mofetil (MMF) use conferred additional risk. SLE had the lowest HZ vaccination rates among age-eligible subjects.[7] Borba et al identified the major trigger factor for this viral infection in SLE as therapy, particularly the concomitant use of corticosteroids and immunosuppressives, and not active disease.[5]

The frequencies of VZV-specific T cells were significantly decreased in patients with SLE, with low frequencies of VZV-specific interferon-γ and tumor necrosis factor-α-positive CD4 T cells relating to disease activity in SLE.[8] Complex genetic and environmental factors related to the pathogenesis of SLE or host immune modulation from interfering drugs might further explain the high incidence rate.

Risk factors associated with the development of HZ in patients with SLE included lymphopenia, anti-Ro antibodies, anti-ribonucleoprotein antibodies, neuropsychiatric manifestations,[9-11] renal involvement, and cyclophosphamide (Cyc) use.[12] Indeed, the presence of specific SLE disease manifestations represents risk factors for the development of HZ.

This study aims to identify risk factors associated with HZ infection among Filipinos with SLE.

2 | METHODS

This is a case-control study. A total of 626 SLE patients seen at the University of Santo Tomas (UST) Hospital and included in the UST SLE Database from January 2009 to December 2014 were reviewed. SLE patients with localized and disseminated HZ infection were identified and their medical records reviewed to confirm the diagnosis and determine the dermatome distribution, use of immunosuppressives, including at least 1 pulse of Cyc, within the last 3 months preceding diagnosis of HZ, SLE disease activity at the time of infection, and HZ outcomes.

The cases were matched to SLE patients without HZ infection according to age, sex, and disease duration in a 1:2 case-control ratio. A case was defined as a patient with SLE with history of HZ any time after the first physician diagnosis of SLE. The diagnosis of HZ was made from the history and documentation of a characteristic rash with associated symptoms in a dermatome distribution. A control was defined as a patient diagnosed with SLE and no history of HZ infection but with history of varicella. Localized HZ was defined as characteristic rash in 1 or 2 dermatomes. Disseminated HZ involves 3 or more dermatomes affected by the rash.

The clinical manifestations, treatment of SLE within the 3 months preceding the HZ episode, disease activity at the time of diagnosis of HZ infection (case group) or the matched disease duration for the non-HZ (control group)-as assessed by the Safety of Estrogens in Lupus Erythematosus National Assessment-Systemic Lupus Erythematosus Disease Activity Index (SELENA-SLEDAI) score, and outcomes including response to anti-viral treatment were recorded. The data were analyzed by STATA version 14.1 (StataCorp), and the results are presented as percentages and means. Comparison of variables was carried out using the Chi-square test or Student's *t* test when appropriate. Multiple conditional logistic regression analysis was used for computation of odds ratios (ORs). Statistical significance was defined as $P < .05$.

3 | RESULTS

A total of 65 patients (61 female, 93.8%) with HZ infection were identified among 626 SLE patients in the database. The mean age was 36.75 years (±1.35; range 19-60 years), and mean duration of SLE at time of HZ diagnosis was 6.15 years (±3.30; range 2-17years). The SLE features, therapies, and HZ outcomes were compared with 130 non-HZ SLE patients matched for age, sex, and disease duration.

There were 23/65 (35.38% ± 0.06) in the HZ group with a SELENA-SLEDAI score of >3 compared to the non-HZ group 58/130 (44.62% ±0.04). Mean SELENA-SLEDAI scores of patients without HZ was 3.86 ± 0.50 (range 0-26) vs that of patients with HZ of 1.63 ± 0.29 (range 0-10), $P = .003$. Lupus nephritis occurrence was 24/65 (36.92% ± 0.06%) for the HZ group and 44/65 (33.85% ± 0.04%) for the non-HZ group with a *P* value of .068, while only 1/130 central nervous system lupus was observed in the non-HZ group and none in the HZ group. There were 64/65 (98.46% ± 0.02%) patients with HZ who received oral prednisone with a mean daily dose of 18.62 mg (±11.48) while 104/130 (80% ± 0.04%) patients in the non-HZ group had oral prednisone exposure with a mean daily dose of 11.73 mg (±1.16); *P* values were <.001 on both prednisone use and mean dose. Exposure to intravenous (IV) Cyc was at 19/65 (29.23% ± 0.06%) among the HZ group and 7/130 (5.38% ± 0.02%) among the non-HZ group, $P < .001$. Seven out of 65 patients (10.77% ± 0.04%) had pulse methylprednisolone (MPSL) and 1/130 (0.77% ± 0.01%) among the non-HZ group, $P < .001$. Azathioprine (AZA) use was 2/65 (3.08% ± 0.02%) patients and 4/130 (3.08% ± 0.02%) patients for HZ and non-HZ groups respectively, $P = 1.00$; mean daily dose among HZ group (n = 2) was 100 mg ± 0 while that of the non-HZ group (n = 4) was 87.5 mg ± 47.87, range 50-150 mg.

Mycophenolate mofetil (MMF) use was 11/65 (16.92% ± 0.05) and the mean dose was 223.08 mg/d (±66.71) for the HZ group compared to the non-HZ group at 30/130 (23.08% ± 0.04%) and a mean dose of 276.92 mg/d (±50.66); $P = .320$ and $P = .531$ for MMF use and mean daily dose, respectively. Hydroxychloroquine (HCQ) was used by 44/65 (67.69% ± 0.06%) in the HZ group compared to 116/130 (89.23% ± 0.03%) in the non-HZ patients, $P < .001$. The mean HCQ dose was significantly higher among the non-HZ group with a mean dose of 193.08 mg/d (±7.42) compared to the HZ group at 156.92 mg/d (±15.50), $P = .018$, see Table 1.

TABLE 1 Clinical characteristics comparing the HZ and non-HZ SLE groups

Characteristics	SLE with HZ infection N = 65	SLE without HZ infection N = 130	*P* value
Mean age in y (± SD)	36.75 (±1.35)	36.75 (± 0.95)	1.00
Sex			
Male n (%)	4 (6.2)	8 (6.2)	1.00
Female n (%)	61 (93.8)	122 (93.8)	1.00
Mean SLE disease duration in y, n (±SD)	6.15 (±3.3)	6.2 (±5.8)	.919
SELENA-SLEDAI > 3, n (% ± SD)	23 (35.38 ± 0.06)	58 (44.62 ± 0.04)	.22
Mean SELENA-SLEDAI score (±SD)	1.63 (±0.29)	3.86 (±0.50)	.027
SLE with nephritis, n (% ± SD)	24 (36.92 ± 0.06)	44 (33.85 ± 0.04)	.068
CNS lupus, n (% ± SD)	0	1 (0.008)	–
Prednisone use, n (% ± SD)	64 (98.46 ± 0.02)	104 (80 ± 0.04)	<.001
Mean prednisone dose in mg/d (±SD)	18.62 (±1.48)	11.73 (±1.16)	<.001
Hydroxychloroquine use, n (% ±SD)	44 (67.70 ± 0.06)	116 (89.23 ± 0.03)	<.001
Mean hydroxychloroquine dose in mg/d (±SD)	156.92 (±15.5)	193.08 (±7.42)	.018
Azathioprine use, n (% ± SD)	2 (3.08 ± 0.02)	4 (3.08 ± 0.02)	1.00
Mean azathioprine dose in mg/d (range)	100 ± 0 (--)	87.5 ± 47.87 (50-150)	.993
Mycophenolate mofetil, n (% ± SD)	11 (16.92 ± 0.05)	30 (23.08 ± 0.04)	.320
Mean MMF dose in mg/d (±SD)	223.08 (±66.71)	276.92 (± 50.66)	.531
Methylprednisolone pulse therapy, n (%)	7 (10.77 ± 0.04)	1 (0.77 ± 0.01)	<.001
IV cyclophosphamide n (%)	19 (29.23 ± 0.06)	7 (5.38 ± 0.02)	<.001

Abbreviations: CNS, Central Nervous System; HZ, herpes zoster; IV, intravenous; MMF, mycophenolate mofetil; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment SLE Disease Activity Index; SLE, systemic lupus erythematosus.

Four (6%) patients had recurrent episodes of HZ infections and 2 (3%) developed disseminated disease. The 2 patients with disseminated disease had active SLE (SLEDAI > 3), received IV Cyc then maintained on AZA, and the other on MMF for lupus nephritis (Table 2).

All 65 patients with HZ received either acyclovir or valacyclovir for treatment, and there were no noted adverse events and morbidities following treatment. There was no record of post-herpetic neuralgia, bacterial superinfection, or death.

In the univariate regression analysis (Table 3), factors that increase the odds for HZ infection risk included Cyc use (OR 7.04, 95% CI 2.61-18.96; *P* < .001); MPSL (OR 14, 95% CI 1.72-113.79; *P* = .014); and prednisone (OR 15.49, 95% CI 2.05-116.89; *P* = .008). The use of HCQ had an OR of 0.25 (95% CI 0.12-0.56; *P* = .001)

TABLE 2 Clinical features of HZ infections

	SLEDAI > 3 n (%)	SLEDAI ≤ 3 n (%)	Total n (%)
Single HZ episode	21 (32.30%)	40 (61.54%)	61 (93.85%)
Recurrent HZ episodes	2 (3.08%)	2 (3.08%)	4 (6.15%)
		Total	65 (100%)
Localized HZ	21 (32.30%)	42 (64.62%)	63 (96.92%)
Disseminated HZ	2 (3.08%)	0	2 (3.08%)
		Total	65 (100%)

Abbreviations: HZ, herpes zoster; SLEDAI, Systemic Lupus Erythematosus Disease Activity Index.

TABLE 3 Univariate regression analysis

Variables	Odds ratio	95% CI	*P* value
Sex	1.00	0.21-4.81	1.000
Azathioprine	1.00	0.18-5.46	1.000
IV cyclophosphamide	7.04	2.61-18.96	<.001
Hydroxychloroquine	0.25	0.12-0.56	.001
Mycophenolate mofetil	0.70	0.33-1.46	.341
Methylprednisolone pulse therapy	14.00	1.72-113.79	.014
Prednisone	15.49	2.05-116.89	.008
SELENA-SLEDAI score > 3	0.65	0.34-1.25	.198
Renal involvement	1.15	0.61-2.14	.670
SLE disease duration	0.99	0.94-1.05	.9143

Abbreviations: IV, intravenous; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment SLE Disease Activity Index; SLE, systemic lupus erythematosus.

conferring decreased odds of having HZ infection. Increased SLE disease activity score >3 (OR 0.65; *P* = .198) and renal involvement (OR 1.15; *P* = .670) did not increase the odds of HZ infection occurrence.

Controlling for the effects of the other variables (Table 4), those who used IV Cyc (adjusted OR [aOR] 295.87; *P* < .001) were 296 times more likely to have HZ infection than those who did not use IV Cyc. Those who used MMF (aOR 26.25; *P* = .14) were 26 times more likely to have HZ infection than those who did not use MMF. Prednisone use (aOR 16.30; *P* = .012) conferred 16 times more risk for HZ infection than those who did not use prednisone. SLE patients on HCQ (aOR 0.13; *P* = .003) were 87% less likely to have HZ infection than those who did not use HCQ. SLE patients with SELENA-SLEDAI scores >3 (aOR 0.37; *P* = .148) were 63% less likely to have HZ infection than those with SELENA-SLEDAI score ≤3. The use of MPSL (aOR 2.34; *P* = .472) did not increase HZ infection risk.

TABLE 4 Full model regression analysis

Variables	Adjusted odds ratio	CI	*P* value
IV cyclophosphamide	295.87	15.02-5825.39	<.001
Hydroxychloroquine	0.13	0.03-0.49	.003
Mycophenolate mofetil	26.25	1.96-350.99	.014
Methylprednisolone pulse therapy	2.34	0.23-23.67	.472
Prednisone	16.30	1.87-142.19	.012
Renal involvement	0.01	0.001-0.22	.001
SELENA-SLEDAI score > 3	0.37	0.15-0.92	.148

Abbreviations: IV, intravenous; SELENA-SLEDAI, Safety of Estrogens in Lupus Erythematosus National Assessment SLE Disease Activity Index.

4 | DISCUSSION

4.1 | HZ risk and SLE disease activity

The SELENA-SLEDAI score was significantly different between the 2 groups (*P* = .027); this result shows there was more active SLE disease among those without HZ infection compared to those with HZ (3.86 [±0.5] vs 1.63 [±0.29], respectively), signifying low disease activity or remission at the time of HZ infection. This finding was relatively different from other reported cohorts, wherein SLE disease activity was correlated with increased occurrence of HZ infection.[13] However, the results of this study support the initial observations by Borba and colleagues where active disease is not a significant trigger factor for HZ occurrence.[5] As seen in the regression analysis models (Tables 3 and 4), having a higher SLE disease activity score of >3 did not increase the odds of HZ infection occurrence. In the earlier study of Kahl et al, the timing of the viral (HZ) infection in SLE patients may not necessarily coincide with the lupus flare and the initial administration of immunosuppressive agent/s. A vast majority (65%) of HZ occurrences were seen during remission or in mild disease flare.[14] On the other hand, Lee and colleagues found that HZ overlaps with higher lupus disease activity among juvenile-onset SLE patients.[15]

4.2 | HZ occurrence in SLE nephritis and immunosuppression

Renal involvement was observed as a risk factor for HZ in other cohorts. Cyc is part of the standard of care for induction of remission among lupus nephritis patients. Immunosuppression, especially with the use of Cyc, may reflect a more severe disease course or act as a marker for lupus activity, which explains its association with HZ infection.[12] In Manzi et al's matched case-control study, they reported that lupus nephritis might increase the risk of HZ infection.[16] The same observation was seen in the retrospective investigation of Lee et al among juvenile-onset SLE patients who had HZ, showing they were more likely to have renal involvement, either previously or concurrently with the viral infection compared with those who did not have HZ.[15] Although this was not observed in our results because the distribution of lupus nephritis cases and controls were almost similar (HZ group 36.92% vs non-HZ group 33.85%; *P* = .068), we infer that nephritis can be an indirect risk factor in the development of HZ infection due to higher doses and aggressive use of immunosuppressives (IV Cyc, MMF and prednisone) to control disease activity and prevent renal damage. We analyzed the combination of therapies with IV Cyc, prednisone and hydroxychloroquine vs MMF, prednisone and hydroxychloroquine among lupus nephritis patients and observed an association with increased HZ infection with the IV Cyc, prednisone and hydroxychloroquine therapy combination compared to the MMF, prednisone and hydroxychloroquine (*P* = .018) treatment. As reported in the cohort of Wolfe and colleagues, they found that immunosuppressive use with Cyc increased the risk of HZ both in lupus and rheumatoid arthritis patients with a hazards ratio of 4.2 (95% CI 1.6-11.5) following adjustment for age, gender, and

functional status.[17] Kang and Park reported the incidence of HZ is higher in lupus patients treated with Cyc than those given MMF.[18] They also held a similar view that the dose-dependent steroid, and immunosuppressant use predisposes the risk for infections in lupus patients including HZ which happens to be the most common viral infection following Cyc and MMF.[18] Similarly, in the observations made by Kahl et al and Borba et al, the occurrence of HZ infections in this study was noted not at the start of initial flare but after consecutive doses of immunosuppressive agents.[5,14]

The results showed that immunosuppressive (IV Cyc, MMF) therapy and prednisone use are risk factors associated with the development of HZ infections among Filipino patients with SLE. In particular, the risk for HZ infection was increased among patients given IV Cyc for management of lupus nephritis. SLE disease activity did not show direct association with HZ infection occurrence, as most HZ cases occurred during remission or mild disease activity and not at the onset of flares.

4.3 | HZ occurrence and use of hydroxychloroquine

Cunha et al reported chloroquine diphosphate could predispose patients with dermatomyositis/polymyositis to develop HZ.[19] However, in this study the aOR for hydroxychloroquine was 0.13 (95% CI 0.03-0.49; P = .003) and more patients were on hydroxychloroquine in the control group (non-HZ group), moreover the dose of hydroxychloroquine was higher in the non-HZ group with a mean daily dose of 193.08 mg (±7.42) compared to the HZ group's mean daily dose of 156.92 mg (±15.5), P = .018; which demonstrates that higher doses of hydroxychloroquine may have an intriguing possible protective effect in preventing HZ infection through an unknown mechanism.

In conclusion, the study demonstrated that exposure to immunosuppressive agents and corticosteroids increased the risk for HZ infection. Hydroxychloroquine, on the other hand, may have a pleiotropic protective action against the development of HZ infection.

One of the limitations of this study is that several risk factors that may interact with the ones considered above were not taken into account, such as lifestyle, depression, living in poverty and adherence to medications. This may have led to the extremely high associations found between HZ infection and use of Cyc, MMF and prednisone.

Finally, an inception cohort of SLE patients will be ideal to observe for development of HZ and other infections important to SLE, and determine associations with other possible risk factors including level of education, economic status, adherence to therapy and access to health care.

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CONFLICT OF INTEREST

All authors declare no conflict of interest.

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Inter-rater reliability of modified hand mobility in scleroderma test

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Abstract

Aim: Systemic sclerosis (SSc) is a chronic autoimmune disease of unknown etiology characterized by excessive collagen production, endothelial cell injury, microvascular obliteration, cutaneous fibrosis and progressive visceral disease. The hands are frequently involved during the progression of the disease, with symmetrical skin thickening as a prominent feature. Modified hand mobility in scleroderma (mHAMIS) test is a measurement method to assess hand mobility in patients with SSc. Knowing the inter-rater reliability of the instrument is important in order for the results from different examiners to be accurately interpreted. The aim of this study was to test inter-rater reliability of the mHAMIS test.

Method: Hand mobility for both hands was assessed in 25 female patients with SSc by 2 physiotherapists who have different years of experience. Patients who had flexion contracture in at least 1 finger and undergone hand surgery in the last year due to any injuries, were excluded from the study since hand mobility was prevented. Inter-rater reliability was determined using intra-class correlation coefficients (ICCs).

Result: The ICCs were excellent between raters for dominant and non-dominant hands. The values were 0.92 and 0.93, respectively.

Conclusion: The inter-rater reliability of the mHAMIS was found to be excellent. This research contributes to the literature by proving that the test can be used without causing bias in clinical trials.

KEYWORDS

hand mobility, inter-rater, mHAMIS, reliability, systemic sclerosis

1 | INTRODUCTION

Systemic sclerosis (SSc) is a systemic, inflammatory and autoimmune disease with an unknown etiology, characterized by damage to various organs as a result of excessive extracellular matrix deposition in the skin and internal organs.[1,2] SSc is divided into 2 main clinical groups according to skin involvement sites. The limited type of scleroderma shows involvement of the face and distal parts of the knee and elbow; diffuse type shows involvement of the whole body. Therefore, symmetrical skin thickening and decrease in hand mobility, which is a prominent feature throughout the course of the disease, are common in both types. In addition to the skin, the involvement of subcutaneous tissue, tendons and synovium in the hands results in contractures in the finger joints.[1] In particular, loss of extension in the proximal interphalangeal joints, abduction of the thumb, loss of opposition and flexion, and loss of wrist movements are the first findings in patients with scleroderma. In addition to these symptoms, Raynaud's phenomenon, digital ulcers, pain in the joints and edema of the fingers are the main indicators that the disease affects the hands.[1] All these structural changes and symptoms

cause grip problems and result in a progressive decrease in hand mobility, which is one of the main causes of rehabilitative problems.[3] As a result of the decrease in hand mobility in these patients, it has been reported that there is a significant decrease in daily living activities and quality of life.[4,5] Therefore, evaluation of hand mobility is clinically important in these patients.[6]

In rheumatologic diseases, hand mobility can be evaluated with performance indexes such as the measurement of range of motion with a goniometer or arthritis hand function test.[2,7] Hand mobility in scleroderma (HAMIS) test was developed specifically for SSc and is used to evaluate hand mobility in patients with SSc.[6] HAMIS was developed by Sandqvist et al in 2000. It is a 9-item test scored by clinicians. It aims to easily reflect problems which are specific to hand mobility. Some special equipment with different shapes and sizes are required for the HAMIS test.[6] A disadvantage of this test is that not all these equipment can be reached by everyone. For this reason, the HAMIS test was modified by the same authors in 2014 and the modified hand mobility in scleroderma (mHAMIS) test, which consists of 4 items, was developed. The equipment used for this test is selected from materials that are easily accessible to everyone. mHAMIS is a short, inexpensive and practical test developed to evaluate the hand mobility of patients with SSc.[8] Because of these advantages, it is frequently used in clinical studies including hand-related evaluations in individuals with SSc.[9-11]

Evaluation of the reliability of the tests/scales used in the field of medical rehabilitation is important in terms of their sensitivity to minimal changes in health status and their use in clinical trials. A low-reliability test/scale provides the basis for biased measurement and in particular, some erroneous decisions in clinical practice. Therefore, it is an important requirement in the field of health that the reliability of the tests/scales used is well known and that even the selected tests/scales should be highly reliable.[12]

Considering that hand involvement is widespread in people with SSc and it consequently decreases hand mobility, the mHAMIS test, which is commonly used to evaluate hand mobility, plays an important role. In the literature, there is no study evaluating the inter-observer reliability of this test. Therefore, the aim of this study was to determine the inter-observer reliability of mHAMIS test for evaluating hand mobility in patients with SSc.

2 | METHODS

This is a prospective study planned and conducted according to the Guidelines for Reporting Reliability and Agreement Studies.[13] The study was approved by the Ethics Committee of Gazi University Health Sciences Institute. In order to participate in the study, 37 patients aged 18-65 years who were diagnosed with SSc according to the classification criteria determined by American Rheumatology Association and European Rheumatism Association were interviewed. Subjects were informed about the study. The study was completed with 25 scleroderma patients because 2 of them refused to participate in the study, 8 of them had flexion contracture in at least 1 finger and 2 of them had digital ulcers in at least 1 finger. All patients were asked to sign the informed consent form. After questioning regarding demographic information and disease-related symptoms of the patients by the first researcher, the test was performed with the participation of 2 other researchers.

Modified hand mobility in scleroderma was developed by Sandqvist et al in 2014 to evaluate hand mobility in patients with SSc. This test was finalized by modifying the 9-item HAMIS test developed by the same researchers in 2000 and reducing it to 4 items.[8] mHAMIS provides assessment of flexion, extension and abduction of the 2nd to 5th fingers and wrist extension of individuals with SSc by occupational therapists, physicians and physiotherapists. In this test, mobility is assessed separately for both hands. The test is performed while the patient is in a sitting position in a chair with his/her back supported. While no material is required to evaluate the abduction of the fingers and extension of the wrist, a pencil with a diameter of 5 mm, a fork, knife or spoon handle with a diameter of 15 mm, a handlebar with a diameter of 30 mm and a table are required to evaluate the flexion and extension of the fingers.[8] In the test, flexion and extension of 2nd to 5th fingers are evaluated, while there is no substance that evaluates thumb movements. Each item is scored between 0 and 3 in the test. As each item goes from 0 to 3, there is loss of mobility for the movement evaluated. The test assesses the fibrotic skin changes that have important roles for patients' daily living activities.[11]

To determine inter-observer reliability, the scoring was performed by 2 physiotherapists, 1 with 19 and the other with 4 years of clinical experience, specializing in rheumatologic rehabilitation. All patients were evaluated in a room with the same temperature and humidity. All evaluations were performed in the afternoon as these patients had morning stiffness which could affect the outcome of the test. The 3rd researcher was in the same room as the observers so that the 2 observers did not consult each other in any way during the test. While the 3rd researcher was standing in front of the patient and describing the movement he/she had to do, the 2 observers standing on the right and left sides of the patient simultaneously and independently scored each patient's test.[14]

2.1 | Statistical analysis

The data obtained from the 2 observers were analyzed by an independent, 4th researcher, who was not present in the evaluation environment, using the Statistical Package for Social Sciences (SPSS) 18.0 computer package program (SPSS Inc). Intra-class correlation coefficient (ICC) method was used for inter-observer reliability analysis.[15] The ICC correlation coefficient above 0.8 indicates that the reliability of the test is excellent, 0.6-0.79 is good, 0.4-0.59 is moderate and below 0.4 is weak. In the study, P values <.05 were considered statistically significant.[16]

3 | RESULTS

The descriptive statistics for the subjects (n = 25) who participated in the research are presented in Table 1. ICCs and associated 95%

CIs, means, standard deviations, minimum and maximum values for each item are presented in Table 2. The ICC values for dominant and non-dominant hands were excellent. The values were 0.92 and 0.93, respectively.

4 | DISCUSSION

When investigating the reliability of a test, the following factors should be taken into consideration: measurement error due to the devices used for the test, the effect of variance due to the patients and examiners and the interactions between these 3 factors.[17] The effect of variance due to the different examiners was tested in this study.

The aim of this study was to investigate the inter-rater reliability of the mHAMIS test in 2 raters with varying experience levels. We found excellent agreement for inter-rater reliability for both hands.[16] The high ICC values obtained from the analyses can be explained by the fact that the test is short and easy to understand.

This study is not interventional research. Since it evaluates inter-observer reliability, it is methodological research. Digital ulcers are common in patients with SSc.[18] However, patients with digital ulcers were excluded from the study. One reason is that digital ulcers are prevalent on the dorsal side of the proximal interphalangeal joints of patients with SSc. When these patients are asked to do finger flexion, the digital ulcers are both painful and the risk of wound opening increases. Another reason for this is that these evaluations are made in the hospital. The patients with digital ulcers were not included into the study due to the non-sterile environment. Researchers wanted to avoid the risk of hospital infection. Because digital ulcers have a risk of infection from the hospital, this alone can be the reason for hospitalization. This increases the number of medicines that patients will take. This may also result in non-healing osteomyelitis. For these reasons, we have not found it ethical to include patients with digital ulcers for only a methodological study.

This test evaluates the 2nd, 3rd, 4th and 5th fingers of the patients together in flexion and extension positions. This is stated in item 1 and 2 of the test.[8] For the patient who had flexion contracture in at least 1 finger, the assessment of finger extension in item 2 could lead to incorrect results. Therefore, we did not include patients with at least 1 finger flexion contracture.

The measurements were carried out by only 2 raters who had different durations of experience. The presence of more raters with different durations of experience contributes to generalizability of the findings.[19] Therefore, the absence of an examiner without experience may be a limitation of this study.

TABLE 1 Descriptive statistics of systemic sclerosis (SSc) patients (n = 25)

Characteristic	n (%)	Mean ± SD	Range
Gender			
Female	25 (100%)		
Male	0 (0%)		
Dominant hand			
Right	25 (100%)		
Left	0 (0%)		
Form of SSc			
Limited	0 (0%)		
Diffuse	25 (100%)		
Age (y)		49 ± 12.73	21-65
Disease duration (mo)		78 ± 48.04	2-186

5 | CONCLUSION

As a result of this study, mHAMIS has been shown to be a reliable test in patients with SSc. As mentioned before, high reliability of tests used in the field of medical rehabilitation is important in terms of not causing bias and they are also sensitive to minimal changes in

TABLE 2 Inter-rater reliability and descriptive statistics for measurements of hands

	Rater A, mean ± SD	Rater A, min-max	Rater B, mean ± SD	Rater B, min-max	ICC	95% CI
Total DH	1.84 ± 1.84	0-6	1.88 ± 1.90	0-6	0.92	0.83-0.96
Total NDH	1.80 ± 1.55	0-5	1.80 ± 1.52	0-5	0.93	0.84-0.96
First item DH	0.68 ± 0.85	0-3	0.60 ± 0.76	0-2	0.94	0.87-0.97
First item NDH	0.56 ± 0.58	0-2	0.60 ± 0.64	0-2	0.72	0.47-0.87
Second item DH	0.48 ± 0.65	0-2	0.56 ± 0.71	0-2	0.82	0.64-0.92
Second item NDH	0.40 ± 0.57	0-2	0.48 ± 0.65	0-2	0.89	0.78-0.95
Third item DH	0.48 ± 0.58	0-2	0.44 ± 0.58	0-2	0.94	0.87-0.97
Third item NDH	0.44 ± 0.58	0-2	0.36 ± 0.48	0-1	0.86	0.72-0.94
Fourth item DH	0.20 ± 0.50	0-2	0.28 ± 0.54	0-2	0.85	0.70-0.93
Fourth item NDH	0.36 ± 0.48	0-1	0.32 ± 0.47	0-1	0.91	0.81-0.96

Abbreviations: DH, dominant hand; ICC, intra-class correlation coefficient; NDH, non-dominant hand.

health status. This research contributes to the literature by proving that the test can be used without causing bias in clinical trials. Intra-rater reliability of this test could not be evaluated because patients could not be reached for a 2nd time in the same time period. It is recommended to this evaluate in future studies.

AUTHOR CONTRIBUTIONS

Nurten Gizem Tore: design of the study, interpretation of the results and writing the manuscript. Fulden Sari, Deran Oskay: data collection. Devrim Can Sarac: data analysis. Songul Baglan Yentur, Hasan Satis, Aslihan Avanoglu Guler, Seminur Haznedaroglu: interpretation of the results and reviewing the manuscript.

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ORIGINAL ARTICLE

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Inhomogeneity of capillaroscopic findings in systemic sclerosis

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Abstract

Background: Despite the great interest in capillaroscopy in systemic sclerosis (SSc), research on the possible combinations of different microvascular phenomena at different fingers in SSc patients have not been performed until now.

Objective: To assess the diversity of capillaroscopic findings in SSc.

Methods: The study includes analysis of the capillaroscopic findings in 40 SSc patients who were divided into the following categories: "scleroderma", type pattern - "early", "active", "late" phase, normal and/or nonspecific findings. The data were analyzed using descriptive statistics and t test.

Results: In 77% of the patients, inhomogeneity of the capillaroscopic findings of the fingers was detected. The most frequent combinations of capillaroscopic patterns were "early + active" (n = 7), "active + late" phase (n = 7), "active" phase + normal and/or nonspecific findings (n = 6), "early + active" phase + normal and/or nonspecific findings (n = 4). Concomitant presence of normal and/or nonspecific findings and "late" phase was detected in only 3 cases.

Conclusion: Inhomogeneity of the capillaroscopic findings in SSc is a frequent phenomenon. The results indicate that combinations of "scleroderma" type capillaroscopic findings from different phases could be observed as well as concomitant appearance of pathological and normal/or nonspecific findings of different digits. This phenomenon could be a result of the complex action of different factors eg, disease duration, severity of Raynaud's phenomenon, presence of digital ulcers, local action of different angiogenic and angiostatic factors, gradual transition from one phase to another due to the extensive capillary area, therapeutic interventions.

KEYWORDS

Inhomogeneity, "scleroderma" type capillaroscopic pattern, systemic sclerosis

1 | INTRODUCTION

The great value of nailfold capillaroscopy in systemic sclerosis (SSc) is linked to the respective disease-specific microvascular changes, which develop in the context of severe Raynaud's phenomenon with profound endothelial damage. The vascular alterations are characterized by presence of giant capillaries, hemorrhages, avascular areas, capillary derangement and neoangiogenesis and are termed "scleroderma" type capillaroscopic pattern.[1] Their early appearance in the disease course determines the crucial role of nailfold capillaroscopy in the early and very early diagnosis of SSc. Currently, the abnormal "scleroderma" type capillaroscopic pattern is a diagnostic criterion for SSc in the updated 2013 ACR/EULAR (American College of Rheumatology/European League Against Rheumatism) classification criteria.[2,3]

Considering the strong diagnostic potential of nailfold capillaroscopy in SSc, we have previously studied nailfold capillaroscopic changes of the toes in a group of 36 SSc patients. Interestingly, whereas in the fingers, a "scleroderma" type capillaroscopic pattern has been found

in 97.2% (35/36) of patients, in the toes, it has been detected in only 66.7% (24/36) of cases ($P < .05$).[4] On the one hand this observation confirms the generalized nature of microangiopathy in SSc; on the other hand, the significantly lower frequency of the "scleroderma" type capillaroscopic pattern of the toes indicates the diversity of the capillaroscopic findings in different nailfold areas. During their research on capillaroscopic findings in SSc, Maricq et al (1981) reported a case of scleroderma, in whom 1 finger showed a normal pattern while another digit of the same patient had the characteristic "scleroderma" pattern. Thus, the necessity of examining all the digits was underlined.[5] Diversity of capillaroscopic changes at different fingers in SSc has been announced in our previous reports.[6,7] Despite the great interest in capillaroscopy in SSc in recent years, research on possible combinations of different microvascular phenomena at different fingers has not been performed. Expanding the knowledge of this topic is important for clinical practice as the inhomogeneity of capillaroscopic findings could affect precision of diagnosis, when not only fingers and toes, but also different fingers are being examined.[5-7]

1.1 | Aim of the study

To assess the diversity of capillaroscopic findings of different fingers in SSc.

2 | METHODS

The current study includes analysis of the data of 40 SSc patients, who had participated in previous studies[4,8] and for whom systematically collected clinical, laboratory and capillaroscopic data were available. The diagnosis SSc was made according to the classification criteria of the ACR (1980).[9] Presence of Raynaud's phenomenon, digital ulcers, telangiectasia and pulmonary arterial hypertension were documented. The global severity of Raynaud's phenomenon was assessed by the patient using a visual analog scale (VAS: 10 cm). The patients were asked by the physician to evaluate the severity and frequency of Raynaud's phenomenon in the last month according to the disability that vasospastic attacks cause to their everyday activities.

Nailfold capillaroscopic pictures were made using a video-capillaroscope Videocap 3.0 (DS Medica) with a magnification of 200-fold. Eight fingers (from 2nd to 5th bilaterally) were examined in each patient. The data were part of a capillaroscopic study that was performed in the Department of Rheumatology and Clinical Immunology, Kerckhoff Clinic, Bad Nauheim, Justus-Liebig University, Giessen, Germany. The study was approved by the local ethics committee and all the patients signed an informed consent.

The normal capillaroscopic findings include regular parallel capillary distribution with 1-3 hair-pin-shaped capillary loops in each dermal papilla, normal number (7-16/mm) without capillary loss. The diameter of the capillaries is within normal values, that is arterial capillary diameter <0.015 mm (= 15 μm) and venous <0.020 mm (= 20 μm).[10] The presence of "normal and/or nonspecific capillaroscopic findings" was assessed as a single category. Nonspecific changes were defined as the following findings: presence of single dilated and tortuous capillaries; traumatic hemorrhages without an association with giant capillaries; single short or elongated capillaries; single neoangiogenic capillaries that are not associated with avascular areas and capillary derangement.[11] Definite features of microangiopathy, that is giant capillaries, hemorrhages that originate from giant capillaries, avascular areas, neoangiogenic capillaries around the areas of capillary loss and capillary derangement, should be absent to define certain capillaroscopic changes as nonspecific.[11]

Capillaroscopic findings were divided into the following categories: "scleroderma" type capillaroscopic pattern - "early", "active", "late" phase (as defined by Cutolo et al, 2000)[12] normal and/or nonspecific findings.[10,11] In the "early" phase "scleroderma" type capillaroscopic pattern, single giant capillaries and single hemorrhages are observed, while capillary distribution is preserved and avascular areas are absent.[12] Presence of giant capillary loops (capillary diameter greater than 0.050 mm [= 50 μm])[10] is a mandatory criterion for definition of the "scleroderma" pattern and it may be an isolated finding.[13] In the "active" phase, there are numerous giant capillaries and hemorrhages, moderate capillary derangement, capillary loss, pericapillary edema. In the "late" phase, severe distortion of the capillary architecture is observed, there are extensive avascular areas and bushy capillaries.[12] Inhomogeneous capillaroscopic findings were considered presence of "scleroderma" type capillaroscopic findings from different phases and their combinations with normal and/or nonspecific findings at different fingers. Capillaroscopic findings of each examined finger were classified separately into 1 of the following categories: (a) "early" (initial changes); (b) "active" (more advanced microvascular changes); (c) "late" phase "scleroderma" pattern (the most advanced severe microangiopathy), (as defined by Cutolo et al, 2000)[12]; and (d) normal and/or nonspecific findings. The presence of the most advanced capillaroscopic changes were previously reported for a part of the patients.[8] This means that in the presence of "early" and "active" phase, more advanced changes, that is "active" phase is essential as it reflects the degree of microangiopathy. Analogously, in the presence of "active" and "late" phase, "late" phase capillaroscopic changes are most advanced and were previously reported.[8] In the current study, the presence of a predominant pattern that was defined as a pattern detected in ≥5 fingers (overall 8 examined digits) was additionally assessed. The exact number of fingers with a distinct capillaroscopic finding has not been calculated.

The data were analyzed using descriptive statistics and t test. The results are presented as mean value/average ± standard deviation. P values < .05 were considered as statistically significant.

3 | RESULTS

The mean age of the patients was 55.5 ± 15.15 years; there were 33 females and seven males. According to the clinical form of the

disease they were distributed into the following categories: 30 patients with limited cutaneous involvement, 8 with diffuse cutaneous involvement and two patients with overlap syndrome. The mean duration of SSc was 10.14 ± 7.78 years (range 0.75-30 years) and the mean duration of Raynaud's phenomenon was 13.27 ± 9.82 years (range 2-50 years). In the previous 3-12 months prior to the capillaroscopic examination, 42.5% of the patients (n = 17) received immunosuppressive treatment (with at least 3 months duration) that included methotrexate, cyclophosphamide (oral and intravenous pulse therapy), azathioprine, cyclosporine, mycophenolate mofetil, leflunomide; 47.5% (n = 19) corticosteroids; 47.5% (n = 19) vasoactive drugs (ie calcium channel blocker and/or sildenafil, excluding intermittent iloprost infusions); 17.5% (n = 7) bosentan.

Raynaud's phenomenon was registered in all of the included patients (100%; 40/40). The global severity of Raynaud's phenomenon assessed by the patient (VAS 10 cm) was 4.95 ± 1.44 cm. Digital ulcers were present in 13 patients (32.5%), telangiectasia in 12 patients (30.0%), pulmonary arterial hypertension in 13 cases (32.5%).

Analysis of the capillaroscopic images was possible in 97.5% of cases (n = 39). One case (2.5%) was excluded from analysis due to poor visualization of the microvessels. A "scleroderma'' type capillaroscopic pattern was found in all of the analyzed images (97.5%; n = 39). In 23% of the analyzed cases (n = 9), the capillaroscopic changes were homogeneous and revealed "active" (n = 8) or "late" phase (n = 1) "scleroderma" pattern. In 77% of the assessed patients (30/39), inhomogeneity of capillaroscopic findings at different fingers was detected. Among patients with inhomogeneous capillaroscopic findings of the fingers (n = 30), the most advanced microvascular changes ("late">"active">"early") was also a predominant capillaroscopic pattern in 67% of the cases (20/30) as follows: "active" pattern in 13 cases and "late" in seven patients. In 33% of the patients with inhomogeneous capillaroscopic pattern (10/30) the predominant pattern was not the most advanced microvascular abnormality ie, normal and/or nonspecific findings were found in most of the fingers in four patients with "active" phase and in three cases with "early" phase of some of the fingers; in three patients "active" phase was a predominant pattern versus "late" phase found at some of the fingers. Analysis of the capillaroscopic inhomogeneity revealed that the most frequent combinations of capillaroscopic changes were "early + active" (n = 7) and "active + late" phase (n = 7), which were found in an equal number of patients (Figures 1 and 2). The other observed combinations are presented in Table 1.

Of note, a combination between "early" and "late" phase "scleroderma" type capillaroscopic changes was not found and concomitant presence of normal and/or nonspecific findings with "late" phase "scleroderma" type capillaroscopic pattern was detected in three cases – 1 case with diffuse and 2 with limited cutaneous involvement. Clinical characteristics and therapeutic regimens of these three patients with unusual combinations of "late" phase + normal and/or nonspecific findings are presented below.

3.1 | Patient 1

Clinical involvement in a 48-year-old female patient with 2-year duration of diffuse cutaneous form of SSc included Raynaud's phenomenon (also with 2-year duration), digital ulcers, skin thickening with Rodnan skin score 27, myositis, initial pulmonary fibrosis, mild proteinuria. Antinuclear antibodies were positive at a titer of 1:12 800/nucleolar fluorescence. Therapeutic interventions that preceded the capillaroscopic examination were methotrexate at the dose of 15 mg weekly subcutaneously for a period of 10 months and bosentan administered with indication digital ulcers in the context of severe Raynaud's phenomenon for 6 months. At capillaroscopic examination, normal findings together with "active" and"late" phase "scleroderma" type capillaroscopic pattern were detected (Figure 3). Presence of "late" phase "scleroderma" pattern in a patient with short disease duration of SSc could possibly be associated with more rapid evolution of microvascular changes in diffuse cutaneous SSc in some areas of microcirculation versus others that have been spared from the pathological process.

3.2 | Patient 2

In a 28-year-old female patient with 8-year duration of limited cutaneous form of SSc, the clinical findings included Raynaud's phenomenon (also with 8-year duration), mild skin thickening with Rodnan skin score 4, recurrent arthritis, history of myositis, initial pulmonary fibrosis, esophageal involvement, telangiectasia, calcinosis. Antinuclear antibodies were positive in a titer of 1:160/nucleolar fluorescence. Therapeutic regimen of the patient prior to the capillaroscopic examination included methotrexate at the dose of 15 mg weekly including parenteral administration for a period of 2 years combined in the last year with mycophenolate mofetil (1000 mg daily) and prednisolone (5 mg daily). The capillaroscopic examination revealed presence of nonspecific findings, "active" and"late" phase "scleroderma" type capillaroscopic changes.

3.3 | Patient 3

Clinical involvement in a 58-year-old female patient with 17-year duration of limited cutaneous form of SSc included Raynaud's phenomenon (with 22-year duration), pulmonary fibrosis, pulmonary arterial hypertension, esophageal involvement. The patient was positive for anti-topoisomerase/anti-Scl-70 antibody. Immunosuppressive and vasoactive treatment of the patient before the capillaroscopic examination included mycophenolate mofetil (2000 mg daily) for 2 years, sildenafil (120 mg daily) for 6 years. The capillaroscopic

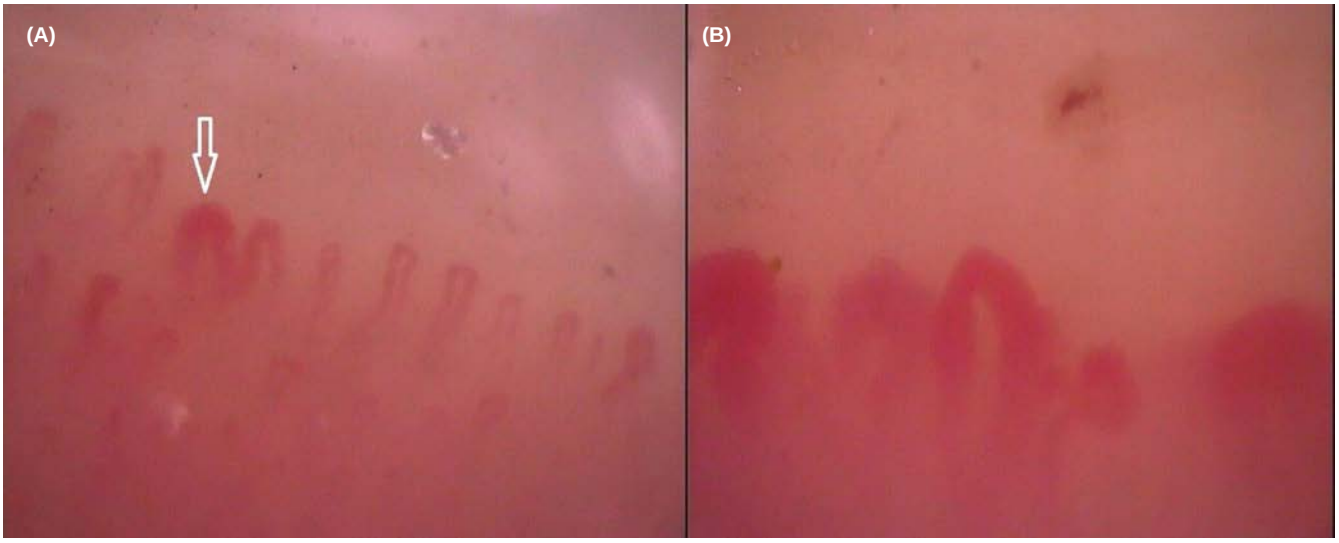

FIGURE 1 Inhomogeneous capillaroscopic findings in a 30-year-old systemic sclerosis (SSc) patient with CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia) syndrome, 9 years duration of Raynaud's phenomenon, 2 years duration of SSc. A, "Early" phase "scleroderma" type capillaroscopic findings with a single giant capillary loop, arrow. B, "Active" phase "scleroderma" type capillaroscopic pattern with giant capillaries – all in the distal row, single hemorrhage and reduced capillary density

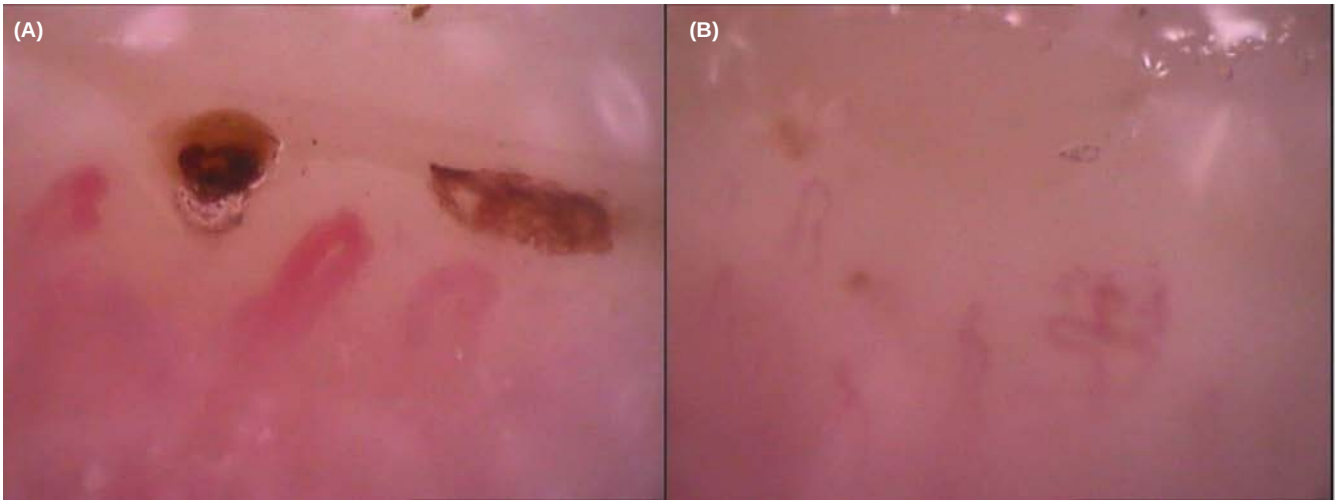

FIGURE 2 Inhomogeneous capillaroscopic findings in a 89-year-old systemic sclerosis (SSc) patient with CREST (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly and telangiectasia) syndrome, 10 years duration of Raynaud's phenomenon, 5 years duration of SSc. A, "Active" phase "scleroderma" type capillaroscopic pattern with giant capillary loops, hemorrhages, derangement and low mean capillary density (B) "Late" phase "scleroderma" type capillaroscopic pattern with avascular areas, derangement, neoangiogenesis

examination revealed concomitant presence of nonspecific findings and "late" phase"scleroderma" type capillaroscopic pattern. Older capillaroscopic images before treatment with the above-mentioned immunosuppressive and vasoactive drugs in these three patients were not available.

The duration of SSc in patients in whom "late" phase capillaroscopic pattern was detected (n = 11) was 13.9 ± 8.76 years which was longer as compared with patients with "early", "active", and normal/nonspecific findings presented in different combinations (n = 28; 8.66 ± 7.14 years), but the difference did not reach statistical significance (P = .061). "Late" pattern of some of the fingers was noted in overall 11 patients (six patients with limited cutaneous involvement, 3 cases with diffuse cutaneous form of the disease and two cases with overlap syndromes). The duration of SSc in the three patients with diffuse cutaneous involvement and "late" phase capillaroscopic changes was as follows: 2, 6 and 23 years. Of note, the shortest disease duration among patients with limited cutaneous form of SSc who presented with "late" pattern was 5 years.

Information about different severity of Raynaud's phenomenon at different fingers was not available. Thus, an association with the degree of microvascular changes could not be assessed in the current study. Interestingly, in all the patients with digital ulcers (n = 13), an "active" phase "scleroderma" pattern was observed at the fingers with active digital ulcers (Figure 4).

TABLE 1 Diversity of capillaroscopic findings of fingers

Capillaroscopic findings of fingers	Total number of the patients analyzed (N = 39)
Nonhomogeneous findings	n = 30 (77%)
"Early + active" phase	7
"Early + active" phase + normal findings and/or nonspecific findings	4
"Early" phase + normal and/or nonspecific findings	3
"Active" phase + normal and/or nonspecific findings	6
"Active + late" phase	7
"Active + late" phase + normal findings and/or nonspecific findings	2
"Late" phase + nonspecific findings	1
Homogeneous findings	n = 9 (23%)
"Active" phase only	8
"Late" phase only	1
Poor visualization/not analyzed	1 (2.5%)

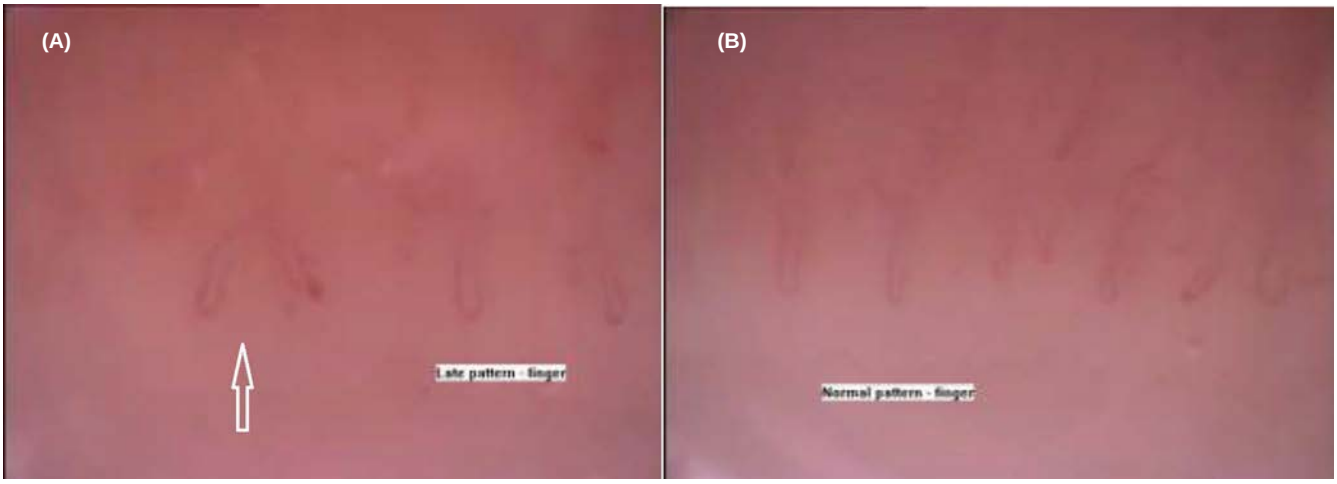

FIGURE 3 Inhomogeneous capillaroscopic findings in a 48-year-old systemic sclerosis (SSc) patient with diffuse cutaneous involvement, 2 years duration of Raynaud's phenomenon, 2 years duration of SSc. A, "Late" phase "scleroderma" type capillaroscopic pattern; low mean capillary density, avascular areas and neoangiogenesis (arrow) are demonstrated. B, Normal capillaroscopic pattern

4 | DISCUSSION

Nailfold capillaroscopic changes of the fingers in SSc are present in the majority of patients (>90%)[1,4,8,14] and are accepted as a diagnostic criterion.[2,3] However, they are inhomogeneous and combinations of "scleroderma" type capillaroscopic changes from different phases could be observed as well as concomitant appearance of pathological and normal and/or nonspecific findings at different digits.[5-7] Inhomogeneity of capillaroscopic changes in SSc indicates that detailed examination of the majority of the fingers is mandatory. Considering the lower capillary visibility of the thumbs, at least fingers from 2nd to 5th (overall 8 fingers) bilaterally should be examined. In addition, it has been found that thumbs are spared in both primary and secondary Raynaud's phenomenon.[15] Of note, thumb involvement has been suggested as a possible indicator of underlying connective tissue disease.[16] Consequently, especially in cases of clinical involvement of the thumbs, they also may be assessed, although milder capillaroscopic changes could be expected that also appear later in the disease course.

In a recent study by Dinsdale et al,[17] the question about capillaroscopic inhomogeneity in SSc has been studied in the light of the diagnostic sensitivity of capillaroscopy. Here, it has been found that the 8-finger gold standard correctly identifies abnormalities in 74.6% of SSc patients. The detection of abnormalities in the analysis included the presence of giant capillary loops and a pathological grade, that is "early", "active" and "late" according to the definitions of Cutolo et al. It has been found that examination of fewer than 8 nailfolds decreases sensitivity to detect capillaroscopic pathology. It has also been found that the best 2-finger combination is examination of both ring fingers, with a sensitivity of 59.8% for detection of either giant vessels or an abnormal grade. A 4-finger combination of middle and ring fingers bilaterally

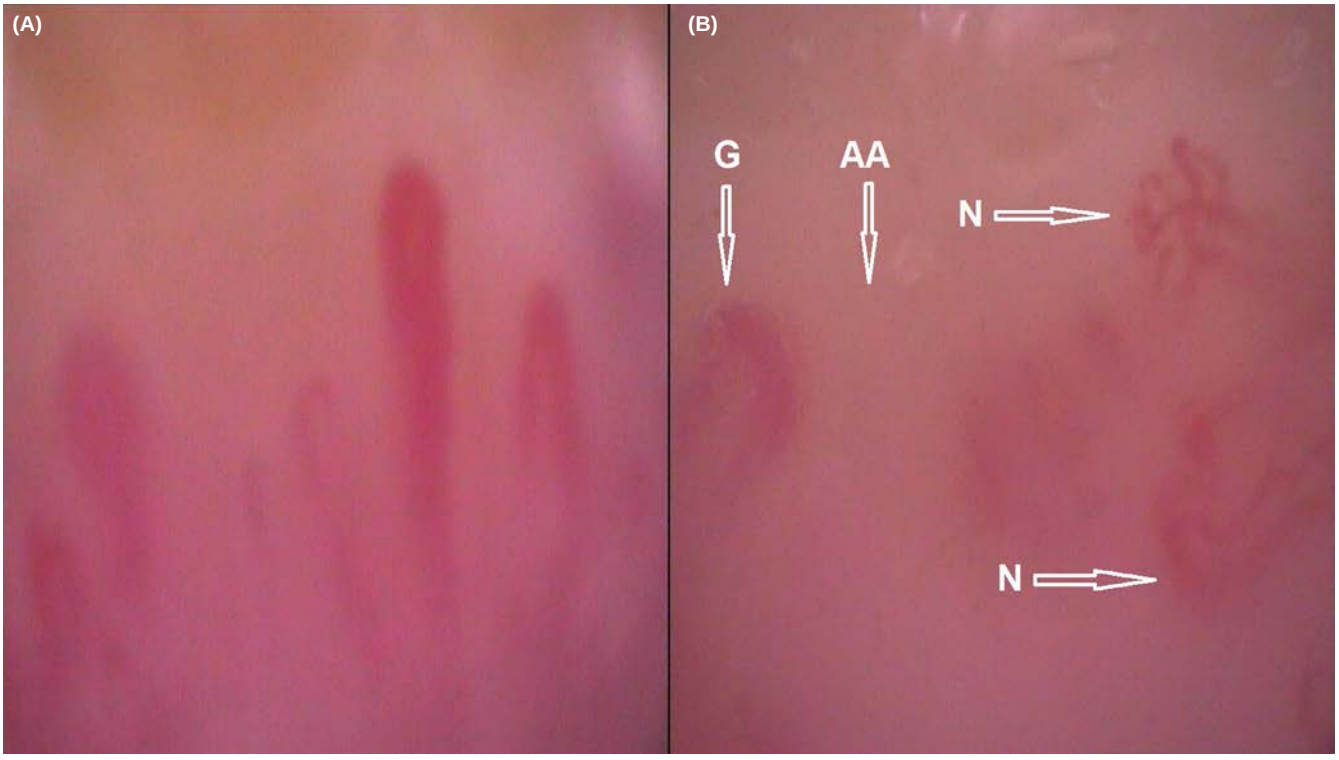

FIGURE 4 Inhomogeneous capillaroscopic findings in a 46-year-old systemic sclerosis (SSc) patient with limited cutaneous involvement, 14 years duration of Raynaud's phenomenon, 14 years duration of SSc. A, "Active" phase "scleroderma" type capillaroscopic pattern of a finger with digital ulcer that demonstrates giant capillaries, pericapillary edema and reduced capillary density. B, "Scleroderma" type capillaroscopic pattern of another finger without digital ulcer. The image demonstrates derangement, low mean capillary density with avascular area (AA), single giant capillary loop (G), neoangiogenic capillaries (N). Concomitant presence of giant capillary loop with severe derangement, extensive capillary loss and neoangiogenesis suggest possible "transition active-to-late" phase "scleroderma" pattern

increased the sensitivity to 66.7%. In cases of a single finger examination, it has been observed that the assessment of the ring finger of the nondominant hand provides 46.6% sensitivity. Thus, the authors concluded that at least a 2-finger combination should be evaluated.[17]

In the current study, diagnostic sensitivity of capillaroscopy using examination of different finger combinations has not been assessed. However, it should be underlined that in 41% of the patients with evaluable capillaroscopic images (16/39), some of the fingers revealed presence of normal and/or nonspecific capillaroscopic findings and examination of a part of the fingers would compromise the diagnostic sensitivity of the method. In 59% (23/39) of the patients, the capillaroscopic examination detected "scleroderma" type microvascular changes of all 8 fingers ie, in 23% (9/39) homogeneous capillaroscopic findings from a single capillaroscopic phase, and in 36% (14/39) inhomogeneous findings that included a different phase of a "scleroderma" type pattern, which were all useful for diagnostic purposes.

The combinations of "scleroderma" type capillaroscopic changes that were commonly observed in the current study were "early-active" and "active-late" phases. This supports the well-known association between capillaroscopic changes and disease duration in SSc whose consequence is "early" 1st stage,"active" 2nd stage,"late" 3rd stage.[12] Of note, in a previous research in SSc patients with duration of the disease less than 4 years, classically an "early" phase was common and was detected in 50% of cases (5/10), while "late" phase was observed in a single patient with diffuse cutaneous involvement (10%).[7] In the current study, the duration of SSc patients, in whom "late" phase capillaroscopic pattern was detected (n = 11) was 13.9 ± 8.76 years that was longer as compared with patients with "early", "active", and normal/nonspecific findings presenting in different combinations (n = 28; 8.66 ± 7.14 years). However, the difference was not statistically significant (P = .061). These results confirm that disease duration is not the sole determining factor for the progression of peripheral microangiopathy in SSc.

"Late" pattern of some of the fingers was evident in 11 patients in the current study. Six of them were cases with limited cutaneous involvement, three cases with diffuse cutaneous form of the disease and two cases with overlap syndromes. The disease duration in SSc patients with diffuse cutaneous involvement and "late" pattern was 2, 6 and 23 years respectively, while the shortest disease duration among patients with limited cutaneous form of SSc who presented with "late" pattern was 5 years. Thus, although all three phases of capillaroscopic changes ("early","active" and"late") could be observed in both limited and diffuse cutaneous form of the disease,[12] the speed of dynamics of microvascular changes probably differs in the 2 subsets of the disease being more rapid and aggressive in the diffuse cutaneous form of SSc (Figure 3).

The severity of Raynaud's phenomenon differs at different fingers.[15] The retrospective nature of the study and the absence of information about the different severity of Raynaud's phenomenon of different fingers excludes the opportunity to analyze its association with the capillaroscopic changes. However, an association between "active" phase "scleroderma" type capillaroscopic pattern and presence of digital ulcers at the same finger was detected (Figure 4). This observation indicates that other contributing factors for the diversity of capillaroscopic changes in SSc are local degree of endothelial damage, different severity of Raynaud's phenomenon at different digits and presence of digital ulcers. In addition, the dynamics of microvascular changes in the different stages of SSc may reflect the action of numerous angiogenic and angiostatic factors that differ in the early and late phases of the disease.[18] In this regard, assessment of the type of microvascular changes in the different phases of skin involvement (ie edematous, indurative and atrophic phases) deserves attention in future studies as different stages of scleroderma cutaneous involvement reflect the local degree of inflammation and tissue fibrosis.

Considering that morphological microvascular changes in SSc correlate with disease duration and develop slowly as well as the great number and total area of capillary microvessels, it can be hypothesized that capillary morphological alterations do not shift simultaneously from one stage to another. Thus, presence of capillaroscopic findings from different stages in different areas of the same SSc patient probably indicates the time of gradual transition from one stage to another. As an example, the appearance of a single giant capillary loop among microvessels with normal characteristics or with nonspecific changes is considered to be one of the earliest features of microangiopathy and confirms that microvascular pathology begins from single capillary vessels and gradually involves larger areas of microcirculation. Logically, it could be suggested that gradual involvement of extensive areas of the capillary network in the pathological process is also a feature of other diseases characterized with microangiopathy and consequently, inhomogeneity of capillaroscopic changes is not unique to SSc. In the majority of SSc patients in the current study, concomitant presence of capillaroscopic changes from different phases as well as an association between pathological and normal and/or nonspecific findings was observed. Moreover, the suggestion that the extensive area of capillary network among other factors leads to gradual transition of capillaroscopic changes from one stage to another, raises also the question about existence of stages of transition or borderline stages. Classically, giant capillaries and hemorrhages are the hallmarks of the "active" phase "scleroderma" pattern. In the "late" phase they disappear and are replaced by extensive avascular areas, neoangiogenesis in the context of severe capillary derangement. Concomitant presence of neoangiogenic and giant capillaries is possible and may represent a "transition active-late" phase in SSc patients (Figure 4). Existence of borderline stages of transition of one stage to another (ie "early-active","active-late" stages) may serve as a possible explanation of the phenomenon of inhomogeneity and requires further purposeful research.

A link between the degree of progression of capillaroscopic findings and the immunological profile has been also hypothesized. In 241 SSc patients, Cutolo et al (2004) found anticentromere antibodies more frequently in the cases with "early" pattern, while in the active" and"late" patterns their frequency was decreased. The presence of anti-topoisomerase/anti-Scl-70 antibodies was significantly more frequent in patients with both the "active" and"late" phase capillaroscopic pattern as compared with those with "early" phase. Thus, it has been hypothesized that although SSc-related autoantibodies (anticentromere and anti-Scl-70) are not directly associated with the development of a distinct subtype "scleroderma" pattern, they supposedly contribute to the rate of progression of scleroderma-related microangiopathy.[19] The absence of available immunological tests in all the patients from the current study excluded the opportunity to assess such an association.

The speed of progression of SSc-related microangiopathy varies in different patients. Timing of transition between capillaroscopic patterns has been evaluated in 38 SSc patients with "early" phase "scleroderma" pattern at baseline for a period of 7 years.[20] At the end of the follow-up, capillaroscopic pattern had been changed in 53% of the cases and the following dynamics was observed: an "active" phase in 13 patients (34%), a "late" phase in five patients (13%), and a normal pattern in two patients (5%). An association between progression of clinical symptoms (that occurred in 60% of the patients) and microangiopathy has been observed. Organ involvement was more frequent in SSc patients with "active" and "late" phase "scleroderma" pattern at the end of follow-up as compared with the frequency of involvement at baseline (when all patients exhibited "early" pattern). Of note, it has been recommended that patients with more rapid progression from "early" to "active" scleroderma pattern for a period shorter than 1 year, should be monitored closely, because of the observation that they are at risk of rapid progression to "late" phase SSc-related microangiopathy that is also associated with progression of clinical symptoms. Although the precise conditions and factors that lead to slower or quicker progression of SSc-related microangiopathy have not been fully identified, it has been suggested that analogous to other autoimmune diseases, potential contributing factors could be certain autoantibodies, genetic factors, as well as hormonal factors, infectious components, stress and mechanical trauma.[20]

Interestingly, a combination between "early" and"late" phase "scleroderma" type capillaroscopic changes was not detected in the current study and simultaneous observation of normal and/or nonspecific findings with "late" phase "scleroderma" type capillaroscopic pattern was observed in only 3 cases. Whether the presence of normal and/or nonspecific findings is primarily an unchanged part of the microcirculation or represents a result of therapy with immunosuppressive or vasoactive drugs in these 3 cases is unclear, as capillaroscopic images before treatment were not available. In the current study, therapy before capillaroscopic examination in the previous 3-12 months (with at least 3-month duration) included immunosuppressive treatment in 42.5% of the patients, corticosteroids in 47.5%, vasoactive drugs (ie calcium channel blocker and/or

sildenafil) in 47.5% and bosentan in 17.5% of patients. Conclusions about influence of the administered treatment on microcirculation could not be done due to the lack of follow-up. Future sequential capillaroscopic examinations in patients treated with vasoactive drugs and/or immunosuppressors could therefore answer the question, which of them could improve the microvasculature state. Of note, microvascular restoration has been observed with reverse order of appearance of the capillaroscopic phases in SSc as a result of therapeutic interventions. It has been reported in a clinical case of SSc that intense immunosuppression and hematopoietic stem cell transplantation has led to a rapid improvement of "scleroderma" type capillaroscopic pattern (with capillary hemorrhages, enlarged capillary loops and avascular areas) to almost normal pattern 5 months after the hematopoietic stem cell transplantation.[21] Of note, a significant improvement of capillaroscopic findings was observed in SSc patients treated with bosentan alone or with a combination of bosentan and sildenafil after 3 and 6 months with reduction of the "late" and "active" phase "scleroderma" pattern and an increase of the "aspecific" findings or "early" pattern.[21] Thus, the "reverse" order of appearance of the capillaroscopic changes is obviously possible and is currently observed after treatment with immunosuppressive drugs, hematopoietic stem cell transplantation and bosentan.[21-24]

Further research on precise interpretation of the dynamics of capillaroscopic changes in SSc is necessary eg, could "reverse" appearance of "active" phase capillaroscopic pattern occur in patients with "late" type capillaroscopic findings in the natural disease course and if so could it indicate disease activity or predict development of digital ulcers? In addition, is there a predilection for development of more advanced microvascular changes at the dominant hand as a result of repetitive microtrauma or at certain digits, remains to be assessed in future studies.

Association of capillaroscopic findings with other vascular manifestations, that is pulmonary arterial hypertension and telangiectasia, could not be assessed in the current study due to the lack of follow-up and the complex potential action of different factors including the effect of treatment. Moreover, the phase capillaroscopic changes of SSc-related microangiopathy are almost a universal feature in scleroderma patients (>90%) and are not specific for a certain type of an accompanying clinical manifestation. However, the speed of progression of microvascular alterations is potentially of prognostic relevance. Thus, the rapid dynamic change of peripheral capillaroscopic findings may indicate disease activity and different types of cutaneous, vascular and/or visceral involvement that should be evaluated and diagnosed in a clinical context.[25]

In conclusion, it could be hypothesized that the capillaroscopic inhomogeneity in SSc is a result of the complex action of different factors ie,

1. disease duration.
2. characteristics of peripheral vascular involvement, for example degree of endothelial damage, severity of Raynaud's phenomenon and presence of digital ulcers.
3. local action of numerous angiogenic and angiostatic factors.
4. gradual transition from 1 phase to another due to the high number and total area of the capillary network.
5. immunological profiles of the patients.
6. therapeutic interventions.

4.1 | How to report the results from capillaroscopic examination?

For diagnostic purposes, the standardized reporting of presence of "scleroderma" type pattern is sufficient. However, precise description and staging of diverging patterns facilitates a further dynamic assessment of microvascular findings during follow-up. Considering, the high frequency of the phenomenon of inhomogeneity, essential for clinical practice is report of the most advanced phase that is observed ie, "late"> "active"> "early" as it reflects the degree of microvascular damage.[8] In the light of the results of the current study, additionally the predominant pattern of most of the digits could be included in the capillaroscopic report, or a detailed description of all the available findings. Here, it should be underlined that presence of initial features of "scleroderma-related" microangiopathy, that is single giant capillaries should be reported as a diagnostic finding even if they are present at a single finger among normal and nonspecific findings of the other digits.

5 | CONCLUSIONS

Despite the high frequency and the diagnostic potential of the capillaroscopic changes in SSc, the results of the present study show that the capillaroscopic inhomogeneity at different fingers is a common finding. More specifically, combinations of "scleroderma" type capillaroscopic changes from different phases as well as concomitant appearance of pathological and normal and/or nonspecific findings of different digits could be observed. Thus, accurate diagnosing and staging in the course of the follow-up requires detailed examination of at least 8 fingers, from the 2nd to the 5th fingers bilaterally considering the poor capillary visibility of the thumbs.

5.1 | Take home messages

1. Inhomogeneity of capillaroscopic changes in SSc is a common finding.
2. "Scleroderma" type changes from different phases or combinations with normal and/or nonspecific findings could be observed.
3. Capillaroscopic inhomogeneity in SSc may be influenced by different factors such as disease duration, presence of digital ulcers and gradual transition of capillary changes from one phase to another.

CONFLICT OF INTEREST

S. Lambova and U. MÜller-Ladner declares that they have no conflict of interest.

ETHICAL APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. All the participants signed an informed consent.

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ORIGINAL ARTICLE

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Adipose-derived stromal/stem cells successfully attenuate the fibrosis of scleroderma mouse models

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Abstract

Aim: Systemic sclerosis (SSc) is an autoimmune disease characterized by skin and lung fibrosis. Although SSc has a high mortality risk, an effective treatment for the disease has not been established yet. Mesenchymal stromal/stem cells (MSCs) are multipotential nonhematopoietic progenitor cells that have the ability to regulate immune responses. Adipose-derived stromal/stem cells (ASCs), one of the types of MSCs, have the advantage of accessibility and potent immunomodulatory effects when compared with other MSCs, such as bone marrow-derived MSCs. This study aimed to investigate the antifibrotic effect of ASCs in scleroderma mouse models, including bleomycin-induced scleroderma and sclerodermatous chronic graft-versus-host disease (Scl-cGVHD) models.

Method: ASCs were intravenously administered to a bleomycin-induced scleroderma or Scl-cGVHD model on day 0. We compared the skin and lung fibrosis of scleroderma model mice between the ASC-treated group and control group.

Results: Administration of ASCs attenuated the skin and lung fibrosis of bleomycin-induced scleroderma and Scl-cGVHD model mice compared to that in the control mice. Immunohistochemical staining showed that ASCs suppressed the infiltration of $CD4^+$, $CD8^+$ T cells and macrophages into the dermis of bleomycin model mice compared to that in control mice. In addition, ASCs attenuated the messenger RNA expression of collagen and fibrogenic cytokines, such as interleukin (IL)-6 and IL-13, in the skin of bleomycin model mice. ASCs also reduced the frequency of fibrogenic cytokine-producing $CD4^+$ T cells and effector B cells in the spleen of bleomycin model mice.

Conclusion: ASCs could prove to be a potential therapeutic agent for use in patients with SSc.

KEYWORDS

adipose-derived stromal/stem cells, cytokine, fibrosis, mesenchymal stromal/stem cells, systemic sclerosis

Okamura and Matsushita contributed equally to this study and share first authorship.

1 | INTRODUCTION

Systemic sclerosis (SSc, also known as scleroderma) is a connective tissue disease characterized by immunologic abnormalities, vascular injury, and increased accumulation of extracellular matrix (ECM) proteins, which are produced by myofibroblasts, in the skin and internal organs.[1,2] Autoantibodies, including anti-DNA topoisomerase I, anticentromere, and anti-RNA polymerase antibodies, are detected in over 90% of SSc patients. However, unfortunately, an effective treatment for SSc has not been established. Emerging evidence indicates that three major abnormalities—autoimmunity, vasculopathy, and fibrosis—are crucial in the pathophysiology of SSc.[3] Immune cells and their components play distinctive roles in SSc development. The levels of T helper (Th)2 cytokines, such as interleukin (IL)-4, IL-6, and IL-13, are elevated in the serum of patients with SSc,[4,5] and promote fibrosis in SSc.[5] Furthermore, IL-6 from B cells also has a disease-promoting role in SSc pathogenesis.[6-8] Therefore, immune cells and their cytokines are thought to be potent therapeutic agents for SSc.

Mesenchymal stromal/stem cells (MSCs) are multipotential non-hematopoietic progenitor cells.[9] MSCs have been shown to regulate immune responses through inhibiting lymphocyte activation/proliferation and proinflammatory cytokine secretion.[10] MSC-based therapy has shown effectiveness in animal models of autoimmunity and human pre-clinical studies, including systemic lupus erythematosus, rheumatoid arthritis, and multiple sclerosis.[10] In addition, MSC-based therapy has been shown to be effective for steroid-refractory acute graft-versus-host disease (GVHD) in a phase II/III study,[11] and has become the approved stem cell drug.[12] Adipose tissue could also be an abundant MSC source and has many advantages over bone marrow tissue as a source of MSCs. Furthermore, adipose tissue is relatively easy and safe to access, and abundant. Adipose-derived stromal/stem cells (ASCs) have also been shown to play an important role in immune regulatory function.[13] In addition, ASCs exhibit more potent immunomodulatory effects compared with bone marrow-derived MSCs (BM-MSCs).[14] Thus, the use of ASCs is a more reasonable treatment strategy for patients with autoimmune diseases, when compared with BM-MSCs. Moreover, cell-based ASC treatment is superior to conventional immunosuppressive therapy in terms of side effects, such as infection and toxicity. Taken together, ASC-based therapy could be a potential treatment strategy for SSc patients.

Here, we investigated the antifibrotic effect of ASCs on scleroderma mouse models, including bleomycin-induced scleroderma and sclerodermatous chronic GVHD (Scl-cGVHD) models.[15] The current study suggests the application of ASCs as a potent therapeutic agent for SSc.

2 | MATERIALS AND METHODS

2.1 | Study design

We performed this study to determine whether ASCs attenuate fibrosis in mouse scleroderma models. We used 2 types of scleroderma model mice, bleomycin-induced scleroderma model and Scl-cGVHD model to establish this study design. In both models, ASC treatment attenuated the skin and lung fibrosis. Subsequent histological analysis confirmed these findings. Sample sizes and end points were selected on the basis of our extensive experience with these systems. In selected experiments, the mice were randomly assigned to treatment groups, and the researchers were blinded to the treatment group during experimental procedures and raw data analysis. All animal experiments were performed according to institutionally approved protocols and in compliance with the guidelines of the Committee on Animal Experimentation of Kanazawa University Graduate School of Medical Sciences. No animals or potential outliers were excluded from the data sets analyzed and presented herein.

2.2 | Mice

Wild-type C57BL/6 mice, B10. D2 (H-2^d) and BALB/c (H-2^d) mice were purchased from Japan SLC (Shizuoka, Japan). For experiments, all mice used were 8-12 weeks of age and housed in a specific pathogen-free barrier facility. The studies and procedures were approved by the Committee of Animal Experimentation of Kanazawa University Graduate School of Medical Science.

2.3 | Bleomycin-induced scleroderma model

Bleomycin (Nippon Kayaku) was dissolved in sterile saline at a concentration of 1 mg/mL. C57BL/6 mice received daily intradermal injections of either bleomycin or saline (300 μL, administered using a 27-gauge needle) into their shaved backs (the para-midline, lower back region) for 4 weeks, as previously described.[16]

2.4 | Scl-cGVHD model (BM transplantation)

In this study, 8-12-week-old male B10.D2 and female BALB/c mice were used as donors and recipients, respectively. BM was T cell depleted with anti-Thy1.2 microbeads (Miltenyi Biotech). BALB/c recipients were irradiated with 400 cGy twice a day (MBR-1520R; Hitachi) at 1 day before transplantation and were injected via the tail vein with 10×10^6 TCD-BM and 10×10^6 splenocytes in 0.5 mL phosphate-buffered saline (PBS) to generate Scl-cGVHD (allogeneic BM transplantation).

2.5 | ASC culture and injection

Cyagen OriCell™ Strain C57BL/6 Mouse Adipose-Derived Mesenchymal Stem Cells (Cyagen) were cultured in OriCell™ Strain C57BL/6 Mouse Adipose-Derived Stem Cell Growth Medium at 37℃ in a 5% CO_2 incubator. ASCs were used before passage 10. At day 0, both in bleomycin-induced scleroderma model and Scl-cGVHD model, 2×10^5 ASCs or PBS were injected into the tail vein.

2.6 | Histologic examination of skin and lung fibrosis

Skin sections were obtained from the bleomycin-injected region (the para-midline, lower back region) from the bleomycin-induced scleroderma model, and from the hairless and hairy area respectively from the Scl-cGVHD model mice. Skin sections were obtained as full-thickness sections extending down to the body wall musculature. Lung sections were also obtained from both the bleomycin-induced scleroderma model and Scl-cGVHD model. The skin and lung samples were fixed in formalin, dehydrated, embedded in paraffin, and used for immunostaining. Sections (6 μm thick) were stained with hematoxylin and eosin (HE) and Masson's trichrome. Dermal thickness, which was defined as the thickness of skin from the top of the granular layer to the junction between the dermis and intradermal fat, was evaluated. The blue-stained area on Masson's trichrome staining, representing collagen was quantified using ImageJ software version 1.51. The severity of lung inflammation was determined by a semiquantitative scoring system as previously described.[17] Briefly, lung fibrosis in randomly chosen fields of sections from the left middle lobe examined at 100× magnification was graded on a scale of 0 (normal lung) to 8 (total fibrous obliteration of fields). All sections were evaluated independently by 2 investigators (TK and SM), in a blinded manner.

2.7 | Immunohistochemical staining of mouse skin

The skin samples from bleomycin-injected mice and Scl-cGVHD mice were removed and frozen in liquid nitrogen using embedding medium for frozen tissue specimens (Tissue-Tek OCT compound; Sakura Finetek) and stored at −70°C until use. Frozen sections (5 μm thick) were immediately fixed in cold acetone and were incubated with rat anti-mouse CD4 monoclonal antibody (mAb) (RM4-5 clone; BD Biosciences), rat anti-mouse CD8 mAb (53-6.7 clone; BD Biosciences), and rat anti-mouse CD11b mAb (M1/70 clone; BD Biosciences). The paraffinized skin sections were applied to slides. All sections were then incubated sequentially with a biotinylated goat anti-rabbit IgG secondary antibody (BD Biosciences), followed by incubation with horseradish peroxidase-conjugated avidin-biotin complex (Vectastain ABC method; Vector Laboratories). Sections were washed three times with PBS between incubations, developed with 3,3′-diaminobenzidine tetrahydrochloride and H_2O_2, and then counterstained with hematoxylin. Positive cells were counted in 5high-power fields (HPF) and the average/HPF was calculated.

2.8 | Reverse transcription–polymerase chain reaction (RT-PCR)

Total RNA was isolated from inflamed skin using RNeasy spin columns (Qiagen) and digested with DNase I (Qiagen) to remove chromosomal DNA. Total RNA was reverse-transcribed to a complementary DNA (cDNA) using a RT system with random hexamers (Promega). Cytokine messenger RNA (mRNA) was analyzed using real-time RT-PCR quantification (Applied Biosystems). Real-time RT-PCR was performed on Quant Studio3 sequence detector (Applied Biosystems). TaqMan probes and primers were purchased from Applied Biosystems. *GAPDH* was used to normalize the mRNA. The relative expression of real-time RT-PCR products was determined according to the ΔΔCt method to compare target gene and *GAPDH* mRNA expression.

2.9 | Flow cytometry analysis

Single-cell leukocyte suspensions from spleens were generated by gentle dissection. The following mAbs were used: fluorescein isothiocyanate-, PE-, PE-Cy5-, PE-Cy7-, PerCP-Cy5.5-, APC-, APC-PECy7-, BV421- conjugated mAbs to mouse CD4 (RM4-5), CD19 (1D3), CD25 (MF-14) from BioLegend. Intracellular staining for FoxP3 (FJK-16s, eBioscience) was performed using the Cytofix/Cytoperm kit (BD Biosciences). For 2- to 6-color immunofluorescence analysis, single cell suspensions (10^6 cells) were stained at 4°C using predetermined optimal concentrations of mAb for 20 minutes. Blood erythrocytes were lysed after staining using Fluorescein-Activated Cell Sorter (FACS)™ Lysing Solution (Becton Dickinson). Dead cells were detected by using LIVE/DEAD Fixable Aqua Dead Cell Kit (Invitrogen-Molecular Probes) before cell-surface staining. Cells with the forward and side light scatter properties of lymphocytes were analyzed using a BD FACSCanto™ II (BD Biosciences). Data were analyzed with FlowJo software (version 10.2; TreeStar).

2.10 | Intracellular cytokine staining

Intracellular cytokine expression was visualized by immunofluorescence staining and analyzed by flow cytometry as described. For interferon (IFN)-γ, tumor necrosis factor (TNF)-α, IL-13, IL-17 detection, cells (2×10^6 cells/mL) were cultured with phorbol 12-myristate 13-acetate (PMA) (50 ng/mL; Sigma-Aldrich), ionomycin (1 μg/mL; Sigma-Aldrich), and brefeldin A (3 μmol/L; BioLegend) for 4 hours. For IL-10 detection, cells (2×10^6 cells/mL) were cultured with lipopolysaccharide (10 μg/mL), PMA (50 ng/mL), ionomycin (500 ng/mL), and brefeldin A (3 μmol/L) for 5 hours. The following mAbs were used: PE-, APC-conjugated mAbs to mouse IFN-γ (XMG1.2), TNF-α (MP6-XT22), IL-17 (TC11-18H10.1), IL-10 (JES5-16E3) from BioLegend and IL-13 (eBio13A) from eBioscience. Fc receptors were blocked with mouse Fc receptor mAb (2.4G2; BD PharMingen) with dead cells detected using a LIVE/DEAD® Fixable Aqua Dead Cell Stain Kit (Invitrogen) before cell surface staining. Stained cells were fixed and permeabilized using a Cytofix/Cytoperm kit (BD PharMingen) according to the manufacturer's instructions.

2.11 | Statistical analysis

Data are presented as means ± SD. Two-tailed Student's *t* test was used for comparisons between 2 groups, and $P < .05$ was considered significant. Comparisons among 3 or more groups were performed with analysis of variance followed by Tukey's multiple comparison test. Data were analyzed with GraphPad Prism (version 5; GraphPad Software).

2.12 | Study approval

Animal studies were approved by the Committee on Animal Experimentation of Kanazawa University Graduate School of Medical Sciences.

3 | RESULTS

3.1 | ASCs attenuated fibrosis in bleomycin-induced scleroderma

To investigate whether ASCs regulate fibrosis, ASCs were intravenously administered to a bleomycin-induced scleroderma model on day 0. The fibrosis of skin and lung in the bleomycin-induced scleroderma model were analyzed on day 28. The skin fibrosis area was analyzed for dermal thickness by HE staining and Masson's trichrome area. The dermal thickness in the bleomycin-induced scleroderma mice treated with ASCs was significantly attenuated ($P < .0001$) compared to that in the PBS-treated group (Figure 1A,B), although ASCs could not improve the dermal fibrosis to the basal levels. In addition, the fibrosis area in the bleomycin-induced scleroderma mice treated with ASCs was also decreased ($P < .01$) compared to that in the PBS-treated group (Figure 1C,D). Lung fibrosis was evaluated with a semiquantitative scoring system, as previously described.[17] The grade of lung fibrosis was significantly lower ($P < .001$) in ASC-treated groups than in the PBS-treated group (Figure 1E,F). Therefore, ASCs attenuate skin and lung fibrosis in bleomycin-induced scleroderma.

3.2 | ASC treatment reduced the infiltration of immune cells into the skin

The infiltration of T cells into the skin plays an important role in skin fibrosis in bleomycin-induced scleroderma.[18] To determine whether ASCs affect the infiltration of immune cells into the skin in bleomycin-induced scleroderma, inflamed skin samples obtained 28 days after bleomycin injection were stained with anti-CD4 and anti-CD8 mAbs, and anti-CD11b mAbs. Immunohistochemical staining (Figure 2A-F) showed that infiltration of $CD4^+$ T cells, $CD8^+$ T cells, and $CD11b^+$ macrophages into the skin were significantly reduced in the ASC-treated group compared to the PBS-treated group (24%, $P < .0001$; 57%, $P < .01$; 49%, $P < .01$; respectively). Thus, ASCs significantly reduce the infiltration of immune cells into the skin in bleomycin-induced scleroderma.

3.3 | ASC treatment reduced mRNA expression of fibrogenic cytokines and type I collagen

Cytokines are critical for the development of tissue fibrosis in SSc and SSc mouse models.[19-21] Previous studies have suggested that some cytokines such as IL-6, IL-13, and TNF-α regulate dermal fibroblast proliferation and collagen.[22,23] By contrast, IFN-γ, a typical Th1 cytokine, can suppress tissue fibrosis in SSc mouse models.[24] To determine whether ASCs regulate cytokine and collagen in the inflamed skin in bleomycin-induced scleroderma, we assessed cytokine and type I collagen gene proα2 (I) collagen (COL1A2) mRNA expression in the skin from bleomycin-induced scleroderma mice by real-time PCR analysis (Figure 2G). Fibrogenic cytokines, such as IL-6 and IL-13, mRNA expression in ASC-treated group were significantly decreased compared to that in the control group (42%, $P < .01$; 29 $P < .05$; respectively, Figure 2G). TNF-α mRNA expression tended to decrease in the ASC-treated group compared to that in the control group ($P < .09$). The expression of IL-10 and IFN-γ mRNA in the skin of the ASC-treated group was comparable with that of the control group ($P < .27$ and $P < .94$; respectively). Consistent with the skin histopathology of bleomycin-induced scleroderma mice, COL1A2 mRNA expression was lower in the ASC-treated group than in the control group (49%, $P < .05$, Figure 2G). Thus, ASC treatment attenuated the production of collagen and expression of fibrogenic cytokines, such as IL-6 and IL-13.

3.4 | ASCs attenuated the frequency of cytokine-producing $CD4^+$ T cells and effector B cells in the spleen of bleomycin-induced scleroderma model

To investigate the mechanisms underlying suppression of bleomycin-induced scleroderma by ASCs, we analyzed the cytokine-producing T cells, regulatory T cells, and effector/regulatory B cells in the spleen of ASC-treated and PBS-treated groups. When compared with ASC-treated and PBS-treated groups, the frequency and number of TNF-α-producing $CD4^+$ T cells, IL-13-producing $CD4^+$ T cells, and IL-17-producing $CD4^+$ T cells were significantly decreased in the ASC-treated bleomycin model compared with that in the PBS-treated bleomycin model (Figure 3A-F). ASCs also reduced the expression levels of IL-13 and IL-17 from $CD4^+$ T cells (Figure S1). Furthermore, ASC treatment significantly decreased the frequency and number of IL-6-producing effector B cells in the bleomycin model (Figure 3I,J). However, ASC treatment did not affect the frequency and number of regulatory T cells and Breg cells (Figure 3G, H, K, L). In the control mice (no bleomycin), ASC treatment only decreased the frequency of IL-13-producing $CD4^+$ T cells (Figure 3D). Therefore, ASCs suppressed cytokine-producing T cells and IL-6-producing effector B cells but not regulatory T and B cells.

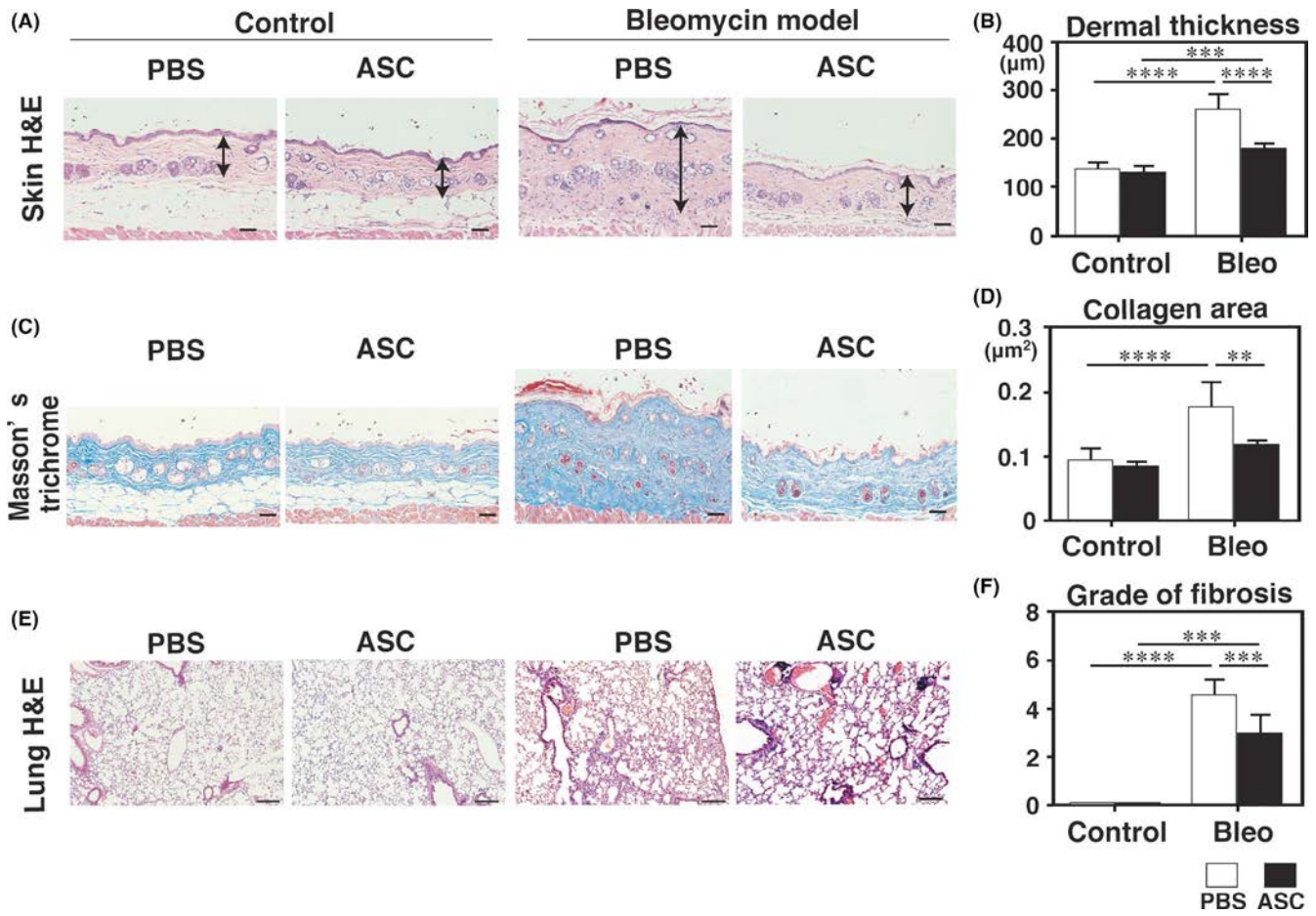

FIGURE 1 Adipose-derived stromal/stem cells (ASCs) attenuate fibrosis in bleomycin-induced scleroderma model. A and B, Dermal thickness was determined by hematoxylin and eosin (HE) staining at day 28 of phosphate-buffered saline (PBS) treated control (control) or bleomycin-induced scleroderma model (Bleo). Arrows indicate dermal thickness. C and D, Skin fibrosis was determined as the collagen area stained by Masson's trichrome at day 28 of PBS-treated control or bleomycin-induced scleroderma model. The blue-stained area, representing collagen, was quantified using ImageJ software. E and F, Lung fibrosis was determined by HE staining at day 28. Data are expressed as means ± SEM (B, D, E). n = 5 mice per group (B, D, F). *P < .05, ** P < .01, *** P < .001, **** P < .0001. Scale bar = 50 μm (A and C). Scale bar = 200 μm (E)

3.5 | ASCs attenuated fibrosis in Scl-cGVHD model

To investigate whether ASCs attenuate fibrosis in another immune-mediated mouse model of SSc, we used a murine Scl-cGVHD model, which is a well-established model for human sclerodermatous chronic GVHD and human SSc.[15,25] Histopathological analysis revealed that dermal thickness was significantly less in the ASC-treated group than in the PBS-treated group (P < .0001, Figure 4A,B). Furthermore, the grade of lung fibrosis was significantly lower in the ASC-treated group than in the control group (P < .001, Figure 4C,D). Thus, ASCs also suppressed fibrosis in the Scl-cGVHD model.

4 | DISCUSSION

The purpose of this study was to determine whether ASCs can regulate fibrosis in scleroderma mouse models, including a bleomycin-induced scleroderma model and murine Scl-cGVHD model. Intravenous ASC injection attenuated the development of skin and lung fibrosis in the bleomycin-induced scleroderma model. Furthermore, ASCs also attenuated skin and lung fibrosis in Scl-cGVHD mice. Infiltration of $CD4^+$ T cells and $CD8^+$ T cells into the skin was significantly lower in the ASC-treated group than in the control group in the bleomycin-induced scleroderma model. ASCs also reduced the mRNA expression of fibrogenic cytokines and collagen in the skin of bleomycin-induced mice. Furthermore, the number of splenic fibrogenic cytokine-producing $CD4^+$ T cells in the bleomycin-induced scleroderma model was significantly lower in the ASC-treated group than in the control group. These results suggest that ASCs are a promising therapeutic agent for human SSc.

In the last decades, immunomodulatory and anti-inflammatory properties of MSCs have been reported. MSCs reportedly suppress T cell and B cell proliferation.[13] Furthermore, MSCs have been shown to attenuate autoimmune disease models, including multiple sclerosis,[26] rheumatoid arthritis,[13] and systemic

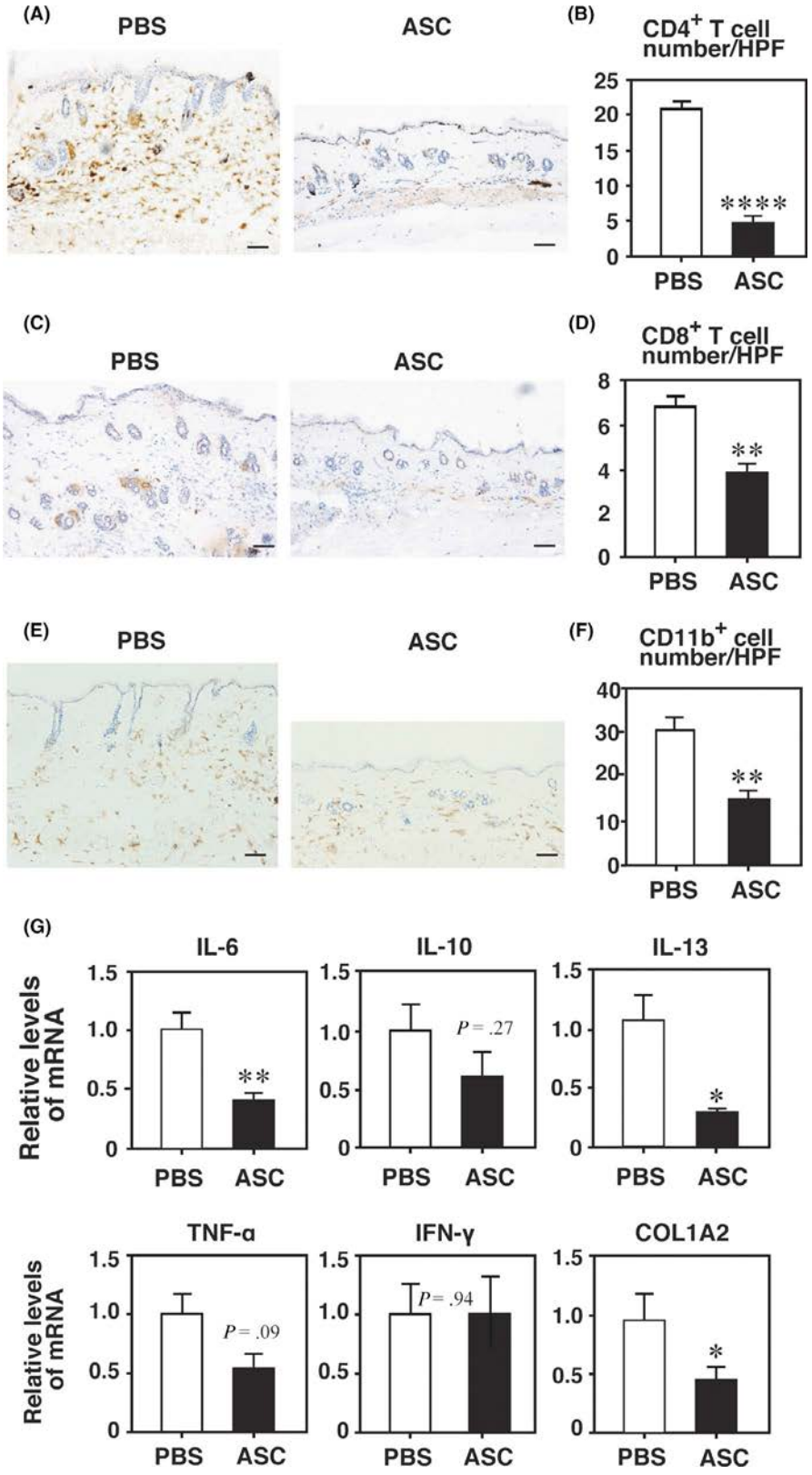

FIGURE 2 Adipose-derived stromal/stem cells (ASCs) suppress the infiltration of immune cells into the skin, and the expression of fibrogenic cytokine (interleukin [IL]-6, IL-13) and collagen in bleomycin-induced scleroderma. A-F, Representative immunohistochemical staining of the skin from bleomycin-induced scleroderma model. Skin tissues were harvested at day 28. The number of $CD4^+$ cells (A and B), and $CD8^+$ T cells (C and D) and $CD11b^+$ cells (E and F) per high-power field (HPF) in immunohistochemical-stained slides from groups of phosphate-buffered saline (PBS)-treated or ASC-treated mice. Data are expressed as means ± SEM (B, D, and F). n = 5 mice per group (B, D, and F). $^{**}P < .01$, $^{****}P < .0001$. Scale bar = 50 μm (A, C, and E). E, Expression of messenger RNA for interleukin (IL)-6, IL-10, IL-13, tumor necrosis factor (TNF)-α, interferon (IFN)-γ, and proα2 (I) collagen (COL1A2) in the skin of bleomycin-induced scleroderma model at day 28. Data are expressed as means ± SEM. n = 5 mice per group. $^{*}P < .05$, $^{**}P < .01$

lupus erythematosus,[27] through decreased cytokine-producing T cells. Cytokines have essential functions in fibrosis in SSc pathogenesis.[28] Previous studies show that cytokines characteristic of Th2/Th17 cells, such as IL-4, IL-6, IL-13, and IL-17, promote the fibrotic process in the pathogenesis of SSc.[20,29,30] The current study shows that ASCs attenuate fibrosis in scleroderma mouse models through reduced production of fibrogenic cytokines and cytokine-producing T cells. However, Treg cells were not

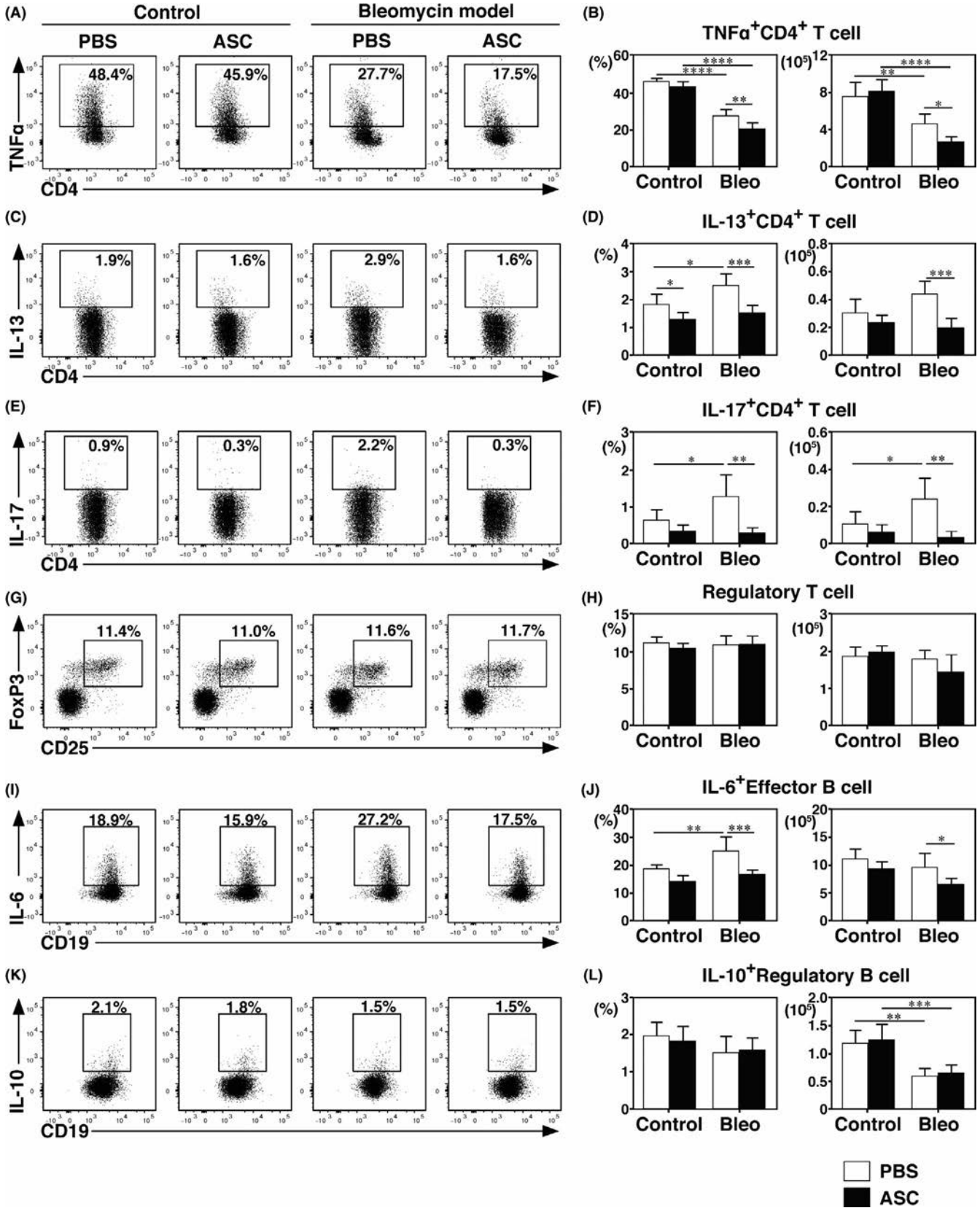

FIGURE 3 Adipose-derived stromal/stem cells (ASCs) attenuate the frequency of tumor necrosis factor (TNF)-α, interleukin (IL)-13, IL-17 producing $CD4^+$ T cells and IL-6 producing B cells of spleen in bleomycin-induced scleroderma. Representative results, the frequency, and numbers of splenic TNF-α^+ $CD4^+$ T cells (A, B), IL-13^+ $CD4^+$ T cells (C, D), IL-17^+ $CD4^+$ T cells (E, F), regulatory T cells (G, H), IL-6^+ effector B cells (I, J), IL-10^+ regulatory B cells (K, L) in phosphate-buffered saline treated control (control) or bleomycin-induced scleroderma model (Bleo) at day 14 are shown. Data are expressed as means ± SEM (B, D, F, H, J, L). n = 5 mice per group. *P < .05, **P < .01, ***P < .001, ****P < .0001

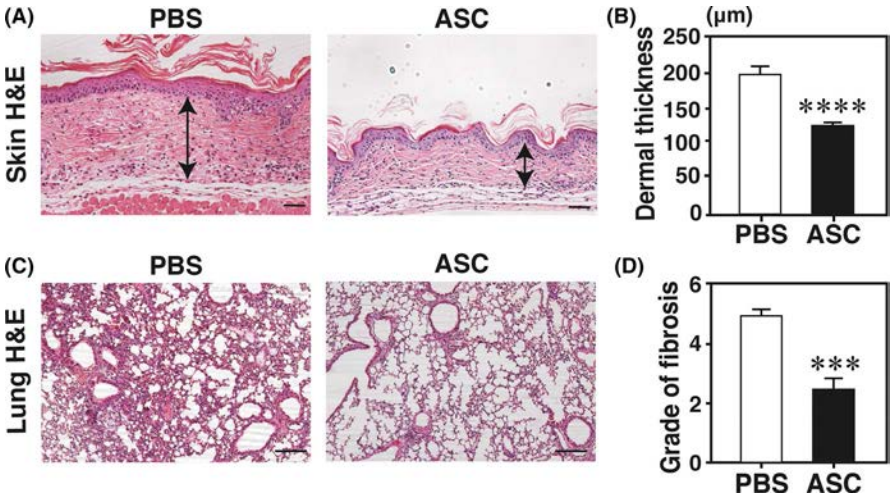

FIGURE 4 Adipose-derived stromal/stem cells (ASCs) attenuate the skin and lung fibrosis in sclerodermatous chronic graft-versus-host disease (Scl-cGVHD) model. A and B, Dermal thickness was determined by hematoxylin and eosin (HE) staining at day 35 after bone marrow transplantation (BMT). Arrows indicate dermal thickness. C and D, Lung fibrosis was determined by HE staining at day 35 after BMT. Data are expressed as means ± SEM (B and D). n = 7 mice per group (B and D). ***P < .001, ****P < .0001. Scale bar = 50μm (A). Scale bar = 200μm (C)

changed with ASC treatment in the scleroderma mouse models. Regulatory B cells (Bregs) have recently been shown to restrain excessive inflammatory responses.[7,31,32] Breg cells play an important role in the suppression of scleroderma mouse models, including Scl-cGVHD[33] and bleomycin-induced models,[6] and human SSc patients.[34] However, ASC treatment has no effect on the frequency of Breg cells in a scleroderma mouse model. By contrast, IL-6 producing effector B cells have a disease-promoting role for a scleroderma mouse model. In the current study, ASC treatment reduced the frequency of IL-6-producing effector B cells in a scleroderma mouse model. Thus, ASCs attenuated the fibrosis of the scleroderma mouse model through reduced production of fibrogenic cytokines and cytokine-producing T cells as well as IL-6 producing effector B cells. Mechanistically, it was reported that MSCs regulate immune cells not only via anti-inflammatory cytokines, such as IL-10 and transforming growth factor-β, but also via cell-cell contact.[35] Importantly, direct cell-cell contact of MSCs and dendritic cells has shown to induce regulatory dendritic cells which have immunomodulatory functions.[36] MSCs have also been shown to suppress T cells via cell-cell contact.[37] It was proposed that lack of costimulatory molecules, such as CD80 and CD86, on MSCs can render T cells anergic.[38] Furthermore, MSCs repress Th17 cells through the PD-1 pathway.[39] Alternatively, there is a possibility that ASC/MSCs directly inhibit the fibrosis without modulating immune cells. However, it was reported that MSCs could not detect the inflamed skin lesion in a hypochlorous acid (HOCL)-induced scleroderma model.[40] MSCs had shown to attenuate skin and lung fibrosis in the HOCL-induced scleroderma model, through the reduction of inflammation and fibrogenic cytokine production.[40] Taken together, ASCs/MSCs exert potent immunomodulatory and antifibrotic effects in pathogenesis of scleroderma through modulating immune cells.

MSCs are immune-privileged; they are able to survive and differentiate in immune-compatibility-mismatched allogenic or even xenogeneic recipients.[41] They are major histocompatibility class II-negative but class I-positive, thus protecting them from natural killer cell-mediated elimination.[9] As a result, MSCs escape recognition by effector $CD4^+$ T cells and avoid an allogenic rejection response.[42] However, it was also reported that transient interaction between ASC/MSCs and immune cells is enough to exert their regulatory role.[14] Thus, it is not necessary for ASC/MSCs to escape from rejection to exert a regulatory effect on inflammation-dependent tissue fibrosis. The immunomodulatory effect by MSCs occurred regardless of the MSC donor origin (autogeneic [auto]-, allo-MSCs). There is no clinical advantage of autologous MSCs over allogeneic MSCs in humans.[43] In addition, it was reported that allo-MSCs are superior to auto-MSCs in the clinical trial for non-ischemic dilated cardiomyopathy.[44] In the current study, the bleomycin-induced scleroderma model is an auto-ASC treatment model, since ASCs derived from C57BL/6 mice were transferred into bleomycin-induced C57BL/6 mice. By contrast, the Scl-cGVHD model is an allo-ASC treatment model, since ASCs derived from C57BL/6 mice were transferred into the Scl-cGVHD model which was induced with BALB/c recipient mice and B10.D2 donor mice. Nonetheless, ASCs attenuated skin and lung fibrosis in a bleomycin-induced scleroderma model (auto-ASCs) and Scl-cGVHD model (allo-ASCs).

To date, ASCs have been reported to show effectiveness in human clinical trials for heart failure, renal failure, and liver cirrhosis.[45-48] In addition, allo-MSC-based therapy for steroid-refractory acute GVHD has been approved in Japan.[11] An open-label phase I trial for patients with SSc, in which auto-ASCs were injected into inflamed fingers, demonstrated a significant improvement in Raynaud's phenomenon, hand disability, and pain.[49,50] Furthermore, intravenous (auto- or allo-) BM-MSC treatment for patients with SSc has shown to improve skin fibrosis and vasculopathy in several cases.[51-53] Taken together, ASCs/MSC-based therapy could be a potent therapeutic strategy for SSc.

In the current study, we have shown that ASCs attenuate skin and lung fibrosis in bleomycin-induced scleroderma and Scl-cGVHD models. ASCs apparently exert an immunosuppressive effect by attenuation of immune cell infiltration into the skin and decreased production of fibrogenic cytokines. The present results suggest ASCs to be potential therapeutic agents for human SSc.

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CONFLICTS OF INTEREST

The authors have declared no conflicting interests.

AUTHOR CONTRIBUTIONS

AO, TM, and KT designed research; AO, TM, AK, TK, and SM conducted research; AO, TM, AK, TK, and SM, and YH analyzed data; AO and TM prepared figures; AO, TM, and KT wrote the paper. AO and TM had primary responsibility for final content. All authors read and approved the final manuscript.

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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ORIGINAL ARTICLE

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Peripheral neuropathies in rheumatic diseases: More diverse and frequent than expected. A cross-sectional study

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Abstract

Background/objective: Peripheral neuropathies (PN) are heterogeneous nerve disorders; frequently rheumatic patients have neuropathic symptoms. In some rheumatic diseases (RD) PN are secondary to nerve compression while others are related to metabolic abnormalities, inflammation or vasculitis. Our aim was to explore the frequency of neuropathic symptoms with three neuropathy questionnaires (NQ) and nerve conduction studies (NCS) in RD.

Methods: This is a cross-sectional study in patients with any RD attending for the first time to a rheumatology outpatient clinic. We included all patients who accepted to participate and who answered three NQ and received a physical evaluation. Twenty patients were randomly selected to perform NCS and 10 healthy subjects were included as controls. The topographic diagnoses were: mononeuropathy, multiplex mononeuropathy, and/or polyneuropathy. Statistical analysis: descriptive statistics (mean, median, standard deviation, interquartile range and frequency, odds ratios and Pearson correlation test).

Results: One hundred patients and 10 healthy subjects were included. Sixty-nine were female, mean age 40.6 ± 15.7 years. Rheumatic diagnoses were: systemic lupus erythematosus (26%), rheumatoid arthritis (16%), gout (14%), and osteoarthritis (11%). Fifty-two patients had neuropathic signs during physical examination and 67% had positive questionnaires with variable scores among several RD. Abnormal NCS was reported in 14 patients (70%): 6 (42.8%) median nerve mononeuropathies, 4 (28.5%) multiplex mononeuropathies and 4 (28.5%) polyneuropathies. None of the healthy subjects had neuropathy (NQ, physical evaluation, or NCS). Risk of being NCS positive is higher when the patients were NQ positive.

Conclusion: PN has variable distribution and high frequency in patients with RD; NQ+ increases the risk of presenting NCS+ for PN.

KEYWORDS

neuropathic symptoms, neuropathy questionnaires, peripheral neuropathy, rheumatic diseases

1 | INTRODUCTION

Peripheral neuropathies (PN) are disorders of the peripheral nervous system secondary to several causes, classified as local or systemic. The clinical manifestations are highly variable, presenting a combination of sensitive changes, pain, muscle weakness, muscle atrophy, and autonomic symptoms.[1] PN diagnosis includes symptoms, questionnaires, physical examination, and nerve conduction studies (NCS) considered as the gold standard for the diagnosis. NCS strongly correlate with underlying structural changes and are the least subjective and most reliable single criterion standard.[2]

NCS have higher sensitivity, specificity, and reproducibility than clinical examination, and also determine the type of affected fibers: motor, sensory, or a combination of both. NCS help to classify the neuropathic distribution: mononeuropathy (MNP) when only one nerve trunk is affected; multiple mononeuropathy (MNPM) when several nerve trunks are involved within an asymmetric distribution; polyneuropathy (PNP) when diffuse and symmetrical involvement of all four limbs is present; and polyradiculopathy (PRP) when proximal affection and diffuse nerve damage is detected. NCS also suggest the possible pathophysiological mechanism, such as demyelination or axonal loss. However, NCS cannot evaluate small fibers or amyelinic fibers. Conventional electromyogram and NCS are noncontributory to diagnose small fiber neuropathy.[3-10]

Questionnaires are useful tools in the evaluation of PN. They are economical and let us identify mild or incipient clinical symptoms frequently referred by rheumatic patients.[11] Douleur Neuropathique en four Questions (DN4),[12] Leeds Assessment of Neuropathic Symptoms and Signs (LANSS),[13] and Michigan Neuropathy Screening Instrument (MNSI),[14] are three neuropathy questionnaires validated in our country with good sensitivity and specificity. However, these questionnaires have not been tested in patients with rheumatic diseases except the LANSS questionnaire, which has been validated in fibromyalgia.[15]

There are many questionnaires designed to detect PN according to its highly variable causes (Table 1). These questionnaires emphasize either neuropathic pain, sensory symptoms, or function limitations, and they differ in the number of items, layout, and structure.[16]

Rheumatic patients frequently attend clinical practice due to numbness or neuropathic pain, and these symptoms are sometimes difficult to distinguish from pain attributed to peripheral inflammation of the joints or other rheumatic symptoms. Recognizing these patients as a distinct subgroup will allow clinicians to improve the management of their symptoms.[17-19]

PN are widely recognized in connective tissue diseases, and are probably secondary to nerve inflammation or vasculitis-mediated microcirculation alterations.[20] The neuropathic distribution and pathophysiological type are known to be variable among RD. In systemic lupus erythematosus (SLE), 1%-13% of the patients had PN, particularly polyneuropathy (55%), and 12% cranial nerves disorders; in Sjögren syndrome, PN ranges between 2%-64%, and the most frequent manifestation is purely sensorial (25%-60%).[21] In RA patients, PN secondary to entrapment occurs in 20%-70%, sensorial PNP in 20%, and sensory-motor PNP in 10% of cases. MNP by entrapment has been reported in 3% of patients with systemic sclerosis.[22,23]

The main aim of this study was to explore the frequency of neuropathic symptoms with three neuropathy questionnaires in 100 consecutive patients with rheumatic diseases, attending for the first time in an outpatient rheumatology department.

2 | METHODS

Our hospital in México City is a public healthcare system which provides partial healthcare coverage to the population. Patients frequently have low socioeconomic status. These patients were referred straight from primary healthcare centers as well as by several specialists from the same hospital.

This is a cross-sectional study where the same rheumatologist evaluated and classified the rheumatic disease in all patients who attended for the first time to the rheumatology department. If the patient met the inclusion criteria (any rheumatic disease: osteoarthritis,[24] RA,[25] SLE,[26] gout,[27] systemic sclerosis,[28] fibromyalgia,[29] ankylosing spondylitis,[30] etc) without pharmacologic treatment (at least 6 months), without chronic or metabolic diseases that affect the peripheral nerve (diabetes, hypothyroidism, Charcot-Marie-Tooth, chronic demyelinating inflammatory polineuropathy, nerve traumatic injury, etc), he or she was invited to participate in this project. All who accepted signed informed consent forms and were referred to the physiatrist to perform clinical evaluation via NQ and NCS. Also we included 10 healthy subjects without chronic, metabolic or traumatic diseases, no substance abuse (alcoholism, smoking or toxic substances). The Hospital General de México Ethics and Research Committees approved this project (ID project: DI/15/404/03/011, approved 6 March, 2015) and was conducted during the period March 2015 until March 2016.

2.1 | Clinical evaluation

Physical evaluation included Semmens Weinstein monofilament testing by nerve territories (lower extremities: sural, superficial peroneal, and saphenous nerves; upper extremities: median, ulnar, and radial nerves), and a 128 Hz tuning fork in lower extremities (feet, knees, and hips) and upper extremities (hands, wrists, elbows, and shoulders). We reported normal or abnormal if the patient felt or did not feel the stimulus.

2.2 | Questionnaires

All patients answered three questionnaires: DN4, LANSS, and MNSI.

The DN4 is a clinician-administered questionnaire that consists of 10 items; seven items are clinical questions related to pain quality, and three items are based on physical examination (ie presence or absence of touch or pinprick hypoesthesia and tactile allodynia). The

TABLE 1 Peripheral neuropathy: classification, etiology and damage

Distribution	Etiology[a]	Peripheral neuropathies[b]	Damage
Focal	Traumatic Focal compression Entrapment	Mononeuropathy	Neurapraxia Axonotmesis Neurotmesis
Systemic	Vasculitic [V]	Mononeuropathy multiplex [V, M]	Axonal loss Demyelination
	Metabolic [M]	Polyneuropathy [M, T, I, A,H]	
	Toxic [T]		
	Infection [I]	Polyradiculopathy [M, T, A, H]	
	Autoimmunity [A]		
	Hereditary [H]	Small fiber neuropathy [M, A, H]	Unknown

[a]Letters [ ] represent proposed mechanisms as etiology.
[b]Letters [ ] represent the mechanisms described for each neuropathy.

questionnaire is positive for neuropathy if the patient has a score equal or higher to four points. The DN4 questionnaire has shown good sensitivity (83%) and specificity (90%) for neuropathy diagnosis[12] and was validated and translated into the Spanish language.[31]

The LANSS Pain Scale is an easily applied clinical instrument developed and validated to recognize neuropathic or nociceptive pain. It contains questions related to five neuropathic sensory disturbance domains, complemented by two sensory examination items. A score equal to or higher than 12 points in this instrument is defined as neuropathy. This questionnaire has good sensitivity (85%) and specificity (80%) to diagnose neuropathy,[13] and was also translated and validated in the Spanish language.[15]

Finally, the MNSI is a widely used questionnaire for diagnosing PN, mainly in patients with diabetic peripheral neuropathy. This questionnaire has 15 items related to neuropathic symptoms, and neuropathy is diagnosed with a score of 7 or higher.[14] This questionnaire has also been previously translated and validated in the Spanish language.[32]

2.3 | NCS

We randomly selected 20 out of the 100 participants and included 10 healthy subjects as controls to conduct the following NCS: sensory nerve action potential, compound motor action potential, and F-waves, using Neuromax XLTEK equipment (Natus Medical Incorporated; Oakville, ON, Canada). We used conventional techniques to determine the presence of median, ulnar, tibial, peroneal, and sural abnormalities. Topographic diagnosis was used to classify neuropathies as MNP, multiplex mononeuropathy (MMNP), or polyneuropathy (PNP).[33]

2.4 | Statistical analysis

Demographic and clinical variables were reported using descriptive statistics: means ± SD for continuous variables and proportions for

TABLE 2 Patients with rheumatic diseases: demographic and clinical variables

Demographic variables	Patients with rheumatic diseases (N = 100)
Age, y, mean (SD)	40.6 (15.7)
Gender number	
Female (%)	69
Male (%)	31
Education level, y, mean (SD)	9.4 (5.0)
Rheumatic disease diagnosis	
Systemic lupus erythematosus, %	26
Rheumatoid arthritis, %	16
Gout, %	14
Osteoarthritis, %	11
Fibromyalgia, %	7
Ankylosing spondylitis, %	6
Others, %	20
Peripheral neuropathy diagnosis	
Clinical evaluation	
Tuning fork, %	47
Monofilament, %	20
Positive questionnaires	67
DN4, %	58
LANSS, %	32
MNSI, %	59
NCS neuropathy distribution, 20 patients	
Normal, number (%)	6 (30)
Mononeuropathy, number (%)	6 (30)
Multiplex mononeuropathy, number (%)	4 (20)
Polineuropathy, number (%)	4 (20)

Abbreviations: DN4, Douleur Neuropathique en 4 Questions; LANSS, Leeds Assessment of Neuropathic Symptoms and Signs; MNSI, Michigan Neuropathy Screening Instrument.

dichotomous or nominal variables. Odds ratios were also calculated for all the symptoms that the patients reported, to determine if they had PN. SPSS for MAC (version 20) was utilized to obtain all statistical estimates.

3 | RESULTS

One hundred patients attending the rheumatology department for RD, as well as 10 healthy subjects who acted as controls for the NCS, participated in this study. These healthy controls were voluntary hospital staff members, and all of them signed informed consent forms.

All patients attended the rheumatology outpatient clinic because of rheumatic complains (pain and/or swollen joints and/or functional impairment). Sixty-nine of the patients were female. The mean age was 40.6 ± 15.7 years, and their average years of education were 9.4 ± 5.0.

The most frequent diagnoses were: SLE (26%), RA (16%), gout (14%), osteoarthritis (11%), fibromyalgia (7%), and ankylosing spondylitis (6%). Twenty percent of the sample had other less frequent diagnoses, such as enthesopathy, unspecified arthropathy, and unspecified vasculitis (20%) (Table 2).

3.1 | Clinical evaluation and questionnaires

Clinically, we diagnosed neuropathy in 52% of the patients (20% with monofilament and 47% with tuning fork). On the other hand, 67% of patients had positive questionnaires for neuropathy (58% were positive in the DN4 questionnaire, 59% in the MNSI, and 32% in the LANSS). Mean questionnaire scores were: 4.4 ± 3.9 for the DN4 (median = 4; interquartile range [IQR] = 1-7), 9.6 ± 6.9 for the LANSS (median = 8.5; IQR = 5-14) and 7.0 ± 4.0 for the MNSI (median = 7; IQR = 3-10). All questionnaires showed high correlation among them (LANSS/DN4 r = .80, P < .001, LANSS/MNSI r = .78, P < .001 and DN4/MNSI r = .86, P < .001). None of the healthy subjects were positive for neuropathy according to the questionnaires (mean DN4 = 0.5 ± 0.97, mean LANSS = 2 ± 2.58, and mean MNSI = 1.5 ± 2.01).

3.2 | NCS

The 20 randomly selected patients who received a NCS had variable scores in their questionnaires and diverse types of RD. Fourteen out of 20 (70%) of the patients had abnormal NCS. All SLE patients (n = 3), half the patients with RA (n = 2), and most patients with fibromyalgia (n = 4) had abnormal NCS. The most frequent type of neuropathy was median nerve MNP (n = 6). MNM and PNP were found in four patients each.

The following neuropathy distribution was observed in each RD type: (a) RA, 1 MMNP and 1 PNP; (b) SLE, 1 median nerve MNP, 1 MMNP and 1 PNP; (c) fibromyalgia: 2 median nerve MNP and 2 MMNP; (d) gout: 1 PNP; and (e) osteoarthritis: 2 median nerve MNP and 1 PNP. One patient with an unspecified arthropathy had a median nerve MNP. All controls had normal NCS (Table 3).

3.3 | Neuropathy risk according to presence of symptoms

We employed all patient data and control subjects to calculate the odds ratios (OR) to present neuropathy according to some of the symptoms and functional characteristics, and we determined neuropathy if the patient was positive in the questionnaires. Difficulty walking (OR = 42.0, CI: 5.1-345.1), "pricking" sensations (OR = 28.6, CI: 2.9-283.1]), "electric shock" sensation (OR = 27.0, CI: 2.7-269.5), and "burning" sensation (OR = 27.0, CI: 2.7-269.5), were all positively associated with presenting neuropathy. The tuning fork clinical test showed a high OR for neuropathy, as defined by NCS, when patients reported no sensation during this test (OR = 25.6, CI: 5.02-602.1).

TABLE 3 Neuropathic diagnosis according to questionnaires and NCS in rheumatic diseases

	Fibromyalgia n = 5	Rheumatoid arthritis n = 4	Gout n = 4	SLE n = 3	Osteoarthritis n = 3	Others n = 1	Healthy subjects n = 10
Questionnaires							
MNS+	4	2	2	3	3	1	0
DN4+	4	2	1	3	2	1	0
LANSS+	2	1	1	1	2	1	0
NCS+	4/5	2/4	1/4	3/3	3/3	1/1	0/10
Neuropathic diagnosis							
MNP	2	0	0	1	2	1	0
MMNP	2	1	0	1	0	0	0
PNP	0	1	1	1	1	0	0

Abbreviations: DN4, Douleur Neuropathique en 4 Questions; LANSS, Leeds Assessment of Neuropathic Symptoms and Signs; MNSI, Michigan Neuropathy Screening Instrument; MNP, mononeuropathy; MMNP, multiplex mononeuropathy; PNP, polyneuropathy; SLE, systemic lupus erythematosus.

Questionnaires are highly predictive of abnormal NCS among rheumatic patients (DN4 positive: OR = 25.6, CI: 3.63-183.41, *P* = .001; MNSI positive: OR = 26, CI: 3.08-183.41, *P* = .001; LANSS positive: OR = 17, CI: 1.53-146.54, *P* = .001) (Table 4).

4 | DISCUSSION

According to our results, the frequency of neuropathy in the studied population with RD and symptoms is high. Between 32% and 59% of the population had PN according to three different questionnaires (32% by LANSS, 58% by DN4 and 59% by MNSI), and 70% of the patients who received NCS had abnormal results (14/20 patients).

Identifying the neurological component is decisive to adapting and customizing treatment in patients with chronic pain, so a better identification of neurological symptoms should improve the therapeutic results.[34] It is important that all the different screening tools to diagnose PN use similar descriptors to differentiate between patients with neuropathic pain or muscle-skeletal pain.[16] Our results support this affirmation, finding that 67% of patients had neuropathic symptoms and 58% were positive for neuropathy in the DN4 questionnaire, 59% in the MNSI, and 32% in the LANSS.

TABLE 4 Risk to peripheral neuropathy according to symptoms and physical evaluation in patients with rheumatic diseases

Variable	Rheumatic diseases patients N = 100	
Symptoms	**OR (95% CI)**	***P***
Difficulty walking	42 (5.1-345.1)	.001
Pricking	28.6 (2.9-283.1)	.001
Electric shocks	27 (2.7-269.5)	.001
Burning	27 (2.7-269.5)	.001
Numbness	26 (3.7-183.4)	.001
Weakness	18 (2.7-117.5)	.001
Difficulty sitting down	17.5 (2.7-114.8)	.002
Itching or stinging	17.5 (2.7-114.8)	.002
Difficulty sleeping	15.9 (2.7-95.2)	.001
Pain	15 (1.4-124.3)	.014
Painful cold	11.25 (1.1-110.5)	.033
Tingling	11 (1.9-60.6)	.005
Muscle cramps	10.8 (0.99-116.4)	.003
Dry	10.8 (1.9-59.8)	.002
Sensitive to touch	8.3 (0.84-86.2)	.033
Spots on skin	8.3 (0.84-83.2)	.033
Ulcer	8.3 (0.84-86.2)	.259
Changes to sensitivity	7 (1.1-42.46)	.044
Physical examination		
Tuning fork	55 (5.02-602.14)	.001
Monofilament	8.3 (0.83-83.16)	.004

Abbreviation: OR, odds ratio.

Median nerve compression is highly frequent in the general population, with a prevalence up to 9.2% in women and 6% in men. One in every five subjects who complains of neuropathic symptoms (ie pain, numbness, and tingling sensation in hands) is expected to have carpal tunnel syndrome, based on clinical examination and electrophysiological testing.[35] Idiopathic carpal tunnel syndrome is the most common diagnosis in patients with symptoms. However, it has been reported that the presence of rheumatic diseases, such as RA and osteoarthritis, increase the risk of presenting with mononeuropathy.[36]

In this study, we found a high frequency of median nerve neuropathy, especially in patients with osteoarthritis (66.6%) and fibromyalgia (40%). There is some association between degenerative radiocarpal and midcarpal osteoarthritis of the wrist with carpal tunnel syndrome; some degenerative changes in this articulation, like osteophytes and/or carpal collapse, could decrease available space within the carpal tunnel and could promote the onset of symptoms.[37] In patients with fibromyalgia, the observance of compression neuropathies may be connected with weight gain, musculoskeletal pain, biomechanical factors secondary to hypermobility, and increased sensitization.[38]

Polyneuropathies (ie symmetric PNP and MMNP) are generalized systemic disorders of the peripheral nervous system which can have a multitude of etiologies and concomitant disorders. There is a prevalence of approximately 5%-8% of PNP in the general population; around 46% have idiopathic etiology. They represent the commonest disorder in this disease group.[39] Consequently, all medical specialists could come across polyneuropathy patients anytime during their practice.[40] In patients with rheumatic diseases, the frequency of peripheral neuropathy is variable, around 5% to 70%, and depends on the disease type, being higher in patients with RA,[41,42] followed by Sjögren's syndrome[43] and then by SLE.[44-46]

In this study, we found a prevalence of 20% for symmetric PNP and 20% for MMNP, both being most frequent in SLE (50%), followed by RA (50%), fibromyalgia (40%), and gout (25%). To our knowledge, there are no previous reports on PNP in patients with gout except for some anecdotal evidence that gout could increase the risk of tophi-related mononeuropathies at the wrists and elbows.[47-55] We reported previously that patients with gout had a higher peripheral neuropathy frequency (65.4%) and the presence of systemic neuropathy is around of 31.5%; the variables associated with PN were higher disability, higher number of tophi, higher age, lower education level, and higher frequency of severe tophaceous gout.[56]

We are not aware of any other study reporting systemic neuropathy in patients with gout. In contrast, for patients with fibromyalgia, one study has reported the prevalence of PNP near 90%;[57] also small fiber neuropathy has been reported.[58] Despite the small numbers of patients in our study we suggest that patients with fibromyalgia and neuropathic symptoms be investigated for peripheral neuropathy.

The pathophysiology, frequency, and clinical manifestation of peripheral neuropathy are as variable as the rheumatic diseases themselves. Consequently, the diagnosis and assessment of these problems remains difficult. Nevertheless, it is important to recognize

that neurological involvement in rheumatic diseases is associated with high comorbidity, and an early assessment and diagnosis of neuropathy in this population is essential for their prompt management.[59,60] Identifying the neurological component is decisive to adapting and customizing treatment in patients with chronic pain; so better identification of neurological symptoms should improve the therapeutic results. Because the therapeutic strategies and prognoses vary depending on the type of neuropathy, a precise diagnosis is important.[61]

5 | CONCLUSION

Peripheral neuropathy occurs with high frequency in patients with rheumatic diseases; the distribution, frequency, and clinical symptoms are variable among the different types of rheumatic conditions. When the patient has a positive NQ, the rate of positive NCS for PN is higher.

CONFLICT OF INTEREST

All the authors declare they have no conflict of interest.

AUTHORS CONTRIBUTION

LLCO: participated in the conception and design of the study as well as the generation, assessments, follow up, collection, assembly, analysis and interpretation of the data. MCML: participated in the analysis and interpretation of nerve conduction studies. SFRC: participated in collection of data. SGLF: participated in the collection of data and assessment of patients. LSA, BVR and PBI: participated in the revision of the final version of the manuscript. VMJ: participated in the conception and design of the study as well as assessment of patients, drafting, revision and approval of the final version of the manuscript.

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ORIGINAL ARTICLE

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Baseline characteristics and long-term outcomes of eosinophilic fasciitis in 89 patients seen at a single center over 20 years

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Abstract

Aim: Eosinophilic fasciitis (EF) is a rare, fibrosing disorder of skin and subcutaneous tissue. This study was undertaken to describe its clinical and laboratory features and identify prognostic factors associated with outcome.

Methods: We conducted a retrospective review of all EF patients evaluated at our institution from 1 January1997 to 30 December 2016. Kaplan-Meier methods were used to determine treatment response rates over time. Potential associations between baseline characteristics and complete response were examined using Cox models adjusted for age and sex. Time-dependent covariates were used to examine treatment effects.

Results: We identified 89 EF patients, with a female-to-male ratio of 1:1. Clinical features included groove sign in 26 (29%), peau d'orange/dimpling in 22 (25%), inflammatory arthritis in 9 (10%) and muscle weakness in 9 (10%). Aldolase was elevated in 11/36 (31%). Complete response rate was 60% (95% confidence interval [CI]: 35-75) at 3 years. Diagnostic delay was inversely associated with treatment response (hazards ratio: 0.84 per 1 month increase; 95% CI: 0.73-0.98). No baseline characteristics correlated with treatment response, but a trend toward positive association of elevated aldolase, hypergammaglobulinemia and presence of hematologic disorders was noted. Methotrexate was the most commonly used immunosuppressant in 79%, hydroxychloroquine in 45%, mycophenolate mofetil in 18% and azathioprine in 8%. No single immunosuppressant agent was associated with a superior response during treatment.

Conclusions: EF is characterized by relatively high response rates. Consensus diagnostic criteria, standardized management algorithms, and large prospective multi-center cohorts are needed to develop an evidence-directed approach to this challenging condition.

KEYWORDS
eosinophilia, eosinophilic fasciitis, sclerosing disorder, thickened skin

1 | INTRODUCTION

Eosinophilic fasciitis (EF), first described by Shulman et al in 1974,[1,2] is a rare disorder characterized by erythema and edema of skin and subcutaneous tissues, followed by induration of the affected areas. Symmetric induration of bilateral extremities is the typical presentation, but unilateral and/or truncal disease may occur. The etiology is unknown but onset may be preceded by strenuous exercise, trauma, infection, medication, systemic autoimmune condition, and even malignancy.[3-6] Absence of systemic involvement, sclerodactyly, and Raynaud phenomenon differentiate EF from systemic sclerosis. Although in the spectrum of fibrosing skin disorders along with morphea profunda, the presentation of EF is clinically distinct, and there are histopathologic features that may help differentiate the 2 disorders.[7] Diagnosis generally depends on biopsy confirmation of the clinical impression, but there are no widely accepted diagnostic or classification criteria. Most published data on EF consist of retrospective case series. We undertook the present study to describe the clinical and laboratory features of EF and identify prognostic factors associated with disease outcomes in a large cohort of patients seen at our tertiary referral center.

2 | METHODS

We identified study subjects by searching the medical records of patients for the term "eosinophilic fasciitis" and who were seen at our institution between 1 January 1997, and 31 December 2016. Patients were included only if they authorized their inclusion in retrospective research studies. Diagnosis of EF was made on suggestive clinical and laboratory findings and supported by biopsy or imaging abnormalities. Patients with systemic sclerosis, graft-versus-host disease, or radiation-induced skin fibrosis were excluded. Patients with concurrent morphea were included, provided that clinical features of EF also were present at the time of evaluation.

A standardized data collection form was used to record clinical features, laboratory and histopathologic findings at the time of initial evaluation at our institution. Baseline variables included age, gender, pertinent physical exam findings and the extent of skin involvement: upper and lower extremities (proximal to elbows or distal to wrists; proximal to knees or distal to ankles respectively), chest, upper, lower abdomen, back and face. Presence of peau d'orange/dimpling (induration of the skin with a dimpling/rippling/puckering or "pseudo-cellulite" appearance) and groove sign (linear depression where veins appear to be sunken within the indurated skin) were recorded. The methods of diagnosis, by biopsy, imaging, or clinical evaluation, were assessed. Laboratory studies abstracted included complete blood count, peripheral eosinophilia, erythrocyte sedimentation rate (ESR), C-reactive protein (CRP), muscle enzymes and serum autoantibodies if performed. Magnetic resonance imaging (MRI) showing presence of myositis, with thickening of fascia with increased T2 signal and enhancement after contrast administration, was noted. Skin biopsies were examined for: the degree, nature, and distribution of inflammation; presence of eosinophils, plasma cells, and edema in the fascia; sclerosis; and eccrine trapping. Newly cut sections obtained from the formalin-fixed, paraffin-embedded tissue blocks were stained with CD34, CD123, and Verhoeff-Van Gieson. All medications used for treatment of EF, glucocorticoids or other immunosuppressive medication used prior to initial evaluation at our institution were recorded. The progress of the disease was determined at each subsequent visit based on evaluation by the treating physician.

Complete response was defined as complete resolution of skin thickening per clinical evaluation, and normalization of acute phase reactants and eosinophilia. Partial response was defined as improved skin thickening in some areas but not all, and worsening or no improvement was recorded as resistant disease. Prognostic analyses were performed in patients who were seen within 1 year of diagnosis at our institution.

The study was approved by our institution's Institutional Review Board.

2.1 | Statistical analysis

Descriptive statistics (means, percentages, etc) were used to summarize the data. Kaplan-Meier methods were used to determine response and recurrence rates over time. Potential associations between baseline characteristics and complete response were examined using Cox models adjusted for age and gender. Time-dependent covariates were used to examine treatment effects. Analyses were performed using SAS version 9.4 (SAS Institute Inc) and R 3.4.2 (R Foundation for Statistical Computing).

3 | RESULTS

EF was diagnosed in 89 patients. The mean age at diagnosis was 51.5 years (range 12-78 years) (Table 1). The female-to-male ratio was 1:1. Median time to diagnosis from symptom onset was 6 months (range 1-45 months). The majority of patients (79; 89%) were diagnosed on the basis of clinical features and biopsy, 3 on clinical and MRI abnormalities, and 7 (8%) on clinical presentation alone. Suspected initial triggers for the diseases were serious illness (n = 1), L-tryptophan (n = 1) and vigorous exercise (n = 19). There were no patients who reported exposure to adulterated oil or infectious triggers. The disease course was rapidly progressive in 64 (83%).

Coexistent morphea was seen in only 3% of patients. Hematologic disorders were diagnosed in 9 patients (10%), including angio-immunoblastic T-cell lymphoma (2), T-cell large granular lymphocytic leukemia (1), acute lymphoblastic leukemia (1), chronic lymphocytic leukemia (1), aplastic anemia (1), lymphocytic-variant hypereosinophilia (1), low-grade lymphoproliferative disorder (1) and T-cell clonal arrangement (1). Diagnosis of hematologic disorder and EF was concurrent in 3 patients, made prior to EF in 3 patients (mean 28 months, range 1-48 months) and followed the diagnosis of EF in 3 (mean 19 months, range 14-26 months). One patient with angio-immunoblastic T-cell lymphoma treated 4 years earlier developed EF concurrent with recurrence of the disease.

TABLE 1 Baseline characteristics of 89 patients with eosinophilic fasciitis

Characteristic	Follow-up cohort (N = 38)	Total cohort (N = 89)
Age at diagnosis, y, mean (SD)	52.8 (14.8)	51.5 (16.2)
Gender, female	23 (61%)	44 (49%)
Length of follow-up, y, median (range)	2.2 (0.4-18.5)	2.2 (0.2-18.5)
Time from symptom onset to diagnosis, mo, median (range)	6.0 (1.0-45.0)	6.0 (1.0-45.0)
Groove sign, specifically mentioned in documentation	13 (34%)	26 (29%)
Peau d'orange, specifically mentioned in documentation	11 (29%)	22 (25%)
Myalgias	7 (18%)	10 (11%)
Muscle weakness	4 (11%)	9 (10%)
Inflammatory arthritis	6 (16%)	9 (10%)
Skin involvement of upper extremity	35 (92%)	82 (92%)
Skin involvement of lower extremity	34 (89%)	77 (87%)
Skin involvement of the trunk	13 (34%)	33 (37%)
Associated malignancy	7 (18%)	10 (11%)
Associated hematologic disorder	7 (18%)	11 (12%)
Laboratory values, n positive/n tested (%)		
Elevated ESR, >29 mm/1 h for females, >22 mm/1 h for males	11/33 (33%)	19/76 (25%)
Abnormal CRP, ≥8 mg/L	18/28 (64%)	36/61 (59%)
Eosinophilia, ≥0.5 × 10^9/mL or ≥7% of total leukocytes	21/36 (58%)	40/79 (51%)
Elevated aldolase, >7.7 units	6/15 (40%)	11/36 (31%)
Polyclonal hypergammaglobulinemia	9/29 (31%)	16/56 (29%)
Elevated ANA, titer ≥1:320 and/or ELISA ≥3 units	4/38 (11%)	7/72 (10%)
Anti-dsDNA	0/11 (0%)	1/23 (4%)
Anti-SSA	1/36 (3%)	2/68 (3%)
Anti-SSB	1/36 (3%)	2/67 (3%)
Anti-Smith	0/36 (0%)	1/66 (2%)
Anti-RNP	1/36 (3%)	2/66 (3%)
Anti-Scl-70	1/38 (3%)	2/71 (3%)
ACPA	1/13 (8%)	4/22 (18%)
EMG consistent with inflammatory myositis	4/11 (36%)	6/18 (33%)

Abbreviations: ACPA, anti-citrullinated protein antibodies; ANA, antinuclear antibodies; CRP, C-reactive protein; dsDNA, double-stranded DNA; ELISA, enzyme-linked immunosorbent assay; EMG, electromyelogram; ESR, erythrocyte sedimentation rate; RNP, ribonuclear protein; SCL-70, scleroderma 70; SSA, Sjögren's syndrome A; SSB, Sjögren's syndrome B.

Other malignancies seen in 7 cases were melanoma (1), testicular seminoma (1), bladder (1), skin cancer (1), prostate (2), and thymoma (1). Concurrent autoimmune diseases occurred in 5 patients, namely, rheumatoid arthritis (2), eosinophilic enteritis (1), Sjögren's syndrome, Hashimoto and celiac disease (1), autoimmune neuropathy and Raynaud phenomenon (1).

3.1 | Physical exam, laboratory features and imaging

The upper extremities were involved in 82 (92%), and lower extremities in 77 patients (87%); truncal involvement was noted in 33 (37%). Isolated upper extremity involvement was seen in 8 (9%) and lower extremity involvement alone in 5 (6%). Groove sign was noted in 26 (29%), (Figure 1) and peau d'orange/dimpling-like changes in 22 (25%) patients. Nine patients (10%) had active inflammatory arthritis (oligoarticular in all) at the time of initial EF evaluation. Joint contractures occurred in 42 (47%).

The median absolute eosinophil count was 0.4 × 10^9/mL (range 0.0-14.4) and peripheral eosinophilia (defined as greater than 0.5 × 10^9/mL or 7% of total leukocytes) was noted in 40 patients (51%). Eleven patients (12%) received steroids prior to diagnosis. Eosinophil counts were available for 8 of these patients and elevated in all. Median ESR was 12.0 mm/1 h (range 0.0-122.0) and CRP 11.6 mg/L (range 0.0-108.3). Elevated ESR was seen in 19/76 (25%) and elevated CRP in 36/61 (59%). Creatine kinase and aldolase were elevated in 2/45 (4%) and 11/36 (31%), respectively. Serum protein electrophoresis (SPEP) showed hypergammaglobulinemia (gamma globulin >1.6 g/dL) in 19/56 (34%). Three of these patients had a monoclonal gammopathy. The monoclonal protein was IgM kappa in 1 patient and IgG kappa in 2 patients.

Low complement C3 (<75 mg/dL) was seen in 1/19 (5%) and low C4 (<14 mg/dL) in 2/20 (10%) patients. High titer positive antinuclear antibodies (≥1:320 or ≥3 units by enzyme-linked immunosorbent assay) was seen in 7/72 (10%), 2 of whom had a positive scleroderma-70 (Scl-70) and 2 had positive Sjögren's syndrome A (SSA) and Sjögren's syndrome B (SSB) antibodies. The titer of anti-Scl-70 was low at 1.4 units (normal <1). The treating physician did not feel there were any features of scleroderma and the clinical examination, biopsy and treatment response supported a diagnosis of EF. Anti-cyclic citrullinated protein antibody was tested in 22 patients and positive in 4 (including 1 with known rheumatoid arthritis).

MRI was performed on 18 patients. Findings included increased T2 signal in the superficial and deep fascia (16/18) and in the muscle (10/18). Electromyogram (EMG) was performed in 18 patients, and showed inflammatory myopathy in 6/18 (33%). Skin biopsies were available in 76 patients and only muscle biopsies in 3 patients. Histopathologic evidence of eosinophilia in subcutaneous tissue was noted in biopsy specimens from 42 patients (47%). Eleven patients had muscles biopsies, 9 consistent with inflammatory myopathy.

The mean time from symptom onset to diagnosis was 6.2 months (range 2-15) in patients with muscle weakness and not different from those without (8.6 months, range 1.0-45.0, P = .33).

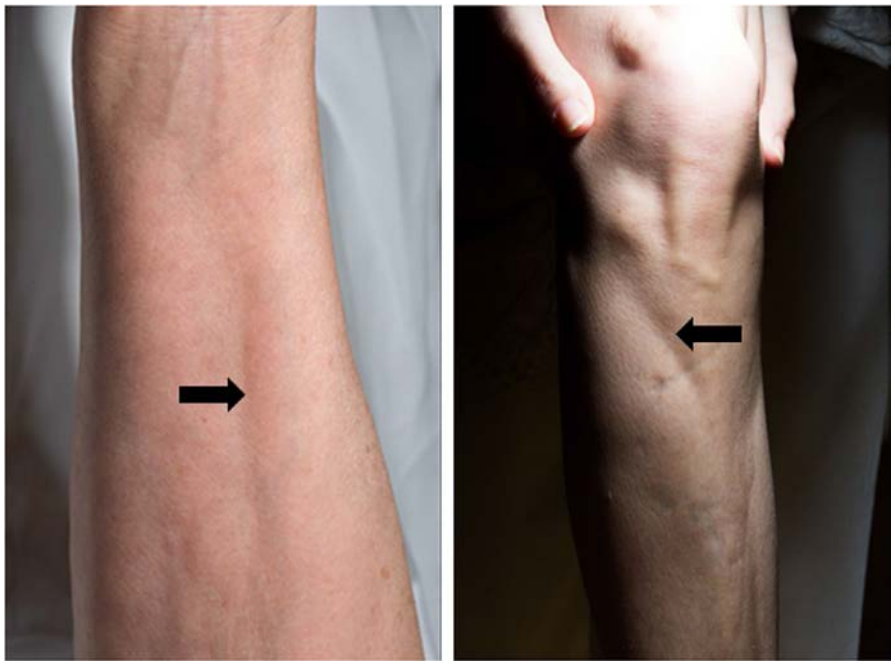

FIGURE 1 Groove sign: Fibrosis of connective tissue around the veins which spares the dermis and epidermis results in superficial layers of skin bowing inward (arrow) which is pronounced when the limb is elevated causing venous pressure to fall

3.2 | Treatment and follow-up

The median follow-up was 2.2 years (interquartile range 0.2-18.5) among 89 patients with at least 1 return visit. Of those, 38 were initially seen at our institution within 1 year of diagnosis, and were included in outcome and prognosis analysis. By 3 years, 60% (95% confidence interval [CI] 35-75) had achieved a complete response with resolution of skin thickening (Figure 2). Treatment included glucocorticoid monotherapy in 4 patients. Methotrexate was the most commonly used immunosuppressant in 79%, hydroxychloroquine in 45%, mycophenolate mofetil in 18% and azathioprine in 8%. The maximum dose of methotrexate was 20 mg once weekly (median, range 7.5-30 mg). At the last follow-up visit, complete response was seen in 39% on methotrexate, 44% on hydroxychloroquine, 67% on mycophenolate mofetil and 25% on azathioprine. No single immunosuppressant agent was associated with a superior response during treatment (Table 2).

Other agents that were used included imatinib (4), cimetidine (3), lefluonamide (2), sulfasalazine (2), and adalimumab, rituximab, intravenous immunoglobulin, dapsone, cyclosporine, thalidomide, everolimus and cyclosporine (1 each). Psoralen and ultraviolet A (PUVA) therapy were administered to 2, UVA-1 to 2 patients and extracorporeal photopheresis to 2. Of the patients treated with imatinib, 1 patient had no response, 1 patient stopped due to abdominal side effects, and 1 reportedly had a complete response.

Table 3 shows the prognostic factors tested for correlation with treatment remission. Elevated aldolase (hazards ratio [HR] 9.37, 95% CI 0.94-93.28), polyclonal hypergammaglobulinemia (HR 5.65, 95% CI 1.37-23.22) and h/o hematologic malignancy (HR, 10.20, 95% CI 2.08-49.93) showed a positive association with complete response with HR > 3, but this did not reach statistical significance. Symptom duration prior to diagnosis was inversely

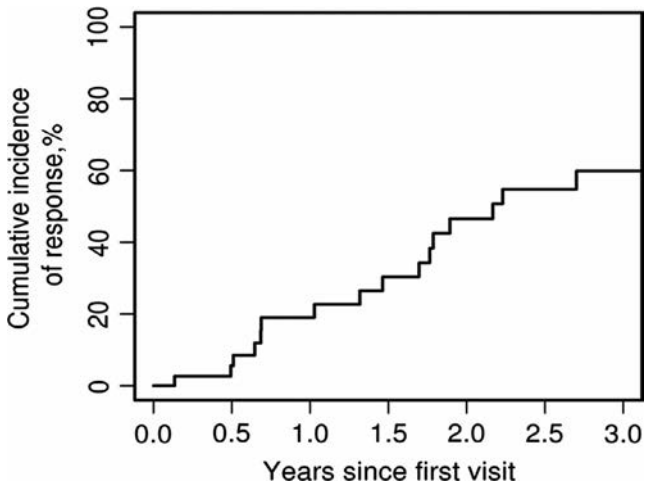

FIGURE 2 Cumulative incidence of complete response

associated with treatment response (HR 0.84 per 1 month increase; 95% CI: 0.73-0.98; P = .022). We did not find any association between the outcomes and age, arthritis, extent or type of skin involvement, elevated acute phase reactants, eosinophilia, and complement levels (data not shown). Eight patients died during the follow-up period. One patient died of a bowel perforation, and another from an apparent reaction to blood. Cause of death was not known for 6 patients.

4 | DISCUSSION

Prior to this study, most information about the features of EF was derived from small retrospective series, and disease rarity

TABLE 2 Association between treatments (time-dependent covariates) and first complete response/resolution (n = 18 events), first complete or partial response (n = 36 events) among 38 patients with follow-up at Mayo and initial presentation within 1 year of diagnosis of eosinophilic fasciitis

	Complete response		Complete or partial response	
Treatment	Hazard ratio[a] (95% CI)	*P* value	Hazard ratio[a] (95% CI)	*P* value
Exposure				
MTX	0.41 (0.14-1.19)	.10	1.01 (0.46-2.24)	.98
HCQ	0.75 (0.28-2.04)	.58	0.84 (0.41-1.72)	.63
MMF	0.74 (0.14-4.11)	.74	0.55 (0.19-1.64)	.29
AZA	0.43 (0.06-3.31)	.41	1.86 (0.54-6.42)	.33
Current use				
MTX	0.43 (0.16-1.15)	.09	0.75 (0.36-1.54)	.38
HCQ	0.59 (0.20-1.74)	.34	0.60 (0.27-1.33)	.21
MMF	1.01 (0.12-8.95)	.99	0.23 (0.03-1.81)	.16
AZA	—	.99	1.86 (0.54-6.42)	.33
MTX, HCQ, MMF or AZA	0.31 (0.10-0.91)	.033	0.55 (0.22-1.36)	.20

Abbreviations: AZA, azathioprine; HCQ, hydroxychloroquine; MMF, mycophenolate mofetil; MTX, methotrexate.

[a]Adjusted for age and gender.

TABLE 3 Association between risk factors of interest at initial presentation and first complete response (n = 18 events) among 38 patients with initial presentation within 1 year of diagnosis of eosinophilic fasciitis

Characteristic	Complete response Hazard ratio[a] (95% CI)
Age, per 10 y increase	1.01 (0.70-1.46)
Symptom duration from onset to diagnosis, per 1 mo increase	0.84 (0.73-0.98)
Inflammatory arthritis	2.30 (0.72-7.39)
Elevated ESR	1.46 (0.46-4.65)
Abnormal CRP	0.95 (0.34-2.63)
Eosinophilia[b]	0.87 (0.32-2.34)
Elevated aldolase >7.7 units	9.37 (0.94-93.28)
Polyclonal hypergammaglobulinemia	
vs normal SPEP – excluding not tested	3.25 (1.03-10.24)
vs normal – adjusted for testing ordering	5.65 (1.37-23.22)
EMG consistent with inflammatory myositis	1.67 (0.06-47.21)
Inflammatory myopathy on muscle biopsy	2.32 (0.61-8.84)
History of hematologic malignancy	10.20 (2.08-49.93)

Abbreviations: CRP, C-reactive protein (≥8 mg/L); EMG, electromyogram; ESR, erythrocyte sedimentation rate (≤29 mm/1 h for females, ≤22 mm/1 h for males); SPEP, serum protein electrophoresis.

[a]Adjusted for age and gender.

[b] ≥0.5×10^9/mL or ≥7% of total leukocytes.

makes identification of prognostic factors difficult. The present study, the largest EF cohort to date, was undertaken to describe clinical and laboratory features and determine prognostic factors for outcomes in EF. Although we did not find any features that significantly predicted complete response, a trend toward association of good outcome with polyclonal hypergammaglobulinemia, elevated aldolase and the presence of hematologic malignancy was noted. Hypergammaglobulinemia seen earlier in disease course normalizes during treatment; it can be speculated that elevated aldolase from muscle involvement may also cause patients to seek early attention. Alternately, these features may identify a subset of patients with heightened immune activation or biologic pathways associated with greater response to immunosuppressive (IS) therapy.

Some studies have shown treatment resistance in patients with hematological disorders unless the underlying blood disorder is corrected.[8] Hematologic malignancies that have been described include thrombocytopenic purpura, myelodysplastic syndrome, myeloproliferative disorder, multiple myeloma, Hodgkin disease, peripheral T-cell lymphoma, chronic lymphocytic leukemia, aplastic anemia and myelomonocytic leukemia. Aplastic anemia, the most common hematologic disorder associated with EF, is usually seen in older men. In a series of 23 patients, none achieved remission of EF when treated with corticosteroid monotherapy without also receiving therapy for aplastic anemia; 67% experienced remission or improvement of their EF after receiving first-line therapies for aplastic anemia.[9] However, not all studies have found an adverse prognostic implication of underlying hematological disorder.[10] In a review of 88 patients, no association of residual fibrosis with hematological disorder was noted.[11] How hematological disorders contribute to EF pathogenesis or resistance to recovery is not known. Postulated mechanisms include elaboration of cytokines by T cells like interleukin (IL)-3, IL-5 and granulocyte-macrophage colony-stimulating factor (GM-CSF) that induce eosinophilia, common immune-mediated pathology with antibodies against hematopoietic stem cells and colony-forming

GM (CFU-GM), burst-forming unit-erythroid and CFU-erythroid and so on.

We show that diagnostic delay is associated with lower likelihood of response. Several series have shown adverse outcomes with delayed diagnosis. A diagnostic delay of >6 months was 14.7 times more likely to be associated with poor outcomes and in another study correlated negatively with physician assessment of damage (but did not reach statistical significance).[6,12] Wright et al[13] showed that treatment within 6 months of diagnosis generally led to better outcomes. The early inflammatory stage of EF may be treatment responsive, while late-stage fibrosis may be treatment resistant. Therefore, we interpret from the known pathogenesis and the observation that early diagnosis correlates with better outcomes that early disease recognition may improve patient outcomes. Imaging modalities like ultrasound, positron emission tomography (PET) and MRI may provide early diagnosis and assessment of disease activity.[14] Berianu et al reported a patient who had symptoms and signs affecting only the left side of the body, but MRI showed bilaterally symmetrical disease.[15] This indicates that MRI may show changes before they are clinically apparent and that the disease can be more extensive than appreciated on clinical exam. PET-computed tomography may have the advantage of excluding the rare chance of an underlying malignancy. The role of imaging in early diagnostic workup warrants further study. Dermal and subcutaneous sclerosis may be reversible in some patients and aggressive therapy should not be withheld even in patients presenting late.[16]

EF is usually treated with a combination of corticosteroids and IS or immunomodulatory medications. Steroid monotherapy and methylprednisolone pulses have been used with good responses.[6] However, a large study that included 64 patients from 3 centers showed more complete responses with the combination of glucocorticoids and methotrexate (64%) vs glucocorticoid monotherapy (30%) or with other combinations (29%).[13] We are unable to comment on responses to steroid monotherapy as the majority of our patients were on combination IS therapy. Methotrexate, hydroxychloroquine, azathioprine and mycophenolate mofetil were the commonly used IS agents and we did not find any particular agent to be superior. Use of any combination therapy showed a lesser likelihood of response which was not statistically significant. However, this finding is potentially influenced by channeling bias where patients with severe conditions tend to receive stronger therapy. Similar to our findings, in a retrospective series, treatment failures were higher in the IS group at 29% vs 12% in glucocorticoids alone and confounding by indication as discussed by the authors, could not be excluded.[6] Prospective studies are needed, guided by standardized protocols and better risk stratification, to determine the optimal combination therapy.

Two other studies have looked at factors affecting outcomes.[11,12] Increased CRP levels, neck and truncal involvement, prolonged time to remission, presence of dermal sclerosis, age <12 years and concurrent morphea, were associated with adverse outcomes. The presence of concurrent morphea is significantly lower in our series compared to others. This likely reflects differences in practice and diagnostic assessment. Our study included only adult patients. We did not find any prognostic associations with age, extent or type of skin involvement, elevated acute phase reactants, eosinophilia, or complement levels.

Our cohort is similar to previously described series in many ways. The average age of onset, prolonged time from symptom onset to diagnosis, and frequency of eosinophilia align with all other previously published cohorts.[4,6,12,13,15] The 1:1 female-to-male ratio seen here approximates the ratios reported by some,[4,6,15] although others have reported a female predominance closer to 2:1.[5,12,13,17] Inflammatory arthritis has been described as a clinical feature seen in EF, and was also seen in this cohort, although at a lower rate than in some previous reports.[4,5] Peripheral blood eosinophilia is not a consistent feature even in patients who have not been treated with glucocorticoids. CRP was elevated in a greater proportion than ESR. The reported rate of complete response is 60%-69% and similar in our study.

The histological features of a subset of these patients have previously been described in detail.[7] This study noted there were no pathognomonic histopathologic features of EF but rather features that may be supportive in the right clinical setting. There is considerable variability in biopsy features, which is based on the age of the clinical lesion biopsied, anatomic location from which it was derived, whether the patient has been treated or not, and so on. The present study was focused on clinical features, treatment and outcomes and it was beyond the scope of this study to assess histopathologic features.

Our study has limitations. The natural heterogeneity of the EF disease course and differences in treatment potentially obscure prognostic signals and conclusions regarding management. The lack of objective measures of disease activity for EF also made determination of disease trajectory ambiguous in some cases. In addition, the nature of our tertiary referral practice may have imparted selection bias. The rarity of EF has made it difficult to describe its full breadth of presentation, and to rigorously evaluate potential treatments. Prospective studies with standardized algorithms may decrease some of the heterogeneity, and allow for definition of additional prognostic factors.

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AUTHOR CONTRIBUTIONS

Robert L Mango, Kubra Bugdayli: study design, data acquisition, data analysis, manuscript writing. Cynthia S. Crowson: study design and data analysis. Lisa A. Drage, David A. Wetter, Julia S. Lehman, Margot S. Peters and Mark D Davis: study design, manuscript writing. Vaidehi R. Chowdhary: study design, data acquisition, data analysis, manuscript writing.

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ORIGINAL ARTICLE

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Predictive factors for work-day loss in Behçet's syndrome: A multi-center study

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Abstract

Objective: The aim of this multi-center study was to assess predictive factors for work-day loss as an indirect cost element in Behçet's syndrome (BS).

Methods: In this cross-sectional, multi-center study, 834 BS patients (F/M: 441/393, age mean: 38.4 ± 10.9 years) were included. Data were collected by a questionnaire regarding treatment protocols, disease duration, smoking pattern, frequency of medical visits during the previous year and self-reported work-day loss during the previous year.

Results: Work-day loss was observed in 16.2% of patients (M/F: 103/32). The percentages of being a smoker (81.8%), using immunosuppressive (IS) medications (82%), and having disease duration <5 years (74%) were higher in male patients with work-day

loss ($P < .05$). The majority of males (90.9%) had more than four clinic visits during the previous year. Moreover, the mean work-day loss (30.8 ± 57.7 days) was higher in patients with vascular involvement (56.1 ± 85.9) than those without (26.4 ± 50.6 days) ($P = .046$). In addition, increased frequency of ocular involvement (25.9%) was also observed in patients with work-day loss compared to others (8.6%) ($P = .059$).

Conclusion: Work-day loss was associated with both vascular and ocular involvement. Close associations were observed among male gender, early period of the disease, frequent medical visits, being a smoker and treatment with IS medications in patients with work-day loss.

KEYWORDS

Behçet's disease, ocular involvement, vascular involvement, work-day loss

1 | INTRODUCTION

The costs of healthcare are categorized as direct or indirect costs. Direct costs are linked with the use of healthcare resources whereas indirect costs are various. In this perspective, work limitation as an indirect cost element is a critical issue for health policies. It has a significant impact on economic life of both employed patients and their employers.[1-5] On this basis, it is necessary to define work limitation-related factors in patients with chronic diseases to improve work performance of patients.[2,6-16]

Behçet's syndrome (BS) is a chronic disease presenting as mild disease course regarding mucocutaneous manifestations and musculoskeletal involvement as well as severe disease course with ocular, vascular, central nervous system and gastrointestinal involvement. A severe disease course is commonly seen in males and treated with immunosuppressive medications (IS).[17,18] Occurrence of unpredictable relapses and life-threatening conditions are crucial components of the disease pattern; workplace problems could be seen in patients with severe organ involvement, especially young males.[9,19-32] Since workplace problems are thought to be an indicator to modify treatment protocols of employed patients for physicians, the evaluation of employment life of BS patients is critical in disease management.[2,24,25] In this perspective, the mean sick leave days or disabled days as workdays lost for the last year were reported as 173 ± 79 for neurological involvement, 134 ± 87 for ocular involvement and 75 ± 100 for vascular involvement in BS in a previous study.[24] When the work performance is previously evaluated by using work productivity and activity impairment (WPAI) scale in BS patients, absenteeism, presenteeism and overall work impairment are assessed in BS patients in a 7-day short period. Weekly working hours are found to be low in BS patients with ocular involvement.[2] In addition, absenteeism evaluated by WPAI is found to be associated with disease activity in BS.[25] However, risk factors for work-day loss have not been previously studied in a long-term assessment in BS patients. Thus, we designed this multi-center study to assess predictive factors for work-day loss as a productivity measure within the previous year in BS.

Since BS has a heterogeneous clinical presentation, disease-related factors and personal factors like age, gender and work-related factors like working hours might be thought as major factors influencing long-term work limitations.[2] Consequently, we aimed to find out whether nature of the disease and personal factors can influence work-day loss in BS patients and also the factors that can be modified to improve the outcomes in working life of BS patients.

2 | METHODS

In this cross-sectional study, 834 BS patients from 12 centers (F/M: 441/393, age mean: 38.4 ± 10.9 years) diagnosed by the International Study Group criteria[26] were included. In the clinical examination, data were collected using a structured questionnaire regarding self-reported work-day loss, treatment protocols, disease duration, smoking pattern and frequency of medical visits during the previous year. Self-reported work-day loss during the previous year was noted if it was related with BS. Primary outcome was to evaluate work-day loss according to organ involvement. Associations among personal factors, smoking habits and disease-related factors on work-day loss were secondary outcomes in the study.

The inclusion criteria were: >18 years of age and being under medical control for BS. Patients with other chronic conditions leading to work impairment and/or irregular medical visits were excluded from the study.

The study was performed according to the principles of the Declaration of Helsinki. It was approved by the Ethics Committee of Marmara University Medical School (14 July 2017; No: 09.2017.497) and informed consent was taken from the study group.

2.1 | Statistical analysis

Data were analyzed by using SPSS 16.0 statistic program (SPSS Inc). Chi-square test and Mann-Whitney *U* test due to non-normal

distribution of data were used in the study. $P \leq .05$ was accepted as statistically significant in the study.

3 | RESULTS

In this cross-sectional study, 834 patients were included from 12 centers in Turkey. The clinical profiles of patients are presented in Table 1. Positive pathergy reaction was observed in 57.7% of the patients (n = 481). Treatment protocols were categorized as non-immuno-suppressive (non-IS) medications regarding colchicine, sulphasalazine, nonsteroidal anti-inflammatory drugs, antibiotics (n = 501, 60.07%) for mild disease course or IS medications (n = 289, 34.65%) such as azathioprine, corticosteroids, anti-tumor necrosis factor-α and interferon-α for severe disease course in the previous year. However, 5.27% of the group (n = 44) were not using any medication.

In the whole group, the mean disease duration was found to be 9.03 ± 7.6 years. Since we aimed to evaluate the effects of early period of the disease,[19] patients were classified into two groups; disease duration less than 5 years (n = 334; 40.04%) vs ≥5 years (n = 484; 58.03%) for the analysis. Yet, no information was available for 16 patients (1.92%) diagnosed in other centers. In addition, patients were also grouped according to smoking habits as current smokers (n = 216, 25.9%) or non-smokers regarding past smokers/never smokers (n = 596, 71.5%). No response was obtained from 22 patients (2.6%).

TABLE 1 Work-day losses according to organ involvement in patients with Behçet's syndrome

	Patients with work-day loss (n = 135)		Patients without work-day loss (n = 699)	
	n	%	n	%
Organ involvement				
Oral ulcer	135	100	699	100
Genital ulcer	115	85.2	595	85.1
Cutaneous	112	83.0	521	74.5
Musculo-skeletal	69	51.1	375	53.6
Ocular[a]	35	25.9	130	8.6
Vascular	20	14.8	86	12.3
Neurological	6	4.4	28	4.01
Gastrointestinal	1	0.7	12	1.7
	Mean ± SD			
Vascular involvement (+), d[b]	56.1 ± 85.9			
Vascular involvement (−), d	26.4 ± 50.6			
Male, d[c]	31.7 ± 54.2			
Female, d	27.9 ± 68.8			

[a]Chi-square test, $P = .059$.
[b]Mann-Whitney U test, $P = .046$.
[c]Mann-Whitney U test, $P = .007$.

Number of medical visits of patients during the previous year was noted. Then, the cut-off point for the number of medical visits (≥4 medical visits [n = 90; 10.79%] vs <4 visits [n = 653; 78.29%]) was determined according to median value. Newly diagnosed patients (n = 91; 10.91%) were not coded.

The ratio of employed patients was 47.48% of the total group (n = 396; F/M: 94/302). Self-reported work-day loss was observed in 16.18% of the group (n = 135; M/F: 103/32) and 34.09% of employed patients. Clinical features of patients are presented whether work-day loss was present or not during the previous year (Table 1).

The mean work-day loss was found to be 30.8 ± 57.7 days in the group. It was higher in males (31.7 ± 54.2) compared to females (27.9 ± 68.8) ($P = .007$) (Table 1). When work-day loss was analyzed according to organ involvement, increases in the work-day loss and the number of medical visits were observed in patients with vascular involvement (M/F: 19/1; 56.1 ± 85.9 days; 5.85 ± 3.6) than without vascular involvement (M/F: 84/31; 26.4 ± 50.6 days; 3.8 ± 3.1) ($P = .046$; $P = .007$, respectively). The ratio of ocular involvement was also higher in patients with work-day loss (n = 35; M/F: 26/9; 25.9%) compared to others (n = 130; M/F: 56/74; 8.6%) ($P = .059$) (Table 1).

Disease severity score was lower in the non-IS group (4.0 ± 1.47) than the IS group (5.6 ± 2.5) ($P = .000$). In the non-IS group (n = 68), the majority of patients had mucocutaneous manifestations and musculoskeletal involvement (n = 58, 85.3%) whereas the other patients had newly diagnosed ocular involvement (n = 10, 14.7%). Regarding these, the work-day loss was significantly higher in patients treated with IS (n = 61, 47.3%) compared to non-IS use (n = 68, 52.75%) (46.29 ± 76.82 vs 18.02 ± 29.9 days; $P = .001$).

Among patients with work-day loss, the mean age, disease duration and age at disease onset were lower ($P < .05$); whereas the number of medical visits and education years were higher than the rest ($P < .05$) (Table 2).

The majority of the patients with work-day loss were males (76.3%). Moreover, smoking habits, treatment protocol, frequency of visits and disease duration were observed to be risk factors for work-day loss ($P < .05$) (Table 3). Then, these factors were analyzed according to gender. The presence of having more than four visits during the previous year (90.9%) as well as being a smoker (81.8%), using IS medications (82%), and having disease duration <5 years (74%) were higher in male patients with work-day loss ($P < .05$) (Table 4) (Figure 1).

4 | DISCUSSION

Absenteeism, loss of productivity and unemployment due to illness may be variable in chronic diseases.[2] In the present study, work-day loss-associated factors were assessed according to patient characteristics like age, gender, treatment protocols, disease duration, smoking habits and frequency of medical visits during the previous year. Male gender was found to be a risk factor for work-day loss. Male gender is a critical prognostic factor in BS, as neutrophils

TABLE 2 Socio-demographic properties and frequency of medical visits in Behçet's syndrome patients with work-day loss

	Patients with work-day loss (n = 135)	Patients without work-day loss (n = 699)	
	Mean ± SD	Mean ± SD	P[a]
Age, y	34.3 ± 8.4	39.2 ± 11.2	.000
Disease duration, y	7.04 ± 6.04	9.4 ± 7.8	.000
Age of disease onset, y	27.2 ± 7.4	29.7 ± 8.8	.009
Number of medical visit/previous year	4.2 ± 3.2	2.9 ± 2.1	.000
Education year	10.1 ± 4.03	8.4 ± 3.9	.000

[a]Mann-Whitney *U* test was used in the analysis.

TABLE 3 Gender and disease-related factors in Behçet's syndrome patients with work-day loss

		Patients with work-day loss (n = 135)		Patients without work-day loss (n = 699)		
		n	%	n	%	P[a]
Gender	Male	103	76.3	290	41.5	.000
	Female	32	23.7	409	58.5	
	Total	135	100	699	100	
Smoking habits	Non-smoker	78	58.6	518	76.3	.000
	Current Smoker	55	41.4	161	23.7	
	Total	133	100	679	100	
Treatment protocols	Non-IS	68	52.7	433	65.5	.007
	IS	61	47.3	228	34.5	
	Total	129	100	661	100	
Examination period/ previous year	<4 visits	97	74.6	556	90.7	.000
	≥4 visits	33	25.4	57	9.3	
	Total	130	100	613	100	
Disease duration	<5 y	73	54.1	261	38.2	.001
	≥5 y	62	45.9	422	61.8	
	Total	135	100	683	100	

Abbreviation: IS, immunosuppressants.

[a]Chi-square test was used in the analysis.

implicated in the pathogenesis could be activated by testosterone, the primary sex hormone in men.[17,18,22,27,28] Vascular and ocular involvements were found to be related to increased work-day loss in male patients. As expected, the use of IS medications were higher among these male patients. Thus male patients with major organ involvement requiring IS use were the risk group for increased work loss.

The work-day loss among those with vascular complaints reaches to almost 2 months during the preceding year. Vasculitis as a primary pathologic feature affects both arterial and venous systems with all sized vessels in BS and venous involvement is reported to be more common in young male patients.[29] Since vascular involvement is a severe health problem leading to mortality and morbidity,[17,19] the primary goal of treatment protocols for vascular disease is to control disease-related symptoms, increase survival and to prevent relapses in BS. Systemic IS medications are used to reduce inflammation and endothelial damage leading to the formation of thrombus. Since venous stasis, leg pain, ulcers on the leg, limitation in walking capacity and mobility are critical problems affecting daily life of patients with vascular involvement,[29] increase in work-day loss could be predicted.

When individuals were classified according to organ involvement, it was also observed that ocular involvement was higher in patients with work-day loss. Ocular involvement is a chronic sight-threating manifestation with a relapsing pattern in BS. Prevention of visual loss, improvement of visual outcomes and decrease in flares of uveitis are the main treatment goals with IS and biologics. Yet, loss of visual acuity could be seen in spite of aggressive therapy protocols.[30-34] Although limited information is available for work limitation in BS, weekly working hours is found to be lower in patients with ocular involvement in our previous study.[2]

TABLE 4 Work-day loss-related factors in Behçet's syndrome patients according to gender

		Patients with work-day loss (n = 135)		Patients without work-day loss (n = 699)		
		n	%	n	%	P^a
Current smokers	Male	45	81.8	96	59.6	.003
	Female	10	19.2	65	40.4	
	Total	55	100	161	100	
Immunosuppressant treatment protocols	Male	50	82	123	53.9	.000
	Female	11	18	105	46.1	
	Total	61	100	228	100	
≥4 medical visits/previous year	Male	30	90.9	25	43.9	—
	Female	3	9.1	32	56.1	
	Total	33	100	57	100	
Disease duration < 5 y	Male	54	74	115	41.1	.000
	Female	19	26	146	55.9	
	Total	73	100	261	100	

[a]Chi-square test was used in the analysis.

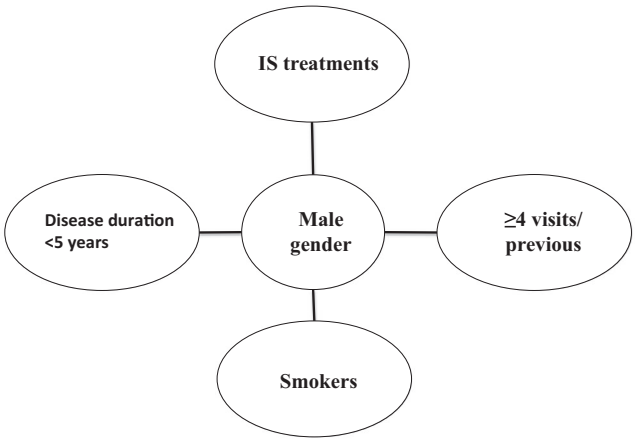

FIGURE 1 Work-day loss-related factors in patients with Behçet's syndrome

An association with frequent visits (≥4 visits during the last year) was found to be a predictive factor for work-day loss, especially in males. Frequency of visits reflects healthcare utilization in the disease management. Multiple visits from different experts are needed in patients with severe disease course such as ocular, vascular, neurological and gastrointestinal involvement due to mortality and morbidity risks.[17,19,20] Therefore, the close relationship between increase in the number of visits and work-day loss could be predicted in the severe disease spectrum.

In the present study, disease duration <5 years and being young were associated with work-day loss. Disease manifestations may not be controlled sufficiently in the early period of the disease following the diagnosis. New vascular events could be seen in one-third of the patients at 5 years.[19] Therefore, exacerbations and remissions of clinical manifestations as well as response to treatments are unpredictable in this period.[35]

Smoking was found to be another risk factor for work-day loss in our study in male patients. Smoking is a well-known risk factor for cardiovascular disease, cancer, infections, various respiratory diseases, intestinal ischemia and renal failure.[36-38] It has a significant impact on direct costs regarding healthcare resource usage as well as indirect costs associated with the decrease in work productivity. Since smoking cessation improves both health status and working life of patients,[39] it could be thought as being a part of the disease management process. Increase in weekly hours worked could be achieved by using integrated disease management programs in heterogeneous clinical manifestations.[3]

As an interesting observation, the education year was higher in patients with work-day loss. Both health problems and work environment may affect work performance.[5] Patients could be unemployed or change their jobs due to reduced work effectiveness. However, work-day loss may also be less due to "fear of job loss" although patients may feel unhealthy and do not work at full capacity.[3-5]

In chronic disease management, effective disease control aims to fulfill both the complex needs of patients as well as to reduce hospitalization and unplanned emergency visits from a health policy perspective.[40] In this perspective, patient-centered[41] and evidence-based effective management programs as well as patient's empowerment improve outcomes in patients with chronic diseases.[40] This study addressed that organ involvement, treatment protocols, disease duration and smoking pattern of employed patients are needed in clinical practice to evaluate working performance, because better outcomes in working lives are achieved by disease management and is an aspect of health policy.[25] BS patients with severe organ involvement

have problems with continuous employability and become an economic burden on society due to increases in work-day losses. More aggressive treatment protocols at acceptable medical cost levels, the modification of life-style and patient empowerment may be options to overcome this problem. In addition multidisciplinary dedicated centers providing patient care maybe helpful.

Despite the fact that our results give some clues about work limitations in BS patients, the study had some limitations. First, the work performance was evaluated by questions on patients' perspective. Second, recall bias may occur due to underestimation or overestimation of self-reported work-day loss in the 1-year period. Third, cultural differences could also affect the gender balance of employed patients. In the perspective of these limitations, further longitudinal studies are necessary to understand how the working life of patients with severe disease course is preserved with coordinated care in different patient populations with BS.

In conclusion, work-day loss as an indirect cost element was associated with vascular and ocular involvement in BS patients. Male gender, early period of the disease, frequent medical visits, being a smoker and treatment with IS medications were more frequently associated with work-day loss in patients with BS.

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ORIGINAL ARTICLE

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Contribution of HLA-B*51:01 and -A*26:01 to Behçet's disease and their clinical association in Thai patients

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Abstract

Aims: To investigate susceptible human leukocyte antigen (HLA) alleles and their associations with clinical features in Thai patients with Behçet's disease (BD).

Method: Eighteen HLA-A and 36 HLA-B alleles were determined in 42 Thai BD patients and 99 healthy controls (HCs) by reverse line blot assay, and reconfirmed by MICRO SSP assay.

Results: The BD patients had significantly higher allele frequency (AF) of HLA-B*51 than the HCs (13.10% vs 5.05%, $P = .025$). The AF of HLA-A*26, -A*26:01 and -B*51:01 also was higher and almost reached statistical significance (5.59% vs 1.52%, $P = .054$, 5.95% vs 1.52%, $P = .054$ and 10.71% vs 4.04%, $P = .051$, respectively). However, the BD patients had significantly higher AF of either HLA-A*26:01 or -B*51:01 (16.67% vs 5.56%, $P = .005$), or -A*26:01 or -B*51X (19.05% vs 6.56%, $P = .003$). The AF of HLA-B*51:01 and -B*51X increased significantly in -A*26:01 non-carrier BD patients (12.16% vs 4.17%, $P = .024$ and 14.86% vs 5.21%, $P = .019$, respectively); and that of HLA-A*26:01 was significantly higher in -B*51X non-carrier BD patients (7.58% vs 1.67%, $P = .034$). HLA-B*51:01 associated significantly with the presence of posterior uveitis and visual impairment (18.18% vs 2.50%, $P = .031$ for both conditions). HLA-B*51:01 was not observed in BD patients with gastrointestinal involvement or arthritis. Furthermore, the AF of HLA-B*51:01 was significantly higher in HLA-A*26:01 non-carrier BD patients without arthritis (17.30% vs 0%, $P = .050$).

Conclusion: HLA-B*51:01 was a susceptible allele for Thai BD patients, and associated with posterior uveitis and visual impairment. HLA-A*26:01 was another susceptible allele in HLA-B*51X non-carrier patients. The protective effect of HLA-B*51:01 on arthritis needs further investigation.

KEYWORDS

Behçet's disease, genetic susceptibility, HLA, MHC class I

1 | INTRODUCTION

Behçet's disease (BD) is a chronic systemic inflammatory disorder characterized by recurrent oral and genital ulcers, skin lesions and ocular inflammations. Furthermore, the disease can involve other tissues or organs, such as blood vessels, and nervous, gastrointestinal and articular systems. The disease has a worldwide distribution, but is more prevalent in countries along the Silk Road, from East Asia (Japan and Korea) to the Middle East and those countries around the Mediterranean basin, particularly Iran and Turkey.[1] Worldwide genetic study has shown that the disease is associated with the presence of human leukocyte antigen (HLA)-B*51, particularly -B*51:01.[2] In East Asia, other HLA loci have been found to associate with BD and they include HLA-A*02:07, -A*26:01 and -A*30:04 from Korea,[3] DRB1*14 from China,[4] and HLA-A*26:01, -A*26:02 and -B*39:01 from Japan.[5,6] In Southeast Asia, including Thailand, BD is considered an uncommon disease,[1,7] and only a few case series on its clinical features have been described from this region.[8,9] Furthermore, to the best of the authors' knowledge, genetic study in BD patients has not been reported from Southeast Asian countries.[3]

This study aimed to ascertain the HLA susceptible alleles in Thai patients with BD, and also to determine the association between susceptible alleles and clinical features of this disease.

2 | MATERIALS AND METHODS

All diagnosed BD patients, who were followed up at the Rheumatology Clinic of Chiang Mai University Hospital between June 2004 and December 2018 were invited to join this study. The diagnosis of BD followed The International Criteria for Behçet's Disease (ICBD).[10] The demographics, current age, age at onset, and cumulative clinical manifestations were recorded. Patients with ocular problems were evaluated by ophthalmologists. The severity of visual impairment was graded according to classification of the World Health Organization, in which visual acuity of less than 6/12, 6/18, 6/60 and 3/60 upon reading the Snellen Chart was considered as mild, moderate, severe visual impairment and blindness, respectively.[11] Healthy controls (HCs) comprised medical personnel, who had no symptoms or signs suggesting any connective tissue diseases. They did not take any regular medications, and were not related to the BD patients. This study was approved by the Ethics Committee of the Faculty of Medicine, Chiang Mai University (Thailand), University of Tokyo (Japan) and Seiei University (Japan), and was performed in accordance with the Declaration of Helsinki. All of the participants gave their written informed consent prior to entering the study.

DNA typing of the HLA-A and B alleles was performed using a reverse line blot assay kit (INNO-LiPA HLA-A Update and INO-LiPA HLA-B Update Plus, Innogenetix) according to the manufacturer's instructions. In brief, generic amplifications of the genes were performed using primers labeled with biotin at the 5′ end. After amplification, the polymerase chain reaction (PCR) products were hybridized with sequence-specific oligonucleotide probes and the hybridization patterns were analyzed using LiRAS (Innogenetics), the interpretation software for LiPA HLA. Reconfirmation of HLA typing was performed using a MICRO SSP HLA DNA Typing Tray (One Lambda Inc, Canoga Park, CA, USA). In this study, 18 HLA-A alleles and 36 HLA-B alleles were determined. The information of primers was partially provided (at http://www.onelambda.com/product-attachment.aspx?c1=molecular&c2=micro-ssp-&c3=allele-specific-trays&c4=2&c5=6&c6=22).

2.1 | Statistical analysis

The SPSS statistical program version 17.0 (SPSS Inc) was used for statistical analysis. Continuous and categorical data were expressed as mean ± standard deviation (SD) and frequency or percent, respectively. Comparison of the HLA allele frequency (AF) and phenotype frequency (PF) between BD patients and HCs, and between HLA susceptible alleles and BD clinical manifestations was determined by using Fisher's exact test. Bonferroni correction was not carried out in this study, due to the small number of patients. A *P* value of less than 0.05 was considered as a statistically significant difference. The odds ratio (OR) with 95% confidential interval (CI) are shown where relevant.

3 | RESULTS

Details of the patient characteristics are shown in Table 1. There were 42 BD patients (19 male and 23 female), who had a mean ± SD age at onset and disease duration of 27.21 ± 9.12 years, and 6.57 ± 5.80 years, respectively. All of the patients met the ICBD criteria with a mean score of 5.33 ± 1.13. Recurrent oral ulcers, ocular involvement (either anterior or posterior uveitis), and recurrent genital ulcers were the three most common findings, followed by arthritis and skin involvement. Intestinal and neurological involvement were not uncommon; but vascular lesions and thrombophlebitis were rare. Epididymitis was seen occasionally in male patients. There was no case of pulmonary involvement. The pathergy test was positive in 7.14% of the cases. The 99 HCs, (48 male and 51 female) in this study had a mean age of 45.6 ± 15.1 years.

The AF and PF of HLA-A and -B alleles among the 42 BD patients and 99 HCs are shown in Table 2. When compared with the HCs, the BD patients had higher AF of HLA-A*26 and -A*26:01 (5.95% vs 1.52%, *P* = .054, OR [95% CI] = 4.11 [0.96-17.63] for both alleles) and PF of HLA-A*26 and -A*26:01 (11.90% vs 3.03%, *P* = .051, OR [95% CI] 4.32 [0.98-19.01] for both alleles). The AF of HLA-B*51 and -B*51:01 also had increased in the BD patients, when compared to that in the HCs (13.10% vs 5.05%, *P* = .025, OR [95% CI] = 2.83 [1.15-6.95] and 10.71% vs 4.04%, *P* = .051, OR [95% CI] 2.85 [1.06-7.66], respectively), but statistical significance was observed only in the -B*51. The PF of HLA-B*51 and -B*51:01 also was higher in the BD patients (21.43% vs 9.09%, *P* = .056, OR [95% CI] = 2.73 [1.00-7.46] and 16.67% vs 8.08%, *P* = .144, OR [95% CI] = 2.28 [0.77-6.74], respectively). The AF

TABLE 1 Clinical characteristics of Behçet's disease in the patients studied

	N = 42
Gender, male:female	19:23
Age, y, mean ± SD	33.78 ± 10.00
Age at onset, y, mean ± SD	27.21 ± 9.12
Disease duration, y, mean ± SD	6.57 ± 5.80
ICBD score, mean ± SD	5.33 ± 1.13
Clinical manifestations	
Recurrent oral ulcers	42 (100.00)
Ocular involvement	31 (73.81)
Anterior uveitis	29 (69.05)
Posterior uveitis	22 (52.38)
Pan-uveitis	20 (47.62)
Visual impairment[a]	
None or mild	9/31 (29.03)
Moderate	9/31 (29.03)
Severe	7/31 (22.58)
Blindness	6/31 (19.35)
Skin involvement	20 (47.62)
Erythema nodosum	14 (33.33)
Folliculitis-like lesion	12 (28.57)
Recurrent genital ulcers	23 (51.76)
Epididymitis, (male = 19)	1/19 (5.26)
Intestinal lesions	5 (11.90)
Neurological involvement	4 (9.52)
Vascular lesions	1 (2.38)
Thrombophlebitis	1 (2.38)
Arthritis	13 (30.95)
Pathergy skin test positive	3 (7.14)
Medication	
Systemic corticosteroids	37 (88.09%)
Colchicine	31 (73.80%)
Immunosuppressive drugs	21 (50.00%)
TNF-inhibitor[b]	2 (4.76%)

Note: Data are expressed as n (%), unless specified.

Abbreviations: ICBD, The International Criteria for Behçet's Disease; TNF, tumor necrosis factor.

[a]Patients with ocular involvement.

[b]In patients who did not respond to immunosuppressive drugs.

and PF of HLA-A*02:07 were similar between the BD patients and HCs. It was interesting that among those patients who carried HLA-A*26:01, none had -B*51:01 or -B*51:02.

The AF of individuals carrying either the HLA-A*26:01 or -B*51:01 allele, or -A*26:01 or -B*51X allele was significantly higher in the BD patients than in the HCs (16.67% vs 5.56%, P = .005, OR [95% CI] = 3.40 [1.47-7.84], and 19.05% vs 6.56%, P = .003, OR [95% CI] = 3.35 [1.53-7.33], respectively). The same pattern also was seen in the PF of those patients carrying either the HLA-A*26:01 or -B*51:01 allele, or -A*26:01 or -B*51X allele (28.57% vs 11.11%, P = .023, OR [95% CI] = 3.20 [1.28-8.01], and 33.33% vs 12.12%, P = .005, OR [95% CI] = 3.63 [1.50-8.75], respectively).

The AF and PF of HLA-A*02:07, -A*26:01 and -B*51X among the subclass of the population studied also were analyzed and are shown in Table 3. Among the HLA-A*26:01 non-carrier patients, the AF of -B*51:01 and -B*51X had increased significantly in the BD patients when compared to that in the HCs (12.16% vs 4.17%, P = .024, OR [95% CI] = 3.19 [1.18-8.60] and 14.86% vs 5.21%, P = .019, OR [95% CI] = 3.18 [1.29-7.84], respectively). The PF of HLA-B*51X, but not -B*51:01 in BD patients, who were HLA-A*26:01 non-carriers, also increased significantly (24.32% vs 9.38%, P = .044, OR [95% CI] = 3.11 [1.12-8.59]). Among the HLA-B*51X non-carrier patients, the AF and PF of HLA-A*26:01 were significantly higher in the BD patients than in the HCs (7.58% vs 1.67%, P = .034, OR [95% CI] = 4.84 [1.12-20.84] and 15.15% vs 3.33%, P = .032, OR [95% CI] = 5.18 [1.16-23.06], respectively). There was no statistical difference in the AF or PF of HLA-A*02:07 among the BD patients who carried neither HLA-A*26:01 nor -B*51X.

Associations between the clinical manifestations of BD and susceptible alleles were determined (Table 4). The presence of either HLA-A*26:01 or -B*51:01 was significantly associated with any uveitis, posterior uveitis, and moderate to severe visual impairment (moderate or severe visual impairment, or blindness) (22.58% vs 0%, P = .016; 27.27% vs 5.00%, P = .008; and 25.00% vs 7.50%, P = .041; respectively). The presence of HLA-B*51:01 alone also was significantly associated with that of posterior uveitis as well as significant visual impairment (18.18% vs 2.50%, P = .031 for both conditions). The association between HLA-B*51:01 in patients who did not carry HLA-A*26:01 also was significantly associated with the presence of any uveitis, posterior uveitis and significant visual impairment (17.31% vs 0%, P = .050; 22.22% vs 2.73%, P = .013; and 21.05% vs 2.78%, P = .029; respectively). However, the presence of HLA-A*26:01 or -B*51X alone, or that of either of these 2 alleles showed no association with any clinical manifestations. In similarity, no association was seen among the clinical manifestations with subgroup of patients who carried HLA-B*51X without carrying HLA-A*26:01 or carried HLA-A*26:01 without carrying HLA-B*51X. It was interesting that none of the patients with arthritis or intestinal involvement carried HLA-B*51:01. The AF of HLA-B*51:01 among the HLA-A*26:01 non-carrier BD patients was significantly lower statistically in those with than those without arthritis (0% vs 17.31%, P = .050).

4 | DISCUSSION

This study found that the AF of HLA-B*51 increased significantly in Thai BD patients, when compared with that in the HCs. The AF of HLA-B*51:01 and PF of HLA-B*51 and -B*51:01 also had increased, but did not reach statistical significance. Subclass analysis showed that among individual HLA-A*26:01 non-carriers, the AF of -B*51:01 and -B*51X and PF of -B*51X were significantly higher in the BD

TABLE 2 Allele frequencies (AF) and phenotype frequencies (PF) of HLA-A, and -B alleles in Thai patients with BD compared with HCs

	AF					PF				
HLA	BD N = 84 (%)	HC N = 198 (%)	*P*	OR	95% CI	BD N = 42 (%)	HC N = 99 (%)	*P*	OR	95% CI
A*02	29 (34.52)	60 (30.30)				23 (54.76)	50 (50.51)			
A*26	5 (5.95)	3 (1.52)	.054	4.11	0.96-17.63	5 (11.90)	3 (3.03)	.051	4.32	0.98-19.01
A*30	0	1 (0.51)				0	1 (1.01)			
A*02:07	13 (15.48)	29 (14.65)				12 (28.57)	26 (26.26)			
A*26:01	5 (5.95)	3 (1.52)	.054	4.11	0.96-17.63	5 (11.90)	3 (3.03)	.051	4.32	0.98-19.01
A*26:02	0	0				0	0			
B*39	3 (3.57)	1 (0.51)				3 (7.14)	1 (1.01)			
B*51	11 (13.10)	10 (5.05)	**.025**	**2.83**	**1.15-6.95**	9 (21.43)	9 (9.09)	.056	2.73	1.00-7.46
B*39:01	3 (3.57)	1 (0.51)				3 (7.14)	1 (1.01)			
B*39:02	0	0				0	0			
B*46:01	21 (25.00)	34 (17.17)	.141			17 (40.48)	30 (30.03)	.068		
B*51:01	9 (10.71)	8 (4.04)	.051	2.85	1.06-7.66	7 (16.67)	8 (8.08)	.144	2.28	0.77-6.74
B*51:02	2 (2.38)	2 (1.01)				2 (4.76)	1 (1.01)			
B*52:01	4 (4.76)	10 (5.05)				3 (7.14)	10 (10.10)			
A*26:01 or B*51:01	14 (16.67)	11 (5.56)	**.005**	**3.40**	**1.47-7.84**	12 (28.57)	11 (11.11)	**.023**	**3.20**	**1.28-8.01**
A*26:01 or B*51X	16 (19.05)	13 (6.56)	**.003**	**3.35**	**1.53-7.33**	14 (33.33)	12 (12.12)	**.005**	**3.63**	**1.50-8.75**

Bold indicates statistical significance.

Abbreviations: BD, Behçet's disease; HC, healthy controls; HLA, human leukocyte antigen; OR, odds ratio; 95% CI, 95% confidence interval.

TABLE 3 Allele frequencies (AF) and phenotype frequencies (PF) of HLA-B*51:01 and -A*26:01 among the subclass of Thai patients with BD compared with healthy controls

	AF					PF				
HLA	BD, N (%)	HC, N (%)	*P*	OR	95% CI	BD, N (%)	HC, N (%)	*P*	OR	95% CI
All patients	84	198				42	99			
A*02:07	13 (15.48)	29 (14.65)	.858	1.07	0.52-2.17	12 (28.57)	26 (26.26)			
A*26:01	5 (5.95)	3 (1.52)	.054	4.11	0.96-17.6	5 (11.90)	3 (3.03)	.051	4.32	0.96-19.01
B*51:01	9 (10.71)	8 (4.04)	.051	2.85	1.06-7.66	7 (16.67)	8 (8.08)	.144		
B*51X	11 (13.10)	10 (5.06)	**.025**	**2.83**	**1.15-6.95**	9 (21.43)	9 (9.09)	.056	2.73	1.00-7.46
A*26:01 non-carriers	74	192				37	96			
A*02:07	13 (17.57)	29 (15.10)	.708	1.20	0.55-2.45	12 (32.43)	26 (27.08)			
B*51:01	9 (12.16)	8 (4.17)	**.024**	**3.19**	**1.18-8.60**	7 (18.92)	8 (8.33)	.123		
B*51X	11 (14.86)	10 (5.21)	**.019**	**3.18**	**1.29-7.84**	9 (24.32)	9 (9.38)	**.044**	**3.11**	**1.12-8.59**
B*51X non-carriers	66	180				33	90			
A*02:07	11 (16.67)	27 (15.00)	.842	1.13	0.53-2.44	10 (30.30)	24 (26.67)			
A*26:01	5 (7.58)	3 (1.67)	**.034**	**4.84**	**1.12-20.84**	5 (15.15)	3 (3.33)	**.032**	**5.18**	**1.16-23.06**
A*26:01 & B*51X non-carriers	56	174				28	87			
A*02:07	11 (19.64)	27 (15.52)	.535	1.33	0.61-2.89	10 (35.71)	24 (27.59)			

Bold indicates statistical significance.

Abbreviations: BD, Behçet's disease; HC, healthy controls; HLA, human leukocyte antigen; OR, odds ratio; 95% CI, 95% confidence interval.

patients. The above findings confirmed that HLA-B*51, particularly -B*51:01, was the susceptible allele in Thai BD patients, which was similar to previous reports and reviews.[1,2,12]

The presence of HLA-B*51:01 in this study also was found to associate with ocular involvement and significant visual impairment. An association between HLA- B*5/B*51/B*51:01 and ocular

TABLE 4 Association between clinical features and potentially significant alleles in 42 Thai patients with Behçet's disease

	All patients (N = 42)										HLA-A*26:01 non-carrier (N = 37)					HLA-A*51X non-carrier (N = 33)		
	A*26:01			B*51:01		B*51X		A*26:01 or B*51:01		A*26:01 or B*51X		B*51:01			B*51X		A*26:01		
Clinical features	(N)/N1	AF+, n (%)	*P*	AF+, n (%)	*P*	AF+, n (%)	*P*	AF+, n (%)	*P*	AF + n, (%)	*P*	(N)/N1	AF+, n (%)	*P*	AF+, n (%)	*P*	(N)/N1	AF+, n (%)	*P*
Any uveitis[a]																			
Yes	31/62	5 (8.06)	.319	9 (14.52)	.104	10 (16.13)	.274	14 (22.58)	**.016**	15 (24.19)	.058	26/52	9 (17.31)	**.050**	10 (19.23)	.157	46	5 (10.87)	.312
No	11/22	0 (0.00)		0 (0.00)		1 (4.54)		0 (0.00)		1 (4.55)		11/22	0 (0.00)		1 (4.55)		20	0 (0.00)	
Anterior uveitis																			
Yes	29/58	5 (8.62)	.318	7 (12.06)	.714	8 (13.79)	1.00	12 (20.69)	.208	13 (22.41)	.369	24/48	7 (14.58)	.480	8 (16.67)	.737	46	5 (10.87)	.312
No	13/26	0 (0.00)		2 (7.69)		3 (11.54)		2 (7.69)		3 (11.54)		13/26	2 (7.69)		3 (11.54)		20	0 (0.00)	
Posterior uveitis																			
Yes	22/44	4 (9.09)	.363	8 (18.18)	**.031**	8 (18.18)	.201	12 (27.27)	**.008**	12 (27.27)	.055	13/36	8 (22.22)	**.013**	8 (22.22)	.108	32	4 (12.50)	.190
No	20/40	1 (2.50)		1 (2.50)		3 (7.50)		2 (5.00)		4 (10.00)		19/38	1 (2.63)		3 (7.89)		34	1 (2.94)	
Severity of visual impairment[b]																			
Moderate or severe	22/44	3 (6.82)	1.00	8 (18.18)	**.031**	8 (18.18)	.201	11 (25.00)	**.041**	11 (25.00)	.173	19/38	8 (21.05)	**.029**	8 (21.05)	.192	32	3 (9.38)	.668
None or mild	20/40	2 (5.00)		1 (2.50)		3 (7.50)		3 (7.50)		5 (12.50)		18/36	1 (2.78)		3 (8.33)		34	2 (5.88)	
Skin involvement[a]																			
Yes	22/44	3 (6.82)	1.00	4 (9.09)	.730	5 (11.36)	.750	7 (15.91)	1.00	8 (18.18)	1.00	19/38	4 (10.53)	.732	5 (13.16)	.751	36	3 (8.33)	1.00
No	20/40	2 (5.00)		5 (12.50)		6 (15.00)		7 (17.50)		8 (20.00)		18/36	5 (13.89)		6 (16.67)		30	2 (6.67)	
Genital ulcers																			
Yes	23/46	2 (4.35)	.654	5 (10.87)	1.00	5 (10.87)	.534	7 (15.22)	.773	7 (15.22)	.406	21/42	5 (11.90)	1.00	5 (11.90)	.515	38	2 (5.26)	.643
No	19/38	3 (7.89)		4 (10.52)		6 (15.79)		7 (18.42)		9 (23.68)		16/32	4 (12.50)		6 (18.75)		28	3 (10.71)	
Intestinal involvement																			
Yes	5/10	1 (10.00)	.478	0 (0.00)	.591	0 (0.00)	.345	1 (10.00)	1.00	1 (10.00)	.679	4/8	0 (0.00)	.584	0 (0.00)	.596	10	1 (10.00)	.573
No	37/74	4 (5.41)		9 (12.16)		11 (14.86)		13 (17.57)		15 (20.27)		33/66	9 (13.64)		11 (16.67)		56	4 (7.14)	
Arthritis																			
Yes	13/26	2 (7.69)	.643	0 (0.00)	.051	1 (3.85)	.160	2 (7.69)	.208	3 (11.54)	.369	11/22	0 (0.00)	**.050**	1 (4.55)	.157	24	2 (8.33)	1.00
No	29/58	3 (5.17)		9 (15.52)		10 (17.24)		12 (20.69)		13 (22.41)		26/52	9 (17.31)		10 (19.23)		42	3 (7.14)	

Bold indicates statistical significance.

Abbreviations: HLA, human leukocyte antigen; (N)/N1, number of patients with clinical features/number of possible maximum positive alleles; n, number of positive alleles.

[a]Anterior or posterior uveitis.

[b]Erythema nodosum and folliculitis-like skin lesions.

TABLE 5 Association between susceptible alleles (HLA-A*26:01 and -B*51:01) and clinical manifestations in patients with Behçet's disease (selected studies)

Alleles	Authors, year, ref.	Country	N	Oral ulcers	Genital ulcers	Ocular involvement	Severity of ocular involvement	Skin involvement	Articular involvement	Intestinal involvement	CNS involvement	Vascular involvement
HLA-B*5/B*51/B*51:01												
HLA-B*5	Lehner et al (1982)[13]	UK	80	NM	NM	Yes	NM	NM	NM	NM	NM	NM
HLA-B*51:01	Koumantaki et al (1998)[16]	Greece	62	NM	NM	No	NM	Yes, EN	NM	NM	No	No
HLA-B*51	Chang et al (2001)[14]	Korea	51	NM	No	Yes	NM	Yes, EN	No	No	No	NM
HLA-B*5/B*51	de Menthon et al (2009)[2]	France	4800[a]	NM	NM	No	NM	NM	NM	NM	No	No
HLA -B*51:01	Kaburaki et al (2010)[20]	Japan	88[b]	NM	NM	ND	No	NM	NM	NM	NM	NM
HLA -B*5/*B51	Maldini et al (2012)[17]	USA	>5790[a]	NM	Yes	Yes	NM	Yes	No	Protective	No	No
HLA -B*51:01	Elfishawi et al (2019)[15]	Egypt	57	NM	NM	NM	Yes	NM	No	NM	Protective	Protective
HLA -B*51:01	Present study (2019)	Thailand	42	No	No	Yes	Yes	No	Protective[c]	No	No	No
HLA-A*26/A*26:01												
HLA -A*26:01	Kaburaki et al (2010)[20]	Japan	88[b]	NM	NM	ND	Yes	NM	NM	NM	NM	NM
HLA -A*26:01	Kang et al (2011)[3]	Korea	223	NM	NM	Yes[d]	NM	NM	NM	NM	NM	NM
HLA -A*26:01	Present study (2019)	Thailand	42	No	No	No	No	No	No	No	No	No

Abbreviations: CNS, central nervous system; EN, erythema nodosum; HLA, human leukocyte antigen; ND, not done; NM, not mentioned.

[a]Systematic review and meta-analysis.

[b]Patients with ocular Behçet's only.

[c]Among patients with HLA-A*2601 non-carrier.

[d]In all Behçet's disease patients and in those with HLA- *51:01 non-carrier.

involvement has been reported in many studies, systematic reviews and meta-analyses, which showed conflicting results. For example, Lehner et al[13] from the UK and Chang et al[14] from Korea found an association between ocular inflammation and HLA-B*5 and -B*51, respectively. A study by Elfishawi et al[15] from Egypt found that HLA-B*51 was associated with severe ocular involvement and blindness. In contrast, Koumantaki et al[16] from Greece found no association between HLA-B*51:01 and ocular involvement. It is interesting that HLA-B*5/B*51 was found to associate with ocular involvement in one systematic review and meta-analysis,[17] but not in others.[2] However, a recent review found that the association between HLA-B*51 and ocular inflammation in BD became stronger in countries located toward the East, along the Silk Road.[18]

The association of HLA-A*26 and -A*26:01 with BD has been reported from eastern and northeast Asian Countries such as Korea[3] and Japan,[5,19] but not in the Middle East or Europe. These alleles also were found to associate with ocular involvement and severity of visual impairment.[3,20] The AF and PF of HLA-A*26 and -A*26:01 in this study were higher and almost reached statistical significance in BD patients when compared with those in the HCs. However, the subclass analysis among HLA-B*51X non-carrier patients found that the AF and PF of -A*26:01 had increased significantly in BD patients. This indicated that the HLA-A*26:01 could be another susceptible allele for Thai BD patients who do not carry -B*51X, similar to that reported from Korea and Japan. Furthermore, although the presence of either HLA-A*26:01 or -B*51:01 in this study was associated with any uveitis, posterior uveitis and significant visual impairment, the subclass analysis found no association between -A*26:01 and ocular involvement or visual impairment among -B*51X non-carrier patients, as seen in the Korean and Japanese reports.[3,19,20] However, the AF of HLA-A*26:01 in this report was higher in BD patients with ocular involvement than those without, regardless of whether the former were HLA-B*51:01 carriers or not, and although this allele did not reach statistical significance, it indicated possible association with ocular involvement in Thai BD patients. An explanation for this might be due to the small number of HLA-A*26:01 carriers in this study. Also, HLA-A*26:01 might not be associated directly with ocular involvement in Thai BD patients, but might play a role by associating with -B*51:01 in the development of ocular inflammation.

Association between HLA-A*26:01 and -B*51:01 and clinical features of BD patients in previously published articles are shown in Table 5.

The association between HLA-A*02:07 and BD has been described in Korean subjects, both in -B*51:01 carrier or non-carrier subgroups, and was associated with skin lesions and arthritis.[3] The AF and PF of HLA-A*02:07 in this study were similar between the BD patients and HCs, and not associated with BD patients in the subclass analysis (those with -A*26:01 or -B*51X non-carriers), indicating that this allele was not associated with BD disease in the Thai population. The prevalence of HLA-A*02:07 was relatively high in the Thai population when compared to that in the general Japanese[21] or Korean population,[3,22] but it was close to the general population of Taiwan,[23-25] and China.[26] A large study in the USA found that this allele presented in only the Asian population, and not in other ethnic groups (African Americans, Caucasians, Hispanics and native North Americans).[27] The AF prevalence of HLA-A*02:07 in Thais, which was close to that in the Chinese, might be due partly to many Thai people having Chinese ancestry.

It is of interest that none of the patients with gastrointestinal involvement or arthritis in this study carried HLA-B*51:01 (Table 4); and this allele was significantly more common among -A*26:01 non-carriers who did not have arthritis. Thus, this allele might be protective against arthritis in Thai BD patients. A recent meta-analysis found that the presence of HLA-B*5/B*51 associated significantly with less gastrointestinal involvement, and less (but non-significant) articular involvement.[17] The protective effect of HLA-B*51:01 on gastrointestinal and articular involvement needs to be investigated further.

As new clinical features may develop or evolve during the course of disease, therefore, the association between susceptible alleles with organ manifestations and severity, or treatment outcomes should be adjusted according to disease duration and the treatment involved. Unfortunately, this adjustment was not performed in this study, as data on the onset of each organ manifestation were not collected at the beginning of the project. In addition, many patients were treated at a local hospital before being referred to us, and the onset of each organ manifestation as well as treatment received was unidentifiable. This made the association between susceptible alleles and clinical manifestations to adjust by disease duration or treatment obtained in this study not possible. Thus, interpretation of these results (Table 4) should be made with caution. It would be interesting for future study to clarify the association between susceptible alleles and organ manifestations and their severity by appropriately collecting data on the disease duration of each organ manifestation and treatment received.

The small number of patients also might affect statistical analysis. Considering that only 42 BD patients were reported in this study over a 15-year period from the rheumatology clinic of the largest university hospital in northern Thailand, and just 23 patients were reported over a 24-year period from the largest and oldest university hospital in this country,[8] suggests that BD is a rare disease among the Thai population. A retrospective study from the Uveitis Clinic at this institution also identified only 50 BD uveitis cases over a 10.5-year period.[28] However, reports involving 254-758 uveitis patients from uveitis clinics of various tertiary medical centers in Thailand found the prevalence of BD uveitis at 6.72%-15.54%.[29-31] These findings suggested that BD in Thailand might not be as rare as initially believed. One explanation might be that the majority of BD patients had ocular problems and therefore tended to visit an ophthalmologist, and if the extra-ocular manifestations were not considered during history taking, BD cases might have been overlooked. The same might be true if patients with recurrent oral or genital ulcers, or arthritis, visited a primary care physician, who was unaware of or unfamiliar with this disease. Nevertheless, BD in the Thai population is still considered uncommon because of its low AF of HLA-B*51/*51:01, when compared with populations in countries along the Silk Road.[1,2]

5 | CONCLUSION

This study confirmed that HLA-B*51:01 is a susceptible allele among Thai BD patients, and associates with ocular problems and severity of visual impairment. The AF and PF of HLA-A*26:01 also increased significantly in Thai BD patients, especially among -B*51X non-carriers, indicating that this allele is another susceptible allele in Thai BD patients. It is interesting that HLA-B*51:01 was not found in patients with gastrointestinal or articular involvement, and the AF of this allele was significantly lower among HLA-A*26:01 non-carrier BD patients with arthritis. Thus, HLA-B*51:01 might be a protective allele against arthritis in Thai BD patients. Further study with a larger number of patients is needed to confirm the findings in this study.

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CONFLICT OF INTEREST

All of the authors declare no conflict of interest.

AUTHOR CONTRIBUTIONS

Study concept and design: Louthrenoo, Takeuchi, Kuwata. Acquisition of data: Louthrenoo, Kasitanon, Wangkaew, Pathanapitoon. HLA typing and analysis: Nishi, Tanaka, Kaburaki, Takeuchi. Analysis and interpretation of data: Louthrenoo, Kasitanon, Takeuchi. Writing original draft preparation: Louthrenoo, Takeuchi. Writing, review and editing, and approval of the final manuscript: All of the authors. Dr Louthrenoo had full access to all of the data in this study, and responsibility for the integrity and analysis of the data.

ETHICS APPROVAL

All procedures performed in studies involving human participants were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki Declaration as revised in Brazil (2013). The Research Committee of the Faculty of Medicine, Chiang Mai University, Thailand. No. 146-2547. The Research Committee of the Tokyo University, Japan. No. G3518 and G10136. The Research Committee of the Tokyo Seiei University, Japan. No. 20160004.

INFORMED CONSENT

All of the participants provided written informed consent prior to entering this study.

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ORIGINAL ARTICLE

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Efficacy of TNFα inhibitors for refractory vascular Behçet's disease: A multicenter observational study of 27 patients and a review of the literature

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Abstract

Objectives: Vascular involvement is one of the major causes of morbidity and mortality in Behçet's disease (BD) patients. Immunosuppressive (IS) agents are the mainstay of vascular BD (VBD) treatment; however, up to one-third of patients relapse under conventional ISs. In this case series, we present the results of tumor necrosis factor-alpha (TNFα) inhibitor use for the treatment of VBD patients who were refractory to conventional ISs and corticosteroids.

Methods: This retrospective multicenter study included 27 refractory VBD patients treated with TNFα inhibitor agents. All data were acquired from patient charts.

Results: Complete clinical remission was achieved in 22 (80%) patients within 3 months of the initiation of TNFα inhibitors. Infliximab was the first choice of TNFα inhibitor in 24 and adalimumab in three patients. The median daily dose of corticosteroids significantly decreased at 3 months. A trend toward a higher rate of complete remission was observed with concomitant IS use compared to monotherapy of TNFα inhibitors (93% vs 67%, $P = .09$). Serious side effects were observed in two patients (one pneumonia and one tuberculosis).

Conclusion: Tumor necrosis factor-alpha inhibitors seem a highly effective option for remission-induction of refractory VBD with an acceptable safety data. Concomitant IS use may achieve higher complete remission rates as compared to TNFα inhibitor monotherapy. Comparative efficacy and safety of biological agents for VBD require further prospective, randomized controlled studies with a longer duration of follow-up.

KEYWORDS

Behçet's disease, TNFα inhibitors, vascular

1 | INTRODUCTION

Behçet's disease (BD) is a systemic inflammatory disorder affecting vessels of all sizes both in the arterial and the venous systems and designated as "variable-vessel" vasculitis in the Chapel Hill definition.[1] Inflammation in vessel walls can cause thrombosis, stenosis, occlusions and aneurysms.[2,3] As the primary pathology leading to thrombosis or aneurysms in BD is inflammation,

the mainstay of treatment is immunosuppressive (IS) agents.[2] According to the European League Against Rheumatism (EULAR) recommendations, IS agents such as corticosteroids (CS), azathioprine, cyclophosphamide or cyclosporine A are recommended for the management of acute deep vein thrombosis (DVT) in BD and cyclophosphamide together with high-dose CSs are recommended for pulmonary arterial, aortic and peripheral arterial aneurysms.[4] However, despite IS treatments, up to one-third of patients with vascular BD (VBD) have recurrent vascular events during their disease course.[2,5,6]

Management of patients who are refractory to the conventional IS treatments is an important problem in daily routine practice. Tumor necrosis factor-alpha (TNFα) inhibitors, especially infliximab (IFX) and adalimumab (ADA), are being increasingly

TABLE 1 Characteristics of patients

Patient	Drug initiation age	Gender	Indication of TNFα inhibitors	Previous treatment	Response at third month	Concomitant IS	Treatment at last visit
1	28	M	PAA, cardiac thrombi	CS, CYC, IFN	CR	No	ADA
2	35	M	PAA, cardiac thrombi	CS, CYC	CR	No	IFX, AC, CS
3	32	M	IVC thrombi	CS, AZA, IFN	PR	No	IFX
4	35	M	DVT	CS, CyS, IFN, AZA	CR	No	IFX
5	30	M	CVT	CS, AZA, IFN	CR	No	IFX
6	39	M	CVT	CS, AZA	PR	No	IFX
7	28	M	DVT (6 times)	CS, AZA	CR	AZA	ADA, AZA, AC
8	36	F	PAT	CS, AZA	CR	AZA	IFX, AZA
9	38	M	PAT, cardiac thrombi	CS, AZA, CYC	CR	No	IFX, CS, AC
10	35	M	PAT	CS, CYC, AZA	CR	AZA	ADA, AZA, AC
11	28	M	IVC	CS, CYC, AZA	CR	AZA	IFX, AZA, AC
12	33	M	DVT	CS, AZA, CyS	CR	No	IFX, AC
13	28	M	DVT	CS, AZA, CyS	CR	AZA	AZA, CS, AC
14	29	M	DVT	CS, AZA	PR	AZA	IFX, AZA, CS
15	42	M	Aorta aneurysm	CS, CYC, AZA	CR	AZA	IFX, AZA, CS
16	39	M	DVT	CS, CYC, AZA,	CR	AZA	IFX, AZA
17	24	M	PAA	CS, CYC, AZA	CR	AZA	IFX, AZA, CS, AC
18	55	M	Celiac-iliac artery, aorta aneurysm	CS, CYC, AZA	CR	AZA	IFX, CS
19	41	M	DVT	CS, CYC, AZA	CR	AZA	IFX, colchicum,
20	35	M	DVT	CS, CYC, AZA	CR	No	IFX, CS, colchicum
21	33	M	PAA	CS, CYC	CR	No	IFX, CS
22	29	F	PAT, cardiac thrombi	CS, CYC, AZA	CR	AZA	IFX, CS
23	30	M	PAT	CS, CYC, AZA	CR	AZA	AZA, CS, voriconazole
24	40	M	SVC	CS, CYC, AZA	CR	AZA	AZA, CS, colchicum
25	50	M	DVT	CS	PR	No	ADA, CS, AC
26	46	F	Aorta aneurysm, femoral artery aneurysm	CS, CYC, AZA, CyS	PR	No	CS, anti-aggregant
27	41	M	Thoracic aorta thrombi	CS, CYC, AZA	CR	AZA	IFX, AZA, CS

Abbreviations: AC, anticoagulation; AZA, azathioprine; CR, complete response; CS, corticosteroid; CyS, cyclosporine; CVT, cerebral vein thrombi; CYC, cyclophosphamide; DVT, deep vein thrombi; IFN, interferon; IS, immunosuppressant; IVC, inferior vena cava; PAA, pulmonary artery aneurysm; PAT, pulmonary artery thrombi; PR, partial response; SVC, superior vena cava; TNFα, tumor necrosis factor - alpha.

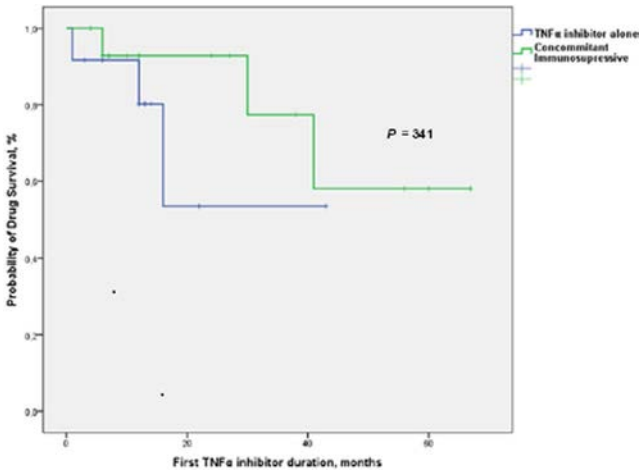

FIGURE 1 Event-free drug survival in vascular Behçet's disease (VBD) patients under tumor necrosis factor-alpha (TNFα) inhibitors

used in BD patients whose disease activity cannot be controlled with conventional ISs. Retrospective studies or case series showed the efficacy of TNFα inhibitor agents in BD patients with especially refractory mucocutaneous, articular, ocular, gastrointestinal and central nervous system involvement.[7] Desbois et al[8] reported the largest series with TNFα inhibitors, showing efficacy and safety in prevention of relapses of VBD. However, published experience with biological agents for vascular involvement in BD is still limited. In this study, we report a multicenter case series of 27 VBD patients, refractory to conventional ISs and treated with TNFα inhibitors.

2 | MATERIALS AND METHODS

We retrospectively collected data on 27 patients with VBD from 4 tertiary rheumatology centers in Turkey. All patients were classified according to International Study Group (ISG) criteria and were refractory to corticosteroids, conventional ISs and were treated with TNFα inhibitors.[9] Conventional treatments were azathioprine for 23, cyclophosphamide for 19 and interferon-α for five patients together with high-dose CSs. Twenty patients (74%) had used at least two ISs before the initiation of TNFα inhibitors (Table 1). Nineteen (70.4%) patients had also used anticoagulant treatment. Clinical, demographic data and treatment outcomes were acquired from the clinical charts.

Activity was assessed by the treating clinician according to clinical manifestations, imaging findings and acute phase reactant results. Complete remission was defined as no new signs and symptoms of vascular disease assessed by a physician, normalized acute phase reactants and CS dose under 10 mg/d at the third month of treatment. Partial response was defined as an improvement of clinical and laboratory parameters and at least 50% reduction of initial CS dose at the third month.

All patients were screened for latent tuberculosis before the initiation of TNFα inhibitors with either purified protein derivative (PPD) or QuantiFERON test, which is the suggested routine practice in Turkey. Patients with PPD >5 mm or positive QuantiFERON test, were given 9 months of isoniazid prophylaxis.

Infliximab was administrated as an induction dose of 5 mg/kg at 0, 2 and 6 weeks followed by every 8 weeks intravenously; ADA was administered as 40 mg every 2 weeks subcutaneously.

TABLE 2 Series with TNFα inhibitor use in the literature

Research	Type of study	No. of patients	Male, %	Time from BD diagnosis to initiation of drug	Indication of TNFα inhibitors	Type of TNFα inhibitors
Desbois [8]	Retrospective	18	89%	21 (0, 181) mo	5 venous, 8 arterials, 5 both	3 ADA/15 IFX
Hamuryudan 2015[14]	Retrospective	13	100%	6.4 ± 4.1 y	3 arteries, 10 both	12 IFX, 1 ADA
Hibi 2016[16]	Retrospective	4	75%	153 ± 85 mo	3 venous, 1 arterial	4 IFX
Vallet, 2015[18]	Retrospective	6	NA	NA	5 venous, 1 arterial	4 IFX, 2 ADA
Vitale[15]	Retrospective	15	NA	NA	NA	15 ADA
Adler, 2012 [13]	Retrospective	7	5/7, 70%	7.4 (0.5-20) y	1 venous, 5 arterial, 1 both	7 IFX
Emmi, 2018[20]	Retrospective	35	19/16, 54%	106.6 ± 107.5 mo	All venous	35 ADA
Our results	Retrospective	27	24, 89%	37 mo	9 arterial, 14 venous, 4 PAI and cardiac thrombi	24 IFX, 3 ADA

Abbreviations: ADA, adalimumab; AZA, azathioprine; CR, complete response; CT, clinical trial; CyS, cyclosporine A; HSV, herpes zoster virus; IFX, infliximab; IS: immunosuppressive drug; MMF, mycophenolate mofetil; MTX, methotrexate; NA, not available; PAI, pulmonary artery involvement; PR, partial response.

2.1 | Statistical analysis

Continuous variables are presented with the median and minimum-maximum. Categorical variables are presented with counts and proportions. Doses of corticosteroids before and after TNFα initiation (at the third month and last visit), as well as C-reactive protein (CRP)-erythrocyte sedimentation rate (ESR), were compared using Wilcoxon's signed rank test. All tests were 2-sided and a *P* value lower than 0.05 was considered as significant. Analyses were performed using SPSS statistical platform, version 21 (IBM).

3 | RESULTS

Infliximab in 24 patients and ADA in three patients were chosen as first-line TNFα inhibitors. Fifteen patients received concomitant ISs (all azathioprine) together with a TNFα inhibitor. Except four cases, all patients received isoniazid prophylaxis for latent tuberculosis infection.

Remission was evaluated at the third month of TNFα inhibitor treatment. Twenty-two (80%) patients achieved complete remission and 5 patients achieved partial response. Although not significant, more patients with concomitant IS use reached complete remission (93%) compared to TNFα monotherapy (67%) (*P* = .09). Duration of first TNFα inhibitor drug survival was also 12.5 (1-43) months and 24 (4-67) months for monotherapy and concomitant IS user groups, respectively (*P* > .05) (Figure 1).

All four patients treated with a TNFα inhibitor drug for PAA together with cardiac thrombi achieved complete remission at the third month of treatment. Ten out of 14 patients (71.4%) treated for venous thrombi and 8 out of 9 patients (89%) for arterial involvement achieved complete responses at the third month. Seven (77.8%) patients with arterial and another 7 (50%) patients with venous involvement used concomitant azathioprine (*P* > .05).

Median methylprednisolone dose was decreased significantly 3 months after TNFα inhibitor initiation (median daily dose at baseline was 16 [4-64] mg vs 4 [0-20] mg at 3 months [*P* = .000] and 2 [0-20] mg at last visit [*P* = .000], respectively) and stopped in seven patients during follow-up without any relapse. Also, 89% of patients discontinued or maintained 4 mg or lower daily of methylprednisolone dosage at the last visit. At the third month evaluation of patients, we detected significant decreases in acute phase reactants as compared with the initiation of TNFα inhibitors: ESR decreased from 24 (2-86) to 10 (1-49) mm/h and CRP from 11 (0.3-89) to 3 (0.3-54) mg/L (*P* < .0001).

Three patients had vascular relapses under the treatment of TNFα inhibitors (2 IFX, 1 ADA), one patient experienced renal vein thrombosis which developed at the 12 months of ADA monotherapy treatment. Hence ADA was switched to IFX. Another two patients had vascular relapses under IFX treatment: one with new aorta involvement at month 41 of IFX with concomitant azathioprine treatment and the other one had DVT at 17 months of IFX monotherapy.

Tumor necrosis factor-alpha inhibitors were stopped with sustained remission in two patients (after 24 and 37 months of treatment). One of the patients relapsed 6 months after cessation of TNFα inhibitor. Another patient was followed in remission under the treatment of azathioprine and low-dose corticosteroids for 48 months.

Concomitant IS drugs	Response	TNFα inhibitor duration, mo	Relapse during TNFα inhibitor treatment	Relapse after withdrawal	Serious infection
7 AZA, 5 MTX, 2 MMF	89% remission (13 CR, 3 PR)	15 (8-161)	2 (1 PAT, 1 peripheric artery aneurysm)	2/2	1 abscess, 1 *C jejuni* infection
8 AZA	11 patients showed good response	19.9 ± 14.7	No relapse	2/4	1 tbc, 1 aspergilloma
0	100% CR	13	No relapse	NA	No serious infection
3	66.7% (50% CR, 16.7% PR)	NA	NA	NA	NA
NA	NA	NA	3 (type?)	NA	NA
2 MTX, 1 AZA, 3 CyS	All patients improved	NA	No relapse	1/2	No serious infection
1 MTX, 7 AZA	97.1% vascular response	25.7 ± 23.2	3	NA	1 pneumonia, 1 HSV infection
15 AZA	80% CR, 20% PR	14 (3-67)	3 (2 venous, 1 arterial)	1/3	1 pneumonia, 1 tuberculosis

After median 14 (3-67) months of follow-up period under TNFα inhibitors, 23 (four ADA, 19 IFX) patients were still under TNFα inhibitors and all were in remission.

Nineteen patients used anticoagulation treatment for a median of 18.5 (3-89) months. There was no association between anticoagulant use and vascular relapses (P = .201) and TNFα inhibitor drug survival (P = .299).

Mortality was observed in 1 patient because of pneumonia under a TNFα inhibitor agent. One patient was diagnosed as having pulmonary tuberculosis at 30 months of TNFα inhibitor treatment, although the patient received 9 months of isoniazid treatment at the initiation period. The patient was under anti-tuberculosis, corticosteroid and azathioprine treatments for 3 months without a relapse. IFX was switched to ADA during follow-up because of allergic reactions in two patients.

3.1 | Literature review

There are four published case series in the English language literature on the use of TNFα inhibitor agents for VBD. There are also one prospective and two retrospective studies on the use of TNFα inhibitors on severe and refractory manifestations of BD patients, which include VBD. Table 2 summarizes these reports. Cumulatively, these reports include 125 patients in our series, most of them were male (between 54%-100%) and IFX (n = 66) and ADA (n = 59) were the two drugs used for VBD patients except for two studies (Table 2): 1 did not have information, the other had low response rate. More than 80% of patients had good vascular response. Only 11 patients relapsed during treatment. In addition, although not included in our literature review, there are case reports which show successfully treated VBD patients.[10-12]

4 | DISCUSSION

There are no randomized controlled trials for the management of major vascular involvement in BD. According to EULAR recommendations monoclonal TNFα inhibitors can be considered for refractory cases[4] as despite all immunosuppressive treatments, about one-third of patients relapse during follow-up.[2,5,6] Therefore, new treatment options are needed. There is now increasing data on TNFα inhibitors for the treatment of all types of refractory VBD.[12-14]

In this report, we present the largest series of VBD, refractory to conventional treatments and successfully treated with TNFα inhibitors. TNFα inhibitors achieved remission in 80% of patients within 3 months with a significant reduction of the relapse rate during median 14 months of follow-up period. Our complete remission rate is in line with the cumulative assessment of all reported series. Desbois et al reported 18 VBD patients treated with TNFα inhibitors who were refractory to conventional immunosuppressants. Clinical remission was achieved in 19 (89%) patients. Relapse risk during 9 months of follow-up was significantly higher with conventional ISs used prior to TNFα inhibitor initiation compared to TNFα inhibitor treatment. Median steroid dosage also significantly decreased at 12 months. Relapse developed in 2 (11%) patients after discontinuation of TNFα inhibitors.[8]

In a retrospective cohort reported by Vitale et al, vascular involvement was the main reason for ADA treatment in 15 of 100 patients. ADA achieved sustain remission during a follow-up 24 months. Relapse developed in only three patients.[15] Hibi et al conducted a multicenter prospective study to determine the efficacy and safety of IFX in 18 BD patients with major organ involvement. Four of 18 patients had VBD refractory or intolerant to conventional treatments. VBD patients showed clinical improvement together with decrease in CRP levels and ESR starting from week 2.[16]

Our results showed a trend toward increased complete remission rates and longer duration of first TNFα agent survival in VBD patients using TNFα inhibitors in combination with ISs compared to monotherapy group. There is no data in the literature comparing TNFα inhibitor monotherapy with a combination therapy using conventional ISs specifically in VBD patients. A literature review regarding the use of TNFα inhibitor agents in 369 BD patients reported that combination of infliximab with conventional ISs (azathioprine and/or cyclosporine A and/or methotrexate) appeared superior to monotherapy for sustained ocular remission.[17] However, in another study from France, including 124 BD patients with uveitis, there was no difference in terms of efficacy when TNFα inhibitor agents were used alone or in combination with conventional ISs.[18]

Adalimumab and IFX are the most commonly used TNFα inhibitor drugs for VBD patients both in the literature and in our study. IFX and ADA are effective during treatment but high relapse rates were detected after the withdrawal of these drugs. For refractory or intolerant cases to IFX or ADA, Lapalco et al presented 13 BD patients treated with certozilumab with three patients having vascular involvement. Although the vascular outcome is not clear in these three patients, 2 out of 3 seem to have changed their treatment to IFX or golimumab, suggesting that the role of certozilumab might be limited in VBD.[19]

In the present study, the methylprednisolone dosage significantly decreased at the third month of TNFα initiation similar to previous reports.[7,14] This is especially important in patients with BD refractory to conventional ISs as these patients usually receive a high cumulative dose of CSs. In our study acute phase reactants were significantly decreased at the third month of treatment as with previous studies, which showed significant decrease of acute phase reactants even 2-4 weeks after initiating TNFα inhibitor drugs.[8,13,16]

The duration of TNFα inhibitor treatment or discontinuation is questionable in VBD. Discontinuation of TNFα inhibitors led to relapses in 1 out of 3 patients in our study. This is like Desbois et al reporting relapses in two patients when TNFα inhibitors are stopped and Hamuryudan et al reporting two relapses in four patients.[8,14] Hamuryudan et al also reported two BD patients who developed pulmonary artery aneurysm while being treated with IFX.[14] In our study, two venous relapses and one arterial relapse occurred under TNFα inhibitor treatment, but pulmonary relapse or new pulmonary vascular events has not been detected. Also, in previous large

reports in BD patients treated with TNFα inhibitors, there were no reported pulmonary aneurysms or thrombi.[17]

Although not reaching the significance level because of small number of patients, our results showed a higher tendency of complete remission for arterial involvement when compared with venous thrombi; however, increased concomitant IS usage for arterial involvement may also contribute to a better response. A study on ADA for the treatment of venous thrombi showed that 76.5% of patients with DVT showed vascular response like our results, and only 7 out of 35 patients had used concomitant ISs.[20]

In both previous reports and our study, no new safety signals were observed during TNFα inhibition in VBD patients. However, like other series, we observed a case of tuberculosis, surprisingly after the completion of 9 months of isoniazid treatment, suggesting a re-infection. In the other major series (information is available for 5 out of 7 studies), there were four serious bacterial infections, one herpes zoster infection and one tuberculosis reported for a total 77 VBD patients treated with TNFα inhibitors (Table 2).[8,13,14,16]

The most important limitation of our study is its retrospective design. Also lack of validated and widely used assessment tools for activity in VBD may be another limitation. But expert opinion for activity assessment with clinical symptoms, signs and acute phase reactants is generally accepted for the assessment of major organ involvement in BD.

In conclusion, TNFα inhibitors seem highly effective options for the management of refractory VBD with acceptable safety data. Concomitant IS drug usage may achieve higher complete remission rates and longer drug survival as compared to TNFα inhibitor monotherapy. However, there is clear need for prospective, randomized controlled studies with long-term follow-up investigating both efficacy/safety and optimal duration of the treatment.

CONFLICT OF INTERESTS

The authors have declared no conflicts of interest.

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APLAR GRAND ROUND CASE

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Cryopyrin-associated periodic fever syndrome in children: A case-based review

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Abstract

Cryopyrin-associated periodic fever syndrome (CAPS) represents an increasingly recognized disease group entity, with varied presentations. CAPS includes 3 clinical entities, namely, familial cold-induced autoinflammatory syndrome (FCAS; MIM #120100), Muckle-Wells syndrome (MWS; MIM #191900) and chronic inflammatory neurologic cutaneous and articular syndrome (CINCA; MIM #607115); which share several overlapping clinical features. These patients often present with early-onset episodes of fever and rash, and variable systemic signs and symptoms, making it a great mimicker of other systemic autoimmune diseases. The episodes are transient and related to exposure to cold temperature and worsen in the winter season. We hereby present a case presenting with recurrent seasonal fever and rash, diagnosed as FCAS/ MWS overlap based on clinical signs and symptoms and positive testing for *NLRP3* gene mutation. We also discuss the clinical presentation and complications of CAPS, chiefly FCAS and MWS, along with the previously described pediatric cases of CAPS. We tried to review the complexities of management of such patients, including the genetic diagnosis and the role of biological therapy. Based on the review of the literature, given the evident broad spectrum of symptoms and signs, use of next-generation sequencing can help in prompt diagnosis and early initiation of biological agents, which may play a great role in reducing the complications that these patients may experience in the long run.

KEYWORDS

autoinflammatory disorders, cryopyrin-associated periodic fever syndrome, familial cold autoinflammatory syndrome, Muckle-Wells syndrome, *NLRP3*, pediatric rheumatology

1 | INTRODUCTION

Cryopyrin-associated periodic syndrome (CAPS) includes a group of genetic conditions, caused by dominantly inherited mutations in the *NLRP3* gene in Muckle-Wells syndrome (MWS) and familial cold autoinflammatory syndrome (FCAS), and de novo mutations in cases of chronic inflammatory neurologic cutaneous and articular syndrome (CINCA). CAPS is characterized by periodic episodes of auto-inflammation and variable clinical findings and classically includes 3 clinically overlapping entities, namely FCAS (MIM #120100), MWS (MIM #191900) and CINCA (MIM #607115).

NLRP3 gene encodes for molecule pyrin, which has its importance in innate immunity where it helps in the cellular response to intracellular danger signals and pathogen-associated molecular patterns. It plays a crucial role in the formation of "inflammasome complex", which also involves several other proteins like a Nod-like receptor protein and an adaptor protein called apoptosis-associated speck-like protein containing caspase recruitment and activating domain (ASC).[1,2] The complex

leads to the activation of procaspase-1 to caspase-1 and leads to further downstream actions. These include activation of cytokines like pro-interleukin (IL)-1beta, which plays a crucial role in the inflammatory response to infection and injury. Mutations in the family of the above genes can result in constitutive activation of the pathways of inflammation resulting in "cryopryinopathies".

It is important to recognize these clinical entities, not only for the diagnosis but also to improve long-term complications and quality of life in such patients, through the early use of biological agents. The drugs useful in this condition include anakinra, canakinumab (IL-1 inhibitors) and rilonacept.

Here, we describe the clinical findings and the typical course of a 10-year-old girl diagnosed with FCAS. The girl was initially diagnosed as having juvenile idiopathic arthritis, but given her joint symptoms and recurrent fever with a seasonal predilection to winter months, cold predilection, we challenged the initial diagnosis and considered autoinflammatory syndrome as one of the differential diagnoses. She underwent genetic testing for *NLRP3* gene, which confirmed the diagnosis of CAPS. We also did a case-based review of the previously described cases of CAPS concerning the clinical characteristics, complications and the response to therapy in children. In this review, we have reviewed the clinical presentation and complexities of management of CAPS, chiefly FCAS and MWS.

2 | CASE DESCRIPTION

A 10-year-old girl came with complaints of recurrent episodes of rash and joint pain, specifically during periods of cold weather since 1 year of age. Rashes were first seen on the face which was erythematous and with hyperpigmentation. Similar rashes occurred in bilateral feet and hands; they were painful and ulcerating. These crops of skin lesions and rashes used to last from several days to weeks during winter (Figure 1).

These episodes are also associated with joint symptoms in the form of periodic erythema and swelling of small joints of hands and feet which subsequently lead to progressive deformities of small joints of hands with fixed flexion deformity of proximal and distal interphalangeal joints. She had episodes of low-grade fever during illness. Eye exam did not reveal any uveitis or evidence of vasculitis. Complete blood counts during periods of exacerbations were normal (hemoglobin 11.2 g/dl, total leukocyte count 9200, N 48%, platelets 1 50 000/mm^3) but the child had high erythrocyte sedimentation rate (ESR) (40 mm/1st h) and C-reactive protein (CRP) (25 mg/L). Antinuclear antibodies, rheumatoid factor, lupus anticoagulant levels, anti-hepatitis C antibodies, serum creatine phosphokinase and serum cryoglobulin levels were negative. Viral markers were negative. X-ray of small joints of hands and feet revealed generalized osteopenia, but no joint erosions were noticed. Urine exam did not reveal any proteinuria or active sediment. Screening for amyloidosis was non-contributory. Nail-fold capillaroscopy was normal. Skin biopsy of the child showed leuco-cytoclastic vasculitis involving the dermal vessels with occasional hemosiderin-laden macrophages (Figure 2). She was managed as having undifferentiated connective tissue disease and was getting methotrexate for the last 2 years and received multiple courses of steroids, which partially relieved her symptoms.

Based on multiple joint involvements, skin lesions and periodicity of symptoms and exacerbation of symptoms during the winter season, an underlying autoinflammatory syndrome was suspected and the child underwent clinical exome sequencing for CAPS. A heterozygous missense variation in exon 3 of the *NLRP3* gene (chr1:247587343G > A; depth: 114×) that results in the amino acid substitution of methionine for valine at codon 200 (p.Val200Met; ENST00000336119) was detected. The in silico prediction # of the variant was damaging by MutationTaster2. The mutation was validated using Sanger sequencing (Figure 3). Given the clinical profile and positive mutation testing, the child's final diagnosis was kept as FCAS/ MWS overlap with heterozygous *NLRP3* gene mutation of uncertain significance.

She was subsequently started on short courses of systemic steroids, which improved her symptoms to a significant extent. The child has shown improvement in her symptoms but continues to experience periods of exacerbations during the winter season. She is planned to be started on seasonal biological agents, given her persistent inflammation during winter and her joint deformities.

3 | SEARCH STRATEGY

We conducted a scoping review of the PubMed, Cochrane, Hindawi and Scopus databases using combinations of the terms "Cryopyrin-associated periodic fever syndrome"; "Familial cold autoinflammatory syndrome"; "Cryopyrin-associated periodic fever syndrome AND genetics"; "Cryopyrin-associated periodic fever syndrome AND complications"; "Muckle-Wells syndrome" and "Cryopyrin-associated periodic fever syndrome AND therapy". Neonatal onset multisystem inflammatory disease/ CINCA were not included in the search strategy as they were not related to the case. The search period was from database inception to 30 May 2019. We included only articles published in the English language and those including the pediatric age group (up to 18 years) in our review. Four hundred and seventy-seven articles were retrieved, and after removing overlapping articles, abstracts of all the articles relevant to the review were reviewed, and 38 articles were included in the study. We could retrieve 24 case reports and case series, which were found relevant to the present study, in addition to the review articles and guidelines which we included in our present study. Details of the previously described cases and case series, concerning MWS and FCAS are summarized in Table 1.

4 | DISCUSSION

The clinical pointers indicating toward the diagnosis of CAPS include early onset and chronic course of urticaria-like rashes and fever with marked periodicity and exacerbation of symptoms during the winter

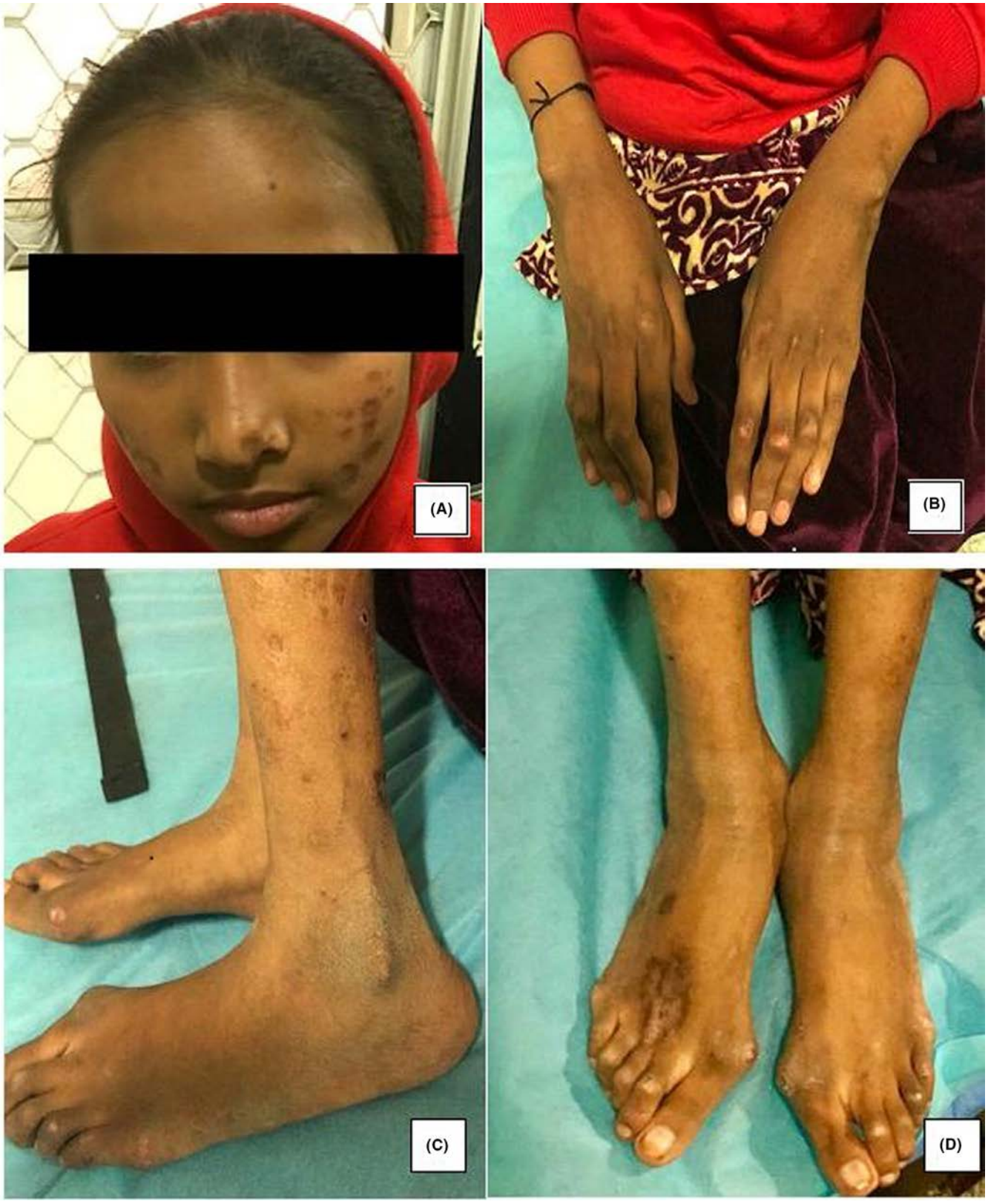

FIGURE 1 Clinical photographs of the case. A, Atrophic scarring of skin over bilateral cheeks and nose; B, progressive fixed flexion deformity of bilateral interphalangeal joints of middle and index fingers with atrophic scarring of skin; C, active ulcerating and vasculitic rash over distal interphalangeal joints of toes, scars of previously active lesions also seen over calf region; D, hallux valgus deformity of bilateral first metatarsophalangeal joints (printed with due permission)

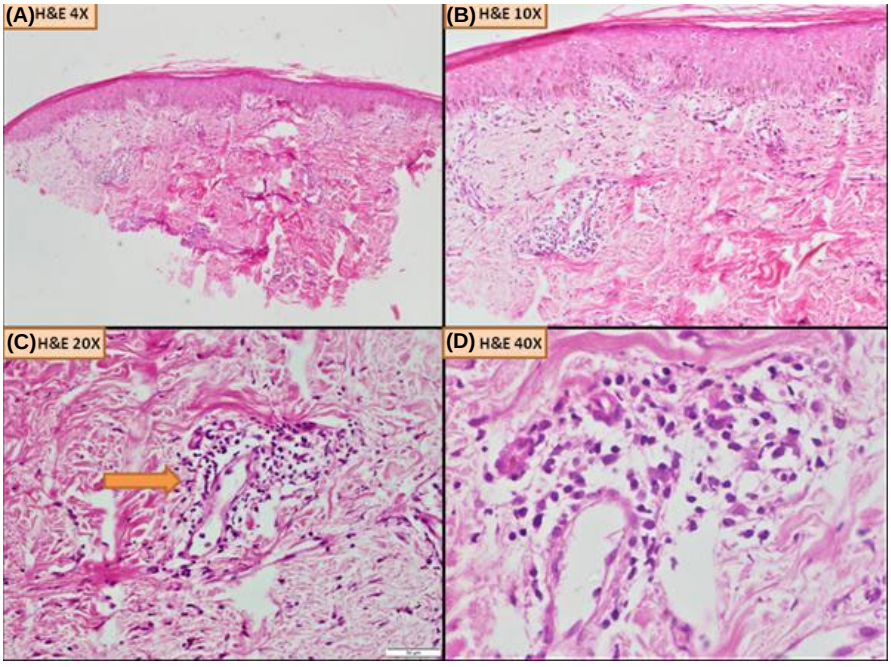

FIGURE 2 A and B, Skin biopsy shows an unremarkable epidermis. Papillary dermis shows edema and minimal chronic inflammation with nuclear debris. Also, occasional hemosiderin-laden macrophages are noted. B, Occasional vessels show leukocytoclastic vasculitis without any definitive evidence of fibrinoid necrosis. C, Higher magnification showing predominantly neutrophils in a perivascular and interstitial pattern

season when the inflammatory markers would also be raised. The exact cause of low temperature-triggered inflammation is still unknown. A standard clinical criterion has been developed for the diagnosis of CAPS.[3] It includes elevation of pro-inflammatory markers (SAA or CRP) as a mandatory criteria along with any 2 or more from 6 of those including urticarial eruption, episodes triggered by the cold, neuro-sensory deafness, musculoskeletal signs like arthralgia, arthritis and myalgia, chronic aseptic meningitis and skeletal abnormalities (hypertrophy of cartilage epiphyseal growth, frontal hump). However, the criterion was not fulfilled in about 59% of cases in a family affected with the condition, as described earlier.[4] Genetic testing, including next-generation sequencing (NGS), may play a much important role in the diagnosis of these cases, especially in case of a milder disease phenotype. NGS helped in the diagnosis of our patient as well, who was earlier mis-labeled with a diagnosis of undifferentiated connective tissue disease and exposed to long-term disease-modifying drugs.

As far as the clinical spectrum of CAPS is concerned, most patients of FCAS have some rash following exposures to cold or decrease in temperature. Other symptoms occur rapidly following exposure to cold, and these include low-grade fever and arthralgia, which follow the occurrence of the rash by a few hours. The symptomatology includes myalgia, conjunctivitis, sweating, drowsiness, headache, extreme thirst, and nausea. Most attacks resolve within a day. MWS is characterized by a more severe course with joint, eye and neurological involvement. The duration of rashes and symptoms is more than a day in MWS. Levy et al reported that the most common symptoms were fever, skin rash, and musculoskeletal involvement (although deforming arthritis is rare) observed in 84%, 97%, and 86% of patients, respectively.[5] A Japanese case review described arthritis in 13/14 CAPS patients.[6] We could not identify typical urticarial lesions in our patient; they looked more like a vasculitic rash with ulcerations and scarring. The skin biopsy confirmed the

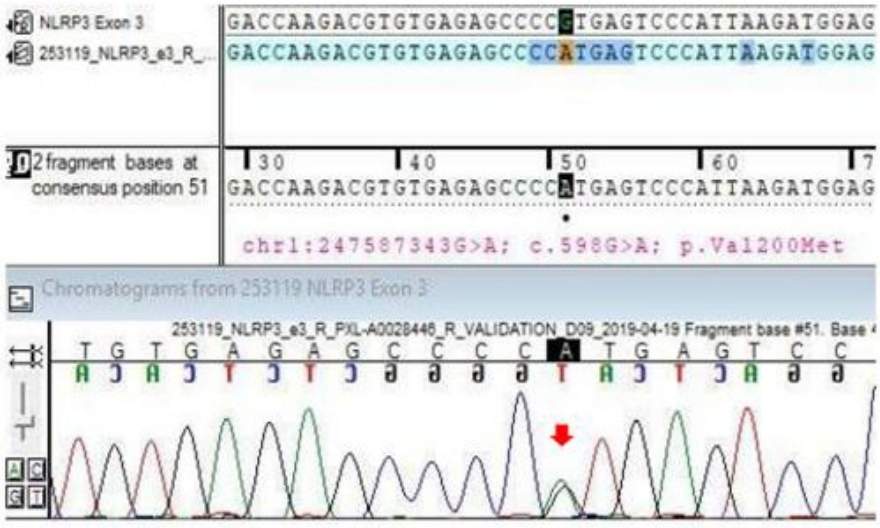

FIGURE 3 Sequence chromatogram and alignment to the reference sequence showing the variation in exon 3 of the *NLRP3* gene (chr1:247587343G > A; c.598G > A; p.Val200Met) of the case

finding of leukocytoclastic vasculitis. Clinically, the index patient did not precisely fit into the diagnosis of FCAS, but rather a phenotype of overlapping features with MWS.

Our case had a heterozygous mutation described previously in a Spanish family.[7] The previously described case was a 10-year-old boy with a similar history in the father but had no arthritis or deformities. Even low-level mosaicism can produce the disease phenotype, and a wide variety of mutations encompassing different genes have been described.[8] This knowledge that the disease genotype may vary and may not be detectable in all the body cells should prompt the clinician to get NGS as the first investigation of choice in suspected patients rather than Sanger sequencing alone.[6] Mutations involving *NLRP12/ NLRP3/ NLRC4/ PLCG2* genes have been associated with CAPS. However, there are several cases of mutation-negative patients with the clinical phenotype of CAPS.[9] A case of mutation-negative FCAS (diagnosed on clinical and cell-based studies confirming inflammasome dysfunction) has been reported previously, confirming the proposition given above.[10] The clinical profile of our patient was worse than the case described in the Spanish cohort, suggesting that even the same genetic mutation can lead to different clinical severities and phenotypes. This heterogeneity in phenotype may be possibly related to the degree of mosaicism in the cells, but such effect of the number of cells testing positive for mutation leading to different phenotypes is uncertain. The patient had significant improvement in response to anakinra and required re-institution of therapy at the arrival of the next cold season. The clinical features, as well as the response to therapy, indicated that the patient might actually be having low-level mosaicism of *NLRP3*, causing a negative mutation testing.

A case study and a recent review have highlighted the neurological complaint that CAPS patients develop on follow up.[11,12] These include headache, papilledema, seizures, and developmental delay. These manifestations occur more commonly in severe cases (CINCA). Long-term complications like optic atrophy and hearing loss have also been reported. A case study described the utility of canakinumab in controlling central nervous system inflammation and reducing the severity of the deafness.[13] Anakinra was used to improve deafness in another case of MWS with no response to canakinumab.[14] Early screening for these issues, therefore, becomes more critical in these cases, for timely diagnosis and rehabilitation. AA amyloidosis is another severe complication occurring in up to 10% of patients, mostly detected after the 3rd decade.[5] Rise in serum amyloid A (SAA) levels by >100-fold is a significant risk factor for the development of secondary amyloidosis, the complication is readily amenable to biological therapy. The treatment prevents, stabilizes and even causes an improvement in secondary amyloidosis.[15] A French review of CAPS described infertility which can develop in poorly controlled cases, probably due to the effect of high IL levels in the ovarian milieu in females and secondary amyloidosis-related effects on testes in males.[16] Higher SAA levels are directly related to the occurrence of infertility, more commonly seen in MWS/CINCA. Three out of 20 patients were hypospermic in a British case series.[17] A Chinese case series looked into the effect of genotype on the severity of symptoms, but they did not find any but one mutation (*D305N*) as highly associated with severe organ involvement.[18] Some of the patients had pulmonary, cardiac, hepatic or renal involvement, but the exact disease pathology in the tissues was not described. A case series of 2 adult siblings with MWS from India has also been described.[19] They presented with rash and short stature. CAPS can, therefore, also be included as a rare differential of short stature.

As far as management of CAPS patients is concerned, an intricate work up and follow up of CAPS patients (even of those on biological agents) should include annual audiometry and ophthalmological examination, a clinical watch for signs and symptoms of amyloidosis and magnetic resonance imaging of the brain at baseline and on detection of new neurological symptoms. At the same time, screening of family members (which may have been missed due to subclinical or milder symptoms) and the prolonged institution of biological therapy are other cornerstones of management.

Biological therapy in CAPS not only leads to control of acute symptoms but also prevents long-term complications. Anakinra has been used as a drug of choice for this disease. The drug produces a significant reduction in clinical symptoms and neurological complications, although the efficacy of this drug in control of chronic complications like systemic amyloidosis and deforming arthritis is ambiguous.[20] There may be poorer clinical response in patients with stable deafness, cartilage or bone hypertrophy, arthritis or chronic renal failure.[19,20] Anakinra has been recommended to be used in a dose of 1-8 mg/kg daily. Dosing depends on the severity of symptoms and can be up-titrated. Agents like rilonacept and canakinumab have also been used, and they provide a window for less frequent dosing (once a week and once every 4-8 weeks respectively).[23] Treating to target rather than prescribing standard doses is one of the key issues, especially in pediatric patients, and such practice leads to better control of symptoms and complications.[24] Steroids may be used for control of acute symptoms but are usually preferred in severe systemic forms of the disease and to control acute symptoms only. Our patient responded well to short courses of steroids and that was perhaps the reason for a delay in diagnosis. Nonsteroidal anti-inflammatory drugs and colchicine were other drugs that have been used to control acute symptoms, although the efficacy of these agents is poor, and these have fallen out of favor. Moreover, with the current availability and efficacy of biologicals, anakinra has become first-line management, not only for acute symptoms but also for long-term management of such patients.

A Finnish case series described by Eskola et al discussed 3 cases of MWS, with good response to biological agents like canakinumab, rilonacept, and anakinra.[25] There is a single case report on the usage of tocilizumab in a Korean patient, with good clinical response.[24] The study highlighted the fact that early recognition by genetic screening and prompt institution of therapy is essential to prevent long-term complications in such cases. Although the efficacy of biological therapy in CAPS has been well established, the data on long-term efficacy is unknown. Most of the cases require escalation of dosing to control symptoms over the long-term follow up.[11] The side effect profile of these agents

TABLE 1 Clinical profile, genetics and therapeutic response profile of previously published case series and case reports of cryopyrin-associated periodic fever syndrome in the pediatric age group[a]

Case series/ case report	Country (no. of subjects)	Age/age group at onset	Gender	Individual diagnosis	Mutation status (*NLRP3*)	Therapy used	Response	Remarks
Johnstone et al (2003)[4]	USA (110, 6 families)	3-36 y/onset at birth	F 52 M 58	FCAS	Positive in 6 patients	NA	NA	Data supported the validity of clinical criterion
Aróstegui et al (2004)[7]	Spain (12)	Neonate – 10 y	F 6 M 6	FCAS 8 CINCA 3 MWS 1	Positive 10/10	NSAIDs Cortico-steroids	Partial	Biologicals not used 5 cases from single family
Ramos et al (2005)[29]	Spain (1)	3 y	M	MWS	Positive	Anakinra	Good	Could not de-escalate therapy
Leslie et al (2006)[17]	Great Britain (22)	Onset in infancy	NA	NA	Positive 22/22	Anakinra in all the patients	Good, CKD due to amyloidosis in 6/22 patients	Anakinra therapy caused a reduction in symptoms and inflammatory parameters and also caused a gradual reduction in amyloid content in those patients who developed amyloidosis
Lainka et al (2010)[30]	Germany (16, 6 children)	0.6-7 y	F 2 M 4	FCAS 1 CINCA 4 MWS 6 Unclassified 3	Positive 16/16	NA	NA	156 patients of suspected periodic fever detected, only 6 had genetic diagnosis and details available
Aoyama et al (2012)[6]	Japan (1 + review of 19 cases)	Birth – childhood	F 8 M 12	FCAS 6 CINCA 9 MWS 5	Positive 9/10	NA	NA	Somatic mosaicism in 1 case Family history positive in 6 cases
Hedrich et al (2012)[10]	Germany (1)	8 y	M	FCAS	Negative by Sanger	Anakinra	Good, rash on exposure to cold water persisted	Mutation-negative FCAS? Mosaicism
Caorsi et al (2013)[11]	Italy (13)	0-9 y	NA	MWS 4 CINCA 7 MWS/CINCA overlap 2	Positive in 10/13	Anakinra and canakinumab	Good 6 Partial 6	12/13 patients treated with canakinumab received anakinra previously, no difference in disease control between the 2
Posch et al (2014)[12]	Austria (1)	9 mo	M	MWS	Positive	Anakinra	Good	Sustained remission at 5 y of follow up
Houx et al (2015)[16]	France (133/33 children)	0-78 y	F 71 M 62	FCAS 20 CINCA 22 MWS 88	Positive in all tested	Anakinra/48 switched to canakinumab	Good	Musculoskeletal symptoms were common, correlated with arthritis and arthralgia. All responded to biological therapy
Abdulla et al (2015)[19]	India (2)	5 and 17 y	M 2	MWS	Positive	Cortico-steroids	Partial	Short stature and clubbing in both cases
Mehr et al (2016)[32]	Australia (18, 12 children)	0-3 y	M 12 F 6	FCAS 2 CINCA 8 MWS 8	Positive in 13/14 tested	Anakinra	Good	Median delay in diagnosis 7.2 y, FCAS patients and 3 MWS not treated
Naz Villalba et al (2016)[33]	Spain (1)	1 y	F	MWS	Positive	Anakinra	Good	Anakinra lead to a reversal of neurological symptoms

(Continues)

TABLE 1 (Continued)

Case series/ case report	Country (no. of subjects)	Age/age group at onset	Gender	Individual diagnosis	Mutation status (*NLRP3*)	Therapy used	Response	Remarks
Xia et al (2016)[9]	China (4)	5-9 mo	F 2 M 2	FCAS	Nonsense *NLRP12*	NA	NA	Novel mutation in *NLRP12*
Li et al (2017)[18]	China (15)	2 d-6 y	F 10 M 5	CAPS (not specified)	Positive 12/15	NA	NA	Largest Chinese case series Mutation-negative cases had multisystem involvement
Wakhlu et al (2017)[31]	India (1)	18 y	F	CAPS (unspecified)	N/A	N/A	N/A	Clinically diagnosed case of CAPS/ favoring MWS phenotype
Lasiglie et al (2017) [8]	Italy (14)	2 mo-10 y	F 7 M 7	FCAS 2 CINCA 3 MWS 9	Positive Somatic mosaicism in 4 patients	Yes (not specified) in 11/14	NA	Somatic mosaicism in patients remained stable over time
Sukumaran, Vijayan (2017)[34]	USA (1)	2 mo	F	MWS	Positive	Anakinra	Good	-
Eskola et al (2018)[25]	Finland (3 + 6 family members)	Birth – 2 mo	F1 M 2	MWS	Positive	Anakinra (2) Canakinumab (1)	Good	First child switched to canakinumab due to arthralgia and side effects
Iida Y et al (2019)[13]	Japan (family of 3)	3 mo-childhood	F 2 M 1	MWS	Positive	Canakinumab	Good	Youngest proband had significant improvement in height gain and deafness
Kilic et al (2019)[35]	Turkey (12)	0.9-4.7 y	F 8 M 4	FCAS 7 CINCA 2 MWS 3	Positive in 9/12	Canakinumab	Good	Neurological complications in 6/12 patients
Marchica et al (2018)[14]	Canada (1)	3 y	M	MWS	Positive	Anakinra	Good	Reversal of hearing loss following the therapy
Han et al (2019)[36]	Korea (2 children)	2 y	F1 M1	FCAS	Positive in 2/2	Anakinra and tocilizumab respectively	Good	The first patient misdiagnosed as Behçet's initially while the second as juvenile idiopathic arthritis, both improved after biological therapy
Fingerhutova et al (2019)[37]	Czech (2 children and 9 other family members)	1.5-4 y	M 6 F 5	MWS	Positive in 2/2	None started	NA	Advocated monitoring of inflammatory activity in young children before initiating anakinra therapy

Abbreviations: CAPS, cryopyrin-associated periodic fever syndrome; CINCA, chronic inflammatory neurologic cutaneous and articular syndrome; FCAS, familial cold-induced autoinflammatory syndrome; MWS, Muckle-Wells syndrome; NA, not available; NSAIDs, nonsteroidal anti-inflammatory drugs.

[a]The table does not include all case series of CINCA/neonatal onset multisystem inflammatory disease, as it was not included in search strategy.

includes bacterial infections, which may require early initiation of antibiotics.[22,23,25,26] The prevention of these infections may require pre-emptive vaccination, but it needs to be balanced against the increased risk of vaccination-related reactions, especially during therapy with biological agents. Vertigo and angle-closure glaucoma have been reported in some CAPS patients on canakinumab.[27] Headache, pyrexia and respiratory infections have been described as common side effects of anakinra therapy in one of the studies.[28] The same study reported serious adverse events like infections (pneumonia and gastroenteritis) and macrophage activation syndrome as serious but rare side effects. These side effects were common in children <2 years of age. Long-term side effects of these agents are still unknown, and cost-related issues may prevent the use of these agents for therapy. There is no available evidence to support the use of one biological agent over the above. Given the fact that search for small molecule therapies continues and oral agents are still not available, there is need to ensure early initiation and compliance to these injectable therapies to provide maximum clinical benefit to the patients. For the index case, due to lack of availability of other biological agents including anakinra in our country and our experience of use of tocilizumab in other rheumatological diseases, we would commence seasonal tocilizumab therapy for the patient and titrate the dosing of the drug as per clinical and biochemical response to the therapy.

To conclude, CAPS is a periodic autoinflammatory syndrome with a broad spectrum of clinical signs and symptoms. Given the myriad of presentations that this disease can have and the delay in diagnosis that occurs so commonly with the disease, it is prudent to consider prompt use of NGS in suspected cases. Early genetic diagnosis would help in early initiation of biological agents, which are the drugs of choice for this condition. There is a need to detect the disease early, not only for the sake of early initiation of therapy but also for the avoidance of unnecessary and prolonged immune suppression. Although these agents help in ameliorating clinical signs and symptoms and improving quality of life, the patients need to be repetitively screened for various complications even during therapy. It becomes crucial, therefore, to counsel the parents/guardians regarding regular screening and follow up.

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CONFLICT OF INTEREST

All authors declare that they have no conflicts of interest.

AUTHOR CONTRIBUTIONS

AG: Data acquisition, literature review, and prepared the initial manuscript. NKB: Concept, design, review and revised the manuscript. SKT: Data collection, patient management, and helped in drafting the manuscript. SA and RHP: Contributed to the histopathological part of the manuscript. All authors approved the final version of the manuscript as submitted and agree to be accountable for all aspects of the work. All authors helped in drafting the article and gave feedback for improving the intellectual content of the article. All the listed authors approved the final manuscript as submitted and agreed to be accountable for all aspects of the work.

RESEARCH INVOLVING HUMAN PARTICIPANTS AND ANIMALS

This article does not contain any studies with human participants or animals performed by any of the authors.

INFORMED CONSENT

Informed consent of the patient concerned was taken in an appropriate format.

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International Journal of Rheumatic Diseases

WILEY

CORRESPONDENCE

An extraordinary manifestation of Behçet's disease in a young male: Urinary meatus ulcer

Dear Editor,

Behçet's disease is a chronic relapsing multisystem disorder characterized by mucocutaneous, ocular and other organ involvement. Genital aphthous ulcers are among the most commonly seen clinical features, and constitute one of the main diagnosis criteria. The most common localization of genital ulcers in men is the scrotum, nearly 90% of all lesions. Corpus penis and glans penis are other involved sites.[1]

Recurrent ulcers in Behçet's disease are also described in the extragenital skin, larynx and esophagus, apart from the genital area.[2-4] It is extremely rare in the uretral orifice.[5]

In this article, we present a young male patient with a complaint of painful voiding, eventually diagnosed with Behçet's disease.

A 27-year-old male patient was referred to the dermatology outpatient clinic by the urology clinic following evaluation of his painful voiding complaint. Dermatological examination revealed a clean ulcer with a diameter of 2 mm at the entrance of the urethra (Figure 1). According to the history, the patient's complaint had been present for about 5 days.

The patient had no history of suspicious sexual intercourse and Venereal Disease Research Laboratory and *Treponema pallidum* hemagglutination tests were negative for syphilis. He had recurrent oral aphthous ulcers, emerging at least once a month for several years. There was also an acneiform rash on the back and gluteal region (Figure 2). Pathergy test was found negative. The eye consultation was normal. There were no clinical and laboratory findings related to other organ involvement. The patient was diagnosed with Behçet's disease based on these findings and was taken to follow-up. A triamcinolone ointment was recommended for the aphthous lesions. The urethral ulcer recovered within a week.

The development of an ulcer at the entrance of the urethra is quite uncommon. In male patients, recurrent ulcers are usually seen in the scrotum. Corpus penis, glans penis are other common areas. The diagnosis of Behçet's disease can be skipped in patients presenting with isolated ulcerations. The patient had a history of oral

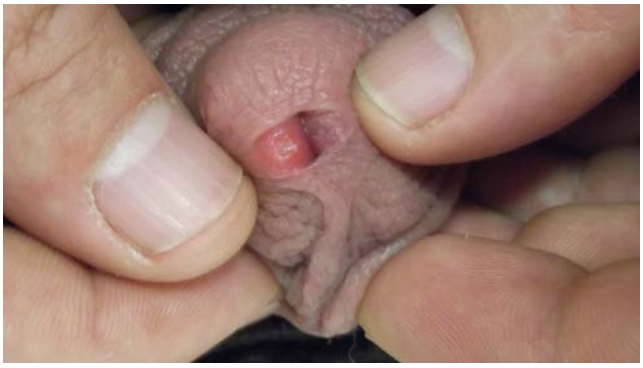

FIGURE 1 A small ulcer in the urinary meatus

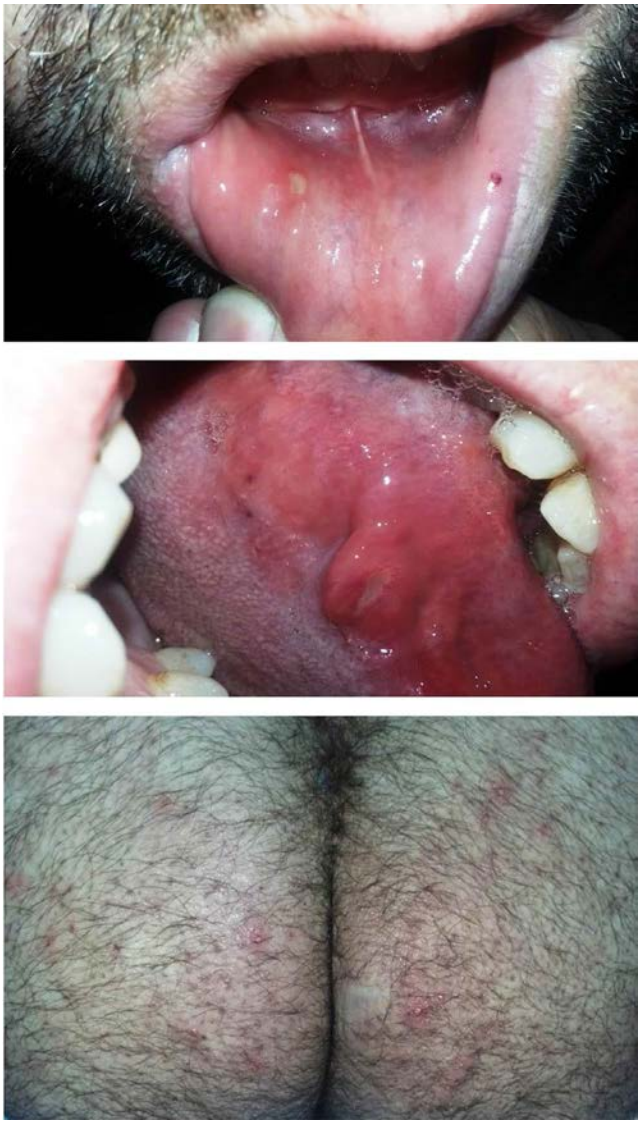

FIGURE 2 Minor aphthous ulcers in the mouth and papulopustular lesions on the buttocks

aphthous ulcers and acneiform skin rashes. A meticulous questioning about the patient's clinical conditions helped to place a diagnosis of Behçet's disease.

The uretral orifice is a risky site for scarring. Genital ulcers usually leave scars after healing because of their depth. In the study by Mat et al, the rate of scarring was found to be 66% in Behçet's patients with genital ulcers.[6] Fortunately, our patient recovered without any sequela.

Ghosh et al reported a 16-year-old boy with Behçet's disease, who had several severe oral and genital aphthous ulcers. This patient had urethral meatal stenosis due to scarring from external urethral meatus ulceration.[7] Our case was not as serious as this.

There is an interesting aspect because eye involvement is rarely seen rare in Behçet's patients with genital ulcers.[8] Hence, eye involvement was not detected in our patient.

This case report emphasizes taking a good clinical history in patients suffering from genital or extragenital ulcers to avoid skipping the diagnosis of important diseases.

CONFLICT OF INTEREST

No conflict of interest.

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International Journal of Rheumatic Diseases WILEY

CORRESPONDENCE

A case of simultaneous onset of anti-melanoma differentiation-associated gene 5 antibody-positive dermatomyositis accompanied by interstitial pneumonia and pulmonary tuberculosis

Dear Editor,

Polymyositis and dermatomyositis are idiopathic inflammatory myopathies.[1] Various antibodies have been identified as associated with polymyositis/dermatomyositis, and characteristic phenotypes have been reported for each.[2,3] Anti-melanoma differentiation-associated gene 5 (*MDA-5*) antibody is associated with rapid progressive interstitial pneumonia, and cases with high ferritin are reported to have an extremely poor prognosis.[4,5] We report a case of simultaneous onset of anti-*MDA-5* antibody-positive dermatomyositis accompanied by interstitial pneumonia and pulmonary tuberculosis.

A 43-year-old man developed anti-*MDA-5* antibody-positive dermatomyositis accompanied by interstitial pneumonia and pulmonary tuberculosis. Simultaneous immunosuppressive therapy and anti-tuberculosis therapy produced a good outcome. He developed erythema on his face as well as muscle pain and weakness of the limbs, especially his lower limbs, in September 2017. He was admitted to hospital because from December 2017 he developed palpitations and dyspnea during exertion. Physical examination demonstrated a body temperature of 38°C, fine crackles in the lower lung fields on both sides, Gottron's papules, and an erythematous rash on his face. Muscle pain in the proximal limb muscles and muscle weakness of about 4/5 on the Manual Muscle Test were confirmed. Laboratory examinations showed creatine kinase (CK) 76 U/L (normal range: 59-248 U/L), aldolase (ALD) 16.8 U/L (normal range: 2.1-6.1 U/L), sialylated carbohydrate antigen Krebs von den Lungen-6 (KL-6) 700 U/mL (normal range: <500 U/mL), ferritin 1337 ng/mL (normal range: 40-360 ng/mL), C-reactive protein (CRP) 0.32 mg/dL (normal range: <0.3 U/mL), and high titer of anti-*MDA-5* antibody (>150) (normal range: <32). Arterial blood gas analysis revealed a PaO_2 of 77.9 mm Hg in room air. Chest computed tomography (CT) revealed a cavity on the left S1 + 2 and consolidations and ground-glass opacities in the bilateral lower lung fields, suggesting a radiologic pattern of non-specific interstitial pneumonia (Figure 1). Because we suspected pulmonary tuberculosis from the cavity, we performed a sputum examination. It was positive by acid-fast bacilli sputum smear and positive by tuberculosis-polymerase chain reaction (Tb-PCR). Based on the above, he was diagnosed as dermatomyositis with interstitial pneumonia coexisting with active pulmonary tuberculosis. On 28 January 2018, he was started on anti-tuberculosis therapy consisting of isoniazid (INH), rifabutin (RBT), ethambutol (EB) and pyrazinamide (PZA). After confirming there were no side effects related to these drugs, prednisolone (PSL) at a dose of 60 mg (1 mg/kg) daily and tacrolimus (TAC), the blood trough concentration of which was adjusted to 5-10 ng/mL, were orally administered. These treatments had an antipyretic effect and improved muscle pain and muscle weakness. After anti-*MDA-5* antibody positivity was observed, intravenous pulse cyclophosphamide (IVCYC) 500 mg/m^2 weekly was initiated. The cavity shrank 1 month after the start of treatment and interstitial pneumonia in the bilateral lower lobes was improved. EB and PZA were discontinued on day 60 as the results of drug susceptibility studies demonstrated that the isolate was susceptible to first-line agents. Because his serum ferritin was still high after 6 cycles of IVCYC, high-dose IV immunoglobulin therapy (IVIg) 20 g daily for 5 days was initiated. We confirmed consecutive negative sputum smears for acid-fast bacillus and improved consolidations and ground-glass opacities on chest CT (Figure 1); therefore, he was discharged on day 95 of hospitalization. Thereafter, there was no exacerbation as an outpatient even though PSL was tapered to 25 mg daily. Furthermore, the serum levels of ferritin and anti-*MDA-5*-antibody decreased to 548 ng/mL and 117 indexes, respectively (Figure 2). One year later, tuberculosis treatment was completed and PSL was tapered to 7.5 mg daily. Anti-*MDA-5*-antibody decreased by 31 indexes.

To the best of our knowledge, this is the first clinical report of a case of simultaneous onset of anti-*MDA-5* antibody-positive dermatomyositis accompanied by interstitial pneumonia and pulmonary tuberculosis. Polymyositis and dermatomyositis are chronic inflammatory disorders that mainly involve muscle and skin lesions. Their clinical features are heterogeneous, with varying degrees of skin manifestations, myositis, and pulmonary involvement. In anti-*MDA-5* antibody-positive dermatomyositis patients, rapidly progressive interstitial pneumonia sometimes develops; this condition is resistant to immunosuppressive treatment and is associated with poor outcomes.[4,5] Immediate and intensive immunosuppressive therapy was required in this patient to avoid a fatal situation and the concomitant use of corticosteroid, calcineurin inhibitor, and cyclophosphamide was indispensable to prevent the progression of interstitial lung disease in anti-*MDA-5* antibody-positive dermatomyositis.[6] Because the effectiveness of IVIg was also reported,

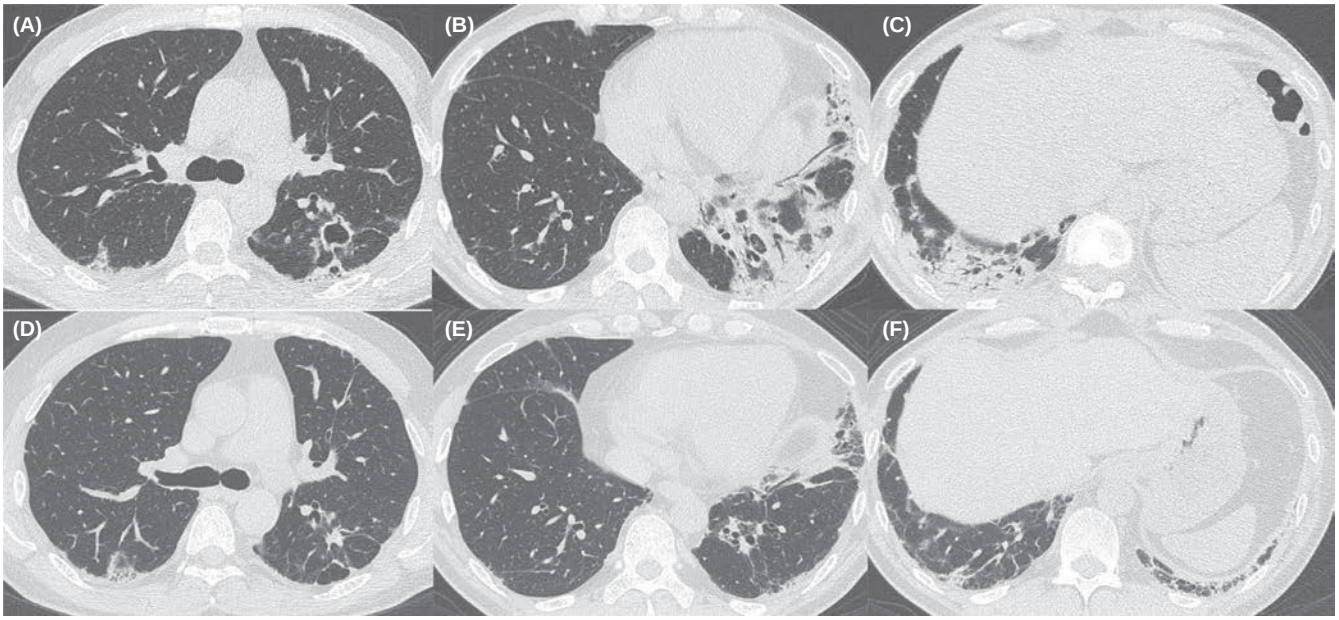

FIGURE 1 A, Chest computed tomography (CT) on admission shows a cavity on the left S1 + 2. B, C, Chest CT on admission shows ground-glass opacities in the bilateral lower lung fields. D-F, Chest CT on the 60th day of hospitalization shows improvement after treatment

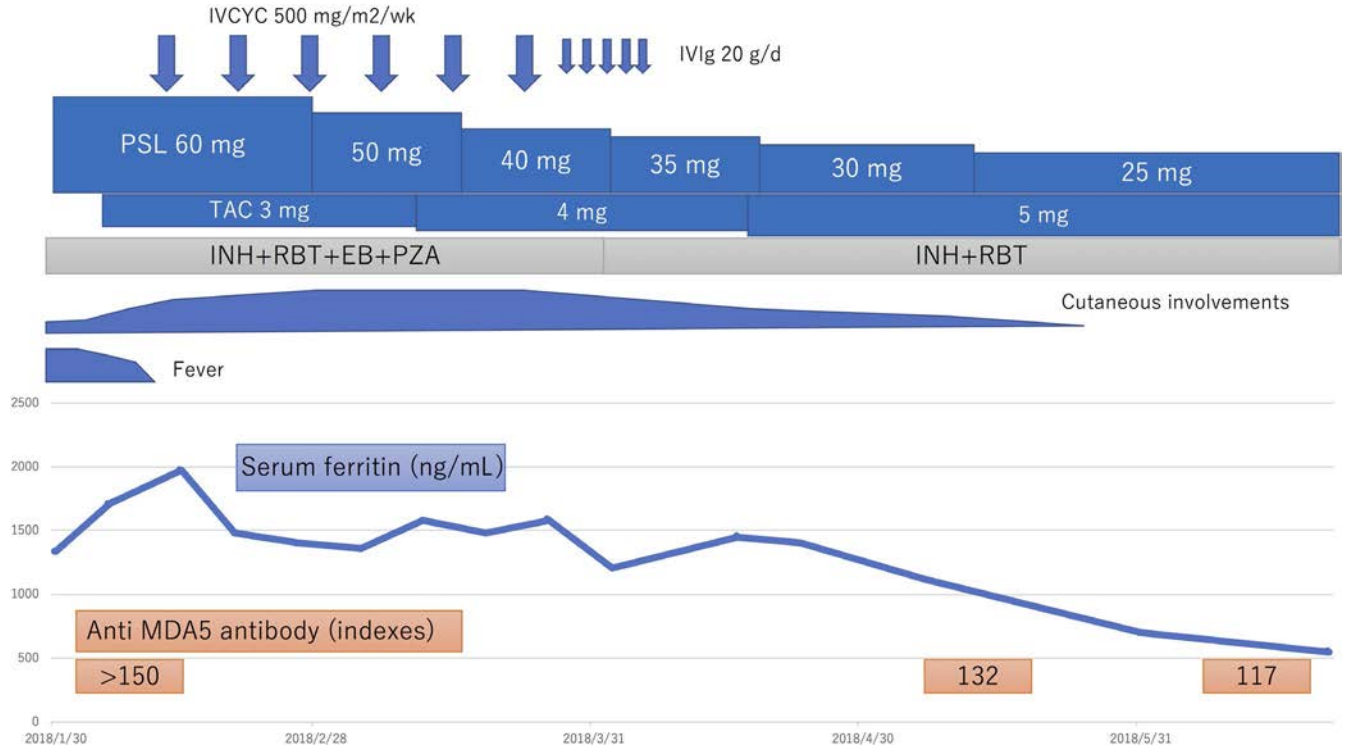

FIGURE 2 Clinical course and changes in the anti-*MDA-5* antibody and serum ferritin levels of this patient. EB, ethambutol; INH, isoniazid; IVCYC, intravenous pulse cyclophosphamide; IVIg, high-dose intravenous immunoglobulin therapy; PSL, prednisolone; PZA, pyrazinamide; RBT, rifabutin; TAC, tacrolimus

it was added to the treatment.[7] Subsequently, his skin and muscle symptoms, and interstitial pneumonia improved. Although this patient initially had a high titer of anti-*MDA-5* antibody (>upper measurable limit) and serum ferritin exceeding 1000 ng/mL, these were reduced by combination therapy. High serum ferritin levels on admission in anti-*MDA-5* antibody-positive dermatomyositis patients were reported to be a poor prognostic marker.[8] Whether anti-*MDA-5* antibody titers are a prognostic factor is controversial, but previous studies reported that anti-*MDA-5* antibody titer was useful for the evaluation of the response to treatment and the status of interstitial pneumonia in patients with anti-*MDA-5* antibody-positive dermatomyositis.[9] Of note, the reduction of high serum ferritin

and anti-*MDA-5* antibody levels after treatment indicated they can predict a successful outcome.[5,10]

There has been no reported case of simultaneous onset of anti-*MDA-5* antibody-positive dermatomyositis and pulmonary tuberculosis. The relationship between dermatomyositis and tuberculosis is unknown. In this case, tuberculosis infection may have triggered the exacerbation of interstitial pneumonia. It is important to report our experience of a patient with anti-*MDA-5* antibody-positive dermatomyositis complicated with interstitial pneumonia with high serum ferritin levels and who, despite the complication of infectious disease, obtained a good outcome after combined treatment. Collagen diseases often accompany lung lesions. Thus, this case highlights that attention should be paid to the coexistence of pulmonary tuberculosis.

CONFLICTS OF INTEREST

The authors have declared no conflicts of interest.

AUTHORS' CONTRIBUTIONS

Shota Fujimoto wrote the initial draft of the manuscript. Keisuke Saito and Kazuyoshi Kuwano assisted in the preparation of the manuscript. All authors approved the final version of the manuscript.

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The 2020 congress will be held on **31 August – 3 September** in Kyoto International Conference Center, Japan. Please do look out for updates by visiting the website.

APLAR aims to improve standards of clinical practice, teaching, and research in rheumatology across Asia Pacific. We are recognising the long-term efforts and dedication of centers in the region with a similar goal for excellence in the field. The certification programme we have initiated will award leading centers in Asia Pacific as Centers of Excellence based on three pillars (research, clinical practice, academia), pre-defined by a list of criteria set by APLAR.

We hope the centers in the region with an excellent track record in any of these pillars will participate in this programme as our goal is to establish reference centers that are best in class models for practice, teaching, and research in rheumatology. We believe this will enhance and enrich the 'best in class' experience for our trainees involved in the APLAR Fellowship programme. Further, this will also help us build a strong network of reference centers for collaborations and consultation within and among countries in the region.

APLAR awarded Centers of Excellence have been updated and information about these centers can be found on the website. Center of Excellence 2020 application will begin in March next year. Application information will be made available through the Member National Organisations of APLAR.

APLAR FELLOWSHIP GRANT

The Asia Pacific League of Associations for Rheumatology (APLAR) had awarded 2 applicants for the Fellowship Grant of 2019. They are embarking on their fellowship programme in the coming months. Successful candidates must have a long-term commitment to continue research or clinical work in his/her own country at the conclusion of the Fellowship. The grant is awarded to cover accommodation and subsistence costs. We congratulate the awardees and wish them a fruitful journey in their career paths.

APLAR RESEARCH GRANT

The Asia Pacific League of Associations for Rheumatology (APLAR) had awarded 2 applicants for the Research Grant of 2019. The grants are to assist the undertaking of research in either adult or paediatric rheumatology. The aims of the grant are to give the researcher an opportunity to start and do research within their own country of residence. In addition, we hope to promote and support basic and clinical research directed to the causes, prevention, and treatment of rheumatic diseases in the APLAR member society countries. This grant is to be used for consumables required for the research and not for salaries or fixed costs. It is expected that the research will be completed within one (1) year of the onset. The awarded candidates are encouraged to publish their work in the APLAR official journal – International Journal of Rheumatic Disease (IJRD) as part of their contribution.

APLAR-COPCORD GRANT

The Asia Pacific League of Associations for Rheumatology (APLAR) did not have any applicant for COPCORD grant 2019. We encourage interested candidates to send in their application during the application period for COPCORD grant 2020. The aims of the grant are to give the researcher an opportunity to study rheumatic disease in the community of their own country of residence. This grant is to be used for consumables required for the research and not for salaries or fixed costs. It is expected that the research will be completed within one (1) year of the onset.

All APLAR Grants are currently open for application. The closing date will be on 21 February 2020. APLAR Grants information on eligibility, criteria and application requirement can be found on the *website*.