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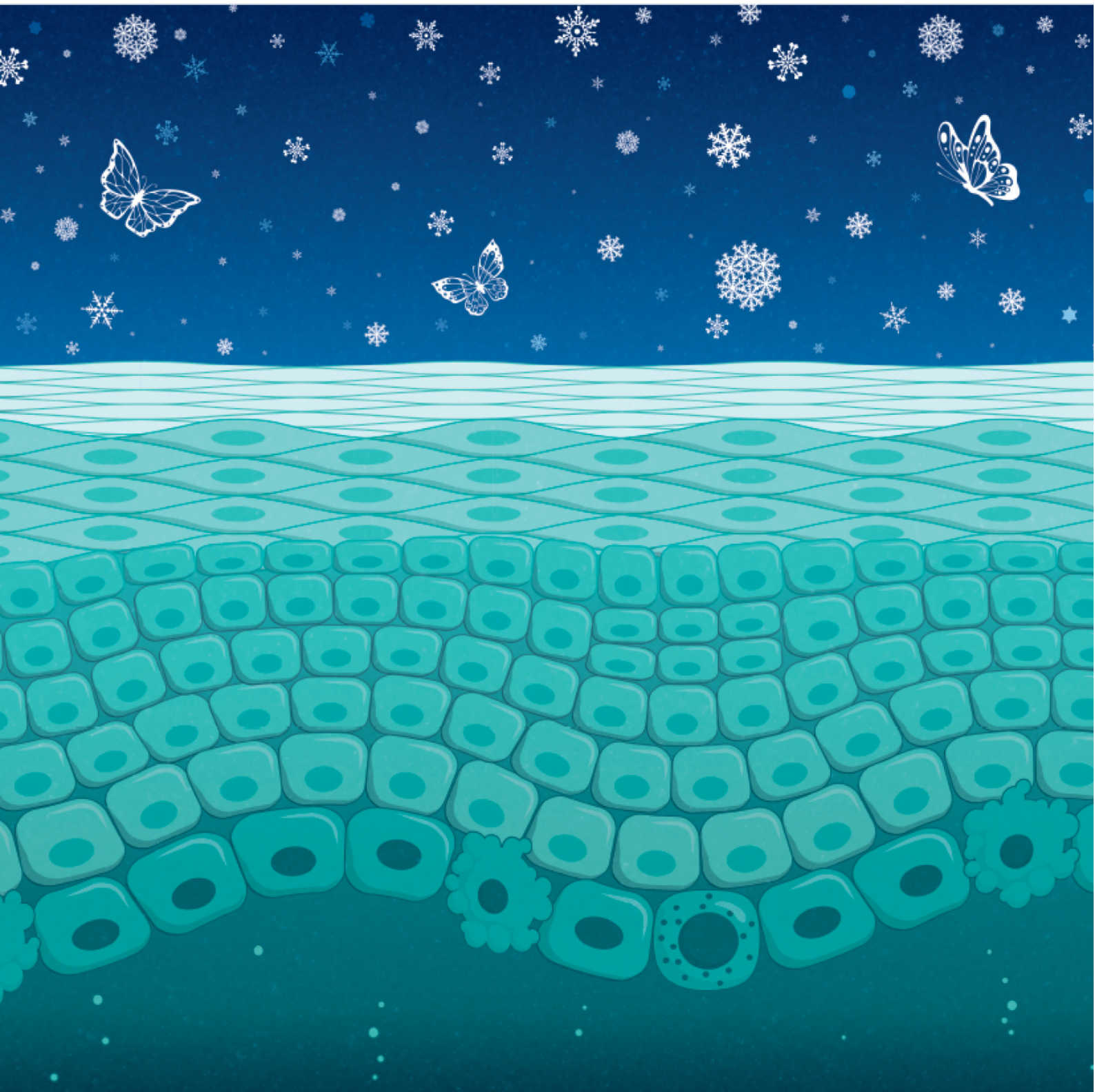

Clinical trials

In vivo CAR-T cell engineering in refractory SLE

Treatment with autologous T cells that are engineered ex vivo to express a chimeric antigen receptor (CAR) is costly, time-consuming, and requires previous lymphodepletion. Ongoing efforts to simplify autologous CAR-T cell therapy have focused on the development of lipid nanoparticles (LNPs) that deliver a CAR mRNA into $CD8^+$ T cells, to achieve generation of CAR-T cells in vivo. In the *New England Journal of Medicine*, Gao-Feng Zha, Georg Schett, Zhu Chen and colleagues report the early results of a clinical trial with in vivo CAR-T cell therapy in five individuals with refractory systemic lupus erythematosus (SLE).

The authors used LNPs that carry a portion of a CD8-targeting monoclonal antibody and encapsulate an mRNA encoding a CD19-specific CAR. Use of these LNPs (which were termed HN2301) in vitro and in non-human primates indicated that they can induce both the expression of CD19-CAR on $CD8^+$ T cells and the depletion of CD19-expressing B cells.

As HN2301 LNPs showed a favourable safety profile in the non-human primate studies, they were administered at two different doses to five individuals with refractory SLE. Treatment with HN2301 induced CD19-CAR expression on approximately 5–50% of circulating $CD8^+$ T cells as early as 6 h after the infusion and was maintained for up to 3 days. Circulating B cells were partly depleted in patients 1 and 2, who received a low dose of HN2301, or fully depleted in patients 3, 4 and 5, who all received a higher dose. Depletion of circulating B cells was observed within 6 h after HN2301 infusion and for up to 10 days. Consistently, levels of anti-nucleosome and anti-double-stranded DNA antibodies were decreased in patients 4 and 5.

The authors report no severe adverse effects, such as grade 3 or 4 cytokine release syndrome, although three patients were treated with a single dose of anti-IL-6 monoclonal antibody (tocilizumab) in response to increased cytokine levels after HN2301 infusion. Importantly, disease activity decreased in all five patients during the 3 months of follow-up. Although long-term follow-up and further data on treatment dose, schedule and responses are still required, the early findings of the study highlight the feasibility of LNPs for in vivo CAR-T cell therapy in B cell-mediated autoimmune conditions.

Maria Papatriantafyllou

Original article: Wang, Q. et al. In vivo CD19 CAR T-cell therapy for refractory systemic lupus erythematosus. *N. Engl. J. Med.* https://doi.org/10.1056/NEJMc2509522 (2025)

Systemic lupus erythematosus

PLD4 variants promote SLE via unchecked TLR activation

Excessive innate immune signalling, particularly via the type I interferon pathway, is a hallmark of systemic lupus erythematosus (SLE) and is associated with overactive Toll-like receptor (TLR) responses. The exonuclease PLD4 helps restrain activation of TLR7 and TLR9 by cleaving their ligands (single-stranded RNA and DNA). In a new study published in *Nature*, researchers have identified loss-of-function variants in *PLD4* in five patients with SLE, linking disruption of this regulatory mechanism with systemic inflammation and autoimmunity.

The study builds on previous work in monogenic SLE that identified causal gain-of-function mutations in *TLR7* and *UNC93B1*, which activate the TLR7 pathway. The newly identified *PLD4* mutations represent a novel genetic cause of monogenic SLE, further underscoring the important role of TLR dysregulation in SLE pathogenesis.

All five patients presented with renal involvement and haematological abnormalities, and some also had skin rashes, arthritis and/or serositis. Whole-exome sequencing revealed biallelic mutations in *PLD4* in all the patients, all located in the catalytic domain and predicted to be deleterious.

Analysis of the peripheral blood mononuclear cells of the patients revealed enhanced type I interferon responses, especially in dendritic cells, and pointed to increased activation of the TLR7 and TLR9 pathways. Further analysis using in vitro and ex vivo assays confirmed that the mutations impaired the exonuclease activity of PLD4.

Mice lacking PLD4 develop an autoimmune phenotype that closely resembles SLE. Mixed-bone marrow chimera experiments showed that the expansion of plasmacytoid dendritic cells and plasma cells in these mice was cell intrinsic. Importantly, treatment with the JAK inhibitor baricitinib ameliorated both the immune phenotype of the mice and the type I interferon hyperactivation observed in the patient-derived cells, highlighting its therapeutic potential for patients with PLD4 deficiency.

"We plan to extend genetic screening in SLE cohorts to identify additional patients with PLD4 mutations and to characterize the clinical spectrum of PLD4 deficiency," explains Zhihong Liu, a corresponding author on the study. "For patient care, our findings highlight the potential value of genetic testing in SLE and support evaluation of interferon-targeted therapies, such as JAK inhibitors, as promising treatment strategies."

Jessica McHugh

Original article: Wang, Q. et al. Loss-of-function mutations in *PLD4* lead to systemic lupus erythematosus. *Nature* https://doi.org/10.1038/s41586-025-09513-x (2025)

Clinical trials

Phase III trial of telitacicept in SLE

Telitacicept, a dual inhibitor of BAFF and APRIL, has now been shown in a phase III randomized controlled trial to improve systemic lupus erythematosus (SLE) disease activity when added to standard therapy. The recombinant fusion protein, which consists of TACI and the Fc portion of human IgG, acts as a soluble decoy receptor for BAFF and APRIL to inhibit B cell activation and survival and is already approved in China for the treatment of SLE.

The trial, conducted at 42 hospitals in China, included 335 adults with moderate-to-severe SLE. All patients received standard therapy plus either telitacicept (160 mg once weekly) or placebo.

At week 52, the rate of clinical response on the modified SLE Responder Index 4 was 67.1% in the telitacicept group, nearly double the response rate in the placebo group (32.7%). The difference in this clinical response between the two groups was apparent by week 4 and sustained to week 52.

Additionally, a reduction of ≥4 points in SELENA-SLEDAI score from baseline to week 52 occurred in 70.1% of the telitacicept group, compared with 40.5% of the placebo group. Notably, however, respiratory tract infections, reductions in serum levels of IgG and IgM and injection-site reactions were more common in the telitacicept group than in the placebo group.

The new findings support the further investigation of telitacicept in other populations of patients with SLE.

Sarah Onuora

Original article: van Vollenhoven, R. F. et al. A phase 3 trial of telitacicept for systemic lupus erythematosus. *N. Engl. J. Med.* **393**, 1475–1485 (2025)

Autoimmunity

SGLT2 inhibitors reduce risk of autoimmune disease

Sodium–glucose cotransporter-2 (SGLT2) inhibitors, originally developed for glycaemic control, are increasingly recognized for providing multisystem benefits, including cardiovascular and renal protection. A new population-based study suggests that these drugs also reduce the risk of autoimmune rheumatic diseases in individuals with type 2 diabetes mellitus.

Using a nationwide health insurance database in South Korea (2012–2022), the investigators compared more than 2 million adults with type 2 diabetes mellitus who initiated either an SGLT2 inhibitor (n = 552,065) or sulfonylurea (n = 1,480,092). Autoimmune rheumatic diseases were defined as a composite of inflammatory arthritis — including rheumatoid arthritis, psoriatic arthritis and spondyloarthritis — and systemic autoimmune rheumatic diseases — including systemic lupus erythematosus, Sjögren disease, systemic sclerosis, idiopathic inflammatory myositis, mixed connective tissue disease, polymyalgia rheumatica and vasculitides.

After propensity score weighting and a median follow-up of 9 months, SGLT2 inhibitor use was associated with an 11% lower risk of incident autoimmune rheumatic disease compared with sulfonylurea use (HR 0.89, 95% CI 0.81–0.98). The reduction in risk was driven by inflammatory arthritis (HR 0.86, 95% CI 0.77–0.97), with no significant difference observed for systemic autoimmune diseases.

Exploratory analyses showed a similar pattern when SGLT2 inhibitors were compared with dipeptidyl peptidase-4 inhibitors, but no significant difference was observed versus glucagon-like peptide-1 receptor agonists, possibly owing to low use of the latter in the study population.

Although the absolute benefit was small, the study provides the first population-level evidence that SGLT2 inhibition might confer protection against autoimmune rheumatic disease. Replication in other populations and longer-term studies will be essential to confirm the immunomodulatory effects of SGLT2 inhibitors.

Jessica McHugh

Original article: Hong, B. et al. Sodium-glucose cotransporter-2 inhibitors and risk of autoimmune rheumatic diseases: population based cohort study. *BMJ* **391**, e085196 (2025)

Related article: Karacabeyli, D. & Lacaille, D. Glucagon-like peptide-1 receptor agonists in arthritis: current insights and future directions. *Nat. Rev. Rheumatol.* **21**, 671–683 (2025)

Epidemiology

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Timing matters in diagnosis of cancer with immune-mediated inflammatory disease

Dongxue Wang & Jianguang Ji

Immune-mediated inflammatory diseases (IMIDs) are associated with cancer risk through mechanisms involving disrupted immune tolerance and dysregulated immune responses. Deng et al. investigated how the timing of IMID diagnosis relative to cancer diagnosis affects patient survival outcomes.

REFERS TO Deng, G. et al. Differential impact of immune-mediated inflammatory diseases before versus after cancer on patient survival: a nationwide cohort study. *Rheumatology* https://doi.org/10.1093/rheumatology/keaf213 (2025).

The association between immune-mediated inflammatory diseases (IMIDs) and cancer is dynamic and bidirectional, largely driven by shared genetic and environmental risk factors. Variants of genes of the HLA complex or other immune regulatory genes, such as cytotoxic T lymphocyte-associated antigen 4 (*CTLA4*), have been strongly associated with susceptibility to various IMIDs and cancers. These variants often confer altered antigen presentation, defects in immune tolerance and dysregulated immune responses[1]. In addition, IMIDs and cancer share non-immune genetic loci, as exemplified by the overlapping mutational profiles between inflammatory bowel disease and colon cancer, which implicate common pathways of immune and cellular dysregulation in IMID and cancer pathogenesis[2]. Environmental factors that promote DNA damage and chronic inflammation and impair immune surveillance, such as smoking, diet, pollution, stress and gut microbiome imbalances, also contribute to the development of both IMIDs and cancer[3]. Medical treatments for IMIDs, such as TNF inhibitors, are likely to increase risk of cancer owing to their immunosuppressive effects[4], whereas surveillance bias might also enhance the frequency of dual IMID and cancer diagnoses[5]. The variations in cancer risk across different IMIDs and anatomical sites highlight the need for precise risk estimation across diverse populations.

Understanding the interplay between IMIDs and cancer might uncover shared disease mechanisms and inform targeted prevention strategies. Moreover, clarifying the effect of IMIDs on cancer survival will guide clinical decision-making towards precision medicine. However, current evidence for cancer survival related to IMIDs remains conflicting and limited. Some studies suggest improved survival in patients with cancer and IMIDs, whereas others report poor outcomes.

Deng et al.[6] explore how the timing of an IMID diagnosis relative to cancer onset might affect survival outcomes. Their findings reveal a striking paradoxical pattern: pre-existing IMIDs are associated with an increased mortality risk, whereas IMIDs diagnosed after the onset of cancer seem to confer a survival advantage. This distinction underscores the dynamic and context-dependent roles of IMIDs in cancer progression and outcomes. This exploration of the temporal sequence between IMIDs and cancer is both thought-provoking and clinically relevant. However, the finding that the timing of IMID onset, whether before or after a cancer diagnosis, has such divergent effects on survival is unexpected and warrants further investigation to confirm these associations and elucidate underlying mechanisms.

Several plausible explanations might account for the elevated mortality risk observed in people with cancer and pre-existing IMIDs. First, these individuals often have poorer baseline health and a higher burden of chronic comorbidities than those with cancer and no other pre-existing conditions, and this might negatively affect cancer prognosis. For example, a previous study demonstrated a significantly reduced survival rate among patients with breast cancer who had previously been hospitalized for over three years due to autoimmune disorders[7]. Second, individuals with IMIDs commonly exhibit immune dysregulation and are likely to tolerate poorly or respond suboptimally to immunotherapy, such as immune checkpoint inhibitors[8]. Third, immunosuppressive treatments used for IMIDs are likely to contribute to cancer progression and thereby to elevated mortality among individuals with a dual diagnosis.

The improved survival among patients diagnosed with IMIDs after the onset of a variety of cancer types, including colorectal, lung, pancreatic, oesophageal and biliary-duct cancers, is interesting and noteworthy. One possible explanation, as suggested by Deng et al.[6], is that the onset of IMIDs after cancer might reflect heightened immune system activation and an enhanced ability of immune cells to recognize and eliminate tumour cells. Indeed, previous research has associated increased lymphocytic activity within tumours with improved prognosis[9]. Similarly, better overall survival has been reported in patients with lung cancer and autoimmune rheumatic diseases compared with patients with lung cancer and without autoimmunity, independent of cancer stage or treatment[10].

Although the study of Deng et al.[6] offers valuable insights, several important challenges must be addressed. In this register-based study, the median interval between a cancer and an IMID diagnosis was just 0.07 years, and this suggests that an unknown number of people are likely to have experienced near-simultaneous diagnoses. The delays in referral from primary to secondary care might obscure the true sequence of disease onset between cancer and IMID, suggesting frequent misclassification of pre-existing undiagnosed conditions as incident cases. Thus, individuals with undiagnosed pre-existing IMIDs might be misclassified as developing IMIDs post-cancer. Future register-based studies should consider excluding those with a small interval between the two diagnoses, such as an interval of one year or less, to avoid such misclassification.

In addition to the lack of detailed information about the time between cancer onset and an IMID diagnosis, detailed analysis of the time interval between the diagnoses would also be required to exclude

immortal time bias in patients who receive an IMID diagnosis long after the onset of cancer. Immortal time bias is a methodological bias in epidemiological and clinical research that frequently leads to the overestimation of survival time in the exposed group, thereby distorting the true association between exposure (in this case, an IMID diagnosis) and clinical outcomes (in this case, survival). As some individuals with cancer must survive long enough to receive an IMID diagnosis, they might have an artificially prolonged survival advantage compared to those with no IMID diagnosis after cancer. In this context, the period between cancer diagnosis and the subsequent onset of IMIDs should be considered a non-exposure interval (that is, as immortal time) to exclude an artificial finding of a protective effect of IMIDs diagnosed after cancer.

Besides detailed analyses of data on time between diagnoses, future studies should investigate associations between specific types of cancer and IMIDs, as well as the effect of the various treatments on survival. The dataset analysed by Deng et al.[6] includes 24 IMIDs and 26 cancer types, but the relatively small sample size for each patient subgroup does not enable detection of significant associations between specific types of cancer and IMIDs. Furthermore, this dataset lacks information about treatment for both IMIDs and cancer, and this might potentially compromise the validity of study conclusions and limit interpretation and clinical application. The observed survival advantage among patients with cancer and subsequent IMID diagnoses might reflect differences in treatment intensity (for example, because of additional targeted treatments following an IMID diagnosis) and frequency of surveillance, or it might stem from biological interactions between immunomodulatory treatments and tumour progression. The inclusion of detailed information about treatment regimens such as immunosuppressants, DMARDs and cancer therapies will help clarify these open questions.

Overall, the study by Deng et al.[6] underscores the potential importance of diagnostic timing and immune system dynamics in cancer outcomes. Although the findings should be interpreted with caution, the study raises important questions that require further investigation to clarify the relationship between IMIDs and cancer survival. Comprehensive evidence based on appropriately reported data will be required to guide clinical decision-making for patients with both IMIDs and cancer.

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Competing interests

The authors declare no competing interests.

Rheumatoid arthritis

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The epidemiology of RA

Axel Finckh

Analysis of regional variations in the epidemiology of rheumatoid arthritis (RA) over the past 40 years indicates that the age-standardized incidence of RA has increased — and is expected to continue rising — while the mortality and morbidity of the disease are decreasing. As a result, the number of years lived with disability and the overall disease burden attributable to RA have increased and are projected to rise further.

Refers to Jin, W. et al. Spatiotemporal distributions and regional disparities of rheumatoid arthritis in 953 global to local locations, 1980-2040, with deep learning-empowered forecasts and evaluation of interventional policies benefits. *Ann. Rheum. Dis.* https://doi.org/10.1016/j.ard.2025.04.009 (2025).

Rheumatoid arthritis (RA) is the most common type of chronic inflammatory arthritis with a global distribution. Jin et al.[1] examined regional variations in the epidemiology of RA from 1980 to 2021 and projected future trends under various scenarios. To do so, the authors used global epidemiological datasets, including publicly available data from the Global Burden of Disease 2021 report, which they analyzed using artificial intelligence-powered advanced deep learning algorithms across 953 locations worldwide.

Key findings indicate that both the age-standardized incidence and the prevalence of RA have continued to rise by 13% and 14%, respectively, in the past 30 years. The age of onset of RA has trended towards younger age groups in the past. Interestingly, regions with higher socio-economic development generally report higher RA incidence rates than less-developed regions. In the period from 1980 to 2021, both the death rates and the number of years of life lost attributable to RA decreased by one third. By contrast, the number of years lived with disability owing to RA increased over the same period.

The overall disease burden attributable to RA was assessed using the 'disability-adjusted life years' (DALY) construct, which pools years of life lost due to premature mortality and years lost due to disability related to the disease. In essence, the DALY construct estimates the quantity of healthy life years lost owing to RA compared with a healthy state, with one DALY unit representing 1 year of healthy life lost[2]. Women with RA generally bear a greater disease burden (as measured by DALY) than men do. Globally, DALY counts attributable to RA nearly doubled over the past 30 years, reflecting a shift from earlier mortality to prolonged disability, as patients now live longer but with more years affected by the disease, relative to some decades ago.

RA-associated disability exhibits marked regional imbalances that seem to be deepening. For example, the Tokyo region has experienced a 22% decline in RA-related disease burden over the past 30 years. The authors propose that factors such as the effectiveness of disease-management programs, changes in environmental exposures and lifestyle modifications potentially explain these regional differences. The example from Japan suggests that proactive healthcare strategies have the potential to reverse RA-associated disability trends.

On the basis of projections for the next 15 years, RA incidence rates and RA disease burden (measured by DALY) are expected to continue to increase. However, the disease burden is predicted to decline in regions with high socio-economic status, probably as a result of improved disease management. The authors project that targeted interventions might further reduce the RA burden by up to 20% and lower RA-related mortality by as much as 17%. Jin et al. thus advocate for health policies and resource allocation to help reduce the burden of RA, emphasizing interventions such as early diagnosis, smoking-control policies, and appropriate use of advanced antirheumatic therapies[1].

A key limitation of this analysis lies in the quality and completeness of the data used for modeling. Although the Global Burden of Disease estimates currently represent the most comprehensive source for global epidemiological studies, the approach relies heavily on complex imputations, especially in regions in which epidemiologic data on RA are sparse or of questionable reliability. Consequently, some of the observed regional disparities in RA estimates, particularly in underserved areas, might reflect deficiencies in healthcare infrastructure and rheumatology care, rather than true epidemiological differences. The validity and relevance of the DALY construct also remains subject to debate[3], partly because some of its key components, such as the 'disability coefficient', are based on arbitrary assumptions. This coefficient, for instance, implies that years lived with certain diseases (such as RA) are inherently less valuable than years lived without disability or disease. Critics argue that such a metric is too disconnected from real-world experience to serve as a reliable basis for setting priorities in resource allocation or informing health policy decisions[4].

Although methodological concerns introduce some uncertainty into specific estimates and outcomes, the overall conclusions of this analysis remain sound. The global incidence and prevalence of RA continue to rise, while both mortality and morbidity associated with the disease are declining — probably reflecting improvements in disease management. As a result, more individuals are living longer with RA, leading to an increase in years lived with disability and, consequently, higher DALY counts. This analysis offers valuable insights into the long-term epidemiological trends of RA. Importantly, it can support health systems in anticipating future demands for RA care and prioritizing resource allocation to measures that are most likely to have the greatest impact.

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Competing interests

The author declares no competing interests.

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Review article

Check for updates

Cutaneous lupus erythematosus — from pathogenesis to targeted therapy

Benjamin Klein[1], Allison C. Billi[2], Lisa Abernathy-Close[1] & J. Michelle Kahlenberg[1,2]

Abstract

Cutaneous lupus erythematosus (CLE) is a complex inflammatory skin disease that presents either in isolation or as a frequent manifestation of systemic lupus erythematosus (SLE). CLE subtypes show clinical heterogeneity and varying associations with SLE. Histologically, CLE is characterized by interface dermatitis, a reaction pattern that involves immune-cell infiltration of the dermo-epidermal junction. In-depth characterization of both non-lesional and lesional lupus skin has reshaped our understanding of pathogenesis. Non-lesional and lesional lupus skin exhibits early and chronic upregulation of type I interferons, which drive photosensitivity, myeloid-cell recruitment and amplification of cytokine responses in both immune and non-immune cells. This detailed understanding of CLE biology has enabled the development of targeted therapies. Ongoing research to identify key pathogenic mechanisms will create opportunities for prevention of CLE and CLE-to-SLE transition.

Sections

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Key points

- Clinical, histological and laboratory findings help to distinguish among subtypes of cutaneous lupus erythematosus (CLE) and can be used to predict potential transition into systemic lupus erythematosus (SLE).
- Type I interferon (IFN) production is an early and persistent finding in non-lesional skin in SLE and CLE.
- Keratinocytes are pro-inflammatory and prone to type I IFN production, even in non-lesional skin.
- Environmental triggers, such as ultraviolet light, over-activate type I IFN and innate immune responses in primed skin of patients with SLE or CLE.
- Plasmacytoid dendritic cells and myeloid-derived cells contribute to the pathogenesis of CLE.
- Absence of the tolerogenic Langerhans cells and dysfunction of regulatory T cells seem to contribute to inflammatory activation in CLE.
- Type I IFN signatures are present in all lesional CLE subtypes, and targeting IFN signaling is a promising way to treat CLE lesions.

Introduction

The outermost barrier of the human body features an orchestrated regulation of epithelial, stromal and immune-cell homeostasis, resulting in a fine-tuned interaction between sensing of external stimuli, regulation of inflammation and repair of damage. The disruption of homeostasis by environmental or pathogen-induced stress, skin injury, impairment of regulatory mechanisms or overdrive of cellular signalling pathways might tip the scale, precipitating or exacerbating skin pathology.

Cutaneous lupus erythematosus (CLE) is a complex inflammatory skin disease with a wide spectrum of lesions ranging from acute and non-scarring lesions to chronic, disfiguring disease (Box 1). CLE occurs either as an isolated skin disease or as a manifestation in about 70–80% of individuals with systemic lupus erythematosus (SLE)[1]. The initial CLE classification by Gilliam and Sontheimer included three major CLE subtypes: acute (ACLE); subacute (SCLE); and chronic CLE (CCLE)[2]. Studies of another rare form of CLE, namely, tumid lupus, have led to the Düsseldorf classification, which distinguishes intermittent CLE as the fourth CLE subtype[3] (Fig. 1). Multiple CLE subtypes may occur in a single patient, although one subtype is usually predominant. CCLE, particularly discoid lupus erythematosus (DLE) is the most common CLE subtype, accounting for up to 80% of all CLE cases[4]. Further subtyping depends on distribution (for example, localized versus generalized ACLE), morphology (for example, annular versus psoriasiform SCLE) and affected skin layers (for example, CLE profundus (also known as CLE panniculitis)) (Fig. 1 and Box 2). Patients with CLE might also develop skin manifestations that are not CLE specific but are observed in many autoimmune diseases, such as vasculitis or non-scarring alopecia[5,6].

CLE is often a devastating disease, and it substantially impacts patient quality of life more than other inflammatory skin lesions[7]. Cross-sectional studies of adults with CLE have demonstrated correlations between reduced quality of life and increased skin disease activity[8,9]. Thus, understanding CLE pathogenesis is crucial for improving treatment of skin inflammation and the lived experience of patients. The factors that contribute to pathogenesis in CLE are manifold. Genetic predisposition, environmental stressors such as ultraviolet (UV) radiation and smoking, and drivers of chronic activation of the immune system, including upregulation of type I interferon (IFN) signalling, prime normal-appearing skin for inflammatory responses. Once triggered, an interplay of humoral and cellular factors drives activation of innate and adaptive immune cells recruited to the dermo-epidermal junction (DEJ). This inflammatory and cytotoxic response culminates in vacuolar degeneration in basal keratinocytes and is mediated and amplified by skin-resident stromal cells, such as keratinocytes and fibroblasts, and immune cells, such as myeloid cells, plasmacytoid dendritic cells (pDCs), T cells, and B cells. Immune complex deposition and a chronic inflammatory circuit then ensues.

In this Review, we discuss CLE pathogenesis with an emphasis on the interplay between chronic IFN cycles, tissue-resident cells and non-tissue-resident cells. Epidemiology of CLE, the potential risk factors of progression to SLE and genetic factors implicated in CLE and SLE are described. We explain the role of type I IFN signalling and non-lesional skin dysfunction in CLE that primes for cutaneous inflammation. We elaborate on triggers that result in provocation or progression of skin lesions such as UV radiation and discuss novel and upcoming therapeutic approaches to targeting these pathways.

Epidemiology of cutaneous lupus erythematosus

Over the past four decades, the incidence of CLE in the USA has remained stable, with no significant trends across sex or age groups[10]. The incidence of CLE in population-based studies is reported at 3.9–4.3 per 100,000 person-years, with prevalence estimates ranging from 70 to 109 per 100,000 (refs. 10–12). In Europe, estimates have been similar[4]. Epidemiological studies of Asia, Africa and Australia are scarce; a Korean study found an estimated incidence of 4.4 per 100,000 (ref. 13). The female-to-male ratio is approximately 3:1, and the mean age at onset is typically in the fifth to sixth decade of life[4]. Notably, CLE is more common than SLE in men and older adults, with the incidence of CLE peaking in the 60–69-year age group[12]. The racial and ethnic demographics of CLE show marked disparities in incidence and disease burden. In the USA, Black individuals have a significantly higher incidence of CCLE, particularly DLE, than white individuals; data from the Georgia Lupus Registry indicate that Black individuals have a 3- to 5-fold increased incidence of CCLE and DLE compared with white individuals[14]. Black patients also tend to experience more severe skin damage and earlier onset of disease than white patients[14]. Studies in other regions demonstrate similar disparities. In New Zealand, Māori and Pacific peoples have a higher relative risk of all types of CLE, especially DLE, than individuals of European ancestry, with a relative risk of 5.96 for DLE for the former[15]. Genetic factors are likely to influence these differences, but socio-environmental factors might also contribute, and further research is required to understand the relative contributions of genetics and environment to CLE and SLE incidence.

Mortality among individuals with isolated CLE is comparable with that of the general population, with one retrospective population-based cohort study reporting a standardized mortality ratio of 1.23 (95% CI, 0.88 to 1.66)[10]. However, a substantial proportion of individuals with CLE either have a concurrent diagnosis of SLE at presentation (approximately 24% in one study) or develop SLE during follow-up (an additional 18%)[4]. Co-occurrence of CLE and SLE increases the risk of morbidity and mortality. A recent systematic review described

Box 1 | Clinical and histological features of cutaneous lupus erythematosus subtypes

Acute cutaneous lupus erythematosus

Localized acute cutaneous lupus erythematosus (ACLE) typically features a malar rash characterized by symmetrical macules and papules that occur on the cheeks and bridge of the nose in the so-called 'butterfly rash' distribution, characteristically sparing the nasolabial folds. This rash is often accompanied by erosions or ulcerations of the nasal mucosa and facial oedema. Generalized ACLE often coincides with organ manifestations and presents as a symmetrical widespread rash sparing the knuckles that resembles a drug eruption or toxic epidermal necrolysis. Histology is characterized by prominent interface dermatitis, potentially with epidermal detachment (toxic epidermal necrolysis-like ACLE). Drug-induced photosensitivity, rosacea, atopic dermatitis, pemphigus erythematosus, contact dermatitis or photocontact dermatitis are differential diagnoses to ACLE.

Subacute cutaneous lupus erythematosus

Subacute cutaneous lupus erythematosus (SCLE) often occurs in a symmetric distribution on sun-exposed areas, usually sparing the central face and the scalp. The eruption initially presents as erythematous papules and macules with a slight scale, evolving into papulosquamous or annular plaques[196]. SCLE shows strong photosensitivity and is often drug induced (for example, by treatment with terbinafine, thiazide diuretics or angiotensin-converting enzyme inhibitors). Lesions sometimes subside with vitiligo-like hypopigmentation but do not scar. Histological features are subtle in SCLE but include interface dermatitis. Psoriasis, dermatomyositis, erythema annulare centrifugum, erythema gyratum repens, photolichenoid drug eruption, granuloma annulare, or pemphigus foliaceus are differential diagnoses to SCLE.

Discoid lupus erythematosus

Discoid lupus erythematosus (DLE) is the most common CLE subtype, and presents either as localized (80%) or as disseminated (20%) rash, with disseminated DLE being more associated with systemic lupus erythematosus (SLE) than localized DLE. DLE is typically distributed on ultraviolet radiation-exposed areas such as the face, ears and scalp, but might involve the extremities when widespread[196]. Lesions typically present as well-demarcated scaly, erythematous, variably hypo- and hyperpigmented macules and papules and indurated plaques that may show characteristic occlusion of follicles with hyperkeratotic plugs — so-called 'follicular plugging'. Lesions frequently eventuate in scarred plaques with central atrophy and hypopigmentation. Histology shows prominent perifollicular and perivascular infiltrates, interface dermatitis and plugging of follicular ostia with keratotic material. Psoriasis, cutaneous T cell lymphoma, polymorphic light eruption, or sarcoidosis are differential diagnoses to DLE.

Profundus cutaneous lupus erythematosus or panniculitis cutaneous lupus erythematosus

Profundus CLE (also known as panniculitis CLE) is characterized by indurated nodules or plaques that resolve with deep lipoatrophy, manifesting as depressed plaques. Histological features of active lesions include lobular panniculitis and mucin deposition between collagen bundles. Involvement of the overlying skin with other forms of CLE might be present. Differential diagnoses include other forms of panniculitis, such as erythema nodosum.

Chilblain cutaneous lupus erythematosus

Chilblain CLE features purple, violaceous, painful plaques in acral areas (primarily the digits of the hands and feet) that are often induced or aggravated by cold exposure but may occur in the absence of these precipitants. Hyperkeratosis and ulceration are common. Differential diagnoses include idiopathic perniosis (chilblains), or secondary chilblains due to other diseases such as cryoglobulinaemia.

Intermittent (tumid) cutaneous lupus erythematosus

Intermittent (tumid) CLE is characterized by erythematous or violaceous firm, indurated, urticaria-like single or multiple plaques without epidermal involvement in sun-exposed areas that spare the knuckles. Histology shows patchy dermal infiltrates (lymphocytes and plasmacytoid dendritic cells) and mucin deposition. Differential diagnoses include reticular erythematous mucinosis, pseudolymphoma and polymorphous light eruption.

progression of isolated CLE to SLE and reported a range of 0% to 42% among adults and 0% to 31% among paediatric populations[16]. Further, progression to SLE may occur both early and late after CLE diagnosis, with substantial variability depending on patient risk factors and study design[4,11,17]. Collectively, these longitudinal studies indicate that the risk of progression from CLE to SLE is clinically substantial, and regular monitoring and early identification of systemic symptoms are recommended for optimal management[16].

Risk of progression to systemic lupus erythematosus

In CLE, many factors have been found to correlate with increased risk of SLE or progression to SLE — most notably, CLE type. ACLE is frequently associated with active SLE. Among other CLE subtypes, risk of progression to SLE is highest among patients with SCLE[18], although generalized DLE, defined as affecting areas both above and below the neck, also confers increased risk of progression to SLE[19,20]. Risk is also stratified by systemic autoimmune markers. These factors include testing positive for antinuclear antibodies (ANAs), especially when high ANA titres are present, haematological abnormalities such as cytopenias, and the presence of additional lupus classification criteria at baseline[16]. Individuals with CLE that test positive for anti-Ro or Sjögren syndrome A (SSA) antibodies also appear to be at an increased risk of progression to SLE, although they have not yet been directly compared with patients with CLE who lack anti-Ro antibodies[21,22].

During assessment of potential risk to progression, it is important to differentiate between progression to mild versus severe SLE. Some patients presenting with CLE receive a consecutive diagnosis of SLE that is only based on the mucocutaneous criteria of previous versions of the ACR classification criteria for SLE[23] — namely, malar rash, discoid rash, enhanced sensitivity to UV radiation (photosensitivity) and oral ulcers but otherwise have mild systemic disease without life-threatening organ involvement[17]. When specifically examining

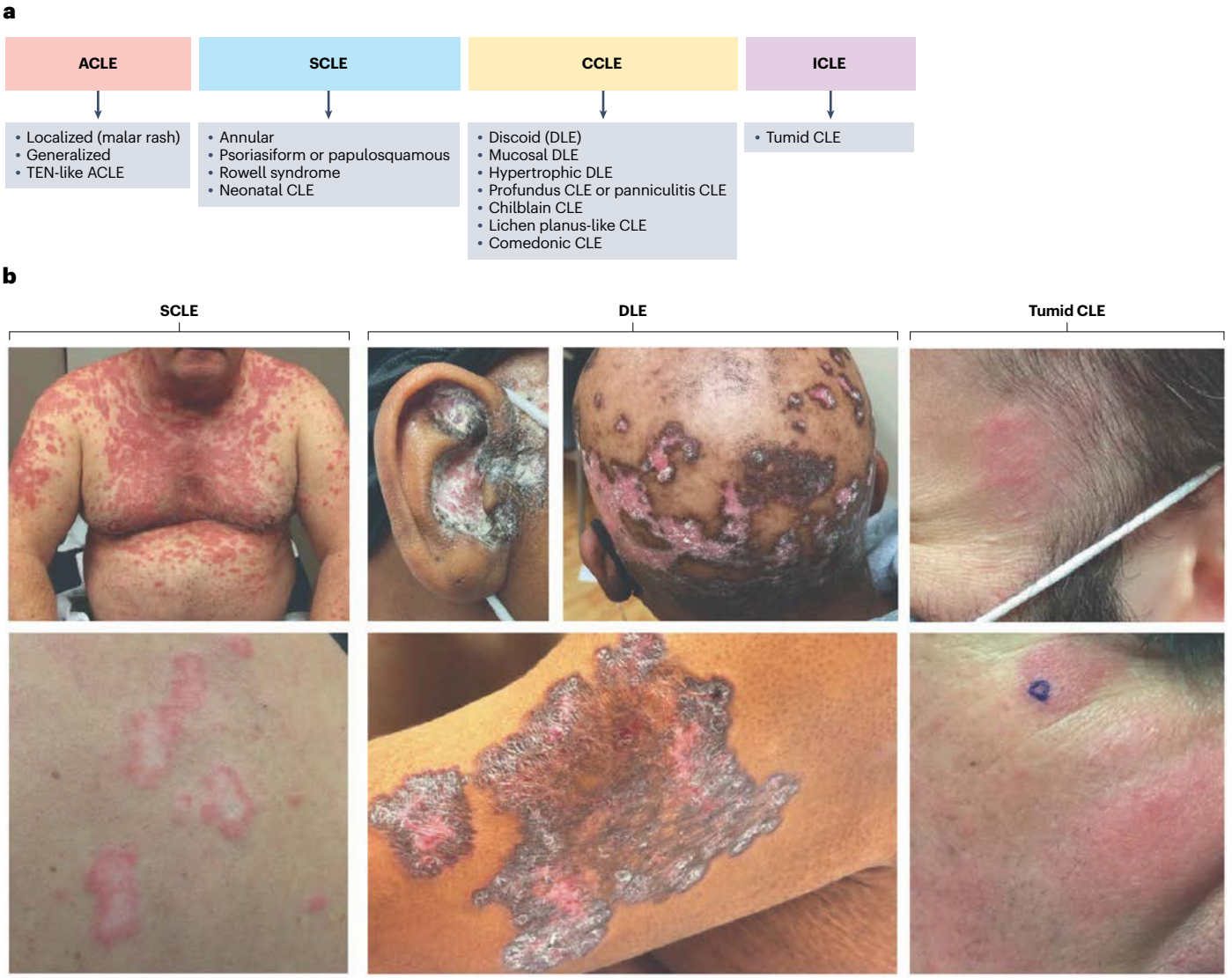


Fig. 1 | Cutaneous lupus erythematosus classification and skin-lesion morphology. a, Cutaneous lupus erythematosus (CLE) classification with four major subtypes according to the Düsseldorf classification[3] and numerous specific subtypes. Acute CLE (ACLE) can be distinguished from subacute (SCLE), chronic (CCLE) and intermediate CLE (ICLE). ACLE presents as localized (malar rash), generalized or toxic epidermal necrolysis (TEN)-like manifestation. SCLE can be divided into annular and psoriasiform subtypes. Rowell syndrome often manifests as erythema multiforme-like skin lesions, accompanied by serological features such as positive ANA (antinuclear antibody), anti-Ro/SSA (Sjögren syndrome A) or anti-La/SSB antibodies. Neonatal CLE might occur in babies born to mothers who test positive for the autoantibodies anti-SSA/Ro, anti-SSB/La or anti-U1RNP. Neonatal CLE typically manifests as annular, SCLE-like lesions on the face. CCLE is divided into multiple subtypes including discoid (DLE), mucosal DLE, hypertrophic DLE, profundus or panniculitis CLE, chilblain CLE, lichen planus-like CLE and comedonic CLE. ICLE is often also referred to as tumid CLE[190]. **b**, Clinical images of SCLE, DLE, and tumid CLE. SCLE features a symmetric distribution on sun-exposed areas with annular or papulosquamous plaques. Annular lesions are often accompanied by central vitiligo-like hypopigmentation. DLE typically occurs on the face, ears and scalp but can occur in sun-exposed areas below the neck when widespread. Note that DLE lesions show a hyperpigmented periphery with depressed central hypopigmented atrophy and scarring. Patients with tumid CLE show indurated, urticaria-like erythematous plaques without epidermal involvement in sun-exposed areas.

the risk of progression from DLE to severe SLE, defined as SLE requiring hospitalization and specific treatment[24], age ≤25 years at the time of DLE diagnosis, ANA titre ≥1:320, and Fitzpatrick phototype V or VI (darker skin types according to a standardized classification of the skin's response to UV exposure[25]) were associated with a significantly increased risk of progression to severe SLE. A follow-up study validated that the absence of these features effectively identified a subset of patients with DLE and no risk of progression to severe SLE[26].

To date, no major rheumatology or dermatology societies have issued formal guidelines advocating a specific method for clinical and laboratory monitoring of patients with CLE for the development of SLE. Clinical monitoring with total body skin examination, including

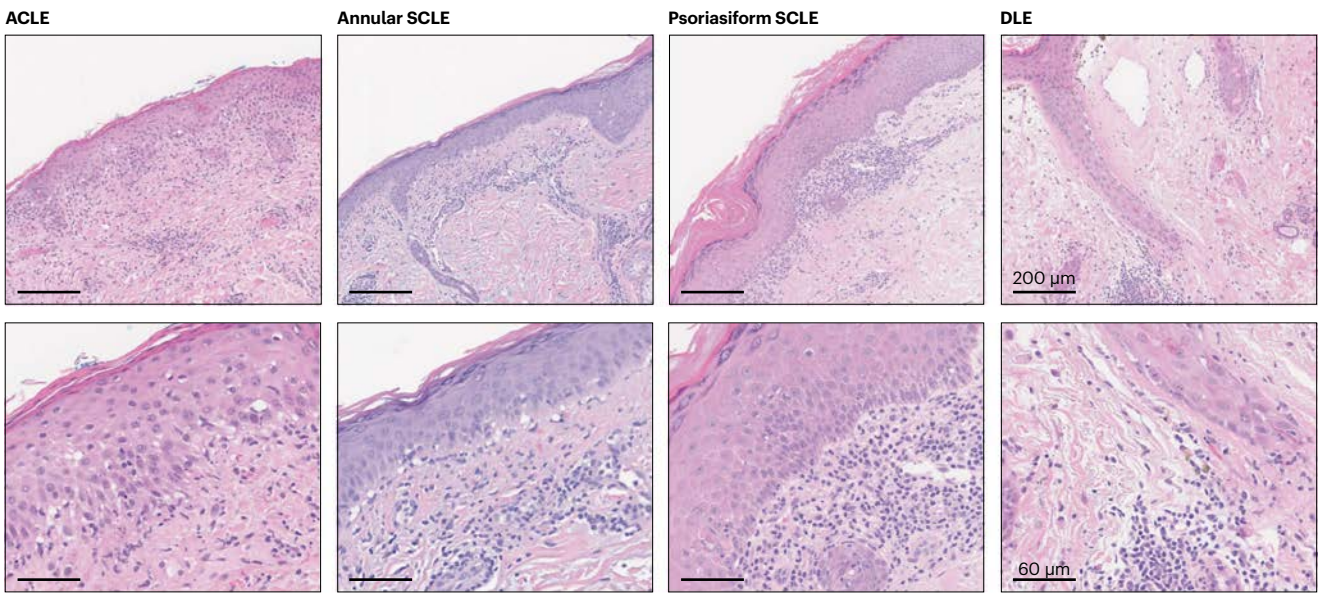
an inspection of mucosal surfaces (oral ulcers) and a complete review of systems, as well as laboratory monitoring, has been recommended[16]. Laboratory monitoring may reasonably include complete blood count and ANA, with positive ANA titres triggering further autoantibody testing including double-stranded DNA (dsDNA) and extractable nuclear antibody tests, with some additionally advocating for urinalysis and renal-function tests[16,19,27]. No studies clearly specify optimal monitoring intervals. This gap in the literature highlights the need for rigorous, high-quality prospective longitudinal research to avoid overscreening in some populations and underscreening in others.

Box 2 | Diagnosis of cutaneous lupus erythematosus

Cutaneous lupus erythematosus (CLE) is diagnosed by a thorough assessment of the onset, duration and morphology of skin lesions, histopathology and laboratory findings. Typical histopathological findings depend on the subtype but generally include dermal mucin deposition and an inflammatory infiltrate along the dermo-epidermal junction (DEJ) that is termed 'interface dermatitis' and is associated with the cell death of basal keratinocytes (see the figure, see also Fetter et al.[197] for a recent review of histopathological features). Of note, tumid lupus does not show interface dermatitis but features mucin deposition, oedema in the papillary dermis and a dermal lymphocytic infiltrate, as well as photosensitivity. This has therapeutic implications, as patients with intermediate CLE (ICLE) are often not included in clinical trials. Diagnostic procedures may further include direct immunofluorescence to detect depositions of IgG, IgM, IgA or complement (C3) at the DEJ — also known as 'the lupus band test' — in lesional CLE skin or in non-lesional, sun-protected skin in systemic lupus erythematosus (SLE). Notably, immune complex deposition at the DEJ can be positive in other dermatological conditions and also in healthy, sun-exposed skin[67]. Photoprovocation, deliberate administration of ultraviolet (UV) radiation, is used to evaluate photosensitivity and to further confirm CLE; in affected patients, UV-induced lesions occur up to 21 days post-exposure and typically persist[78].

During the diagnostic work-up, a complete review of systems is recommended to evaluate for associated SLE: physical examination including evaluation of skin and mucosa for worsening of CLE and oral ulcers lasting for more than 2 weeks; and laboratory evaluation including complete blood count, serum creatinine, urine protein and anti-nuclear antibody testing with subsequent testing for autoantibodies to double-stranded DNA (dsDNA) and extractable nuclear antigens, if the anti-nuclear antibody test is positive[198]. In SCLE, anti-Ro/Sjögren syndrome A and anti-La/Sjögren syndrome B are often positive, whereas anti-Smith or anti-dsDNA antibodies are frequently seen in SLE-associated CLE. After establishment of a CLE diagnosis, the activity of disease is assessed by using the Cutaneous Lupus erythematosus disease Area and Severity Index (CLASI), an instrument developed for scoring CLE skin activity and damage[199]. In Europe, the revised CLASI (RCLASI) is used as the primary scoring system. The RCLASI emphasizes morphological criteria, for example, including oedema, which is an important and often underrecognized clinical sign. Further assessments include the degree of pain and itch as well as skin-disease-associated quality of life[7,8,200–202].

The box figure shows representative histopathology images of haemotoxylin and eosin (H&E)-stained acute CLE (ACLE), annular subacute CLE (SCLE), psoriasiform SCLE and discoid lupus erythematosus (DLE). Enlarged area depicts features of each subtype. All subtypes show interface dermatitis with vacuolar degeneration of basal keratinocytes. Note the differences in the epidermal thickness in annular versus psoriasiform SCLE. DLE shows deep dermal and periadnexal inflammatory infiltrate and pigment incontinence. Scale bars top row, 200 µm. Scale bars bottom row, 60 µm.



The pathogenesis of CLE

Type I interferon signalling

CLE lesions are characterized by a cytotoxic immune response against the epidermis. Previous studies have suggested that during CLE pathogenesis an inflammatory trigger (for example, UV light) leads to the formation of a lesion through externalization of antigens that are recognized by pathogenic autoantibodies. However, pathogenesis of CLE is likely to be more complex than this model, as not all disease subtypes are associated with known autoantibodies. Importantly, all subtypes of CLE are associated with an activation of the type I IFN pathway that promotes the cytotoxic epidermal reaction. Type I IFNs signal through the IFN-α/β receptor (IFNAR) to activate Janus kinase 1 (JAK1) and tyrosine kinase 2 (TYK2). This leads to phosphorylation of signal transducer and activator of transcription 1 (STAT1) and STAT2, which form a complex with interferon regulatory factor 9 (IRF9) to then translocate to the nucleus to induce expression of IFN-stimulated genes via binding to interferon-stimulation response elements[28]. Chronic upregulation of IFN-stimulated genes is referred to as the 'IFN signature'. This type I IFN signature is robustly detected in lesional and non-lesional, sun-protected skin in patients with a history of CLE[29] (Fig. 2). Moreover, IFN signatures are increased, even in patients with so-called 'incomplete lupus', who have detectable antinuclear antibodies but do not meet SLE criteria[30,31].

Type I IFNs are crucial mediators of inflammation through their effects on activation and metabolic reprogramming of myeloid cells, T cell polarization and sensitization of tissues to environmental stimuli[32–35]. The importance of type I IFN in CLE pathogenesis is further highlighted by the striking beneficial effects of drugs targeting

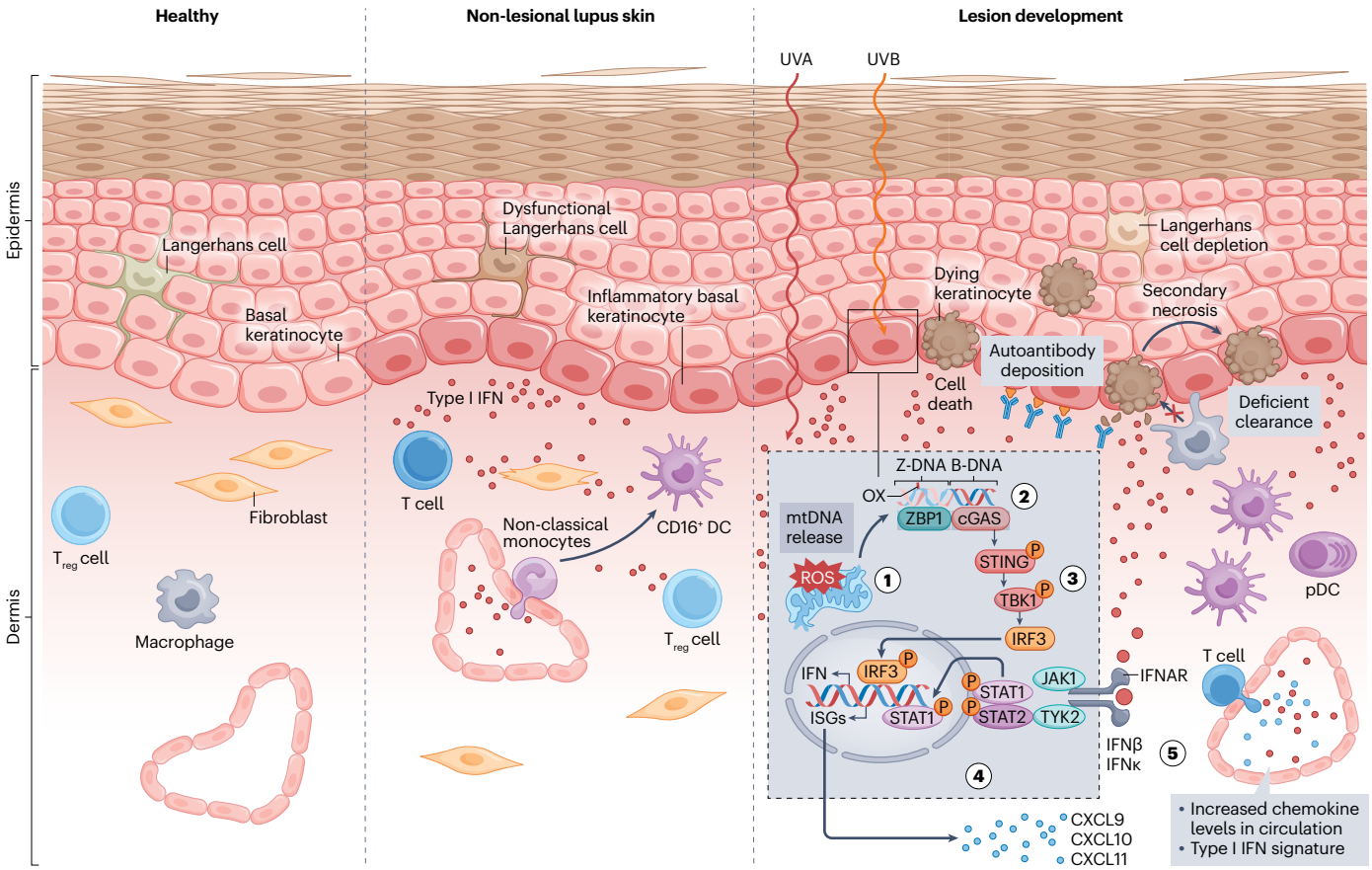


Fig. 2 | Non-lesional skin dysfunction and photosensitivity. Non-lesional skin of patients with cutaneous lupus erythematosus or systemic lupus erythematosus exhibits increased type I interferon (IFN) levels, dysfunctional Langerhans cells and increased numbers of CD16$^+$ dendritic cells (DCs) that probably derive from non-classical monocytes. Exposure to ultraviolet (UV) light triggers lesion development through UVB-mediated effects on keratinocytes. First, mitochondrial damage and production of reactive oxygen species (ROS) results in release of oxidized mitochondrial DNA (mtDNA) in the Z-conformation (Z-DNA) (1). Second, Z-DNA is stabilized by IFN-induced Z-DNA binding protein 1 (ZBP1) and further recognized by cyclic GMP-AMP synthase (cGAS) (2). Third, cGAS activates a signalling cascade that includes activation of stimulator of interferon genes (STING) and TANK-binding kinase 1 (TBK1), to promote interferon regulatory factor 3 (IRF3)-dependent expression of IFN (3). Fourth, type I IFNs get released and bind to interferon-α/β receptor (IFNAR), and this leads to signal transducer and activator of transcription 1 (STAT1) phosphorylation and expression of interferon-stimulated genes (ISGs) and release of chemokines (CXCL9, CXCL10 and CXCL11) (4). Secreted chemokines recruit CXCR3$^+$ T cells, plasmacytoid dendritic cells (pDCs) and myeloid cells into the skin, and myeloid cells potentiate type I IFN secretion, subsequently migrating to skin-draining lymph nodes (5). In addition to cytokine and chemokine secretion, UVB causes keratinocyte cell death in all epidermal layers, leading to autoantigen expression on the surface. Deficient clearance of cellular debris leads to secondary necrosis and release of autoantigens that form immune complexes with autoantibodies. This inflammatory circuit is further promoted by the dysfunction of regulatory T (T_{reg}) cells. JAK1, Janus kinase 1; TYK2, tyrosine kinase 2.

IFN signalling, even in refractory cases[36–38] (see section on therapeutic approaches). Epithelial, stromal and immune cells produce type I IFN. Keratinocytes express a broad range of type I IFNs including *IFNB, IFNK*, *IFNE* and type III IFNs (*IFNL*)[39]. Myeloid cells (monocytes, monocyte-derived dendritic cells and macrophages) and pDCs secrete large amounts of type I IFN[40,41] and have been identified in both non-lesional and lesional lupus skin[41–44] (Fig. 2). However, recent studies suggest $CD16^+$ myeloid cells rather than pDCs to be prominent producers of type I IFN in lupus skin[41].

Type I IFN production is triggered by activation of endogenous antimicrobial machinery that detects nucleic acids from varying sources. Recognition of double-stranded RNA (dsRNA) through Toll-like receptor 3 (TLR3) and single-stranded RNA (ssRNA) through TLR7 and TLR8 induces type I IFN expression via nuclear translocation of pIRF3 (ref. 28). Cytosolic RNA is sensed by RIG1 and MDA5, which promote type I IFN expression through MAVS. Cytosolic DNA from microbial and endogenous sources is recognized by cyclic GMP-AMP synthase (cGAS), which produces cyclic GMP-AMP (cGAMP), leading to downstream activation and phosphorylation of stimulator of interferon genes (STING)–TANK-binding kinase 1 (TBK1) and IRF3 (ref. 28). Another sensor that promotes type I IFN signalling and cell-death responses is Z-DNA binding protein 1 (ZBP1), which binds cytosolic DNA in the Z-conformation[45]. The expression, trafficking and signalling of these sensors are tightly regulated, and disruption of inhibitory factors or chronic overexpression are assumed to drive the chronic type I IFN loop that characterizes lupus skin. Notably, nucleic acid sensors such as cGAS and ZBP1 are themselves induced by stimulation with IFN[45–48], resulting in a feedforward autocrine loop that might underlie chronic activation of type I IFN signalling. Our understanding of these pathways is evolving rapidly, and further translational and clinical studies are needed to decipher what nucleic acids and nucleic acid sensors mostly drive IFN production in the skin of patients with CLE and SLE.

Genetic associations in cutaneous lupus erythematosus

Multiple genetic factors have been associated with CLE, with subtypes exhibiting overlapping and unique genetic associations. Monogenic CLE and monogenic SLE have been mostly associated with chronic activation of the type I IFN pathway, and are collectively termed 'interferonopathies'[49,50]. Monogenic CLE is primarily manifested as familial chilblain lupus. Many individuals with monogenic CLE have heterozygous mutations in *TREX1* (refs. 51–54). This gene encodes a cytosolic 3′–5′ exonuclease involved in clearing cytosolic DNA; decreased TREX1 function leads to accumulation of cytosolic DNA, which is sensed by the cGAS–STING pathway, triggering chronic type I IFN production[55,56]. Patients with TREX1-associated CLE exhibit signs of systemic immune activation including production of autoantibodies, a systemic type I IFN signature and photosensitivity due to enhanced DNA damage and cGAS activation in response to UV radiation[52,57]. Mutations in *SAMHD1*, a regulator of intracellular deoxynucleotide triphosphate (dNTP) levels, cause another form of familial chilblain lupus phenotypically characterized by violaceous plaques, nail dystrophy and vasculitis[58]. TLR7 signalling is also affected in some individuals with monogenic SLE. Missense mutations in *TLR7* and in *UNC93B1*, which is involved in TLR7 trafficking and function, have been shown to cause SLE with cutaneous manifestations including chilblain lupus, whereas TLR mutations have been associated with malar rash[59–61].

Non-monogenic CLE exhibits complex genetic associations[58] with HLA-associated genes, as well as genes involved in antigen presentation, complement, apoptosis, DNA processing and IFN responses. A genome-wide association study of 183 patients with CLE and 1,288 healthy individuals identified 4 CLE-associated SNPs that are all located within the major histocompatibility complex region of chromosome 6, in proximity to genes implicated in other autoimmune diseases such as HLA-DQ alpha chain 1 (*HLADQA1*), *TRIM39* and *RPP21* (ref. 62). Genetic associations with propensity for skin involvement in SLE were further identified for variants in *ITGAM*, *FCGR2A*, *VDR* and *STK17A*[63–65]. *IFNK* represents another risk locus for the development of both CLE and SLE[66]. Further genetic associations and functions of individual proteins are reported by Chen et al.[58].

Non-lesional skin dysfunction in cutaneous and systemic lupus erythematosus

The idea that non-lesional lupus skin might be primed for inflammation was introduced in the 1960s, when non-lesional skin was found to feature immunoglobulins along the DEJ in up to 70% of patients with SLE[67]. Now we know that there is intrinsic dysregulation of keratinocytes in non-lesional lupus that persists in culture and is likely to be driven by epigenetic modifications[68,69]. Some of this dysfunction is driven by chronic upregulation of *IFNK* expression, as blockade of IFNκ normalizes pro-inflammatory responses to UV light[42,68,70,71]. A recent single-cell RNA-sequencing study of lesional and non-lesional skin and circulating immune cells from patients with CLE and SLE confirmed that the IFN-rich environment generated by non-lesional lupus keratinocytes influences gene expression in skin-infiltrating non-classical monocytes, which thereby acquire pro-inflammatory properties and become $CD16^+$ DCs, a pathogenic immune-cell subset in the skin of patients with CLE[42]. Additional studies have identified epigenetic dysregulation of Hippo signalling pathways in non-lesional skin that contribute to a propensity towards apoptosis[69]. Further, repression of peroxisome proliferator-activated receptor (PPARγ) levels have been observed in basal keratinocytes from the skin of patients with SLE, and PPARγ expression in keratinocytes is also likely to contribute to enhanced IFN production in these cells[72,73]. IFNs released from dysregulated keratinocytes in non-lesional skin activate DCs[35] and are likely to promote inflammatory phenotypes of skin-infiltrating myeloid cells[42] (Fig. 2). Collectively, these data support a model in which chronic secretion of type I IFN by dysfunctional keratinocytes in non-lesional skin places individuals at risk of developing hyperinflammatory responses after additional external stimuli such as UV light.

Triggers for development of skin lesions

Ultraviolet radiation. Photosensitivity to UV radiation is one of the most important features of CLE, reported in up to 81% of patients, regardless of skin colour[74]. Other inflammatory skin diseases, such as atopic dermatitis and psoriasis, can be treated by narrowband (311 nm) UVB radiation, but UV exposure can provoke CLE and lead to severe systemic flares, including lupus nephritis, when SLE is present[74–76]. Clinically, photosensitivity in CLE and SLE is defined as photo-distributed rash histologically consistent with CLE or systemic symptoms such as fatigue or arthritis with a delayed onset (up to 3 weeks)[77,78]. This must be distinguished from acute photosensitive rashes, immediately following UV radiation exposure, such as sunburn, solar urticaria, polymorphic light eruption and other non-rheumatic diseases. In a study using self-report, reaction patterns in photosensitive individuals with CLE are variable, ranging from pruritic sensations (60%) to a direct sun-induced CLE flare (86%) or even systemic reactions (36%)[74].

The mechanisms underlying photosensitivity in CLE and SLE are under investigation. UVB is mainly absorbed by the epidermal

compartment, whereas UVA reaches the dermis. Both UVB and UVA were shown to induce CLE lesions[78,79]. However, histologically, skin from patients with CLE exhibits increased abundance of dying keratinocytes across all layers of the epidermis after exposure to UV light[80] (Fig. 2). Thus, keratinocytes are likely to be involved in initiation of the reaction. Keratinocytes from non-lesional skin of patients with SLE and a history of CLE in vitro exhibit hyperinflammatory immune responses after UVB exposure, including enhanced IFN and chemokine secretion[35,81,82] (Fig. 2). IFN has been implicated in priming inflammatory responses, showing a pathogenic role in increased cell death and T cell activation after exposure of human non-lesional lupus keratinocytes to UV light in vitro[35] and in mouse models[83]. In mouse models, epidermal *IFNK* overexpression enhances epidermal cell death through activation of caspase 8 (ref. 81), skin inflammation and systemic T cell activation after exposure to UV light[84].

Mechanistically, we are now starting to understand why type I IFN production is amplified in the skin of patients with CLE or SLE after UVB exposure. In mice, early inflammatory responses to UV radiation are cGAS dependent, and high doses of UV radiation result in neutrophil-mediated kidney inflammation[85,86]. Type I IFNs, which are high in the skin of patients with non-lesional CLE, further skew this process through a crucial IFN-inducible rheostat, ZBP1 (Fig. 2). UV radiation causes mitochondrial stress and release of mitochondrial DNA in the Z-conformation, most likely through generation of oxidized bases (8-oxodG) that favour Z-DNA conformation over the more conventional B-conformation[32,87]. Oxidized DNA staining colocalizes with IFN-induced genes in skin lesions of patients with CLE[88], but type I IFN does not increase oxidation per se[32]. Importantly, in keratinocytes, UV-induced mitochondrial Z-DNA and ZBP1 act as a ligand–receptor pair driving enhanced early inflammatory responses in autoimmune photosensitivity[32] (Fig. 2). ZBP1 is upregulated in CLE, as well as in other photosensitive diseases, such as dermatomyositis[32,45]. Knockdown of ZBP1 reduces IFN responses after UV, whereas overexpression results in spontaneous Z-DNA accumulation and a type I IFN signature[32]. Similar to oxidized DNA, Z-DNA is resistant against intracellular nucleases[89], suggesting that this nucleic acid conformation might overcome cellular DNA degradation through TREX1. Thus, Z-DNA and ZBP1 cause strong activation of cGAS, leading to robust type I IFN and inflammatory cytokine production (Fig. 2).

UV light also affects autoantigen exposure on dying cells, which may alter downstream activation of immune responses. After UV radiation, apoptotic keratinocytes present autoantigens such as Ro52/SSA and La/SSB on their cell surface that can subsequently be bound by autoantibodies, thereby forming immune complexes[90]. UV-induced reactive oxygen species increase expression of autoantigens on the cell surface of keratinocytes but also oxidize them to increase autoantigen immunogenicity[91,92]. Translocation of La/SSB from the nucleus to the cytoplasm is induced by UV-dependent conformational changes of La[93,94]. These autoantigens can then be recognized by antibodies, forming immune complexes, triggering tissue damage.

Type I IFNs also act via epidermal Langerhans cells to abolish protection of keratinocytes from UVB-induced cell death. In healthy skin, Langerhans cells provide epidermal growth factor receptor (EGFR) ligands through a disintegrin and metalloproteinase 17 (ADAM17)-mediated activation, and EGFR signalling in keratinocytes promotes survival despite exposure to UVB light[95]. In mouse models of lupus, Langerhans cells are dysfunctional and the type I IFN-rich environment limits sheddase activity of ADAM17, thereby amplifying photosensitive responses[96] (Fig. 2).

Beyond the epidermis, data from mouse models have shown that type I IFN also regulates photosensitive responses via the activation of inflammatory monocytes and their migration to local lymph nodes, where they prime adaptive immune cells[97]. In IFNAR-knockout mice, this response and associated photosensitivity were found to be substantially reduced. Consistently, type I IFN-dependent migration of myeloid-derived DCs to the skin and draining lymph nodes was more pronounced in lupus-prone mice than in non-lupus prone controls[98]. Increased activation of myeloid-derived DCs was also seen in an IFN-high model generated by deletion of *Trim21*, the gene that encodes for Ro/SSA. In these mice, UVB radiation leads to enhanced systemic inflammation with an increase in inflammatory monocytes[99]. Thus, environments with high levels of type I IFNs, such as those seen in lupus-prone mouse models, skew myeloid-cell recruitment and generate a pro-inflammatory response. Similarly, IFN-associated genes are expressed in FOXP3$^+$ regulatory T (T_{reg}) cells from patients with CLE but not in T_{reg} cells from healthy individuals[42]. Indeed, chronic type I IFN results in T_{reg} cell dysfunction and T cell activation in the skin-draining lymph nodes after UV exposure in mice, further accelerating UV-induced inflammatory responses[83]. In addition to IFN signalling, lymphatic flow, which is reduced in lupus-prone mice, might also contribute to autoimmune photosensitivity[100]. Improved lymphatic flow restrains B cell responses through activation of stromal CCL2, leading to depletion of plasmablasts[100].

In summary, the IFN-rich epidermis in non-lesional lupus skin primes for photosensitive responses that are mediated by hyperinflammatory responses of keratinocytes and immune cells, compounded by the absence of tolerogenic factors.

***Staphylococcus aureus*.** Patients with SLE have a distinct skin microbiome compared with healthy individuals[101]. *Staphylococcus aureus* is a dynamic colonizer of 30% of the US population[102], and has been shown to promote SLE-like autoimmune inflammation[103]. *S. aureus* is likely to also contribute to development of CLE[104–107]. Individuals with SLE are disproportionately colonized by *S. aureus*[108], and nasal carriage of *S. aureus* increases the risk of skin disease flare in individuals with SLE[106]. Importantly, CLE lesions are frequently colonized by *S. aureus*[105,107]. *S. aureus* adheres more robustly to keratinocytes in patients with SLE than to those in healthy individuals and produces mediators that induce inflammatory signalling and type I IFN production, which contributes to skin barrier disruption[105]. Treating CLE lesions with 2% mupirocin, a topical antibiotic, to decrease *S. aureus* colonization, was accompanied by decreased type I IFN-stimulated gene expression[109]. Reduction of staphylococcal burden in CLE lesions correlated with a decrease in IFN pathway signalling, in inflammatory gene expression and in barrier dysfunction in lesional skin. Interestingly, mupirocin-associated decreases in lesional monocytes also correlated with decreased inflammatory gene expression[109]. These studies suggest that colonization of CLE lesions by *S. aureus* contributes to a feedforward loop wherein type I IFNs drive a skin environment that is conducive to colonization, which in turn further increases IFN production.

Chronic exposure to *S. aureus* proteins via repeated injection induces development of lupus-like disease manifestations in wild-type mice[110]. Additional mouse models show that *S. aureus* colonization of mouse-bladder catheters with *S. aureus* prompts sterile inflammatory-cell infiltration in the absence of bacteraemia in diverse organs, such as the kidney and lung[111]. Emerging evidence demonstrates that *S. aureus* regularly breaches the epidermis, even in normal

skin[112], and this process is enhanced when skin-barrier proteins, such as filaggrin[113], are dysfunctional or absent. Increased type I IFN expression in the skin might further promote infiltration by the spread of *S. aureus*, as cutaneous inoculation resulted in increased lung-isolated *S. aureus* in mice overexpressing *Ifnk* in their epidermis as compared with wild type[33]. Furthermore, other environmental CLE triggers, such as UV radiation[76] and smoking[114], are also implicated in damaging skin-barrier integrity, thereby potentially promoting increased *S. aureus* adherence[115,116]. Thus, overall skin health, barrier function and underlying IFN production are crucial for microbial interactions and require further study to understand how manipulation of the cutaneous microbiome might exacerbate or benefit CLE lesions.

Cigarette smoking. Cigarette smoking increases the risk and disease activity of CLE[114,117] and SLE[118,119]. Intriguingly, smoking at the onset of SLE was associated with DLE (odds ratio (OR) 2.05), tumid CLE (OR 4.5) and photosensitivity (OR 2.07)[120]. Current smokers with SLE or CLE have more severe disease and worse quality of life than non-smokers, and smoke exposure increases cutaneous inflammation and damage in a dose-dependent manner[114]. Cigarette smoking also has negative effects on treatment responses for CLE. Smoking decreases the efficacy of antimalarials in patients with SLE and CLE[121]. Current smokers with CLE are more often treated with hydroxychloroquine (HCQ) plus quinacrine than non-smokers[114] suggesting that additional drugs might be required to overcome the effects of smoking or that smoking is associated with increased disease activity. Indeed, in patients with CLE, the antimalarial response rate is significantly lower for smokers (40%) than for non-smokers (90%)[122]. A meta-analysis of the literature revealed that smoking is associated with a 2-fold decrease in the proportion of patients with CLE achieving resolution of cutaneous disease with antimalarials[123]. Furthermore, smoking limits efficacy of other immunosuppressant medications such as methotrexate and mycophenolate[124]. The mechanisms by which smoking impacts therapeutic responses and drives skin disease in SLE are currently under investigation. A cross-sectional study in patients with SLE found that smoking is independently associated with increased skin manifestations (for example, with Raynaud's phenomenon), increased levels of B cell-activating factor (BAFF) and decreased levels of IFNγ[125]. Further studies are required to identify SLE- and CLE-associated pathways triggered by smoking. Regardless, current evidence highlights the importance of smoking cessation messaging as an approach to improving skin-disease outcomes in patients with SLE and CLE.

Lesional skin

Inflammatory circuits in lesional skin. CLE lesions are marked by a prominent autocrine inflammatory loop at the DEJ that relies on crosstalk between keratinocytes, fibroblasts, myeloid cells, T cells and B cells. Keratinocytes robustly express chemokines such as CXCL9, CXCL10 and CXCL11, thereby recruiting $CXCR3^+$ cytotoxic T cells to the site of inflammation[34,126] (Fig. 3). Keratinocyte-derived type III IFNs (IFNλ1–4) might contribute to this chemokine excess, as IFNλ1 is enhanced in serum from patients with active CLE, and stimulation of keratinocytes with IFNλ1 results in enhanced production of CXCL9 (ref. 127). Vacuolar degeneration of basal keratinocytes and insufficient uptake of apoptotic material by macrophages lead to persistence of cellular debris, including nucleic acids. This insufficient disposal of cellular waste has been suggested to amplify the lesional inflammation in CLE and further activate innate immune pathways in lesional keratinocytes and immune cells[128]. Lesional CLE features deposition of immunocomplexes at the DEJ, probably through autoantigen exposure on the surface of keratinocytes and insufficient efferocytosis of dying keratinocytes[129] (Fig. 3). Notably, tumour necrosis factor (TNF) can increase the surface expression of Ro52/SS-A and La/SS-B on keratinocytes and is highly expressed in CLE, especially in therapy-refractory cases[44,130].

Among immune cells, T cell numbers are increased in CLE lesions. $CD8^+$ T cells have been identified to promote skin damage through release of cytotoxic factors such as granzyme B and perforin[126,131] (Fig. 3). Cytotoxicity of both $CD4^+$ and $CD8^+$ T cells expressing granzyme B is regulated by hypoxia-inducing factor 1 (HIF-1), which is highly expressed in lesional CLE[131] (Fig. 3). CLE $CD4^+$ T cells are predominantly polarized towards a T helper 1 (T_H1) phenotype, and this T cell phenotype correlates with type I IFN signalling[34]. In CLE, T cells exhibit very elevated and sustained type I IFN signatures compared with T cells from healthy individuals[42,132,133]. The downstream effects of this IFN exposure remain uncertain, as CLE lesional T cells exhibit reduced activation and cytotoxicity when compared with T cells from lupus nephritis biopsies[132]. Further, exhaustion signatures have been reported in T cells from CLE lesions[134]. In contrast to human CLE, mouse models of CLE exhibit T_H17 cell polarization[131]. Both DLE and SCLE lesions were shown to exhibit increased IL-17A expression compared with healthy skin[135,136]. However, transcriptomic analysis of CLE lesion samples revealed that the levels of IL-17A are minimal compared with levels of other cytokines[137,138]. Targeting of IL-17 signalling through blockade of upstream IL-12 and IL-23 using ustekinumab did not result in greater improvement in skin activity, as measured by Cutaneous Lupus erythematosus disease Area and Severity Index (CLASI) scores, compared with placebo in a phase III placebo-controlled multi-centre study in patients with active SLE[139]. Thus, IL-17 signalling might not be clinically relevant in CLE. Overall, more research is needed to fully understand the pathogenic contributions of T cells in CLE.

Myeloid cells are less abundant than T cells in CLE but participate substantially in the inflammatory loop in CLE lesions (Fig. 3). pDCs are able to produce high amounts of IFNα upon TLR stimulation[140,141]. As pDC numbers are low in the blood of patients with SLE, for many decades they were thought to be localized in the tissue and serve as the main contributors to the IFN signature observed in SLE and CLE. Stimulation of peripheral blood mononuclear cells from patients with SLE with autoantibodies and plasmid DNA or immune complexes together with apoptotic material have been shown to mount robust type I IFN responses[142,143]. However, sources of type I IFN other than pDCs have been identified, and pDCs were found to have lower IFNα expression levels than myeloid-derived dendritic cells or epithelial cells, such as keratinocytes, especially in lesional CLE biopsies[30,41]. The low numbers of pDCs in peripheral blood of patients with SLE did not correlate with disease activity, and these pDCs exhibited lower production of IFNα and TNF after TLR stimulation than pDCs isolated from healthy individuals, despite equivalent levels of receptor expression[30]. Furthermore, pDCs isolated from patients with SLE did not activate T cells as effectively as pDCs from healthy individuals[30]. The compromised capacity for in vitro IFN production of blood-derived pDCs from patients with SLE was reproduced using pDCs from skin lesions of patients with CLE[41]. These results suggest that pDCs in SLE feature an exhausted phenotype and more research is needed to understand their role in SLE and CLE. pDCs might have roles beyond IFN production in SLE and CLE, as they express granzyme B, which promotes their interaction with T cells[41]. Indeed, clinical trials using litifilimab, a monoclonal antibody against the pDC marker BDCA2, have indicated that pDC blockade

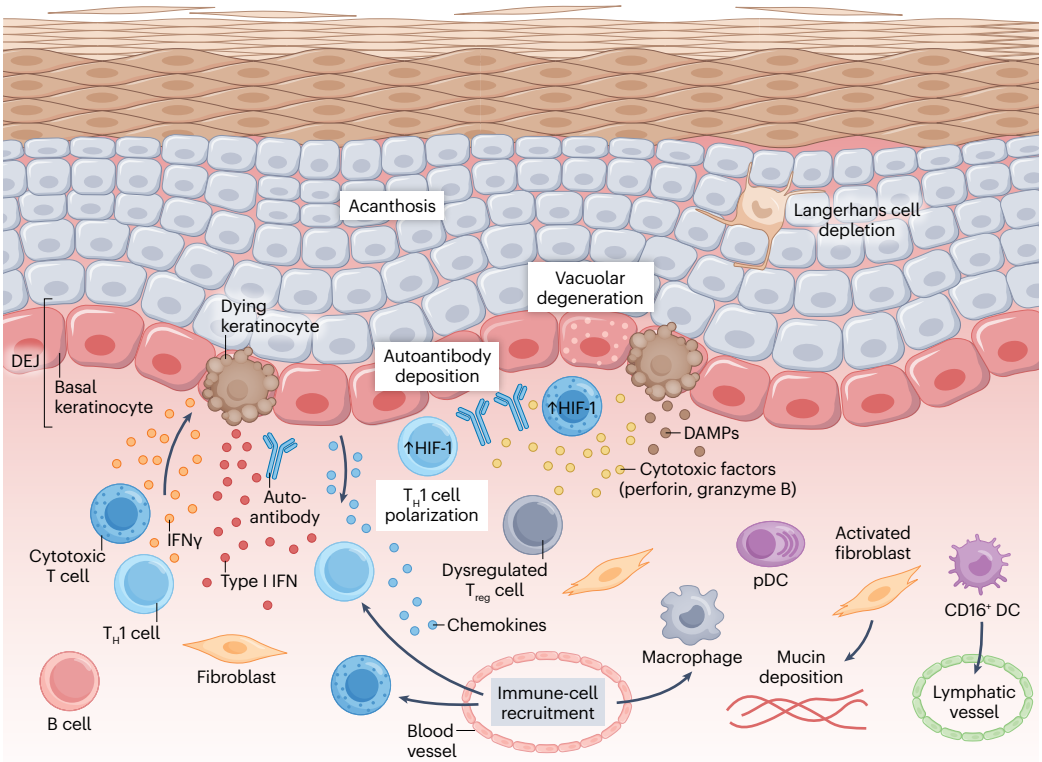


Fig. 3 | Inflammatory circuits in lesional lupus skin. Lesional lupus skin is characterized by infiltration of the dermo-epidermal (interface dermatitis) by T cells, marked by vacuolar degeneration of basal keratinocytes, leading to release of danger-associated molecular patterns (DAMPs) and autoantibody deposition. This cytotoxic response is mediated by $CD8^+$ T cells and $CD4^+$ T cells, particularly T helper 1 (T_H1) cells, which all exhibit upregulation of the transcription factor hypoxia-inducible factor 1 (HIF-1). A chronic cytokine crosstalk is established by keratinocytes, myeloid cells and T cells, resulting in robust chemokine and type I interferon (IFN) signatures in lesional skin, leading to further immune-cell recruitment. Absence of tolerogenic Langerhans cells and the presence of dysfunctional regulatory T (T_{reg}) cells result in dampened immune tolerance, leading to a chronic hyperinflammatory environment. Fibroblasts exhibit immune-cell crosstalk and become activated, ultimately leading to dermal mucin deposition[191]. Antigen-presenting cells migrate through lymphatic vessels to skin-draining lymph nodes, promoting adaptive immune responses. DC, dendritic cell; DEJ, dermo-epidermal junction; pDC, plasmacytoid DC.

leads to amelioration of CLE lesions[144], accompanied by reduction of MX1 expression in skin lesions[145]. However, BDCA2 might also be expressed on dendritic-cell subsets[146], and the specificity of litifilimab against pDCs remains to be validated. We will learn more about the role and targeting of pDCs in CLE when data from the phase III trial using litifilimab are released.

Inflammation in lesional skin is further amplified by the absence of tolerogenic factors. Epidermal Langerhans cells are depleted in lesional CLE[42,95,147] (Fig. 3), which is a finding relatively unique to CLE, as other inflammatory skin diseases that feature interface dermatitis, such as lichen planus, exhibit increased numbers of Langerhans cells[147]. T_{reg} cells, known to dampen T cell activation, are similar in numbers in CLE lesions and skin samples of healthy individuals, but are dysfunctional in CLE[42,134] (Fig. 3). T_{reg} cells in CLE skin exhibit a high type I IFN signature and a high exhaustion score[132,134], especially in non-lesional skin. As the immunosuppressive capacity of T_{reg} cells is also strongly inhibited by type I IFNs following UV exposure in lupus-prone mice[83], it is tempting to speculate that high levels of IFNs in CLE skin contribute to T_{reg} cell dysfunction. Other relevant pathways contributing to this T_{reg} cell phenotype include metabolic shifts that result in increased glycolysis, overdrive of oxidative phosphorylation and repression of the pentose phosphate pathway[148,149]. Intriguingly, a small study that treated CLE lesions with gluconolactone, a metabolite of the pentose phosphate pathway, to restore activity of T_{reg} cells resulted in moderate improvement of CLE lesions after 2 weeks of treatment[149]. Further studies will be needed to investigate if T_{reg} cell function is improved after reduction in IFN signatures in CLE and SLE skin.

Discoid lupus erythematosus versus subacute cutaneous lupus erythematosus. The two best studied subtypes of CLE lesions are DLE and SCLE. These lesions have interesting contrasting phenotypes, but drivers for this difference in lesional behaviour have not yet been identified. DLE lesions manifest as inflammatory plaques, often resulting in atrophic scars with dyspigmentation[150], whereas SCLE lesions are characterized by non-scarring, non-atrophying inflammation[151]. Both subtypes are characterized by type I IFN signatures, and these signatures are stronger in DLE versus SCLE, regardless of whether associated with SLE[152,153]. Comparisons of immunophenotypes in DLE versus SCLE via mass cytometry revealed similar levels of skin infiltration by myeloid cells and T cells[41]. SCLE showed slightly enhanced T_H2 cell-to-T_H17 cell ratios compared with DLE[41], potentially reflecting similarity to psoriasiform inflammation. Overall, DLE is more cellular and inflammatory than SCLE, which may explain the higher IFN scores in DLE[41,153].

In SLE, dermal fibroblasts are poised to hyper-respond to inflammation, and fibroblast responses differ between patients with SLE and a history of SCLE versus patients with DLE[154]. Transforming growth factor-β (TGFβ) has been identified as a crucial upstream regulator for inflammatory fibroblasts in DLE lesions, whereas inflammatory pathways were more prominent in patients with a history of SCLE. Further, when stimulated with TGFβ, DLE fibroblasts responded with increased upregulation of collagen transcripts, whereas SCLE fibroblasts mounted inflammatory responses[154]. Some of these differences might underlie variable propensity for scar formation.

B cell profiles also differ between the two lesional subtypes. In DLE, B cells are enriched, coinciding with an upregulation of BAFF, whereas SCLE lesions have very few B cells[152,155,156]. Peripheral B cell analysis in patients with DLE identified less overlap with SLE B cell phenotypes when there were few lesions but more overlap with SLE when there were widespread lesions, suggesting that isolated DLE might have distinct B cell activation patterns that are less 'SLE like'[157]. B cell immunophenotyping in DLE and SCLE skin lesions compared with healthy skin revealed increased abundance of $CD20^+$ B cells, $CD38^+$ B cells, but not plasma cells in DLE versus SCLE[158]. Together, it remains to be determined whether B cells contribute to differences between the DLE and SCLE phenotypes.

Therapy for cutaneous lupus erythematosus

Treatment of CLE requires a multimodal approach that includes avoidance of triggering factors and use of topical and systemic treatments based on individual factors such as CLE subtype and patient comorbidities (Fig. 4). Until recently, treatment options were limited, and, to date, there are still no FDA-approved therapies beyond HCQ for treatment of CLE. However, inhibition of type I IFN signalling is especially effective in treating SLE-associated cutaneous lesions[159], highlighting the importance of this pathway for disease pathogenesis. Ongoing trials of new therapies for SLE and CLE have promising early data, and we anticipate that treatment algorithms for CLE will change as these data emerge.

Conventional therapies

First-line therapies for CLE are topical corticosteroids and topical calcineurin inhibitors for localized disease, and antimalarial medications (HCQ, chloroquine and quinacrine) for more extensive or refractory cases (Fig. 4). Topical corticosteroids are the mainstay for limited skin involvement, with generally good efficacy but a risk of local side effects, such as atrophy and telangiectasia, especially with prolonged use. Topical calcineurin inhibitors, for example, tacrolimus

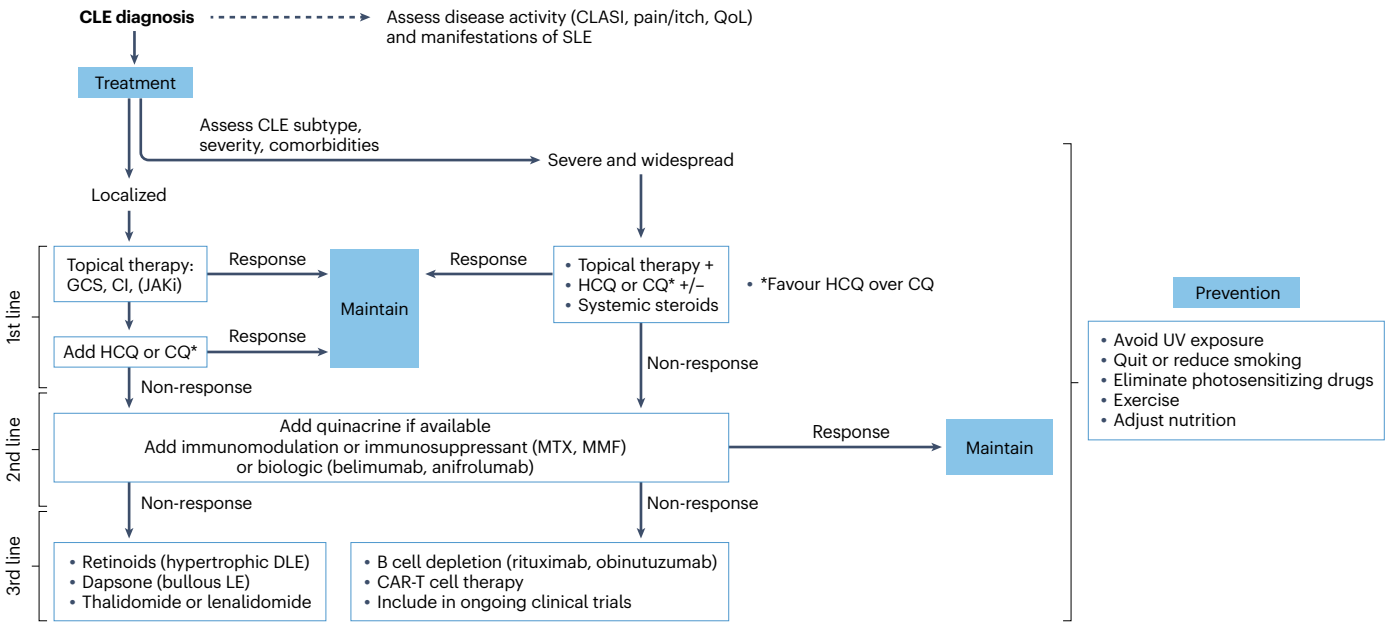


Fig. 4 | Treatment algorithm for cutaneous lupus erythematosus. Treating cutaneous lupus erythematosus (CLE) should include a specific treatment strategy that is based on individual factors such as subtype, disease severity, comorbidities, lifestyle and patient preference. It is recommended to combine topical and systemic therapies for improved outcome if initial topical treatment is not successful[192–195]. Preventative factors should accompany any therapeutic approach (avoid ultraviolet (UV) exposure, quit/reduce smoking, eliminate photosensitizing drugs, exercise, healthy nutrition). When treating CLE, patients need to be assessed for disease distribution, disease activity (as assessed by the Cutaneous Lupus erythematosus disease Area and Severity Index (CLASI) or revised CLASI (RCLASI)), pain, itch, quality of life (QoL) and manifestations of systemic lupus erythematosus (SLE) including potential risk of progression to SLE. Localized disease should be treated topically with glucocorticosteroids (GCS), calcineurin inhibitors (CI) or topical JAK inhibitors (JAKi), if available. Non-responders should receive hydroxychloroquine (HCQ) or chloroquine (CQ) systemically, where hydroxychloroquine is preferred because of the retinal toxicity risk of chloroquine. In severe and widespread disease, first-line therapy includes both topical and systemic treatment. If available, quinacrine should be added to hydroxychloroquine or chloroquine. Second-line treatments include immunomodulatory or immunosuppressant drugs (methotrexate (MTX), or mycophenolate mofetil (MMF) are recommended) or biologic DMARDs (such as belimumab or anifrolumab), especially when SLE is present. Non-responders should be interdisciplinarily discussed and might benefit from retinoids (hypertrophic discoid lupus erythematosus (DLE)), dapsone (bullous CLE), thalidomide/lenalidomide or B cell depletion (for example, with rituximab or obinutuzumab). Inclusion in ongoing clinical trials (clinicaltrials.gov), including chimeric antigen receptor (CAR)-T cell studies, is an option for difficult-to-treat patients. Responders to therapy should maintain their current therapeutic regimen and be regularly assessed for sustained efficacy or possible transition to SLE.

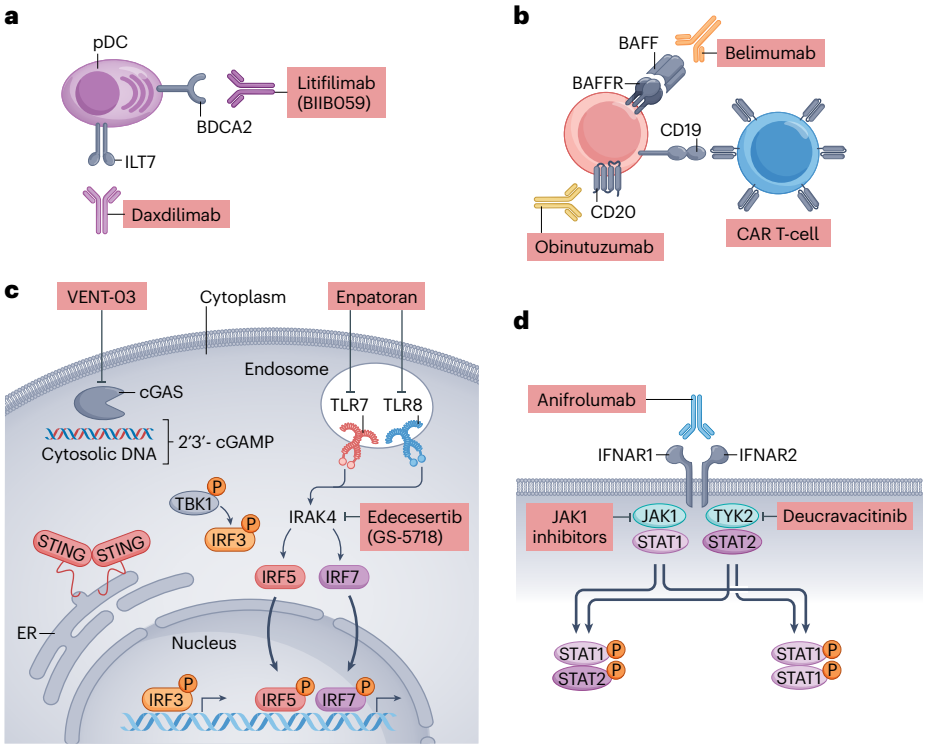


Fig. 5 | Emerging therapies in cutaneous lupus erythematosus. a, Drugs targeting plasmacytoid dendritic cells (pDCs) include the anti-BDCA2 monoclonal antibody litifilimab (BIIB059) and anti-ILT7 monoclonal antibody daxdilimab. **b**, B cells are targeted by the anti-BAFF (B cell-activating factor) antibody belimumab, the anti-CD20 antibody obinutuzumab and chimeric antigen receptor (CAR)-T cell therapy. **c**, Drugs targeting intracellular signal transduction upstream of interferon (IFN) gene expression are small molecules inhibiting cyclic GMP-AMP synthase (cGAS) (VENT-03), Toll-like receptor 7/8 (TLR7/8) (enpatoran) and interleukin-1 receptor-associated kinase 4 (IRAK4) (edecesertib (GS-5718)). **d**, IFN signalling is targeted by monoclonal antibody anifrolumab targeting interferon-α/β receptor 1 (IFNAR1) and downstream signalling via Janus kinase 1 (JAK1) inhibition (for example, baricitinib, upadacitinib) as well as tyrosine kinase 2 (TYK2) inhibitors (deucravacitinib). BAFFR, BAFF receptor; ER, endoplasmic reticulum; IRF, interferon regulatory factor; STAT, signal transducer and activator of transcription; STING, stimulator of interferon genes; TBK1, TANK-binding kinase 1.

or pimecrolimus, are effective steroid-sparing agents, particularly for sensitive areas such as the face and intertriginous zones and are supported by moderate evidence of efficacy in CLE[160–166]. Among antimalarials, HCQ is the first-line systemic treatment with favourable efficacy and safety profile[167] and is supported by moderate-quality evidence for reducing clinical flares compared with placebo[168] (Fig. 4). The mechanism of action involves modulating immune system activity, particularly through inhibition of TLR signalling and reduced pro-inflammatory cytokine production. HCQ accumulates in lysosomes, increasing the lysosomal pH and interfering with antigen processing and presentation, thereby dampening the activation of autoreactive T cells and B cells. This leads to decreased production of type I IFN and other cytokines implicated in CLE pathogenesis[169]. Addition of quinacrine in patients for whom HCQ monotherapy fails is associated with higher response rates[170]. For patients with an inadequate response to antimalarials, escalation to immunosuppressive agents such as methotrexate is recommended[168]. Methotrexate has demonstrated superiority to placebo in achieving complete clinical response and was found to be non-inferior to chloroquine in head-to-head trials[168] (Fig. 4). Methotrexate is a chemotherapy agent that inhibits dihydrofolate reductase to exert an antiproliferative effect; however, at the low doses used in treatment of autoimmune diseases, methotrexate principally acts to modulate immune responses, suppressing T cell activation, reducing pro-inflammatory cytokine production, and interfering with purine metabolism and, thus, increasing the release of adenosine, which has broad anti-inflammatory effects[171]. Methotrexate efficacy in psoriasis was linked with methotrexate ability to inhibit transport of bacterial peptidoglycans into keratinocytes[172]. Cyclosporine and azathioprine are also used as steroid-sparing agents in SLE, with similar efficacy in treating cutaneous disease[168].

Autoantibody positivity correlates not only with risk of disease progression but also with CLE therapeutic response[173]. In a study of 390 patients with CLE, antimalarials and topical steroids were the most common treatments (86% and 85% of participants, respectively), but only 63% of CLE patients responded to antimalarials and 50% to topical steroids. Low response rates to these first-line therapies were observed in patients with ACLE and SLE; when controlling for CLE subtype and the presence of SLE, poor response to antimalarials was observed among participants with anti-dsDNA (OR 0.5), anti-Smith (OR 0.5), or anti-chromatin (OR 0.6) autoantibodies[173]. Cellular and molecular disease characteristics also correlate with therapeutic response. One study comparing responses to HCQ and the antimalarial quinacrine reported that increased numbers of myeloid dendritic cells with high TNF expression in cutaneous lesions might contribute to HCQ refractoriness but was associated with improved response to quinacrine; this is likely to explain the differential effects of these two medications on the levels of inflammatory cytokines[44].

Emerging therapies for cutaneous lupus erythematosus

The development and validation of provider- and patient-reported disease severity metrics for CLE have facilitated incorporation of primary or secondary CLE outcomes in trials, accelerating discovery in this area. Emerging therapies for CLE focus primarily on targeted immunomodulation (Fig. 5). Recent advances include monoclonal antibodies and small molecules that specifically inhibit key pathogenic pathways in CLE. Type I IFN pathway blockade is a major area of development. Anifrolumab, a monoclonal antibody targeting IFNAR, has demonstrated efficacy in reducing cutaneous disease activity in SLE trials, with significant improvement in skin-specific outcomes, and is now being evaluated in CLE-only populations[37,159,174].

Belimumab, a monoclonal antibody against BAFF, is approved for SLE and has shown benefit in cutaneous domains[175], although its efficacy in CLE without systemic involvement is still under investigation. Litifilimab, an anti-BDCA2 antibody that depletes pDCs, has shown promising results in a phase II trial, significantly reducing skin disease activity in patients with CLE[144]. Other agents in development include deucravacitinib (a selective TYK2 inhibitor approved for psoriasis)[176] and enpatoran[177], a TLR7 and TLR8 inhibitor, which have shown promise in phase II data. Edecesertib (GS-5718), an inhibitor of IRAK4, a kinase that is activated downstream of TLRs, and VENT-03, a cGAS inhibitor, are currently under investigation in phase II trials (Fig. 5). Although some therapeutics did not meet CLE endpoints, such as the selective JAK1 inhibitor filgotinib and the SYK inhibitor lanraplenib[178], select subgroups were found to benefit, suggesting possible disease heterogeneity. Indeed, meta-analyses indicate that the effect of JAK inhibitors such as baricitinib on CLE is uncertain[179–181], but baricitinib was highly effective in a small case series of patients with familial chilblain lupus who carried *TREX1* mutations[182].

Other emerging therapies that might show efficacy on CLE lesions include those aiming at 'immune reset' through deep B cell depletion. Case reports of patients with SLE with active CLE as part of their disease have shown complete reduction in SLEDAI activity with CD19-directed chimeric antigen receptor (CAR)-T cell therapy[183,184] (Fig. 5), suggesting that skin manifestations are also improving. Other methods of B cell depletion, including bi-specific T cell engager therapy, are also showing promise with improvement in skin manifestations in other autoimmune diseases[185], but data in SLE or CLE are still lacking. The next 5 years will rapidly provide insight into how B cell depletion affects CLE.

Moving from treatment to prevention

Inflammatory changes in the skin are found early, potentially before lesions appear. Epigenetic modifications of non-lesional keratinocytes have been reported[69], but we still know very little about the connections between CLE and the development of SLE. Type I IFNs are sufficient to drive CLE phenotypes and immune activation in mice[84]. Type I IFNs also accelerate SLE onset[186,187]. Skin exposure to UV light causes both CLE and SLE flares. However, we still know very little about how CLE starts, whether CLE is a driver of SLE, or how the skin activates systemic autoimmunity. Mouse models support systemic immune activation by UV exposure or skin inflammation, especially in the context of lupus-prone, IFN-rich environments[83–86,188]. Thus, treatment of isolated CLE has long been hypothesized to reduce the likelihood of progression to SLE. An observational study of 286 patients with isolated CLE treated with HCQ or topical corticosteroids or with calcineurin inhibitors reported that early initiation of HCQ was associated with an 87% reduction in SLE risk over time, regardless of CLE severity and baseline antinuclear antibody status. HCQ use was also associated with a lower risk of severe SLE with end-organ involvement[189]. Definitive determination of the effects of CLE treatment on progression to SLE will require prospective, longitudinal studies and high-quality, skin-focused randomized controlled trials. As therapeutic options expand with new agents that target potential drivers of disease onset and progression — such as type I IFNs — the prospect of treating CLE to prevent SLE transition might be drawing closer.

Conclusions

The future for patients with CLE has never been brighter. The understanding of CLE continues to evolve but has already led to potentially life-changing therapies for patients who are affected by this disease. Future research will help to clarify the definitive pathogenic cell populations in CLE and whether they differ by disease subtype. This, coupled with a wave of targeted therapies, will offer the opportunity for personalized therapeutics and potentially immune reset or cure. Support and growth of research in autoimmune diseases is crucial for this transformational work to happen.

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Review article

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Challenges in the diagnosis, classification and prognosis of ANCA-associated vasculitis

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Abstract

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) encompasses three rare yet interrelated diseases: granulomatosis with polyangiitis (GPA), microscopic polyangiitis (MPA) and eosinophilic granulomatosis with polyangiitis (EGPA). Despite increasing recognition, the diagnosis of AAV remains challenging, even in specialized medical centres, owing to its clinical heterogeneity, overlap with mimicking conditions, and the variable performance of ANCA testing. The assessment of a patient suspected of AAV requires a timely synthesis of symptoms, physical examination, laboratory tests, histopathology and imaging data to substantiate the diagnosis, exclude alternative diagnoses, assess disease activity and extent, and enable rapid initiation of appropriate therapies. Classification is similarly complex, and evolving classification systems are based on clinical phenotype, ANCA specificity or a combination of both, each with implications for disease monitoring, therapeutic decisions and trial design. Assessing disease severity and predicting prognosis are fundamental but complicated by the diverse patterns of organ involvement, relapsing–remitting course and co-morbidities. Although validated tools exist for measuring disease activity, organ damage and prognosis, many limitations remain, particularly in identifying smouldering disease, irreversible damage and risk of relapse. Emerging therapies have improved outcomes, with recovery of kidney function, better overall survival and improved glucocorticoid-related toxicity, but patients with AAV continue to experience high risks of chronic morbidity and early mortality. This Review explores current challenges and opportunities in the diagnosis, classification and prognostic assessment of AAV, and outlines a structured framework to support personalized and outcome-focused care.

Sections

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Key points

- Diagnosing ANCA-associated vasculitis (AAV) can be challenging owing to the heterogeneity of the syndromes, the absence of a gold standard and criteria for diagnosis, and the overlapping features with other conditions.
- The development and revision of classification criteria for AAV have been essential for enhancing the accuracy and consistency of research studies.
- As research into the genetic and immunological basis of AAV progresses, classification criteria will continue to evolve, assisting patient stratification and personalized treatment.
- Although the standardized tools — BVAS, VDI and AAV-PRO — have improved our ability to assess disease activity, organ damage and patient quality of life, respectively, comprehensive measures that integrate all these factors remain to be developed.
- Improved disease stratification, combined with patient-centred approaches, will help to refine prognosis, to personalize treatment and ultimately to improve outcomes for patients with AAV.
- An integrated, multifaceted approach to assess AAV is essential for improving patient care, including understanding diagnostic tools, classifying disease severity and predicting outcomes based on a combination of factors.

Introduction

Anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) is a group of three related, rare, challenging and complex conditions with overlapping clinical presentations: granulomatosis with polyangiitis (GPA); microscopic polyangiitis (MPA); and eosinophilic granulomatosis with polyangiitis (EGPA). The outcome of systemic vasculitis has improved from an invariably fatal course to a chronic relapsing–remitting disorder, with survival rates close to 90% after remission-induction treatment[1–3]. Following the introduction of cyclophosphamide in the 1960s, the management of AAV progressed from optimizing glucocorticoid-based and other immune-suppressive regimens to targeted therapies, including rituximab, the complement C5a receptor inhibitor avacopan, for GPA and MPA[4–8], and interleukin-5 (IL-5) inhibition for EGPA[9,10]. Achieving remission, resolving acute life-threatening disease manifestations and markedly reducing the risk of organ damage is now possible for most people with AAV. The frequency of adverse outcomes, including death and end-stage kidney disease, is declining owing to earlier diagnosis and advances in therapy[11,12]. However, substantial mortality and morbidity associated with both the disease and treatment, and reduced life expectancy, remain a reality for many people with AAV[11].

Classification criteria for GPA and EGPA were initially developed by the American College of Rheumatology (ACR) in 1990, were updated in 2022 to include MPA, and improved standardization of patient recruitment for clinical trials[13–15]. Additionally, definitions of AAV were established through the Chapel Hill Consensus Conferences process in 1993 and updated in 2012 (ref. 15). However, these classification criteria and definitions are not designed for diagnosing AAV, and formal diagnostic criteria have not yet been established for AAV. Disease activity and extent in AAV has been quantified for clinical trials using various iterations of the Birmingham vasculitis activity score (BVAS). Organ damage resulting from initial vasculitic activity, disease relapse, adverse effects of treatment or other co-morbidities are captured using damage assessment instruments, including the vasculitis damage index (VDI) and the combined damage assessment (CDA). Finally, so-called generic patient-reported outcomes (PROs) have been studied and validated for use to assess the impact of AAV on physical, mental, and social well-being. A disease-specific PRO for AAV has been developed[16–18]. Consequently, a cohesive and integrated approach that combines the evaluation of the diagnosis, classification, severity, damage and PROs is strongly recommended when studying AAV[6,19].

Despite advances in the treatment of AAV and progresses made in disease classification and assessment, challenges remain in ensuring timely diagnosis, consistent disease assessment, and appropriate treatment stratification[20]. Existing classification criteria and disease activity scores have facilitated research and clinical decision-making, but their limitations — particularly in real-world settings — have become apparent. As precision medicine gains traction and clinical trials become increasingly tailored to patient subgroups, there is a pressing need to reassess how we define, measure and monitor AAV. Recent updates to classification criteria, emerging targeted therapies and a growing emphasis on precision medicine all call for accurate and adaptable tools for diagnosis, assessment and outcome measurement in AAV. Therefore, the field needs to critically examine the current tools used for classification and disease assessment, explore their clinical and research implications, and highlight opportunities for refinement to improve outcomes for patients with AAV.

This Review outlines an integrated approach to evaluation of AAV that considers diagnosis, classification, assessment of severity and prognosis. Discussions include ongoing challenges of diagnosing AAV in the absence of validated diagnostic criteria, followed by development and application of classification criteria and disease definitions. Furthermore, we review current tools for assessing disease activity, organ damage, and patient-reported outcomes, and their utility in both clinical practice and research. Finally, we highlight emerging opportunities to refine these instruments in the context of precision medicine, with the goal of improving disease stratification, treatment individualization and long-term outcomes for individuals living with AAV.

Approach to AAV diagnosis

The frequent occurrence of nonspecific presenting signs and symptoms of AAV and the absence of established diagnostic criteria often result in delays in diagnosis and postponement of the start of treatment, both potentially leading to development of irreversible organ damage[21,22]. AAV symptoms might range from nonspecific constitutional features (such as malaise, fatigue, weight loss, fever, arthralgia and myalgia) to organ-related manifestations (such as pulmonary disease or neuropathy). Incidentally discovered findings such as impaired kidney function, urinary findings suggestive of glomerulonephritis, or radiographic abnormalities suggesting pulmonary disease also prompt evaluation for AAV in otherwise asymptomatic individuals. The diagnosis of AAV is based on a synthesis of data based on clinical presentation, radiographic testing, pathology, and laboratory tests[1,23] (Fig. 1 and Supplementary Fig. 1). Differences in organ manifestations, ANCA specificity, and the presence or absence of peripheral and tissue eosinophilia help to distinguish among the three subtypes of AAV.

The development of diagnostic criteria for AAV has been challenged by protean nature and heterogeneity of the disease combined with the absence of a gold standard. Ideally, such diagnostic criteria should be adaptable to the various clinical contexts, yet sufficiently broad to encompass many potential features and variations in disease severity, while achieving high levels of sensitivity and specificity[24]. This is complicated by the fact that individuals with AAV are often ANCA-negative, whereas common clinical features of AAV, such as constitutional symptoms, are not specific to vasculitis[24,25]. Potentially, deeper understanding of the pathogenesis of AAV, including genetic factors, cytokine profiles, mechanisms leading to loss of immune tolerance, and immune cell signatures associated with GPA, MPA or EGPA, might help to develop biomarkers with the potential to guide diagnostic criteria and improve diagnostic accuracy.

Typical clinical manifestations of AAV subtypes

Disease manifestations, ANCA specificity and histopathology largely overlap among the three subtypes of AAV. However, a large amount of medical literature in the AAV spectrum support clinical use of the three disease subtypes.

Granulomatosis with polyangiitis. Granulomatosis with polyangiitis (GPA) is a small-vessel vasculitis that typically involves the upper and lower respiratory tract and presents with granulomatous inflammation. Common clinical manifestations include nasal crusting, epistaxis, sinusitis, otitis, conductive hearing loss and capillaritis with vasculitis, alveolar haemorrhage, and kidney involvement with glomerulonephritis[26] (Fig. 1a). In patients with severe ear, nose and throat (ENT) involvement, GPA leads to nasal septum perforation and saddle nose deformity. Orbital pseudotumors and subglottic stenosis are also highly suggestive of GPA[27,28]. Although GPA typically presents with upper respiratory tract involvement that is likely to progress to affect the lungs and kidneys, isolated involvement of the lungs is a common presentation[29–31]. The presence of proteinase 3 (PR3)-specific ANCA, is strongly associated with GPA. However, some individuals with GPA are ANCA-negative (10–50%), and the absence of ANCA might delay the diagnosis and is associated with chronic damage at the time of presentation[21,32–34].

Microscopic polyangiitis. Microscopic polyangiitis (MPA) is a small-vessel vasculitis often associated with myeloperoxidase (MPO)-specific ANCA and involves the kidney in 75–100% of cases, whereas clinical manifestations related to granulomatous inflammation such as lung nodules or retroorbital masses are absent as per the 2012 Chapel Hill Consensus Conference (CHCC) disease definition[35–37] (Table 1 and Fig. 1b). Lung involvement in MPA is likely to present in various ways, including pulmonary capillaritis with alveolar haemorrhage or as fibrotic parenchymal disease manifesting as interstitial lung disease[38,39].

Eosinophilic granulomatosis with polyangiitis. Eosinophilic granulomatosis with polyangiitis (EGPA) is a small-vessel vasculitis often accompanied by eosinophilic infiltration and granuloma formation (Fig. 1c). Clinically, EGPA typically presents with a prodromal phase marked by asthma and nasal polyposis, which often precede systemic manifestations by months or years[40]. Blood eosinophilia is consistently present[41] (Table 1). Although the disease is named for eosinophilic granulomatous inflammation, histological identification of eosinophilic granuloma is exceedingly rare.

Manifestations of EGPA can be broadly categorized into two groups: eosinophilic and vasculitic[40]. The eosinophilic manifestations include asthma, nasal polyposis, lung infiltrates and cardiac involvement, particularly myocarditis, which is common and potentially severe[42]. Pleuritis and pericarditis are also more common in EGPA than in GPA or MPA, although they are probably underdiagnosed[43]. The vasculitic features include peripheral nervous system involvement most often presenting with mononeuritis multiplex in 50–70% of patients. Mononeuritis multiplex typically causes sensory deficits, but motor symptoms might also occur. Nerve conduction studies show an axonal damage pattern in EGPA with mononeuritis multiplex, and the frequency of neuropathy is higher in EGPA than in GPA or MPA[44–46]. Kidney involvement is relatively uncommon in EGPA, but possible[47–49].

Stratification by ANCA status reveals distinct phenotypic patterns in EGPA. Positive MPO-ANCA, found in approximately 40% of patients with EGPA, is frequently associated with vasculitic features, such as neuropathy and glomerulonephritis, whereas ANCA-negative EGPA is usually associated with eosinophilic manifestations, including cardiomyopathy and lung infiltrates[47–51]. These clinical differences are supported by genetic studies, which have linked ANCA-positive and ANCA-negative EGPA with partially distinct susceptibility loci: gene variants associated with barrier dysfunction have been implicated in ANCA-negative disease and HLA polymorphisms have been identified in individuals with ANCA-positive EGPA[50,51]. However, both EGPA subsets share a genetic predisposition to eosinophilia and, rather than representing two distinct diseases, EGPA subsets are best understood as a spectrum of overlapping features[50,51].

Laboratory, serological, histopathology and imaging profiles

The inflammatory marker C-reactive protein and erythrocyte sedimentation rate are commonly increased in patients with active disease but are not specific for AAV. Assessment of ANCA titers aids in the diagnosis of AAV, particularly when clinical features are supportive, but their correlation with disease activity or severity remains inconsistent. Perinuclear ANCA and cytoplasmatic ANCA patterns in indirect immunofluorescence of blood samples are still used for ANCA detection and AAV diagnosis despite their low predictive value. ANCA-specificity testing, particularly for MPO and PR3, is crucial for diagnosing AAV and occasionally has a supportive role in predicting risk of relapse (Fig. 1). Current guidelines recommend using third-generation antigen-specificity tests to detect MPO-ANCA and PR3-ANCA, such as enzyme-linked immunosorbent assay (ELISA) or bead assays, which provide more reliable information and have higher specificity (91.4–95.6% and 96.8–98.3%, respectively) than previous generation assays or indirect immunofluorescence, decreasing the false-positive rates[52–54]. Furthermore, ANCA-specificity tests have improved correlation with disease phenotype, standardization, and reproducibility[52–54]. Positive MPO-ANCA has been frequently associated with interstitial lung disease and increased risk of progression from acute or chronic kidney injury to end-stage kidney disease, whereas positive PR3-ANCA has been associated with the presence of lung nodules, ENT involvement and acute kidney injury[55–58]. In terms of treatment response, patients with positive PR3-ANCA and patients with GPA tend to have a higher relapse risk than patients with positive MPO-ANCA or individuals with MPA[59–61].

In the absence of vasculitis, ANCA tests can be positive in patients with inflammatory bowel disease, malignancies, or infections; in infective endocarditis 8% of the patients test positive for ANCA[62] (Box 1). Moreover, manifestations of vasculitis and ANCA seropositivity might

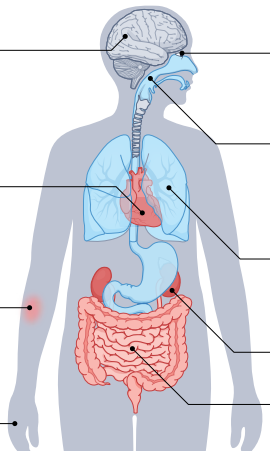
a Granulomatosis with polyangiitis

Central nervous system
Headache, stroke, intracranial haemorrhage
(0%–18%)

Heart
Pericarditis, pericardial effusion, cardiomyopathy, coronary artery disease, heart failure
(2%–15%)

Skin
Palpable purpura, livedo reticularis
(10%–50%)

Peripheral nervous system
Vasculitic neuropathy, mononeuritis multiplex
(14%–40%)



Eyes
Episcleritis, uveitis, optic neuropathy, nerve palsy, retinal vasculitis
(1%–9%)

Ear, nose, throat
Rhinosinusitis, chronic otitis media, sensorineural hearing loss, subglottic stenosis, saddle nose deformity after rhinosinuitis
(75%–99%)

Lungs
Nodules, cavities and pulmonary infilrates: alveolar haemorrhage and pleurisy
(62%–94%)

Kidneys
Acute kidney injury with pauci-immune necrotizing glomerulonephritis (38%–85%)

Gastrointestinal tract:
Abdominal pain, bleeding, diarrhoea, pancreatitis
(0%–7%)

Limited disease (often ANCA-negative)

- Necrotizing granulomatous inflammation usually involves the upper and lower respiratory tract
- Necrotizing vasculitis predominantly affects small to medium vessels
- Necrotizing glomerulonephritis is common

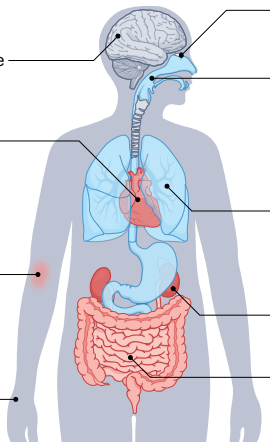
b Microscopic polyangiitis

Central nervous system
Headache, stroke, intracranial haemorrhage
(0%–18%)

Heart
Pericarditis, pericardial effusion, cardiomyopathy, coronary artery disease, heart failure
(2%–15%)

Skin
Palpable purpura, livedo reticularis, nodules, urticarial lesions
(30%–60%)

Peripheral nervous system
Vasculitic neuropathy, mononeuritis multiplex
(14%–40%)



Eyes
Episcleritis, uveitis, optic neuropathy, nerve palsy, retinal vasculitis
(1%–9%)

Ear, nose, throat
Non-granulomatous and non-erosive sinus inflammation, sensorineural hearing loss
(9%–30%)

Lungs
Diffuse alveolar haemorrhage, interstitial pneumonitis or pulmonary fibrosis
(25%–66%)

Kidneys
Acute kidney injury with pauci-immune necrotizing glomerulonephritis (75%–100%)

Gastrointestinal tract
Abdominal pain, bleeding, diarrhoea, abnormal liver tests, cholecystitis, appendicitis
(2%–56%)

- Necrotizing vasculitis predominantly affects small vessels (capillaries, venules or arterioles)
- Necrotizing glomerulonephritis is very common
- Pulmonary capillaritis is common

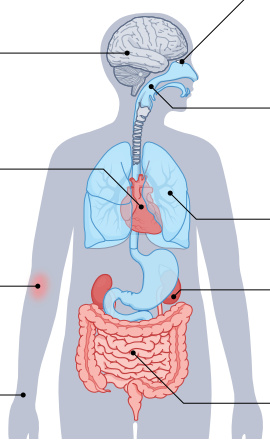
c Eosinophilic granulomatosis with polyangiitis

Central nervous system
Eosinophilia in cerebrospinal fluid, vasculitis, stroke, cranial nerve palsy, cognitive impairment (5%–15%)

Heart
Pericarditis, pericardial effusion, cardiomyopathy, coronary artery disease, heart failure, arrhythmia
(14%–58%)

Skin
Aseptic nodules, palpable purpura, livedo reticularis, urticarial lesions
(30%–69%)

Peripheral nervous system
Vasculitic neuropathy, mononeuritis multiplex
(50%–92%)



Eyes
Orbital granuloma, episcleritis, uveitis, optic neuropathy, nerve palsy, retinal vasculitis
(3%–11%)

Ear nose and throat
Allergic rhinitis, sinusitis, polyposis, otitis media, sensorineural hearing loss
(48%–98%)

Lungs
Asthma
(91%–100%)
Pulmonary infiltrates, pleural effusion, nodules/cavities
(61%–91%)

Kidneys
Interstitial nephritis, less severe pauci-immune necrotizing glomerulonephritis
(10%–27%)

Gastrointestinal tract
Organ perforation, mesenteric ischaemia, colitis
(6%–44%)

EGPA triad: asthma, nasal polyposis, eosinophilia

- Eosinophil-rich and necrotizing granulomatous inflammation involving the respiratory tract
- Necrotizing vasculitis predominantly affects small to medium vessels
- Associated with asthma and eosinophilia

Fig. 1 | Systematic approach to the diagnosis in ANCA-associated vasculitis. The initial assessment of a patient with suspected anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) requires a systematic approach to establish the degree of organ involvement, of which there are several common organ manifestations that present with differing frequencies. The most common manifestations are shaded blue for granulomatosis with polyangiitis (GPA) (**a**), shaded pink for microscopic polyangiitis (MPA) (**b**) and shaded purple for eosinophilic granulomatosis with polyangiitis (EGPA) (**c**). According to the signs and symptoms at AAV presentation, tests will be performed to ascertain the involvement of each probable organ affected. For instance, patients with respiratory tract involvement, particularly ear, nose and throat manifestations such as nasal crusting, epistaxis, sinusitis, otitis and hearing loss, are most likely to be diagnosed with GPA and are frequently evaluated by ear, nose and throat specialists who therefore perform specific ear, nose and throat-related investigations (**a**). By contrast, patients presenting with acute kidney injury are likely to be diagnosed with MPA, and a kidney biopsy will be performed early in the evaluation (**b**). Patients with EGPA frequently present with asthma and therefore pulmonary function tests are usually performed first (**c**). Life-threatening manifestations (yellow shading) involve capillaritis in GPA and MPA. Limited disease can be ANCA-negative in 10–50% of patients with GPA (**a**). As depicted, the heterogeneous clinical presentation of AAV and clinical syndromes hampers the establishment of a standardized first diagnostic evaluation of these patients.

occur in patients with other primary autoimmune diseases, including systemic sclerosis, Sjögren syndrome and rheumatoid arthritis[1,63–66].

A range of laboratory tests are essential to support diagnosis, assess organ involvement, and identify comorbid conditions prior to initiating treatment in AAV. Urinary findings, such as proteinuria, dysmorphic erythrocytes, or red blood cell casts, are indicative of glomerulonephritis. Anti-glomerular basement membrane antibodies are detected in about 6% of patients with AAV and glomerulonephritis[67], and support dual diagnoses of AAV and anti-glomerular basement membrane disease. Troponins and B-type natriuretic peptide can be useful biomarkers when there is suspected cardiac involvement, particularly in EGPA, although not specific to vasculitis-associated disease[68]. Screening for hepatitis B, hepatitis C and human immunodeficiency virus (HIV), as well as other infectious diseases (as, for example, tuberculosis, schistosomiasis and strongyloidiasis in endemic areas) is recommended prior to starting treatment[1,69,70].

Histological findings of vasculitis have been useful in AAV diagnosis and in developing disease definitions and classification. In suspected kidney involvement, biopsy can confirm the hallmark finding of AAV-associated glomerulonephritis (AAV-GN) — that is necrotizing and crescentic glomerulonephritis with absence or minimal presence of immune deposits affecting small vessels, including glomeruli[15,58] — but also permits exclusion of other causes of kidney diseases, such as drug toxicity, IgA vasculitis, or cryoglobulinaemia. Kidney biopsy, as performed in experienced centres, has a high diagnostic yield (sensitivity ≥99%) and is particularly important when patients test negative for PR3-ANCA or MPO-ANCA or when there are doubts about the diagnosis[1]. Furthermore, kidney histology is an important predictor of long-term kidney function in AAV[71]. By contrast, nasal and sinus biopsies have a low diagnostic yield (sensitivity 28–37%) for vasculitis or granuloma[72]. Transbronchial biopsies in GPA also have limited diagnostic value (sensitivity <50%), and are typically used to exclude infection or malignancy[73]. Electromyography might be helpful in mapping any affected nerves and muscles. Nerve and muscle biopsies (as, for example, biopsies of the superficial peroneal nerve) show 60–75% sensitivity for vasculitic neuropathy, which most frequently occurs in patients with EGPA. However, nerve biopsies might lead to sensory impairment, usually mild[74,75]. Skin biopsies, though nonspecific for the type of vasculitis, can support the presence of vasculitis in a patient with suspected AAV.

Imaging is used to assess organ involvement in AAV and is performed based on clinical symptoms or as part of a systematic disease evaluation protocol. Non-contrast high-resolution computed tomography should be considered a routine test to evaluate suspected lung involvement[76,77]. In some cases, chest imaging is also useful in distinguishing between AAV subtypes, as certain lung lesions, such as honeycombing and peripheral reticulation, are often associated with MPO-ANCA positivity, whereas nodular opacities are seen frequently when PR3-ANCA is detectable[55,78]. Furthermore, pulmonary function tests with bronchodilation are mandatory in patients with EGPA who present with asthma. For potential cardiac involvement, a step-up approach starting with an electrocardiogram, followed by echocardiography, and cardiac magnetic resonance imaging, is used to increase the detection rate of cardiac involvement, particularly in EGPA[79].

Differential diagnosis and mimickers of ANCA-associated vasculitis

Other diseases associated with ANCA positivity, such as non-AAV vasculitides, autoimmune diseases[80,81], secondary vasculitis, or mimics of vasculitis[1,62,82] (Box 1), need to be excluded before classifying a patient with GPA, MPA or EGPA. In essence, a broad differential diagnosis exists for most organ manifestations of AAV.

For instance, acute kidney injury with haematuria and proteinuria might be present in several glomerular diseases such as anti-glomerular basement membrane disease, lupus nephritis, IgA nephropathy, cryoglobulinaemic glomerulonephritis, and drug-induced interstitial nephritis[83,84]. In the differential diagnosis of AAV with lung nodules, pulmonary infiltrates or alveolar haemorrhage, conditions such as infections (such as bacterial pneumonia, tuberculosis and fungal infections), malignancy (including primary lung cancer and metastatic disease), other vasculitides (such as anti-glomerular-basement-membrane disease or Behçet's disease), sarcoidosis, pulmonary embolism and drug-induced pneumonitis must be considered. Diagnosing EGPA remains challenging as many conditions share the features of asthma, eosinophilia and pulmonary infiltrates: hypereosinophilic syndrome, allergic bronchopulmonary aspergillosis, parasitic infections, drug reactions, and idiopathic eosinophilic pneumonia. In the absence of ANCA, distinction between these differential diagnoses and EGPA can be difficult[40]. In such cases, the presence of both eosinophilic and vasculitic features — such as peripheral neuropathy, purpura or biopsy-proven vasculitis — is required for establishing the diagnosis of EGPA.

Classification criteria

Classification criteria are essential for defining homogeneous patient groups for enrolment into clinical studies, ensuring that cohorts are uniform and comparable across studies and geographical regions[24]. The 2022 revision of the classification criteria for AAV was prompted by several key factors, including the recognition of the problems with the performance of the 1990 ACR criteria, the increasing contribution of ANCA testing to diagnosis, and advancement in imaging techniques[85–90].

Table 1 | Domains of ANCA-associated vasculitis and associated assessment tool scores

Index	Description	Domains
Disease activity		
BVAS/GPA (2001)[106]	List of items that typically occur in patients with active GPA, providing an overall measure of disease activity using a score from 0 to 68	Organ involvement (general; cutaneous; mucous membranes and eyes; ENT; cardiovascular; gastrointestinal; pulmonary; renal; nervous system) major versus minor disease manifestationsa; new or deteriorated disease within the previous 28 days versus persistent disease; disease status (severe disease or flare[b]; limited disease or flare[c]; persistent disease or flare[d]; remission[e]); physician's global assessment[f] (only in BVAS/GPA)
BVAS V3.0 (2009)[107]	List of items that typically occur in patients with active systemic vasculitis, providing an overall measure of disease activity using a score from 0 to 63	
Damage		
VDI (1997)[113]	The VDI is used to score damage that has been accrued since the onset of vasculitis using a score from 0 to 64 (each item scores 1). Comorbidities present before developing vasculitis should not be scored. The score can either increase or remain the same over time	Organ damage (musculoskeletal; skin or mucous membranes; ocular; ENT; pulmonary; cardiovascular; peripheral vascular disease; gastrointestinal; renal; neuropsychiatric; other)
CDA (2007)[114]	The CDA has 135 individual items in 17 categories and includes some bilaterality for items involving the eyes and ears; 8 items assign gradation. The CDA tool has been developed to improve the description of damage to provide more detail and to consider the possibility of reversibility of some damaged items	Organ damage (musculoskeletal; skin or mucous membranes; ocular; ear; nose; sinuses; subglottic stenosis; pulmonary; cardiac; vascular disease; gastrointestinal; renal; neurologic; psychiatric; endocrine; haematology or oncology; other)
Patient-reported outcomes		
ANCA-associated vasculitis PROs (2017)[16]	Questionnaire composed of 29 items. Each item has 5 answers scored from 0 to 4 (the higher the score, the higher the severity) distributed in 6 domains using a score from 0 to 600	Organ-specific symptoms; systemic symptoms; treatment side effects; physical function; social and emotional impact; concerns about the future
PROs Measurement Information System (PROMIS)[126]	A set of person-centred measures that evaluates and monitors physical, mental and social health in adults and children; it can be used with the general population and with individuals living with chronic conditions	Standardized measures of health status, including pain (intensity, interference), fatigue, emotional distress (depression, anxiety), physical function, sleep disturbance, social roles, cognitive function, and global health
Short Form 36 (SF-36)[127]	A 36-item, patient-reported survey of patient health. The SF-36 is usually used in health economics as a variable in the quality-adjusted life year calculation to determine the cost-effectiveness of a health treatment. The SF-36 is also often utilized in health psychology research to examine the burden of disease The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight. The lower the score the more disability	Assesses health-related quality of life across eight domains: physical functioning, role-physical, bodily pain, general health, vitality, social functioning, role-emotional, and mental health

AAV, ANCA-associated vasculitis; ANCA, anti-neutrophil cytoplasmic antibody; BVAS, Birmingham vasculitis activity score; CDA, combined damage assessment; ENT, ear, nose and throat; GPA, granulomatosis with polyangiitis; PRO, patient-reported outcomes; VDI, vasculitis damage index. Disease activity denotes the spectrum of clinical manifestations, which may range from acute and severe episodes to persistent, insidious symptoms; Damage denotes the resultant tissue damage that can induce chronic signs and symptoms reminiscent of active disease, although not necessarily attributable to ongoing inflammatory activity. Patient-reported outcome encompass the overall effect of the disease on physical, social, and psychological domains, including quality of life and employment. [a]Major disease manifestations were those that constitute an immediate threat to the patient's life or to the function of a vital organ (urinary red blood cell casts, pulmonary haemorrhage, and mononeuritis multiplex); minor items do not constitute immediate threats to vital organs or patients' lives and would normally be managed as limited GPA. [b]Severe disease/flare: occurrence of any new/worse item that is major. [c]Limited disease/flare: any new/worse item that is minor. [d]Persistent disease: presence of 1 item representing active disease that has continued since the patient's previous evaluation. [e]Remission: no active disease; that is, no new/worse and no persistent items present. [f]The degree of GPA disease activity within the 28 days prior to the evaluation by marking a vertical line on the 10-cm visual analogue scale.

Classification by clinical subtypes versus ANCA specificity

A debate exists regarding whether to categorize patients with AAV based on clinical disease (GPA, MPA, and EGPA) or based on ANCA specificity (PR3-ANCA versus MPO-ANCA)[91] (Fig. 2). Studies show that patients with positive PR3-ANCA might have different responses to treatment, relapse rates, and long-term outcomes compared with patients that test positive for MPO-ANCA[61,92–98]. Research also highlights that the genetic distinctions among patients with AAV are more closely aligned with ANCA serotype than with clinical or histopathological features[99]. In EGPA, clinical and genetic studies found differences between MPO-ANCA-positive and ANCA-negative individuals, in both clinical features and gene variants that are associated with ANCA status, and this further enhances differences in pathogenesis with implications for patient classification[50,100,101]. Classifying AAV using both clinical disease name and ANCA specificity might better reflect the phenotypic spectrum of AAV[36,97,102]. Observational studies and post hoc analyses have shown that such an approach enhances prognostic accuracy, enables tailored treatment strategies, and helps to improve disease monitoring. However, large-scale prospective studies are lacking, constituting a barrier to adoption of this type of classification. These challenges underline the limitations of relying solely on ANCA positivity, especially given the lack of assay standardization and the presence of ANCA-negative patients with AAV.

Current classification criteria

The 2022 ACR–European Alliance of Associations for Rheumatology (EULAR) criteria have improved sensitivity and specificity for distinguishing AAV from other similar forms of vasculitis when a diagnosis of small- or medium-vessel vasculitis has been made. These criteria also incorporate ANCA specificity (PR3-ANCA and MPO-ANCA) and provide a reliable framework for classifying patients based on both clinical presentation and laboratory results[103] (Box 2). Consequently, patients

can be classified as having GPA in the absence of any granulomatous inflammation (for instance a patient with isolated pauci-immune glomerulonephritis and PR3-ANCA), or as having MPA despite the presence of granulomatous inflammation (for instance a patient with lung nodules and MPO-ANCA)[104]. This is natural because classification criteria are based on a probabilistic scoring that integrates various scenarios and combinations in the context of overlapping clinical and pathological features, a context that is frequent in AAV. The applicability of these criteria might differ across the various ethnic backgrounds. Therefore, the 2022 ACR–EULAR criteria might require additional validation, particularly in populations under-represented in the derivation process research, such as those originating from Africa, Latin America and Asia[103]. Importantly, neither the 2022 ACR–EULAR classification criteria, nor the 2012 CHCC definitions are appropriate for use as diagnostic criteria.

Assessment of disease activity, damage and health-related quality of life

Outcome Measures in Rheumatology (OMERACT) developed a core set of outcome domains and matching instruments for use in clinical trials in AAV[19]. This set includes the domains of disease activity, disease damage, PROs and mortality[19]. The clinical evaluation of disease activity in AAV is complex, given the variable clinical manifestations and involvement of multiple organ systems[105]. There is no consensus on how to grade severity of presentations of AAV, with several proposed systems that have not gained universal approval. The 2022 EULAR recommendations for the management of AAV avoided use of the word 'severe' and referred to disease activity that was, or was not, directly threatening organ function[5]. However, the outcome of a presumably non-life-threatening manifestation is hard to predict and might still contribute to accumulation of organ damage in an individual. The term 'severe' was adopted by the US Food and Drug Administration agency for the approval of avacopan for GPA and MPA. Thus, a comprehensive definition of disease extent and severity in AAV, incorporating BVAS, damage assessment and PROs, would improve patient stratification, risk assessment and the evaluation of treatment responses and outcomes (remission and relapse).

Disease activity in ANCA-associated vasculitis

The BVAS has been widely used to assess disease activity and severity in clinical research in AAV. Several versions of BVAS have been developed for clinical trials. Items are scored only if judged to stem from active disease, with new or worsening symptoms over the preceding

Box 1 | Main differential diagnoses of ANCA-associated vasculitis and diseases associated with ANCA seropositivity

Other small/medium vessel vasculitides: monogenic autoinflammatory diseases; inborn errors associated with anti-neutrophil cytoplasmic antibody (ANCA) positivity; polyarteritis nodosa; and Behçet's disease.

Non-vasculitic systemic rheumatic diseases: systemic lupus erythematosus; sarcoidosis; rheumatoid arthritis; Sjögren's disease; inflammatory myopathies; juvenile chronic arthritis; reactive arthritis; relapsing polychondritis; systemic sclerosis; and antiphospholipid syndrome.

Anti-glomerular-basement-membrane disease: dual positivity of AAV and anti-glomerular basement membrane disease is common; present in 6% of patients with AAV and 30–40% of patients with anti-glomerular basement membrane disease.

Other concurrent glomerular diseases: membranous nephropathy; lupus nephritis; IgA nephropathy; cryoglobulinaemia; and bacterial infection-related glomerulonephritis.

Interstitial nephritis: may be seen when the vasculitis involves the renal medulla.

Drug-induced ANCA-associated vasculitis (AAV): usually occurring within the first year of exposure to the causal agent(s), more likely to affect women than men and individuals who test positive for multiple autoantibodies, including ANCA; mostly specific to myeloperoxidase (MPO), anti-nuclear antibodies and anti-histone antibodies. The most common agents associated with drug-induced AAV are hydralazine, propylthiouracil, thiamazole and carbimazole. Vasculitis occurs in only a minority of the patients.

- **Cocaine-induced AAV:** can lead to midline destructive lesions of the face with a high incidence of nasal septal perforation or oronasal fistulae; systemic involvement is rare in cocaine-induced GPA, but when it occurs, patients may test positive for proteinase-3 (PR3)-specific ANCA
- **Cocaine+levamisole-induced AAV:** skin lesions predominate and both PR3- and MPO-ANCA can be present

Autoimmune gastrointestinal disorders: inflammatory bowel diseases are often associated with positive cytoplasmic ANCA (up to 40%).

Infection: differentiating infective endocarditis from AAV can be particularly challenging, because 8% of these patients test positive for PR3-ANCA, sometimes with high ANCA titres. Other infections (such as bacterial pneumonia, tuberculosis, allergic bronchopulmonary aspergillosis and parasitic infections) might be considered in the appropriate context (for example, in the presence of lung nodules or suspected eosinophilic granulomatosis with polyangiitis, EGPA).

Malignancy: primary lung cancer; metastatic disease; lymphoma; leukaemia; myeloproliferative and myelodysplastic disorders; and hypereosinophilic syndromes.

Cystic fibrosis: non-MPO perinuclear ANCA are common in patients with cystic fibrosis, particularly among those with bacterial airway infections. The ANCA is directed against bactericidal/permeability-increasing protein (BPI), with a strong association with *Pseudomonas aeruginosa* infection and colonization.

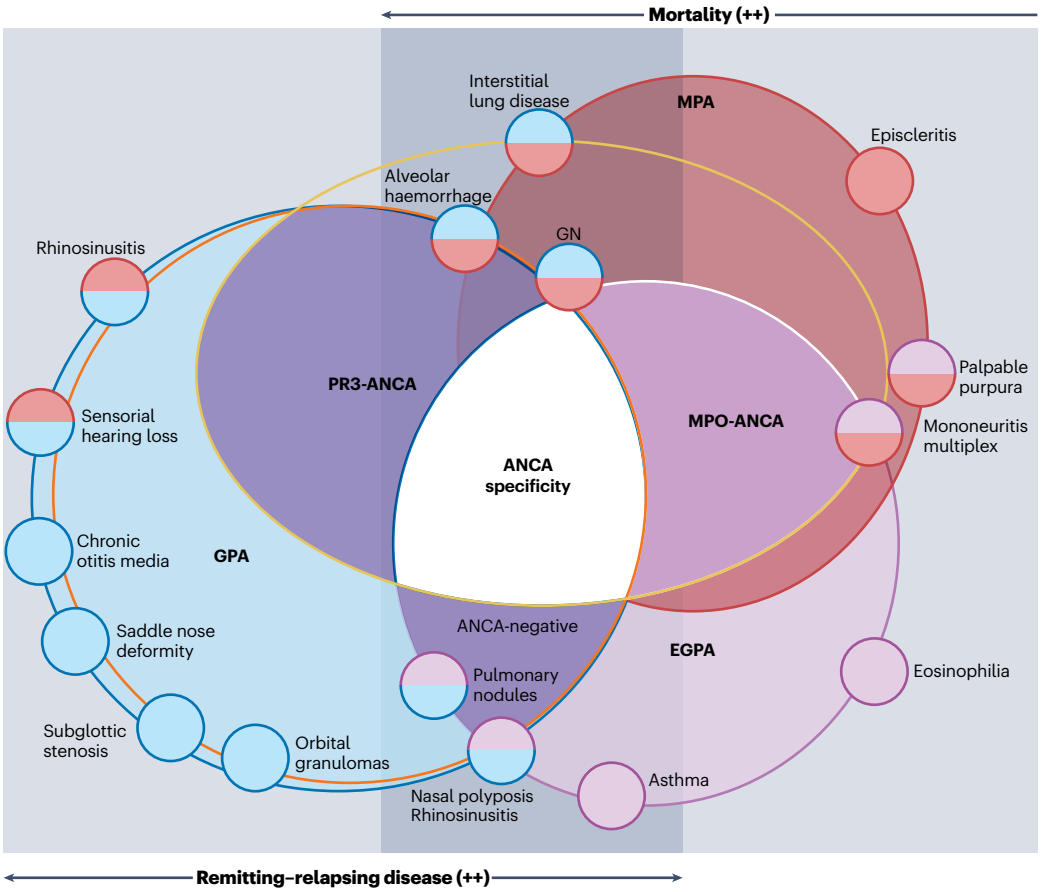


Fig. 2 | Classification by clinical presentation versus autoantibody specificity in ANCA-associated vasculitis. Classification criteria were developed to recruit individuals with anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) into clinical trials and other clinical research studies based on specific disease phenotypes so that homogeneous study cohorts can be ensured. There is an ongoing debate on whether patients with AAV should be classified according to their clinical presentation, as in previous practice, or according to antigen specificity of anti-neutrophil cytoplasmic antibody (ANCA). ANCAs are usually specific against proteinase 3 (PR3) or myeloperoxidase (MPO). The initial concept of eosinophilic granulomatosis with polyangiitis (EGPA; shown in purple), granulomatosis with polyangiitis (GPA; shown in blue) and microscopic polyangiitis (MPA; shown in red) under AAV recognized their overlapping clinical and histopathological characteristics, as well as their strong association with positive ANCA serology. The central challenge in developing classification criteria lies in the clinical and biological heterogeneity of AAV. Patients often present with overlapping AAV syndromes and variable ANCA status (PR3-ANCA, MPO-ANCA or ANCA-negative). For example, clinical manifestations typical of GPA almost always overlap with PR3-ANCA or ANCA-negative (outlined by orange circle). By contrast, clinical manifestations of MPA overlap less perfectly with MPO-ANCA and are more heterogeneous (outlined by yellow oval). These overlaps complicate clear distinctions between syndromes and contribute to difficulties in classification. Mortality increases when capillaritis develops, occurring as a relapse of the disease in some patients (darker grey area). Over the years, the importance of ANCA specificity has been highlighted, and now they are included in the classification criteria. ANCA-specificity provides additional prognostic and pathogenic insights. AAV is a relapsing–remitting disease and patients with GPA and PR3-ANCA positivity are at a particularly high risk of relapse, whereas severity of the presentation and mortality are higher in patients with MPA and MPO-ANCA. This highlights the importance of patient phenotype for prediction of prognosis. Integrating both clinical features and ANCA specificity allows for objective and reproducible classification of AAV, advancing research consistency and enabling more accurate patient stratification in clinical trials. GN, glomerulonephritis.

4 weeks contributing to the score[106]. Symptoms that occurred in the past 1–3 months are mentioned but not scored, unless they are still active[106]. BVAS version 3 (BVAS V3.0), provides a score from 0 to 63 based on common manifestations of active vasculitis. The BVAS-GPA, a revised version of BVAS V2 used in several trials of GPA and MPA, distinguishes between major manifestations, which threaten vital organ function, and minor manifestations, which are less severe[107] (Table 1). Major manifestations are assigned 3 points, whereas minor ones are given 1 point, reflecting clinical severity. Across the BVAS versions, weighting of items is based on expert opinion and total scores are not generalizable. High BVAS scores at presentation correlate with poor prognosis, and during follow-up, worsening or new symptoms often lead to escalation of treatment[19,106–109]. However, the BVAS system is almost always used in trials in a dichotomous manner to distinguish

active disease (score ≥1) from remission (score 0), with no reliable manner of scoring intermediate disease states or responses. Nevertheless, BVAS has been a useful tool in the conduct of clinical trials that led to changes in practice.

The BVAS system has several drawbacks, including its subjectivity and variability in clinical assessments, and its limited sensitivity to chronic damage or mild disease. BVAS also lacks any PRO measures. Therefore, combining BVAS with other tools, such as novel biomarkers, damage indexes and PROs, might mitigate some of these limitations and better characterize disease activity and severity (Fig. 3). The limitations of BVAS in accurately estimating disease severity are particularly evident in EGPA (Fig. 3). This is largely due to challenges in scoring asthma and asthma-associated exacerbations, the underrepresentation of ENT symptoms in the BVAS scoring system, and the underestimation of the clinical need to escalate immunosuppression even when BVAS scores remain low. In EGPA, a more accurate assessment of disease

Box 2 | Classification criteria for ANCA-associated vasculitis

The first attempt to develop any structured classification system was made in 1952 by Pearl Zeek[194], who proposed that vasculitis should be classified according to the size of the vessels affected: small, medium or large. Then, Donato Alárcon-Segovia in 1977[195] and Anthony Fauci in 1978[196] proposed classifications based on vessel size and pathophysiology. A set of classification criteria for several types of systemic vasculitis was developed by the American College of Rheumatology (ACR) in 1990 following previous proposals for sub-categorization of vasculitis disease. The Chapel Hill Consensus Conference (CHCC) in 1993 achieved international agreement on a set of definitions of the various vasculitides. In 2007, a four-step algorithm, integrating ACR 1990 and CHCC 1993 criteria in a hierarchic way, categorized patients into a single classification[197]. A revision of the CHCC definitions in 2012 adopted the term 'ANCA-associated vasculitis'. These disease definitions are also used to define patient cohorts for clinical research studies. The classification criteria were revisited by a subsequent classification initiative to produce diagnostic and classification criteria for vasculitis (DCVAS), a large, multinational prospective observational study that included data from over 6,900 patients with vasculitis across 136 sites and 32 countries[88–90,198]. The updated criteria were developed using regression modelling and expert consensus, incorporating both clinical and laboratory data, with weighted criteria that reflect the importance of specific features)[88–90].

Granulomatosis with polyangiitis (GPA)

- Upper and lower respiratory tract symptoms with granulomatous inflammation and typically seropositivity for proteinase-3-specific anti-neutrophil cytoplasmic antibodies (PR3-ANCA). Individuals who present with only one organ manifestation such as ear, nose and throat or lung involvement test negative for ANCA.

2012 CHCC

- Necrotizing granulomatous inflammation usually involving the upper and lower respiratory tract, and necrotizing vasculitis affecting predominantly small to medium vessels (such as capillaries, venules, arterioles, arteries and veins); necrotizing glomerulonephritis is common[15].

2022 American College of Rheumatology (ACR)–European Alliance of Associations for Rheumatology (EULAR) classification criteria (presence of at least 5 points)

- **Clinical criteria**: Bloody nasal discharge, ulcers, crusting, congestion or blockage, or septal defect/perforation (3 points); cartilaginous involvement (2 points); conductive or sensorineural hearing loss (1 point)[88].
- **Laboratory, imaging and biopsy criteria:** Cytoplasmic ANCA or PR3-ANCA (5 points); pulmonary nodules, mass or cavitation on chest imaging (2 points); granuloma, extravascular granulomatous inflammation or giant cells on biopsy (2 points); inflammation, consolidation or effusion of the nasal or paranasal sinuses on imaging (1 point); pauci-immune glomerulonephritis on biopsy (1 point); perinuclear ANCA or myeloperoxidase-specific ANCA (MPO-ANCA) (–1 point); blood eosinophil count ≥1×10^9 per litre (–4 points)[88].

Microscopic polyangiitis (MPA)

- Acute kidney injury with glomerulonephritis, typically, generally testing positive for MPO-ANCA, with or without pulmonary capillaritis and absence of granulomatous inflammation.

2022 ACR–EULAR classification criteria (presence of at least 5 points)[89]

- **Clinical criteria**: Bloody nasal discharge, ulcers, crusting, congestion or blockage, or septal defect or perforation (–3 points).
- **Laboratory, imaging and biopsy criteria:** perinuclear ANCA or MPO-ANCA (6 points); fibrosis or interstitial lung disease on chest imaging (3 points); pauci-immune glomerulonephritis on biopsy (3 points); cytoplasmatic ANCA or PR3-ANCA (–1 point); blood eosinophil count ≥1×10^9 per litre (–4 points).

Eosinophilic granulomatosis with polyangiitis (EGPA)

- Upper respiratory tract involvement with nasal polyposis associated with asthma and eosinophilia, usually testing positive for MPO-ANCA, although ANCA-negative disease is frequent.

2012 CHCC

- Eosinophil-rich and necrotizing granulomatous inflammation often involving the respiratory tract, and necrotizing vasculitis predominantly affecting small to medium vessels, and associated with asthma and eosinophilia. ANCA is more frequent when glomerulonephritis is present[15].

2022 ACR–EULAR classification criteria (presence of at least 6 points)

- **Clinical criteria**: Obstructive airways diseases (3 points); nasal polyps (3 points); mononeuritis multiplex (1 point)[90].
- **Laboratory, imaging and biopsy criteria:** Blood eosinophil count ≥1×10^9 per litre (5 points); Extravascular eosinophilic-predominant inflammation on biopsy (2 points); cytoplasmatic ANCA or PR3-ANCA (–3 points); haematuria (–1 point)[90].

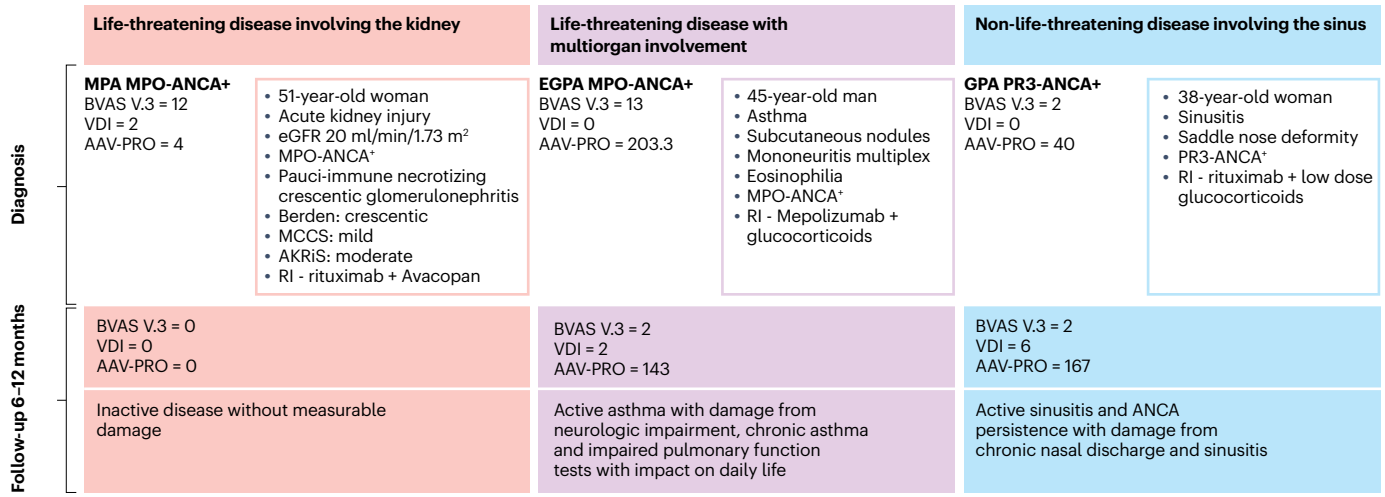


Fig. 3 | Combined assessment of disease activity, organ damage and patient-reported outcomes can help to characterize severity in three stereotypical cases of ANCA-associated vasculitis. Shown are three examples of stereotypical cases of anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) and how life-threatening versus non-life-threatening and 'limited' versus systemic presentation can affect outcomes differently, particularly in the context of damage (as assessed by the vasculitis damage index (VDI) and patient-reported outcomes (as assessed by AAV-patient-reported outcomes (AAV-PRO). Three representative cases illustrate the spectrum of disease presentation, follow-up and long-term outlook. In a case of microscopic polyangiitis (MPA, MPO-ANCA+), a 38-year-old woman presented with acute kidney injury, haematuria and pauci-immune crescentic glomerulonephritis. At baseline, disease was assessed with a Birmingham vasculitis activity score (BVAS) V3.0 of 12, a VDI of 0, and an AAV-PRO of 4. Treatment with rituximab and avacopan achieved remission, with stable kidney function and no relapse over 24 months. Despite life-threatening kidney involvement at onset, the patient achieved inactive disease without measurable damage. In a case of eosinophilic granulomatosis with polyangiitis (EGPA, MPO-ANCA+), a 45-year-old man presented with asthma, subcutaneous nodules, mononeuritis multiplex and eosinophilia. At baseline, disease was assessed with BVAS V3.0 = 13, VDI = 0 and AAV-PRO = 203.3. He was treated with mepolizumab and glucocorticoids. Over 24 months, asthma relapses required treatment with glucocorticoids, and long-term follow-up showed BVAS v.3 = 2, VDI = 2 and AAV-PRO = 143, reflecting damage related to chronic asthma and motor impairment, with substantial impact on quality of life. In a case of granulomatosis with polyangiitis (GPA, PR3-ANCA+), a 56-year-old woman presented with sinusitis and PR3-ANCA+ tests. At baseline, disease was assessed with BVAS V3.0 = 2, VDI = 0 and AAV-PRO = 40. Despite treatment with rituximab and low-dose glucocorticoids, she persistently tested positive for ANCA and had sinus disease with chronic nasal discharge. At 24 months, relapse required intravenous glucocorticoids, and her follow-up scores were BVAS v.3 = 2, VDI = 6 and AAV-PRO = 167, reflecting damage related to sinus disease and glucocorticoid toxicity. The figure emphasizes that prognosis in AAV depends not only on disease activity, extent and severity at presentation, but also on the accrual of damage and the influence of patient-related factors and comorbidities throughout the disease course. AKRiS, ANCA kidney risk score; eGFR, estimated glomerular filtration rate; MCCS, Mayo Clinic chronicity score; MPO, myeloperoxidase; PR3, proteinase 3; RI, remission induction.

severity requires the use of targeted tools such as the SNOT-22 (ref. 110) and the Asthma Control Questionnaire[111], both of which capture the disease's respiratory and sinonasal burden better than BVAS.

Organ damage

Persistent organ damage in AAV results from disease activity, cumulative relapses, treatment side effects and comorbidities. Damage is quantified using standardized and validated assessment tools. The VDI assesses features persisting for at least three months post-diagnosis after appropriate treatment on a scale from 0 to 64[112,113] (Table 1). A cumulative VDI ≥ 5 correlates with increased mortality risk after two years[112]. An alternative instrument, the CDA score was developed specifically for AAV and has been used in clinical trials such as PEXIVAS, RITAZAREM and ABROGATE[114].

Differentiating between organ damage and disease activity is crucial to avoid unnecessary immunosuppressive treatment[112]. Organ damage mostly occurs within the first 6–12 months, with slower progression thereafter, driven by relapses and therapy[115]. Long-term damage is associated with disease severity, age at presentation, relapse frequency and glucocorticoid use[115]. There is interest in differentiating disease-related from treatment-related damage, given that the latter is predictable and preventable[116].

Glucocorticoid-related toxicity. Despite important advances in treatment, glucocorticoids remain a cornerstone of treating AAV. In practice, glucocorticoids tend to be maintained at higher doses and for longer time than in clinical trials. Patients in practice are often left on a maintenance dose of glucocorticoids. For these reasons, patients are likely to receive substantially more glucocorticoids than the data from clinical trials might suggest is indicated. In the long term, treatment-related damage, especially from glucocorticoids, rivals the damage imposed by the disease itself[115,117].

There is now great interest in reducing glucocorticoid-related toxicity in AAV. In the PEXIVAS trial comparing standard versus reduced-dose glucocorticoid regimens for severe AAV, the efficacy of the two treatments were equivalent but the reduced-dose glucocorticoid arm had significantly (hazard ratio 0.69, 95% confidence interval 0.52–0.93) fewer serious infections in the first year of treatment[7]. The ADVOCATE trial demonstrated that a strategy using avacopan allows for reduced dosing of glucocorticoids and subsequent reduced glucocorticoid-related toxicity as measured by the glucocorticoid toxicity index (GTI)[118] compared to standard prednisone tapering[119,120]. In EGPA, glucocorticoid needs were the highest, mainly due to persistent and severe asthma symptoms, but treatment with anti-IL5 has shown an effective sparing effect[10,121].

Patient-reported outcomes

People with AAV often rate the importance of various manifestations of vasculitis differently from physicians[122,123]. As with all diseases, the perspectives of people with AAV should be respected and incorporated into assessment of any treatment plan and judgement of efficacy of interventions (see Supplementary Box 1). AAV impairs daily functioning across physical, social and psychological domains, affecting health-related quality of life (HRQoL) and employment[112]. Patients with AAV experience reductions in HRQoL that are comparable with HRQoL decreases experienced by patients with other chronic diseases. So-called generic measures of HRQoL, especially the SF-36, have been validated and used regularly to study AAV[18,124,125]. In addition, the disease-specific tool AAV-PRO was developed to more comprehensively capture patients' experiences with AAV[16,126] (Table 1). AAV-PRO domain scores do not correlate with disease activity and damage assessment (including the BVAS and the VDI), and, so AAV-PRO represents an outcome measure that complements clinician-reported endpoints in clinical trials, and aims to be reflective of the specific needs of patients[17] (Fig. 3). Other generic tools such as EQ-5D and PROMIS are also used to estimate PROs in AAV research[127,128]. In the ADVOCATE trial, patients with AAV receiving avacopan showed improvements in HRQoL, as measured by SF-36, EQ-5D-5L and SF-6D, compared with those receiving oral glucocorticoids[8,129]. In patients with EGPA, mepolizumab was associated with a quick and remarkable improvement of HRQoL as measured by the AAV-PRO[129]. These and other findings suggest that treatment, particularly if accompanied by reduced glucocorticoid exposure, can enhance HRQoL in people with AAV. People experience AAV in ways that are poorly measured by BVAS and other clinician-reported outcomes, and their concerns are often ignored[130,131].

Prognosis

Advances in treatment regimens have improved survival in AAV, and the emphasis in clinical management has shifted towards long-term health, preventing disease flares, minimizing treatment toxicity and enhancing HRQoL. Severe comorbidities, such as thromboembolic events and cardiovascular diseases, suggest a complex interaction between the pathogenesis of vasculitis, persistent inflammatory activity and clinical manifestations that do not appear to be direct consequences of vasculitis[132,133]. Comorbidities have thus become central concerns for clinicians.

AAV is characterized by considerable heterogeneity in age at onset, organ involvement, disease severity, treatment response and risk of comorbidity, all of which affect individual prognoses[134]. Long-term outcomes of great interest include remission, relapse, mortality, survival and accrual of damage, particularly progression to end-stage kidney disease or respiratory failure[134]. Additionally, comorbidities such as severe infections, thromboembolic events, cardiovascular risk, malignancy, fertility issues, secondary immunodeficiency and mental health issues must be considered[134].

Remission

Remission of AAV is achieved in 70–90% of cases (Supplementary Table 1). Achieving a BVAS of zero at 3 months correlates with improved survival, reduced risk of end-stage kidney disease, and less damage[135]. Sustained remission for at least 3–6 months predicts favourable outcomes, and is a key end point in interventional trials[134]. Such sustained remission is more difficult to obtain in people with EGPA than in people with other subtypes of AAV, because recurrent respiratory symptoms occur in the former once treatment is reduced[136,137]. PR3-ANCA positivity and increased baseline disease activity are inversely correlated with likelihood of remission in newly diagnosed patients. Refractory disease substantially heightens the risk of early mortality, primarily owing to alveolar haemorrhage and end-stage kidney disease[138].

Relapse

Relapse occurs in 42–57% of people with AAV within 5 years of diagnosis[12,139,140] (Supplementary Table 1). Depending on the AAV severity score used, relapses are classified as major or minor, although untreated minor relapses often progress to major ones[141]. Disease activity at relapse is typically less severe than disease activity at initial diagnosis, as a result of early detection and ongoing immunosuppression[142]. The optimal duration of maintenance therapy and the role of ANCA titres in the prediction of relapse remain key research areas[143–145]. Current guidelines do not recommend treatment adjustments based solely on ANCA levels[4]. However, a rise in ANCA levels, the persistence of a positive test for ANCA, and the reappearance of a positive test for ANCA all correlate with relapse in AAV-GN[145,146]. These findings pertain to people with AAV and kidney involvement, and it remains unclear whether similar findings are observed in other well defined disease clusters (such as AAV with ENT involvement). Emerging biomarkers, such as urinary soluble CD163 (which is already available in clinical practice), urinary levels of $CD4^+$ T cells, and serum complement markers show promise for prediction of relapse but require further validation[147–149].

Kidney outcomes

Kidney involvement in AAV is associated with high morbidity and mortality. Despite therapeutic advances, 25% of people with AAV progress to end-stage kidney disease at 5 years after diagnosis[26,36,94,150–155]. Outcomes are influenced by the timing of obtaining a diagnosis and baseline kidney function. People with GPA are generally diagnosed earlier than patients with MPA owing to extrarenal manifestations. Therefore people with MPA, especially in cases where disease is present only in the kidneys, often present later and with advanced chronic kidney disease[36,153].

Several tools, including the Berden histological classification, the Mayo Clinic chronicity score (MCCS), the ANCA renal risk score (ARRS) and its revised version the ANCA kidney risk score (AKRiS), as well as the percentage of ANCA crescentic score (PACS) help to predict end-stage kidney disease in AAV[71,156–159] (Fig. 4 and Supplementary Table 1). Of these, AKRiS, which includes baseline kidney function as well as histopathological features, is the most reliable predictor of end-stage kidney disease[71,160]. However, these tools do not address the chance of recovery of kidney function, an important outcome given that patients frequently present with severe kidney disease and an eGFR <15 ml min^{-1} per 1.73 m^2 and require acute dialysis. The percentage of normal glomeruli on kidney biopsy was found to help to predict kidney recovery in people with AAV-GN, but this observation needs validation in prospective studies[161]. Recovery of kidney function is not yet an established end point in clinical trials, although it is being explored in current studies. The ADVOCATE trial demonstrated that avacopan improved eGFR in people with baseline eGFR <20 ml min^{-1} per 1.73 m^2, with a significant between-group (active drug versus placebo) difference of 8.4 ml min^{-1} per 1.73 m^2 at 52 weeks[131]. Definitions of kidney function recovery, such as eGFR ≥ 15 ml min^{-1} per 1.73 m^2 or a change in the category of chronic kidney disease, require further validation[162]. Notably, recovery of eGFR continues beyond 52 weeks, as reported in observational studies, underscoring the importance of long-term follow-up in clinical trials[162,163]. Severe chronic kidney disease and the requirement for kidney replacement therapy have profound effects on cardiovascular events, thromboembolism, infection risk, HRQoL and mortality[164–166].

Screening for comorbidities

Patients with AAV are at increased risk of developing comorbidities. Some comorbidities, such as infection[167] and thromboembolic events[168,169], occur early in the disease course (23% in the first year), and others, including cardiovascular disease[1,170,171], osteoporosis[172] and malignancy[134,173,174], occur during long-term follow-up (37% at 10 years). Fertility issues[175] and reduced HRQoL[134] might persist throughout the duration of the disease (Supplementary Table 1). It is unclear whether comorbidities are attributable to immunosuppression, underlying disease or both. Anticipating comorbidities can help to mitigate the metabolic effects of treatments (by using lower-dose glucocorticoid regimens, or alternatives such as avacopan) or the impact on fertility and pregnancy (through counselling and treatment with fertility- and pregnancy-compatible immunosuppression)[176]. Routine prophylaxis against *Pneumocystis jirovecii* pneumonia is recommended and might also reduce the frequency of other bacterial infections[2]. People with AAV that are on rituximab maintenance therapy are at risk for secondary immunodeficiency and should have serum immunoglobulins checked prior to infusion. Cardiovascular disease is the leading cause of mortality in AAV, and screening for cardiovascular risk factors can support prevention of cardiovascular disease and early AAV treatment[2]. Also, age- and sex-adjusted malignancy screening is recommended. People with AAV treated with cyclophosphamide are at increased risk of non-melanoma skin cancer and urothelial malignancy, and screening for haematuria and skin malignancy in these individuals should be lifelong[173,177,178].

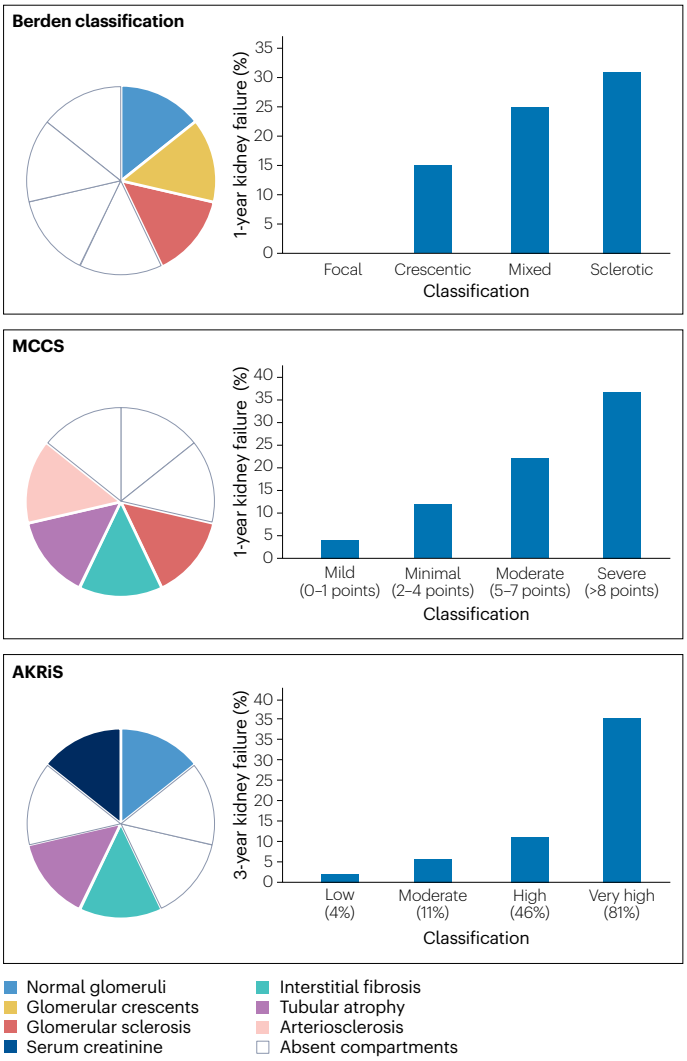


Fig. 4 | Histopathological assessment of kidney for end-stage kidney disease prediction in AAV-associated glomerulonephritis. Various histopathological scores assess kidney histopathological patterns. Berden classification and ANCA kidney risk score (AKRiS) have been developed specifically for the assessment of glomerulonephritis in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV-GN). The Mayo Clinic chronicity score (MCCS) is used in a broad spectrum of diseases with kidney involvement. Berden classification evaluates only glomerular compartment; the MCCS evaluates glomerular and interstitial compartment with additional grading of interstitial fibrosis and tubular atrophy and arteriosclerosis; and the AKRiS combines the evaluation of the glomerular and interstitial compartments with estimated glomerular filtration rate (eGFR). The risk of progression to end-stage kidney disease (eGFR <15 ml min^{-1} per 1.73 m^2 or dialysis) at 12 months and 3 years is shown for each classification (left). In the MCCS and AKRiS, biopsy findings are graded, and patients are assigned to a category according to the total score obtained. The implementation of at least one of the scores in a routine histopathological report is warranted, and the Berden score has been used here in the past by most pathology services.

Early mortality

Early mortality in AAV is driven primarily by infections and other treatment-related adverse effects. A 'therapy burden' tool can be used to effectively predict risk of early mortality (Supplementary Table 1). Other prognostic factors include markedly reduced kidney function — specifically a baseline eGFR below 30 ml min^{-1} per 1.73 m^2 — which portends poorer kidney survival, and cumulative cyclophosphamide exposure (exceeding ~36 g of cyclophosmamide), which might lead to long-term complications, including malignancy. Advanced age, chronic kidney disease and MPO-ANCA positivity consistently predict poorer survival. Despite improved survival, based on data from cohorts from 2002 to 2017 the overall mortality rate in people with AAV remains 2.7-fold higher than the rate in the general population[179,180].

Long-term outcomes

The five-year survival rate for AAV has risen to 70–80%, a marked improvement from previous decades, owing to earlier diagnosis, effectiveness of immunosuppressive therapies, new treatments, wide availability of ANCA testing and improved supportive care[12]. Similarly, there has been a reduction in the rate of end-stage kidney disease over the past several decades[12,181]. Although mortality rates have decreased, there is still a higher-than-expected mortality compared to the general population, largely caused by complications arising from the disease or its treatment[182]. The five-factor score (FFS) is a prediction system based on the presence of four positive items such as age >65 years, creatinine ≥2.7 mg dl^{-1}, and central nervous system and cardiac involvement, and one negative item, ENT involvement, at the time of diagnosis of vasculitis. The FFS predicts mortality across several types of vasculitis, including AAV[183,184] with a score of above 2 associated with worse outcomes at five years[183,184].

Outlook

An integrated, multifaceted approach to assess AAV is essential for improving patient care (Box 3). This includes understanding diagnostic tools, classifying disease, estimating severity, and predicting outcomes. By better addressing comorbidities, side effects of treatment, and disease progression, clinicians can optimize care and enhance the prognosis for patients living with AAV.

Multidisciplinary management in specialized centres and international collaboration

Multidisciplinary management in specialized centres with vasculitis expertise is considered an overarching principle in treatment guidelines for AAV[4]. Rapid access to multidisciplinary diagnostic evaluation and treatment for an early and accurate diagnosis is often necessary. In addition, patients with relapsing or refractory AAV might need improved access to clinical trials testing new drugs. Dedicated vasculitis centres with appropriately trained healthcare providers experienced in AAV can support patients and provide patient education. Some retrospective studies showed improved outcomes for patients with centre-based management, but prospective studies are needed[185–187].

In addition, collaborative efforts across international research centres, clinical registries and patient populations have the potential to expand knowledge about AAV pathogenesis and management. Global exchange of clinical experience and patient data will clarify differences in presentation and prognosis of AAV on a global scale, enabling the identification of novel biomarkers, treatment strategies and clinical guidelines. Incorporating mechanistic endpoints into clinical trials, such as evaluating the role of specific immune pathways, genetic markers, and immune cell populations, might provide deeper insights into the mechanisms driving disease activity and relapse.

Refinement of classification criteria

The development and revision of classification criteria for AAV have been important for enhancing the accuracy and consistency of research studies. The 2022 ACR–EULAR criteria offer substantial improvements over previous versions, addressing the challenges posed by the diverse clinical and serological features of AAV. ANCA-specificity testing has been shown to predict risk of relapse and has the potential to guide decisions about treatment duration. This underlines the need to analyse clinical trial outcomes based on ANCA specificity[59,145]. Understanding the relative contributions of clinical phenotypes and ANCA specificity is necessary for personalizing treatment and improving outcomes of patients with AAV[36] (Fig. 2).

Integrated view of disease activity, organ damage and PROs

The development of the standardized tools BVAS, VDI and AAV-PRO has advanced the ability to assess disease activity, damage and HRQoL. However, integration of these tools into daily care and assessment of disease activity and damage in AAV has proved difficult. This is particularly evident in patients with EGPA, because estimation of disease activity and damage in EGPA needs to incorporate the assessment of ENT manifestations and asthma more precisely. Current measures of disease activity and damage, especially kidney involvement, might lack sufficient granularity to correctly estimate severity and, thus, to stratify patients in prognostic categories. For instance, the BVAS V3.0 assigns the same score of 12 in the presence of haematuria and proteinuria regardless of whether a patient presents with a creatinine level of 1.54 or 7.50 mg dl^{-1}. The VDI records damage based on eGFR ≤ 50 ml min^{-1} per 1.73 m^2 or significant proteinuria but this does not account for improvements in kidney function[188,189]. The comprehensive end organ and integrated

Box 3 | Future steps towards an integrative approach to the assessment of ANCA-associated vasculitis

An integrated assessment in anti-neutrophil cytoplasmic antibody (ANCA)-associated vasculitis (AAV) should take into consideration diagnostic approaches, classification criteria and assessment of disease severity and prognosis. The aim is to achieve discriminative assessment with improved identification of patients at a high risk of specific outcomes. This would help to tailor treatments and would bring the field a step closer to personalized medicine in AAV.

Diagnosis

- Developing diagnostic criteria would be beneficial for improved accuracy in stratification and personalization of treatment of AAV

Classification

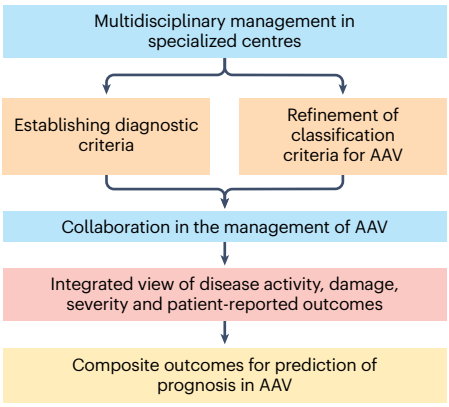
- Validation of the American College of Rheumatology (ACR)–European Alliance of Associations for Rheumatology (EULAR) classification criteria in populations under-represented in initial studies
- Continued international collaborations to perform investigator-initiated clinical trials, but also observational studies

Disease assessment

- Developing a definition of disease extent and severity that combines the activity and damage assessment, and patient-reported outcomes to improve patient stratification, risk assessment, and evaluate response to treatment and outcomes (remission, relapse) in AAV
- Improved granularity when assessing the severity and damage of certain organ manifestations

Outcomes and prognosis

- Inclusion of biomarkers and genetic data in the evaluation of individuals with AAV, especially for prediction of future relapse risk
- Development of composite assessment tools to evaluate response to treatment in AAV



Glossary

Alveolar haemorrhage
The presence of blood within the alveoli (air sacs) of the lungs, often caused by injury or disease; it can lead to difficulties in breathing, coughing up blood and impaired gas exchange.

Capillaritis
An inflammatory process that primarily affects capillaries (the smallest blood vessels in the body) and is characterized histologically by neutrophilic infiltration of the capillary walls, leukocytoclastic vasculitis, fibrinoid necrosis of the vessel and erythrocyte extravasation.

Conductive hearing loss
A type of hearing loss that occurs when sound waves cannot efficiently travel through the outer ear, eardrum or middle ear.

Eosinophilia
Eosinophilia is characterized by an increased number of eosinophils in the blood, defined by an absolute eosinophil count greater than 500 cells per microlitre or an eosinophil percentage that exceeds 10% of the total white blood cell count.

Gold standard
The most reliable and accurate method for diagnosing a condition, testing a procedure or assessing treatment effectiveness; it serves as the benchmark against which other methods or treatments are compared.

Granulomatous inflammation
A chronic inflammatory response characterized by the formation of granulomas, which are aggregates of macrophages, often surrounded by lymphocytes and other immune cells; this type of inflammation typically occurs in response to persistent infections, foreign bodies or certain diseases, such as tuberculosis, sarcoidosis and leprosy.

Interstitial lung disease
A group of pulmonary disorders characterized by inflammation and fibrosis of the lung interstitium, leading to impaired gas exchange and respiratory dysfunction; it can result from various causes, including autoimmune diseases, environmental exposures and medications.

Mononeuritis multiplex
Mononeuritis multiplex is characterized by the simultaneous or sequential inflammation and damage of two or more peripheral nerves, typically affecting different anatomical areas; it often results from systemic diseases such as autoimmune disorders, vasculitis or infections; symptoms include pain, weakness and sensory disturbances like numbness or tingling.

Necrotizing and crescentic glomerulonephritis
A severe kidney disorder characterized by rapid glomerular damage and crescent formation, often leading to acute kidney failure; it is often associated with autoimmune diseases and vasculitis.

Orbital pseudotumours
A benign, non-infectious inflammatory condition of the orbit that causes swelling, pain and potential vision changes, often resembling a tumour.

Saddle nose deformity
A condition characterized by a collapse or depression of the nasal bridge, creating a saddle-like appearance. It can result from trauma, congenital conditions, or diseases like syphilis or granulomatosis with polyangiitis (GPA).

Subglottic stenosis
A narrowing of the airway in the subglottic region, located between the vocal cords and the first tracheal ring; symptoms may include inspiratory stridor, dyspnea and voice abnormalities.

Vasculitis
Inflammation of the blood vessels; it can affect the arteries, veins or capillaries, leading to a variety of symptoms, depending on which vessels and organs are involved.

assessment of disease activity and damage could be used as a measure of AAV severity, because different treatment regimes are needed for a person who has overcome acute kidney failure and a person who progressed to end-stage kidney disease shortly after diagnosis (Fig. 3). Similarly, risk of relapse differs between individuals with AAV, and relapse contributes to cumulative damage (Fig. 3). PROs are not part of the standard assessments, but they are important to understand patients' perceptions of the disease, adherence to the management plan and would help with patient inclusion in an integrated approach towards personalized care (Fig. 3; Supplementary Box 1). In addition, the lack of reliable biomarkers for disease assessment in AAV disconnects evaluation of disease state and pathophysiology, but their integration on combined assessment might help to tailor treatment in the appropriate setting. For example, MPO-ANCA testing could be integrated with clinic and laboratory data to guide maintenance or treatment strategies in people with AAV-GN. Future research should focus on combining disease assessment tools with PROs and biomarkers to better characterize disease and assess outcomes in AAV (Fig. 3).

Composite outcomes for prediction of prognosis

Composite assessment tools have been proposed to improve assessment of response to treatment and outcomes in AAV. These tools integrate various disease measures, including disease activity, damage and treatment toxicity[190,191]. The OMERACT Vasculitis Working Group is developing a composite tool that captures the full disease burden across multiple domains[190,191]. This approach might provide a more holistic assessment of AAV, including assessment of the potential increase in frailty and the long-term consequences of persistent organ damage, and might help to guide clinical trials and patient management in the future[190,191]. Such composite assessment tools could incorporate PROs, biomarkers and genetic data. Genetic data are emerging as a potential biomarker for refining patient management. For instance, polymorphisms in the *PRTN3* gene might increase the amount of PR3 in patients with AAV or increase the risk of relapse in patients with PR3-ANCA[192,193]. Although this approach holds promise, more research is needed to validate the utility of genetic markers in clinical practice, and their integration into personalized treatment strategies will require further refinement. An increased understanding of the pathogenesis of AAV might also help individual risks to be evaluated by integrating genetic and immunological information.

Conclusions

An integrated approach to assessing and managing AAV is essential for improving outcomes. This includes the use of diagnostic tools, accurate disease classification, biomarkers and PROs to personalize treatment. Ongoing international collaborations and clinical registries will help to refine treatment strategies, biomarkers and classification systems. Future clinical trials focused on mechanistic endpoints will further enhance our understanding of the pathophysiology of this complex

disease. By incorporating these strategies, clinicians will be able to personalize and optimize care, reduce complications and improve prognosis for patients with AAV.

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Author contributions

M.C.M. and A.K. had the idea for this review paper, conceptualized the proposal and the manuscript that generated this work, and coordinated the project. P.A.M. and D.J. provided initial review of, and input into, the proposal and the manuscript. All authors contributed to writing and revising the paper.

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Review article

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Advances in the pathophysiology, diagnosis and treatment of Takayasu arteritis

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Abstract

Takayasu arteritis (TAK) is a rare, chronic, large-vessel vasculitis that primarily targets the aorta and its major branches, leading to vascular stenosis, occlusion and aneurysm formation. TAK, which is characterized by granulomatous inflammation of the arterial wall, predominantly affects women, with peak onset typically occurring between 20 and 40 years of age. The disease exhibits substantial geographic variability in prevalence, with emerging evidence suggesting that these differences are partly owing to variations in genetic susceptibility loci, particularly within immune-related genes; however, the role of environmental factors in the disease aetiology remains poorly understood. Non-invasive imaging techniques have become central to both diagnosis and disease monitoring. Furthermore, the development of biomarkers holds promise for more accurate assessment of disease activity. The management of TAK is evolving, driven by an improved understanding of disease pathogenesis. The growing use of biologic agents is providing new treatment options, particularly for patients with refractory or relapsing disease. By integrating these developments, this Review is aimed at serving as a comprehensive resource for clinicians and researchers dedicated to improving the understanding and management of TAK.

Sections

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Key points

- Takayasu arteritis (TAK) is a rare large-vessel vasculitis with a global incidence of 1.11 per million person-years, which predominantly affects young women 20–40 years of age.
- The pathogenesis of TAK involves multiple interconnected immune-mediated processes that ultimately result in vascular fibrosis and stenosis.
- Over 100 genetic susceptibility loci, including *HLA-B*52*, have been identified, contributing to geographic differences in disease prevalence.
- Non-invasive imaging is central to diagnosis and monitoring; ^{18}F-fluorodeoxyglucose-PET uptake in the arterial wall predicts future stenotic lesions better than wall thickness alone.
- Serum pentraxin-3 shows promise as a biomarker of disease activity, particularly when IL-6 blockers are used.
- Glucocorticoids combined with conventional immunosuppressive therapy remain the cornerstone of treatment; relapse rates with glucocorticoid monotherapy reach 60–77% within 1 year.
- Biologic agents, including TNF inhibitors and tocilizumab, can be effective in refractory TAK; therapies such as secukinumab and Janus kinase inhibitors are emerging options.

Introduction

Takayasu arteritis (hereafter also referred to as TAK), first described by the Japanese ophthalmologist Mikito Takayasu in 1908, is characterized by chronic granulomatous inflammation of the arterial wall that can lead to stenosis, occlusion and aneurysm formation[1]. These vascular changes can result in ischaemic symptoms and the characteristic loss of pulses, hence why TAK is sometimes referred to as 'pulseless disease'. Disruption of blood flow through crucial arteries to the brain, heart and other organs can be life threatening.

TAK is more common in women than in men; reported ratios vary between 2:1 and 9:1 (ref. 2). Although disease onset is typically 20–40 years of age, childhood-onset disease and onset after 40 years of age can occur[3]. TAK is a rare disease; the estimated global incidence of TAK is 1.11 per million person-years, although incidence rates vary considerably among different populations[4]. The disease is most common in East Asian populations, with the highest prevalence rates reported in Japan (40 per million)[5]. However, the disease can affect individuals of any genetic ancestry. Studies suggest that inter-population differences in disease prevalence are, at least in part, caused by variation in allele frequencies at disease-associated genetic susceptibility loci[6]. The role of environmental factors in the aetiology of TAK is less clear.

Given its complex and often insidious onset, TAK requires a high index of clinical suspicion and a multidisciplinary approach to diagnosis and management. In this Review, we comprehensively examine advances in the pathophysiology, clinical features, diagnostic strategies and therapeutic approaches with regard to TAK.

Pathology and immunopathogenesis

In TAK, the arterial tissue has a granulomatous pan-arteritis with prominent adventitial fibrosis, neovascularization, disruption of the elastic laminae and intima-media thickening (Fig. 1). Environmental factors, particularly infectious triggers, are thought to contribute to disease development. This section explores the immunopathological mechanisms underlying TAK, including the roles of microbial exposure, dysregulated innate and adaptive immune-cell activation, cytokine signalling and tissue remodelling, which lead to arterial fibrosis.

Environmental factors

Indirect evidence suggests an association between TAK and infections; for example, a high frequency of tuberculosis occurs in patients with TAK (including those not on immunosuppressive therapy)[7,8]. In addition, the common pathology of granulomatous inflammation, reports of primary immunodeficiency disorders associated with paediatric-onset TAK and the role of T helper 17 (T_H17) cells in TAK (a cell type that is linked to viral infections) make it reasonable to hypothesize that an aberrant immune response to prior infection with tuberculosis, viruses or other infections might trigger TAK[7–12]. Compared with atherosclerotic arteries, the arterial wall is inflamed in TAK and shows increased MHC class I polypeptide-related sequence A (MICA) expression, which can be induced by infections and can activate infiltrating γδ T cells and natural-killer (NK) cells via the NKG2D receptor[13–20]. In TAK, a greater abundance of *Streptococcus* and *Campylobacter* species has been reported in the gut microbiota, and in the blood, Clostridia, Cytophagia and Deltaproteobacteria are increased, whereas Bacilli classes are reduced compared with healthy individuals[21,22].

Innate immunity

The activation of γδ T cells and NK cells in TAK arterial tissue is hypothesized to stimulate their cytotoxic activity and is also associated with higher expression of the co-stimulatory molecules CD137 (also known as 4-1BB) and Fas in the arterial wall, which in turn enhance T cell activation[19,20] (Fig. 1). Vascular smooth-muscle cells in patients with TAK have a senescent phenotype with mitochondrial dysfunction, driven by IL-6 (ref. 23).

The gene *ETS2*, which regulates monocyte and macrophage activation, has been identified as a common genetic association between TAK, ankylosing spondylitis and inflammatory bowel diseases, which are also linked through their shared MHC-I associations (referred to as MHC-I-opathies)[24,25]. However, clinical and molecular characteristics suggest that TAK belongs to a distinct subset of MHC-I-opathies[25], demonstrated by the lack of an association with ERAP1 or ERAP2 in contrast with other MHC-I-opathies (A.H.S., unpublished observations). A polymorphism (rs2069837) in the *IL6* enhancer region that alters the expression of glycoprotein non-metastatic melanoma protein B (GPNMB), a negative regulator of monocyte and macrophage activation, has been linked with TAK susceptibility[26]. Keeping in mind the continuum between M1-like and M2-like macrophage polarization within biological systems, patients with TAK who are not on immunosuppressive therapy show a predominant infiltration of M1-like macrophages and the chemoattractant protein CCL2 is detected in the adventitia, whereas those who are on immunosuppressants have primarily M2-like macrophage infiltration and CCL2 reported in the media layer[27]. These findings indicate a shift to a predominantly fibrotic M2-like phenotype in patients with TAK receiving immunosuppressive therapy, which corresponds

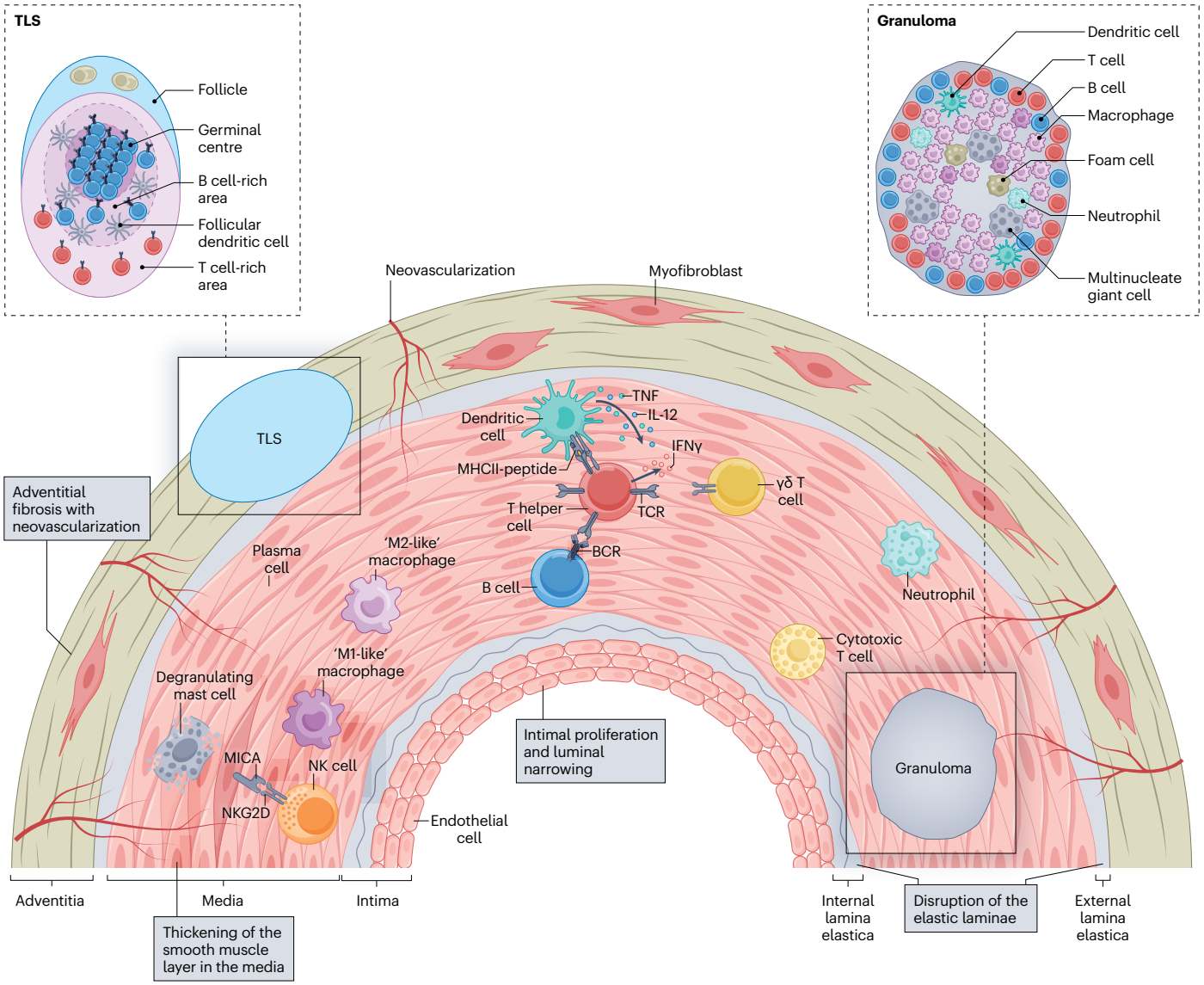

Fig. 1 | Pathology of Takayasu arteritis. The pathology of Takayasu arteritis (TAK) is a pan-arteritis, believed to begin in the adventitial layer, initially through vasa vasorum affliction, before involving the media and intima, resulting in intimal hyperplasia, disruption of the elastic laminae and adventitial thickening with fibrosis and neovascularization[13,14]. Cellular infiltrates in the arterial wall include T cells, B cells, plasma cells, γδ T cells, natural killer (NK) cells, dendritic cells, neutrophils and macrophages[13,15]. Granulomatous arteritis is common to TAK and giant-cell arteritis (GCA). Granulomas with multinucleate giant cells in the TAK arterial wall are often found in the intima and media. The arteries from patients with TAK show a dominant infiltration of $CD8^+$ T cells and NK cells[14]. Tertiary lymphoid structures (TLS) have been identified in the adventitia of TAK arteries[16,17]. Arterial-wall fibrosis (which results in arterial stenosis) is prominent in TAK, unlike GCA, in which aneurysms are more common[18]. BCR, B cell receptor; MICA, MHC class I polypeptide-related sequence A; TCR, T cell receptor. The original version of this figure was created with BioRender.com.

with the stenosing behaviour of arteritis in TAK[18]. Patients with active TAK have higher frequencies of circulating total monocytes and classical and intermediate sub-populations than healthy people, and levels of the monocyte chemokine CCL22 are elevated compared with those with inactive TAK[28]. Arterial-wall macrophage infiltration detection in vivo using somatostatin-2 receptor PET, which targets the somatostatin-2 receptor expressed on inflammatory macrophages, merits evaluation as a novel disease activity measure for TAK[29].

Adaptive immunity

Dendritic cells infiltrating affected arteries might bridge innate and adaptative immunity in TAK[13]. T_H1 and T_H17 cells, via secretion of IFNγ and IL-17, respectively, drive granuloma formation and arteritis in TAK[10,25,30]. In TAK, the activation of mammalian target organ of rapamycin (mTOR), particularly mTOR complex 1 (mTORC1) in $CD4^+$ T cells is driven by Notch-1, which promotes T_H1 and T_H17 cell activation[31,32]. Unlike in giant-cell arteritis (GCA), another form of large-vessel

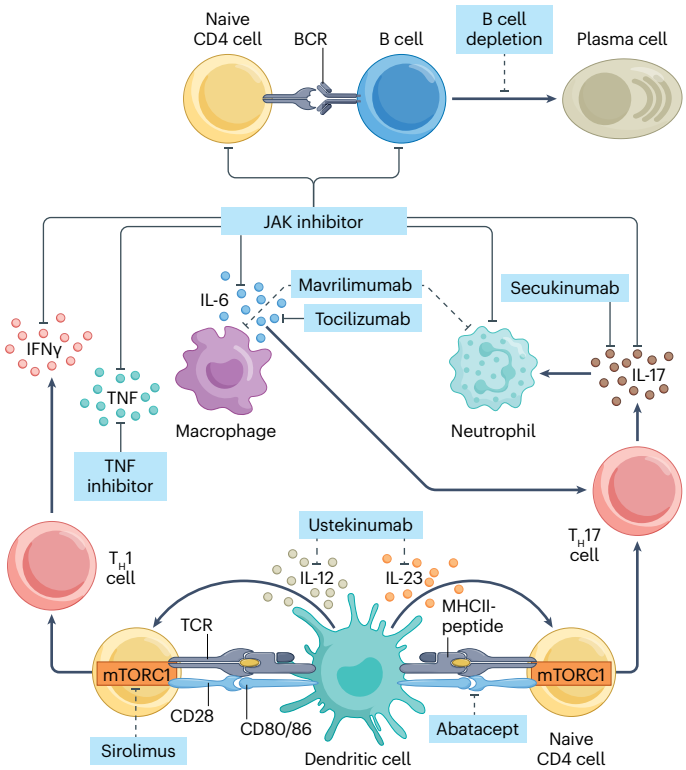

Fig. 2 | Therapeutic targets in Takayasu arteritis. Observational data and the secondary end point of a randomized controlled trial (RCT) support the use of IL-6 inhibition with tocilizumab in Takayasu arteritis (TAK)[40,41]. The use of TNF inhibitors and secukinumab for TAK is also supported in observational studies[41,42]. Costimulatory blockade with abatacept and IL12p40 inhibition with ustekinumab failed to demonstrate benefits versus placebo in RCTs, although methodological issues and premature termination rendered the trial of ustekinumab at a high risk of bias[43–45]. Despite literature supporting the role of B cells in the arterial pathology of TAK, observational data reveal the ineffectiveness of rituximab in TAK, although other B cell-depleting therapies, such as obinutuzumab and inebilizumab, remain unexplored[46]. Sirolimus blocks mTORC1, which drives T helper 1 (T_H1) cell and T_H17 cell differentiation in TAK, and is a potential treatment target for future exploration[32]. Mavrilimumab blocks granulocyte-macrophage colony-stimulating factor receptor which activates macrophages and neutrophils[201]; it has been proven effective in an RCT of giant-cell arteritis, although it remains unexplored in TAK[202]. Observational studies have reported the effectiveness of Janus kinase (JAK) inhibitors in TAK and these drugs target multiple cytokines and immune cells. The solid lines indicate therapies that are commonly used with some evidence to support their use in patients with TAK. The dotted lines indicate potential future therapies based on an understanding of the pathogenesis of TAK or therapies that have a mechanistic basis but have not yet been proven to be effective in patients with TAK. CD80/86, CD80 or CD86; mTORC1, mammalian target organ of rapamycin complex 1; TCR, T cell receptor; BCR, B cell receptor. The original version of this figure was created with BioRender.com.

vasculitis, the expansion of T_H17 cells in the peripheral blood in TAK is not inhibited by glucocorticoids[10,30]. T_H17.1 cells have been reported in TAK; these cells secrete both IFNγ and IL-17 and thus share phenotypic characteristics of T_H1 and T_H17 cells, and also express the drug efflux protein p-glycoprotein, which might explain the resistance of T_H17 cells to glucocorticoids in this context[11,33]. Circulating $CD4^+$ T cells and T_H17 cells that express the exhaustion marker PD1 are also elevated in TAK. These cells drive fibrosis in other disease states, and might contribute to arterial-wall fibrosis in TAK, although these cell populations have not yet been studied in arterial tissue from patients with TAK[11,18]. Infiltrating $CD8^+$ cytotoxic T cells in TAK have increased T cell receptor activation and are important sources of IFNγ[34,35].

The role of B cells in TAK is emerging. Tertiary lymphoid structures (TLSs) comprising follicular dendritic cells, memory B cells and T cells, with enrichment of antigen-experienced T follicular helper cells, are more prevalent in the arterial wall of TAK than GCA, particularly in active TAK[16,17]. In arterial tissue from patients with GCA and in a functional mouse model of GCA, stem-like $CD4^+$ T cells expressing TCF1 were crucial for TLS formation; however, this aspect remains unexplored in TAK[36]. Sera from patients with TAK can activate mTORC1 in endothelial cells in vitro[37]. Autoantibodies that target endothelial protein C receptor and scavenger receptor class B type I block these proteins from inhibiting endothelial-cell and T_H17-cell activation, thereby driving inflammation in TAK[38]. Novel autoantibodies against proline-rich protein HaeIII subfamily 2, dihydropteridine reductase and spermatogenesis-associated 7 proteins were identified in 2021 using serum proteomics that distinguished samples from people with TAK from samples from healthy individuals, but these results require further validation[39].

Arterial-wall fibrosis

The inflamed TAK artery heals and becomes a fibrosed, stenosed artery. M2-like macrophages, mast cells, T cells (particularly PD1-expressing T_H17 cells) and the cytokines IL-6 and IL-17A are postulated to drive fibroblast activation in the TAK artery. As arterial inflammation in TAK can result in fibrosis, using in vitro and preclinical models of disease to test if combining immunosuppressive and antifibrotic therapies can reduce subsequent arterial stenosis is important[18]. Several targeted therapies for TAK have been developed on the basis of the current understanding of disease pathogenesis[32,40–46] (Fig. 2).

Animal models of Takayasu arteritis

Animal models that replicate the pathology of TAK are sparse. One model, which was first described in GCA and is now also used as a model of TAK, involves implanting human arteries from cadavers into immunodeficient NOD-SCID mice followed by infusion of peripheral-blood mononuclear cells from patients with active TAK, and results in immune-cell engraftment in the implanted artery[32]. Other models of TAK include aortitis induced by knocking out IRF4-binding protein, IL-1 receptor antagonist knockout mice or bioengineered human arteries engrafted with monocytes, macrophages and dendritic cells[47,48].

Taken together, the interplay of environmental triggers, dysregulated innate and adaptive immune responses, and maladaptive tissue repair drives the vascular pathology of TAK, underscoring the importance of mechanistic insights for the development of targeted therapies.

Genetics of Takayasu arteritis

The pathogenesis of TAK remains incompletely understood. Given the substantial heterogeneity observed between different patients, there might be multiple causal factors that contribute to disease pathogenesis. Evidence of a genetic contribution to the disease aetiology comes from differences between populations in the prevalence of TAK, familial case occurrence and the confirmed genetic associations within and outside of the HLA region[6]. Unbiased genome-wide association studies have

been performed in TAK that characterize the genetic landscape of the disease[49–53]. Currently, over 100 genetic susceptibility loci for TAK have been identified, including a number of loci established in multiple cohorts with a genome-wide association studies level of significance (Table 1).

Genetic susceptibility loci in Takayasu arteritis

The most well-established genetic association in TAK is within the HLA class I region. Specifically, *HLA-B*52* has been consistently linked to increased disease susceptibility across different populations[54–56]. Furthermore, *HLA-B*52* is associated with earlier disease onset and a more aggressive disease course, including increased rates of aortic regurgitation and left ventricular dysfunction in TAK[55,57,58]. Fine-mapping studies within the HLA region have led to the identification of an additional genetic association in the HLA class II region, specifically localized to *HLA-DQB1* and *HLA-DRB1* in TAK[49]. This association appears to be independent of *HLA-B*52*, albeit much less robust. Interestingly, similar genetic associations within both HLA class I and class II regions have been reported in GCA[59]; however, in GCA, the genetic association is stronger in the HLA class II region. These findings suggest that the relative contribution of associations in HLA class I versus class II regions might influence if a patient predisposed to large-vessel vasculitis develops TAK or GCA.

Beyond the HLA region, multiple non-HLA loci have been implicated in TAK, primarily genes involved in immune-system regulation[6]. Among these, *IL12B* encodes the p40 subunit of IL-12 and IL-23, both of which have key roles in pro-inflammatory immune responses[49,50]. Another important cytokine-related gene, *IL6*, has been associated with TAK, with functional studies indicating that genetic variants in this region might alter the expression of pro-inflammatory mediators in monocytes and macrophages[26,51].

Other associated loci include *FCGR2A* and *FCGR3A*, which encode Fc receptors involved in immune-complex clearance, and *ETS2*, a transcription factor that regulates macrophage-driven inflammation[24,49,53]. Additional susceptibility loci that have been identified include *DUSP22*, *PTK2B*, *KLHL33*, *RPS9/LILRB3*, *LILR3A*, *SVEP1*, *CFL2* and *VPS8*, many of which are involved in immune signalling, vascular biology and inflammatory responses[51–53].

Functional implications of susceptibility variants

Similar to other immune-mediated diseases, the majority of genetic susceptibility loci in TAK are located in non-protein-coding regions and are instead found in regulatory regions that influence gene expression and chromatin structure[6,53]. Functional genomic analyses show that TAK-associated variants are enriched in enhancer and promoter regions, particularly in monocytes, suggesting their role in modulating immune responses[53]. Further enrichment of genetic susceptibility loci within regulatory chromatin regions in B cells also suggests a role for B cells in the pathogenesis of TAK[53].

The disease-risk allele in a key disease-associated genetic variant within *IL6* suppresses the expression of *GPNMB*, an anti-inflammatory gene, through chromatin looping and recruitment of the MEF2–HDAC repressive complex in monocyte-derived macrophages[26]. Risk alleles in the disease-associated chr21q22 locus enhance the expression of *ETS2*, a transcription factor implicated in macrophage-mediated inflammation[24,53]. These findings highlight how non-coding genetic variation contributes to disease pathogenesis by altering immune-cell activity in TAK.

Transcription factor binding analysis has shown that TAK-associated variants are enriched in binding sites for STAT and RUNX family transcription factors, which are critical regulators of immune responses[6]. This finding suggests that genetic variants associated with TAK might influence the activation of key inflammatory pathways and therefore provide novel potential therapeutic targets for TAK.

Genetic-risk score and population differences

A cumulative genetic-risk score (GRS) analysis has provided insights into the genetic burden of TAK across populations[6]. The highest genetic risk has been observed in East Asian populations, where TAK prevalence is highest. South Asian and African populations also exhibit a relatively high GRS, whereas European and admixed American populations are at a lower genetic risk. These findings suggest that genetic factors at least partly underlie the differences in TAK prevalence across populations. However, it should be noted that the use of a GRS alone in immune-mediated diseases in individual patients is limited, largely owing to the fact that GRSs are based mainly on common genetic variants.

Clinical implications

The identification of genetic risk loci in TAK has potential clinical applications, including biomarker development, risk stratification and personalized-medicine approaches. Moreover, genetic studies in TAK can identify promising new therapeutic targets; for example, the genetic association with *IL12B* suggests that ustekinumab might warrant consideration as a candidate for future clinical evaluation in TAK[44,45,60]. The IL-6 pathway is already a target of existing biologic therapies, such as tocilizumab, which is used in the treatment of TAK[26,51]. Evidence from functional genetic studies suggests that targeting ETS2-driven macrophage inflammation could offer novel therapeutic strategies in TAK and other ch21q22-associated diseases[24]. Finally, drug-repurposing analyses based on genetic-association studies

Table 1 | Genetic susceptibility loci in Takayasu arteritis

Gene	Odds ratio	Loci
HLA-B and *MICA*	3.28	HLA
MUC21	2.71	HLA
CCHCR1	2.44	HLA
HLA-DQB1 and *HLA-DRB1*	2.34	HLA
IL6	2.07	Non-HLA
PTK2B	1.94	Non-HLA
chr13q21	2.02	Non-HLA
FCGR2A and *FCGR3A*	1.81	Non-HLA
RPS9 and *LILRB3*	1.64	Non-HLA
CFL2	1.62	Non-HLA
chr21q22	1.56	Non-HLA
KLHL33	1.55	Non-HLA
IL12B	1.54	Non-HLA
LILR3A	1.53	Non-HLA
DUSP22	1.52	Non-HLA
VPS8	1.51	Non-HLA
SVEP1	1.45	Non-HLA
HLA-G	1.43	HLA

Loci within and outside of the HLA region that have been associated with the susceptibility to Takayasu arteritis with a genome-wide association studies level of significance ($P<5\times10^{-8}$) are depicted[6].

have identified medications such as fostamatinib and leflunomide as potential treatments for TAK[61].

In summary, integrating genetic discoveries with functional genomics and clinical data will be essential for advancing understanding of the molecular mechanisms underlying TAK. Future research into the genetics of TAK should also focus on understanding gene–environment interactions in the development of TAK.

Clinical features and differential diagnosis

The clinical presentation of patients with TAK depends on the stage of the disease and the distribution of vascular lesions. Classically, the natural history of TAK progresses through three stages: the first stage is characterized by the presence of non-specific constitutional symptoms (that is, non-specific symptoms that indicate generalized disease and do not signify specific organ pathology) caused by systemic inflammation; the second stage is vascular inflammation that presents with features such as carotidynia; the final stage is vascular insufficiency[62]. However, less than one-fifth of patients progress sequentially through such a triphasic disease[63].

Most patients present with clinical features suggestive of underlying vascular inflammation and vascular insufficiency. The symptoms of vascular insufficiency, including limb claudication, absent pulses, vascular bruit and hypertension, are by far the most common presenting features, reported in more than 50% of patients with TAK[64]. Although some symptoms, including limb claudication, reflect the underlying vascular area of stenosis, many of the symptoms are multifactorial. For instance, breathlessness, cough and chest pain might be manifestations of multiple pathologies, including aortic regurgitation, cardiac failure, coronary heart disease, systemic hypertension and rarely pericarditis, pulmonary hypertension or aortic dissection[65]. A few patients might present with features of subclavian steal syndrome, which includes light-headedness, presyncope or syncope along with features of upper limb claudication[66].

Around 30% of patients with severe narrowing of large arteries present with complications that include stroke or transient ischaemic attacks, hypertensive emergency, myocardial ischaemia, heart failure, aortic regurgitation, ocular blindness and, rarely, digital gangrene[64,67,68]. Patients can also present with features of left-ventricular dysfunction and pulmonary hypertension, including haemoptysis, but these features are rare[69–71]. Visual symptoms, such as amaurosis fugax and monocular or bilateral visual loss, are common and generally indicate advanced disease[72]. In many patients, extensive vascular damage is already present at the time of diagnosis, and life-threatening or organ-threatening complications might be the initial presenting features[63,65,66,68,73].

In long-standing disease, the risk of cardiovascular disease, including stroke and transient ischaemic attack, is increased, with an estimated pooled prevalence of 15.8% (refs. 74–76). Coronary-artery lesions have also been described in TAK[77]; coronary-artery involvement occurs in ~5% to 50% of patients with adult-onset TAK, whereas the frequency in paediatric TAK varies from ~8% to 40% (ref. 78). For more than two thirds of patients, involvement occurs primarily in the proximal region and ostia of the coronary artery, whereas the middle and distal regions are rarely affected. Skip lesions (segmental areas of vascular inflammation separated by normal-appearing artery) are also characteristic of TAK-associated coronary-artery lesions[79]. Coronary-artery involvement is associated with a high frequency of major cardiovascular events, and this frequency is increased further with disease involving the coronary-artery ostia, ≥70% luminal stenosis and high disease activity[79]. Multi-detector CT imaging is the preferred method for detecting coronary involvement[80]. Given the high frequency of coronary-artery lesions in TAK and the considerable impact of coronary lesions on cardiovascular mortality, it might be prudent to assess the coronary arteries of patients with TAK at least at diagnosis.

Carotidynia, a characteristic symptom of vascular inflammation, is described in 5% to 15% of patients with TAK. Up to one third of patients with TAK present with fatigue, fever, myalgia and malaise, which indicates systemic inflammation along with features of vascular inflammation or ischaemia. However, constitutional symptoms alone occur in less than 10% of patients[62,64]. The absence of ischaemic symptoms in these patients can lead to diagnostic delay[81]. Skin lesions, including erythema nodosum, pyoderma gangrenosum and cutaneous vasculitis, are uncommon and often indicate overlap with other autoimmune conditions[82–84]. A few (<10%) patients are asymptomatic and are diagnosed incidentally during evaluations for other medical conditions[63]. Some patients only present with vascular bruit (an abnormal sound heard over an artery caused by turbulent blood flow, usually owing to stenosis or other vascular irregularities), pulse asymmetry or blood-pressure abnormalities during examination.

The frequency of symptoms differs slightly with age at onset. Although constitutional symptoms, abdominal pain, hypertension, cardiomyopathy and renal failure are more common in childhood TAK, symptoms of peripheral ischaemia, including limb claudication, is more frequently observed in patients with adult-onset disease[85]. However, pulse abnormality and hypertension are still the commonest clinical presentations in children[64]. Infants most commonly present with hypertension, blood-pressure inequality between limbs and fever[86]. Aortic regurgitation and stroke are more frequently observed in adult TAK (approximately 7.5%) than in childhood-onset TAK[64].

The co-occurrence of other immune-mediated diseases with TAK is not uncommon. The most common associations include spondyloarthritis (referred to as TAK-SPA) and inflammatory bowel disease, which are observed in approximately 6%–20% and 2%–6% of patients with TAK, respectively[87]. These conditions share common genetic susceptibility loci, including MHC class I and *IL12B*. The TAK-SPA group of patients present at a younger age and require biologic drugs more frequently than patients with TAK without SPA[87].

Differential diagnosis of Takayasu arteritis

Although imaging abnormalities in TAK are quite characteristic, many other autoimmune and non-autoimmune diseases might present with overlapping features and therefore need to be ruled out[88] (Table 2). The most common differential diagnosis is GCA. Older age at onset, more frequent cranial and constitutional symptoms (including polymyalgia rheumatica) and higher and persistent metabolic activity on PET scans, with less severe thickening of the involved areas, differentiate GCA from TAK[89,90]. In addition, patients with GCA generally do not present with lower-limb claudication and carotidynia[88,91]. Although the carotid and subclavian arteries can be involved in both diseases, longer segment and tapering stenotic lesions are more often found in GCA than in TAK[92]. IgG4-related peri-aortitis is another condition that can also mimic TAK[93–95] (Table 2). Atherosclerosis is yet another common mimic, particularly in older individuals; in contrast to the smooth long segment concentric mural thickening in TAK, atherosclerosis is characterized by eccentric thickening of the aorta or its branches with focal, low-intensity uptake in fluorodeoxyglucose (FDG)-PET studies[96]. Atherosclerosis preferentially involves the distal portions of the carotids and its branches[96]. Some infections can also resemble TAK; tuberculosis

Table 2 | Differential diagnosis of Takayasu arteritis

Disease(s) or disorder(s)	Prominent features	Vascular imaging findings	Refs.
Autoimmune and inflammatory diseases			
Giant-cell arteritis	Older age at disease onset than in TAK Frequent constitutional and cranial symptoms	Superficial temporal arteries and cranial and axillary arteries are commonly affected PET-CT scans show higher and persistent metabolic activity with less severe mural thickening of the involved arteries than in TAK	89,90
IgG4-related peri-aortitis	Other organ involvement The presence of retroperitoneal fibrosis	The aorta and coronary arteries are most affected, followed by iliac arteries Diffuse or patchy mural thickening of often >2 mm along with homogenous delayed wall enhancement ('mantle sign') with either aneurysms or stenosis Periaortic soft-tissue thickening and absence of mural calcifications differentiate IgG4-related peri-aortitis from TAK FDG-PET scans show no or minimal metabolic activity in the aortic wall but metabolic activity is present in peri-aortic and arterial tissues	93–95
Associated with other autoimmune rheumatic conditions[a]	Disease-specific features that are indicative of other organ involvement and the presence of autoantibodies specific for other rheumatic diseases	Small to large vessel involvement Behçet disease might lead to both aneurysms and stenosis with involvement of the pulmonary arteries, the aorta and aortic branches Ascending aorta involvement with aortic insufficiency is a common feature of Cogan's syndrome	88,89
Antiphospholipid antibody-associated vasculopathy	Previous pregnancy loss or pregnancy complications Vascular thrombosis Associated with neurological involvement Normal inflammatory markers	Involvement of any of the aortic-arch branches, including carotids with the internal carotid artery, innominate and subclavian arteries Usually non-inflammatory with no or minimal metabolic activity	188
Erdheim–Chester disease	Clinical features that reflect the involvement of other organs, including the lungs, eyes, long bones, skin, pituitary gland and brain Retroperitoneal fibrosis	Circumferential wall thickening of the aorta (coated aorta), the entire aorta is involved in 50% of patients Descending thoracic aorta and renal ostial stenosis Periarteritis is common	189–191
Non-infectious non-autoimmune diseases			
Atherosclerosis	Affects older patients Absence of symptoms such as carotidynia Normal or mildly elevated inflammatory markers	The disease might extend up to and beyond the carotid bifurcation, which are usually spared in TAK Subclavian arteries are less commonly involved The aortic-wall thickening is focal, eccentric and irregular in atherosclerosis, whereas smooth, concentric and long-segment thickening is the typical involvement in TAK Calcified plaques on CT angiography are more common than in TAK FDG uptake is less intense, with an SUV max of <2	96
Fibromuscular dysplasia	Primarily affects young women Usually presents with hypertension or mid-aortic syndrome, stroke Normal inflammatory markers	Typically characterized by symmetrical involvement of bilateral renal and distal carotid arteries, predominantly the extra-cranial portion of the internal carotid artery Characteristic 'string of beads' appearance, owing to areas of focal stenosis and aneurysms	192
Segmental mediolysis	Abdominal pain is a frequent symptom	Affects medium-sized arteries, including involvement of the superior mesenteric and coeliac axis, whereas the main aorta is usually spared Characterized by non-inflammatory dissecting aneurysms Aneurysms and dissecting haematoma lesions can also be observed	193,194
Hereditary elastic fibrous disorders			
Vascular Ehlers–Danlos syndrome, Loeys–Dietz syndrome and Marfan syndrome	Positive family history Characteristic clinical features, including tall stature, ectopia lentis and hyperextensibility of skin and joints	Involvement of the infra-diaphragmatic aorta and infra-diaphragmatic aorta branches Multiple arterial dissections and aneurysms, and rarely occlusions No or low metabolic activity on PET scans	195
Neurofibromatosis-1 vasculopathy	Characteristic features, including symptoms suggestive of compression of the gastrointestinal tract, pulmonary and urinary tracts by neurofibroma	Arterial aneurysms of the aorta, renal, carotid or mesenteric arteries with or without stenosis Arterio-venous malformation	196

Table 2 (continued) | Differential diagnosis of Takayasu arteritis

Disease(s) or disorder(s)	Prominent features	Vascular imaging findings	Refs.
Infectious aortitis disorders			
Mycobacterium tuberculous arteritis, syphilitic aortitis and bacterial aortitis	These disorders typically present with non-specific constitutional symptoms, including fever, weight loss, malaise and myalgia Lymphadenopathy	Abdominal aorta is primarily involved, followed by descending thoracic aorta and renal arteries Multiple saccular aneurysms without substantial wall thickening can be observed in tuberculous arteritis Arterial-wall erosions might occur (uncommon in TAK) Non-homogenous contrast-medium uptake, perivascular inflammation with perilesional lymphadenopathy FDG-PET uptake in large arteries can be patchy	97,98,197
Miscellaneous diseases involving a single large vessel			
Transient perivascular inflammation of the carotid artery syndrome	Acute neck pain with transient neurological symptoms	Only carotid abnormality with peri-arterial infiltration with focal soft plaque (30% of people) and luminal narrowing (15% of people) All findings resolve or are substantially reduced within days or months	198
Thoracic outlet syndrome	Symptoms related to the vascular area involved	Typically affects the mid-distal segment of the subclavian artery	
Congenital hypoplasia of the carotid or subclavian arteries	Symptoms related to the vascular area involved	Usually presents as isolated long-segment stenosis or 'string appearance'	199
Post-radiation carotid stenosis	History of radiation with only carotid involvement	Carotid involvement	200

[a]Including Cogan's syndrome, relapsing polychondritis, anti-neutrophil cytoplasm antibody-associated vasculitis, sarcoidosis, Behçet disease, axial spondyloarthritis and Sjögren disease. SUV, standard uptake value; TAK, Takayasu arteritis; FDG, fluorodeoxyglucose.

is the most common mimic of TAK, especially in developing countries[97]. The presence of constitutional symptoms and multiple aneurysms on imaging studies can indicate possible tuberculous arteritis[97,98]. In patients with predominantly aneurysmal lesions, inherited disorders of connective tissue, such as Ehlers–Danlos syndrome or Loeys–Dietz syndrome, merit consideration. Many other differential diagnoses exist for TAK, and knowledge of the clinical and imaging features of each might prevent misdiagnosis (Table 2).

Imaging in the diagnosis and management of Takayasu arteritis

Imaging has a central role in the diagnosis, classification and management of TAK. Advances in imaging technology have transformed how clinicians detect vascular inflammation, monitor disease progression and assess response to treatment. The following section highlights the evolving role of vascular imaging in TAK.

Importance of imaging

In 2022, the classification criteria for TAK were updated[99]. Compared with the original 1990 classification criteria for TAK[100], the updated criteria more strongly reflect the increasing importance of vascular imaging to define and characterize TAK. An absolute requirement of the updated criteria is that, to be classified as TAK, a patient must have imaging evidence suggestive of vasculitis in the aorta or branch arteries. Although the criteria permit confirmation of vasculitis by many different imaging techniques (angiography, PET or ultrasonography), this mandated requirement emphasizes the role that imaging has as a complementary assessment to the vascular physical examination in TAK[101].

Vascular-imaging modalities

Multiple imaging techniques can be used to assess the large arteries. Non-invasive angiography by MRI or CT has largely replaced catheter-based angiography, except for instances in which concomitant direct measurement of central arteries is desirable or during endovascular interventions. PET imaging can be used to assess arterial ^{18}F-FDG uptake as a surrogate measure for vascular inflammation, typically coupled with either CT- or MR-based anatomical imaging[102,103]. Ultrasonography is an inexpensive way of assessing parts of the vasculature at the bedside. Each modality has specific advantages and limitations; consequently, multimodal imaging can be used to assess patients comprehensively, particularly when there are unexpected findings by one form of imaging assessment[104]. Consensus-based recommendations for the use of imaging in large-vessel vasculitis have been proposed to standardize image acquisition and interpretation[105,106].

The purpose of vascular imaging in TAK is to identify luminal disease (for example, aneurysm, stenosis or occlusion) and to characterize morphological abnormalities of the vascular wall (such as increased wall thickness or oedema). Differentiating vascular damage from active disease can be challenging but has important treatment implications[107]. Increased wall thickness might reflect ongoing vascular inflammation, prior damage or vascular remodelling, whereas vascular oedema on MR angiography or increased arterial FDG uptake by PET is more suggestive of active vasculitis[108]. Technological advances in imaging will continue to improve the ability to monitor disease at the vascular level. Specific MRI sequences aid the visualization of wall thickness (such as black blood imaging) or oedema (such as signal tau inversion recovery). Novel radioligands that target specific immune-cell populations, such as fibroblast-activating protein inhibitor for fibroblast activation and somatostatin 2 receptor to indicate macrophage infiltration, might improve the specificity of PET by detecting and defining inflammation within the vascular wall compared with FDG[109]. Newer-generation PET scanners will enable faster imaging with less radiation and define the kinetics of radiotracer distribution within the vascular compartment[110].

Angiographic patterns

Various classification patterns have been proposed to define subgroups of patients with TAK with different angiographic patterns of disease. The Lupi-Herrera classification scheme, a modification of

the Ueno classification[111], divides patients into four subtypes on the basis of involvement of the aortic-arch branch vessels, descending thoracic, abdominal, and pulmonary arteries[62]. The Numano classification groups patients into five subtypes on the basis of involvement of the aortic arch, aortic-arch branch vessels, ascending aorta, descending thoracic aorta, abdominal aorta and renal arteries[112].

Data-driven classification patterns were developed by assessing differences in angiographic patterns of damage from over 800 patients with TAK from India and North America. Three clusters were identified: involvement of the abdominal aorta and its branches; involvement of the aortic arch and its branches; and asymmetric, focal disease[113] (Fig. 3). Angiographic patterns differ among patients with TAK in different parts of the world. Patients in India have more frequent abdominal vasculature involvement, whereas patients from Japan and North America are more likely to have involvement of the aortic arch and its branches[112–114]. Ongoing studies are assessing the extent to which genetics might influence angiographic patterns of disease.

Imaging to monitor disease activity

Discordance between clinical symptoms and imaging findings can occur when assessing disease activity in patients with TAK. New or worsening areas of arterial damage have been noted on serial angiography in patients with TAK during periods of apparent clinical remission[115]. Given the concern for 'silent' angiographic progression of disease, some guidelines recommend that patients with TAK undergo regularly scheduled non-invasive angiography to assess for changes in vascular damage over time, even in the absence of clinical symptoms of disease activity; however, the optimal timing for repeat imaging is not specified owing to limited evidence[116]. The development of a new lesion in a previously unaffected vascular area is of greater concern, as it indicates active disease, compared with worsening of existing arterial stenosis, which can be secondary to changes in scar tissue within the arterial wall (that is, 'healing fibrosis')[116].

Changes in the vessel wall on imaging that might suggest active disease include vascular oedema, contrast enhancement and increased wall thickening on CT or MR imaging, or vascular FDG uptake in the arterial wall on FDG-PET. These imaging sequences can be complementary to clinical assessment in TAK, and particularly helpful for instances in which there is clinical uncertainty about disease activity; however, these findings are not always specific indicators of active disease, and other factors, such as vascular remodelling and atherosclerosis, can contribute to wall-morphology changes and vascular FDG uptake[106,108,117,118]. FDG uptake in the arterial wall better predicts future stenotic lesions in TAK than wall thickness alone[119], but the majority of arterial regions with FDG uptake do not develop stenosis (>90%)[117]. Arteries with wall thickening and oedema on MRI and concomitant FDG uptake on PET are at a high risk of angiographic progression[117]. In the absence of prospective studies to inform specific guidelines regarding serial imaging to monitor disease activity, these decisions should be individualized to each practitioner in alignment with institutional resources and capabilities.

Scoring systems have been proposed to quantify changes in the vessel wall on imaging over time (such as the PET Vascular Activity Score[102] or Vasculitis Activity using MRI and PET scores[120]), but these have mainly been used in research settings and are not routinely incorporated into clinical practice. Novel disease indices that integrate clinical and imaging assessments in TAK have also been proposed, including the TAK Integrated Disease Activity Index. This index evaluates clinical, imaging and laboratory findings in a hierarchical manner, and vascular FDG uptake on PET is only scored if a patient has a corresponding disease-associated clinical symptom[121]. Incorporating vascular imaging as an outcome measure will probably occur with increasing frequency in future therapeutic trials, and these data will be important to determine the extent to which serial imaging is helpful in assessing response to therapy and guiding management.

Biomarkers and disease-activity monitoring

Identifying accurate and reliable biomarkers to assess disease activity in TAK remains challenging. Traditional inflammatory markers, such

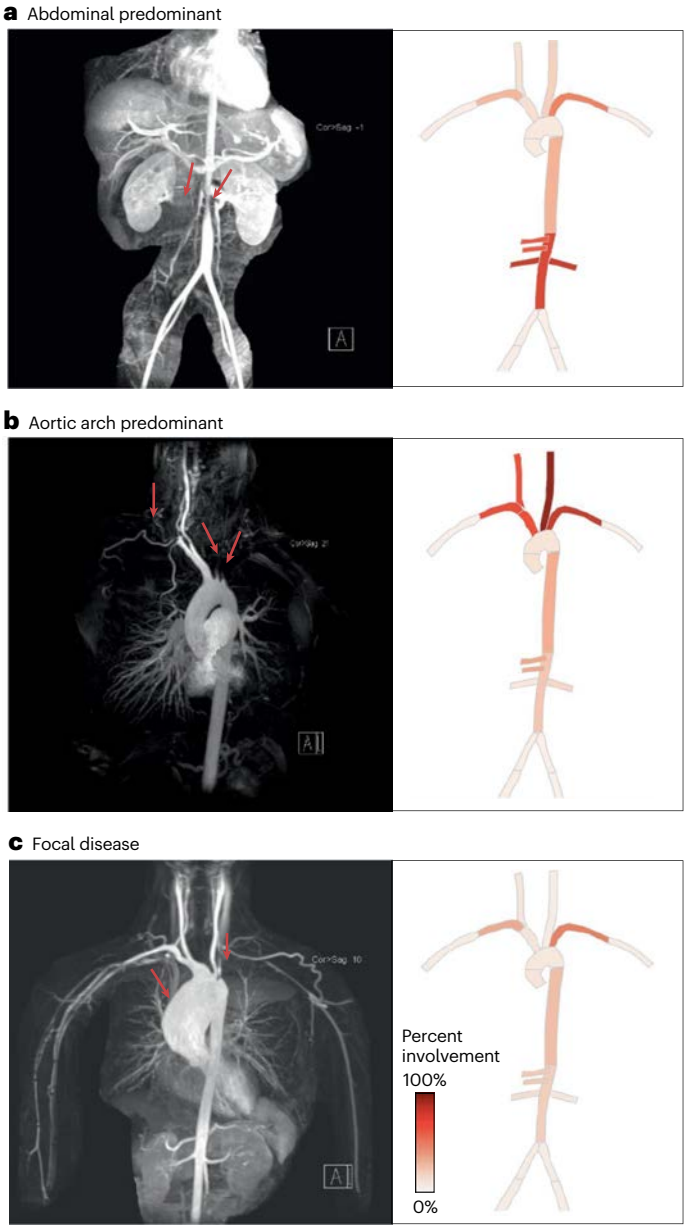

Fig. 3 | Angiographic patterns of Takayasu arteritis. Using k-means clustering, three angiographic clusters have been identified and validated in TAK: **a**, abdominal predominant; **b**, aortic-arch predominant; **c**, focal disease. Representative angiograms of a patient in each cluster are depicted with sites of vascular damage identified by red arrows. Heatmaps of the large arteries indicate the percentage of patients in each cluster with involvement of each artery. Aadapted with permission from ref. 203, Wiley.

Box 1 | Biomarkers of active disease in Takayasu arteritis

Acute-phase reactants
- Erythrocyte sedimentation rate
- C-reactive protein
- Pentraxin-3
- Serum amyloid A
- Complement C4-binding protein
- Complement 3
- Complement 1q

Cytokines
- IL-6
- IL-18
- IL-2
- IL-17A
- Soluble IL-6 receptor
- IFNγ

Endothelial-damage markers
- Circulating endothelial progenitor cell
- Vascular endothelial growth factor
- Endothelin-1

Chemokines
- CCL5 (also known as RANTES)
- Monocyte chemotactic protein-1
- CCL2
- CCL20
- CCL22
- CXCL8
- CXCL10

Matrix metalloproteinases (MMP)
- MMP-3
- MMP- 9

Autoantibodies
- Anti-endothelial cell antibody
- Anti-cardiolipin antibody
- Anti-annexin V antibody

Others
- T helper (T_H) 1 cells
- T_H17 cells and $T_H17.1$ cells
- Macrophage inflammatory protein-1β
- Leucine-rich α2-glycoprotein
- Platelet-to-lymphocyte ratio
- Neutrophil-to-lymphocyte ratio
- Plateletcrit

as erythrocyte sedimentation rate (ESR) and C-reactive protein (CRP), are widely used[122], but lack sufficient sensitivity and specificity[123,124]. Active disease can be present in up to one third of patients with normal ESR and CRP levels[63,125]. Moreover, ESR levels can be high in 44% of patients who have achieved remission[126]. When the levels of different acute-phase proteins in patients with TAK were assessed, only serum amyloid A (SAA) and complement C4-binding protein (C4BP) levels were increased in patients with active TAK compared with patients with inactive disease and healthy individuals[127]. Another study confirmed that SAA levels were higher in patients with active disease than in those with stable disease and decreased after treatment[128]. These findings suggest that SAA might be a reliable biomarker for assessing disease activity and response to treatment in TAK.

Several cytokines, chemokines, autoantibodies and growth factors are increased in TAK, but they are not disease specific[129]. Among these markers, IL-6, IL-18, CCL5 (also known as RANTES), monocyte chemotactic protein-1, CCL2, CCL20, CCL22, CXCL8, CXCL10, matrix metalloproteinase-3, matrix metalloproteinase-9, anti-endothelial cell antibody, anti-cardiolipin antibody, anti-annexin V antibody, serum C1q levels and leucine-rich α-2 glycoprotein were associated with clinical disease activity[27,28,130–138] (Box 1). Higher complement protein C3 levels occur in patients with active disease than in those with inactive disease (sensitivity of 69.9%, specificity of 66.7%) and can better indicate active TAK than IL-6 levels[139]. However, all these biomarkers need to be investigated further before they can be applied in clinical settings.

A 2024 systematic review and meta-analysis reported that IL-6 levels were increased in patients with active TAK compared with those with inactive disease and healthy individuals[140]. In another study, soluble IL-6 receptor levels were also increased in patients with active but not inactive TAK compared with healthy individuals and could be a potential biomarker for disease activity[141]. Prospective longitudinal studies are needed to assess the clinical use of IL-6 as a biomarker of disease activity in TAK.

The pentraxin (PTX) superfamily is a group of proteins that function as acute-phase reactants during exogenous pathogen recognition. PTX-3 is a long pentraxin that is secreted independently of IL-6 stimulation and has been proposed as a potential marker for active disease in TAK[142–147]. However, two large studies found no difference in PTX-3 levels between patients with active and inactive disease[148,149]. By contrast, another study reported elevated PTX-3 levels in a subgroup of patients with TAK who showed signs of active inflammation on vascular imaging[149]. In addition, PTX-3 levels correlate strongly with disease activity, as assessed by PET imaging and standardized indices such as the NIH criteria and ITAS2010 (ref. 150). Furthermore, PTX-3 levels show stronger correlation with activity scores in PET scans and ITAS2010 than ESR and CRP[151]. In addition, results of a systematic review and meta-analysis of eight studies indicate that PTX-3 might be more valuable than CRP for the assessment of disease activity in TAK[152]; however, this result should be interpreted cautiously owing to the heterogeneity and potential publication bias of this meta-analysis. Furthermore, although PTX-3 seems to be a promising biomarker for disease activity in TAK, its use in clinical practice and correlation with disease activity in imaging studies need to be evaluated in prospective follow-up studies.

Thus, reliable biomarkers for assessing active disease in TAK remain limited, largely owing to conflicting findings across studies; however, PTX-3 seems to be the most promising biomarker for monitoring disease activity in TAK. CRP, ESR and SAA are still the most commonly used biomarkers to assess disease activity in TAK, but it should be noted that these biomarkers are non-specific and might not accurately reflect disease activity. Moreover, they are usually suppressed with IL-6-blocking agents, which are commonly used in the management of TAK.

Identifying biomarkers of arterial-wall fibrosis and damage in TAK is an area of increasing interest. Higher Enhanced Liver Fibrosis scores (used to assess fibrosis in liver diseases) and TAK-associated polymorphisms in *IL12B* have been shown to predict more vascular damage in patients with TAK[153,154].

Management of Takayasu arteritis

Effective management of TAK requires a carefully balanced approach to control inflammation while minimizing treatment-related risks. This section reviews current therapeutic strategies, including the use of glucocorticoids, conventional immunosuppressive agents and biologic therapies, highlighting evolving recommendations in TAK treatment (Fig. 4).

Glucocorticoids are the mainstay treatment for remission induction in TAK[155]. However, glucocorticoid monotherapy for remission induction is associated with frequent relapses after drug withdrawal and is not recommended in current management guidelines[116,156–160]. Most guidelines suggest doses of 0.5–1 mg/kg per day (40–80 mg per day) prednisone or prednisolone as the initial therapy[116,156–159,161,162], except for

milder, single lesions, for which lower doses 25–30 mg per day might be used[159,162]. Similar complete remission and relapse rates were shown in patients receiving 0.5 mg/kg per day and 1 mg/kg per day as the initial glucocorticoid dose when a second immunosuppressive agent is used[163]. No studies have compared the efficacy of high-dose glucocorticoid versus pulse glucocorticoid treatments for TAK; however, pulse glucocorticoids are suggested for refractory, life-threatening or organ-threatening disease[116,160,161]. Although there is no standard glucocorticoid dose-reduction regimen for TAK, most guidelines recommend lowering prednisone doses to <10 mg per day, and some guidelines from the past 3 years recommend aiming for <5 mg per day after 1 year[116,156,157,159–162]. Low-dose or discontinuation of glucocorticoid monotherapy, especially in the first year, led to relapses in 60–77% of patients during two randomized controlled trials (RCTs)[40,43].

Owing to the toxicity risk that can occur with long-term glucocorticoid use and high relapse rates with glucocorticoid monotherapy, additional immunosuppressive agents are recommended from the initial remission-induction phase[116,156,157,159,160]. Efficacy of methotrexate, azathioprine, leflunomide and mycophenolate mofetil on induction of remission and prevention of relapses were shown in various observational studies and meta-analysis[164–166]. Methotrexate and azathioprine have a similar efficacy, with low long-term retention rates as first-line immunosuppressive drugs[167]. Mycophenolate mofetil and methotrexate combination therapy was shown to be superior to cyclophosphamide and azathioprine sequential therapy[168]. Owing to the serious adverse effects of cyclophosphamide and the lack of the proven superiority of this drug against other conventional immunosuppressive drugs, cyclophosphamide is only recommended for severe life- or organ-threatening disease[157,162,169].

Clinical or angiographically refractory disease to conventional immunosuppressive drugs or frequent flares are a clinical challenge in the management of TAK. Biologic therapies are recommended in these patients in all current guidelines; however, using biologic drugs from the onset in patients with a severe disease course is also recommended in some guidelines[116,157,162]. The efficacy of TNF inhibitors for remission induction and prevention of relapses in TAK was demonstrated in multiple observational studies[170]. Retrospective, comparative data indicate that using TNF inhibitors can lead to a better disease course, without new vascular lesions, than glucocorticoid monotherapy and immunosuppressive agents[171]. Despite an RCT of tocilizumab (an anti-IL-6 receptor antagonist) versus placebo failing to meet its primary end point of time to first relapse[40], the efficacy of tocilizumab has been shown in numerous observational studies[41]. There are only a limited number of retrospective studies that compare TNF inhibitors and tocilizumab, with no clear evidence of superiority between them[172,173]. However, one prospective, comparative trial demonstrated better outcomes with adalimumab (a TNF inhibitor) at 24 weeks[174]. Although most recommendations do not make a preferential choice between the two classes of biologic drugs[156–159,162], the American College of Rheumatology guidelines recommend TNF inhibitors owing to greater clinical experience and more available data, and the challenge of using acute-phase reactants to monitor disease activity in TAK when treated with tocilizumab. Unlike TNF inhibitors, tocilizumab can inhibit the acute-phase response (such as C-reactive protein production), even in the presence of clinically active disease[116].

For refractory disease or patients who are intolerant to TNF inhibitors or tocilizumab, new alternative agents are emerging. Secukinumab (an IL-17 inhibitor) was shown to have similar efficacy to TNF inhibitors in a small prospective trial[42]. Among Janus kinase (JAK) inhibitors, tofacitinib has the most comprehensive data, favouring its use over methotrexate but not over leflunomide for TAK[175,176]. A prospective case series with another JAK inhibitor, baricitinib, showed favourable results[177]. Abatacept has shown negative results, and data on rituximab are limited; therefore, the use of these drugs is not currently recommended for TAK[43,157]. Data for ustekinumab in a 2025 RCT were inconclusive, as patient numbers were too low, owing to recruitment challenges[44,45].

The optimal duration of immunosuppressive therapy for TAK is unknown[157]. Use of immunosuppressive agents, lower cumulative glucocorticoid dose and earlier disease onset are associated with reduced long-term disease-associated and treatment-associated damage in TAK[178]. Clinicians should be aware of risks associated with long-term glucocorticoid therapy and discontinuation of glucocorticoids should

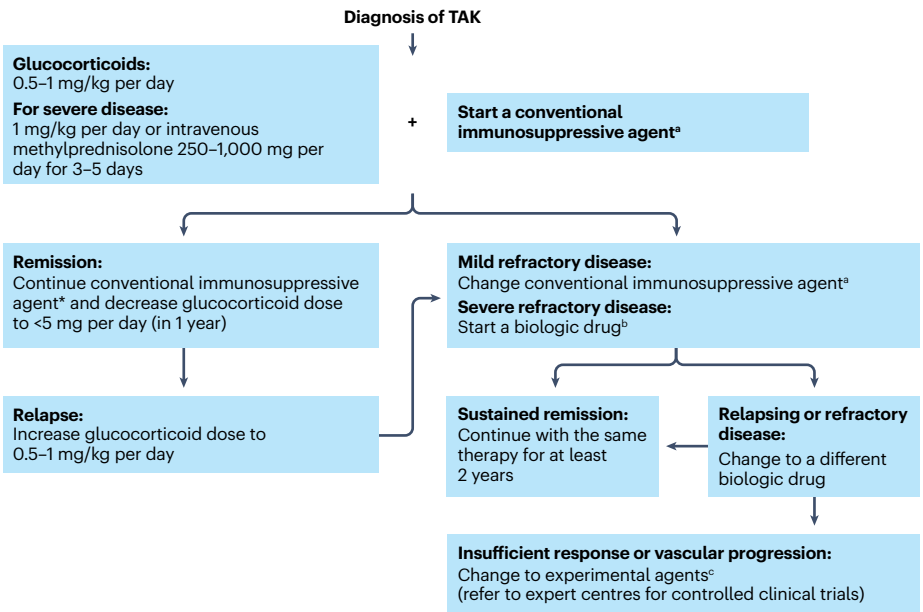

Fig. 4 | Therapeutic approaches to Takayasu arteritis. Current treatment strategies for Takayasu arteritis (TAK) include glucocorticoids, conventional immunosuppressive agents and biologic therapies, which reflects the evolving recommendations in TAK management. [a]Methotrexate, azathioprine, leflunomide, mycophenolate mofetil or cyclophosphamide; [b]TNF inhibitors or tocilizumab; [c]Janus kinase inhibitors, secukinumab, calcineurin inhibitors, sirolimus or rituximab.

be considered in patients with sustained remission for longer than 6–12 months. Addition of immunosuppressive agents, especially biologic agents, might decrease the relapse rates to less than 10% and enable glucocorticoid doses to be reduced to <10 mg per day[179]. In our opinion, immunosuppressive agents should be used for a minimum of 2 years after remission is achieved. Tapering of immunosuppressive drugs should also be slow, especially in patients with frequent relapses and organ- or life-threatening manifestations. Whether routine imaging should be used before immunosuppressive agent tapering or drug discontinuation is debatable, with no high-quality evidence. Evidence to support the routine use of low-dose aspirin and statins in all patients with TAK for primary cardiovascular prevention is insufficient. In our opinion, the use of these treatments should be limited to patients with conventional cardiovascular risk factors; however, in those with high-risk arterial involvement, such as coronary or cerebral arteries, these therapies might be considered.

Vascular interventions are considered mainly for patients with haemodynamically severe vascular stenosis or occlusions, such as cranial arterial or coronary disease, renal-artery stenosis or aortic aneurysms with a rupture risk, especially those with a progressive disease course, despite effective treatment with immunosuppressive drugs[162]. However, the American College of Rheumatology guidelines emphasize a more conservative approach, advocating for the escalation of immunosuppressive drugs or biologic therapies in cases of progressive vascular disease before considering vascular interventions[116]. Patients undergoing vascular interventions should be on lifelong antiplatelet agents[180].

Vascular interventions should be planned, if possible, during clinical remission and with adequate immunosuppressive agents or biologic therapy before the procedure. In emergency situations, vascular interventions should be performed under the protection of a perioperative high-dose glucocorticoid therapy to prevent postoperative complications such as stenosis or occlusions[160,181]. However, risk of infection and possible impairment of wound healing with high-dose glucocorticoids should be assessed for each individual patient. The type of vascular intervention (open surgery versus endovascular procedure) in TAK can vary depending on the affected vascular region[160]. Open surgeries, such as bypasses, have a high postoperative rate of patency and are preferred in complicated and long-segment, occlusive lesions[160]. However, the risk of early perioperative mortality and complications are high with open surgeries. Endovascular therapies such as balloon angioplasty and stent implantation are minimally invasive, effective in short-segment lesions, but their long-term restenosis rates are higher[159]. However, repeat percutaneous interventions are possible, and patency has been shown to increase from 49% to 83% in obstructive lesions in a large study from India[182]. For patients with renal-artery involvement, endovascular intervention should be prioritized over open surgery, with balloon angioplasty preferred to stenting owing to its lower restenosis rate[159,160,183,184].

Given the risk of complications such as stroke and death, endovascular intervention should also be the primary option for patients with supra-aortic artery involvement. For coronary-artery involvement, open surgery seems generally more successful than percutaneous coronary interventions and might be the preferred option[185]. However, the retrospective nature of these data and possible selection bias for patients with severe disease for endovascular interventions limit the interpretation of these observations. In patients with stable upper-extremity claudication, vascular interventions are generally not preferred, as the risk of critical ischaemia is low owing to extensive collateral circulation[116].

Patients with TAK treated with glucocorticoids and immunosuppressive agents are at a greater risk of osteoporosis, infections and cardiovascular events. Such comorbid conditions should be managed as per standard recommendations[186,187]. Hypertension is another important manifestation of TAK that requires management. The presence of anatomical or functional (stenosis of suprarenal abdominal aorta or descending thoracic aorta) bilateral renal-artery stenosis in a substantial proportion of people with TAK precludes the use of angiotensin-converting enzyme inhibitors or angiotensin receptor blockers for managing hypertension[180].

In summary, although additional evidence from clinical trials is needed, current data suggest that early and aggressive use of glucocorticoids with immunosuppressive or biologic agents results in better outcomes for patients with TAK, with reduced morbidity and mortality.

Conclusion

Perturbations in innate and adaptive immune mechanisms, which are driven at least in part by genetic factors, promote the pan-arteritis observed in TAK. Extracranial giant-cell arteritis and atherosclerosis are important differential diagnoses, particularly in older individuals. Imaging is the cornerstone for diagnosing TAK and can help to delineate luminal narrowing and wall thickening. ^{18}F-FDG uptake in the arterial wall is increasingly recognized to denote active disease and arterial segments at a risk of future stenosis. Despite a lack of quality evidence from RCTs, glucocorticoids, along with conventional, biologic or targeted synthetic immunosuppressive agents, remain the cornerstone of the management of TAK.

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Inborn errors of immunity and AAV: a complex picture

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We read with great interest the manuscript by Gül et al. on monogenic systemic vasculitis (Gül, A. et al. The pathogenesis, clinical presentations and treatment of monogenic systemic vasculitis. *Nat. Rev. Rheumatol.* **21**, 414–425 (2025))[1]. We thank the authors for presenting a detailed synthesis of current knowledge on the clinical features of these genetic disorders and the putative mechanisms that link different genetic defects to vascular inflammation. Gül et al.[1] also discuss the potential relevance of these genes (and their associated pathways) for the sporadic forms of vasculitis that they clinically resemble. We would like to provide further comments on the genetic defects associated with anti-neutrophil cytoplasmic antibodies (ANCA)-associated vasculitis (AAV).

First, although a robust link between AAV and specific genetic disorders (particularly among type I interferonopathies) is emerging, much progress is still needed to better understand the nature of this association[2]. For instance, ANCA specificity and titres are lacking in many studies that describe these conditions, as is their association with specific small vessel vasculitis manifestations (such as alveolar vasculitis and pauci-immune glomerulonephritis). These aspects are indeed crucial to assess the pathogenic value of ANCA (that is, the presence of true AAV), as opposed to an unspecific biological sign of autoimmunity.

Second, in addition to mutations in *COPA* and *STING1* genes, deficiency in DNASE1L3 (deoxyribonuclease 1L3), which usually results in lupus-like phenotypes with hypocomplementemic urticarial vasculitis, should be added as a classic aetiology for an early-onset AAV-like phenotype; 55–85% of patients with biallelic mutations in the *DNASE1L3* gene and consequent DNASE1L3 deficiency are ANCA-positive, which is associated with pulmonary haemorrhage and/or interstitial lung disease or pauci-immune glomerulonephritis in a subset of patients[3–5]. In contrast to the two other conditions (that is, COPA syndrome and STING-associated vasculopathy with onset in infancy (SAVI)), which are considered classical type I interferonopathies, DNASE1L3 deficiency has only been associated with transiently increased expression of interferon-stimulated genes[4]. Increasing evidence also suggests that patients with gain-of-function mutations in *PIK3CD* can present with an AAV-like phenotype[6–8]. Links to type I interferon have not yet been specifically investigated in the latter condition. Therefore, absence of increased interferon-stimulated gene expression does not rule out an underlying monogenic disorder in a patient with AAV.

We also want to share two observations regarding the diagnosis and management of individuals with these inborn errors of immunity and features of AAV. First, it should be noted that some patients will present with overlap syndromes with mixed clinical, serological and histological features of AAV and other conditions, in particular systemic lupus erythematosus[3]. Second, the treatment of AAV in patients with underlying monogenic disorders has not been specifically studied and is challenging in practice. Standard therapies and protocols for sporadic AAV should generally be used for such patients, potentially in combination with other therapies such as Janus kinase inhibitors.

Finally, as mentioned by Gül et al.[1], the mechanistic link between genetically driven, excessive type I interferon signalling and AAV remains unclear at this stage, and other distinct dysregulated pathways might have a role. Therefore, drawing parallels on possible shared pathophysiology between monogenic disorders that have an increased risk of AAV and the sporadic forms of AAV remains thus far hypothetical[3].

There is a reply to this letter by Gül, A. et al. *Nat. Rev. Rheumatol.* https://doi.org/10.1038/s41584-025-01298-7 (2025).

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Reply to 'Inborn errors of immunity and AAV: a complex picture'

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We thank Clément Triaille, Marie-Louise Frémond and Augusto Vaglio for their interest in our Review (Gül, A et al. The pathogenesis, clinical presentations and treatment of monogenic systemic vasculitis. *Nat. Rev. Rheumatol.* **21**, 414–425 (2025))[1], and for providing additional examples of monogenic disorders that can be associated with the development of anti-neutrophil cytoplasm antibodies (ANCA) and vasculitic manifestations (Triaille, C., Frémond, M. L. & Vaglio, A. Inborn errors of immunity and AAV: a complex picture. *Nat. Rev. Rheumatol.* https://doi.org/10.1038/s41584-025-01299-6 (2025))[2].

In our Review[1], we focused on monogenic autoinflammatory diseases that present with findings of vasculitis involving blood vessels of all sizes and types. The pathogenic mechanisms underlying these conditions are complex and include the activation of myeloid cells, type I interferon-driven autoimmune responses, dysregulated adaptive immunity, endothelial dysfunction and injury and thrombotic vasculopathies.

Among these mechanisms, ANCA can be detected particularly in disorders characterized by dysregulated adaptive immunity and/or type I interferon-driven autoimmunity, mainly classified as interferonopathies. As noted by Triaille et al.[2], ANCA can also develop in association with immunodeficiencies[3,4]; however, the relationship between ANCA positivity and the development of vascular pathology remains unclear in many of these instances[2].

We are grateful to Triaille et al.[2] for suggesting the inclusion of patients with *DNASE1L3* variants in the spectrum of monogenic vasculitis. These patients typically exhibit a systemic lupus erythematosus (SLE)-like phenotype[2,5]. Reduced DNASE1L3 enzymatic activity impairs the clearance of extracellular chromatin from apoptotic bodies, which triggers disease activity associated with a transient type I interferon response[6]. A considerable proportion of patients with *DNASE1L3* variants also develop hypocomplementemic urticarial vasculitis, with urticarial rash often being the initial manifestation[7]. Thus, *DNASE1L3*-related disease can be considered a form of monogenic vasculitis, particularly in patients with early-onset SLE-like features. Although ANCA screening has not been uniformly performed in these patients, reports describe ANCA positivity alongside anti-nuclear antibodies and anti-double-stranded DNA antibodies[6]; the specific contribution of ANCA to disease manifestations, however, remains to be elucidated.

In this context, hereditary complement deficiencies, such as C1q and C2 deficiency, can also be included in the spectrum of monogenic vasculitis and SLE-like disease[5]. These disorders can also present with hypocomplementemic urticarial vasculitis, but can also involve vasculitic neuropathy and central nervous system vasculitis[8,9].

Activated PI3Kδ syndrome is a combined form of immunodeficiency that is associated with increased susceptibility to sinopulmonary infections, Epstein–Barr virus and cytomegalovirus viremia, enteropathy, increased risk of malignancy and autoimmunity[3,4]. As noted by Triaille et al.[2], patients with type 1 activated PI3Kδ syndrome owing to *PIK3CD* variants can develop ANCA, along with some clinical findings that resemble ANCA-associated vasculitis[3,4]. In such settings, various factors, including infections, can contribute to vascular pathology.

In summary, beyond monogenic autoinflammatory disorders, other monogenic diseases can also lead to systemic vascular involvement through diverse mechanisms, not limited to ANCA. Increasing awareness of these rare monogenic disorders is essential, as early recognition can offer opportunities for timely and targeted management. We fully agree with our colleagues that translating current observations from monogenic diseases to multifactorial disorders is challenging; however, we hope that further investigation of these rare conditions will enhance understanding of the pathogenic mechanisms underlying more common forms of systemic vasculitis.

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Potential benefit of anticoagulation in Behçet syndrome

We read with great interest the comprehensive Review by Bello et al. published in *Nature Reviews Rheumatology*[1]. The authors stated that four retrospective studies have shown that the addition of anticoagulation to immunosuppressants does not seem to significantly reduce the recurrence of vascular events in Behçet syndrome compared with treatment with DMARDs alone. However, in our study[2], which is one of the studies cited by the authors, recurrent venous thromboembolism was statistically significantly lower in the group treated with immunosuppressants plus anticogulation than in the group treated with immunosuppressants alone. Also, some case reports[3] and a 2021 study[4] report successful prevention of recurrence of venous thromboembolism with anticoagulation in these patients.

Thromboinflammation is the main mechanism underlying the vascular complications of Behçet syndrome. Thus, immunosuppressives are the mainstay of management. However, as previous studies revealed, there is a possibility of hypercoagulation and thrombophilia in these patients[5–8]. Therefore, adding anticoagulants might help to lower the risk of thrombosis in Behçet syndrome.

There is a reply to this letter by Fagni, F. et al. *Nat. Rev. Rheumatol.* https://doi.org/10.1038/s41584-025-01317-7 (2025).

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Reply to 'Potential benefit of anticoagulation in Behçet syndrome'

We thank Serhat Erol et al. for their interest in our Review article (Bello, F. et al. Arterial and venous thrombosis in systemic and monogenic vasculitis. *Nat. Rev. Rheumatol.* **21**, 355–369 (2025))[1] and for raising important points regarding the role of anticoagulation in Behçet syndrome with vascular involvement[2]. We appreciate the opportunity to clarify these points.

The study by Erol et al.[3] that we cited in our Review reported 27 recurrent venous thrombotic events among 22 of 40 (55%) patients with Behçet syndrome. Of these 27 events, 15 (55.5%) occurred while patients were on immunosuppressants alone, 2 (7.4%) occurred on combined immunosuppressants and anticoagulation, and 2 (7.4%) occurred on anticoagulation alone. The recurrence rate was significantly lower in the group receiving the combination therapy than in the group receiving immunosuppressants only, suggestive of a potential benefit of combination therapy in selected cases.

In our Review[1], we emphasized that endothelial activation and the neutrophil-mediated immune response (that is, thromboinflammation), rather than hypercoagulability, is a central mechanism underlying vascular complications in Behçet syndrome. Immunosuppressants therefore remain the mainstay of treatment, particularly in preventing new inflammatory thrombotic events, as is also recommended by the 2018 EULAR guidelines[4] and the recent 2025 update (G. Hatemi, personal communication).

However, we recognize that the interplay between inflammation and coagulation is complex and that some patients could indeed benefit from adjunctive anticoagulation. As highlighted in the Correspondence[2], some studies suggest a potential benefit of anticoagulation in selected patients with Behçet syndrome, due to prothrombotic factors and a hypercoagulable state. However, larger retrospective studies have not confirmed this finding[5,6], and the risk of haemorrhagic complications, particularly with arterial involvement or pulmonary artery aneurysms[7,8], remains relevant. Alibaz-Oner et al.[5] reported similar rates of new vascular events in patients treated with immunosuppressants alone or combined with anticoagulation, and Emmi et al.[6] likewise found no improvement in venous thromboembotic event-free survival.

We also believe that the data presented by Erol et al.[3] should be interpreted with appropriate caution. The study reports a relatively high rate of pulmonary embolism (52.5% of the cohort), including a considerable proportion of cases with concomitant deep vein thrombosis and pulmonary embolism (37.5%). Although these findings are quite well documented within their cohort, such a frequency is somewhat higher than what is commonly reported in the literature, where pulmonary embolism is considered an uncommon manifestation of Behçet syndrome. These observations might reflect specific features of the local population or referral bias, and thus merit further investigation in larger prospective studies.

We believe the question of anticoagulation in Behçet syndrome remains nuanced. While immunosuppression is essential, adding anticoagulants should be decided individually, considering clinical context, bleeding risk and imaging findings. Current recommendations also endorse a case-by-case approach[4], given the lack of randomized trials showing reduced relapse or post-thrombotic syndrome.

We are grateful to the authors for drawing attention to the more detailed results of their study and for referencing additional relevant literature. Their contribution underscores the need for further high-quality research to guide anticoagulation strategies in Behçet syndrome.

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Competing interests

The authors declare no competing interests.

Author Correction: Parathyroid hormone receptor agonists in the management of osteoporosis

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In the version of the article initially published, in Fig. 1, the box reading "↑ OPG" should have read "↓ OPG". In the Fig. 1 caption, the text "…results in increased expression of receptor activator of NF-κB ligand (RANKL) and osteoprotegerin (OPG) in osteoclasts, and sustained RANKL–OPG signalling supports osteoclast activation, resulting in bone resorption" should have read "…results in increased expression of receptor activator of NF-κB ligand (RANKL) and downregulation of osteoprotegerin (OPG) in osteoclasts, leading to osteoclast activation, and resultant bone resorption". These corrections have now been made to the HTML and PDF versions of the article.