RHEUMATOID ARTHRITIS
and
INFECTIOUS DISEASES

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- There are **several reasons** why RA may be associated with an **increased incidence** of infection.

- **Disturbance** of the immune system in RA **per se** may reduce the ability to resist infection.

1. **Decreased spontaneous and stimulated IgM production** associated with increased spontaneous IgM RF production.

Boling EP, Ohishi T, Wahl SM, Misiti J, Wistar RJr, Wilder RL. Humoral immune function in severe, active rheumatoid arthritis, **Clin Immunol Immunopathol , 1987**, 43 ;185-94.

2. Functionality of the immune system is **tightly linked** to the receptor diversity or repertoire of the T-cell pool.

Studies of patients with RA have shown *marked contraction of T-cell repertoires* with *decreased diversity*, which may predispose to infection.

Yang H, Rittner H, Weyand CM, Goronzy JJ. Aberrations in the primary T-cell receptor repertoire as a predisposition for synovial inflammation in rheumatoid arthritis, **J Investig Med , 1999**, 47;236-45.

- RA disease **severity** and the **chronic immune activation** associated with inflammation may impair immune function.

- … and powerful immunosuppressive agents

BURDEN OF INFECTION IN RHEUMATOID ARTHRITIS-TREATED BIOLOGIC PATIENTS

- The increased risk of infection seen in RA is **complex** and likely **multifactorial**.

  – **High disease activity**,
  – **multi-morbidity**,
  – **treatment/disease-related immunosuppression**
  – **polypharmacy**

  all likely contribute.

- Serious infections are defined as events resulting in hospitalization or death.

- A UK-based real-world study that surveyed RA patients reported **8%** required hospitalization because of serious infection **each year**; however, hospitalized infections are likely to be an under-representation when considering the overall burden of infections.

Subesinghe S, Rutherford AI, Ibrahim F, et al. A large two-centre study in to rates of influenza and pneumococcal vaccination and infection burden in rheumatoid arthritis in the UK. **BMC Musculoskelet Disord 2016**; 17:322.

- A recent cross-sectional study in RA patients reported a **tripling of sepsis rates** between 1993 and 2013 in the United States (1.9–6.4%) [3], consistent with other sepsis studies in the US general population.

- This may be attributed to an **aging population** with **more comorbidities**, **increased use** of immunosuppressant drugs, spread of **multi-resistant pathogens** or to **better** International Classification of Diseases-9 **coding of sepsis over time**.

Jinno S, Lu N, Jafarzadeh SR, et al. Trends in hospitalizations for serious infections in patients with rheumatoid arthritis in the US between 1993 and 2013. **Arthritis Care Res (Hoboken) 2018**; 70:652–658.

- Anti-TNF therapies are known to be associated with an **increased serious infection risk** in comparison to csDMARDs, with a time varying risk highest in the **first 6–12 months** of treatment.

Askling J, Dixon W. The safety of antitumour necrosis factor therapy in rheumatoid arthritis. **Curr Opin Rheumatol 2008**; 20:138–144.

Galloway JB, Hyrich KL, Mercer LK, et al. Anti-TNF therapy is associated with an increased risk of serious infections in patients with rheumatoid arthritis especially in the first 6 months of treatment: updated results from the British Society for Rheumatology Biologics Register with special EMPH. **Rheumatology (Oxford) 2011**; 50:124–131.

- One of the largest meta-analyses to date, reported a **31% increased risk** of serious infections in **standard dose** biologic-treated RA patients compared to csDMARDs (**OR: 1.31;** 1.09, 1.58).

- In the clinical trial population studied, the **absolute increase** in number of serious infections associated with biologics was reported as **six per 1000 patients** treated **per year** for standard dose biologics.

Singh JA, Cameron C, Noorbaloochi S, et al. Risk of serious infection in biological treatment of patients with rheumatoid arthritis: a systematic review and meta-analysis. Lancet 2015; 386:258–265.

STRATIFICATION OF INFECTION RISK

Patient demographics:

- increasing age,
- comorbidities (such as chronic obstructive airways disease, interstitial lung disease and chronic renal failure)

Types of infection:

- The most common types of serious infections overall in biologic-treated RA patients are:
  - respiratory infections [22/1000 patient-years (p/yrs)],
  - skin and soft tissue (11/1000 p/yrs),
  - genitourinary (6.2/1000 p/yrs) and
  - bone/joint infections (5.4/1000 p/yrs)

- Thirty-day mortality following serious infection remains is also high, with **mortality rate of 10.4%** (95% CI 9.2, 11.6%) observed within the British Society for Rheumatology Biologics Register for RA (BSRBR-RA).
  - **Sepsis/bacteraemia** was associated with the highest 30-day **mortality at 45%** (95% CI 33%, 61%)

Rutherford AI, Subesinghe S, Hyrich KL, et al. Serious infection across biologic-treated patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. **Ann Rheum Dis 2018;** 77:905–910.

Between tumour necrosis factor inhibitor drugs

- An infection type that appears to have a clear differential risk across available TNFi therapies is **tuberculosis (TB**).

- The risk of TB reactivation **appears lower** in etanercept-treated patients compared with the monoclonal antibodies such as infliximab and adalimumab, as observed in several studies.

- In patients with risk factors for TB, etanercept may be the TNFi drug of **choice**.

Tumour necrosis factor inhibitors versus non-tumour necrosis factor inhibitor biologics

- For the most common types of serious infections, the majority of studies **do not** conclude a clinically meaningful difference between classes of drugs, after adjustment for baseline differences between patients.

- However, interpreting the evidence with available data sources can be **challenging**.

- A previous large meta-analysis of biologics in RA reported a **significantly higher rate** of serious infection with **anakinra** and **certolizumab** pegol compared with a control population

Conventional synthetic disease-modifying anti-rheumatic drugs and glucocorticoids

- csDMARDs such as methotrexate **are not associated** with an increased infection risk in RA patients, **without the use of glucocorticoids**.

- However, glucocorticoid use is likely to be **one of the most important** factors in terms of risk stratification of infection before starting and during biologic therapy.

- **Dose, recency** and **duration** of glucocorticoid prescription have been shown to be the most important factors when considering the risk of serious infection in RA patients.

- For instance, a patient with a prescription of prednisolone of 5 mg for 3 months has a **30% increased serious infection risk** but this goes up to **100%** if used continuously for 3 years (in the absence of a co-prescribed biologic).

Opioids

- Risk of serious infection was **higher** with use of **long-acting opioids**, **immunosuppressive opioids** (*codeine, morphine, transdermal fentanyl*) and those with a daily morphine milligram equivalent (**MME**) dose of at least **60 mg**.

  - to be an independent risk factor of **invasive pneumococcal disease**, which include serious infection such as **bacteraemia**, **meningitis** and **invasive pneumonia.**

Infection risk with TNF alpha inhibitors

- Four anti-TNF-α monoclonal antibodies (mAbs)
  - **infliximab,**
  - **adalimumab,**
  - **golimumab and**
  - **certolizumab pegol**

- One fusion protein that acts as a “decoy receptor” for TNF-α (**etanercept**)

Bacterial infections

- Tuberculosis risk: what news?

- Several studies were conducted to assess the **true risk** of TB infection or reactivation in patients treated with TNF-α inhibitors.

- a systematic literature search for randomized controlled trials (RCTs)/ up to December 2015/
  - The treatment with TNF-α inhibitors was associated with an **increased occurrence of TB** especially in rheumatoid arthritis (RA) patients compared with control groups ($p=0.03$).
  - Nevertheless, the risk of TB **was not related** to the **type** of TNF-α inhibitors administered.

BMJ Open. 2017 Mar 22;7(3):e012567. doi: 10.1136/bmjopen-2016-012567.

Risk of tuberculosis in patients treated with TNF-α antagonists: a systematic review and meta-analysis of randomised controlled trials.

Zhang Z[1], Fan W[1,2], Yang G[3], Xu Z[2], Wang J[1], Cheng Q[1], Yu M[1,3].

Author information

Abstract

OBJECTIVES: An increased risk of tuberculosis (TB) has been reported in patients treated with TNF-α antagonists, an issue that has been highlighted in a WHO black box warning. This review aimed to assess the risk of TB in patients undergoing TNF-α antagonists treatment.

METHODS: A systematic literature search for randomised controlled trials (RCTs) was performed in MEDLINE, Embase and Cochrane library and studies selected for inclusion according to predefined criteria. ORs with 95% CIs were calculated using the random-effect model. Subgroup analyses considered the effects of drug type, disease and TB endemicity. The quality of evidence was assessed using the Grades of Recommendation, Assessment, Development and Evaluation (GRADE) approach.

RESULTS: 29 RCTs involving 11 879 patients were included (14 for infliximab, 9 for adalimumab, 2 for golimumab, 1 for etanercept and 3 for certolizumab pegol). Of 7912 patients allocated to TNF-α antagonists, 45 (0.57%) developed TB, while only 3 cases occurred in 3967 patients allocated to control groups, resulting in an OR of 1.94 (95% CI 1.10 to 3.44, p=0.02). Subgroup analyses indicated that patients of rheumatoid arthritis (RA) had a higher increased risk of TB when treated with TNF-α antagonists (OR 2.29 (1.09 to 4.78), p=0.03). The level of the evidence was recommended as 'low' by the GRADE system.

CONCLUSIONS: Findings from our meta-analysis indicate that the risk of TB may be significantly increased in patients treated with TNF-α antagonists. However, further studies are needed to reveal the biological mechanism of the increased TB risk caused by TNF-α antagonists treatment.

- TB, it still remains **unclear whether** RA in conjunction with common treatments is, in itself, a risk factor.

- However, with patients being treated with any TNF-α inhibitors for any disease included, the risk of TB was almost doubled compared with those in normal care or placebo comparator arms.

- A systematic literature review to update the evidence for the safety of **csDMARDs, bDMARDs** and **tsDMARDs** in patients with RA

- Seven studies/ **moderate or high risk of bias/**

- An increased risk of TB in patients on TNF-α inhibitors (no studies for other sDMARDS), both compared with the general population and to patients on csDMARDs (**aHR 2.7 to 12.5** per study)

Ramiro S, Sepriano A, Chatzidionysiou K, et al. Safety of synthetic and biological DMARDs: a systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis. **Ann Rheum Dis**. 2017;76(6):1101-36.

Ann Rheum Dis. 2017 Jun;76(6):1101-1136. doi: 10.1136/annrheumdis-2016-210708. Epub 2017 Mar 15.

Safety of synthetic and biological DMARDs: a systematic literature review informing the 2016 update of the EULAR recommendations for management of rheumatoid arthritis.

Ramiro S[1], Sepriano A[1,2], Chatzidionysiou K[3], Nam JL[4,5], Smolen JS[6,7], van der Heijde D[1], Dougados M[8], van Vollenhoven R[9], Bijlsma JW[10], Burmester GR[11], Scholte-Voshaar M[12,13], Falzon L[14], Landewé RBM[9,15].

Author information

Abstract

OBJECTIVES: To assess the safety of synthetic (s) and biological (b) disease-modifying antirheumatic drugs (DMARDs) for the management of rheumatoid arthritis (RA) to inform the European League Against Rheumatism recommendations for the management of RA.

METHODS: Systematic literature review (SLR) of observational studies comparing any DMARD with another intervention for the management of patients with RA. All safety outcomes were included. A comparator group was required for the study to be included. Risk of bias was assessed with the Hayden's tool.

RESULTS: Twenty-six observational studies addressing diverse safety outcomes of therapy with bDMARDs met eligibility criteria (15 on serious infections, 4 on malignancies). Substantial heterogeneity precluded meta-analysis. Together with the evidence from the 2013 SLR, based on 15 studies, 7 at low risk of bias, patients on bDMARDs compared with patients on conventional sDMARDs had a higher risk of serious infections (adjusted HR (aHR) 1.1 to 1.8)-without differences across bDMARDs-a higher risk of tuberculosis (aHR 2.7 to 12.5), but no increased risk of infection by herpes zoster. Patients on bDMARDs did not have an increased risk of malignancies in general, lymphoma or non-melanoma skin cancer, but the risk of melanoma may be slightly increased (aHR 1.5).

CONCLUSIONS: These findings confirm the known safety pattern of bDMARDs, including both tumour necrosis factor-α inhibitor (TNFi) and non-TNFi, for the treatment of RA.

– The pooled analysis of six studies:

- Etanercept had a **lower risk** of favoring TB infection or re-activation LTB whether we took mono-antibodies as a whole or analyzed **infliximab** independently [**RR=0.19** (0.06–0.56), P=0.003].
- However, it was not statistically different when compared with **adalimumab** [RR=0.58 (0.13– 2.61), P=0.48]

- These findings confirmed **the greater safety of the etanercept**.

Liao H, Zhong Z, Liu Z, Zou X. Comparison of the risk of infections in different anti-TNF agents: a meta- analysis. **Int J Rheum Dis. 2017**;20(2):161-8.

	No. of studies	Fixed-effects model	
		OR	95% CI
Serious infections			
–All RCTs	58	1.41	1.16, 1.73
–RCT high-dose arms*	58	1.46	1.19, 1.79
–OLE studies	6	1.33	0.77, 2.29
Tuberculosis			
–All RCTs	19	3.53	1.58, 7.85
–RCT high-dose arms*	19	3.32	1.54, 7.15
Opportunistic infections			
–All RCTs	6	0.94	0.33, 2.64
–RCT high-dose arms*	6	0.98	0.35, 2.73
Any infection			
–All RCTs	37	1.20	1.10, 1.30
–RCT high-dose arms*	37	1.21	1.11, 1.32
–OLE studies	6	1.69	1.31, 2.18

- A statistically **significant threefold increase** in the risk of TB

- The subgroup analysis by the type of TNF-α inhibitors **did not reveal** any difference among the drug specific effect estimates.

- The power of this analysis is typically **low.**

Minozzi S, Bonovas S, Lytras T, et al. Risk of infections using anti-TNF agents in rheumatoid arthritis, psoriatic arthritis, and ankylosing spondylitis: a systematic review and meta-analysis. **Expert Opin Drug Saf. 2016**;15(sup1):11-34.

Practical Approach

- Screening for TB before starting a biologic

1

- **All patients** require screening for tuberculosis (TB) before starting a biologic
    - (grade 1B, SOA 98%).

2

Screening for TB should include checking for

- previous TB **exposure** and **treatment**,
- **performing a clinical examination**,
- **chest X-ray** (CXR) and
- either a **TST or an IGRA or both**,

as appropriate

- (grade 2C, SOA 98%).

- Patients with an **abnormal** CXR, **previous history of TB** or **TB treatment** *should be* **referred to a specialist** with an interest in TB prior to commencing a biologic

    - (grade 2C, SOA 99%).

- Immunocompromised patients screened for latent TB with an IGRA alone or together with a TST and found to have **a positive result** in **either test** should be considered for **treatment prior to starting biologic therapy**

    - (grade 2C, SOA 96%).

- **Repeating the TST** (booster effect) **has not** been shown to improve the sensitivity of the test in IMIDs, and reduces its specificity; therefore, it is not currently recommended, as IGRA techniques are available.

    - (CIII)

- Blood for IGRA tests should be extracted **before the TST**, due to the **booster effect** identified on IGRA tests.

    - (AIII)

- The specificity and sensitivity of both IGRA techniques for the diagnosis of LTBI is **similar** in patients with IMID, although the sensitivity of the **T-SPOT.TB** is somewhat greater in patients treated with **corticosteroids**.
- Its use should therefore be assessed in these patients.

    - (BIII)

- **Indeterminate** results in IGRA tests should always **be confirmed with a second test**, which is usually negative in most cases
    - (AIII)
- A negative result in the **TST and IGRA** tests **does not rule out** the presence of an LTBI
    - (AIII)

- Patients should be treated with prophylactic anti-TB treatment **prior to commencing a biologic**
    - (grade 1B, SOA 99%);

- The recommended treatment regimen is **INH for 9 months**.

- In exceptional cases only, treatment with **INH+RIF for 3 months** may be indicated

    - (AIII)

- Treatment should be monitored each month. In the event of **INH-induced hepatotoxicity**, an alternative regimen with **RIF for 4 months** is recommended.

    - (AIII)

- According to current data, study and screening of the LTBI **after the start of and during anti-TNF treatment are not indicated** as a strategy for diagnosing initial false negatives.

- The screening study **should only be repeated** if there are changes in the **clinical symptoms** or **after possible exposure** to *M. tuberculosis* on travel to highly endemic areas.

    - (AIII)

- Therapy may be commenced after completing **at least 1 month of anti-TB treatment**
    - (grade 2C, SOA 91%)

- Patients who have had **previous inadequate** treatment for active TB **should be investigated for active TB**.

- In these individuals *even when active disease has been excluded*, the annual risk of TB (reactivation) is **much higher** than the general population rate, so the risk-benefit analysis favours **chemoprophylaxis**

    - (grade 1C, SOA 98%).

- As TB reactivation risk is higher with anti-TNF mAb drugs (notably ADA and INF) than for ETN, **consider ETN** in preference for those who require anti-TNF therapy and are at high risk of TB reactivation

    - (grade 1B, SOA 99%).

- The risk of relapse in patients who have **correctly completed tuberculosis treatment** does not seem to be higher after starting anti-TNF treatment.

    - (AIII)

- Patients with evidence of active TB should be treated **before starting** a biologic

    - (1C, SOA 99%);

- Therapy may be commenced after completing **at least 3 months** of anti-TB treatment and there is evidence that the patient **is improving with evidence of culture negativity**

    - (grade 2C, SOA 91%).

Low (DAS28: ≤3.2)	**NSAIDs, analgesics, ICLR, SSZ.** **Restart biologics after 6 months of therapy for active TB.**
Moderate (DAS28: 3.3–5.0)	**After 2-month of therapy for active TB, it is possible to use CS (as low as possible dose) + MTX or CsA.** **Restart biologics after 6 months of therapy for active TB.**
High (DAS28: ≥5.1)	**After 2-month therapy for active TB it is possible to restart a low risk biologic: ANK, TCZ, RTX, and ABA for RA.**

Cantini F, et al, Guidance for the management of patientswith latent tuberculosis infection requiring biologic therapy in rheumatology and dermatol..., **Autoimmun Rev (2015)**, http://dx.doi.org/10.1016/j.autrev.2015.01.011

Pneumocystis jirovecii

- There is **wide diversity** in the diseases under the general category of connective tissue disorders.
- The frequency of PCP **varies greatly** from disease to disease.
- Pneumocystis jirovecii infection increased to **80%**, especially when **CD4+ T-lymphocyte** counts were **<100 cells/µl**.

- Ward et al. determined a frequency of PCP infections for *granulomatosis with polyangiitis (GPA)* to be **89 cases per 10,000** hospitalizations/year versus **2 per 10,000** in *rheumatoid arthritis (RA).*

- The incidence of Pneumocystis jirovecii among patients receiving **TNF-α inhibitors** varies widely:
-

between **<0.01/1000** PYs in North America to **8.8/1000** PYs in Japan

Ward MM, Donald F. Pneumocystis carinii pneumonia in patients with connective tissue diseases: the role of hospital experience in diagnosis and mortality. **Arthritis Rheum. 1999**;42(4):780–9.
Grubbs JA, Baddley JW. Pneumocystis jirovecii pneumonia in patients receiving tumor-necrosis-factor- inhibitor therapy: implications for chemoprophylaxis. **Curr Rheumatol Rep. 2014**;16(10):445.

- **Up to a quarter** of patients with RA have been reported to be **asymptomatically colonized** with Pneumocystis jirovecii.

- Risk factors for colonization include
  - **methotrexate and**
  - **corticosteroid use** and
  - **infliximab treatment for >3 years**

Arnold TM, Sears CR, Hage CA. Invasive fungal infections in the era of biologics. **Clin Chest Med. 2009**;30(2):279–86.

Established	Suspected[a]	Possible
Low CD4+ count	Glucocorticoids	Younger age[b]
Lymphopenia	Cyclophosphamide	Male[b]
	Rituximab	Hispanic decent[b]
	Methotrexate	Asian decent[b]
	Anti-TNF inhibitors	Private medical insurance[b]
	Azathioprine	Interstitial pulmonary fibrosis[c]
		Caucasian decent[d]
		Australian autumnal season[d]

Wolfe RM, Peacock JE Jr. Pneumocystis Pneumonia and the Rheumatologist: Which Patients Are At Risk and How Can PCP Be Prevented? **Curr Rheumatol Rep. 2017**;19(6):35.

- When presenting with Pneumocystis jirovecii, patients with chronic immune-mediated inflammatory diseases tend to have:
  - **A shorter duration of symptoms** (about 1 week as opposed to about 1 month in HIV-infected persons) and
  - lower beta-D glucan and
  - **higher C-reactive protein levels.**

Tokuda H, Sakai F, Yamada H, et al. Clinical and radiological features of Pneumocystis pneumonia in patients with rheumatoid arthritis, in comparison with methotrexate pneumonitis and Pneumocystis pneumonia in acquired immunodeficiency syndrome: a multicenter study. **Intern Med. 2008**;47(10):915–23.

- Several scientific articles reported the **occurrence** of P. jirovecii pneumonia (PCP) in patients with RA and CD **receiving infliximab** with or without concomitant immunosuppressive drugs.

- Bruce et al. confirmed that PCP is a **rare** infection in patients receiving TNF-α inhibitors, analyzing data from the British Society for Rheumatology Biologics Register for RA (BSRBR-RA), a national prospective observational cohort study.

Bruce ES, Kearsley-Fleet L, Watson KD, et al. Risk of Pneumocystis jirovecii pneumonia in patients with rheumatoid arthritis treated with inhibitors of tumour necrosis factor α: results from the British Society for Rheumatology Biologics Register for Rheumatoid Arthritis. **Rheumatology (Oxford). 2016**;55(7):1336-7.

- Prophylaxis with trimethoprim/sulfamethoxazole for Pneumocystis jirovecii **is not indicated** given the **low incidence** of infectious risk.

- It is essential to assess the risk factors for PCP including:
  (before starting TNF-α inhibitors)

  - **the concomitant use of corticosteroids** (especially >8 weeks),
  - advance age (>65 years),
  - lung disease or fibrosis,
  - **leucopenia <500/µl**,
  - hypoalbuminemia and
  - **lymphopenia**,
  - in the setting of an **outbreak of PCP** among RA or IBD patients (in which person-to-person transmission is thought to occur)

Grubbs JA, Baddley JW. Pneumocystis jirovecii pneumonia in patients receiving tumor-necrosis-factor- inhibitor therapy: implications for chemoprophylaxis. **Curr Rheumatol Rep. 2014**;16(10):445.
Mori S, Sugimoto M. Pneumocystis jirovecii infection: an emerging threat to patients with rheumatoid arthritis. **Rheumatology (Oxford). 2012**;51:2120-2130.

- Demoruelle et al. proposed PCP prophylaxis in patients with **CTD** and **2 or more** of the following:
- (1) steroids ≥20 mg/day for >4 weeks,
- (2) current use of ≥2 DMARDs,
- (3) absolute lymphocyte count ≤350 cells/mm3, or
- (4) underlying lung parenchymal disease

	Dose	Selected side effects/cautions
First line		
Trimethoprim-sulfamethoxazole (oral)	1 single-strength (SS) daily 1 double-strength (DS) daily 1 DS three times weekly	Nausea, GI discomfort, hypersensitivity reactions (rashes, fever), elevated creatinine, hyperkalemia, Stevens-Johnson syndrome (rare)
Second line		
Dapsone (oral)	100 mg daily	Check for G6PD deficiency prior to starting therapy. Anemia, hemolysis, methemoglobinemia
Atovaquone (oral)	1500 mg daily	Give with food. Nausea, diarrhea, rash, hepatitis (rarely)
Pentamidine (aerosolized)	300 mg every 4 weeks	Cough, dyspnea, bronchospasm, wheezing, pancreatitis, fever, dysglycemia, pneumothorax

Disease	Prophylaxis?	To whom?	Conditional factors[b]
GPA	Yes	All patients undergoing induction therapy	
SLE	Conditional[a]	High dose GC	Lymphopenia Low CD4+ count Immunosuppressive regimen
PM/DM	Conditional[a]	High-dose GC	Lymphopenia Low CD4+ count More severe disease
PAN, AAV	Conditional[a]	During induction therapy and/or high dose GC	Lymphopenia Low CD4+ count
RA	No	–	–
GCA	No	–	–
Scleroderma	No	–	–

Hepatitis B and C virus infections

- Patients should be screened for hepatitis B and C viral infection
    - (grade 1C, SOA 98%).

- In patients who are HBV positive, **a risk-benefit assessment** should be undertaken, as biologics may be safe if appropriate anti-viral treatment is given, working closely with a hepatologist.

    - (grade 1C, SOA 99%)

AASLD 2018

- **HBsAg-positive, anti-HBc–positive** patients are at high risk of HBV reactivation, especially with HBV DNA elevation
  - Antiviral prophylaxis is recommended **before or at the start of immunosuppressive or cytotoxic therapy**

- HBsAg-negative, anti-HBc–positive patients generally at lower risk of HBV reactivation
  - Monitor ALT, HBV DNA, and HBsAg, initiating therapy at the first sign of HBV reactivation
  - Exception: patients **undergoing SCT or receiving anti-CD20 therapy (e.g. rituximab)** should initiate HBV prophylaxis even if HBsAg negative

- When HBV prophylaxis is indicated:
  - Tenofovir DF, tenofovir AF, or entecavir are preferred for their high resistance barriers
  - Once started, anti-HBV prophylaxis should continue during immunosuppressive therapy and for **at least 6 months** (or for **at least 12 months** for patients receiving anti-CD20 therapies) after completion of immunosuppressive therapy.

AGA 2015

- The **high-risk group** was defined by anticipated incidence of HBVr in **>10%** of cases and included the following:

- 1.**HBsAg-positive/anti-HBc–positive** or HBsAg-negative/**anti-HBc–positive** patients treated with B cell–depleting agents (eg, rituximab, ofatumumab)

- 2.**HBsAg-positive/anti-HBc–positive** patients treated with anthracycline derivatives (eg, doxorubicin, epirubicin)

- 3.**HBsAg-positive/anti-HBc–positive** patients treated with moderate-dose (10–20 mg prednisone daily or equivalent) or high-dose (>20 mg prednisone daily or equivalent) corticosteroids daily **for ≥4 weeks**

- The AGA recommends **antiviral prophylaxis** over no prophylaxis for patients at high risk undergoing immunosuppressive drug therapy. *(Strong recommendation, Moderate-quality evidence)*

- Comments: *Treatment should be continued for **at least 6 months after discontinuation** of immunosuppressive therapy (at least 12 months for B cell–depleting agents).*

- The **moderate-risk** group was defined by anticipated incidence of HBVr of **1% to 10%** of cases and included the following:

- 1.**HBsAg-positive/anti-HBc–positive** or **HBsAg-negative/anti-HBc–positive** patients treated with **tumor necrosis factor alpha inhibitors** (eg, etanercept, adalimumab, certolizumab, infliximab)

- 2.**HBsAg-positive/anti-HBc–positive** or **HBsAg-negative/anti-HBc–positive** patients treated with **other cytokine or integrin inhibitors** (eg, abatacept, ustekinumab, natalizumab, vedolizumab)

- 3.**HBsAg-positive/anti-HBc–positive** or **HBsAg-negative/anti-HBc–positive** patients treated with **tyrosine kinase inhibitors** (eg, imatinib, nilotinib)

- 4.**HBsAg-positive/anti-HBc–positive** patients treated with **low-dose (<10 mg prednisone daily or equivalent) corticosteroids** for duration of **≥4 weeks**

- 5.**HBsAg-negative/anti-HBc–positive** patients treated with **moderate-dose (10–20 mg prednisone daily or equivalent**) or **high-dose (>20 mg prednisone daily or equivalent) corticosteroids** daily for **≥4 weeks**

- 6.**HBsAg-negative/anti-HBc–positive** patients treated with **anthracycline derivatives** (eg, doxorubicin, epirubicin)

- The AGA **suggests** **antiviral prophylaxis over monitoring** for patients at moderate risk undergoing immunosuppressive drug therapy. (*Weak recommendation; Moderate-quality evidence)*

- Comments: *Treatment should be **continued for 6 months after discontinuation** of immunosuppressive therapy.*
- *Patients who place a higher value on avoiding long-term use of antiviral therapy and the cost associated with its use and a lower value on avoiding the small risk of reactivation (*particularly in those who are HBsAg negative*) may reasonably select **no prophylaxis** over antiviral prophylaxis.*

- The **low-risk group** was defined by anticipated incidence of HBVr of **<1%** of cases and included the following:

- 1.**HBsAg-positive/anti-HBc–positive** or **HBsAg-negative/anti-HBc–positive** patients treated with **traditional immunosuppressive** agents (eg, **azathioprine, 6-mercaptopurine, methotrexate**)
- 2.**HBsAg-positive/anti-HBc–positive** or **HBsAg-negative/anti-HBc–positive** patients treated with **intra-articular corticosteroids**

- 3.**HBsAg-positive/anti-HBc–positive** or **HBsAg-negative/anti-HBc–positive** patients treated with **any dose of oral corticosteroids daily for ≤1 week**

- 4.**HBsAg-negative/anti-HBc–positive** patients treated with **low-dose (<10 mg prednisone or equivalent) corticosteroids** for **≥4 weeks.**

- The AGA suggests against routinely using antiviral prophylaxis in patients undergoing immunosuppressive drug therapy who are at low risk for HBVr. (*Weak recommendation; Moderate-quality evidence*)

- The AGA suggests use of antiviral drugs with **a high barrier to resistance** over lamivudine for prophylaxis in patients undergoing immunosuppressive drug therapy. (Weak recommendation; Moderate-quality evidence)

EASL 2017

- HBsAg+ candidates for **chemotherapy** and **immunosuppressive therapy** should receive entecavir, tenofovir DF, or tenofovir AF as treatment or prophylaxis (regardless of HBV DNA levels);

- Assess HBV DNA and ALT levels periodically;

- Discontinue therapy for patients with HBsAg loss ± anti-HBs seroconversion or for noncirrhotic patients with stable HBeAg seroconversion and undetectable HBV DNA after 12 mos of consolidation therapy or with ≥ 3 yrs of virologic suppression, if close monitoring is guaranteed

- For patients with **chronic HBV infection** without hepatitis, prophylaxis with entecavir, tenofovir DF, or tenofovir AF is recommended for **≥ 12 mos after cessation of immunosuppressive therapy or 18 mos after rituximab**;
- Discontinue only if disease is under remission;
- HBV DNA and liver function should be monitored every 3-6 mos during and 12 mos following anti-HBV treatment

- **Viremic HBsAg-/anti-HBc+** patients at high risk for HBV reactivation (> 10%), including those undergoing **stem cell transplantation** or **receiving rituximab and/or combined regimens for hematologic malignancies**, should be treated the same as HBsAg+ patients, with prophylaxis continuing for **≥ 18 mos** and monitoring continuing for 12 mos after stopping anti-HBV treatment;
- some experts recommend prophylaxis with lamivudine in this setting, but resistance has been reported

- **HBsAg-/anti-HBc+** patients at moderate (< 10%) or low (< 1%) risk for HBV reactivation should receive **preemptive** (not prophylactic) entecavir, tenofovir DF, or tenofovir AF therapy in the event that they become HBsAg+ or HBV DNA+ **during immunosuppressive therapy**; monitor every 1-3 mos

- **After a week of antiviral treatment**, with clinical and biochemical stability demonstrated, **TNF-α inhibitors** can be administered.

Carroll MB, Forgione MA. Use of tumor necrosis factor alpha inhibitors in hepatitis B surface antigen- positive patients: a literature review and potential mechanisms of action. **Clin Rheumatol 2010**;29(9):1021-9.

HCV infection

- Studies to date suggest that though biologic therapy **does not appear** to have a detrimental effect on HCV infection, it should **continue to be used only with caution** in such patients, following a risk-benefit decision made with a hepatologist.

    - (grade 1C, SOA 96%)

Vaccinations

- HBV immunization should be considered for at risk patients.
    - (grade 2C, SOA 94%)

- Since the respiratory tract is the most common source in bacterial infections observed in registries, age-appropriate **pneumococcal vaccination** (ideally including **conjugate** vaccine formulations) should be encouraged for patients.

- Similar rationale supports the seasonal administration of the trivalent **inactivated influenza vaccine**.

- Patients **>50 years** should undergo vaccination against **herpes zoster** assuming there are no contraindications

  (e.g. treatment **within the past 3 months**
  - with >40 mg prednisolone per day for >1 week,
  - >20 mg prednisolone per day for >14 days,
  - MTX >25 mg/week,
  - AZA >3.0 mg/kg/day).

- This should be administered preferably **>14 days** before starting biologic therapy .

  - (grade 2C, SOA 97%)

- Patients who **do not have a positive history** of **varicella zoster (chickenpox) infection should** have a varicella zoster virus antibody test.

- If this is **negative**, and there are **no contraindications**, varicella zoster vaccination **should be offered** prior to biologic commencement.

    - (grade 2C, SOA 98%)

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