2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases

George E Fragoulis , ^{1,2} Elena Nikiphorou , ^{3,4} Mrinalini Dey , ^{5,6} Sizheng Steven Zhao, Delphine Sophie Courvoisier , ⁸ Laurent Arnaud , ⁹ Fabiola Atzeni, Georg MN Behrens, MD Bijlsma, Peter Böhm, Scostas A Constantinou, MS Silvia Garcia-Diaz, Meliha Crnkic Kapetanovic, Kim Lauper , ^{7,17} Mariana Luís , ¹⁸ Jacques Morel, György Nagy , ^{20,21,22} Eva Polverino, Mariana Luís , Marco Sebastiani , ²⁵ Anja Strangfeld , ²⁶ Annette de Thurah , ^{27,28} James Galloway , ^{3,4} Kimme L Hyrich , ^{7,29}

Handling editor Josef S Smolen

▶ Additional supplemental material is published online only. To view, please visit the journal online (http://dx. doi.org/10.1136/ard-2022-223335).

For numbered affiliations see end of article.

Correspondence to

Professor Kimme L Hyrich, Centre for Epidemiology Versus Arthritis, Division of Musculoskeletal and Dermatological Science, The University of Manchester, Manchester, Manchester, UK; kimme.hyrich@manchester.ac. uk

Received 8 September 2022 Accepted 11 October 2022 Published Online First 3 November 2022



© Author(s) (or their employer(s)) 2023. No commercial re-use. See rights and permissions. Published by BMJ.

To cite: Fragoulis GE, Nikiphorou E, Dey M, et al. Ann Rheum Dis 2023;**82**:742–753.

ABSTRACT

Objectives To develop EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in patients with autoimmune inflammatory rheumatic diseases (AIIRD).

Methods An international Task Force (TF) (22 members/15 countries) formulated recommendations, supported by systematic literature review findings. Level of evidence and grade of recommendation were assigned for each recommendation. Level of agreement was provided anonymously by each TF member.

Results Four overarching principles (OAP) and eight recommendations were developed. The OAPs highlight the need for infections to be discussed with patients and with other medical specialties, in accordance with national regulations. In addition to biologic/ targeted synthetic disease-modifying antirheumatic drugs (DMARDs) for which screening for latent tuberculosis (TB) should be performed, screening could be considered also before conventional synthetic DMARDs, glucocorticoids and immunosuppressants. Interferon gamma release assay should be preferred over tuberculin skin test, where available. Hepatitis B (HBV) antiviral treatment should be guided by HBV status defined prior to starting antirheumatic drugs. All patients positive for hepatitis-C-RNA should be referred for antiviral treatment. Also, patients who are non-immune to varicella zoster virus should be informed about the availability of postexposure prophylaxis should they have contact with this pathogen. Prophylaxis against *Pneumocystis jirovecii* seems to be beneficial in patients treated with daily doses >15-30 mg of prednisolone or equivalent for >2-4 weeks.

Conclusions These recommendations provide guidance on the screening and prevention of chronic and opportunistic infections. Their adoption in clinical practice is recommended to standardise and optimise care to reduce the burden of opportunistic infections in people living with AIIRD.

INTRODUCTION

Opportunistic and chronic infections, that is, those which present more commonly or more severely in people who are immunocompromised, are encountered in the setting of autoimmune inflammatory rheumatic diseases (AIIRD) and are often associated with immunosuppressive and immunomodulatory treatments used for these diseases. Although it is recognised that screening procedures and prophylactic measures should be followed, clinical practice is largely heterogeneous and relevant recommendations are often lacking or are disparately located across the literature. There is, therefore, a need for collating evidence for different AIIRD and treatment regimens to be used as a single point of reference in routine clinical practice. ^{2 3}

Setting a single set of guidelines for infection screening and prophylaxis is challenging, as recommendations and procedures cannot be unified across all infections and organisms due to differences in area of residence, type of AIIRD and associated risk, the antirheumatic treatment received and other factors that may present additional layers of complexity, such as age and comorbidities. ⁴⁻⁶ Our goal was to formulate a set of recommendations, taking these challenges into account, to inform rheumatologists and healthcare providers in their decision making when caring for people living with AIIRD, to ensure that these infections can be identified and adequately managed.

A EULAR Task Force (TF) has been formed, comprised healthcare professionals and patients across different disciplines and countries, to develop the first EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in patients living with AIIRD based on the best available scientific evidence. This manuscript presents the work of this TF and the final set of recommendations.

METHODS

The EULAR standardised operating procedures (SOP)⁷ were followed throughout the undertaking of this work. The project was approved by the EULAR executive committee (No: CLI 118).

The steering committee included a main convenor (KLH) and a co-convenor (JG), one methodologist (EN), a co-methodologist (DSC) and a main fellow (GEF). Two co-fellows (MD and SSZ) supported the undertaking of the systematic literature review (SLR), especially during validation steps (see below). TF members were selected based on their experience in the field of infections in the setting of AIIRD, considering also gender and regional equity. The final TF consisted of 22 people (including steering committee members) from 15 different European countries. Two patient research partners, two healthcare professionals in rheumatology, two infectious disease doctors with an interest in rheumatology and one pulmonologist were included in addition to rheumatologists/epidemiologists (including two Emerging EULAR Network (EMEUNET) members).

In preparation of the first TF meeting, the steering group identified research questions of interest and relevance, leading to a scoping review (available on request) by the fellow (GEF). The scoping review provided an overview of the existing literature on chronic and opportunistic infections in AIIRD. During the first TF meeting, which was held virtually in September 2020, the results of the scoping review were presented and the research questions for the main SLR were discussed and modified as deemed appropriate by the TF. In addition, there was review and discussion on the pathogens that would be included in the subsequent SLR (presented in online supplemental material 1), based on the findings of the scoping review as well as expert opinion of TF members including the two infectious disease doctors who reviewed separately the list of pathogens.

Afterwards, the steering committee transformed the research questions (online supplemental material 1) into epidemiological questions that were addressed via the SLR. The latter was registered in PROSPERO (No: CRD42021244732) and was performed as *per guidance* provided in the Cochrane Handbook. The SLR results were reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines. ¹⁰

The SLR was performed for studies published from inception up to 5 December 2021. However, new studies that were published after this date and up until the date of the second TF meeting (18 January 2022) were also considered, where these provided additional evidence relevant to the research questions. The SLR focused on studies examining the efficacy of screening and prophylaxis for chronic and opportunistic infections. Results as well as details about the methodology of the SLR are presented separately. The results of the SLR were presented in the second virtual meeting (split over December 2021 and January 2022) during which the overarching principles (OAPs) and the recommendations were formulated and voted on. Recommendations and OAPs were accepted if ≥75% of the members agreed in a first round of anonymised voting; if this agreement was not reached, the recommendation/OAPs were reworded with a voting cut-off of \geq 67%. If this was not achieved, voting in favour by >50% of the TF members was required as part of a third and final round of voting, after rephrasing. As per EULAR guidance, the Oxford Evidence Based Medicine categorisation was followed for applying level of evidence and grade of recommendation (GoR). 11 A research agenda was formed, based on the identified unmet need and gaps in the literature found via the SLR and in discussions between TF members. Finally, after the second meeting, TF members provided their level of agreement which each OAP and recommendation from 0

(=no agreement) to 10 (=full agreement), via an anonymised online survey.

RESULTS

These recommendations address the screening procedures and prevention measures that should be followed in people living with AIIRD, treated (or about to be treated) with antirheumatic drugs. After the identification of the pathogens that were covered in the respective SLR, extensive discussions took place (during the second meeting) about the nomenclature that should be followed for the various antirheumatic drugs used. The TF reached consensus (agreed by 88% of the TF members) on the use of a four-category system as follows: (1) biological (b) and targeted synthetic (ts)-disease-modifying antirheumatic drugs (DMARDs): all biological and ts-DMARDs (except apremilast), (2) conventional synthetic (cs)DMARDs: methotrexate, leflunomide. Sulfasalazine and hydroxychloroquine were exempted from this category, and the TF members agreed to name them specifically, if needed, as it was thought that they only have a mild immunomodulatory/immunosuppressive effect. (3) other immunosuppressants: cyclophosphamide, mycophenolate mofetil, azathioprine, ciclosporin, tacrolimus. (4) glucocorticoids. These categories were adopted, with some modifications from recently published expert opinion and other consensus papers. It is recognised that the rheumatology community should discuss and reach a final consensus about the terminology used to describe these drugs. 12-14 The term 'antirheumatic treatment/drugs' is also used in this manuscript, encompassing all the above-mentioned categories. The TF meetings resulted in the formulation of four OAPs and eight recommendations (table 1).

Overarching principles

OAPs form the basis on which the recommendations were built. They reflect the rationale behind the development of this set of recommendations and they highlight key concepts in the management of AIIRD. In total, four OAPs that apply across all recommendations were formulated and met with high consensus by the TF (table 1).

The risk of chronic and opportunistic infections should be considered and discussed with all patients with AIIRD prior to treatment with csDMARDs, tsDMARDs, bDMARDs, immunosuppressants and/or glucocorticoids and reassessed periodically

Chronic and opportunistic infections are an important aspect of AIIRD and a significant cause of morbidity and mortality. 15 16 This principle was regarded as the cornerstone of all formulated recommendations. Antirheumatic treatment is a widely accepted risk for infections and thus the respective risk should be explained and discussed with patients, including how these risks can be minimised. The association of high disease activity with increased infection rates should also be considered. ¹⁷ 18 Shared-decision making is increasingly recognised as an important component of good clinical care in the management of people living with AIIRD, 19-22 who should also be educated to identify promptly signs and symptoms of infections and how to seek relevant medical attention. Considering also that escalation or change in treatment might be necessary and late reactivation of latent infections is possible, the respective risk should be reassessed and discussed periodically.

Table 1 The EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases

,			
Overarching principles	LoE	GoR	LoA mean (SD)
(A) The risk of chronic and opportunistic infections should be considered and discussed with all patients with AIIRD prior to treatment with csDMARDs, tsDMARDs, bDMARDs, immunosuppressants and/or glucocorticoids and reassessed periodically.	NA	NA	9.5 (1.0)
(B) Collaboration between rheumatologists and other specialists including but not limited to infectious disease doctors, gastroenterologists, hepatologists and pulmonologists is important.	NA	NA	9.6 (0.8)
(C) Individual risk factors should be considered in the decision for screening and prophylaxis of chronic and opportunistic infections and reassessed periodically.	NA	NA	9.8 (0.7)
(D) National guidelines and recommendations, among other country/region-level factors pertaining to endemic infectious diseases, should be considered.	NA	NA	9.7 (0.8)
Recommendations			
(1) Screening for latent tuberculosis is recommended in patients prior to starting bDMARDs or tsDMARDs*. Screening should also be considered in patients with increased risk for latent tuberculosis prior to starting csDMARDs, immunosuppressants* and/or glucocorticoids (according to dose and duration).	2b 5*	B D*	9.5 (0.9)
(2) Screening for latent tuberculosis should follow national and/or international guidelines and would typically include a chest X-ray* and Interferon-gamma release assay over tuberculin skin test where available.	2b 5*	B D*	9.5 (0.8)
(3) Choice and timing of latent tuberculosis therapy should be guided by national and/or international guidelines. Special attention should be given to interactions with drugs commonly used to treat AIIRD.	5	D	9.3 (1.4)
(4) All patients being considered for treatment with csDMARDs, bDMARDs, tsDMARDs*, immunosuppressants* and glucocorticoids (according to dose and duration) should be screened for HBV.	2a 2b*	C C*	9.1 (1.3)
(5) Screening for chronic hepatitis C should be considered in patients prior to starting csDMARDs, bDMARDs, tsDMARDs*, immunosuppressants and glucocorticoids* (according to dose and duration). Screening is recommended for patients with elevated alanine aminotransferase or those with known risk factors.	2b 5*	C D*	9.0 (1.3)
(6) Screening for HIV is recommended prior to treatment with bDMARDs and should be considered prior to treatment with csDMARDs, tsDMARDs, immunosuppressants and glucocorticoids (according to dose and duration).	5	D	8.9 (1.6)
(7) All patients commencing csDMARDs, bDMARDs, tsDMARDs, immunosuppressants and/or glucocorticoids (according to dose and duration) who are non-immune to VZV should be informed about post-exposure prophylaxis following contact with VZV.	5	D	8.9 (1.5)
(8) Prophylaxis against PCP should be considered in patients with AlIRD in whom high doses of glucocorticoids are used, especially in combination with immunosuppressants* and depending on the risk-benefit ratio.	2b 5*	B D*	9.2 (1.1)

^{*}Denotes separate LoE and GoR, where this is different from the rest of the statement.

AIIRD, autoimmune inflammatory rheumatic diseases; bDMARDs, biological disease-modifying antirheumatic drugs; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; GoR, grade of recommendation; HBV, hepatitis B virus; LoA, level of agreement; LoE, level of evidence; NA, not applicable; PCP, pneumocystis pneumonia; tsDMARDs, targeted synthetic DMARDs; VZV, varicella zoster virus.

Collaboration between rheumatologists and other specialists including but not limited to infectious disease doctors,

gastroenterologists, hepatologists and pulmonologists is important Rheumatologists carry primary responsibility when it comes to the treatment of people living with AIIRD and should work in close collaboration with other specialties when planning prevention or management of chronic and opportunistic infections in patients receiving antirheumatic drugs. This is an important component of multidisciplinary care and particularly relevant in the setting of these recommendations. Given that tuberculosis (TB) and hepatitis are among the most commonly discussed infections in people with AIIRD, teamwork with pulmonologists and hepatologists/gastroenterologist, respectively, is important. Other specialties including infectious disease doctors, radiologists, haematologists and microbiologists also have a crucial role in guiding the screening and prophylaxis of chronic and opportunistic infections in patients with AIIRD.

Individual risk factors should be considered in the decision for screening and prophylaxis of chronic and opportunistic infections and reassessed periodically

An individualised approach has been identified as a key principle of this set of recommendations, since several factors are known to increase the susceptibility for specific preventable infections. 4-6 23-25 These include, but are not limited to, age, comorbidities (eg, lung disease), cotreatment with other medications and travelling/living in endemic areas. Given that these parameters can change, and that escalation in the treatment of AIIRD is not unusual (OAP A), the presence of risk factors for chronic and opportunistic infections should be reassessed periodically. From this point of view, medical history including previous infections,

lifestyle (eg, frequent travelling), habits (eg, smoking), vaccination status and previous countries of residence should be taken into account.

National guidelines and recommendations, among other country/ region-level factors pertaining to endemic infectious diseases, should be considered

It was recognised by the TF members that there are significant variations in the strategies followed across different regions/ countries. This might reflect differences in the geoepidemiology of certain pathogens, as well as in factors related to cost and/or availability. To give an example, TB is more prevalent in specific areas of the world and/or resistance of *Mycobacterium tuberculosis* varies across countries, ²⁶ reflecting in the use of different therapeutic regimes/schemes for prophylaxis against latent TB reactivation. From this point of view, the TF thought it appropriate to have as an OAP that national/regional recommendations should always be taken into consideration in addition to these recommendations.

Recommendations

Screening for latent tuberculosis is recommended in patients prior to starting bDMARDs or tsDMARDs. Screening should also be considered in patients with increased risk for latent tuberculosis prior to starting csDMARDs, immunosuppressants and/or glucocorticoids (according to dose and duration).

Screening for latent TB before starting bDMARDs is included in screening programmes of most national and international rheumatology associations, while the same applies for tsDMARDs, although there is less evidence. ^{27–32} On the other hand, there is some evidence that patients with AIIRD under treatment with csDMARDs and/or glucocorticoids have also increased

risk for latent TB reactivation.^{29 33-37} The minimum dose/duration of glucocorticoids above which latent TB screening should be performed, is unknown. A number of studies and other guidelines have suggested that screening should be considered particularly in those patients likely to receive >15 mg of prednisolone (or equivalent)/day for longer periods of time (eg, >4 weeks). 34 35 38 39 In addition, screening for latent TB before commencement of these drugs should be considered in patients who also have accompanying TB risk factors like alcohol abuse, smoking, living with people with TB, living in endemic countries and others. 23 40 Finally, despite being suggested that cyclophosphamide might associate with TB development in some AIIRD, ²³ ⁴¹ evidence specifically addressing the impact of immunosuppressants is lacking. Recommendation for immunosuppressants at the time of drafting these recommendations, is only based on expert opinion.

Screening for latent tuberculosis should follow national and/or international guidelines and would typically include a chest X-ray, and interferon-gamma release assay (IGRA) over tuberculin skin test (TST) where available.

Evidence suggests that IGRA performs better than TST in the diagnosis of latent TB and is less affected by treatment with glucocorticoids, DMARDs or immunosuppressants. 42-51 From this point of view, IGRA should be preferred over TST for TB screening. Given the low agreement between TST and IGRA, 42 44 52-71 performing both tests can also be considered in cases of high suspicion for latent TB and/or in high-endemic countries. $^{58\,70\,72}$ Concordance between different IGRAs (Quantiferon and EliSPOT) is good thus one is not recommended over the other. 47 73-75 In addition, although there is no robust evidence for the usefulness of chest X-Ray, the TF considered it appropriate that this should be included in the TB- screening procedures, especially as a negative IGRA or TST cannot exclude active TB or rule out latent TB. 76 Finally, as discussed in the SLR informing current recommendations, conversion (from negative to positive) of TST or IGRA after treatment with bDMARDs has been reported. 63 70 77-89 Therefore, periodic rescreening could be considered, especially if risk factors exist or develop over time. 23 40 There are no robust data to define how often re-screening should be performed and/or if there is a need to rescreen patients who switch bDMARDs or tsDMARDs; this issue has been added in the research agenda. As stated, given the regional differences in TB-burden and also issues (eg, cost) that might affect the availability of some investigations (eg, Quantiferon), national and international guidelines should also be followed, where available.

Choice and timing of latent tuberculosis therapy should be guided by national and/or international guidelines. Special attention should be given to interactions with drugs commonly used to treat AllRD. Various therapeutic schemes have been used for the treatment of latent TB. These include isoniazid for 6–12 months, combination of rifampicin/isoniazid for 3–4 months, rifampicin for 4 months and once-weekly therapy of isoniazid plus rifapentine. ^{29 72 77 83 90-107} Given differences in the TB-burden and drug resistances among regions/countries, the TF members advise adhering to relevant national guidelines.

Interactions between drugs used to treat AIIRD and those used as treatment for latent TB should be considered. Monitoring of liver function tests (LFTs) is necessary in patients cotreated with isoniazid and hepatotoxic drugs like methotrexate and leflunomide. ^{96 108 109} In addition, pharmacokinetics

of JAK-inhibitors and glucocorticoids might be affected by coadministration with rifampicin. 110 111

All patients being considered for treatment with csDMARDs, bDMARDs, tsDMARDs, immunosuppressants and glucocorticoids (according to dose and duration) should be screened for hepatitis B virus

The risk of hepatitis B virus (HBV) reactivation (appearance/rise in HBV-DNA or conversion from HBsAg-negative to HBsAg-positive)¹¹² depends on the HBV-status (unexposed, vaccinated, carrier (ie, HBsAg-positive) and resolved-HBV (anti-HBcore-positive and HBsAg-negative)) and this should be determined before the treatment for AIIRD is commenced. HBV-status would also help identify patients at risk (eg, from their occupation) who should be vaccinated. ¹¹³ Due to the complex nature of this recommendation, the TF decided to include a figure outlining the suggested procedures according to the HBV status of the patient (figure 1).

Evidence suggests that HBV carriers (HBsAg-positive) would benefit from prophylactic treatment, and thus it is advised that they should be referred to hepatologist for antiviral prophylactic treatment. As outlined in the SLR informing these recommendations, data are less robust for drugs 116-125 other than bDMARDs. However, for non-bDMARDs users, referral to a hepatologist for consideration of anti-viral prophylaxis is also recommended. The exact dose and duration of glucocorticoids that would increase HBV reactivation risk cannot be inferred from existing studies. Patients receiving at least 10 mg of prednisolone or equivalent for ≥4 weeks are regarded by the American Gastroenterology Association as a high-risk group for HBV reactivation, also supported by expert opinion. 138 139

For patients who have resolved-HBV (anti-HBcorepositive and HBsAg-negative), risk for HBV reactivation is lower. 119 121-123 140-148 Baseline measurement of LFT and HBV-DNA levels and then regular (eg, every 3-6 months) monitoring of LFT and HBV-DNA levels over universal prophylaxis is advised. 132 149-152 Referral to a hepatologist is also recommended for all patients, but is imperative for those with detectable HBV-DNA. Special attention should be given to patients considered as high-risk for HBV reactivation. These are mainly patients treated with rituximab; some investigators as well as rheumatology and/or hepatology societies have suggested that these patients should be referred to a hepatologist for consideration of prophylactic treatment irrespective of HBV-DNA levels. 153-157 Of note, compared with people with high titres of anti-HBs antibodies, those with low titres have also been linked with greater risk of reactivation. 158-163 In terms of prophylaxis, the TF did not suggest any antiviral drug in favour of the other, as this is a decision that should be made by the treating hepatologist. There are no data to support a recommendation about the timing of anti-viral treatment, but it is reasonable to start ideally before or at least simultaneously with the treatment administered for AIIRD and continuing for least 6-12 months after discontinuation of antirheumatic treatment, as has been proposed in recommendations from rheumatology and hepatology/gastroenterology societies. 137 153 155 157 164 165 This proposed time window for prophylaxis continuation might be longer for patients treated with rituximab. 137 153 157 165 Given the lack of data, the TF did not make a specific recommendation related to this. Instead, a relevant research agenda item has been agreed (see below).

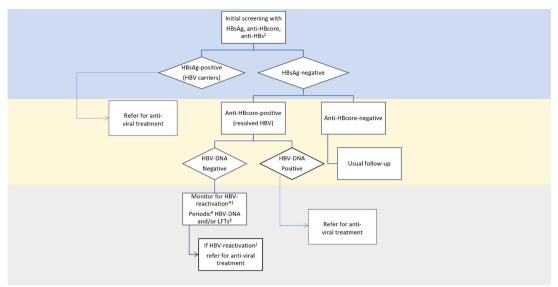


Figure 1 Typical screening for hepatitis B virus (HBV) status include HBsAg, anti-HBcore and anti-HBs. HBsAg-positive patients (HBV carriers) would benefit from prophylactic treatment, and thus it is advised that they should be referred to hepatologist for anti-viral prophylactic treatment. For those who are anti-HBcore-positive and HBsAg-negative (resolved HBV), measurement of HBV-DNA and liver function tests at baseline and then regular monitoring is advised. If HBV reactivation is suspected, based on these tests, referral to hepatologist for anti-viral treatment is recommended. For high-risk patients (eg, commencing treatment with anti-CD20 regimes) prophylactic treatment, irrespective of DNA levels might be considered. ‡Positive anti-HBs without positive HBsAg or anti-HBcore is consistent with prior vaccination. If all three (HBsAg, anti-HBcore, anti-HBs) are negative, means no previous exposure to HBV. *Consider referral for antiviral prophylaxis for those commencing rituximab, having also low titers of anti-HBs. Risk is assessed on an individual basis. J HBV-reactivation: rise or appearance of HBV-DNA, or conversion from HBsAg-negative to HBsAg-positive. #Periodic: there are no data to specify the exact time at which re-screening for HBV-reactivation should be performed. However, every 3–6 months is the standard for many national guidelines. Risk factors and cost should also be considered. §Referral to hepatologists is also recommended.

Screening for chronic hepatitis C should be considered in patients prior to starting csDMARDs, bDMARDs, tsDMARDs, immunosuppressants and glucocorticoids (according to dose and duration). Screening is recommended for patients with elevated alanine aminotransferase or those with known risk factors Most of the studies examining hepatitis C virus (HCV) reactivation pertain to treatment with bDMARDs, particularly TNF inhibitors, and show that HCV reactivation does occur, although in a low number of patients. 166-170 Of note, most of these studies were published before newer, more effective drugs against HCV (eg, direct acting antivirals) were widely available. In the interest of public health, the TF suggests that screening should be considered in AIIRD patients before starting treatment. Considering also cost-effectiveness and geographical variations, the threshold for screening should be lower for patients with concurrent HCV risk factors (eg, intravenous use of drugs) and/or abnormal LFTs, especially ALT. No data exist regarding HCV screening and glucocorticoids or immunosuppressants. Therefore, recommendation for these drug categories is based on expert opinion. Screening for HCV includes anti-HCV antibodies and if these are present, measurement of HCV-RNA levels. 164 171 172 Patients with detectable HCV-RNA should be referred for consideration of antiviral treatment. In these patients, regular monitoring with LFTs and viral load is also advised. 166 170 173-175

Screening for HIV is recommended prior to treatment with bDMARDs and should be considered prior to treatment with csDMARDs, tsDMARDs, immunosuppressants and glucocorticoids (according to dose and duration)

No robust data exist for the safety of treatment with DMARDs, immunosuppressants or glucocorticoids in patients with HIV; however, the TF supported that screening for HIV should be undertaken prior to treatment with bDMARDs, with

appropriate HIV care and treatment given where indicated. Taking also into account the importance of addressing public health and depending on cost-effectiveness and national guidelines, screening of HIV could be performed before commencing other antirheumatic drugs as suggested in other recommendations for specific AIIRD or drugs. ¹⁷⁶ 177

All patients commencing csDMARDs, bDMARDs, tsDMARDs, immunosuppressants and/or glucocorticoids (according to dose and duration) who are non-immune to varicella zoster virus (VZV) should be informed about post-exposure prophylaxis following contact with VZV

In the TF meeting, it was discussed whether AIIRD patients should have serological screening for VZV immunity. Acknowledging that status of VZV-immunity can be affected by various factors, including national regulations, access to testing, as well as previous vaccination or infection history, it was considered appropriate not to formulate a specific recommendation on this issue; however, the TF advocates the importance of establishing VZV-immunity status through a detailed past medical history of previous exposure, for example, chickenpox. Mainly based on published expert opinion 178 179 the TF agreed that those identified as non-immune or where there is doubt about their immunity status, should be informed in advance about post-exposure prophylaxis and offered prophylaxis after contact with a person with chickenpox or shingles, according to local guidelines. There is no evidence about the level of immunosuppression/immunomodulation (type of treatment) above which, patients would have a benefit from postexposure prophylaxis. This has been noted in the research agenda.

Prophylaxis with antivirals against reactivation of herpes zoster infection (shingles), as has been suggested by some in the literature (largely expert opinion), 179–181 could not be

recommended routinely at this stage. It has been suggested that this might benefit patients with AIIRD with a history of recurrent herpes zoster infections; however, the TF considered that there was not enough evidence to support such a recommendation at this stage.

Prophylaxis against *Pneumocystis jirovecii* pneumonia (PCP) should be considered in patients with AIIRD in whom high doses of glucocorticoids are used, especially in combination with immunosuppressants* and depending on the risk-benefit ratio. Prophylaxis for PCP has been mostly examined in AIIRD patients treated with glucocorticoids. Although the minimum dose and duration of glucocorticoid treatment above which prophylaxis is recommended is not defined, evidence suggests that in daily doses > 15–30 mg of prednisolone or equivalent for > 2–4 weeks, prophylaxis is beneficial. 182-186 Most studies do not focus on a specific AIIRD. Therefore, it was not possible to make recommendations for PCP prophylaxis in individual diseases although the risk for PCP infection might be significantly different.¹ Data specifically addressing the contribution of other antirheumatic drugs in PCP development are limited. 188 189 On the other hand, it has been shown that coadministration of immunosuppressants with glucocorticoids 184 185 190 increase the risk for PCP. Other features including persistent lymphopenia,^{5 6 184 185} older age and pre-existing lung disease are also considered risk factors for PCP.4-6

The most commonly used prophylaxis scheme is trimethoprim/sulfamethoxazole (TMP-SMX) 480 mg/day (single-strength) or 960 mg three times a week; of note, there is some evidence that reduced doses (eg, half-strength, daily) may also be effective and associated with fewer adverse events . ^{191–195} It should be noted that adverse events related to TMP-SMX (eg, nausea, headache, rash) are common, affecting about 20% of patients. ¹⁹⁶ Concerns for higher adverse event rates have been expressed for individuals treated with methotrexate (in specific relation to the combination of TMP and MTX and the risk of cytopenia) or in patients with systemic lupus erythematosus (SLE). ¹⁸⁷ ¹⁹⁷

Alternative prophylactic medications include atovaquone, dapsone or nebulised pentamidine. Although there is some disagreement in the literature, ¹⁹⁸ it seems that they are equally effective compared with TMP-SMX^{199–201}; however, their usage is limited by factors like cost or need for hospital administration.²

DISCUSSION

This is the first set of EULAR recommendations on the screening and prophylaxis of opportunistic and chronic infections in AIIRD. The four OAPs comprise the cornerstones of the eight recommendations produced. The latter are presented and grouped per infectious agent (rather than per underlying rheumatic disease or by individual antirheumatic treatments) as the steering group and the members of the TF concluded that this was the best way to present the evidence in the respective SLR and subsequently formulate the recommendations. They should be considered as a whole for each patient.

During the development of these recommendations, we faced several challenges, mainly pertaining to the variations across different types of AIIRD or antirheumatic drugs used. Initially, we had to decide which pathogens should be included in these recommendations. As discussed, our scoping review identified the bulk of these pathogens, and the TF members made their additions based on their expertise. Contribution of the two infectious disease doctors who participated in this TF and reviewed the list of studies regarding pathogens was crucial. We also reviewed an

authoritative consensus about opportunistic infections reporting during clinical trials and post-marketing surveillance of biological therapies in immune-mediated diseases¹ and found it to be consistent with the pathogens that were included in our SLR. Of note, infection with SARS-CoV2 was not included in these recommendations, as it is covered by EULAR recommendations dedicated to this topic.²⁰²

Some infections are traditionally linked with a specific drug class (eg, TB with TNF-inhibitors) which creates a risk of underestimating the importance of screening before commencing treatment with other drug categories (ie, csDMARDs and glucocorticoids in the example of TB). Stronger recommendations for specific treatments could not always be made as there is a lack of data for many of the commonly used drugs in rheumatology. This includes newer medications such as the JAK-inhibitors but also well-established immunosuppressants, such as cyclophosphamide. In these cases, level and GoR were low, and the respective unmet needs are captured in the research agenda.

To add another level of complexity, there is heterogeneity on clinical grounds about the screening and prevention strategies followed currently across different AIIRD. For example, prophylactic treatment for PCP with TMP-SMX is recommended in patients with ANCA-associated vasculitis²⁰³ but not in patients with SLE, as the evidence about the latter is limited thus far.²⁰⁴ As regards treatment with glucocorticoids, risk for specific infections like TB or HBV reactivation differs in relation to dose and duration of treatment. Therefore, where there was evidence available, specific doses/duration of glucocorticoids are proposed in this set of recommendations as a cut-off, in accordance with guidance from other societies.³⁸ 137

Finally, some pathogens are more prevalent in specific areas of the world, so special attention should be paid in these cases. Extensive discussions took place during the TF meetings about whether a separate recommendation should be included for rarer pathogens like Histoplasma spp, Coccidioides spp, Strongyloides spp and others which are more prevalent in specific geographical areas. As discussed in the respective SLR, relevant evidence was scarce, despite several expert opinion articles. Eighty-two per cent of the members voted that no recommendation can be formulated at this stage for these less common organisms. On the other hand, TF members agreed, as has been shown, ²⁰⁵ that people living with AIIRD benefit when provided with general dietary and environmental advice to reduce their risk of infection from specific pathogens (eg, Listeria spp, Salmonella spp) while receiving treatment with bDMARDs, tsDMARDs, immunosuppressants and high-doses of glucocorticoids. In addition, patients commencing any antirheumatic therapies should be counselled about infection risk as part of self-management. 19 Furthermore, increased awareness for atypical or rarer infections (eg, Histoplasma spp) is proposed for patients living or travelling from high-endemic areas. 206 207

Considering differences between countries and consistently with other EULAR recommendations²¹ and EULAR SOP,⁷ cost-effectiveness was also taken into account in the discussions that took place during the TF meetings, although such formal assessments were not conducted. As captured in the OAPs of this set of recommendation, national regulations, where they exist, should also be considered as a guidance for screening/therapeutic decisions. OAPs were phrased to stress that decision and were made on a case-by-case basis, considering concurrent risk factors (eg, treatment with other medications, comorbidities). Importantly, screening and prophylactic procedures should be reassessed periodically. The importance of the multidisciplinary approach is also highlighted. Even though rheumatologists should always

Box 1 Research agenda

General

- ⇒ Does the risk of opportunistic and chronic infections differ between the different classes of disease-modifying antirheumatic drugs (DMARDs) or immunosuppressive drugs?
- ⇒ What is the dose and duration of glucocorticoids above which the risk of opportunistic and chronic infections starts to increase compared to those patients not receiving glucocorticoids? Does this differ by pathogen?
- ⇒ How often should people with autoimmune inflammatory rheumatic diseases (AIIRD) receiving antirheumatic therapies be rescreened for chronic and opportunistic infections?
- ⇒ Is screening and prophylaxis for opportunistic and chronic infections in people with AIIRD receiving antirheumatic therapies cost-effective?

Tuberculosis

- ⇒ Should patients starting immunosuppressants (eg, cyclophosphamide) be screened routinely for latent tuberculosis (TB)?
- ⇒ Should patients starting antirheumatic therapies be screened for non-tuberculous mycobacteria? What is the most effective way to screen for these infections?
- ⇒ How often should patients who have already been tested for tuberculosis, be rescreened? In relation to that, is there a need to rescreen patients who switch biological DMARDs or targeted synthetic-DMARDs?

Hepatitis

- ⇒ When should hepatitis antiviral treatment be started in people living with AIIRD commencing antirheumatic treatment found to be at risk of hepatitis reactivation?
- ⇒ For how long should hepatitis antiviral prophylaxis be continued in patients at risk for hepatitis reactivation after antirheumatic treatment is stopped?
- ⇒ Should patients with chronic or resolved hepatitis B also be screened for hepatitis D?

Other viruses

- ⇒ Is it safe to treat people living with HIV with antirheumatic treatments?
- ⇒ When should antiviral prophylaxis be considered in people with AIIRD who have recurrent herpes zoster infections?
- ⇒ Is postexposure prophylaxis for patients non-immune to VZV who are exposed to VZV beneficial?
- ⇒ Should patients with AIIRD starting antirheumatic therapy be screened for cytomegalovirus?

Pneumocystis jirovecii pneumonia (PCP)

- ⇒ Does the risk of *Pneumocystis jirovecii* pneumonia (PCP) differ according to underlying AIIRD (eg, giant cell arteritis, systematic literature review, ANCA-associated vasculitis, etc)?
- ⇒ What is the added risk of PCP in patients treated with combination glucocorticoids/immunosuppressive therapies compared to those receiving glucocorticoids along?
- ⇒ What is the safest and most effective regimen for PCP prophylaxis?
- \Rightarrow How long should patients at risk for PCP receive prophylaxis? Other pathogens
- ⇒ Does avoidance of certain foods (eg, unpasteurised cheese) reduce the risk of opportunistic and severe infections in patients with AIIRD receiving antirheumatic treatments?
- ⇒ Should people with AIIRD starting antirheumatic therapies living in endemic areas be screened for *Leishmania*, *Histoplasma or Coccidioides*?

Continued

Box 1 Continued

⇒ Should people with AIIRD starting antirheumatic therapies be screened for fungal infections?

be in close collaboration and refer where appropriate to other professions, the TF underscores the central role of the rheumatologist in the management of chronic and opportunistic infections arising in the context of AIIRD and relating to the antirheumatic treatment received. For example, in HBV reactivation, rheumatologists should be able to understand the meaning of the various HBV screening tests and refer the patient on as appropriate. Our TF included clinicians from other disciplines (eg, infectious diseases, pulmonology) and although recommendations/guidelines from other non-rheumatology societies were not included specifically in our SLR, their views were taken into account. ³⁸ ¹³⁷ ¹⁵⁵ ¹⁵⁷

In these recommendations, despite discussing prevention strategies, we did not include or discuss studies about vaccination, as this is covered by another set of EULAR recommendations²⁰⁸; however, screening strategies proposed herein might identify individuals who are candidates for vaccinations.

During the TF meetings, it was discussed that the TF members, in collaboration with EULAR, will help towards the implementation of this set of recommendation in clinical practice. As outlined in the EULAR SOR, there are various implementation strategies, including audits and inclusion of recommendations in quality indicators. It is expected that apart from EULAR and EMEUNET, the TF members will help in the dissemination of this set of recommendations, in the first instance via their national rheumatology societies. Apart from rheumatologists and health policy makers, HPRs should be also aware of these recommendations given their active role in the education and monitoring of people living with AIIRD.²⁰⁹ It is also important that patient associations and people living with AIIRD, who are encouraged to play an active role in shared decision making and their care pathway, are also aware of these recommendations. 19 We believe that implementation of these recommendations will lead to better outcomes for patients, as it has been shown, for example, that rates of TB were significantly decreased after screening recommendations were issued at a national level. 102

For some infectious diseases (eg, fungal infections) data are still scarce. Most of these are recognised in the work presented here and in the respective SLR and are captured in the research agenda. Hopefully these issues will be the subject of future research and will be answered in time.

In summary, this is the first set of EULAR recommendations addressing the need for guidance about screening and prophylaxis in people living with AIIRD. Variations relating to treatment, geographical and other differences were taken into account. We believe that these recommendations will be a useful aid for decision making for people living in many countries and working in different healthcare systems.

Research agenda

A research agenda was considered during and after the second TF meeting. Items collected for the research agenda are shown in box 1

Author affiliations

¹Joint Academic Rheumatology Program, First Department of Propaedeutic and Internal Medicine, National and Kapodistrian University of Athens, Athens, Greece

²Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow,

³Centre for Rheumatic Diseases, King's College London, London, UK ⁴Rheumatology Department, King's College London, London, UK

⁵Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, UK ⁶Rheumatology Department, Countess of Chester Hospital NHS Foundation Trust, Chester, UK

⁷Centre for Epidemiology Versus Arthritis, Division of Musculoskeletal and Dermatological Science, The University of Manchester, Manchester, UK ⁸Division of Rheumatology, Geneva University Hospitals, Geneve, Switzerland ⁹Department of Rheumatology, National Reference Center for Autoimmune Diseases (RESO), University Hospitals Strasbourg, Strasbourg, France

⁰Rheumatology Unit, Department of Experimental and Internal Medicine, University of Messina, Messina, Italy

Department for Rheumatology and Immunology, Hannover Medical School, Hannover, Germany

¹²Dept of Rheumatology & Clinical Immunology, University Medical Center Utrecht, Utrecht, Netherlands

¹³Forschungspartner, German League against rheumatism, Bonn, Germany

¹⁴Department of Internal Medicine, Nicosia General Hospital, Leukosia, Cyprus ¹⁵Rheumatology Department, Complex Hospitalari Moises Broggi, Barcelona, Spain ¹⁶Skåne University Hospital, Department of Clinical Sciences Lund, Lund University,

⁷Division of Rheumatology, University of Geneva, Geneva, Switzerland ¹⁸Rheumatology, Centro Hospitalar e Universitário de Coimbra EPE, Coimbra,

¹⁹Department of Rheumatology, Montpellier University Hospital, University of Montpellier, Montpellier, France

²⁰Department of Rheumatology and Clinical Immunology, Department of Internal Medicine and Oncology, Semmelweis University, Budapest, Hungary ¹Heart and Vascular Center, Semmelweis University, Budapest, Hungary

²²Department of Genetics, Cell- and Immunobiology, Semmelweis University, Budapest, Hungary

²³Pneumology Department, Hospital Universitari Vall d'Hebron, Vall d'Hebron Institut de Recerca (VHIR), Vall d'Hebron Barcelona Hospital Campus, Ciber de Enfermedades Respiratorias CIBERES, Barcelona, Spain

²⁴Belgium Patient Partner Program, EULAR People with Arthritis/Rheumatism across Europe (PARE), Antwerpen, Belgium

²⁵Rheumatology Unit, University of Modena and Reggio Emilia, Modena, Italy ²⁶Epidemiology and Health Services Research, German Rheumatism Research Centre (DRFZ) Berlin and Charite University Medicine, Berlin, Germany

²⁷Department of Rheumatology, Aarhus University Hospital, Aarhus, Denmark ²⁸Department of Clinical Medicine, Aarhus University Hospital, Aarhus, Denmark ²⁹National Institute of Health Research Manchester Biomedical Research Centre,

Manchester Academic Health Science Centre, Manchester NHS Foundation Trust, Manchester, UK **Correction notice** This article has been corrected since it published Online First.

The affiliations for Prof G Nagy and Prof Eva Polverino have been corrected as well as Prof Polverino's name.

Twitter George E Fragoulis @FragoulisGeorge, Elena Nikiphorou @ElenaNikiUK, Mrinalini Dey @DrMiniDey, Delphine Sophie Courvoisier @delcourvoisier and Mariana Luís @maryanaluys

Contributors All authors contributed and finally approved the current manuscript.

Funding The systematic literature review was funded as part of the EULAR Quality of Care Committee (CI118) project for the 2022 EULAR recommendations on the screening and prophylaxis of chronic and opportunistic infections. KLH is also supported by the NIHR Manchester Biomedical Research Centre.

Competing interests GEF: Consulting fees/honoraria: Pfizer, Abbvie, Novartis, UCB, AENorasis, Janssen, Pharmaserv-Lilly. EN: speaker fees/honoraria: Celltrion, Pfizer, Sanofi, Gilead, Galapagos, AbbVie, Lilly, Fresenius. Research funding: Pfizer, Lilly. MD: none SZ: consulting fees: UCBDC: None. LA: has received consulting fees and/or research funding from Astra-Zeneca, GSK, Pfizer. FA: none. GMNB: has received consulting fees/honoraria as speaker from Gilead, ViiV Healthcare, Janssen, MSD, Roche, Moderna unrelated to this work. JWJB: none PB: none CAC: none SG-D: none MCK: none KL: has received consulting/ speaker fees from Pfizer, Viatris, Celltrion outside of the submitted work. ML: none. JM: none GN: consulting fees/honoraria as speaker from AbbVie, Amgen, Boehringer Ingelheim, Janssen, Miltenyi Biotech, Lilly, Pfizer, Roche unrelated to this work. EP: consulting fees/honoraria as speaker from Bayer, Menarini, Grifols, Zambon, Pfizer, Chiesi, Teva, Shire, Shionogi, Insmed, Boehringer-Ingelheim, unrelated to this work. JvR: none MS: consulting fees: BMS, Boehringer-Ingheleim, Eli Lilly, Celltrion, Amgen, Pfizer, Janssen Cilag. AS: has received consulting fees/honoraria as speaker from AbbVie, Amgen, BMS, Celltrion, Janssen, Lilly, MSD, Pfizer, Roche unrelated to this workAdT: none JG: speaker fees/honoraria: Abbvie, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer, UCB.

Research funding: Abbvie, Astrazeneca, Galapagos, Gilead, Gritstone, Janssen, Moderna, Novovax, PfizerKH: honoraria from Abbvie; grant income from Pfizer and BMS.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

Supplemental material This content has been supplied by the author(s). It has not been vetted by BMJ Publishing Group Limited (BMJ) and may not have been peer-reviewed. Any opinions or recommendations discussed are solely those of the author(s) and are not endorsed by BMJ. BMJ disclaims all liability and responsibility arising from any reliance placed on the content. Where the content includes any translated material, BMJ does not warrant the accuracy and reliability of the translations (including but not limited to local regulations, clinical guidelines, terminology, drug names and drug dosages), and is not responsible for any error and/or omissions arising from translation and adaptation or otherwise.

George E Fragoulis http://orcid.org/0000-0003-4932-7023 Elena Nikiphorou http://orcid.org/0000-0001-6847-3726 Mrinalini Dey http://orcid.org/0000-0001-6858-4338 Delphine Sophie Courvoisier http://orcid.org/0000-0002-1956-2607 Laurent Arnaud http://orcid.org/0000-0002-8077-8394 Kim Lauper http://orcid.org/0000-0002-4315-9009 Mariana Luís http://orcid.org/0000-0001-9581-7088 György Nagy http://orcid.org/0000-0003-1198-3228 Marco Sebastiani http://orcid.org/0000-0002-1294-6421 Anja Strangfeld http://orcid.org/0000-0002-6233-022X Annette de Thurah http://orcid.org/0000-0003-0103-4328 James Galloway http://orcid.org/0000-0002-1230-2781 Kimme L Hyrich http://orcid.org/0000-0001-8242-9262

REFERENCES

- 1 Winthrop KL, Novosad SA, Baddley JW, et al. Opportunistic infections and biologic therapies in immune-mediated inflammatory diseases: consensus recommendations for infection reporting during clinical trials and postmarketing surveillance. Ann Rheum Dis 2015;74:2107-16.
- Stamp LK, Hurst M. Is there a role for consensus guidelines for P. jiroveci pneumonia prophylaxis in immunosuppressed patients with rheumatic diseases? J Rheumatol
- Park JW, Curtis JR, Lee EB. Response to: 'Can we prescribe TMP/SMX prophylaxis without any concerns equally for all patients with rheumatic disease?' by Suyama and Okada. Ann Rheum Dis 2019;78:e18.
- Mecoli CA, Danoff SK. Pneumocystis jirovecii pneumonia and other infections in idiopathic inflammatory myositis. Curr Rheumatol Rep 2020;22:7.
- Hsu H-C, Chang Y-S, Hou T-Y, et al. Pneumocystis jirovecii pneumonia in autoimmune rheumatic diseases: a nationwide population-based study. Clin Rheumatol 2021:40:3755-63
- Mori S, Sugimoto M. Pneumocystis jirovecii pneumonia in rheumatoid arthritis patients: risks and prophylaxis recommendations. Clin Med Insights Circ Respir Pulm Med 2015;9:29-40.
- van der Heijde D, Aletaha D, Carmona L, et al. 2014 update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. Ann Rheum Dis 2015;74:8-13.
- Sepriano A, Kerschbaumer A, Bergstra SA, et al. Safety of synthetic and biological DMARDs: a systematic literature review Informing the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis. Ann Rheum Dis 2023:82:107-18.
- Cochrane. Cochrane Handbook for systematic reviews of interventions. 6.3 ed.
- Moher D, Liberati A, Tetzlaff J, et al. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. PLoS Med 2009;6:e1000097.
- Oxford centre for evidence-based Medicine—Levels of evidence, 2009 [Accessed March 2022].
- Isaacs JD, Burmester GR. Smart battles: immunosuppression versus immunomodulation in the inflammatory RMDs. Ann Rheum Dis 2020;79:991–3.
- Machado PM, Lawson-Tovey S, Strangfeld A, et al. Safety of vaccination against SARS-CoV-2 in people with rheumatic and musculoskeletal diseases; results from the EULAR coronavirus vaccine (COVAX) physician-reported registry. Ann Rheum Dis 2022:81:695-709.
- 14 Strangfeld A, Schäfer M, Gianfrancesco MA, et al. Factors associated with COVID-19related death in people with rheumatic diseases: results from the COVID-19 global rheumatology alliance physician-reported registry. Ann Rheum Dis 2021;80:930–42.
- Fragoulis GE, Sipsas NV. When rheumatology and infectious disease come together. Ther Adv Musculoskelet Dis 2019;11:1759720X19868901.
- Hsu C-Y, Ko C-H, Wang J-L, et al. Comparing the burdens of opportunistic infections among patients with systemic rheumatic diseases: a nationally representative cohort study. Arthritis Res Ther 2019;21:211.

- 17 Accortt NA, Lesperance T, Liu M, et al. Impact of sustained remission on the risk of serious infection in patients with rheumatoid arthritis. Arthritis Care Res 2018;70:679–84.
- 18 Au K, Reed G, Curtis JR, et al. High disease activity is associated with an increased risk of infection in patients with rheumatoid arthritis. Ann Rheum Dis 2011:70:785–91
- 19 Nikiphorou E, Santos EJF, Marques A, et al. 2021 EULAR recommendations for the implementation of self-management strategies in patients with inflammatory arthritis. Ann Rheum Dis 2021;80:1278–85.
- 20 Ritschl V, Stamm TA, Aletaha D, et al. 2020 EULAR points to consider for the prevention, screening, assessment and management of non-adherence to treatment in people with rheumatic and musculoskeletal diseases for use in clinical practice. Ann Rheum Dis 2021;80:707–13.
- 21 Smolen JS, Landewé RBM, Bijlsma JWJ, et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2019 update. Ann Rheum Dis 2020;79:685–99.
- 22 Toupin-April K, Décary S, de Wit M, et al. Endorsement of the OMERACT core domain set for shared decision making interventions in rheumatology trials: results from a multi-stepped consensus-building approach. Semin Arthritis Rheum 2021:51:593–600
- 23 Xiao X, Da G, Xie X, et al. Tuberculosis in patients with systemic lupus erythematosus-a 37-year longitudinal survey-based study. J Intern Med 2021:290:101–15.
- 24 Curtis JR, Xie F, Yang S, et al. Risk for herpes zoster in Tofacitinib-Treated rheumatoid arthritis patients with and without concomitant methotrexate and glucocorticoids. Arthritis Care Res 2019;71:1249–54.
- 25 Lertnawapan R, Totemchokchyakarn K, Nantiruj K, et al. Risk factors of Pneumocystis jeroveci pneumonia in patients with systemic lupus erythematosus. Rheumatol Int 2009:29:491–6.
- 26 Ektefaie Y, Dixit A, Freschi L, et al. Globally diverse Mycobacterium tuberculosis resistance acquisition: a retrospective geographical and temporal analysis of whole genome sequences. Lancet Microbe 2021;2:e96–104.
- 27 Evangelatos G, Koulouri V, Iliopoulos A, et al. Tuberculosis and targeted synthetic or biologic DMARDs, beyond tumor necrosis factor inhibitors. Ther Adv Musculoskelet Dis 2020;12:1759720X20930116.
- 28 Winthrop KL, Harigai M, Genovese MC, et al. Infections in baricitinib clinical trials for patients with active rheumatoid arthritis. Ann Rheum Dis 2020;79:1290–7.
- 29 Winthrop KL, Park S-H, Gul A, et al. Tuberculosis and other opportunistic infections in tofacitinib-treated patients with rheumatoid arthritis. Ann Rheum Dis 2016;75:1133–8.
- 30 Ji X, Hu L, Wang Y, et al. Risk of tuberculosis in patients with rheumatoid arthritis treated with biological and targeted drugs: meta-analysis of randomized clinical trials. Chin Med J 2022;135:409–15.
- 31 Cantini F, Blandizzi C, Niccoli L, et al. Systematic review on tuberculosis risk in patients with rheumatoid arthritis receiving inhibitors of Janus kinases. Expert Opin Drug Saf 2020:19:861–72.
- 32 Cohen SB, van Vollenhoven RF, Winthrop KL, et al. Safety profile of upadacitinib in rheumatoid arthritis: integrated analysis from the select phase III clinical programme. Ann Rheum Dis 2021;80:304–11.
- 33 Brassard P, Lowe A-M, Bernatsky S, et al. Rheumatoid arthritis, its treatments, and the risk of tuberculosis in Quebec, Canada. Arthritis Rheum 2009;61:300–4.
- 34 Long W, Cai F, Wang X, et al. High risk of activation of latent tuberculosis infection in rheumatic disease patients. Infect Dis 2020;52:80–6.
- 35 Jick SS, Lieberman ES, Rahman MU, et al. Glucocorticoid use, other associated factors, and the risk of tuberculosis. Arthritis Rheum 2006;55:19–26.
- 36 Fragoulis GE, Constantinou CA, Sipsas NV. Tuberculosis in inflammatory arthritis. are biologics the only culprits? *Lancet Rheumatology* 2019. Accepted for publication.
- 37 Brode SK, Jamieson FB, Ng R, et al. Increased risk of mycobacterial infections associated with anti-rheumatic medications. Thorax 2015;70:677–82.
- 38 Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American thoracic Society was adopted by the ats board of directors, July 1999. this is a joint statement of the American thoracic Society (ats) and the centers for disease control and prevention (CDC). this statement was endorsed by the Council of the infectious diseases Society of America. (IDSA), September 1999, and the sections of this statement. Am J Respir Crit Care Med;2000:S221–47.
- 39 Prevention CfDCa, National Center for HIV/AIDS VH, STD, and TB Prevention, Elimination DoT. Latent tuberculosis infection: A guide for primary health 2020 [Publication Number 22-0468]. Available: https://www.cdc.gov/tb/publications/ltbi/default.htm [Accessed 13 July 2022].
- 40 Cantini F, Niccoli L, Capone A, et al. Risk of tuberculosis reactivation associated with traditional disease modifying anti-rheumatic drugs and non-anti-tumor necrosis factor biologics in patients with rheumatic disorders and suggestion for clinical practice. Expert Opin Drug Saf 2019;18:415–25.
- 41 Balbi GGM, Machado-Ribeiro F, Marques CDL, et al. The interplay between tuberculosis and systemic lupus erythematosus. Curr Opin Rheumatol 2018;30:395–402.

- 42 Ruan Q, Zhang S, Ai J, et al. Screening of latent tuberculosis infection by interferon-γ release assays in rheumatic patients: a systemic review and meta-analysis. Clin Rheumatol 2016;35:417–25.
- 43 Hsia EC, Schluger N, Cush JJ, et al. Interferon-γ release assay versus tuberculin skin test prior to treatment with golimumab, a human anti-tumor necrosis factor antibody, in patients with rheumatoid arthritis, psoriatic arthritis, or ankylosing spondylitis. Arthritis Rheum 2012;64:2068–77.
- 44 Maeda T, Banno S, Maeda S, et al. Comparison of QuantiFERON-TB gold and the tuberculin skin test for detecting previous tuberculosis infection evaluated by chest CT findings in Japanese rheumatoid arthritis patients. J Infect Chemother 2011;17:842–8.
- 45 Matulis G, Jüni P, Villiger PM, et al. Detection of latent tuberculosis in immunosuppressed patients with autoimmune diseases: performance of a Mycobacterium tuberculosis antigen-specific interferon gamma assay. Ann Rheum Dis 2008;67:84–90.
- 46 Sargın G, Şentürk T, Ceylan E, et al. TST, QuantiFERON-TB gold test and T-SPOT.TB test for detecting latent tuberculosis infection in patients with rheumatic disease prior to anti-TNF therapy. *Tuberk Toraks* 2018;66:136–43.
- 47 Vassilopoulos D, Tsikrika S, Hatzara C, et al. Comparison of two gamma interferon release assays and tuberculin skin testing for tuberculosis screening in a cohort of patients with rheumatic diseases starting anti-tumor necrosis factor therapy. Clin Vaccine Immunol 2011;18:2102–8.
- 48 Jiang B, Ding H, Zhou L, et al. Evaluation of interferon-gamma release assay (T-SPOT. TB(™)) for diagnosis of tuberculosis infection in rheumatic disease patients. Int J Rheum Dis 2016;19:38–42.
- 49 Lee H, Park HY, Jeon K, et al. Quantiferon-Tb gold in-tube assay for screening arthritis patients for latent tuberculosis infection before starting anti-tumor necrosis factor treatment. PLoS One 2015;10:e0119260.
- 50 Marques CDL, ALBP D, Barros de Lorena VM. Attenuated response to PPD in the diagnosis of latent tuberculosis infection in patients with rheumatoid arthritis. Revista Brasileira de Reumatologia 2009;49:121–31.
- 51 Bélard E, Semb S, Ruhwald M, *et al.* Prednisolone treatment affects the performance of the quantiferon gold In-Tube test and the tuberculin skin test in patients with autoimmune disorders screened for latent tuberculosis infection. *Inflamm Bowel Dis* 2011:17:2340–9.
- 52 Cho H, Kim YW, Suh C-H, *et al.* Concordance between the tuberculin skin test and interferon gamma release assay (IGRA) for diagnosing latent tuberculosis infection in patients with systemic lupus erythematosus and patient characteristics associated with an indeterminate IGRA. *Lupus* 2016;25:1341–8.
- 53 Escalante P, Kooda KJ, Khan R, et al. Diagnosis of latent tuberculosis infection with T-SPOT(®).TB in a predominantly immigrant population with rheumatologic disorders. Lung 2015;193:3–11.
- 54 Girlanda S, Mantegani P, Baldissera E, et al. ELISPOT-IFN-gamma assay instead of tuberculin skin test for detecting latent Mycobacterium tuberculosis infection in rheumatic patients candidate to anti-TNF-alpha treatment. Clin Rheumatol 2010:29:1135–41.
- 55 Gogus F, Günendi Z, Karakus R, et al. Comparison of tuberculin skin test and QuantiFERON-TB gold in tube test in patients with chronic inflammatory diseases living in a tuberculosis endemic population. Clin Exp Med 2010;10:173–7.
- 56 Hanta I, Ozbek S, Kuleci S, et al. Detection of latent tuberculosis infection in rheumatologic diseases before anti-TNFα therapy: tuberculin skin test versus IFN-γ assay. Rheumatol Int 2012;32:3599–603.
- 57 Inanc N, Aydin SZ, Karakurt S, et al. Agreement between QuantiFERON-TB gold test and tuberculin skin test in the identification of latent tuberculosis infection in patients with rheumatoid arthritis and ankylosing spondylitis. J Rheumatol 2009;36:2675–81.
- 58 Kim J-H, Cho S-K, Han M, et al. Factors influencing discrepancies between the QuantiFERON-TB gold in tube test and the tuberculin skin test in Korean patients with rheumatic diseases. Semin Arthritis Rheum 2013;42:424–32.
- 59 Klein M, Jarosová K, Forejtová S, et al. Quantiferon TB gold and tuberculin skin tests for the detection of latent tuberculosis infection in patients treated with tumour necrosis factor alpha blocking agents. Clin Exp Rheumatol 2013;31:111–7.
- 60 Lee J-H, Sohn HS, Chun JH, et al. Poor agreement between QuantiFERON-TB gold test and tuberculin skin test results for the diagnosis of latent tuberculosis infection in rheumatoid arthritis patients and healthy controls. Korean J Intern Med 2014;29:76–84.
- 61 Mínguez S, Latorre I, Mateo L, et al. Interferon-Gamma release assays in the detection of latent tuberculosis infection in patients with inflammatory arthritis scheduled for anti-tumour necrosis factor treatment. Clin Rheumatol 2012;31:785–94.
- 62 Paluch-Oleś J, Magryś A, Kozioł-Montewka M, et al. Identification of latent tuberculosis infection in rheumatic patients under consideration for treatment with anti-TNF-α agents. Arch Med Sci 2013;9:112–7.
- 63 Park JH, Seo GY, Lee JS, et al. Positive conversion of tuberculin skin test and performance of interferon release assay to detect hidden tuberculosis infection during anti-tumor necrosis factor agent trial. J Rheumatol 2009;36:2158–63.

- 64 Pyo J, Cho S-K, Kim D, et al. Systemic review: agreement between the latent tuberculosis screening tests among patients with rheumatic diseases. Korean J Intern Med 2018;33:1241–51.
- 65 Scrivo R, Sauzullo I, Mengoni F. Mycobacterial interferon-gamma release variations during longterm treatment with tumor necrosis factor blockers: lack of correlation with clinical outcome. *Journal of Rheumatology* 2013;40:157–65.
- 66 Tang I, So H, Luk L, et al. Comparison of single and dual latent tuberculosis screening strategies before biologic and targeted therapy in patients with rheumatic diseases: a retrospective cohort study. Hong Kong Med J 2020:26:111–9
- 67 Vassilopoulos D. Should we routinely treat patients with autoimmune/rheumatic diseases and chronic hepatitis B virus infection starting biologic therapies with antiviral agents? Yes. Eur J Intern Med 2011;22:572–5.
- 68 Vassilopoulos D, Stamoulis N, Hadziyannis E, et al. Usefulness of enzyme-linked immunospot assay (Elispot) compared to tuberculin skin testing for latent tuberculosis screening in rheumatic patients scheduled for anti-tumor necrosis factor treatment. J Rheumatol 2008;35:1271–6.
- 69 Wu X, Chen P, Wei W. Diagnostic value of the interferon-gamma release assay for tuberculosis infection in patients with Behcet's disease. BMC Infectious Diseases 2019:19
- 70 Xie X, Chen J-W, Li F, et al. A T-cell-based enzyme-linked immunospot assay for tuberculosis screening in Chinese patients with rheumatic diseases receiving infliximab therapy. Clin Exp Med 2011;11:155–61.
- 71 So H, Yuen CS, Yip RM. Comparison of a commercial interferon-gamma release assay and tuberculin skin test for the detection of latent tuberculosis infection in Hong Kong arthritis patients who are candidates for biologic agents. Hong Kong Med J 2017;23:246–50.
- 72 Malaviya AN, Thakaran R, Rawat R. Real life experience of a screening strategy for latent tuberculosis before treatment with biologicals in Indian patients with rheumatic diseases. *Indian Journal of Rheumatology* 2018;13:233–9.
- 73 Iwagaitsu S, Naniwa T, Maeda S, et al. A comparative analysis of two interferon-γ releasing assays to detect past tuberculosis infections in Japanese rheumatoid arthritis patients. Mod Rheumatol 2016;26:690–5.
- 74 Martin J, Walsh C, Gibbs A, et al. Comparison of interferon (gamma) release assays and conventional screening tests before tumour necrosis factor (alpha) blockade in patients with inflammatory arthritis. Ann Rheum Dis 2010;69:181–5.
- 75 Melath S, Ismajli M, Smith R, et al. Screening for latent TB in patients with rheumatic disorders prior to biologic agents in a 'high-risk' TB population: comparison of two interferon gamma release assays. Rheumatol Int 2014;34:149–50.
- 76 Kang J, Jeong DH, Yoo B, et al. The usefulness of routine chest radiograph examinations in patients treated with TNF inhibitors for inflammatory arthritis in South Korea. Respir Med 2018;143:109–15.
- 77 Bonfiglioli KR, Ribeiro ACM, Moraes JCB. LTBI screening in rheumatoid arthritis patients prior to anti-TNF treatment in an endemic area. *International Journal of Tuberculosis and Lung Disease* 2014;18:905–11.
- 78 Busquets-Pérez N, Ponce A, Ortiz-Santamaria V, et al. How many patients with rheumatic diseases and TNF inhibitors treatment have latent tuberculosis? *Reumatol Clin* 2017;13:282–6.
- 79 Cerda OL, de Los Angeles Correa M, Granel A, et al. Tuberculin test conversion in patients with chronic inflammatory arthritis receiving biological therapy. Eur J Rheumatol 2019;6:19–22.
- 80 Chen D-Y, Shen G-H, Hsieh T-Y, et al. Effectiveness of the combination of a wholeblood interferon-gamma assay and the tuberculin skin test in detecting latent tuberculosis infection in rheumatoid arthritis patients receiving adalimumab therapy. Arthritis Rheum 2008;59:800–6.
- 81 Goel N, Torralba K, Downey C, et al. Screening for acquired latent tuberculosis in rheumatoid arthritis patients on tumor necrosis factor inhibition therapy in southern California. Clin Rheumatol 2020;39:2291–7.
- 82 Hatzara C, Hadziyannis E, Kandili A, *et al.* Frequent conversion of tuberculosis screening tests during anti-tumour necrosis factor therapy in patients with rheumatic diseases. *Ann Rheum Dis* 2015;74:1848–53.
- 83 He D, Bai F, Zhang S, et al. High incidence of tuberculosis infection in rheumatic diseases and impact for chemoprophylactic prevention of tuberculosis activation during biologics therapy. Clin Vaccine Immunol 2013;20:842–7.
- 84 Hejazi M-E, Ahmadzadeh A, Khabbazi A, et al. Tuberculin skin test conversion in patients under treatment with anti-tumor necrotizing factor alpha agents. BMC Infect Dis 2020;20:464.
- 85 Kim HW, Kwon OC, Han SH, et al. Positive conversion of interferon-γ release assay in patients with rheumatic diseases treated with biologics. Rheumatol Int 2020:40:471–9.
- 86 Scrivo R, Sauzullo I, Mengoni F, et al. Mycobacterial interferon-γ release variations during longterm treatment with tumor necrosis factor blockers: lack of correlation with clinical outcome. J Rheumatol 2013;40:157–65.
- 87 Son C-N, Jun J-B, Kim J-H, et al. Follow-Up testing of interferon-gamma release assays are useful in ankylosing spondylitis patients receiving anti-tumor necrosis factor alpha for latent tuberculosis infection. J Korean Med Sci 2014;29:1090–3.
- 88 Thomas K, Hadziyannis E, Hatzara C, et al. Conversion and reversion rates of tuberculosis screening assays in patients with rheumatic diseases and

- negative baseline screening under long-term biologic treatment. *Pathog Immun* 2020;5:34–51.
- 89 Cuomo G, D'Abrosca V, Iacono D, et al. The conversion rate of tuberculosis screening tests during biological therapies in patients with rheumatoid arthritis. Clin Rheumatol 2017:36:457–61.
- Aggarwal R, Manadan AM, Poliyedath A, et al. Safety of etanercept in patients at high risk for mycobacterial tuberculosis infections. J Rheumatol 2009;36:914–7.
- 91 Carmona L, Gómez-Reino JJ, Rodríguez-Valverde V, et al. Effectiveness of recommendations to prevent reactivation of latent tuberculosis infection in patients treated with tumor necrosis factor antagonists. Arthritis Rheum 2005;52:1766–72.
- 92 Hernández-Cruz B, Sifuentes-Osornio J, Ponce-de-León Rosales S, et al. Mycobacterium tuberculosis infection in patients with systemic rheumatic diseases. A case-series. Clin Exp Rheumatol 1999;17:289–96.
- 93 Hsia EC, Cush JJ, Matteson EL, et al. Comprehensive tuberculosis screening program in patients with inflammatory arthritides treated with golimumab, a human anti-tumor necrosis factor antibody, in phase III clinical trials. Arthritis Care Res 2013;65:309–13.
- 94 Kurt OK, Kurt B, Talay F, et al. Intermediate to long-term follow-up results of INH chemoprophylaxis prior to anti-TNF-alpha therapy in a high-risk area for tuberculosis. Wien Klin Wochenschr 2013;125:616–20.
- 95 Valls V, Ena J. Short-Course treatment of latent tuberculosis infection in patients with rheumatic conditions proposed for anti-TNF therapy. Clin Rheumatol 2015;34:29–34
- 96 Bray M-G, Poulain C, Dougados M, et al. Frequency and tolerance of antituberculosis treatment according to national guidelines for prevention of risk of tuberculosis due to tumor necrosis factor blocker treatment. Joint Bone Spine 2010;77:135–41.
- 97 Hazlewood GS, Naimark D, Gardam M, et al. Prophylaxis for latent tuberculosis infection prior to anti–tumor necrosis factor therapy in low-risk elderly patients with rheumatoid arthritis: a decision analysis. Arthritis Care Res 2013;65:1722–31.
- 98 Shen Y, Ma H-F, Luo D, et al. The T-SPOT.TB assay used for screening and monitoring of latent tuberculosis infection in patients with Behçet's disease pre- and post-anti-TNF treatment: a retrospective study. J Chin Med Assoc 2019;82:375–80.
- 99 Sichletidis L, Settas L, Spyratos D, et al. Tuberculosis in patients receiving anti-TNF agents despite chemoprophylaxis. Int J Tuberc Lung Dis 2006;10:1127–32.
- 100 Thomas K, Vassilopoulos D. Infections in patients with rheumatoid arthritis in the era of targeted synthetic therapies. *Mediterr J Rheumatol* 2020;31:129–36.
- 101 Watanabe A, Matsumoto T, Igari H, et al. Risk of developing active tuberculosis in rheumatoid arthritis patients on adalimumab in Japan. Int J Tuberc Lung Dis 2016:20:101–8.
- 102 Gómez-Reino JJ, Carmona L, Angel Descalzo M, et al. Risk of tuberculosis in patients treated with tumor necrosis factor antagonists due to incomplete prevention of reactivation of latent infection. Arthritis Rheum 2007;57:756–61.
- 103 Chen Y-M, Liao T-L, Chen H-H, et al. Three months of once-weekly isoniazid plus rifapentine (3Hp) in treating latent tuberculosis infection is feasible in patients with rheumatoid arthritis. Ann Rheum Dis 2018;77:1688–9.
- 104 Gaitonde S, Pathan E, Sule A, et al. Efficacy of isoniazid prophylaxis in patients with systemic lupus erythematosus receiving long term steroid treatment. Ann Rheum Dis 2002;61:251–3.
- 105 Shobha V, Chandrashekara S, Rao V, et al. Biologics and risk of tuberculosis in autoimmune rheumatic diseases: a real-world clinical experience from India. Int J Rheum Dis 2019;22:280–7.
- 106 Shobha V, Rao V, Desai A. Prescribing patterns and safety of biologics in immunemediated rheumatic diseases: Karnataka biologics cohort study Group experience. *Indian Journal of Rheumatology* 2019;14:17–20.
- 107 Song YJ, Cho SK, Kim H, et al. Risk of tuberculosis development in patients with rheumatoid arthritis receiving targeted therapy: a prospective single center cohort study. J Korean Med Sci 2021;36:e70.
- 108 Bourré-Tessier J, Arino-Torregrosa M, Choquette D. Increased incidence of liver enzymes abnormalities in patients treated with isoniazid in combination with disease modifying and/or biologic agents. Clin Rheumatol 2014;33:1049–53.
- 109 Vanhoof J, Landewe S, Van Wijngaerden E, et al. High incidence of hepatotoxicity of isoniazid treatment for tuberculosis chemoprophylaxis in patients with rheumatoid arthritis treated with methotrexate or sulfasalazine and anti-tumour necrosis factor inhibitors. Ann Rheum Dis 2003;62:1241–2.
- 110 Nam SH, Oh JS, Hong S, et al. Early discontinuation of tofacitinib in patients with rheumatoid arthritis co-treated with rifampin for latent tuberculosis. *Joint Bone* Spine 2020;87:475–9.
- 111 McAllister WA, Thompson PJ, Al-Habet SM, et al. Rifampicin reduces effectiveness and bioavailability of prednisolone. Br Med J 1983;286:923–5.
- 112 Myint A, Tong MJ, Beaven SW. Reactivation of hepatitis B virus: a review of clinical guidelines. Clin Liver Dis 2020;15:162–7.
- 113 Rondaan C, Furer V, Heijstek MW, et al. Efficacy, immunogenicity and safety of vaccination in adult patients with autoimmune inflammatory rheumatic diseases: a systematic literature review for the 2019 update of EULAR recommendations. RMD Open 2019;5:e001035.
- 114 Lin T-C, Yoshida K, Tedeschi SK, et al. Risk of hepatitis B virus reactivation in patients with inflammatory arthritis receiving disease-modifying antirheumatic drugs: a systematic review and meta-analysis. Arthritis Care Res 2018;70:724–31.

- 115 Su J, Long L, Zou K. Antiviral prophylaxis for preventing reactivation of hepatitis B virus in rheumatic patients: a systematic review and meta-analysis. *Clin Rheumatol* 2018;37:3201–14.
- 116 Kalyoncu U, Emmungil H, Onat AM, et al. Current antiviral practice and course of hepatitis B virus infection in inflammatory arthritis: a multicentric observational study (A + HBV study). Eur J Rheumatol 2015;2:149–54.
- 117 Kalyoncu U, Yonem O, Calguneri M, et al. Prophylactic use of lamivudine with chronic immunosuppressive therapy for rheumatologic disorders. Rheumatol Int 2009:29:777–80
- 118 Lin WT, Chen YM, Chen DY, et al. Increased risk of hepatitis B virus reactivation in systemic lupus erythematosus patients receiving immunosuppressants: a retrospective cohort study. Lupus 2018;27:66–75.
- 119 Matsuzaki T, Eguchi K, Nagao N, et al. Hepatitis B virus reactivation in patients with rheumatoid arthritis: a single-center study. Mod Rheumatol 2018;28:808–13.
- 120 Mo Y-Q, Liang A-Q, Ma J-D, et al. Discontinuation of antiviral prophylaxis correlates with high prevalence of hepatitis B virus (HBV) reactivation in rheumatoid arthritis patients with HBV carrier state: a real-world clinical practice. BMC Musculoskelet Disord 2014;15:449.
- 121 Tan J, Zhou J, Zhao P, et al. Prospective study of HBV reactivation risk in rheumatoid arthritis patients who received conventional disease-modifying antirheumatic drugs. Clin Rheumatol 2012;31:1169–75.
- 122 Chen M-H, Wu C-S, Chen M-H, et al. High risk of viral reactivation in hepatitis B patients with systemic lupus erythematosus. Int J Mol Sci 2021;22. doi:10.3390/ijms22179116. [Epub ahead of print: 24 Aug 2021].
- 123 Ming-Xu H, Chen M, Cai Y, et al. Clinical outcomes of low-dose leflunomide for rheumatoid arthritis complicated with hepatitis B virus carriage and safety observation. Pak J Med Sci 2015;31:320–4.
- 124 Chen M-H, Chen M-H, Liu C-Y, et al. Hepatitis B virus reactivation in rheumatoid arthritis patients undergoing biologics treatment. J Infect Dis 2017;215:566–73.
- 125 Jeong W, Choe J, Song BC. Effect of low-dose corticosteroid use on HBV reactivation in HBsAg-positive rheumatoid arthritis patients. The Open Rheumatology Journal 2021:15:39—46.
- 126 Chen L-F, Mo Y-Q, Jing J, et al. Short-Course tocilizumab increases risk of hepatitis B virus reactivation in patients with rheumatoid arthritis: a prospective clinical observation. Int J Rheum Dis 2017;20:859–69.
- 127 Giardina AR, Ferraro D, Ciccia F, et al. No detection of occult HBV-DNA in patients with various rheumatic diseases treated with anti-TNF agents: a two-year prospective study. Clin Exp Rheumatol 2013;31:25–30.
- Kuo MH, Tseng C-W, Lu M-C, et al. Risk of hepatitis B virus reactivation in rheumatoid arthritis patients undergoing Tocilizumab-Containing treatment. Dig Dis Sci 2021:66:4026–34.
- 129 Lan J-L, Chen Y-M, Hsieh T-Y, et al. Kinetics of viral loads and risk of hepatitis B virus reactivation in hepatitis B core antibody-positive rheumatoid arthritis patients undergoing anti-tumour necrosis factor alpha therapy. Ann Rheum Dis 2011;70:1719–25.
- 130 Padovan M, Filippini M, Tincani A, et al. Safety of abatacept in rheumatoid arthritis with serologic evidence of past or present hepatitis B virus infection. Arthritis Care Res 2016:68:738–43.
- 131 Vassilopoulos D, Apostolopoulou A, Hadziyannis E, et al. Long-Term safety of anti-TNF treatment in patients with rheumatic diseases and chronic or resolved hepatitis B virus infection. Ann Rheum Dis 2010;69:1352–5.
- 132 Ye H, Zhang X-wu, Mu R, et al. Anti-TNF therapy in patients with HBV infection-analysis of 87 patients with inflammatory arthritis. Clin Rheumatol 2014;33:119–23.
- 133 Zingarelli S, Frassi M, Bazzani C, *et al*. Use of tumor necrosis factor-alpha-blocking agents in hepatitis B virus-positive patients: reports of 3 cases and review of the literature. *J Rheumatol* 2009;36:1188–94.
- 134 Ryu HH, Lee EY, Shin K, *et al.* Hepatitis B virus reactivation in rheumatoid arthritis and ankylosing spondylitis patients treated with anti-TNFα agents: a retrospective analysis of 49 cases. *Clin Rheumatol* 2012;31:931–6.
- 135 Wang S-T, Tseng C-W, Hsu C-W, et al. Reactivation of hepatitis B virus infection in patients with rheumatoid arthritis receiving tofacitinib. Int J Rheum Dis 2021;24:1362–9.
- 136 Chen Y-M, Huang W-N, Wu Y-D, et al. Reactivation of hepatitis B virus infection in patients with rheumatoid arthritis receiving tofacitinib: a real-world study. Ann Rheum Dis 2018;77:780–2.
- 137 Reddy KR, Beavers KL, Hammond SP, et al. American gastroenterological association Institute guideline on the prevention and treatment of hepatitis B virus reactivation during immunosuppressive drug therapy. Gastroenterology 2015;148:215–9. quiz e16-7.
- 138 Koutsianas C, Thomas K, Vassilopoulos D. Reactivation of hepatitis B virus infection in rheumatic diseases: risk and management considerations. *Ther Adv Musculoskelet Dis* 2020;12:1759720x20912646.
- 139 Sasadeusz J, Grigg A, Hughes PD, et al. Screening and prophylaxis to prevent hepatitis B reactivation: other populations and newer agents. Clin Liver Dis 2019:23:521–34.
- 140 Barone M, Notarnicola A, Lopalco G, et al. Safety of long-term biologic therapy in rheumatologic patients with a previously resolved hepatitis B viral infection. Hepatology 2015;62:40–6.

- 141 Fukuda W, Hanyu T, Katayama M, et al. Incidence of hepatitis B virus reactivation in patients with resolved infection on immunosuppressive therapy for rheumatic disease: a multicentre, prospective, observational study in Japan. Ann Rheum Dis 2017;76:1051–6.
- 142 Fukuda W, Hanyu T, Katayama M, et al. Risk stratification and clinical course of hepatitis B virus reactivation in rheumatoid arthritis patients with resolved infection: final report of a multicenter prospective observational study at Japanese red cross Hospital. Arthritis Res Ther 2019;21:255.
- 143 Laohapand C, Arromdee E, Tanwandee T. Long-Term use of methotrexate does not result in hepatitis B reactivation in rheumatologic patients. *Hepatol Int* 2015;9:202
- 144 Schwaneck EC, Krone M, Kreissl-Kemmer S, et al. Management of anti-HBc-positive patients with rheumatic diseases treated with disease-modifying antirheumatic drugs-a single-center analysis of 2054 patients. Clin Rheumatol 2018;37:2963–70.
- 145 Cantini F, Boccia S, Goletti D, et al. Hbv reactivation in patients treated with antitumor necrosis factor-alpha (TNF-α) agents for rheumatic and dermatologic conditions: a systematic review and meta-analysis. Int J Rheumatol 2014;2014:926836.
- 146 Mori S. Do low titers of antibody against hepatitis B surface antigen carry a risk of viral reactivation during immunosuppressive therapy for rheumatic diseases? J Rheumatol 2012;39:1292–3.
- 147 Chen M-H, Chen M-H, Chou C-T, et al. Low but long-lasting risk of reversal of seroconversion in patients with rheumatoid arthritis receiving immunosuppressive therapy. Clin Gastroenterol Hepatol 2020;18:2573–81.
- 148 Urata Y, Uesato R, Tanaka D, et al. Prevalence of reactivation of hepatitis B virus replication in rheumatoid arthritis patients. Mod Rheumatol 2011;21:16–23.
- 149 Caporali R, Bobbio-Pallavicini F, Atzeni F, et al. Safety of tumor necrosis factor alpha blockers in hepatitis B virus occult carriers (hepatitis B surface antigen negative/ anti-hepatitis B core antigen positive) with rheumatic diseases. Arthritis Care Res 2010;62:749–54.
- 150 Charpin C, Guis S, Colson P, et al. Safety of TNF-blocking agents in rheumatic patients with serology suggesting past hepatitis B state: results from a cohort of 21 patients. Arthritis Res Ther 2009;11:R179.
- 151 Giannitti C, Lopalco G, Vitale A, et al. Long-Term safety of anti-TNF agents on the liver of patients with spondyloarthritis and potential occult hepatitis B viral infection: an observational multicentre study. Clin Exp Rheumatol 2017;35:93–7.
- 152 Kim YJ, Bae S-C, Sung Y-K, et al. Possible reactivation of potential hepatitis B virus occult infection by tumor necrosis factor-alpha blocker in the treatment of rheumatic diseases. J Rheumatol 2010;37:346–50.
- 153 Lau CS, Chia F, Dans L, et al. 2018 update of the APLAR recommendations for treatment of rheumatoid arthritis. Int J Rheum Dis 2019;22:357–75.
- 154 Fraenkel L, Bathon JM, England BR. American College of rheumatology guideline for the treatment of rheumatoid arthritis. Arthritis Rheumatol 2021;2021:1108–23.
- 155 European Association for the Study of the Liver. Electronic address eee, European association for the study of the L. EASL 2017 clinical practice guidelines on the management of hepatitis B virus infection. J Hepatol 2017;67:370–98.
- 156 Mok CC. Hepatitis B and C infection in patients undergoing biologic and targeted therapies for rheumatic diseases. Best Pract Res Clin Rheumatol 2018;32:767–80.
- 157 Terrault NA, Lok ASF, McMahon BJ, et al. Update on prevention, diagnosis, and treatment of chronic hepatitis B: AASLD 2018 hepatitis B guidance. Hepatology 2018;67:1560–99.
- 158 Chen Y-M, Chen H-H, Huang W-N, et al. Reactivation of hepatitis B virus infection following rituximab treatment in HBsAg-negative, HBcAb-positive rheumatoid arthritis patients: a long-term, real-world observation. Int J Rheum Dis 2019;22:1145–51.
- 159 Kuo MH, Tseng C-W, Lee C-H, et al. Moderate Risk of Hepatitis B Virus Reactivation in HBsAg'/HBcAb⁺ Carriers Receiving Rituximab for Rheumatoid Arthritis. Sci Rep 2020:10:2456
- 160 Watanabe T, Fukae J, Fukaya S, et al. Incidence and risk factors for reactivation from resolved hepatitis B virus in rheumatoid arthritis patients treated with biological disease-modifying antirheumatic drugs. Int J Rheum Dis 2019:22:574–82.
- 161 Tien Y-C, Yen H-H, Li C-F, et al. Changes in hepatitis B virus surface antibody titer and risk of hepatitis B reactivation in HBsAg-negative/HBcAb-positive patients undergoing biologic therapy for rheumatic diseases: a prospective cohort study. Arthritis Res Ther 2018;20:246.
- 162 Chen M-H, Lee I-C, Chen M-H, et al. Abatacept is second to rituximab at risk of HBsAg reverse seroconversion in patients with rheumatic disease. Ann Rheum Dis 2021;80:1393–9.
- 163 Kato M, Atsumi T, Kurita T, et al. Hepatitis B virus reactivation by immunosuppressive therapy in patients with autoimmune diseases: risk analysis in hepatitis B surface antigen-negative cases. J Rheumatol 2011;38:2209–14.
- 64 Karadağ Ömer, Kaşifoğlu T, Özer B, *et al*. Viral hepatitis screening guideline before biological drug use in rheumatic patients. *Eur J Rheumatol* 2016;3:25–8.
- 165 Sebastiani M, Atzeni F, Milazzo L, et al. Italian consensus guidelines for the management of hepatitis B virus infections in patients with rheumatoid arthritis. Joint Bone Spine 2017:84:525–30.
- 166 Brunasso AMG, Puntoni M, Gulia A, et al. Safety of anti-tumour necrosis factor agents in patients with chronic hepatitis C infection: a systematic review. Rheumatology 2011;50:1700–11.

- 167 Costa L, Caso F, Atteno M, et al. Long-Term safety of anti-TNF-α in PSA patients with concomitant HCV infection: a retrospective observational multicenter study on 15 patients. Clin Rheumatol 2014;33:273–6.
- 168 Parke FA, Reveille JD. Anti-Tumor necrosis factor agents for rheumatoid arthritis in the setting of chronic hepatitis C infection. *Arthritis Rheum* 2004;51:800–4.
- 169 Peterson JR, Hsu FC, Simkin PA, et al. Effect of tumour necrosis factor alpha antagonists on serum transaminases and viraemia in patients with rheumatoid arthritis and chronic hepatitis C infection. Ann Rheum Dis 2003;62:1078–82.
- 170 Gandhi NP, Manadan AM, Block JA. Retrospective study of patients on etanercept therapy for rheumatic diseases in patients with chronic hepatitis C virus. J Clin Rheumatol 2017;23:252–7.
- 171 Holroyd CR, Seth R, Bukhari M, et al. The British Society for rheumatology biologic DMARD safety quidelines in inflammatory arthritis. Rheumatology 2019;58:e3–42.
- 172 Sebastiani M, Milazzo L, Atzeni F, et al. Italian consensus recommendations for the management of hepatitis C infection in patients with rheumatoid arthritis. Mod Rheumatol 2019;29:895–902.
- 173 Chen M-H, Chen M-H, Tsai C-Y, et al. Incidence and antiviral response of hepatitis C virus reactivation in lupus patients undergoing immunosuppressive therapy. Lupus 2015;24:1029–36.
- 174 Lin K-M, Cheng T-T, Lin J-C, et al. Tumor necrosis factor-α antagonist therapy for concomitant rheumatoid arthritis and hepatitis C virus infection: a case series study. Clin Rheumatol 2015;34:1039–46.
- 175 Caso F, Cantarini L, Morisco F, et al. Current evidence in the field of the management with TNF-α inhibitors in psoriatic arthritis and concomitant hepatitis C virus infection. Expert Opin Biol Ther 2015;15:641–50.
- 176 Mosca M, Tani C, Aringer M, et al. European League against rheumatism recommendations for monitoring patients with systemic lupus erythematosus in clinical practice and in observational studies. Ann Rheum Dis 2010;69:1269–74.
- 177 Visser K, Katchamart W, Loza E, et al. Multinational evidence-based recommendations for the use of methotrexate in rheumatic disorders with a focus on rheumatoid arthritis: integrating systematic literature research and expert opinion of a broad international panel of rheumatologists in the 3E initiative. Ann Rheum Dis 2009;68:1086–93.
- 178 Cates M, Donati M, Gillet S, et al. Managing varicella zoster virus contact and infection in patients on anti-rheumatic therapy. Rheumatology 2018;57:596–605.
- 179 Winthrop KL, Tanaka Y, Lee EB, et al. Prevention and management of herpes zoster in patients with rheumatoid arthritis and psoriatic arthritis: a clinical review. Clin Exp Rheumatol 2022;40:162–72.
- 180 Guillevin L. Infections in vasculitis. Best Pract Res Clin Rheumatol 2013;27:19–31.
- 181 Lortholary O, Fernandez-Ruiz M, Baddley JW, et al. Infectious complications of rheumatoid arthritis and psoriatic arthritis during targeted and biological therapies: a viewpoint in 2020. Ann Rheum Dis 2020;79:1532–43.
- 182 Honda N, Tagashira Y, Kawai S, et al. Reduction of Pneumocystis jirovecii pneumonia and bloodstream infections by trimethoprim-sulfamethoxazole prophylaxis in patients with rheumatic diseases. Scand J Rheumatol 2021;50:1–7.
- Park JW, Curtis JR, Kim MJ, et al. Pneumocystis pneumonia in patients with rheumatic diseases receiving prolonged, non-high-dose steroids-clinical implication of primary prophylaxis using trimethoprim-sulfamethoxazole. Arthritis Res Ther 2019:21:207.
- 184 Park JW, Curtis JR, Moon J, et al. Prophylactic effect of trimethoprimsulfamethoxazole for Pneumocystis pneumonia in patients with rheumatic diseases exposed to prolonged high-dose glucocorticoids. Ann Rheum Dis 2018;77:644–9.
- 185 Ogawa J, Harigai M, Nagasaka K, et al. Prediction of and prophylaxis against Pneumocystis pneumonia in patients with connective tissue diseases undergoing medium- or high-dose corticosteroid therapy. Mod Rheumatol 2005;15:91–6.
- 186 Vananuvat P, Suwannalai P, Sungkanuparph S, et al. Primary prophylaxis for Pneumocystis jirovecii pneumonia in patients with connective tissue diseases. Semin Arthritis Rheum 2011;41:497–502.
- 187 Wolfe RM, Peacock JE. Pneumocystis pneumonia and the rheumatologist: which patients are at risk and how can PCP be prevented? Curr Rheumatol Rep 2017;19:35.
- 188 Katsuyama T, Saito K, Kubo S, et al. Prophylaxis for Pneumocystis pneumonia in patients with rheumatoid arthritis treated with biologics, based on risk factors found in a retrospective study. Arthritis Res Ther 2014;16:R43.

- 189 Meuli K, Chapman P, O'Donnell J, et al. Audit of Pneumocystis pneumonia in patients seen by the Christchurch Hospital rheumatology service over a 5-year period. Intern Med J 2007;37:687–92.
- 190 Vela Casasempere P, Ruiz Torregrosa P, García Sevila R. Pneumocystis jirovecii in immunocompromised patients with rheumatic diseases. *Reumatol Clin* 2021:17:290–6.
- 191 Harada T, Kato R, Sueda Y, et al. The efficacy and safety of reduced-dose sulfamethoxazole-trimethoprim for chemoprophylaxis of *Pneumocystis* pneumonia in patients with rheumatic diseases. Mod Rheumatol 2021;31:1–7.
- 192 Takenaka K, Komiya Y, Ota M, et al. A dose-escalation regimen of trimethoprimsulfamethoxazole is tolerable for prophylaxis against Pneumocystis jiroveci pneumonia in rheumatic diseases. Mod Rheumatol 2013;23:752–8.
- 193 Utsunomiya M, Dobashi H, Odani T, et al. An open-label, randomized controlled trial of sulfamethoxazole-trimethoprim for *Pneumocystis* prophylaxis: results of 52-week follow-up. *Rheumatol Adv Pract* 2020;4:rkaa029.
- 194 Utsunomiya M, Dobashi H, Odani T, et al. Optimal regimens of sulfamethoxazoletrimethoprim for chemoprophylaxis of Pneumocystis pneumonia in patients with systemic rheumatic diseases: results from a non-blinded, randomized controlled trial. Arthritis Res Ther 2017;19:7.
- 195 Suyama Y, Okada M, Rokutanda R, et al. Safety and efficacy of upfront graded administration of trimethoprim-sulfamethoxazole in systemic lupus erythematosus: a retrospective cohort study. Mod Rheumatol 2016;26:557–61.
- 196 Wallace ZS, Choi H, Stone JH. Risk of severe infection following rituximab and the efficacy of antimicrobial prophylaxis. *Ann Rheum Dis* 2020;79:e40.
- 197 Suyama Y, Okada M. Can we prescribe TMP/SMX prophylaxis without any concerns equally for all patients with rheumatic disease? *Ann Rheum Dis* 2019;78:e17.
- 198 Sonomoto K, Tanaka H, Nguyen TM. Prophylaxis against Pneumocystis pneumonia in rheumatoid arthritis patients treated with b/tsDMARDs: insights from 3,787 cases in first registry. Rheumatology 2021.
- 199 Jinno S, Akashi K, Onishi A, et al. Comparative effectiveness of trimethoprimsulfamethoxazole versus atovaquone for the prophylaxis of Pneumocystis pneumonia in patients with connective tissue diseases receiving prolonged high-dose glucocorticoids. Rheumatol Int 2022;42:1403–9.
- 200 Kitazawa T, Seo K, Yoshino Y, et al. Efficacies of atovaquone, pentamidine, and trimethoprim/sulfamethoxazole for the prevention of Pneumocystis jirovecii pneumonia in patients with connective tissue diseases. J Infect Chemother 2019;25:351–4.
- 201 Schmajuk G, Jafri K, Evans M, et al. Pneumocystis jirovecii pneumonia (PJP) prophylaxis patterns among patients with rheumatic diseases receiving high-risk immunosuppressant drugs. Semin Arthritis Rheum 2019;48:1087–92.
- 202 Landewé RBM, Kroon FPB, Alunno A, et al. EULAR recommendations for the management and vaccination of people with rheumatic and musculoskeletal diseases in the context of SARS-CoV-2: the November 2021 update. Ann Rheum Dis 2022;81:1628–39.
- 203 Yates M, Watts RA, Bajema IM, et al. EULAR/ERA-EDTA recommendations for the management of ANCA-associated vasculitis. Ann Rheum Dis 2016;75:1583–94.
- 204 Fanouriakis A, Kostopoulou M, Alunno A. Update of the EULAR recommendations for the management of systemic lupus erythematosus. *Ann Rheum Dis* 2019:2019:736–45.
- 205 Davies R, Dixon WG, Watson KD, et al. Influence of anti-TNF patient warning regarding avoidance of high risk foods on rates of Listeria and Salmonella infections in the UK. Ann Rheum Dis 2013;72:461–2.
- 206 Bradshaw MJ, Cho TA, Chow FC. Central nervous system infections associated with immunosuppressive therapy for rheumatic disease. Rheum Dis Clin North Am 2017:43:607–19.
- 207 Orenstein R, Matteson EL. Opportunistic infections associated with TNF-α treatment. Fut Rheumatol 2007;2:567–76.
- 208 Furer V, Rondaan C, Heijstek MW. Update of EULAR recommendations for vaccination in adult patients with autoimmune inflammatory rheumatic diseases. *Ann Rheum Dis* 2020;79:39–52.
- 209 Edelaar L, Nikiphorou E, Fragoulis GE. EULAR recommendations for the generic core competences of health professionals in rheumatology. *Ann Rheum Dis* 2020;79:53–60.