RMD Open
Rheumatic & Musculoskeletal Diseases

REVIEW

Systematic literature review informing the 2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases

George E Fragoulis ,[1,2] Mrinalini Dey ,[3,4] Sizheng Zhao,[5] Jan Schoones,[6] Delphine Courvoisier ,[7] James Galloway ,[8,9] Kimme L Hyrich,[5,10] Elena Nikiphorou [8,9]

To cite: Fragoulis GE, Dey M, Zhao S, *et al*. Systematic literature review informing the 2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases. *RMD Open* 2022;**8**:e002726. doi:10.1136/rmdopen-2022-002726

► Additional supplemental material is published online only. To view, please visit the journal online (http://dx.doi.org/10.1136/rmdopen-2022-002726).

Received 10 September 2022
Accepted 12 October 2022

For numbered affiliations see end of article.

Correspondence to
Dr Elena Nikiphorou;
enikiphorou@gmail.com

ABSTRACT

Objective To conduct a systematic literature review (SLR) on the screening and prophylaxis of opportunistic and chronic infections in autoimmune inflammatory rheumatic diseases (AIIRD).

Methods SLR (inception-12/2021) based on the following search domains: (1) infectious agents, (2) AIIRD, (3) immunosuppressives/immunomodulators used in rheumatology, (4) screening terms and (5) prophylaxis terms. Articles were retrieved having the terms from (1) AND (2) AND (3) plus terms from (4) OR(5). Databases searched: PubMed, Embase and Cochrane Library. Exclusion criteria: studies on postoperative infections, paediatric AIIRD, COVID-19, vaccinations and non-English literature. Study quality was assessed with Newcastle-Ottawa scale for non-randomised controlled trials (RCTs), RoB-Cochrane for RCTs, AMSTAR2 for SLRs.

Results From 5641 studies were retrieved, 568 full-text articles were assessed for eligibility, with 194 articles finally included. For tuberculosis, tuberculin skin test (TST) is affected by treatment with glucocorticoids and conventional synthetic disease modifying anti-rheumatic drugs (DMARDs) and its performance is inferior to interferon gamma release assay (IGRA). Agreement between TST and IGRA is moderate to low. For hepatitis B virus (HBV): risk of reactivation is increased in patients positive for hepatitis B surface antigen. Anti-HBcore positive patients are at low risk for reactivation but should be monitored periodically with liver function tests and/or HBV-viral load. Risk for Hepatitis C reactivation is existing but low in patients treated with biological DMARDs. For *Pneumocystis jirovecii*, prophylaxis treatment should be considered in patients treated with prednisolone ≥15–30 mg/day for >2–4 weeks.

Conclusions Different screening and prophylaxis approaches are described in the literature, partly determined by individual patient and disease characteristics.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Opportunistic and chronic infections are relatively common in the setting of autoimmune inflammatory rheumatic diseases (AIIRD). However, recommendations for the screening and prophylaxis of such infections are lacking, at least at European level.

WHAT THIS STUDY ADDS

This systematic literature review (SLR) highlights that:

⇒ Interferon gamma release assay performs better than tuberculin skin test for latent tuberculosis screening.

⇒ Risk of hepatitis B virus (HBV) reactivation is higher in patients positive for HBV surface antigen (HBsAg) compared with those positive for antibody against HBV core antigen (anti-HBcore).

⇒ Prophylaxis against Pneumocystis jirovecii should be considered in patients treated with prednisolone ≥15–30 mg/day for >2–4 weeks.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This SLR is the first to address the specific topic and has been used to inform the 2022 European Alliance of Associations for Rheumatology recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases (AIIRD).

INTRODUCTION

There is a strong association between auto-Immune inflammatory rheumatic diseases (AIIRD) and the occurrence of infections. The reasons behind this are multifactorial and relate to several factors including the underlying mechanistic pathways that lead to

dysregulation of the immune system as well as the effects of treatments used.[1 2] Infections are associated with significant morbidity and mortality and additionally come with a substantial cost-burden for healthcare systems largely due to additional treatment and hospitalisation needs.[3] Furthermore, treatment of AIIRD may need to be put on hold when infections occur.

Opportunistic and chronic infections in AIIRD often arise in the context of immunosuppressive/immunomodulatory treatment, although it is thought that some of these infections may be preventable if appropriate steps are taken. It is unanimously recognised that screening procedures and prophylactic measures should be followed. However, due to several reasons including geo-epidemiological differences between countries/regions, relevant recommendations are disparately located across the literature or have not been developed at all in the context of AIIRD.[4 5] As a result, diverse screening and prevention strategies are being followed currently among AIIRD in clinical settings. The latter relates also, at least in part, to the different pharmacological therapies used, with guidelines often developed specifically for certain treatments only (eg, biological disease modifying antirheumatic drugs (bDMARDs)).

Recognising the lack of or variability in guidance for clinicians for the screening and prophylaxis of chronic and opportunistic infections in AIIRD, a European Alliance of Associations for Rheumatology (EULAR) Task Force (TF) was convened with the task of developing recommendations at European level. As part of this work, a systematic literature review (SLR) focusing on screening procedures and prophylactic measures for chronic and opportunistic infections in the setting of AIIRD was undertaken to inform the '2022 EULAR recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with AIIRD'.

METHODS

The review protocol for this SLR was developed by the steering committee of the taskforce, in a Patients, Intervention, Comparator or Control, Outcome, (PICO) structure, as per the EULAR Standard Operating Procedure.[6] The SLR was undertaken according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines and was registered in PROSPERO (No: CRD42021244732).

Eligibility criteria and literature search

During the first TF meeting, two research questions were agreed as important and relevant to address as part of the topic under study: Research question 1: Which opportunistic and chronic infections in people with AIIRD can and should we screen for? Research question 2: What screening and prophylaxis can we use and does it work? The following PICO structure was agreed: P—People with AIIRD, I—Immunosuppression/immunomodulation (including steroids), C—People with AIIRD not on immunosuppression, O1—screening and prophylaxis, O2—effectiveness of screening and prophylaxis.

The population of interest was patients ≥18 years with any AIIRD. The latter included: Systemic lupus erythematosus (SLE), antiphospholipid syndrome, Sjogren's syndrome, rheumatoid arthritis (RA), psoriatic arthritis (PsA), seronegative spondyloarthritis, ankylosing spondylitis, Behcet's disease, ANCA-vasculitis (AAV), cryoglobulinaemic vasculitis, polymyalgia rheumatica, Takayasu arteritis, giant-cell arteritis, polyarteritis nodosa, inflammatory myopathy, dermatomyositis, IgG4-related disease, relapsing polychondritis, autoinflammatory diseases (including familial Mediterranean fever, Still's disease), systemic sclerosis. The intervention was any drugs used to treat AIIRD that supress or modulate the immune system including glucocorticoids. The nomenclature followed in this SLR was extensively discussed by the TF and consensus was reached on the following terms, which adopted a modified version of recently published expert opinions and studies[7–9]: biologic- targeted synthetic DMARDs (b-ts-DMARDs): all b-ts-DMARDs, conventional synthetic (cs) DMARDs: methotrexate, leflunomide, sulfasalazine and hydroxychloroquine, other immunosuppressants: cyclophosphamide, mycophenolate mofetil, azathioprine, cyclosposrin and tacrolimus.

Preliminary work included an initial scoping review presented during the first TF meeting which identified the pathogens that can and should be screened for in patients with AIIRD. TF members, including experts in infectious diseases, pulmonologists and rheumatologists with a special interest in infectious diseases, reviewed the list and added any other pathogens that were deemed relevant to include. Screening and prophylaxis strategies for these pathogens were indicated as the outcomes to focus on (online supplemental material 1).

The search strategy for the SLR consisted of the combination of the five concepts (Infection AND AIIRD AND Immunosuppression AND (Screening OR Prophylaxis)), using all relevant keyword variations, not only keyword variations in the controlled vocabularies of the consulted databases, but the free text word variations of these concepts too. The search strategy was optimised for all databases, taking into account the differences of the various controlled vocabularies as well as the differences of database-specific technical variations (eg, the use of quotation marks). The following databases were used: PubMed, Embase (OVID version) and Cochrane Library (details are provided in the online supplemental material 1).

Study selection, data extraction and quality assessment

Studies that had information relevant to the PICO questions and published in the English language from inception to 5 December 2021 were included, excluding articles concerning perioperative or postoperative infections, vaccinations, COVID-19, infections in non-AIIRD patients (eg, septic arthritis), procedures other than screening and prophylaxis in AIIRD. Case reports and meeting abstract references were also excluded.

Titles and abstracts and the full text, if necessary, were screened for eligibility by the main fellow (GEF) with a second fellow (MD) screening independently a random 20% sample. Data extraction was undertaken in the same way, with the main fellow (GF) completing data extraction on all articles and a second fellow (SZ) repeating the extraction on a random 20% sample, as part of a validation exercise. Any disagreements in the cross-validation exercises above were discussed and resolved with the TF methodologists (EN and DC). References from included studies were searched manually to identify any additional articles.

The quality of the studies selected was assessed by the main fellow (GEF) with the other two fellows (MD and SZ) assessing independently a random 40% (20% each) sample. The following tools were used: the Cochrane risk-of-bias tool[10] (score for risk of bias: low, high and some concerns) for randomised controlled trials (RCTs); the Newcastle-Ottawa scale (score 0–9) for cohort and case-control studies[11]; the AMSTAR 2 tool (quality score: critically low, low, moderate and high) for SLRs.[12]

RESULTS

A total of 5641 articles were retrieved from the initial search. Following deduplication, 3929 articles were screened and 568 full-text articles were assessed for eligibility, where eventually 194 articles were included in the SLR (Supplementary Figure 1). Agreement between assessors was high (98%) for the title/abstract and full text screening of articles, as well as for data extraction and 97% for the assessment of the quality of the studies. Retrieved articles were categorised by type of organism under study. Namely: tuberculosis (TB), hepatitis B virus (HBV), hepatitis C virus (HCV), *Pneumocystis jirovecii*, other viruses and other pathogens.

Tuberculosis

Screening for TB in clinical practice typically includes a chest-X-ray with a tuberculin skin test (TST) and/or Interferon gamma release assays (IGRA). Studies suggest the use of different screening strategies, depending on national guidelines and TB burden for each region.

Previous BCG vaccination seems to be associated with false positive TST,[13–15] although this association was attenuated in multivariable analysis in one study.[16] The association of previous BCG vaccination with TST has also been reported in a meta-analysis including 11 studies with a total of 1940 patients.[17] Similarly, most[15 18–22 23] but not all[16 24 25] studies, including a meta-analysis[17] suggest that treatment with glucocorticoids (even at low doses) could lead to false negative TST tests (table 1). Studies are inconclusive for a possible effect of csDMARD use on the performance of TST[16 18 19 24 26] (table 1), while bDMARD use does not seem to lead to false-positive results.[27–29]

For IGRA, although it has been suggested that a recent TST could produce a false-positive IGRA result, this has not been confirmed. In a study examining IGRA responses before and after TST, it was found that interferon response was augmented; however, IGRA remained negative.[18] As shown in a meta-analysis, IGRA do not seem to be affected by concurrent treatment with csDMARDs or glucocorticoids.[17 14 30 31 26] However, some evidence suggests that glucocorticoid use might lead to more frequent indeterminate IGRA results.[20 22] As regard to treatment with bDMARDs, one study suggested that treatment with TNF-inhibitors associates with false negative IGRA results,[30] which is in contrast to the findings of three other observational studies which found no effect.[27 28 32]

Several studies have shown that agreement between TST and IGRA is moderate (agreement range: 61%–88%)[14 15 17 18 33–50] (table 2). Disagreement between TST and IGRA has led some authors to suggest that both tests should be performed in high-risk patients (travelling or coming from endemic regions) and/or in countries with high TB-burden.[39 49 51] On the other hand, Quantiferon and enzyme-linked immunosorbent spot (ELISpot), two IGRA test platforms, appear to have good concordance[52–55] (table 2). Several studies have shown that IGRA display a better performance compared with TST, having better sensitivity and specificity and being associated more closely with TB risk factors.[13 14 17 19 25 30 55–57] Conversion of these tests from negative to positive after treatment with bDMARDs is not uncommon, varying from 2% to 33%,[43 45 49 58–69] possibly related to different TB burden across regions (online supplemental table 1).

Although screening is always performed before treatment with b-ts-DMARDs, there is some evidence that the risk of TB is also increased in patients treated with glucocorticoids, csDMARDs or other immunosuppressives. Brassard *et al*[70] obtained data from around 25 000 patients with RA. Fifty of them had TB (age-standardised incidence rate: 45.8/100.00 persons-year) and were compared, using a nested control analysis, with matched control subjects from the same cohort. It was found that the rate ratio (RR) for TB was 2.4 (95% CI 1.1 to 5.4) and 3.0 (95% CI 1.6 to 5.8) for treatment with glucocorticoids and csDMARDs, respectively. Use of csDMARDs was associated with TB occurrence (RR, 1.2; 95% CI 1.0 to 1.5, using the same methodology (comparison between TB cases with matched control subjects) and analysing data from 112 300 patients with RA.[71] Brode *et al*[72] analysed data from 56 269 patients with RA aged 67 years or older. Thirty-seven TB cases were identified and were compared with 363 matched controls. It was found that apart from treatment with TNF-inhibitors, treatment with leflunomide (adjusted OR 4.02 (95% CI 1.08 to 15.0) p=0.04) and with other drugs including cyclophosphamide, azathioprine, ciclosporin, mycophenolate and chlorambucil (adjusted OR 23.0 (95% CI 2.88 to 184) p=0.003) was associated with TB. Long *et al*[73] in a study of 1788 patients with AIIRD treated with glucocorticoids for at least 4 weeks, showed that development of TB (without receiving prophylaxis for latent TB reactivation) was more common (5.2%) in those having positive

Table 1 Factors affecting performance of tuberculosis screening tests

Author-year/country	Patients (N)	Disease	Association with TST			RoB
			BCG	GC	csDMARDs	
Ruan *et al*[17] 2016/NA*	1940	AIIRD	Positive OR: 1.64 (95% CI 1.06 to 2.53)	Negative OR 0.45 (95% CI 0.30 to 0.69)	–	High quality
Reitblat *et al*[24] 2018/ Israel	65	RA	–	No	No	7
Agarwal *et al*[23] 2014/USA	250	RA	–	Negative (mean dose†: 6.4), (p=0.002)	No	7
Hsia *et al*[13] 2012/ multinational	2303	IA	Positive (p<0.0002 vs IGRA)	–	–	7
Klein *et al*[18] 2013/Czech	305	AIIRD	–	Negative, (p=0.0172)	Negative (combination with GC) (p=0.0003)	6
Belard *et al* [22] 2011/ Denmark	248	AIIRD‡	–	Negative (p=0.018)	–	6
Soborg *et al*[20] 2009/ Denmark	302	IA	–	Negative RR 0.4 (95% CI 0.1 to 1.0), (p=0.04)	–	6
Tamborenea *et al*[21] *2009/Argentina*	105	RA	–	Negative (mean dose: 6 mg/day), OR 0.72 (95% CI 0.55 to 0.95), p=0.021	–	6
Vassilopoulos *et al*[15] 2008/Greece	70	AIIRD	Positive§	Negative (mean dose: 6.8 mg)¶	–	6
Arias-Guillen *et al*[26] 2018/Spain	393	IA	–	–	Positive (MTX) OR 2.15 (95% CI 1.05 to 4.44)	5
Maeda *et al*[14] 2011/ Japan	97	RA	Positive (14/19 false-positive TST)	–	–	5
Sargin *et al*[25] 2018/ Turkey	109	IA	–	No	–	4
Lee *et al*[16] 2012/South Korea	81	RA	No	–	–	4
Lee *et al*[16] 2012/South Korea	81	RA	–	No	No	4

Author-year/country	Patients (N)	Disease	Association** with IGRA	RoB
Ruan *et al*[17] 2016/NA	1940	AIIRD	No (GC, csDMARDs)	High quality
Vassilopoulos *et al*[55] 2011/Greece	155	AIIRD	Negative (GC, mean GC dose: 6.8 mg), (OR=0.31 95% CI 0.1 to 0.96; p=0.04)	6
Belard 2011 *et al*[22] / Dennmark	248	AIIRD‡	With indeterminate IGRA (GC), OR=6.1 95% CI 4.1 to 63.2; p<0.001)	6
Soborg *et al*[20] 2009/ Denmark	302	IA	With indeterminate IGRA (GC), RR 4.2 (95% CI 1.6 to 10.7, p=0.04)	6
Arias-Guillen *et al*[26] 2018/Spain	393	IA	No (MTX)	5
Maeda *et al*[14] 2011/ Japan	97	RA	No (GC, (mean dose prednisolone: 5.7 mg), MTX)	5
Shovman *et al*[31] 2009/ Israel	35	RA	No (GC, (mean dose prednisolone: 8.3 mg), MTX)	5
Matulis *et al*[30] 2008/UK	142	IMID	No (GC, csDMARDs)	5

Continued

Table 1 Continued

Author-year/country	Patients (N)	Disease	Association** with IGRA	RoB

*Meta-analysis.
†GC dose: prednisolone or equivalent.
‡93/244 patients had inflammatory bowel disease.
§BCG associated with TST-positive/IGRA-negative discordant status (p=0.01).
¶Associated with TST-negative/IGRA-positive discordant status (p=0.04).
**Association of GC or csDMARDs with IGRA.
AIIRD, autoimmune inflammatory rheumatic disease; csDMARDs, conventional synthetic DMARD; DMARDs, disease modifying anti-rheumatic drugs; GC, glucocorticoids; IA, inflammatory arthritis; IGRA, interferon releasee gamma assay; IMID, immune mediated disease; MTX, methotrexate; NA, not available; RA, rheumatoid arthritis; RoB, risk of bias; RR, risk ratio; TST, tuberculin skin test.

IGRA at baseline compared with those who did not (5.2% vs 0.45%, respectively, p<0.05) over a 2-year follow-up period. Treatment with prednisolone at doses greater than 15 mg/day was found to be a risk factor for TB reactivation. Another study, in patients with various diseases (including AIIRD and non-AIIRD patients) found that use of glucocorticoids was independently associated with TB (adjusted OR 4.9 (95% CI 2.9 to 8.3)). This association was stronger in patients receiving at least 15 mg of prednisone (OR) 7.7 (95% CI 2.8 to 21.4) compared with those receiving less than15 mg of prednisolone (or equivalent) (OR) 2.8 (95% CI 1.0 to 7.9).[74]

Various therapeutic regimes have been found to be effective for latent TB prophylaxis. In low TB-endemic countries[75] these include: isoniazid for 6–9 months; combination of rifampicin/isoniazid for 3 months; rifampicin for 4 months[76–89] (online supplemental table 2). For medium-to-high TB-endemic countries[75]: isoniazid 6–12 months; rifampicin/isoniazid for 3–4 months; rifampicin for 6 months alone and once-weekly therapy of isoniazid plus rifapentine for 3 months[51 58 64 90–94] (online supplemental table 3). Of note, in high-endemic countries prophylaxis for patients treated with steroids (usually more than 15 mg prednisolone or equivalent) has been suggested, irrespective of screening tests.[91 95] However, findings across studies remain contradictory.[96 97]

Hepatitis B

Screening for HBV would typically include HBV surface antigen (HBsAg), antibody against HBV core antigen (anti-HBcore) and antibody against HBV surface antigen (anti-HBs). Several studies have shown that patients who are positive for HBsAg are at high risk for reactivation, on treatment with DMARDs or other immunosuppressants. Data for prophylaxis are more robust for patients treated with bDMARDs[98–108] compared with other drug categories.[109–118] Coadministration of glucocorticoids has been identified as an additional risk factor.[111 115 117 119 120] Data from a meta-analysis show that reactivation was decreased in HBsAg-positive inflammatory arthritis patients who received antiviral prophylaxis compared with those who did not. A subanalysis showed that this was more evident for patients treated with TNF-inhibitors but not in those treated with csDMARDs.[121] Similar results were reported by Su *et al*[122] who showed that antiviral prophylaxis was effective for HBsAg-positive, patients with AIIRD in general, with the effect being more pronounced in patients treated with bDMARDs (online supplemental table 4).

For anti-HBcore-positive (but HBsAg-negative) patients, observational studies have shown that risk for reactivation on treatment with csDMARDs, other immunosuppressants or combination of anti-rheumatic drugs (including bDMARDs) is low, ranging from 0% to 10%[112 114–116 123–131] (table 3). In a prospective study including 188 anti-HBcore-positive patients with RA treated with csDMARDs without co-administration of prophylactic treatment, only two (1.1%) experienced HBV reactivation.[114] In another study, none of the 65 anti-HBcore-positive patients with RA treated with methotrexate experienced HBV reactivation over a 10-year period.[126] Similarly, in 36 anti-HBcore-positive patients with RA treated with leflunomide, no case of HBV reactivation was recorded.[116] Finally, in another study 3.2% of 63 anti-HBcore-positive SLE patients, experienced HBV reactivation on treatment with glucocorticoids or immunosuppressants. Of note, receiving glucocorticoids and specifically more than 10 mg of prednisolone or equivalent was an independent risk factor for HBV reactivation in this study.[115]

Evidence for the effect of glucocorticoids remains generally scarce.[120 132–136] A study published after the time frame of this SLR, showed that anti-HBcore-positive patients with uveitis, treated with time-weighted (cumulative dose/drug duration (days)) prednisone more than 20 mg/day were at high risk (incidence more than 10/100 persons-years) of HBV reactivation.[137] Treatment with bDMARDs, other than rituximab, was also associated with low risk of HBV reactivation, as shown by several observational studies[98–104 138–146147] (table 4). A meta-analysis of nine studies with a total of 468 anti-HBcore-positive patients with AIIRD treated with TNF inhibitors (and with only one study (n=19) using prophylaxis), reactivation was observed in 1.8% of patients.[148]

Reactivation appears to be more common in anti-HBcore-positive patients treated with rituximab (table 4). In a retrospective study, 9.1% of 44 patients with RA treated with rituximab experienced HBV reactivation[149] during a follow-up period of 3.4±1.7 years form the first rituximab infusion. Similar results are reported in the study of Kuo *et al*[150] in which 8% of patients with RA

Table 2 Agreement between TST (TST-IGRA and among IGRA)

Author-year/country	Patients (N)	Disease	Agreement with TST	RoB
Ruan *et al*[17] 2016/NA*	1940	AIIRD	72% (QTF) 75% (T-Spot)	High quality
Pyo *et al*[44] 2018/NA*	5224	AIIRD	73% (QTF) 75% (T-Spot)	Medium quality
Escalante *et al*[34] 2015/USA	101	AIIRD	81% (T-Spot)	7
Tang *et al*[46] 2020/Hong Kong	217	AIIRD	74.4% (QTF)	6
Wu *et al*[48] 2019/China	173	BD	0.391† (T-Spot)	6
Klein *et al*[18] 2013/Czech	305	AIIRD	66% (QTF)	6
Vassilopoulos *et al*[55] 2011/ Greece	155	AIIRD	64% (QTF) 71% (T-Spot)	6
Park *et al* [43] 2009/South Korea	86	AIIRD	68.6% (IGRA)	6
Vassilopoulos *et al*[15] 2008/ Greece	70	AIIRD	72.8% (T-Spot)	6
Cho *et al*[33] 2016/South Korea	136/66	SLE/RA	84.6%/78.8% (QTF)	5
Kim *et al*[39] 2013/South Korea	724	IA	0.285† (QTF)	5
Lee *et al*[40] 2013/South Korea	64	RA	75% (QTF)	5
Minguez *et al*[41] 2012/Spain	53	IA	77.3% (QTF)	5
Scrivo *et al*[45] 2013/Italy	102	AIIRD	88% (QTF)	5
Paluch-oles *et al*[42] 2013/Poland	90	IA	82% (QTF)	5
Maeda *et al*[14] 2011/Japan	97	RA	50.5% (QTF)	5
Inanc *et al*[38] 2009/Turkey	140	IA	61% (QTF)	4
Girlanda *et al*[35] 2010/Italy	69	AIIRD	0.341† (T-Spot)	4
Gogus *et al*[36] 2010/Tureky	45	IA	0.188† (QTF)	4
Xie *et al*[49] 2011/China	58	AIIRD	88.2% (T-Spot)	4
Hanta *et al*[37] 2012/Turkey	90	IA	0.12† (QTF)	4
So *et al*[50] 2017/Hong Kong	38	RA	73.7% (QTF)	4
Author-year/country	**Patients (N)**	**Disease**	**Agreement among IGRA**	**RoB**
Vassilopoulos *et al*[55] 2011/ Greece	155	AIIRD	81%	6
Martin *et al*[53] 2010/Ireland	150	AIIRD	98%	6
Iwagaitsu *et al*[52] 2016/Japan	68	RA	0.68†	4
Melath *et al*[54] 2014/UK	76	AIIRD	91%	4

*Meta-analysis.
†Only k coefficient is available.
AIIRD, autoimmune inflammatory rheumatic diseases; BD, Bechet's disease; IA, inflammatory arthritis; IGRA, interferon gamma release assay; IMID, immune mediated inflammatory disease; N, number; NA, not applicable; QTF, quantiferon; RA, rheumatoid arthritis; RoB, risk of bias; SLE, systemic lupus erythematosus; TST, tuberculin skin test.

treated with rituximab exhibited HBV reactivation within 1–4 years after the first dose of the drug. On the other hand, in an Italian study, seroconversion and positive HBV-DNA levels were recorded in 0% and 3%, respectively, in 33 patients with RA treated with rituximab.[151] In another study, HBV reactivation was not seen in 44 RA, anti-HBcore-positive patients treated with rituximab.[152] A recent study, examining 489 patients with resolved HBV, also showed that treatment with rituximab or abatacept were independent risk factors for HBsAg conversion (HR 87.76, 95% CI 11.50 to 669.73, p<0.001; HR 60.57, 95% CI 6.99 to 525.15, respectively) in patients with resolved HBV.[153] Data on tsDMARDs are limited. Observational studies have shown that HBV reactivation in patients treated with tsDMARDs was uncommon, ranging from 0% to 3.1%[107 108 154 155] (table 4).

Absence and/or low titres of anti-HBs appear to be risk factors for HBV reactivation in anti-HBcore-positive patients. From 103 patients with RA treated with rituximab, 20% from those who were anti-HBs-negative and anti-HBcore-positive developed HBV reactivation, in contrast with 4.8% of patients who were positive for both

Table 3 Antiviral prophylaxis and HBV reactivation in anti-HBcore-positive patients treated with cDMARDs, immunosuppressants or combination of antirheumatic drugs

Author-year/country	Patients (N)	Disease	Treatment	Prophylaxis N (%)	Reactivation N (%)	RoB
Su *et al*[122] 2018/NA*	2162 patients (53 studies)	AIIRD	Anti-rheumatic drugs†	Not effective for chronic/occult infection	Relative risk (95% CI) 0.89 (0.05 to 16.36)	Medium quality
Fukuda *et al*[125] 2019/Japan	1127‡	RA	Anti-rheumatic drugs†	ND	57 (5.1)	8
Schwaneck *et al*[127] 2018/ Germany	84	AIIRD	Anti-rheumatic drugs†	1 (1.2)	8/84 (9.6)	8
Fukuda *et al*[124] 2017/Japan	1042‡	AIIRD	Anti-rheumatic drugs†	0 (0)	35 (3.4)	8
Barone *et al*[123] 2015/Italy	179	AIIRD	Anti-rheumatic drugs†	0 (0)	(0)	8
Matzusaki *et al*[112] 2018/ Japan	360‡	RA	Anti-rheumatic drugs†	0 (0)	6/238 (2.5)ˆ	7
Tan *et al*[114] 2012/China	188	RA	csDMARDs	0 (0)	2 (1.1)	7
Chen *et al*[115] 2021/Taiwan	63	SLE	Immunosuppressants/GC	0 (0)	2 (3.2)	6
Chen *et al*[130] 2020/Taiwan	925	RA	Anti-rheumatic drugs†	0 (0)	17 (1.8)	6
Laohapand *et al*[126] 2015/ Thailand	65	AIIRD	Methotrexate	0 (0)	(0)	6
Mori *et al*[129] 2012/Japan	62‡	RA	Anti-rheumatic drugs†	ND	(0)	5
Urata *et al*[131] 2010/Japan	135‡	RA	Anti-rheumatic drugs†	0 (0)	7 (5.2)	5
Xu *et al*[116] 2015/China	115§	RA	Leflunomide	ND	(0)	3

*Meta-analysis.
†Various types of anti-rheumatic drugs used.
‡Anti-HBc (+) and/or Anti-HBs (+), ˆ 238 are the patients who were HBV-DNA-negative.
§36 Anti-HBc-positive or Anti-HBe-positive.
AIIRD, autoimmune inflammatory rheumatic diseases; bDMARDs, biological DMARDs; csDMARDs, conventional synthetic DMARDs; DMARDs, disease modifying anti-rheumatic drugs; GC, glucocorticoids; HBV, hepatitis B virus; IA, inflammatory arthritis; NA, not available; ND, not defined; RA, rheumatoid arthritis; RoB, risk of bias; SLE, systemic lupus erythematosus; TNFi, TNF-inhibitors.

anti-HBs and anti-HBcore.[156] Similarly, examining 152 patients with RA treated with bDMARDs, reactivation was significantly more common in those who were negative for anti-HBs (p=0.013).[157] In a study of 35 patients with various AIIRD and treated with a wide range of drug regimens, anti-HBs titres at baseline were lower in those who exhibited HBV reactivation compared with those who did not (2.83 (0.24–168.50) mIU/mL vs 99.94 (range 0.00–5342.98) mIU/mL, respectively (p=0.036)).[158] Furthermore, in a study of 50 patients with resolved HBV treated with rituximab, reactivation was more common in patients negative for anti-HBs compared with those positive (30% vs 4%, p=0.02).[150] Finally, in another study, negativity for anti-HBs was found to be an independent risk factor (HR 5.15, 95% CI 2.21 to 12.02) for conversion of HBsAg in patients with resolved HBV.[153]

Hepatitis C

Most data for HCV pertain to patients with RA or PsA treated with bDMARDs. More specifically, there have been a handful of observational studies and a systematic review about the outcomes in HCV-RNA-positive patients with RA or PsA, treated with TNF-inhibitors, most of which show that liver function tests (LFTs) and/or viral load increase in a small number of patients[159–163] (table 5). In addition, in a randomised trial, 29 patients with RA with HCV infection were randomised to receive methotrexate alone, etanercept alone or a combination of these drugs.[164] LFTs and viral load did not change significantly in any of the groups. In another study examining patients with RA treated with various anti-rheumatic drugs, it was shown that hepatotoxicity (defined in this study as alanine transaminase (ALT) elevation ≥100 IU/L or increase in HCV RNA of 1 log or more) was seen in 3.4% of the patients with RA enrolled and it was more frequent in patients treated with bDMARDs than in those receiving csDMARDs[165] (table 5). Furthermore, examining data from 26 patients with RA and HCV infection, viral load remained stable in patients treated with TNF-inhibitors (n=20) but increased in patients treated with rituximab (n=6).[166] Less data exist for people with AIIRD other than RA or PsA. In a small retrospective study, 10/26 (38.5%) of SLE patients treated with various immunosuppressives exhibited HCV reactivation (threefold increase in ALT with an increase of HCV RNA>1 log10 IU/mL or HCV RNA >5 log10 IU/mL).[167]

It should be noted that in most of the above-mentioned studies a very small percentage of patients were on concurrent treatment with antiviral drugs (table 5). It is worth noting that these studies were conducted before direct acting antiviral drugs were widely available.

Pneumocystis jirovecii

Efficacy of prophylaxis for *P. jirovecii* pneumonia (PCP) has mostly been examined in patients receiving treatment with glucocorticoids. The exact dose and duration

Table 4 Antiviral prophylaxis and HBV reactivation in anti-HBcore-positive patients treated with b-ts-DMARDs

Author-year/country	Patients (N)	Disease	Treatment	Prophylaxis N (%)	Reactivation N (%)	RoB
Lee *et al*[16 148] 2012/South Korea*	468 patients (9 studies)	IA	TNFi	0 (0)†	8 (1.7)	Low quality
Harigai *et al*[155] 2020/Multi	215	RA	Baricitinib	0 (0)	4 (1.9)	8
Papalopoulos et al[144] 2018/Greece	212	AIIRD	bDMARDs	8 (3.8)	2 (2)	8
Lan *et al*[101] 2011/Taiwan	88	RA	TNFi	0 (0)	1/70‡ (1.4)	8
Charpin *et al*[141] 2009/France	21	IA	TNFi	0 (0)	0 (0)	8
Ahn *et al*[138] 2018/South Korea	15	RA	Tocilizumab	0 (0)	0 (0)	7
Vassilopoulos *et al*[103] 2010/Greece	19	IMID	TNFi	0 (0)	0 (0)	7
Serling-Boyd *et al*[154] 2021/USA	24	AIIRD	Tocilizumab, Tofacitinib	6 (25.0)	0 (0)	6
Wang *et al*[107] 2021/Taiwan[107]	64	RA	Tofacitinib	0 (0)	2 (3.1)	6
Kuo *et al*[150] 2020/Taiwan	64	RA	Tocilizumab	0 (0)	1 (1.6)	6
Chen et al[108] 2018/Taiwan	75	RA	Tofacitinib	0 (0)	0 (0)	6
Chen et al[98] 2017/China	41	RA	Tocilizumab	0 (0)	0 (0)	6
Gianniti et al[142] 2017/Italy	131	SpA	TNFi	0 (0)	0 (0)	6
Padovan *et al*[102] 2016/Italy	21	RA	Abatacept	4 (19.1)	0 (0)	6
Nakamura et al[143] 2016/Japan	57§	RA	bDMARDs	0 (0)	3 (5.3)	6
Biondo *et al*[139] 2014/Italy	20	IA	TNFi	0 (0)	0 (0)	6
Giardina *et al*[99] 2013/Italy	7	IA	TNFi	0 (0)	0 (0)	6
Caporalli et al[140] 2010/Italy	67	IA	TNFi	0 (0)	0 (0)	6
Zhang *et al*[145] 2013/China	41	RA	Infliximab	0 (0)	0/30 (0)	5
Ye *et al*[104] 2014/China	50	IA	TNFi	0 (0)	0 (0)	4
Chen *et al*[156] 2019/Taiwan	103	RA	Rituximab	0 (0)	9 (8.7)	8
Kuo *et al*[150] 2020/Taiwan	50	RA	Rituximab	0 (0)	4 (8)	7
Tien *et al*[149] 2017/Taiwan	44	RA	Rituximab	0 (0)	4 (9.1)	7
Varisco *et* al[151] 2016/Italy	33	RA	Rituximab	0 (0)	0 (0)¶	7
Mitroulis et al[147] 2013/Greece	12	AIIRD	Rituximab	0 (0)	0 (0)	6
Barone *et al*[152] 2021/Italy	44	AIIRD	Rituximab	0 (0)	0 (0)	5

*Meta-analysis.
†Prophylaxis was given only in 1 study with 19 patients.
‡18 patients were HBsAg-positive.
§Anti-core and/or anti-HBs (+).
¶3% became HBV-DNA (+).
AIIRD, autoimmune inflammatory rheumatic diseases; bDMARDs, biological DMARDs; HBV, hepatitis B virus; IA, inflammatory arthritis; RA, rheumatoid arthritis; RoB, risk of bias; SLE, systemic lupus erythematosus; SpA, Spondyloarthritis; TNFi, TNF-inhibitors; tsDMARDs, targeted synthetic disease modifying anti-rheumatic drugs.

Table 5 Hepatotoxicity and reactivation of hepatitis C in patients treated with DMARDs or immunosuppressants

Author-year/country	Patients (N)	Concurrent antivirals* (%)	Disease	Treatment	Increase in LFTs N (%)	Increase in viral load N (%)	RoB
Iannone *et al*[164] 2014/ Italy†	29	0%	RA	Etanercept or MTX or combination	0 (0)	0 (0)	Some concerns
Burton *et al*[165] 2017/USA	748‡	4.6%	RA	DMARDs	37 (3.4)	0 (0)	7
Chen et al[166] 2015/ Taiwan	26§	NS	SLE	Immunosuppressants	10 (38.5)¶	10 (38.5)¶	6
Costa *et al*[160] 2014/Italy	15	NS	PsA	TNFi	0 (0)	0 (0)	6
Parke *et al*[161] 2004/USA	5	0%	RA	TNFi	0 (0)	1 (20)**	6
Peterson *et al*[162] 2003/ USA	24	0%	RA	Etanercept or Infliximab	0 (0)	6/22 (27.3)††	6
Gandhi et al[163] 2017/ USA	14‡‡	14.3%	RA, PsA	Etanercept	7 (50.0)	5/10 (50.0)	5

*Patients concurrently treated with antivirals.
†Randomised controled trial.
‡1097 treatment-episodes.
§Anti-HCV+, baseline RNA not stated.
¶Increase in viral load or LFTs.
**Was not combined with liver injury.
††No significant differences were seen between the mean viral loads at baseline and follow-up.
‡‡5/7 were RNA-positive.
DMARDs, disease modifying anti-rheumatic drug; HCV, hepatitis C virus; IMID, immune-mediated diseases; LFTs, liver function tests; MTX, methotrexate; NS, not significant; PsA, psoriatic arthritis; RA, rheumatoid arthritis; RoB, risk of bias.

of treatment with glucocorticoids cannot be defined based on the available data thus far. However, prophylaxis in patients with various AIIRD receiving prednisolone more than 15–30 mg/day for more than 2–4 weeks, has been found to reduce episodes of PCP and associated mortality[168–172] (table 6). On the other hand, in a study enrolling 184 patients with giant cell arteritis treated with high doses of glucocorticoids (average starting dose of 47 mg of prednisone/day), no PCP cases were recorded, while prophylaxis for PCP was given in only 5 patients.[173]

Data for other antirheumatic treatments beyond glucocorticoids are very limited. Katsuyama *et al*[174] found that patients with RA treated with bDMARDs, having also specific risk factors for PCP development, might benefit from prophylaxis for PCP. In 214patients with RA who received prophylaxis for PCP based on the presence of at least two risk factors (age ≥65 years, coexisting pulmonary disease and use of glucocorticoids), no PCP cases were reported, compared with the incidence observed (0.93/100 000) for patients with the same characteristics in whom prophylaxis for PCP was administered based on physician's discretion. In addition, in a small retrospective study, it was shown that annual incidence of PCP was lower in patients treated with cyclophosphamide who received PCP prophylaxis (5.33% (95% CI 0.65% to 19.24%)), compared with those who did not (9.50% (95% CI 1.15% to 34.33%)).[175] Of note, in all but one of these patients, glucocorticoids were coadministered (mean maximum dose of prednisone: 39 mg/day). The most common prophylactic scheme in clinical practice

Table 6 Prophylaxis with trimethoprim-sulfamethoxazole for PCP in patients treated with GC

Author-year/country	Patients (N)	GC scheme	Prophylaxis* N (%)	Outcome of prophylaxis	RoB
Park et al[170] 2018/South Korea	1092 (1522 episodes†)	≥30 mg/day for ≥4 weeks	262 (24.0)	Reduced PCP incidence HR=0.07 (95% CI 0.01 to 0.53), p=0.01	8
Honda et al[168] 2019/Japan	437	≥50 mg/day	376 (86.0)	Reduced PCP incidence OR=0 (95% CI 0.00 to 0.38), p=0.003	7
Park *et al*[169] 2019/South Korea	735 (1065 episodes†)	≥15 mg and <30 mg for ≥4 weeks	45 (6.1)	Reduced PCP incidence in high risk-group‡ HR=0.2 (0.001–2.3)	7
Ogawa *et al*[171] 2005/Japan	124	≥30 mg/day	46 (37.1)	Effective in high-risk patients§, p=0.039	7
Vananuvat *et al*[172] 2011/ Thailand	132 (138 episodes†)	≥20 prednisolone for >2 weeks	59 (44.7)	Reduced PCP incidence, p=0.038	6

*Prophylaxis given in (% episodes): trimethoprim-sulfamethoxazole 480 mg/day or three tablets of 480 mg, weekly.
†Episode: a patient could be treated with these doses of glucocorticoids more than once.
‡High-risk group: GC-pulse treatment and/or lymphopenia.
§Risk was calculated using a prediction model.
AIIRD, autoimmune inflammatory rheumatic diseases; GC, glucocorticoids; PCP, pneumocystis pneumonia; RoB, risk of bias.

and in published studies is trimethoprim/sulfamethoxazole (TMP/SMX) 480 mg/day or 960 mg three times a week. However, there are a handful of studies, including a RCT, suggesting that reduced dosing regimes (eg, 480 mg every other day) are equally effective and have fewer adverse effects[176–180] (online supplemental table 5).

Alternative regimens such as atovaquone or pentamidine may also be effective.[181–183] However, a recent large retrospective study examining PCP prophylaxis in patients with R treated with ts-b-DMARDs showed that TMP/SMX was more effective compared with pentamidine[184] (online supplemental table 6).

Other viruses

To date, there are no robust data to support screening or prophylaxis for viruses other than HBV and HCV in patients with AIIRD treated with immunosuppressive/immunomodulatory drugs. For HIV, a small study that included eight HIV patients with CD4 cells more than 200 mm^3 and viral load less than 60 000 copies/mm^3, treated with TNF-inhibitors showed stable CD4 counts and viral load over a 2-year follow-up period.[185]

For cytomegalovirus (CMV), in a retrospective study of patients with SLE receiving various immunosuppressives including glucocorticoids, prophylaxis in a selected group of patients with ganciclovir or valganciclovir led to numerically less CMV organ invasive disease, compared with those who did not receive prophylaxis.[186] Similar results were reported by Lim *et al*[187] in a study including 119 patients with glomerulonephritis or renal vasculitis.

No studies were retrieved by this SLR that addressed specifically the issue of prophylaxis (pre-exposure or postexposure) for Varicella Zoster Virus (VZV). In a study with 110 SLE and AAV patients, 19 individuals (17.2%) received prophylaxis with valaciclovir (500 mg, once or twice a day). Among these, none developed VZV in contrast to 10 patients who did not receive prophylaxis and developed VZV during a mean follow-up of 3.4 years (overall incidence of 27.9/1000 patient-years (95% CI 15.2 to 50.6).[188]

Other pathogens

For other pathogens, including those which are more commonly encountered in certain regions such as *Trypanosoma cruzi* in Latin America or *Coccidioides* in southwestern USA, data from literature in patients with AIIRD remain scarce and screening/prophylaxis procedures are mainly based on expert opinion and collaboration with other disciplines (eg, infectious disease physicians). Of note, a study enrolling 1951 patients with immune-mediated diseases living in an area endemic for coccidioides treated with TNF-inhibitors found that patients who had serology screening for *Coccidioides*, compared with those who did not, were less likely to have symptomatic coccidiomycosis (11/861 vs 35/1025, p<0.01).[189] Another study examining rates of infections with *listeria* or *salmonella* in more than 10 000 patients with RA starting treatment with TNF-inhibitors showed that these infections dropped significantly after dietary advice was included in standard patient leaflets advising avoidance of certain foods like raw eggs and poultry.[190]

DISCUSSION

To our knowledge, this is the first SLR undertaken to date that focuses on the screening and prophylaxis of chronic and opportunistic infections in the setting of AIIRD. Despite the lack of evidence in some cases (ie, for more rare pathogens), several studies were identified for common pathogens. As mentioned, the risk for reactivation or new-onset infection differs depending on various factors, including type of AIIRD and immunosuppressive/immunomodulatory treatment used.

Since TB is a major concern in patients with AIIRD receiving immunosuppressive/immunomodulatory medication, it is not surprising that there is a wealth of data for this pathogen in the field of AIIRD. In TB, IGRA seems to perform better than TST and appears to be less affected by factors such as previous vaccination with BCG or concurrent treatment with glucocorticoids. In terms of TB prophylaxis, various prophylactic schemes have been used, driven largely by national regulations and differences in the geoepidemiology of infections.

HBV is another much-discussed pathogen as reactivation is not unusual in patients with AIIRD treated with immunosuppressive/immunomodulatory drugs. Antiviral prophylaxis has proven to be beneficial, especially in certain subgroups such as patients who are HBsAg-positive. The latter should be referred for prophylaxis with antiviral drugs like lamivudine, entecavir and tenofovir, especially when treated with bDMARDs. For patients who are anti-HBcore-positive, close monitoring with LFTs and measurement of viral load seems reasonable, while prophylaxis (irrespective of these tests) might be considered for patients treated with rituximab. Presence/high titres of anti-HBs appear to be protective against HBV-reactivation.

Reactivation of HCV appears to be less common compared with HBV. The treatment landscape for HCV has changed over the last years with the development of newer (direct-acting) antiviral drugs. Notably, most of the studies examining HCV reactivation in patients with AIIRD were conducted before direct acting antiviral drugs were widely available. Although more data are needed, treatment with bDMARDs appears to be relatively safe in patients who are HCV-RNA positive, as a small percentage of them will exhibit an increase in viral loads or levels of transaminases. There is much less evidence for other drug categories.

Finally, treatment with glucocorticoids (although the exact dose/duration of treatment is not well defined) appears to be a significant risk factor for PCP development and therefore prophylaxis with TMP/SMX is a reasonable approach for these patients. Evidence for other pathogens which are more endemic is specific geographic areas is not enough thus far to draw

solid conclusions. There are several expert opinions, supported by a small number of studies suggesting that life-style and environmental advice could reduce the incidence of certain pathogens like listeria.[190–193]

This SLR has some limitations. First, the complete screening and data extraction was led by one fellow (GEF). However, this was deemed adequate by the steering group, due to the high concordance (more than 97%) in the validating process, performed for 20% of the studies. Second, although quality of the studies was not low overall, most of the data were derived from observational studies, while RCTs or meta-analyses are lacking. This highlights the need for more studies in the field of chronic and opportunistic infections in patients with AIIRD. Third, there is a significant heterogeneity regarding different AIIRD and treatment received, preventing meta-analyses currently. We opted to group and present data per pathogen, considering also the different drugs used. To ensure clarity and consistency throughout the manuscript but also with the current nomenclature, we used a modified version of a recently proposed terminology for the various immunosuppressive/immunomodulatory drugs used in rheumatology.[7–9]

There are, however, also important strengths to this SLR. This is the first registered SLR in the field of rheumatology addressing this topic and forming the basis for EULAR recommendations. This was a systematic review led by a TF of multiple experts from across not just rheumatology, but also infectious diseases and pulmonology, as part of the attempt to ensure information was retrieved on all relevant pathogens and screening and prophylaxis practices in routine clinical settings across countries. Also, an expert librarian (JS) supported the search strategy and undertook the database searches. The scoping review was also supported by the librarian and the methodologists and informed the main SLR, ensuring this was focused and pragmatic.

In conclusion, this SLR provides evidence on current knowledge on the screening and prophylaxis for chronic and opportunistic infections in patients with AIIRD. The review discusses the existing evidence based on different types of pathogens, addressing regional and other variations in the screening and treatment regimens used for prophylaxis, also highlighting the unmet needs. This SLR was used to inform the 2022 EULAR recommendations for the screening and prophylaxis of chronic and opportunistic infections.

Author affiliations
[1]Joint Academic Rheumatology Program, National and Kapodistrian University of Athens, First Department of Propaedeutic and Internal Medicine, National and Kapodistrian University of Athens, Athens, Greece
[2]Institute of Infection, Immunity and Inflammation, University of Glasgow, Glasgow, UK
[3]Institute of Life Course and Medical Sciences, University of Liverpool, Liverpool, UK
[4]Department of Rheumatology, Countess of Chester Hospital NHS Foundation Trust, Chester, UK
[5]Centre for Epidemiology Versus Arthritis, Centre for Musculoskeletal Research, The University of Manchester, Manchester, UK
[6]Directorate of Research Policy, Leiden University Medical Center, Leiden, The Netherlands
[7]Division of Rheumatology, Geneva University Hospitals, Geneve, Switzerland
[8]Centre for Rheumatic Diseases, King's College London, London, UK
[9]Rheumatology Department, King's College London, London, UK
[10]National Institute of Health Research Manchester Biomedical Research Centre, Manchester University NHS Foundation Trust, Manchester, UK

Twitter Elena Nikiphorou @ElenaNikiUK

Acknowledgements We would like to thank all members of the Task Force for the '2022 EULAR Recommendations for screening and prophylaxis of chronic and opportunistic infections in adults with autoimmune inflammatory rheumatic diseases'.

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.

Competing interests GEF: speaker fees/honoraria: Pfizer, UCB, Novartis, Abbvie, Aenorasis, Genesis. MD: None. SSZ: consulting fees: UCB. JS: none. DSC: none. JG: speaker fees/honoraria: Abbvie, Galapagos, Gilead, Janssen, Lilly, Novartis, Pfizer, UCB. Research funding: Abbvie, Astrazeneca, Galapagos, Gilead, Gritstone, Janssen, Moderna, Novovax, Pfizer. KH: honoraria from Abbvie; grant income from Pfizer and BMS. EN: speaker fees/honoraria: Celltrion, Pfizer, Sanofi, Gilead, Galapagos, AbbVie, Lilly, Fresenius. Research funding: Pfizer, Lilly.

Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

ORCID iDs
George E Fragoulis http://orcid.org/0000-0003-4932-7023
Mrinalini Dey http://orcid.org/0000-0001-6858-4338
Delphine Courvoisier http://orcid.org/0000-0002-1956-2607
James Galloway http://orcid.org/0000-0002-1230-2781
Elena Nikiphorou http://orcid.org/0000-0001-6847-3726

REFERENCES

1 Fragoulis GE, Sipsas NV. When rheumatology and infectious disease come together. *Ther Adv Musculoskelet Dis* 2019;11:19868901.
2 Shamriz O, Shoenfeld Y. Infections: a double-edge sword in autoimmunity. *Curr Opin Rheumatol* 2018;30:365–72.
3 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.
4 McGeoch L, Twilt M, Famorca L, *et al*. CanVasc recommendations for the management of antineutrophil cytoplasm antibody-associated vasculitides. *J Rheumatol* 2016;43:97–120.
5 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.
6 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.
7 Isaacs JD, Burmester GR. Smart battles: immunosuppression versus immunomodulation in the inflammatory RMDs. *Ann Rheum Dis* 2020;79:991–3.

8 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.
9 Strangfeld A, Schäfer M, Gianfrancesco MA, *et al*. Factors associated with COVID-19-related death in people with rheumatic diseases: results from the COVID-19 global rheumatology alliance physician-reported registry. *Ann Rheum Dis* 2021;80:930–42.
10 Sterne JAC, Savović J, Page MJ, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. *BMJ* 2019;366:l4898.
11 Wells G, Shea B, O'Connell D. The Newcastle-Ottawa scale (NOS) for assessing the quality of nonrandomised studies in meta-analyses. Available: http://www.ohri.ca/programs/clinical_epidemiology/oxford.asp [Accessed 08 Mar 2022].
12 Shea BJ, Reeves BC, Wells G, *et al*. AMSTAR 2: a critical appraisal tool for systematic reviews that include randomised or non-randomised studies of healthcare interventions, or both. *BMJ* 2017;358:j4008.
13 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.
14 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.
15 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.
16 Lee K-H, Jung S-Y, Ha Y-J, *et al*. Tuberculin reaction is not attenuated in patients with rheumatoid arthritis living in a region with intermediate burden of tuberculosis. *Rheumatol Int* 2012;32:1421–4.
17 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.
18 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.
19 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.
20 Soborg B, Ruhwald M, Hetland ML, *et al*. Comparison of screening procedures for Mycobacterium tuberculosis infection among patients with inflammatory diseases. *J Rheumatol* 2009;36:1876–84.
21 Tamborenea MN, Tate G, Mysler E, *et al*. Prevalence of positive PPD in a cohort of rheumatoid arthritis patients. *Rheumatol Int* 2010;30:613–6.
22 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.
23 Agarwal S, Das SK, Agarwal GG. Steroids decrease prevalence of positive tuberculin skin test in rheumatoid arthritis: implications on anti-TNF therapies. *Interdiscip Perspect Infect Dis* 2014;2014:430134–5.
24 Reitblat O, Lerman TT, Cohen O, *et al*. The effect of prednisone on tuberculin skin test reaction in patients with rheumatoid arthritis. *Int J Rheumatol* 2018;2018:2586916.
25 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.
26 Arias-Guillén M, Sánchez Menéndez MM, Alperi M, *et al*. High rates of tuberculin skin test positivity due to methotrexate therapy: false positive results? *Semin Arthritis Rheum* 2018;48:538–46.
27 Hatemi G, Melikoglu M, Fresko I, *et al*. Infliximab does not suppress the tuberculin skin test (purified protein derivative). *J Rheumatol* 2007;34:474–80.
28 Ringrose JS, Sanche SE, Taylor-Gjevre RM. Detecting latent tuberculosis infection during anti-tumor necrosis factor therapy. *Clin Exp Rheumatol* 2011;29:790–4.
29 Yamamoto S, Nagatani K, Sato T, *et al*. Unaffected reaction level in tuberculin skin test by long-term therapy with tumor necrosis factor inhibitors for rheumatoid arthritis. *Int J Rheum Dis* 2017;20:584–8.
30 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.
31 Shovman O, Anouk M, Vinnitsky N, *et al*. Quantiferon-Tb gold in the identification of latent tuberculosis infection in rheumatoid arthritis: a pilot study. *Int J Tuberc Lung Dis* 2009;13:1427–32.
32 Chen Y-M, Chen H-H, Lai K-L, *et al*. The effects of rituximab therapy on released interferon-γ levels in the QuantiFERON assay among RA patients with different status of Mycobacterium tuberculosis infection. *Rheumatology* 2013;52:697–704.
33 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.
34 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.
35 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.
36 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.
37 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.
38 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.
39 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.
40 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.
41 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.
42 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.
43 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.
44 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.
45 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.
46 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.
47 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.
48 Wu X, Chen P, Wei W, *et al*. Diagnostic value of the interferon-γ release assay for tuberculosis infection in patients with Behçet's disease. *BMC Infect Dis* 2019;19.
49 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.
50 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.
51 Malaviya A, Thakaran R, Rawat R, *et al*. Real life experience of a screening strategy for latent tuberculosis before treatment with biologicals in Indian patients with rheumatic diseases. *Indian J Rheumatol* 2018;13:233–9.
52 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.
53 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.
54 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.
55 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.
56 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.
57 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.
58 Bonfiglioli KR, Ribeiro ACM, Moraes JCB, *et al*. LTBI screening in rheumatoid arthritis patients prior to anti-TNF treatment in an endemic area. *Int J Tuberc Lung Dis* 2014;18:905–11.
59 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.
60 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.
61 Chen D-Y, Shen G-H, Hsieh T-Y, *et al*. Effectiveness of the combination of a whole-blood 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.
62 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.
63 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.
64 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.
65 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.
66 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.
67 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.
68 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.
69 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.
70 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.
71 Brassard P, Kezouh A, Suissa S. Antirheumatic drugs and the risk of tuberculosis. *Clin Infect Dis* 2006;43:717–22.
72 Brode SK, Jamieson FB, Ng R, *et al*. Increased risk of mycobacterial infections associated with anti-rheumatic medications. *Thorax* 2015;70:677–82.
73 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.
74 Jick SS, Lieberman ES, Rahman MU, *et al*. Glucocorticoid use, other associated factors, and the risk of tuberculosis. *Arthritis Rheum* 2006;55:19–26.
75 WHO. *WHO global Lists of high burden countries for tuberculosis (TB), TB/HIV and multidrug/rifampicin-resistant TB (MDR/RR-TB), 2021–2025*, 2021.
76 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.
77 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.
78 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.
79 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.
80 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.
81 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.
82 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.
83 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.
84 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.
85 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.
86 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.
87 Thomas K, Vassilopoulos D. Infections in patients with rheumatoid arthritis in the era of targeted synthetic therapies. *Mediterr J Rheumatol* 2020;31:129–36.
88 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.
89 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.
90 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.
91 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.
92 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.
93 Shobha V, Rao V, Desai A, *et al*. Prescribing patterns and safety of biologics in immune-mediated rheumatic diseases: Karnataka biologics cohort study group experience. *Indian J Rheumatol* 2019;14:17–20.
94 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.
95 Hernández-Cruz B, Ponce-de-León-Rosales S, Sifuentes-Osornio J. Tuberculosis prophylaxis in patients with steroid treatment and systemic rheumatic diseases. A case-control study. *Clin Exp Rheumatol* 1999;17:81–7.
96 Mok MY, Lo Y, Chan TM, *et al*. Tuberculosis in systemic lupus erythematosus in an endemic area and the role of isoniazid prophylaxis during corticosteroid therapy. *J Rheumatol* 2005;32:609–15.
97 Park JW, Curtis JR, Lee H, *et al*. Risk-benefit analysis of isoniazid monotherapy to prevent tuberculosis in patients with rheumatic diseases exposed to prolonged, high-dose glucocorticoids. *PLoS One* 2020;15:e0244239.
98 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.
99 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.
100 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.
101 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.
102 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.
103 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.
104 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.
105 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.
106 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.
107 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.
108 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.
109 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.
110 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.
111 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.
112 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.
113 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.
114 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.
115 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].
116 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.
117 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.
118 Jeong W, Choe J-Y, Song B-C, *et al*. Effect of low-dose corticosteroid use on HBV reactivation in HBsAg-positive rheumatoid arthritis patients. *Open Rheumatol J* 2021;15:39–44.
119 Yang C-H, Wu T-S, Chiu C-T. Chronic hepatitis B reactivation: a word of caution regarding the use of systemic glucocorticosteroid therapy. *Br J Dermatol* 2007;157:587–90.
120 Xuan D, Yu Y, Shao L, *et al*. Hepatitis reactivation in patients with rheumatic diseases after immunosuppressive therapy--a report of long-term follow-up of serial cases and literature review. *Clin Rheumatol* 2014;33:577–86.
121 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.
122 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.
123 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.
124 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.
125 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.
126 Laohapand C, Arromdee E, Tanwandee T. Long-term use of methotrexate does not result in hepatitis B reactivation in rheumatologic patients. *Hepatol Int* 2015;9:202–8.
127 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.
128 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.
129 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.
130 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.
131 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.
132 Cheng J, Li J-B, Sun Q-L, *et al*. Reactivation of hepatitis B virus after steroid treatment in rheumatic diseases. *J Rheumatol* 2011;38:181–2.
133 Hatano M, Mimura T, Shimada A, *et al*. Hepatitis B virus reactivation with corticosteroid therapy in patients with adrenal insufficiency. *Endocrinol Diabetes Metab* 2019;2:e00071.
134 Luís M, Freitas J, Costa F, *et al*. An updated review of glucocorticoid-related adverse events in patients with rheumatoid arthritis. *Expert Opin Drug Saf* 2019;18:581–90.
135 Yang S-S, Hung C-T, Li S-F, *et al*. Hepatitis B virus-related mortality in rheumatoid arthritis patients undergoing long-term low-dose glucocorticoid treatment: a population-based study. *J Formos Med Assoc* 2018;117:566–71.
136 Lin Y-C, Chen Y-J, Lee S-W, *et al*. Long-term safety in HBsAg-negative, HBcAb-Positive patients with rheumatic diseases receiving maintained steroid therapy after pulse therapy. *J Clin Med* 2021;10. doi:10.3390/jcm10153296. [Epub ahead of print: 26 07 2021].
137 Zhong Z, Liao W, Dai L, *et al*. Average corticosteroid dose and risk for HBV reactivation and hepatitis flare in patients with resolved hepatitis B infection. *Ann Rheum Dis* 2022;81:584–91.
138 Ahn SS, Jung SM, Song JJ, *et al*. Safety of tocilizumab in rheumatoid arthritis patients with resolved hepatitis B virus

infection: data from real-world experience. *Yonsei Med J* 2018;59:452–6.
139 Biondo MI, Germano V, Pietrosanti M, *et al*. Lack of hepatitis B virus reactivation after anti-tumour necrosis factor treatment in potential occult carriers with chronic inflammatory arthropathies. *Eur J Intern Med* 2014;25:482–4.
140 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.
141 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.
142 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.
143 Nakamura J, Nagashima T, Nagatani K, *et al*. Reactivation of hepatitis B virus in rheumatoid arthritis patients treated with biological disease-modifying antirheumatic drugs. *Int J Rheum Dis* 2016;19:470–5.
144 Papalopoulos I, Fanouriakis A, Kougkas N, *et al*. Liver safety of non-tumour necrosis factor inhibitors in rheumatic patients with past hepatitis B virus infection: an observational, controlled, long-term study. *Clin Exp Rheumatol* 2018;36:102–9.
145 Zhang X, Zhang F, Wu D, *et al*. Safety of infliximab therapy in rheumatoid arthritis patients with previous exposure to hepatitis B virus. *Int J Rheum Dis* 2013;16:408–12.
146 Laurenti R, Giovannangeli F, Gubinelli E, *et al*. Long-term safety of anti-TNF adalimumab in HBc antibody-positive psoriatic arthritis patients: a retrospective case series of 8 patients. *Clin Dev Immunol* 2013;2013:410521.
147 Mitroulis I, Hatzara C, Kandili A, *et al*. Long-Term safety of rituximab in patients with rheumatic diseases and chronic or resolved hepatitis B virus infection. *Ann Rheum Dis* 2013;72:308–10.
148 Lee YH, Bae S-C, Song GG. Hepatitis B virus (HBV) reactivation in rheumatic patients with hepatitis core antigen (HBV occult carriers) undergoing anti-tumor necrosis factor therapy. *Clin Exp Rheumatol* 2013;31:118–21.
149 Tien Y-C, Yen H-H, Chiu Y-M. Incidence and clinical characteristics of hepatitis B virus reactivation in HBsAg-negative/HBcAb-positive patients receiving rituximab for rheumatoid arthritis. *Clin Exp Rheumatol* 2017;35:831–6.
150 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.
151 Varisco V, Viganò M, Batticciotto A, *et al*. Low risk of hepatitis B virus reactivation in HBsAg-negative/Anti-HBc-positive carriers receiving rituximab for rheumatoid arthritis: a retrospective multicenter Italian study. *J Rheumatol* 2016;43:869–74.
152 Barone M, Venerito V, Paolillo R, *et al*. Long-term safety of rituximab in rheumatic patients with previously resolved hepatitis B virus infection. *Intern Emerg Med* 2022;17:475–80.
153 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.
154 Serling-Boyd N, Mohareb AM, Kim AY, *et al*. The use of tocilizumab and tofacitinib in patients with resolved hepatitis B infection: a case series. *Ann Rheum Dis* 2021;80:274–6.
155 Harigai M, Winthrop K, Takeuchi T, *et al*. Evaluation of hepatitis B virus in clinical trials of baricitinib in rheumatoid arthritis. *RMD Open* 2020;6.
156 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.
157 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.
158 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.
159 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.
160 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.
161 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.
162 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.
163 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.
164 Iannone F, La Montagna G, Bagnato G, *et al*. Safety of etanercept and methotrexate in patients with rheumatoid arthritis and hepatitis C virus infection: a multicenter randomized clinical trial. *J Rheumatol* 2014;41:286–92.
165 Burton MJ, Curtis JR, Yang S, *et al*. Safety of biologic and nonbiologic disease-modifying antirheumatic drug therapy in veterans with rheumatoid arthritis and hepatitis C virus infection. *J Rheumatol* 2017;44:565–70.
166 Chen Y-M, Chen H-H, Chen Y-H, *et al*. A comparison of safety profiles of tumour necrosis factor α inhibitors and rituximab therapy in patients with rheumatoid arthritis and chronic hepatitis C. *Ann Rheum Dis* 2015;74:626–7.
167 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.
168 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.
169 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.
170 Park JW, Curtis JR, Moon J, *et al*. Prophylactic effect of trimethoprim-sulfamethoxazole for pneumocystis pneumonia in patients with rheumatic diseases exposed to prolonged high-dose glucocorticoids. *Ann Rheum Dis* 2018;77:644–9.
171 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.
172 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.
173 Krijthe BP, Hogendoorn-van Zwienen EG, van Zeben D. Pneumocystis pneumonia in patients with giant cell arteritis treated with high dose steroids: is there an indication for prophylaxis? *Clin Exp Rheumatol* 2021;39 Suppl 129:189.
174 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.
175 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.
176 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.
177 Takenaka K, Komiya Y, Ota M, *et al*. A dose-escalation regimen of trimethoprim-sulfamethoxazole is tolerable for prophylaxis against Pneumocystis jiroveci pneumonia in rheumatic diseases. *Mod Rheumatol* 2013;23:752–8.
178 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.
179 Utsunomiya M, Dobashi H, Odani T, *et al*. Optimal regimens of sulfamethoxazole-trimethoprim 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.
180 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.

181 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.
182 Jinno S, Akashi K, Onishi A, *et al*. Comparative effectiveness of trimethoprim-sulfamethoxazole 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.
183 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.
184 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.
185 Cepeda EJ, Williams FM, Ishimori ML, *et al*. The use of anti-tumour necrosis factor therapy in HIV-positive individuals with rheumatic disease. *Ann Rheum Dis* 2008;67:710–2.
186 Tan HZ, Choo JCJ, Tan BH, *et al*. Cytomegalovirus preventive strategies in lupus nephritis and renal vasculitis treated with immunosuppressants. *Lupus* 2020;29:351–2.
187 Lim CC, Tan BH, Tung YT, *et al*. Risk-stratified approach to anti-viral prophylaxis against cytomegalovirus disease in glomerulonephritis and renal vasculitis treated with potent immunosuppressants. *Infect Dis* 2019;51:745–52.
188 Garnier C, Ribes D, Chauveau D, *et al*. Zoster after cyclophosphamide for systemic lupus erythematosus or vasculitis: incidence, risk factors, and effect of antiviral prophylaxis. *J Rheumatol* 2018;45:1541–8.
189 Choi K, Deval N, Vyas A, *et al*. The utility of screening for coccidioidomycosis in recipients of inhibitors of tumor necrosis factor α. *Clin Infect Dis* 2019;68:1024–30.
190 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.
191 Orenstein R, Matteson EL. Opportunistic infections associated with TNF-α treatment. *Fut Rheumatol* 2007;2:567–76.
192 Santiago M, Leitão B. Prevention of Strongyloides hyperinfection syndrome: a rheumatological point of view. *Eur J Intern Med* 2009;20:744–8.
193 Winthrop KL. Infections and biologic therapy in rheumatoid arthritis: our changing understanding of risk and prevention. *Rheum Dis Clin North Am* 2012;38:727–45.