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

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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 anti-rheumatic 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, cyclosporin 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**			**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 than 15 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[98–104 138–146 147] (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 (+), ˆ238 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 214 patients 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.

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