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 Nikipherou8,9

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, and 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 HBV surface antigen (HBsAg) compared with those positive for antibody against HBV core antigen (anti-HBcore). 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.

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 autoimmune 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. 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. 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. 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. 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, ankyllosing spondylitis, Behcet’s disease, ANCA-vasculitis (AAV), cryoglobulinemic 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 suppress 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: biologic-targeted synthetic DMARDs (b-DMARDs); all b-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 tool10 (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 studies11; 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, most18–22 but not all23–25 studies, including a meta-analysis,26 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 TST16–18,19,21,24–26 (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,17,19,31–36 However, some evidence suggests that glucocorticoid use might lead to more frequent indeterminate IGRA results.30,32 As regards 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.27–29

Several studies have shown that agreement between TST and IGRA is moderate (agreement range: 61%–88%).14,15,17,18,33–36 (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 al70 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.18 Brode et al52 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, cyclosporin, mycophenolate and chlorambucil (adjusted OR 23.0 (95% CI 2.88 to 184) p=0.003) was associated with TB. Long et al68 in a study of 1788 patients with AIRD 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

<table>
<thead>
<tr>
<th>Author-year/country</th>
<th>Patients (N)</th>
<th>Disease</th>
<th>Association with TST</th>
<th>BCG</th>
<th>GC</th>
<th>csDMARDs</th>
<th>RoB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruan et al(^1) 2016/NA*</td>
<td>1940</td>
<td>AIRD</td>
<td>Positive</td>
<td>OR: 1.64 (95% CI 1.06 to 2.53)</td>
<td>Negative OR 0.45 (95% CI 0.30 to 0.69)</td>
<td>–</td>
<td>High quality</td>
</tr>
<tr>
<td>Reitblat et al(^2) 2018/Israel</td>
<td>65</td>
<td>RA</td>
<td>–</td>
<td>No</td>
<td>No</td>
<td>–</td>
<td>7</td>
</tr>
<tr>
<td>Agarwal et al(^3) 2014/USA</td>
<td>250</td>
<td>RA</td>
<td>–</td>
<td>Negative OR 6.4 (95% CI 0.30 to 0.69)</td>
<td>–</td>
<td>–</td>
<td>7</td>
</tr>
<tr>
<td>Hsia et al(^4) 2012/multinational</td>
<td>2303</td>
<td>IA</td>
<td>Positive (p&lt;0.0002 vs IGRA)</td>
<td>–</td>
<td>–</td>
<td>–</td>
<td>7</td>
</tr>
<tr>
<td>Klein et al(^5) 2013/Czech</td>
<td>305</td>
<td>AIRD</td>
<td>–</td>
<td>Negative, (p=0.0172)</td>
<td>Negative (combination with GC) (p=0.0003)</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Belard et al(^6) 2011/Denmark</td>
<td>248</td>
<td>AIRD‡</td>
<td>–</td>
<td>Negative (p=0.018)</td>
<td>–</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Soborg et al(^7) 2009/Denmark</td>
<td>302</td>
<td>IA</td>
<td>–</td>
<td>Negative RR 0.4 (95% CI 0.1 to 1.0), (p=0.04)</td>
<td>–</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Tamborenea et al(^8) 2009/Argentina</td>
<td>105</td>
<td>RA</td>
<td>–</td>
<td>Negative (mean dose: 6mg/day, OR 0.72 (95% CI 0.55 to 0.95), (p=0.021)</td>
<td>–</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Vassilopoulos et al(^9) 2008/Greece</td>
<td>70</td>
<td>AIRD</td>
<td>Positive§</td>
<td>Negative (mean dose: 6.8mg§)</td>
<td>–</td>
<td>6</td>
<td></td>
</tr>
<tr>
<td>Vassilopoulos et al(^{10}) 2008/Greece</td>
<td>393</td>
<td>IA</td>
<td>–</td>
<td>–</td>
<td>Positive (MTX OR 2.15 (95% CI 1.05 to 4.44)</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Maeda et al(^{11}) 2011/Japan</td>
<td>97</td>
<td>RA</td>
<td>Positive (14/19 false-positive TST)</td>
<td>–</td>
<td>–</td>
<td>5</td>
<td></td>
</tr>
<tr>
<td>Sargin et al(^{12}) 2018/Turkey</td>
<td>109</td>
<td>IA</td>
<td>–</td>
<td>No</td>
<td>–</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Lee et al(^{13}) 2012/South Korea</td>
<td>81</td>
<td>RA</td>
<td>No</td>
<td>–</td>
<td>–</td>
<td>4</td>
<td></td>
</tr>
<tr>
<td>Lee et al(^{14}) 2012/South Korea</td>
<td>81</td>
<td>RA</td>
<td>No</td>
<td>–</td>
<td>No</td>
<td>4</td>
<td></td>
</tr>
</tbody>
</table>

**Author-year/country** | **Patients (N)** | **Disease** | **Association** with IGRA | **RoB** |
<table>
<thead>
<tr>
<th></th>
<th></th>
<th></th>
<th></th>
<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruan et al(^1) 2016/NA*</td>
<td>1940</td>
<td>AIRD</td>
<td>No (GC, csDMARDs)</td>
<td>High quality</td>
</tr>
<tr>
<td>Vassilopoulos et al(^{15}) 2011/Greece</td>
<td>155</td>
<td>AIRD</td>
<td>Negative (GC, mean GC dose: 6.8mg), (OR=0.31 95% CI 0.1 to 0.96; p=0.04)</td>
<td>6</td>
</tr>
<tr>
<td>Belard 2011 et al(^{16}) /Denmark</td>
<td>248</td>
<td>AIRD‡</td>
<td>With indeterminate IGRA (GC), OR=6.1 95% CI 4.1 to 63.2, (p=0.001)</td>
<td>6</td>
</tr>
<tr>
<td>Soborg et al(^{17}) 2009/Denmark</td>
<td>302</td>
<td>IA</td>
<td>With indeterminate IGRA (GC), RR 4.2 (95% CI 1.6 to 10.7, (p=0.04)</td>
<td>6</td>
</tr>
<tr>
<td>Arias-Guillen et al(^{18}) 2018/Spain</td>
<td>393</td>
<td>IA</td>
<td>No (MTX)</td>
<td>5</td>
</tr>
<tr>
<td>Maeda et al(^{14}) 2011/Japan</td>
<td>97</td>
<td>RA</td>
<td>No (GC, (mean dose prednisolone: 5.7 mg), MTX)</td>
<td>5</td>
</tr>
<tr>
<td>Shovman et al(^{19}) 2009/Israel</td>
<td>35</td>
<td>RA</td>
<td>No (GC, (mean dose prednisolone: 8.3 mg), MTX)</td>
<td>5</td>
</tr>
<tr>
<td>Matulis et al(^{20}) 2008/UK</td>
<td>142</td>
<td>IMID</td>
<td>No (GC, csDMARDs)</td>
<td>5</td>
</tr>
</tbody>
</table>

Continued
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 countries75 these include: isoniazid for 6–9 months; combination of rifampicin/isoniazid for 3 months; rifampicin for 4 months76-89 (online supplemental table 2). For medium-to-high TB-endemic countries75: 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 months51 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 bDMARDs88-108 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 al122 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 studies98-104 138-141 147 (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 reactivation149 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 al150 in which 8% of patients with RA

<table>
<thead>
<tr>
<th>Author-year/country</th>
<th>Patients (N)</th>
<th>Disease</th>
<th>Association** with IGRA</th>
<th>RoB</th>
</tr>
</thead>
<tbody>
<tr>
<td>*Meta-analysis.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>†GC dose: prednisolone or equivalent.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>§CG associated with TST-positive/IGRA-negative discordant status (p=0.01).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>¶Associated with TST-negative/IGRA-positive discordant status (p=0.04).</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>**Association of GC or csDMARDs with IGRA.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>AIIRD, autoimmune inflammatory rheumatic disease; csDMARDs, conventional synthetic DMARD; DMARDs, disease modifying anti-rheumatic drugs; GC, glucocorticoids; IA, inflammatory arthritis; IGRA, interferon release 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.</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>
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. In another study, HBV reactivation was not seen in 44 RA, anti-HBcore-positive patients treated with rituximab. A recent study, examining 489 patients with resolved HBV, 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. 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%. 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 2 Agreement between TST (TST-IGRA and among IGRA)

<table>
<thead>
<tr>
<th>Author-year/country</th>
<th>Patients (N)</th>
<th>Disease</th>
<th>Agreement with TST</th>
<th>RoB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ruan et al17 2016/NA*</td>
<td>1940</td>
<td>AIIRD</td>
<td>72% (QTF) 75% (T-Spot)</td>
<td>High quality</td>
</tr>
<tr>
<td>Pyo et al44 2018/NA*</td>
<td>5224</td>
<td>AIIRD</td>
<td>73% (QTF) 75% (T-Spot)</td>
<td>Medium quality</td>
</tr>
<tr>
<td>Escalante et al44 2015/USA</td>
<td>101</td>
<td>AIIRD</td>
<td>81% (T-Spot)</td>
<td>7</td>
</tr>
<tr>
<td>Tang et al46 2020/Hong Kong</td>
<td>217</td>
<td>AIIRD</td>
<td>74.4% (QTF)</td>
<td>6</td>
</tr>
<tr>
<td>Wu et al48 2019/China</td>
<td>173</td>
<td>BD</td>
<td>0.391† (T-Spot)</td>
<td>6</td>
</tr>
<tr>
<td>Klein et al18 2013/Czech</td>
<td>305</td>
<td>AIIRD</td>
<td>66% (QTF)</td>
<td>6</td>
</tr>
<tr>
<td>Vassiliopoulos et al35 2011/Greece</td>
<td>155</td>
<td>AIIRD</td>
<td>64% (QTF) 71% (T-Spot)</td>
<td>6</td>
</tr>
<tr>
<td>Park et al 43 2009/South Korea</td>
<td>86</td>
<td>AIIRD</td>
<td>68.6% (IGRA)</td>
<td>6</td>
</tr>
<tr>
<td>Vassiliopoulos et al35 2008/Greece</td>
<td>70</td>
<td>AIIRD</td>
<td>72.8% (T-Spot)</td>
<td>6</td>
</tr>
<tr>
<td>Cho et al33 2016/South Korea</td>
<td>136/66</td>
<td>SLE/RA</td>
<td>84.6%/78.8% (QTF)</td>
<td>5</td>
</tr>
<tr>
<td>Kim et al39 2013/South Korea</td>
<td>724</td>
<td>IA</td>
<td>0.285† (QTF)</td>
<td>5</td>
</tr>
<tr>
<td>Lee et al40 2013/South Korea</td>
<td>64</td>
<td>RA</td>
<td>75% (QTF)</td>
<td>5</td>
</tr>
<tr>
<td>Minguez et al41 2012/Spain</td>
<td>53</td>
<td>IA</td>
<td>77.3% (QTF)</td>
<td>5</td>
</tr>
<tr>
<td>Scivo et al45 2013/Italy</td>
<td>102</td>
<td>AIIRD</td>
<td>88% (T-Spot)</td>
<td>5</td>
</tr>
<tr>
<td>Paluch-oles et al42 2013/Poland</td>
<td>90</td>
<td>IA</td>
<td>82% (QTF)</td>
<td>5</td>
</tr>
<tr>
<td>Maeda et al14 2011/Japan</td>
<td>97</td>
<td>RA</td>
<td>50.5% (QTF)</td>
<td>5</td>
</tr>
<tr>
<td>Inanc et al38 2009/Turkey</td>
<td>140</td>
<td>IA</td>
<td>61% (QTF)</td>
<td>4</td>
</tr>
<tr>
<td>Girlanda et al35 2010/Italy</td>
<td>69</td>
<td>AIIRD</td>
<td>0.341† (T-Spot)</td>
<td>4</td>
</tr>
<tr>
<td>Gogus et al36 2010/Tureky</td>
<td>45</td>
<td>IA</td>
<td>0.188† (QTF)</td>
<td>4</td>
</tr>
<tr>
<td>Xie et al49 2011/China</td>
<td>58</td>
<td>AIIRD</td>
<td>88.2% (T-Spot)</td>
<td>4</td>
</tr>
<tr>
<td>Hanta et al37 2012/Turkey</td>
<td>90</td>
<td>IA</td>
<td>0.121 (QTF)</td>
<td>4</td>
</tr>
<tr>
<td>So et al50 2017/Hong Kong</td>
<td>38</td>
<td>RA</td>
<td>73.7% (QTF)</td>
<td>4</td>
</tr>
<tr>
<td>Vassiliopoulos et al35 2011/Greece</td>
<td>155</td>
<td>AIIRD</td>
<td>81%</td>
<td>6</td>
</tr>
<tr>
<td>Martin et al33 2010/Ireland</td>
<td>150</td>
<td>AIIRD</td>
<td>98%</td>
<td>6</td>
</tr>
<tr>
<td>Iwagaisru et al62 2016/Japan</td>
<td>68</td>
<td>RA</td>
<td>0.68†</td>
<td>4</td>
</tr>
<tr>
<td>Melath et al34 2014/UK</td>
<td>76</td>
<td>AIIRD</td>
<td>91%</td>
<td>4</td>
</tr>
</tbody>
</table>

*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.

anti-HBs and anti-HBc.\(^ {156} \) 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).\(^ {159} \) 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.\(^ {155} \)

### 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\(^ {90–163} \) (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 (threifold 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 3  Antiviral prophylaxis and HBV reactivation in anti-HBcore-positive patients treated with cDMARDs, immunosuppressants or combination of antirheumatic drugs

<table>
<thead>
<tr>
<th>Author-year/country</th>
<th>Patients (N)</th>
<th>Disease</th>
<th>Treatment</th>
<th>Prophylaxis N (%)</th>
<th>Reactivation N (%)</th>
<th>RoB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Su et al(^ {122} ) 2018/NA*</td>
<td>2162 patients (53 studies)</td>
<td>AIIRD</td>
<td>Anti-rheumatic drugs†</td>
<td>Not effective for chronic/occult infection</td>
<td>Relative risk (95% CI)</td>
<td>Medium quality</td>
</tr>
<tr>
<td>Fukuda et al(^ {25} ) 2019/Japan</td>
<td>1127‡</td>
<td>RA</td>
<td>Anti-rheumatic drugs†</td>
<td>ND</td>
<td>57 (5.1)</td>
<td>8</td>
</tr>
<tr>
<td>Schwanek et al(^ {22} ) 2018/ Germany</td>
<td>84</td>
<td>AIIRD</td>
<td>Anti-rheumatic drugs†</td>
<td>1 (1.2)</td>
<td>8/84 (9.6)</td>
<td>8</td>
</tr>
<tr>
<td>Fukuda et al(^ {24} ) 2017/Japan</td>
<td>1042‡</td>
<td>AIIRD</td>
<td>Anti-rheumatic drugs†</td>
<td>0 (0)</td>
<td>35 (3.4)</td>
<td>8</td>
</tr>
<tr>
<td>Barone et al(^ {123} ) 2015/Italy</td>
<td>179</td>
<td>AIIRD</td>
<td>Anti-rheumatic drugs†</td>
<td>0 (0)</td>
<td>(0)</td>
<td>8</td>
</tr>
<tr>
<td>Matzusaki et al(^ {112} ) 2018/ Japan</td>
<td>360‡</td>
<td>RA</td>
<td>Anti-rheumatic drugs†</td>
<td>0 (0)</td>
<td>6/238 (2.5)</td>
<td>7</td>
</tr>
<tr>
<td>Tan et al(^ {114} ) 2012/China</td>
<td>188</td>
<td>RA</td>
<td>csDMARDs</td>
<td>0 (0)</td>
<td>2 (1.1)</td>
<td>7</td>
</tr>
<tr>
<td>Chen et al(^ {115} ) 2021/Taiwan</td>
<td>63</td>
<td>SLE</td>
<td>Immunosuppressants/GC</td>
<td>0 (0)</td>
<td>2 (3.2)</td>
<td>6</td>
</tr>
<tr>
<td>Chen et al(^ {130} ) 2020/Taiwan</td>
<td>925</td>
<td>RA</td>
<td>Anti-rheumatic drugs†</td>
<td>0 (0)</td>
<td>17 (1.8)</td>
<td>6</td>
</tr>
<tr>
<td>Laohapand et al(^ {126} ) 2015/Thailand</td>
<td>65</td>
<td>AIIRD</td>
<td>Methotrexate</td>
<td>0 (0)</td>
<td>(0)</td>
<td>6</td>
</tr>
<tr>
<td>Mori et al(^ {129} ) 2012/Japan</td>
<td>62‡</td>
<td>RA</td>
<td>Anti-rheumatic drugs†</td>
<td>ND</td>
<td>(0)</td>
<td>5</td>
</tr>
<tr>
<td>Urama et al(^ {131} ) 2010/Japan</td>
<td>135‡</td>
<td>RA</td>
<td>Anti-rheumatic drugs†</td>
<td>0 (0)</td>
<td>7 (5.2)</td>
<td>5</td>
</tr>
<tr>
<td>Xu et al(^ {116} ) 2015/China</td>
<td>115§</td>
<td>RA</td>
<td>Leflunomide</td>
<td>ND</td>
<td>(0)</td>
<td>3</td>
</tr>
</tbody>
</table>

*Meta-analysis.
†Various types of anti-rheumatic drugs used.
‡Anti-HBC (+) and/or Anti-HBs (+), * 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.
Table 4  Antiviral prophylaxis and HBV reactivation in anti-HBcore-positive patients treated with b-ts-DMARDs

<table>
<thead>
<tr>
<th>Author-year/country</th>
<th>Patients (N)</th>
<th>Disease</th>
<th>Treatment</th>
<th>Prophylaxis N (%)</th>
<th>Reactivation N (%)</th>
<th>RoB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Lee et al&lt;sup&gt;16,18&lt;/sup&gt; 2012/South Korea*</td>
<td>468 patients (9 studies)</td>
<td>IA</td>
<td>TNFi</td>
<td>0 (0)&lt;sup&gt;†&lt;/sup&gt;</td>
<td>8 (1.7)</td>
<td>Low quality</td>
</tr>
<tr>
<td>Harigai et al&lt;sup&gt;55&lt;/sup&gt; 2020/Multi</td>
<td>215</td>
<td>RA</td>
<td>Baricitinib</td>
<td>0 (0)</td>
<td>4 (1.9)</td>
<td>8</td>
</tr>
<tr>
<td>Papalopoulos et al&lt;sup&gt;144&lt;/sup&gt; 2018/Greece</td>
<td>212</td>
<td>AIIRD</td>
<td>bDMARDs</td>
<td>8 (3.6)</td>
<td>2 (2)</td>
<td>8</td>
</tr>
<tr>
<td>Lan et al&lt;sup&gt;101&lt;/sup&gt; 2011/Taiwan</td>
<td>88</td>
<td>RA</td>
<td>TNFi</td>
<td>0 (0)</td>
<td>1/70‡ (1.4)</td>
<td>8</td>
</tr>
<tr>
<td>Charpin et al&lt;sup&gt;141&lt;/sup&gt; 2009/France</td>
<td>21</td>
<td>IA</td>
<td>TNFi</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>8</td>
</tr>
<tr>
<td>Ahn et al&lt;sup&gt;138&lt;/sup&gt; 2018/South Korea</td>
<td>15</td>
<td>RA</td>
<td>Tocilizumab</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>7</td>
</tr>
<tr>
<td>Vassilopoulos et al&lt;sup&gt;103&lt;/sup&gt; 2010/Greece</td>
<td>19</td>
<td>IMID</td>
<td>TNFi</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>7</td>
</tr>
<tr>
<td>Serling-Boyd et al&lt;sup&gt;154&lt;/sup&gt; 2021/USA</td>
<td>24</td>
<td>AIIRD</td>
<td>Tocilizumab, Tofacitinib</td>
<td>6 (25.0)</td>
<td>0 (0)</td>
<td>6</td>
</tr>
<tr>
<td>Wang et al&lt;sup&gt;107&lt;/sup&gt; 2021/Taiwan</td>
<td>64</td>
<td>RA</td>
<td>Tofacitinib</td>
<td>0 (0)</td>
<td>2 (3.1)</td>
<td>6</td>
</tr>
<tr>
<td>Kuo et al&lt;sup&gt;150&lt;/sup&gt; 2020/Taiwan</td>
<td>64</td>
<td>RA</td>
<td>Tocilizumab</td>
<td>0 (0)</td>
<td>1 (1.6)</td>
<td>6</td>
</tr>
<tr>
<td>Chen et al&lt;sup&gt;108&lt;/sup&gt; 2018/Taiwan</td>
<td>75</td>
<td>RA</td>
<td>Tofacitinib</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6</td>
</tr>
<tr>
<td>Chen et al&lt;sup&gt;98&lt;/sup&gt; 2017/China</td>
<td>41</td>
<td>RA</td>
<td>Tocilizumab</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6</td>
</tr>
<tr>
<td>Gianniti et al&lt;sup&gt;140&lt;/sup&gt; 2017/Italy</td>
<td>131</td>
<td>SpA</td>
<td>TNFi</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6</td>
</tr>
<tr>
<td>Padovan et al&lt;sup&gt;102&lt;/sup&gt; 2016/Italy</td>
<td>21</td>
<td>RA</td>
<td>Abatacept</td>
<td>4 (19.1)</td>
<td>0 (0)</td>
<td>6</td>
</tr>
<tr>
<td>Nakamura et al&lt;sup&gt;143&lt;/sup&gt; 2016/Japan</td>
<td>57§</td>
<td>RA</td>
<td>bDMARDs</td>
<td>0 (0)</td>
<td>3 (5.3)</td>
<td>6</td>
</tr>
<tr>
<td>Biondo et al&lt;sup&gt;139&lt;/sup&gt; 2014/Italy</td>
<td>20</td>
<td>IA</td>
<td>TNFi</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6</td>
</tr>
<tr>
<td>Giardina et al&lt;sup&gt;85&lt;/sup&gt; 2013/Italy</td>
<td>7</td>
<td>IA</td>
<td>TNFi</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6</td>
</tr>
<tr>
<td>Caporalli et al&lt;sup&gt;140&lt;/sup&gt; 2010/Italy</td>
<td>67</td>
<td>IA</td>
<td>TNFi</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6</td>
</tr>
<tr>
<td>Zhang et al&lt;sup&gt;145&lt;/sup&gt; 2013/China</td>
<td>41</td>
<td>RA</td>
<td>Infliximab</td>
<td>0 (0)</td>
<td>0/30 (0)</td>
<td>5</td>
</tr>
<tr>
<td>Ye et al&lt;sup&gt;104&lt;/sup&gt; 2014/China</td>
<td>50</td>
<td>IA</td>
<td>TNFi</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>4</td>
</tr>
<tr>
<td>Chen et al&lt;sup&gt;156&lt;/sup&gt; 2019/Taiwan</td>
<td>103</td>
<td>RA</td>
<td>Rituximab</td>
<td>0 (0)</td>
<td>9 (8.7)</td>
<td>8</td>
</tr>
<tr>
<td>Kuo et al&lt;sup&gt;150&lt;/sup&gt; 2020/Taiwan</td>
<td>50</td>
<td>RA</td>
<td>Rituximab</td>
<td>0 (0)</td>
<td>4 (8)</td>
<td>7</td>
</tr>
<tr>
<td>Tien et al&lt;sup&gt;149&lt;/sup&gt; 2017/Taiwan</td>
<td>44</td>
<td>RA</td>
<td>Rituximab</td>
<td>0 (0)</td>
<td>4 (9.1)</td>
<td>7</td>
</tr>
<tr>
<td>Varisco et al&lt;sup&gt;151&lt;/sup&gt; 2016/Italy</td>
<td>33</td>
<td>RA</td>
<td>Rituximab</td>
<td>0 (0)</td>
<td>0 (0)&lt;sup&gt;¶&lt;/sup&gt;</td>
<td>7</td>
</tr>
<tr>
<td>Mitroulis et al&lt;sup&gt;147&lt;/sup&gt; 2013/Greece</td>
<td>12</td>
<td>AIIRD</td>
<td>Rituximab</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6</td>
</tr>
<tr>
<td>Barone et al&lt;sup&gt;155&lt;/sup&gt; 2021/Italy</td>
<td>44</td>
<td>AIIRD</td>
<td>Rituximab</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>5</td>
</tr>
</tbody>
</table>

*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.
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\textsuperscript{168–172} (table 6). On the other hand, in a study enrolling 184 patients with giant cell arteritis treated with glucocorticoids, Katsuyama \textsuperscript{174} found that glucocorticoids were coadministered in only 5 patients.\textsuperscript{173}

Data for other antirheumatic treatments beyond glucocorticoids are very limited. Katsuyama \textsuperscript{et al}\textsuperscript{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\%)).\textsuperscript{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 5  Hepatotoxicity and reactivation of hepatitis C in patients treated with DMARDs or immunosuppressants

<table>
<thead>
<tr>
<th>Author-year/country</th>
<th>Patients (N)</th>
<th>Concurrent antivirals* (%)</th>
<th>Disease</th>
<th>Treatment</th>
<th>Increase in LFTs N (%)</th>
<th>Increase in viral load N (%)</th>
<th>RoB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Iannone et al\textsuperscript{164} 2014/Italy\textsuperscript{†}</td>
<td>29</td>
<td>0%</td>
<td>RA</td>
<td>Etanercept or MTX or combination</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>Some concerns</td>
</tr>
<tr>
<td>Burton et al\textsuperscript{165} 2017/USA</td>
<td>748\‡</td>
<td>4.6%</td>
<td>RA</td>
<td>DMARDs</td>
<td>37 (3.4)</td>
<td>0 (0)</td>
<td>7</td>
</tr>
<tr>
<td>Chen et al\textsuperscript{166} 2015/Taiwan</td>
<td>26§</td>
<td>NS</td>
<td>SLE</td>
<td>Immunosuppressants</td>
<td>10 (38.5)§</td>
<td>10 (38.5)§</td>
<td>6</td>
</tr>
<tr>
<td>Costa et al\textsuperscript{169} 2014/Italy</td>
<td>15</td>
<td>NS</td>
<td>PsA</td>
<td>TNFi</td>
<td>0 (0)</td>
<td>0 (0)</td>
<td>6</td>
</tr>
<tr>
<td>Parke et al\textsuperscript{161} 2004/USA</td>
<td>5</td>
<td>0%</td>
<td>RA</td>
<td>TNFi</td>
<td>0 (0)</td>
<td>1 (20)\‡</td>
<td>6</td>
</tr>
<tr>
<td>Peterson et al\textsuperscript{162} 2003/USA</td>
<td>24</td>
<td>0%</td>
<td>RA</td>
<td>Etanercept or Infliximab</td>
<td>0 (0)</td>
<td>6/22 (27.3)\†</td>
<td>6</td>
</tr>
<tr>
<td>Gandhi et al\textsuperscript{163} 2017/USA</td>
<td>14\‡‡</td>
<td>14.3%</td>
<td>RA, PsA</td>
<td>Etanercept</td>
<td>7 (50.0)</td>
<td>5/10 (50.0)</td>
<td>5</td>
</tr>
</tbody>
</table>

*Patients concurrently treated with antivirals.
†Randomised controlled trial.
‡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.
†‡1097 treatment-episodes.
‡‡5/7 were 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.

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

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

*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 trimethoprime/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\(^{76-180}\) (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 RA 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 immunemediated 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 coccidioidomycosis (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 geopandemiaology of infections.

HBV is another much-discussed pathogen as reactivation is not unusual in patients with AIIRD treated with immunosuppressive/immunomodulatory drugs. Anti-viral 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.

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 AIRD. Third, there is a significant heterogeneity regarding different AIRD 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.

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 AIRD. 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

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

Twitter Elena Nikiphorou @ElenaNikUK

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 (C1118) project for the 2022 EULAR recommendations on the screening and prophylaxis of chronic and opportunistic infections.


Patient consent for publication Not applicable.

Provenance and peer review Not commissioned; externally peer reviewed.

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

Open access This is an open access article distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on different terms, provided the original work is properly cited, appropriate credit is given, any changes made indicated, and the use is non-commercial. See: http://creativecommons.org/licenses/by-nc/4.0/.

ORCID ids

George E Fragoulis http://orcid.org/0000-0003-4932-7023
Minralini Dey http://orcid.org/0000-0001-6858-4338
Delphine Courvoisier http://orcid.org/0000-0002-1956-2607
James Galloway http://orcid.org/0000-0002-1239-2781
Elena Nikiphorou http://orcid.org/0000-0001-6847-3726

REFERENCES


50 So H, Yuen CS, Yp 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.
94 Song YJ, Cho SK, Kim H, et al. Risk of tuberculosis development in patients with rheumatoid arthritis receiving targeted therapy:


