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Rheumatoid arthritis

Safety of synthetic and biological DMARDs: a systematic literature review informing the 2025 update of the EULAR recommendations for the management of rheumatoid arthritis

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ABSTRACT

Objectives: This study aims to perform a systematic literature review (SLR) concerning the safety of synthetic and biological disease-modifying antirheumatic drugs (DMARDs) for the 2025 update of European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of rheumatoid arthritis (RA).

Methods: Medline, Embase, Cochrane CENTRAL, and Web of Science were searched for observational and randomised controlled trials with a primary endpoint of DMARD safety on the conventional synthetic (cs-), biological (b-), and targeted synthetic-DMARDs, as well as glucocorticoids, published between January 14, 2022, and January 22, 2025. Separate searches on DMARD monitoring were conducted from database inception to January 22, 2025. A comparator group was required for inclusion. All safety outcomes were included.

Results: A total of 3837 articles were identified, with 321 selected for full-text review; 71 articles were included. Across the evidence base, infections were the most frequently assessed outcome: 13 studies examined serious or hospitalised infections, usually as composite endpoints of bacterial, opportunistic, and herpes zoster infection, while 1 addressed nonserious infections. Serious infections were more common with bDMARDs than csDMARDs. Janus kinase inhibitors (JAKis) showed a higher herpes zoster risk than bDMARDs. Tuberculosis risk was not increased with JAKis compared with bDMARDs, but was higher with infliximab and adalimumab compared with etanercept. Fifteen studies evaluated malignancy, split evenly between analyses of any malignancy and those excluding nonmelanoma skin cancer (NMSC); 2 focused on melanoma and 2 on NMSC. Increased NMSC was noted in patients with RA using DMARDs compared with the general population, with no link to a specific DMARD. Cardiovascular and thromboembolic events were reported in 20 studies. No consistent evidence of increased major adverse cardiovascular events risk with JAKis compared with bDMARDs was identified. Venous thromboembolism risk appeared elevated with JAKis compared with bDMARDs, driven mainly by pulmonary embolism. Fourteen studies reported retention and adverse event–related withdrawals, and 8 assessed other specific adverse events. Gastrointestinal perforation and demyelinating disease were each reported in 3 studies. No eligible articles were identified in searches on DMARD monitoring.

Conclusions: There has been a notable increase in studies evaluating safety outcomes, with the majority of these being observational studies focusing primarily on malignancy, thromboembolic, and cardiovascular events, with most studies pertaining to JAKi safety. A substantial proportion of studies in this SLR relied on claims databases to evaluate safety outcomes, a practice that carries important methodological limitations for safety research. Surprisingly, not many studies looked into glucocorticoid safety outcomes over the past 3 years. This SLR, along with the SLR on efficacy of DMARDs, informed the 2025 update of the EULAR recommendations for management of RA with synthetic and biological DMARDs.

INTRODUCTION

In comparison with the general population, patients with rheumatoid arthritis (RA) are at an increased risk of morbidity and mortality, particularly those with more severe disease activity [1,2]. Disease-modifying antirheumatic drugs (DMARDs) provide effective treatment for RA that can alleviate pain, joint damage, and disability [3]. DMARDs currently approved for RA include conventional synthetic DMARDs (csDMARDs), biological DMARDs (bDMARDs), and targeted synthetic DMARDs (tsDMARDs) [4]. DMARDs is an umbrella term including drugs with different modes of action and molecular targets such as tumour necrosis factor (TNF) alpha, interleukin (IL)-6 receptor, T-cell costimulation (CD80/86), and B-cells (CD20). So far, Janus kinase inhibitors (JAKis) are the only tsDMARDs approved by the U.S. Food and Drug Administration and European Medicines Agency (EMA) for RA. Exploring the associated safety aspects of DMARDs remains clinically important as they influence clinical decision-making. This is particularly important following the recent regulatory changes made by EMA in its recommendations of JAKi use in immune-mediated diseases due to concerns over the increased risk of cardiovascular (CV) and thromboembolic events, and malignancies [5]. Previous systematic literature reviews (SLRs) have shed light on the safety and efficacy aspects of drugs used to treat RA, with the latest being published in 2022 [6,7]. It is important to update the evidence on safety that has become available from randomised controlled trials (RCTs) and real-world data analyses since then.

Safety concerns associated with many DMARDs can be mitigated by the early identification of toxicity through routine laboratory monitoring [8]. Significant variation in blood monitoring frequency when using DMARDs is described [9]. Current recommendations adopt a cautious stance regarding DMARD blood monitoring frequency, primarily based on clinical trial safety data [10,11]. Considering these gaps, an SLR on DMARD monitoring was incorporated, prompted by the steering committee's decision to broaden the scope of inquiry to encompass previously underexplored aspects of clinical practice.

In order to inform the task force responsible for the 2025 update of the European Alliance of Associations for Rheumatology (EULAR) RA management recommendations, we performed an SLR to update evidence on the safety of csDMARDs, bDMARDs, and tsDMARDs in patients with RA, building upon the previous SLR performed for the corresponding 2022 update [6]. The safety SLR, as well as the SLR on DMARD monitoring, is

WHAT IS ALREADY KNOWN ON THIS TOPIC

- Since the 2022 European Alliance of Associations for Rheumatology (EULAR) recommendations for the management of rheumatoid arthritis (RA), new evidence has emerged on the safety of synthetic and biological DMARDs (bDMARDs) in RA.

WHAT THIS STUDY ADDS

- Serious infections continue to be shown to be more common with bDMARDs when compared to conventional synthetic DMARDs (csDMARDs), while Janus kinase inhibitors (JAKis) show a higher herpes zoster risk than bDMARDs.
- The risk of serious infections was found to be the same for bDMARDs and JAKis; higher rates of serious infections were reported with JAKis compared with interleukin-6 inhibitors in 1 study.
- The risk of malignancy, excluding nonmelanoma skin cancer, was similar between csDMARDs and bDMARDs and across different bDMARDs, and it was not increased with JAKi compared with tumour necrosis factor inhibitors.
- Increased nonmelanoma skin cancer was noted in patients with RA using DMARDs compared with the general population, with no link to a specific DMARD.
- In observational studies, no consistent new evidence of increased major adverse cardiovascular events risk was demonstrated for JAKi when compared with bDMARDs. No new randomised controlled trials investigating safety outcomes as a primary endpoint on JAKi have been published since the last update.
- Venous thromboembolic, mainly pulmonary embolism, risk appeared to be increased in patients treated with JAKi when compared with bDMARDs.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

- This review informed the 2025 EULAR recommendations for the management of RA, highlighting new evidence on the safety of synthetic and bDMARDs.

included in this manuscript, while an SLR on efficacy, RA-associated interstitial lung disease, and pre-RA is published separately [12]. Both SLRs provided the task force with the current state of evidence.

METHODS

EULAR standard operating procedures for the development of recommendations and points to consider, as well as the Cochrane Handbook for SLRs and Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines, were adhered to in this project [13–16].

Literature search

The scope of the review was defined during an initial steering committee meeting held on November 16, 2024. Research questions were defined in Population, Intervention, Comparator, Outcome (PICO) format, and a study protocol was distributed among all committee members. Based on these, a literature search strategy was developed by an experienced librarian (JWS), and Medline, Embase, The Cochrane Central Register of Controlled Trials (CENTRAL), and Web of Science, as well as conference abstracts from the 2023 and 2024 EULAR and American College of Rheumatology annual meetings, were screened for all relevant articles without language restrictions.

PICO questions and the detailed search strategies used are provided in the Supplementary Material (Section S1). Seven research questions were formulated for the safety SLR. Observational studies, namely cohort studies/registries with >50 participants, were the main study type in the previous and current SLRs. Studies were only eligible if they included an adequate comparator group (either another DMARD or a combination DMARD therapy strategy); the sole exception was a study that used the general population as a comparator due to a lack of other available studies on pregnancy-related outcomes. Additionally, RCTs with a primary safety outcome were included. Safety data of RCTs (and related long-term extension studies), selected in the accompanying SLR addressing efficacy [12], were also included to assess the safety of drugs with or without available real-world data. Unlike the previous update, no separate SLR on glucocorticoids (GCs) was conducted, but respective trials on GCs were included in the efficacy and safety SLRs.

For the separate SLR focused on DMARD monitoring in patients with RA, both randomised controlled and observational, namely cohort, studies with at least 30 participants were included. Studies were only eligible if they included an adequate comparator group (either another DMARD or a combination DMARD therapy strategy). Details on the additional search are provided in the Supplementary Material (Section S1.2). Ten research questions were formulated for DMARD monitoring (Supplementary Material, Section S1.6).

For all other searches, study duration of at least 6 months and a sample size of at least 50 participants were considered, but smaller trials or studies were also included if the former were not available for specific research questions. Published manuscripts and conference abstracts were considered without language restriction. Publications were included from January 14, 2022, to January 22, 2025, for the update of the SLR for safety of DMARDs; for the DMARD monitoring SLR, we included all search results from database inception until January 22, 2025, as monitoring had not been examined in previous SLRs. Details on complete search strategies are provided in the Supplementary Material.

Data extraction

Two researchers (FL and VK) screened 10% of all articles in duplicates. If an agreement rate of >90% was achieved, the remaining articles were screened by 1 researcher (FL), and uncertainties were discussed with the methodologists (AK and RBML). Selected articles were fully assessed for eligibility, study and baseline characteristics, as well as safety/monitoring outcomes from the finally included articles extracted using a previously prepared data extraction form.

Assessment of risk of bias

The risk of bias (RoB) of each included study was assessed using the 'Hayden tool' for observational studies and The Cochrane Collaboration's tool for RCTs (RoB 2) [17–19].

The RoB assessment in this SLR was conducted using the Hayden tool, which provides a structured framework for evaluating observational studies across key domains, including study participation, attrition, measurement of prognostic factors and outcomes, confounding, and statistical analysis. Applying this tool to real-world evidence presented several challenges, particularly given the variability in exposure and outcome definitions and the frequent presence of residual confounding that could not be fully assessed. Studies rated as high RoB commonly

demonstrated limited representativeness of the underlying population and insufficient reporting on the handling of missing data. A further recurring limitation was the lack of clarity in outcome measurement, which hindered the ability to reliably compare findings across studies.

No meta-analyses were conducted due to the high heterogeneity of studies and patient populations included. Decisions on study selection, extraction, and RoB assessment were discussed with a methodologist (either AK or RBML) whenever necessary.

RESULTS

Safety SLR

For the safety SLR, a total of 3837 abstracts were obtained from the database search, of which 3502 were screened following deduplication. A total of 321 articles were selected for full-text review, and 71 articles were finally included. No RCTs with a primary safety outcome were identified; in total, 13 RCTs from the efficacy SLR were included. Thirteen RCTs investigating DMARDs with efficacy as a primary endpoint were included; these studies were selected from the efficacy SLR that was also submitted separately [12]. We investigated the reported safety events from these RCTs, but no RCTs with a primary endpoint of a safety outcome were identified.

For DMARD monitoring, 3835 abstracts were obtained, with 3698 screened following deduplication. Thirty articles were sought for retrieval and assessment of eligibility, of which none were deemed eligible for inclusion. Flowcharts of these 2 literature searches are provided in Figures 1 and 2. Studies were heterogeneous, precluding meta-analysis; therefore, results are presented descriptively.

A summary of all outcomes examined and the total number of studies included for each outcome in the safety SLR is shown in Table 1. A summary of the number of included publications in the efficacy SLR for the different classes of drugs is shown in Table 2. Detailed overviews of all studies included, as well as RoB analyses, baseline characteristics, and safety outcomes, are provided in the Supplementary Material.

Observational studies

Infections

Twenty-one studies evaluated the risk of infections:

Thirteen studies evaluated the risk of serious infections (5 low [20–24], 2 moderate [25,26], and 6 high RoB [27–32]), and 2 studies examined the risk of opportunistic infections (high and moderate RoB, respectively [26,33]).

Six studies evaluated the risk of herpes zoster infection (1 low [24], 1 moderate [26], and 4 high RoB [28,32,34,35]), and 4 evaluated the risk of tuberculosis (TB) (1 low RoB [20], 3 high RoB [36–38]). One study assessed the risk of nonserious infections [34] (high RoB), and 2 assessed the risk of COVID-19 infection [39,40] (both high RoB). No studies examined the risk of pneumocystis pneumonia since the last SLR.

Serious infections

The risk of serious infection was increased with bDMARDs compared with csDMARDs in 2 studies (adjusted hazard ratio [aHR]: 1.74 [1.07-2.81] and 2.3 [1.6-3.3]) [21,23], with the risk remaining increased when compared with non–TNF inhibitor (TNFi) (2.3 [1.2-4.1]) and TNFi (1.9 [1.3,3.0]) separately [21] (Table 3) [20–32]. These studies investigated the risk of *Staphylococcus aureus* bacteraemia [21] and osteoarticular infection post Staphylococcus bacteraemia [23]. These represent an extended follow-up of the same cohort. No increased risk was observed in a study comparing leflunomide and tacrolimus with TNFi (aHR 1.03 [0.87-1.22] and 0.91 [0.77-1.08], respectively) (2 of them at low RoB) [20,22,28].

Five studies that compared different bDMARDs showed overall similar risk of serious infection across different bDMARDs [20,24,27,30,31]. In 2 low RoB studies, the risk of serious infection was similar across different bDMARDs, including TNFi, IL-6 inhibitor (IL-6i), and rituximab, while a lower risk was reported with certolizumab and sarilumab [20,24].

One study, at high RoB, showed different levels of risk across different bDMARDs compared with IL-6i; with TNFis (etanercept, adalimumab, and golimumab), the risk was increased compared with IL-6i (tocilizumab) (aHR 2.40 [1.24-4.61], 1.90 [0.75-4.83], and 1.21 [0.66-2.23], respectively), while with

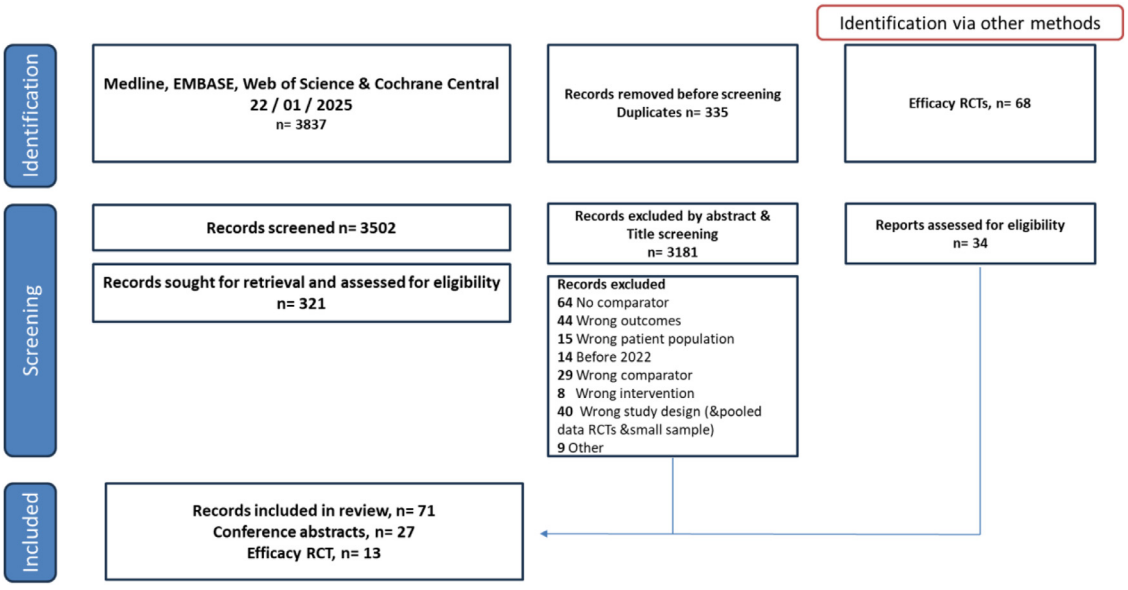

Figure 1. PRISMA chart illustrating the systematic literature review (SLR) and study selection process for the DMARD safety SLR. DMARD, disease-modifying antirheumatic drug; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCT, randomised controlled trial.

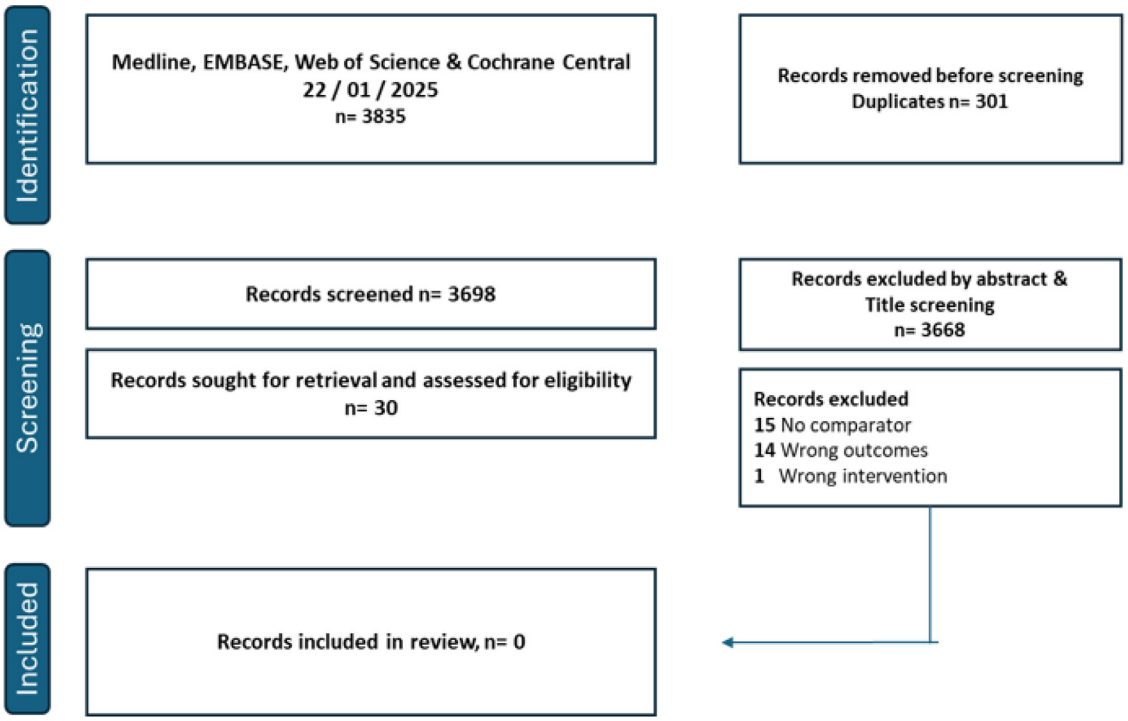

Figure 2. PRISMA chart illustrating the systematic literature review (SLR) and study selection process for the DMARD Monitoring SLR. No articles were identified via other methods (manual search). DMARD, disease-modifying antirheumatic drug; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

abatacept, the risk was reduced (aHR 0.89 [0.49-1.62]) [27]. Lower risk with abatacept compared with TNFi was also seen in a high RoB study (aHR 0.610 [0.247-1.508]), while the risk was increased with tocilizumab compared with TNFi (aHR 2.493 [1.275-4.876]) [31].

Five studies compared the risk of serious infections between bDMARDs and JAKi [22,25,26,28,32] (1 study at low RoB [22]); the risk was similar to bDMARDs with JAKi [22,25,26,28], apart from 1 study where the risk was increased when JAKis were compared with IL-6i (aHR 3.45 [1.48-9.04]) (high RoB [32]). In 1 study, the risk of a serious infection was increased in older individuals aged >76 years with tofacitinib compared with bDMARDs [22].

Four studies on serious infections performed subgroup analysis and looked for age-specific associations; 1 study reports the hazard of a first serious infection due to tofacitinib compared with bDMARDs to be increased with increasing age by a factor of 1.05 (95% CI 1.00-1.11) per year, although the relationship was not statistically significant [22]. The increased risk for a serious infection on tofacitinib becomes convincing and potentially clinically relevant after the age of 69 (1.99 [95% CI 1.02-3.90] and 2.05 [95% CI 1.04-4.05], left and right date imputation), while at the age of 76, the risk is higher (2.85 [95% CI 1.27-6.38] and 2.87 [95% CI 1.27-6.52], left and right date imputation); results below age 65 are too uncertain to interpret [22]. Three studies report no significant differences in the incidence or risk of serious infections between JAKis and TNFis for patients aged >65 years with at least 1 atherosclerotic risk factor [25], a similar risk for serious bacterial infections and opportunistic infections among those aged ≥60 [26], and, for those aged ≥75 treated with different bDMARDs, the risk remained similar except for etanercept compared with tocilizumab (adjusted risk ratio (aRR) 0.30 [0.11-0.85] for <65 years, aRR 0.99 [0.50-1.98] for 65-74 years, and aRR 2.40 [1.24-4.61] for >75 years) [27].

Herpes zoster

The risk for herpes zoster (HZ) was found to be more than 3 times higher among patients with RA on b/tsDMARDs compared with the general population (aHR 3.65 [3.13-4.25]) [24] (Table 4) [24,26,28,32,34,35]. The risk of HZ was assessed in 6 studies in total [24,26,28,32,34,35] (1 low RoB [24]). Two studies examined the risk of HZ across different bDMARDs and JAKis compared with etanercept [24,35]; HZ risk was increased in all studies comparing JAKis to TNFis [26,28,32,34], abatacept [35], or IL-6i [32]. The risk of serious HZ was examined only in 1 high RoB study (aHR 7.43 [3.91-14.11]) [26] comparing JAKis to TNFis. On individual JAKi, the HZ risk was found to be increased with tofacitinib (aHR 2.06 [1.38-3.08] [35] and 4.00 [1.59-10.06]) [24] and baricitinib (aHR 3.82 [2.05-7.09]) [24], while no published data on any other JAKis were identified.

When looking into recurrent HZ infection (defined as active HZ infection on DMARDs with a history of HZ infection pre-DMARD initiation), the relationship remained the same, with an increased risk observed with tofacitinib vs etanercept (aHR 3.01 [1.49-6.11]) or abatacept (aHR 3.69 [1.77-7.69]) [35]. The risk for HZ was the same with baricitinib compared with tofacitinib [28,34] in 2 studies, whereas in 1 study the risk was found to be increased with tofacitinib compared with baricitinib (aHR 1.92 [0.43-8.51]) [32].

Infliximab (aHR 1.36 [1.06-1.74]) and adalimumab (aHR 1.29 [1.02-1.64]) were associated with a significantly increased HZ risk compared with abatacept [34].

Tuberculosis

The risk of TB, although a rare event, was found to be more than 3 times higher among patients with RA on b/tsDMARDs

Table 1
Number of all observational studies and outcomes included in the current safety literature review

2022-2025 SLR Observational studies	
Main outcome	No. of studies n = 71
Infections	
Serious infections	12 (+1)
Any opportunistic infection	1 (+1)
Herpes zoster	2 (+4)
Tuberculosis	3 (+1)
Pneumocystis jirovecii	0
Hospitalisation due to infection	(+1)
Reactivation of hepatitis B	0
Nonserious infections	1
COVID-19	2
Malignancies	
Any malignancy	9
Any excluding NMSC	5
Any lymphoma	(+1)
Any haematological	(+3)
Leukaemia	0
Any skin	1
Melanoma	(+2)
NMSC	(+3)
Mortality	9
Cardiovascular events	
Cardiovascular events	5
MACE combined (MI, stroke, CV death)	11
Heart failure	1 (+1)
MI	1 (+5)
Stroke	(+6)
Arrhythmia	1 (+2)
Venous thromboembolism	1 (+6)
Gastrointestinal perforation	2
Neuroinflammatory events	1
Pregnancy outcomes	1[a]
Withdrawals due to AEs	14
Glucocorticoid-associated AEs	3[b]
Any AE	8[c]

AE, adverse event; CV, cardiovascular; MACE, major adverse cardiovascular events; MI, myocardial infarction; NMSC, nonmelanoma skin cancer; SLR, systematic literature review.
()(in brackets) to indicate studies that examined more than one outcome.
[a] Pre-eclampsia.
[b] Infection, cardiovascular events, diabetes, fracture.
[c] Dyslipidaemia, peripheral oedema, nonsteatosis liver disease, depression, suicide, autoimmune thyroid disease, diabetes, bone mineral density loss and fractures.

compared with the general population (aHR 3.14 [1.60-6.14]) [23]. TB was assessed in 4 studies (1 low RoB) [20]. The risk of TB was not increased with JAKis compared with TNFis or bDMARDs [37,41]. Infliximab and adalimumab increased the risk of TB compared with etanercept (aHR 3.4 [1.6-7.3] and aHR 3.3 [1.4-7.8], respectively) [20] or IL-6i (aHR 3.07 [1.33-7.1]) [36].

Opportunistic infections

Nontuberculous mycobacterial infection was assessed in 1 high RoB study; the risk was not found to be increased with TNFis compared with csDMARDs (aHR 0.517 [0.205-1.301]) [33]. Similarly, the risk of opportunistic infection (including TB, nontuberculous mycobacterial infection, and systemic fungal infections; the majority being TB) was lower with JAKis compared with TNFis (aHR 0.25 [0.09-0.73]) [26].

No *Pneumocystis jirovecii* pneumonia infection was reported in any studies.

COVID-19 infection was assessed in 2 studies; the risk of COVID-19 infection was not increased with JAKis or IL-6i compared with TNFis [39], but hospitalisation, intensive care unit admission, and severe/fatal events due to COVID-19 infection were increased with rituximab (aHR 2.14 [1.51-3.04], 5.22 [1.77-15.41], and 1.66 [0.89-3.08], respectively) compared with csDMARDs [40].

Malignancy

Fifteen studies evaluated the risk of malignancy, of which 14 evaluated the risk of any type of malignancy (Table 5). Of those 14, 5 studies included any type of malignancy except nonmelanoma skin cancer (NMSC) (1 low [42], 1 moderate [43], and 3 high RoB [44–46]); 1 included any malignancy except haematological malignancy [28] (high RoB), and 1 included any malignancy except skin malignancy [47] (moderate RoB). Two studies examined the risk of melanoma [44,48] (high RoB). Three studies examined the risk of haematological malignancy alone [43,44,49] (high and moderate RoB). Two studies examined the risk of NMSC only [43,45], and 1 study examined the risk between methotrexate and hydroxychloroquine (HCQ) users for any new skin malignancy [48] (high and moderate RoB).

Any type of malignancy

Six studies assessed the risk of any malignancy. The risk of malignancy was similar with csDMARDs and bDMARDs [50,51], including 1 low RoB study [50]. The risk was increased with rituximab, abatacept, and JAKis compared with TNFis in 1 high RoB study [52], whereas the same risk was not found in another study examining different bDMARDs and JAKis vs TNFis [53]; in the latter, risk was increased with IL-6i and cytotoxic T-lymphocyte–associated protein 4 immunoglobulin fusion proteins (CTL4-IgG) compared with TNFis [53]. Similar risk was found between JAKis and TNFis in 3 studies [25,38,49].

Any type of malignancy except NMSC

Seven studies assessed the risk of malignancy excluding NMSC. The risk was similar between csDMARDs and bDMARDs [44,47] and across different bDMARDs [47], while an increased incidence rate was reported with JAKis compared with IL-6i (incidence rate ratio (IRR) 2.13 [0.67-7.42]) (high RoB study and not statistically significant) [46]. The risk was not increased with JAKis compared with TNFis (aHR range from 0.385 [0.095-1.552] to 1.41 [0.76-2.37]) [28,42,43,45,47], while numerically increased risk estimates were detected in 1 study with low RoB [42].

NMSC and melanoma

NMSC incidences in the JAKi, TNFi, and non-TNFi groups were all higher than in the general population [43]; the risk of NMSC has been shown to be increased with JAKis compared with TNFis in 2 studies of moderate (aHR 1.39 [1.01-1.91]) and high RoB (aHR 1.38 [0.39-4.88]); however, no differences were observed among different csDMARDs [43,45,48].

Similarly, no difference was found for the risk of melanoma with bDMARDs compared with csDMARDs, or among different csDMARDs [44,48].

Haematological malignancy

The risk of all haematological malignancies was increased with JAKis compared with TNFis in 2 studies (both high RoB) (aHR 1.90 [0.70-5.16] [42] and aHR 2.86 [0.41-20.00]) [49], while the risk was similar with bDMARDs (aHR 1.35 [0.72-2.53]), TNFi-exposed (aHR 0.77 [0.42-1.43]), and csDMARDs or in combination (aHR 1.18 [0.55-2.52]) [44].

Table 2
Number of included publications in the efficacy SLR for the different classes of drugs

Drug class	No. of publications	No. of RCTs	No. of LTEs	No. of PBO-controlled	No. of biosimilar studies
csDMARDs					
MTX	1	1			
bDMARDs					
PD-1 agonist	1	1		1	
TNFi	3				3
CD40L	1	1		1	
GM-CSF	2	2	2	2	
IL-6Ri	4	4	1		3
CD80/86	1	1		1	
tsDMARDs					
JAKi 1-3	1	1		1	
BTK	1	1		1	
JAK1	1	1	1	1	
Total	16	13	4	8	6

bDMARD, biological disease-modifying antirheumatic drug; BTK, Bruton's tyrosine kinase inhibitor; CD80/86, cluster of differentiation 80/86; csDMARD, conventional disease-modifying antirheumatic drug; CD40L, CD40 ligand; GM-CSF, granulocyte-macrophage colony-stimulating factor; IL-6Ri, interleukin-6 receptor inhibitor; JAK1, Janus kinase 1; JAKi, Janus kinase inhibitor; LTE, long-term extension; MTX, methotrexate; PBO, placebo-controlled; PD-1, programmed death-1; RCT, randomised controlled trial; SLR, systematic literature review; TNFi, tumour necrosis factor inhibitor; tsDMARD, targeted synthetic disease-modifying antirheumatic drug.

Table 3
Serious infections, comparison between different DMARDs (observational studies)

Study ID	Registry	Intervention	Control	aHR/OR	RoB
Shin et al [29], 2022	Claims database	LEF	TNFi	1.03 (0.87-1.22)	High
		TAC		0.91 (0.77-1.08)	
Harigai et al [27], 2024	MDV[c]	ETA	TCZ	2.40 (1.24-4.61)	High
		ADA		1.90 (0.75-4.83)	
		GOL		1.21 (0.66-2.23)	
		ABA		0.89 (0.49-1.62)	
Dieperink et al [21], 2022	DANBIO	bDMARDs	Non-bDMARD users	2.3 (1.6-3.3)	Low
		TNFi		1.9 (1.3-3.0)	
		non-TNFi		2.3 (1.2-4.1)	
Lauper et al [20], 2024	BSRBR-RA	ADA	ETA	1.1 (1.0-1.3)	Low
		IFX		1.3 (1.1-1.5)	
		CERT		0.8 (0.5-1.1)	
		RTX		1.0 (0.8-1.1)	
		TCZ		1.2 (1.0-1.4)	
		ABA		1.2 (0.8-1.7)	
Frisell et al [24], 2023	ARTIS	ADA	ETA	1.12 (0.96-1.31)	Low
		IFX		1.32 (1.09-1.60)	
		CERT		1.10 (0.91-1.33)	
		GOL		1.07 (0.86-1.32)	
		ABA		1.08 (0.91-1.29)	
		RTX		1.31 (1.15-1.50)	
		TCZ		0.98 (0.80-1.19)	
		SAR		0.61 (0.24-1.53)	
		BARI		0.98 (0.75-1.29)	
		TOFA		0.89 (0.47-1.69)	
Ota et al [30], 2024	Claims database	TNFi	IL-6i	0.66 (0.36-1.20)	High
Bellan et al [31], 2022	Claims database	ABA	TNFi	0.61 (0.247-1.508)	High
		TCZ		2.49 (1.275-4.876)	
Dieperink et al [23], 2024	DANBIO	bDMARDs	Non-bDMARD users	1.74 (1.07-2.81)	Low
		Current user		2.27(1.29-3.98)	
Riek et al [22], 2023	SCQM	bDMARDs	TOFA	1.05 (1.00-1.11)	Low
Mok et al [25], 2024	HK registry	JAKi	TNFi	1.08 (0.84-1.39)	Moderate
Uchida et al [28], 2023	Rheumatology departments[a]	JAKi	TNFi	0.79 (0.417-1.502)	High
Choi et al [26], 2023	Claim database	JAKi	TNFi	1.04 (0.71-1.52)	Moderate
Yoshida et al [32], 2024	FMU Rheumatology[b]	JAKi	IL-6i	3.45 (1.48-9.04)	High

ABA, abatacept; ADA, adalimumab; aHR, adjusted hazard ratio; ARTIS, Anti-Rheumatic Therapy in Sweden, BARI, baricitinib; bDMARD, biological disease-modifying antirheumatic drug; BSRBR-RA, British Society of Rheumatology Biologics Register for Rheumatoid Arthritis; c, control; CERT, certolizumab pegol; DANBIO, Danish nationwide quality registry; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; FMU, Fukushima Medical University; GOL, golimumab; HK, Hong Kong biologic registry; i, intervention; IFX, infliximab; IL-6i, interleukin-6 inhibitor; JAKi, Janus kinase inhibitor; LEF, leflunomide; OR, odds ratio; RoB, risk of bias; RTX, rituximab; SAR, sarilumab; SCQM, Swiss Clinical Quality Management in Rheumatic diseases; TAC, tacrolimus; TCZ, tocilizumab; TNFi, tumour necrosis factor inhibitor; TOFA, tofacitinib.

[a] Nagasaki University Hospital, Sasebo Chuo Hospital, or Ureshino Medical Center.

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[c] Medical Data Vision Co., Ltd (Tokyo, Japan)

Table 4
Herpes zoster, comparison between different DMARDs (observational studies)

Study ID	Registry	Intervention	Control	aHR	RoB
Frisell et al [24], 2023	ARTIS	ADA	ETA	1.48 (0.90-2.43)	Low
		IFX		1.64 (0.90-2.99)	
		CERT		1.32 (0.73-2.38)	
		GOL		1.20 (0.63-2.28)	
		ABA		0.89 (0.49-1.64)	
		RTX		1.21 (0.77-1.91)	
		TCZ		1.06 (0.52-2.17)	
		SAR		N/A	
		BARI		3.82 (2.05-7.09)	
		TOFA		4.00 (1.59-10.06)	
Jeong et al [35], 2022	Claims database	INF	ETA	1.14 (0.95-1.36)	High
		ADA		1.09 (0.94-1.25)	
		GOL		0.89 (0.69-1.14)	
		TOC		0.74 (0.58-0.94)	
		RTX		1.01 (0.52-1.97)	
		TOFA		2.06 (1.38-3.08)	
		ABA		0.84 (0.66-1.06)	
Uchida et al [28], 2023	Rheumatology departments[a]	JAKi	TNFi	0.20 (0.08-0.52)	High
Choi et al [26], 2023	Claims database	JAKi	TNFi	2.37 (2.00-2.80)	Moderate
Opdam et al [34], 2024	Claims database	JAKi	bDMARDs	2.65 (1.94-3.60)	High
Yoshida et al [32], 2024	Rheumatology departments	JAKi	IL-6i	2.83 (0.87-10.96)	High

ABA, abatacept; ADA, adalimumab; aHR, adjusted hazard ratio; ARTIS, Anti-Rheumatic Therapy in Sweden; BARI, baricitinib; bDMARD, biological disease-modifying antirheumatic drug; c, control; CERT, certolizumab pegol; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; GOL, golimumab; i, intervention; IFX, infliximab; IL-6i, interleukin-6 inhibitor; JAKi, Janus kinase inhibitor; RoB, risk of bias; RTX, rituximab; SAR, sarilumab; TCZ, tocilizumab; TNFi, tumour necrosis factor inhibitor; TOFA, tofacitinib.
[a] Nagasaki University Hospital, Sasebo Chuo Hospital, or Ureshino Medical Center.

Nine studies assessed the risk of malignancy while also performing subgroup analysis and looked for age-specific associations; no statistically significant trends in younger and older groups were observed [25,38,44,45,47,49–51]. Analyses stratified by age displayed numerically increased yet statistically not significant hazard ratios (HRs) between age groups (aHR 1.47 [0.79-2.74] in 50+, 1.35 [0.61-2.97] in 65+ years of age, and 1.50 [0.83-2.72] in all ages) in a study examining JAKis compared with TNFis [42].

Cardiovascular events

Twenty studies investigated the risk of CV events (major adverse cardiovascular events [MACE], heart failure, myocardial infarction, stroke, arrhythmias) (4 low RoB [24,54–56] and 16 moderate or high RoB [25,38,43,46,57–64]). Two studies described the risk of heart failure [63,65] (1 low and 1 high RoB, respectively), 6 studies assessed the risk of myocardial infarction (2 low [56,65] and 4 high RoB [45,58,63,65,66]) and stroke (2 low [56,65] and 4 high RoB [41,45,58,63]), while arrhythmias were assessed in 3 studies (1 low [65] and 2 high RoB [63,67]).

MACE

Twelve studies examined the risk of MACE, and 4 studies assessed the risk of CV events (myocardial infarction and/or heart failure, and stroke, but no CV death); the definition of a CV event varied among them [38,58,61,64] (Table 6). The risk of MACE is similar between different csDMARDs (methotrexate [MTX] vs HCQ: aHR 1.07 [0.97-1.18] [59,63]; csDMARDs with MTX vs MTX only: aHR 0.859 [0.375-1.97]; csDMARDs vs MTX: aHR 1.552 [0.766-3.144]) or between csDMARDs and bDMARDs [54–56,59]. No difference was observed with TNFis compared with csDMARDs alone (aHR 0.91 [0.72-1.17] and aHR 0.65 [0.40-1.05]) [54,55].

Similar risk of MACE was found across different bDMARDs with a reported higher rate for certolizumab (aHR 1.31 [0.99-1.73]) and rituximab (aHR 1.27 [1.04-1.55]) compared with etanercept in 1 study [24,56].

The risk of MACE was increased with JAKis compared with TNFis and IL-6i in 2 studies, 1 of moderate and 1 of high RoB (aHR 2.09 [1.10-3.95] [25] and 3.03 [0.77-15.21] [46], respectively), whereas 7 studies reported no increased risk with JAKis compared with TNFis or any bDMARDs (including 3 low RoB studies) [24,45,55–57,60,62].

No significant differences were found across different DMARDs regarding the isolated risk of heart failure, stroke, myocardial infarction, or arrhythmias.

Eight studies on MACE performed subgroup analysis and looked for age-specific associations; age-specific subgroup analysis of patients aged ≥65 years did not find an increased risk of MACE for JAKis compared with TNFis [45], JAKis compared with adalimumab [60], tofacitinib compared with TNFis [57], or JAKis, other bDMARDs and csDMARDs compared with TNFis [55], whereas the risk was found to be similar in patients >60 years of age and in those aged 50+ with a presence of at least 1 CV risk factor when JAKis were compared with TNFis [25,68]. In a high RoB study, the risk of CV disease, not specifically MACE, tended to increase with JAKis compared with that with bDMARDs in patients aged ≥65 years (aHR 1.83 [0.36-9.31] vs 1.13 [0.39-3.30] in patients <65); it is important to report that approximately 90% of participants on JAKis were aged <65, and wide CIs were seen [62]. Finally, for coronary heart disease, the incidence rates between JAKis and TNFis were insignificant in those aged ≥50 (HR 0.68 [0.26-1.81]) and in those <50 years of age (HR 1.03 [0.45-2.36]; high RoB) [38].

Venous thromboembolism

Seven studies examined the risk of thromboembolic events among patients on JAKis and bDMARDs (2 low RoB [65,69] and 5 moderate/high RoB [25,41,45,58,60]) (Table 6).

Table 5
Malignancies, comparison between different DMARDs (observational studies)

Study ID	Registry	Intervention	Control	aHR	RoB
Any malignancy					
Simon et al [50], 2024	ARTIS, BC, FORWARD, RABBIT	csDMARDs	ABA	1.1 (0.8-1.5)	Low
		bDMARDs		1.0 (0.8-1.3)	
Choi et al [51], 2022	Claims database	TNFi	nbDMARDs	0.37 (0.255-0.563)	High
Song et al [49], 2022	Claims database	JAKi	TNFi	0.83 (0.55-1.27)	High
Fang et al [38], 2022	TNHIRD/TDR	JAKi	TNFi	1.10 (0.44-2.78)	High
Molina-Collada et al [53], 2024	BIOBADASER	JAKi	TNFi	0.7 (0.2-2.7)	
		Anti-CD20		0.3 (0.1-1.3)	
		Anti-IL-6		1.7 (0.6-4.3)	
		CTLA4-Ig		1.9 (0.8-4.7)	
		Anti-IL-17		N/A	
Sendaydiego et al [52], 2024	Claims database	RTX	TNFi	1.91 (1.17-3.14)	High
		IL-6i		1.04 (0.57-1.92)	
		ABA		1.47 (1.03-2.11)	
		JAKi		1.36 (0.94-1.96)	
Mok et al [25], 2024	HK Biologic registry	JAKi	TNFi	0.87 (0.39-1.95)	Moderate
Any malignancy except NMSC					
Seror et al [44], 2022	Claims database	bDMARDs	csDMARDs	0.99 (0.86-1.14)	High
		bDMARD + csDMARD		0.98 (0.83-1.16)	
		TNFi exposed		1.03 (0.88-1.21)	
Westermann et al [42], 2024	DANBIO	JAKi	bDMARDs	1.41 (0.76-2.37)	Low
		TNFi	bDMARDs naïve	1.0 (0.9-1.0)	
		RTX		1.0 (0.9-1.1)	
		ABA		1.15 (0.98-1.34)	
		JAKi		1.0 (0.8-1.2)	
Uchida et al [28], 2023	Rheumatology departments[a]	JAKi	TNFi	0.38 (0.095-1.552)	High
Min et al [45], 2023	Claims database	JAKi naïve	TNFi	1.53 (0.81-2.87)	High
		JAKi treated		1.02 (0.81-1.29)	
Huss et al [47], 2022	SRQ	TOFA	TNFi	1.08 (0.52-2.24)	Moderate
		BARI		0.92 (0.61-1.38)	
		JAKi		0.94 (0.65-1.38)	
		Non-TNFi		1.12 (0.88-1.43)	
Yoshida et al [46], 2023	Rheumatology departments[b]	JAKi	IL-6i	2.13 (0.67-7.42)	High
Melanoma					
Lee et al [48], 2023	Claims database	MTX	HCQ	1.39 (0.87-2.21)	High
Seror et al [44], 2022	Claims database	bDMARDs	csDMARDs	0.91 (0.43-1.79)	
		TNFi exposed		0.73 (0.33-1.62)	High
NMSC					
Lee et al [48], 2023	Claims database	MTX	HCQ	1.01 (0.90-1.12)	High
Huss et al [47], 2022	SRQ	JAKi	TNFi	1.39 (1.01-1.91)	Moderate
		TOFA		1.56 (0.83-2.92)	
		BARI		1.37 (0.97-1.92)	
		Non-TNFi		1.00 (0.78-1.28)	
Min et al [45], 2023	Claims database	JAKi	TNFi	1.38 (0.39-4.88)	High
Haematological malignancy					
Seror et al [44], 2022	Claims database	bDMARDs	csDMARDs	1.35 (0.72-2.53)	High
		bDMARDs & csDMARDs		1.18 (0.55-2.52)	
		TNFi exposed		0.77 (0.42-1.43)	
Huss et al [47], 2022	SRQ	JAKi	TNFi	1.90 (0.70-5.16)	Moderate
		TOFA		N/A	
		BARI		1.96 (0.66-5.79)	
		Non-TNFi		1.04 (0.48-2.25)	
Song et al [49], 2022	Claims database	JAKi	TNFi	2.86 (0.41-20.00)	High

ABA, abatacept; aHR, adjusted hazard ratio; ARTIS, Anti-Rheumatic Therapy in Sweden, BC, British Columbia Canadian RA Cohort; bDMARD, biological disease-modifying antirheumatic drug; BIOBADASER, Safety Register of the Spanish Society of Rheumatology; c, control; csDMARD, conventional disease-modifying antirheumatic drug; DANBIO, Danish nationwide quality registry; DMARD, disease-modifying antirheumatic drug; FORWARD, National Databank for Rheumatic Diseases longitudinal prospective observational study; HCQ, hydroxychloroquine; HK, Hong Kong biologic registry; i, intervention; IL-17, interleukin-17; IL-6i, interleukin-6 inhibitor; JAKi, Janus kinase inhibitor; MTX, methotrexate; N/A, Not applicable; nbDMARD, nonbiologic disease-modifying antirheumatic drug; NMSC, nonmelanoma skin cancer; RABBIT, Rheumatoid Arthritis Observation of Biologic Therapy registry; RoB, risk of bias; RTX, rituximab; SRQ, Swedish Rheumatology Quality Register; TNFi, tumour necrosis factor inhibitor; TNHIRD/TDR, Taiwan National Health Insurance Research Database/Taiwan Death Registry; TOFA, tofacitinib.

[a] Nagasaki University Hospital, Sasebo Chuo Hospital, or Ureshino Medical Center.

[b] Department of Rheumatology of Fukushima Medical University Hospital, Japanese Red Cross Fukushima Hospital, and Ohta Nishinouchi General Hospital Foundation.

The risk of thromboembolic events was increased with JAKis and IL-6i compared with TNFis or other bDMARDs in 5 studies [25,38,45,58,65,69], while in 1 high RoB study, the risk was similar between JAKi and adalimumab [60]. The risk of overall venous thromboembolism (VTE) was increased primarily secondary to pulmonary embolism events (aHR 3.21 [2.11-4.88]) and not deep vein thrombosis (aHR 0.83 [0.47-1.45]) in 1 low RoB study [69]. When studying specific JAKis, the risk was

increased with upadacitinib and baricitinib compared with tofacitinib (low RoB) [65].

Gastrointestinal perforation and demyelinating disease

Intestinal perforations and neuroinflammatory events were assessed in 3 studies, including patients on JAKis and bDMARDs [70–72].

In both studies evaluating the risk of gastrointestinal perforation (GIP) with JAKis compared with other bDMARDs, the risk was found to be increased with any JAKi (Reporting odds ratio (ROR) 1.98 [1.69-2.31]) and with each JAKi: baricitinib (ROR 5.38 [3.46-8.37] and aHR 2 [1.2-3.4]), upadacitinib (ROR 2.73 [2.17-3.44] and aHR 2.8 [1.1-7.2]) and tofacitinib (ROR 1.52 [1.25-1.85] and aHR 1.7 [0.9-3.1]) [70,71]. Both were high RoB studies.

No risk was observed for neuroinflammatory diseases with other TNFis compared with etanercept [72].

Others

Mortality was assessed as a primary endpoint in 3 studies, while in 6 studies it was assessed as a secondary endpoint; 7 studies examined all-cause mortality [24,38,45,53,57,62,67] (2 low and 5 high RoB), while in 2 studies, CV-related mortality was assessed [56,64] (1 low and 1 high RoB, respectively).

Fourteen studies assessed retention rates and withdrawals due to adverse events (11 low RoB [24,73–82] and 3 high RoB [25,83,84]).

Eight studies examined any other adverse events, including dyslipidaemia (high RoB), peripheral oedema [65] (low RoB), nonsteatosis liver disease, depression, suicide [24] (low RoB), autoimmune thyroid disease (high RoB), diabetes [85] (high RoB), and osteoporosis [86–88] (high RoB).

Only 1 study reported the risk of preeclampsia in patients on csDMARDs, bDMARDs, or GCs [89] (high RoB, control was the general population), and 3 studies evaluated GC-associated risks (1 low [20] and 2 high RoB [90,91]). Additional information and details on respective studies are available in the Supplementary Material (Sections S3.1.7-3.111, pages 102-128).

RCTs

Thirteen low RoB RCTs described in the efficacy SLR are included in the safety SLR. One trial evaluated csDMARDs, more specifically, methotrexate [92]. Two phase 2 [93,94] and 4 phase 3 [95–97] trials examined bDMARDs, while 1 phase 2 [98] and 1 phase 3 [99] trials included patients on tsDMARDs. Six RCTs on biosimilars are also included in this SLR [100–104]. Most RCTs were not designed and, therefore, not powered to evaluate safety outcomes. The incidence of major adverse events was low and mostly comparable between active treatment, placebo, or active comparator. No RCTs with a primary safety outcome were found.

Infections

In the sole RCT examining the risk of serious infections comparing oral methotrexate to subcutaneous methotrexate, the risk was equal in both formulations (15.4% vs 18%, respectively). No serious infections were reported in phase 2 bDMARD trials [93,94].

In phase 3 bDMARD trials, and more specifically in CONTRAST 1, comparing otilimab with tofacitinib, the risk of serious infections was similar across different doses of otilimab and equally common to tofacitinib (range <1%-1% in week 0-12 and 3%-4% in week 12-52) or placebo (1% at week 0-12) [95]. Similar results were seen in CONTRAST 2 (range <1%-1% in week 0-12 and 2%-4% in week 12-52) [95]. When comparing otilimab with sarilumab in CONTRAST 3, more common serious infections were noted in otilimab low dose in weeks 0-24 (3%) compared with sarilumab (1%), while no serious infections were reported in high-dose otilimab. The frequency of serious infections in weeks 0-12 was reported to be the same between otilimab and sarilumab (<1%), while there were no serious infection reports in the placebo group. No reports of serious infections were reported in the AVERT 2 trial when comparing placebo with abatacept [105].

One episode of HZ was reported in the placebo group when compared with peresolimab (death protein 1 [PD-1] inhibitor) [93]. HZ was similarly common when comparing placebo with ivarmacitinib (range 0.6%-2.6%); higher dose of ivarmacitinib resulted in a slightly higher incidence of HZ (1.6% at weeks 0-24, 1.8% in weeks 24-52 for 4 mg ivarmacitinib vs 2.6 % and 2.3%, respectively) [99]. From the biosimilar studies, only 1 HZ case (0.4%) was reported in the infliximab generic group [106].

Three opportunistic infections were reported in CONTRAST 1 in the high-dose otilimab group only (1 in weeks 0-12 and 2 in weeks 12-52), while 4 were reported in the otilimab group (3 in the low dose and 1 in the high dose) in CONTRAST 2, compared with 5 cases reported in the tofacitinib group by week 52.

Incidences of TB were similar between otilimab, tofacitinib, or sarilumab, but more common compared with placebo (2%-4% vs 0%, respectively) [95,96].

Malignancy

No malignancies were reported when comparing oral with subcutaneous methotrexate (0% and 0%, respectively) [92], or dazodalibep with placebo (0% and 0%, respectively) [94]. One episode of malignancy was reported in the placebo group when compared with peresolimab (4% vs 0%, respectively) [93].

No malignancies were reported in the abatacept group compared with placebo, where the rate of malignancy was numerically higher (0 [0%] vs 3 [0.7%]) [105]. One episode of malignancy was reported in the placebo group when compared with BMS-986142 (Bruton's tyrosine kinase inhibitor) (1 [<1%] vs 0 [0%]) [98].

Compared with otilimab, the incidence of malignancy was similar to that with sarilumab and tofacitinib in 2 RCTs by week 12 (<1% in all groups), but was numerically slightly higher in patients on tofacitinib by week 52 only (<1% vs 2%, respectively) and compared with placebo (<1%) [95,96]. Malignancy was also numerically higher in ivarmacitinib (0.5% by week 24 and 1.1% by weeks 24-52) compared with placebo (0% by week 24 and weeks 24-52) in 1 RCT [99].

The number of malignancies reported in biosimilar studies was also similar for infliximab, tocilizumab, and adalimumab (range 0.4%-<1%) [100,101,103,104,107,108].

VTE

No thromboembolic events were reported in csDMARDs [92], phase 2 bDMARDs studies [93,94] or tsDMARDs [98,99]. In phase 3 bDMARDs studies, 3 thromboembolic events were reported by week 12 with otilimab 150 mg QW (<1%) compared with no events with tofacitinib (0%), sarilumab (0%), or placebo (0%) [95,96]. One thromboembolic event was reported with

otilimab 90 mg QW (<1%) compared with tofacitinib (0 [0%]) by week 52, while no thromboembolic events were reported by week 24 in otilimab vs sarilumab groups (0% for both groups) [96].

MACE

CV events were reported in the sole trial on csDMARDs in both methotrexate arms (5.8% and 4% for oral and subcutaneous MTX, respectively) [92].

CV events were reported in both the placebo (<1%-1%), and otilimab groups (range 0-<1); by week 12 in csDMARD inadequate response (IR)/bDMARD IR population, 3 events (<1%) were reported with otilimab 90 mg and 150 mg, while no events were reported with placebo (0%), tofacitinib (0%), or sarilumab (0%) [95,96]. By week 52, in the MTX IR population, 4 events (<1%) were reported in otilimab 90 mg compared with 1 event (<1%) in placebo and no events in the tofacitinib group (0%) [95]. Additionally, by week 52, in csDMARD IR/bDMARD IR populations, 5 events were reported (<1%) in the otilimab 90 mg group and 3 events (<1%) in the otilimab 150 mg group compared with no events in the tofacitinib and sarilumab groups (0 [0%]) [95]. No CV events were reported in the otilimab or sarilumab groups (0%) compared with 1 event in the placebo group (1 [1%]) by week 24 [96]. One CV event (1.3%) was reported with low-dose BMS-986142 compared with placebo (0%) [98]. One event was also reported with high-dose ivarmacitinib 8 mg (0.5%) compared with placebo (0%) by week 24, and 1 event in the switch group from placebo to ivarmacitinib 4 mg from week 24 to 52 (0.6) compared with no events in the groups that continued on ivarmacitinib at 4 and 8 mg (0%) [99].

No CV events were reported with peresolimab (0%) and dazodalibep (0%) vs placebo (0%) [93,94]. Low rates of CV events were noted with biosimilar tocilizumab studies only (0.3%-1%) [100,101,108].

Mortality

One death (1 [5.9%]) was reported in the MIDORA trial, in the dazodalibep group only [94]. In CONTRAST trials 1 and 2, 34 deaths were reported in total in all groups, including 4 in the placebo group; none of these deaths was considered treatment-related, while 8 of them were COVID-19-related [95]. Deaths were equally common in CONTRAST trial 3 and the AVERT trial between intervention groups (otilimab and sarilumab [<1%], abatacept [<1%]) [96,97]. No deaths were reported in csDMARDs and tsDMARDs studies [92,98,99].

Gastrointestinal perforations

GIPs were only reported in bDMARD studies comparing otilimab with tofacitinib (1 [<1%] by week 12 with tofacitinib, and 1 [<1%] by week 52 with otilimab) [95]. GIPs were more common with higher dose ivarmacitinib compared with placebo (6 [3.2%] vs 3 [1.6%], respectively) and compared with ivarmacitinib lower dose (6 [3.2%] vs 2 [1.1%]) by week 24, while they increased numerically by week 52 (range 1.8%-48%) [99]. Two GIP events were reported in 2 tocilizumab biosimilar studies [101,107].

DMARD monitoring SLR

No RCTs or observational studies addressed the clinical utility of long-term routine laboratory toxicity surveillance.

DISCUSSION

Since the publication of the last SLR on the safety of DMARDs in 2022 [6], particularly following concerns raised by the ORAL surveillance study [109] regarding the safety of tsDMARDs, there has been a notable increase in studies evaluating safety outcomes, with the majority of these observational studies focusing primarily on malignancy, thromboembolic and CV events. However, no new RCTs evaluating the comparative safety of JAKis vs other bDMARDs with regard to MACE, VTE, or malignancy risks have been published since the last update.

Consistent with previous findings [6], the risk of serious infections remains elevated with bDMARDs compared with csDMARDs, although the risk appeared comparable across different classes of bDMARDs and tsDMARDs. Notably, higher rates of serious infections were reported with JAKi compared with IL-6i in 1 study only [32]. In line with the previous SLR, HZ was more frequently observed with JAKis than with bDMARDs [6]. In comparison, in a high-risk-of-bias study, the risk of serious infections and HZ infection was found to be lower with JAKis compared with TNFis (HR 0.79 [0.417-1.502] and HR 0.20 [0.08-0.52], respectively). These results were incongruous with the broader literature [28]. Future efforts to estimate and compare HZ risk across different JAKis are likely to be constrained by several methodological challenges. Chief among these are the widespread uptake of the recombinant zoster vaccine, synchronous and overlapping prescribing trajectories of JAKis, and vaccine availability in different health care settings and systems [110]. Together, these factors may complicate attempts to disentangle drug-specific risk profiles among JAKis and may limit the precision of comparative safety assessments. Additionally, we did not find new data published on HZ risk with filgotinib, but rather with JAKi overall or with baricitinib and tofacitinib specifically. This could reflect current clinical practice, as the latter 2 JAKis were the first JAKis approved and studied extensively [111]. The 2016 SLR suggested an increased risk of TB associated with TNFis [112]; however, while the most recent 2022 SLR found no supporting evidence for this association, recent data from a low-risk-of-bias study indicated that infliximab and adalimumab are still associated with an increased TB risk [20], while no significant differences were observed between JAKis and bDMARDs. It is important to note that most cases in the study occurred before comprehensive TB screening, including interferon γ (IFN-γ) –based immunological testing, was routinely recommended before initiating b/tsDMARDs and information on prior treatment for latent TB was not available [20]. With these in mind, it remains important to monitor for TB reactivation risk, but the overall risk remains low if mandatory screening is in place before b/tsDMARD initiation.

Another important finding that arose from the ORAL surveillance study was the higher incidence of malignancy in patients receiving tofacitinib [109]; in the open-label study of ORAL surveillance, patients with a history of CV disease and CV risk factors were at increased risk of malignancies excluding NMSC, and at increased risk of NMSC alone with tofacitinib vs TNFis [113]. Similar analysis has since been undertaken in cohort studies to assess malignancy risk in patients on different DMARDs. The risk of malignancy has been found to be lower with csDMARDs than with bDMARDs, although the risk appears consistent across different bDMARDs. Conflicting evidence regarding abatacept was noted in the previous SLR [6]; however, these findings were not corroborated in the current review. In recent years, the association between DMARD use and skin malignancies has garnered increased attention [114]. An

elevated risk of both melanoma and NMSCs has been reported among patients with RA treated with DMARDs, and specifically TNFi [112]. Nevertheless, no significant differences in NMSC have been observed between various groups of bDMARDs, while the risk of NMSC alone was found to be increased with JAKis compared with TNFis [43,45]. However, it must be noted that both studies were assessed as having at least a moderate RoB, and wide CIs associated with a moderately increased aHR. Substantial differences in the characteristics between patients initiating a JAKi and those initiating a TNFi were found, as well as a short follow-up period, which is why these results have to be interpreted with caution [43,45]. Assessing malignancy risk with DMARDs, particularly JAKi, requires long-term follow-up; thus, a well-controlled prospective study excluding confounders like smoking, cancer risk factors, and geographic variability would be valuable in understanding this risk. Another challenge lies in appropriately accounting for varying time exposure and risk within observational studies, as both treatment patterns and outcome hazard evolve over time, and observational studies may not capture these changes [115].

The previous systematic review placed significant emphasis on CV and thromboembolic events, particularly in response to safety concerns raised by the ORAL surveillance study [6,109]. Since the ORAL surveillance study was published, several observational studies have sought to address these concerns and generate evidence based on clinical practice using observational studies and real-world clinical data, included in this SLR; however, no additional RCTs have been conducted to date addressing safety outcomes as a primary endpoint.

Evidence from studies with low RoB indicates no increased risk of MACE with JAKis compared with bDMARDs. In contrast, 2 high RoB studies reported an increased risk of MACE with JAKis relative to TNFis and IL-6i [25,46]. Inflammation has been recognised as a central process in the development of CV disease, and the excess inflammation present in RA has been hypothesised to be a determinant of the observed higher risk in RA [116–119]; patients receiving JAKis might have longer disease duration at treatment start, accompanied with higher disease burden, which potentially increases overall CV risk in this patient population. These results may offer cautious reassurance to clinicians and patients engaged in shared decision-making regarding the initiation and continuation of JAKi therapy. JAKi use in patients with risk factors remains a shared decision between physician and informed patient, given the modest risk increase observed in individuals with a CV history, while further investigations outside robust RCTs may offer limited additional insights, as current guidance appears to be reasonably well established. Additionally, no CV benefit was observed with TNFis compared with csDMARDs, corroborating earlier safety findings [6,54,55].

One important safety signal identified in the 2022 SLR was the increased risk of VTE associated with high doses of tofacitinib, primarily based on data from the ORAL surveillance study [109]; these data led the regulatory authorities to recommend caution when JAKis are prescribed, especially in patients with risk factors for VTE [120]. Subsequently, real-world studies have further explored that risk since the last SLR. The risk of VTE was increased in all but 1 high RoB study with JAKis compared to bDMARDs (where the risk was found to be comparable), specifically for pulmonary embolism as reported in 1 low RoB study [69]. Interestingly, the risk was found to be increased with upadacitinib and baricitinib compared with tofacitinib [65]. The cause of this observed risk remains unclear, and future research should aim to understand the underlying mechanism/aetiology of the above-mentioned association, though further exploration beyond well-designed RCTs may yield limited incremental insight given the current strength of available evidence.

A number of observational studies, included in this SLR, investigated age-specific associations, particularly in relation to serious infections, MACE, and malignancy, guided by the ORAL surveillance study results in relation to increased risk of the above-mentioned outcomes in patients over the age of 75 years. Across studies evaluating age-stratified risks, JAKis generally did not show increased rates of MACE, malignancy, or serious infection compared with TNFis or other bDMARDs, aside from results derived from a low RoB study notifying of a higher serious infection risk with tofacitinib at ≥70 years, while this risk is shown to be increased with increasing age [22]. It is, though, important to continue investigating age-specific associations to guide biologic selection in clinical practice.

A critical methodological consideration in synthesising safety data is the consistent definition of clinical outcomes across studies; for example, in the current SLR, many of the included studies failed to clearly define CV events, thereby limiting the interpretability and comparability of findings related to specific safety outcomes. This lack of standardisation underscores the need for harmonised outcome definitions in future research to enable more robust meta-analyses and evidence synthesis. Additionally, many studies in this SLR based their safety analyses on claims databases, which poses notable methodological risks given the limited clinical granularity, potential coding inaccuracies and incomplete ascertainment of adverse events inherent to such data [121].

A related issue concerns the distinction between RoB classification and the precision of study findings. It has to be highlighted that, while assessing RoB and study quality in this SLR was based on the Hayden tool, the correct interpretation of measures of uncertainty (eg, CIs) in context of the respective effect sizes is a crucial component for interpreting evidence of observational studies correctly. Large real-world data studies, in particular, may yield highly precise estimates, often reflected in narrow CIs around effect sizes, while still being vulnerable to substantial systematic bias. Such estimates (eg, odds ratios close to 1 with very tight CIs) can be misinterpreted as clinically meaningful solely on the basis of statistical significance. However, high precision does not compensate for underlying bias, and small effect sizes should be interpreted cautiously unless baseline risks are sufficiently high to confer meaningful impact.

Beyond effect sizes and their precision, the metric of association should also be considered when estimating effect magnitudes and evaluating the relevance of any study's finding in regard to its clinical relevance. In contrast to RCTs, predefined assumptions of effect sizes (or their differences) are critical, which is largely absent in observational studies. The primary aim of our safety systematic review is to identify potential safety signals rather than to adjudicate their magnitude. The identification of a signal, does not itself, determine its clinical significance. This distinction underscores the necessary step from detecting a potential association to evaluating its practical relevance for patient care.

On the other hand, the additional SLR on DMARD monitoring revealed a notable evidence gap, as no RCTs or observational studies addressed the clinical utility of long-term routine laboratory toxicity surveillance. This paucity of data has contributed to the widespread adoption of frequent monitoring practices in clinical settings derived primarily from safety data from phase 3 RCTs that then translate into label texts. Current recommendations advocate for intensive

Table 6
MACE and VTE, comparison between different DMARDs (observational studies)

Study ID	Registry	Intervention	Control	aHR/OR	RoB
MACE					
D'Andrea et al [63], 2022	Claims database	HCQ	MTX	1.07 (0.97-1.18)	High
Yoshida et al [54], 2023	CorEvitas RA[a]	TNFi & MTX NDE	MTX	0.77 (0.60-1.00)	Low
		TNFi & MTX CDE		0.91 (0.72-1.17)	
Huang et al [59], 2024	Claims database	TNFi + MTX	MTX	1.30 (0.578-2.952)	High
		Non-TNFi + MTX		0.84 (0.157-4.547)	
		csDMARDs + MTX		0.85 (0.375-1.97)	
		TNFi		1.37 (0.627-3.032)	
		Non-TNFi		0.92 (0.299-2.859)	
		csDMARDs		1.55 (0.766-3.144)	
Frisell et al [24], 2023	ARTIS	ADA	ETA	1.12 (0.89-1.41)	Low
		IFX		1.00 (0.72-1.39)	
		CERT		1.31 (0.99-1.73)	
		GOL		1.14 (0.82-1.58)	
		ABA		1.14 (0.87-1.48)	
		RTX		1.27 (1.04-1.55)	
		TCZ		0.97 (0.70-1.33)	
		SAR		N/A	
		BARI		0.83 (0.49-1.42)	
		TOFA		0.78 (0.31-1.99)	
Bower et al [56], 2023	SRQ	JAKi	TNFi	0.71 (0.51-0.99)	Low
		TOFA		0.78 (0.39-1.55)	
		BARI		0.70 (0.49-1.01)	
		UPA		N/A	
		Non-TNFi		0.98 (0.78-1.23)	
Mok et al [25], 2024	HK Biologic registry	JAKi	TNFi	2.09 (1.10-3.95)	Moderate
Min et al [45], 2023	Claims database	JAKi naïve	TNFi	0.69 (0.42-1.14)	High
		JAKi treated		0.84 (0.70-1.00)	
Yoshida et al [46], 2023	Rheumatology departments[b]	JAKi	IL-6i	3.03 (0.77-15.21)	High
Ma et al [57], 2024	Claims database	TOFA	ADA	0.99 et al [0.760-1.303]	High
Hoisnard et al [60], 2023	SNDS	JAKi	ADA	1.0 (0.7-1.5)	High
Song et al [62], 2023	Claims database	JAKi	bDMARDs	1.28 (0.53-3.11)	High
Meissner et al [55], 2023	RABBIT	JAKi	TNFi	0.89 (0.52-1.52)	Low
		Other bDMARDs		0.76 (0.45-1.27)	
		csDMARDs		1.36 (0.85-2.19)	
VTE					
Molander et al [69], 2023	SRQ	RTX	TNFi	0.94 (0.74-1.20)	Low
		IL-6i		1.25 (0.94-1.67)	
		ABA		0.89 (0.66-1.21)	
		JAKi		1.73 (1.24-2.42)	
Goldman et al [65], 2024	Claim database	JAKi	bDMARDs	2.11 (1.97-2.25)	Low
Mok et al [25], 2024	HK Biologic registry	JAKi	TNFi	3.90 (0.20-78.1)	Moderate
Min et al [45], 2023	Claim database	JAKi naïve	TNFi	1.46 (0.70-3.03)	High
		JAKi treated		1.35 (0.92-1.97)	
Fang et al [38], 2022	TNHIRD/TDR	JAKi	TNFi	0.65 (0.25-1.70)	High
Sakai et al [58], 2024	Claim database	JAKi	TNFi	2.08 (1.47-2.93)	High
Hoisnard et al [60], 2023	SNDS	JAKi	ADA	1.1 (0.7-1.6)	High

ABA, abatacept; ADA, adalimumab; aHR, adjusted hazard ratio; ARTIS, Anti-Rheumatic Therapy in Sweden, bDMARD, biological disease-modifying antirheumatic drug; BARI, baricitinib; c, control; CDE, Controlled direct effect nalyses; CERT, certolizumab; csDMARD, conventional disease-modifying antirheumatic drug; GOL, Golimumab; HCQ, hydroxychloroquine; HK, Hong Kong biologic registry; i, intervention; IL-6i, interleukin-6 inhibitor; IFX, infliximab; JAKi, Janus kinase inhibitor; MACE, major adverse cardiovascular events; MTX, methotrexate; NDE, Natural direct effect analyses; OR, odds ratio; RABBIT, Rheumatoid Arthritis Observation of Biologic Therapy registry; RoB, risk of bias; RTX, rituximab; SAR, sarilumab; SNDS, Système National des Données de Santé, France; SRQ, Swedish Rheumatology Quality Register; TCZ, tocilizumab; TNFi, tumour necrosis factor inhibitor; TOFA, tofacitinib; UPA, upadacitinib; VTE, venous thromboembolism.
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laboratory monitoring during the initial 6 months of DMARD therapy, a period associated with elevated risk of adverse reactions, followed by a transition to less frequent assessments throughout the remainder of treatment, which may extend for decades or even a lifetime [10,11,122]. To date, no studies have systematically compared alternative blood or laboratory monitoring strategies in terms of their influence on clinically meaningful outcomes. Emerging data studies suggest that intensive long-term blood monitoring offers limited benefit, indicating that this practice may warrant reconsideration in future guideline updates [8]. Future research should investigate both patient and physician perspectives on monitoring practices, including the possibility that routine testing, despite limited medical necessity, may foster medication adherence by providing reassurance regarding drug safety. Additionally, further inquiry is warranted to identify potential legal implications and practical challenges that could impede the implementation of revised clinical guidelines.

Randomisation is the cornerstone of RCTs, rendering them the gold standard for evaluating differences in outcomes across treatment groups [123]. By randomly allocating participants, RCTs achieve a balanced distribution of both measured and unmeasured confounding variables, thereby minimising bias and enhancing internal validity [123]. Typically, the primary endpoint in RCTs pertains to efficacy, while formal comparisons of safety outcomes are often constrained by limited statistical power [123]. Moreover, RCTs frequently exclude individuals at elevated risk for adverse events and are generally of insufficient duration to detect outcomes with extended latency periods, such as malignancies [123].

Consequently, observational studies, particularly those involving unselected patient populations monitored over prolonged periods, serve as the principal source of evidence in this SLR for assessing drug safety. While these studies offer valuable insights into real-world safety profiles, they are inherently limited by the absence of randomisation [124]. This introduces the potential for confounding by indication, wherein baseline differences in risk factors between treatment groups may influence observed outcomes [125]. Safety findings from the ORAL Surveillance RCT trial demonstrated a clear dose-dependent signal [109]. However, observational studies may be limited in their ability to investigate dose-response associations with JAKis, given the use of fixed dosing regimens in certain agents (eg, upadacitinib) and restricted dose variability in some regions globally. This constraint hampers the validation of dose-response relationships in real-world settings and could represent a limitation for comparative safety evaluations. Another limitation is the geographic heterogeneity due to differences in healthcare systems, screening and prescribing practices, and vaccination schedules observed when comparing studies, which could limit generalisability [126].

Despite these limitations, observational studies remain indispensable for evaluating safety, especially for outcomes that are rare or manifest over long time horizons [127]. Ideally, a hybrid approach that integrates the methodological rigour of experimental designs with the external validity of observational research would provide the most comprehensive assessment of treatment safety. In the current systematic review, no RCTs were found to have safety events as primary endpoints.

Conclusion

Overall, the conclusions drawn from this SLR are consistent with those reported in the 2022 review, which is reassuring and reinforces the evolving consensus regarding the safety profiles of cs-, b-, and tsDMARDs in the treatment of RA. The accumulating body of evidence supports the notion that these agents can be employed with safety in clinical practice. Importantly, this SLR, when considered alongside the corresponding efficacy review, provides a comprehensive evidence base that strengthens the EULAR recommendations for the management of RA with DMARDs. Moreover, it offers a substantive reaffirmation of the theoretical framework and guiding principles upon which these clinical guidelines are founded.

Competing interests

FL received speaker fees from Alfasigma. VK received speaker's or consultancy fees from Eli Lilly, AbbVie, and AstraZeneca. JSS received honoraria for consultancies and/or speaking engagements from Abbott, AbbVie, Anaptys, Ananda, AstraZeneca, Celltrion, Chugai, Immunovant, Lilly, R-Pharma, Samsung, Sandoz, Shattuck labs, and UCB. CJE received honoraria, advisory boards, speaker's bureau, and research support from AbbVie, Alphasigma, AstraZeneca, BMS, Biogen, Boehringer Ingelheim, Celgene, Celltrion, Fresenius, Gilead, GSK, Janssen, Lilly, Pfizer, MSD, Novartis, Roche, Samsung, Sanofi, and UCB. DA received honoraria from Advanz, Janssen/Johnsen & Johnsen, Sanofi, Mitsubishi Tanabe, UCB, and AstraZeneca, and grants to his institution from Lilly and Johnson & Johnson. DvdH received consulting fees from AbbVie, Alfasigma, ArgenX, BMS, Elly-Lilly, Grey-Wolf Therapeutics, Janssen, Novartis, Pfizer, Takeda, and UCB Pharma, and is associate editor of *Annals Rheumatic Diseases*, editorial board member of *Journal of Rheumatology*, and director of Imaging Rheumatology. KLW received honoraria for consulting from AbbVie, AstraZeneca, BMS, Eli Lilly, Galapagos, Gilead, GlaxoSmithKline (GSK), Moderna, Novartis, Roche, Sanofi, Union Chimique Belge (UCB), Zurabio, Takeda, Ouros, and Otsuka. TT received speaker's or consultancy fees from AbbVie GK, Chugai, Eli Lilly Japan, Eisai, Gilead Sciences Inc, Pfizer Japan Inc, Mitsubishi Tanabe, and Taisho Pharma. RC received consultancy and speaker fees from AbbVie, Alfasigma, AstraZeneca, GSK, Eli Lilly, Galapagos, Janssen, Novartis, Pfizer, and UCB. PV received research grants from Alfasigma and Pfizer; speaker or consultancy fees from Alfasigma, AbbVie, Galapagos, Eli Lilly, Cytrill, and Boehringer Ingelheim; and support for attending meetings from Fresenius Kabi and AbbVie. JaP declares no conflicts. KH received speaker's fees from AbbVie, grants from Pfizer and BMS, and serves as associate Editor for *Annals of the Rheumatic Diseases*. SdS declares no conflicts. JeP received speaker fees from Pfizer and Eli Lilly. JWS declares no conflicts. RBML received honoraria for lectures and payments for advisory boards from AbbVie, Jansen Pharma, Galapagos, Novartis, and UCB, and is director of Joint Imaging BV. AK received consulting fees from AbbVie, Lilly, Gilead, Janssen, and UCB; lecture fees from Lilly, Galapagos, Janssen, MSD, Novartis, and Pfizer; and congress support from Boehringer Ingelheim, Lilly, and UCB.

CRediT authorship contribution statement

Faidra Laskou: Writing – review & editing, Writing – original draft, Methodology, Formal analysis, Data curation, Conceptualization. **Victoria Konzett:** Writing – review & editing, Conceptualization. **Josef S Smolen:** Writing – review & editing, Supervision, Conceptualization. **Christopher J Edwards:** Writing – review & editing, Supervision, Conceptualization. **Daniel Aletaha:** Writing – review & editing, Conceptualization. **Désirée van der Heijde:** Writing – review & editing, Conceptualization. **Kevin L Winthrop:** Writing – review & editing, Conceptualization. **Tsutomu Takeuchi:** Writing – review & editing, Conceptualization. **Roberto Caporali:** Writing – review & editing, Conceptualization. **Patrick Verschueren:** Writing – review & editing, Conceptualization. **Janet E Pope:** Writing – review & editing, Conceptualization. **Kimme Hyrich:** Writing – review & editing, Conceptualization. **Savia de Souza:** Writing – review & editing, Conceptualization. **Tanja A Stamm:** Writing – review & editing, Conceptualization. **Jette Primdahl:** Writing – review & editing, Conceptualization. **Jan W Schoones:** Data curation. **Robert BM Landewé:** Writing – review & editing, Supervision, Methodology, Conceptualization. **Andreas Kerschbaumer:** Writing – review & editing, Supervision, Methodology, Conceptualization.

Contributors

All authors contributed and finally approved the current manuscript. FL is the guarantor of the study. The guarantor accepts full responsibility for the finished work and the conduct of the study, had access to the data, and controlled the decision to publish the manuscript together with the methodologists (AK and RBML) and the convenors of the taskforce (JSS and CJE).

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Because of the nature of the analyses, this is not applicable for the current work. All patients gave informed consent to participation in the studies included and publication of study results.

Ethics approval

Because of the nature of the analyses performed here, this is not applicable to the current project. All studies included in this work were approved by the respective ethics committees.

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Data availability statement

Not applicable, as no datasets were generated for this study. All data relevant to the study are available in public and are included in the article or uploaded as online supplemental information.

Patient and public involvement

One patient research partner (SdS) participated in the steering group and task force, and 2 additional patients contributed to the task force that developed the guidelines. Patients and/or the public were otherwise not involved in the design, or conduct, or reporting, or dissemination plans of this research. Details are provided in the Methods section.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ard.2026.02.024.

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