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CLINICAL SCIENCE

Safety of synthetic and biological DMARDs: a systematic literature review informing the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis

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ABSTRACT

Objectives To perform a systematic literature review (SLR) concerning the safety of synthetic (s) and biological (b) disease-modifying anti rheumatic dugs (DMARDs) to inform the 2019 update of the EULAR recommendations for the management of rheumatoid arthritis (RA).

Methods An SLR of observational studies comparing safety outcomes of any DMARD with another intervention for the management of RA. A comparator group was required for inclusion. For treatments still without registry data (eg, sarilumab and the Janus kinase (JAK) inhibitors baricitinib, upadacitinib), randomised controlled trials (RCTs) and long-term extensions (LTEs) were used. Risk of bias (RoB) was assessed according to standard procedures.

Results Forty-two observational studies fulfilled the inclusion criteria, addressing safety outcomes with bDMARDs and sDMARDs. Nine studies showed no difference in the risk of serious infections across bDMARDs and two studies (high RoB) showed an increased risk with bDMARDs compared with conventional synthetic (cs) DMARDs (adjusted incidence rate ratio 3.1–3.9). The risk of Herpes zoster infection was similar across bDMARDs, but one study showed an increased risk with tofacitinib compared with abatacept (adjusted HR (aHR) 2.0). Five studies showed no increased risk of cancer for bDMARDs compared with csDMARDs. An increased risk of lower intestinal perforation was found for tocilizumab compared with csDMARDs (aHR 4.5) and tumour necrosis factor inhibitor (TNFi) (aHR 2.6–4.0). Sixty manuscripts reported safety data from RCTs/LTEs. Overall, no unexpected safety outcomes were found, except for the possibly increased risk of venous thromboembolism (VTE) with JAK inhibitors.

Conclusion Data obtained by this SLR confirm the known safety profile of bDMARDs. The risk of VTE in RA, especially in patients on JAK inhibitors, needs further evaluation.

INTRODUCTION

Over the past 20 years, a large number of treatment options have become available for people with rheumatoid arthritis (RA). This is especially important since many patients will need to receive multiple drugs over the course of their disease, in order to attain and maintain adequate control.

Treatment options for RA include drugs with different modes of action formally categorised as conventional synthetic disease-modifying antirheumatic dugs (csDMARDs), biological DMARDs (bDMARDs), including both biological original (boDMARDs) and biosimilar DMARDs (bsDMARDs) and also targeted synthetic DMARDs (tsDMARDs); in RA, the only currently approved tsDMARDs are Janus kinase (JAK) inhibitors (JAKis).[1] With the increasing number of available drugs, many with direct or indirect evidence of similar efficacy stemming from randomised controlled trials (RCTs), safety plays an increasingly important role in decision-making.[2]

On a daily basis, clinicians decide which drug to choose as first-line therapy and what is the more efficacious second option when the first fails. Patients' characteristics (eg, comorbidities) are also important to inform these decisions and reflect, to a certain extent, perceived differences in safety across drugs.[3] In principle, drug development programme is designed to capture relevant safety signals early, which *in extremis* may lead to programme cessation before approval. These early safety signals are also key to inform future research, for drugs that do succeed. But despite tight regulations, RCTs have important intrinsic limitations in evaluating the safety of interventions (eg, limited numbers of strictly selected patients not necessarily representing 'real-world' practice) that render postmarketing monitoring especially relevant.[4] This includes safety assessments in (unselected) patients from cohorts and registries that are followed for long periods and, as such, better capture less frequent adverse events or risks related to certain comorbidities.

In order to inform the task force responsible for the 2019 update of the European League Against Rheumatism (EULAR) RA management recommendations,[2] we performed a systematic literature review (SLR) to update the evidence for the safety of csDMARDs, tsDMARDs and bDMARDs in patients with RA. This SLR is an extension of the SLR performed previously for the corresponding 2016 update.[3] The results of this and another SLR

focusing on efficacy[5] provided the task force with the current state of evidence.

METHODS

Literature search

The steering group of the EULAR task force for the 2019 update of the RA management recommendations outlined the scope of the literature search according to the Population, Intervention, Comparator, Outcomes (PICO) format and defined the criteria for a study being eligible.[6] The search was performed in MEDLINE, Embase and the Cochrane CENTRAL Register of Controlled Trials (Central), without language restrictions, and comprised publications from 2016 until 8 March 2019, as an update of the previous SLR.[3] Studies published after 8 March 2019 were not included and thus not presented to the task force. Details on complete search strategies are provided in online supplementary text 1. The literature search addressed the safety of DMARDs. Observational studies, namely, cohort studies or registries with >30 cases were the main study type. Participants were adults (≥18 years old) with a clinical diagnosis of RA. Studies including patients with other diagnoses were eligible only if results from patients with RA were presented separately. The intervention was any DMARD (csDMARD, bDMARD—including biosimilars—or tsDMARD), including all drugs (methotrexate, leflunomide, hydroxychloroquine, sulfasalazine, gold, azathioprine, chlorambucil, chloroquine, ciclosporin, cyclophosphamide, mycophenolate, minocycline, penicillamine, tacrolimus, anakinra, infliximab, etanercept, adalimumab, golimumab, certolizumab pegol, rituximab, abatacept, tocilizumab, sarilumab, sirukumab, olokizumab, ixekizumab, guselkumab, ustekinumab, mavrilimumab, tofacitinib, baricitinib, peficitinib, filgotinib, upadacitinib or fostamatinib), formulations and duration. Glucocorticoids were also included. The comparator was another bDMARD, sDMARD, glucocorticoid, combination therapy or the general population. Studies were only eligible if they included a comparator group. All safety outcomes were considered, namely, infections (including serious infections (SIs), opportunistic infections (OIs) such as tuberculosis and herpes zoster (HZ)), malignancies, mortality, major cardiovascular events (MACEs) including venous thromboembolism/pulmonary embolism (VTE/PE), change in lipid levels, elevation of creatine phosphokinase, impairment in renal function, elevation of liver enzymes, haematological abnormalities, gastrointestinal side effects, demyelinating disease, induction of autoimmune disease and teratogenicity.

In addition, RCTs and long-term extensions (LTEs) selected in the accompanying SLR addressing efficacy[5] were also included to assess safety of drugs yet without registry data available.

Selection of studies, data extraction and assessment of risk of bias

Two reviewers (AS and AK) independently screened titles and abstracts, and if necessary, the full text, for eligibility. Data from eligible studies were extracted regarding study and population characteristics, inclusion/exclusion criteria, follow-up time, interventions, outcome definition and outcome measures using a standardised data extraction form. The same two reviewers independently assessed the risk of bias (RoB) of each included study using the 'Hayden-tool' for observational studies and the Cochrane Collaboration's tool for RCTs.[7 8] A brief tutorial on how to use the 'Hayden-tool' is provided elsewhere.[9] For study selection, extraction and RoB assessment, disagreements were discussed until consensus was achieved, and a third reviewer (RL) was involved whenever necessary.

RESULTS

Of a total of 3886 references (after deduplication), 155 were selected for a full-text review and 42 observational studies fulfilled the inclusion criteria. In addition, 60 RCTs/LTEs were included from the efficacy SLR (flow chart in online supplementary figure S1).

Safety aspects from observational studies

Of the 42 observational studies, 16 addressed the risk of infections in patients receiving bDMARDs (3 also included patients on tofacitinib),[10–25] 8 studies focused on malignancies,[16 26–32] with all except one (comparing MTX to the general population),[27] assessing patients on bDMARDs. The risk of MACEs was evaluated in 10 studies, all performed in patients treated with bDMARDs,[16 33–41] with one also including patients on tofacitinib.[33] Three studies addressed the risk of lower intestinal perforations (LIPs),[42–44] five addressed the risk of withdrawal due to adverse events,[45–49] and two addressed the risk of immunological reactions,[50 51] all in patients treated with bDMARDs (online supplementary table S1). Studies were very heterogeneous; thus, data pooling was not possible, and the results are presented descriptively.

Infections

Out of 16 studies addressing the risk of infections, 3 compared bDMARDs with csDMARDs,[10 21 25] and 13 compared the risk across bDMARDs (table 1 and online supplementary tables S2–S31).[11–20 22–24] Three of these studies also compared tofacitinib with bDMARDs.[14 17 18]

Two studies have shown an increased risk of SIs both with tumour necrosis factor inhibitor (TNFi) (adjusted incidence rate ratio (aIRR) 3.1; p<0.001; one study at moderate RoB)[12] and non-TNFi (aIRR 3.9 (95% CI 1.2; 24.3); one study at high RoB)[25] compared with csDMARDs. Another study, at moderate RoB, showed that the risk of sepsis (complicating an SI) is lower in patients treated with bDMARDs compared with those on csDMARDs at the time of the SI. However, it is unclear whether this finding reflects an underlying biological mechanism or residual confounding.[21]

Most new evidence on the risk of SI stems from studies comparing bDMARDs (nine studies, four at low RoB) and, overall, no major differences were found (table 1). In addition, no significantly increased risk of SI (HR 1.54 (95% CI 0.93; 2.56)) was found comparing tofacitinib with TNFi (one study at high RoB).[18] Two studies (one at low RoB) reported no difference in the risk of any OIs between tocilizumab and TNFi.[20 22] One of these studies also found no difference between rituximab and TNFi (aHR 0.96 (95%CI 0.62; 1.50)).[22] Two studies, both at high RoB, found no difference in the risk of HZ infection between TNFi and non-TNFi, but in one study, an increased risk with tofacitinib compared with abatacept was reported (aHR 2.01 (95% CI 1.40; 2.88)). One study showed an increased risk of tuberculosis with monoclonal TNFi antibodies (as a group) compared with etanercept (aOR 2.49 (95% CI 1.45; 4.25)) and another for adalimumab against etanercept (aIRR 1.87 (95% CI 1.27; 2.73)), both at high RoB. One study (at low RoB) reported a decreased risk of tuberculosis in patients treated with rituximab compared with those on TNFi (HR 0.16 (95% CI 0.04; 0.67)).

Table 1 Serious infections, comparison between different bDMARDs/tsDMARDs (observational studies)

Study ID	Registry	Intervention	Control	aHR (I vs C)	Risk of bias
Serious infections					
Carrara 2019 Clin Exp Rheumatol[11]	RECORD	ADA	ETA	1.4 (1.0; 2.0)	High
		IFX		1.0 (0.6; 1.6)	
		CZP		1.3 (0.5; 3.6)	
		GOL		1.1 (0.4; 3.2)	
		ABA		**0.3 (0.1; 0.8)**	
		RTX		1.0 (0.5; 1.9)	
		TCZ		1.2 (0.6; 2.6)	
Cecconi 2018 J Clin Rheumatol[12]	BIOBADABRASIL	ADA	IFX	**aIRR: 0.5 (0.4; 0.8)**	Moderate
		ETA		aIRR: 0.8 (0.6; 1.2)	
Grøn 2019 Ann Rheum Dis[15]	DANBIO and ARTIS	ABA	RTX	aIRR: 0.9 (0.7; 1.1)	Low
		TCZ		aIRR: 0.8 (0.6; 1.0)	
Harrold 2018 Arthritis Res Ther[16]	CORRONA	CZP	Other TNFi	aIRR: 1.3 (0.8; 1.9)	Low
Machado 2018 Arthritis Res Ther[18]	Claims database	TNFi	Non-TNFi	1.1 (1.0; 1.4)	High
		TOFA		1.5 (0.9; 2.6)	
Mori 2017 PLoS One[19]	SARABA	IFX	ETA	1.5 (0.8; 3.0)	Moderate
		ADA		1.7 (0.9; 3.3)	
		ABA		1.1 (0.6; 2.2)	
		TCZ		1.0 (0.6; 1.9)	
Pawar 2019 Ann Rheum Dis[20]	Claims database	TCZ	TNFi	1.1 (1.0; 1.2)	High
		ABA		1.4 (1.2; 1.6)	
Rutherford 2018 Ann Rheum Dis[23]	BSRBR-RA	IFX	ETA	0.9 (0.8; 1.0)	Low
		ADA		1.0 (0.9; 1.1)	
		RTX		0.9 (0.8; 1.0)	
		TCZ		**1.2 (1.0; 1.5)**	
		CZP		**0.8 (0.6; 1.0)**	
Silva-Fernández 2018 Rheumatology (Oxford)[24]	BSRBR-RA	RTX	TNFi	1.0 (0.7; 1.4)	Low
Opportunistic infections					
Pawar 2019 Ann Rheum Dis[20]	Claims database	TCZ	TNFi	1.0 (0.6; 1.8)	High
		ABA		NR	
Rutherford 2018 Rheumatology (Oxford)[22]	BSRBR-RA	RTX	TNFi	1.0 (0.6; 1.5)	Low
		TCZ		0.5 (0.2; 1.7)	
Herpes zoster					
Pawar 2019 Ann Rheum Dis[20]	Claims database	TCZ	TNFi	0.9 (0.5; 1.7)	High
		ABA		NR	
Curtis 2016 Ann Rheum Dis[14]	Claims database	ADA	ABA	1.0 (0.8; 1.3)	High
		CZP		1.1 (0.9; 1.5)	
		ETA		1.1 (0.9; 1.3)	
		GOL		1.1 (0.8; 1.6)	
		IFX		1.2 (1.0; 1.4)	
		RTX		1.1 (0.9; 1.4)	
		TCZ		1.1 (0.9; 1.4)	
		TOFA		**2.0 (1.4; 2.9)**	
Tuberculosis					
Cho 2017 Semin Arthritis Rheum[13]	Claims database	Monoclonal AB (ADA; GOL; IFX)	ETA	**aOR: 2.5 (1.5; 4.3)**	High
Lim 2017 Plos one[17]	Files from Taichung Veterans General Hospital	ADA	ETA	**aIRR: 1.9 (1.3; 2.7)***	High
		GOL		†	
		TCZ		†	
		ABA		†	
		TOFA		†	
Pawar 2019 Ann Rheum Dis[20]	Claims database	TCZ	TNFi	†	High
		ABA		NR	
Rutherford 2018 Rheumatology (Oxford)[22]	BSRBR-RA	RTX	TNFi	**0.2 (0.0; 0.7)**	Low
		TCZ		0.4 (0.1; 2.6)	

Continued

Table 1 Continued

Study ID	Registry	Intervention	Control	aHR (I vs C)	Risk of bias
***Pneumocystis jirovecii* pneumonia**					
Rutherford 2018 Rheumatology (Oxford)[22]	BSRBR-RA	RTX	TNFi	**3.2 (1.4; 7.5)**	Low
		TCZ		NR	

*Including only patients without history of tuberculosis (effect not significant if including all patients irrespective of history).
†No cases of tuberculosis occurred so comparisons are not possible. Values in bold reflect a statistically significantly effect (ie, ratio different from 1). Additional details in online supplementary tables S2–31
ABA, abatacept; ADA, adalimumab; aHR, adjusted HR; aIRR, adjusted incidence rate ratio; aOR, adjusted OR; ARSTIS, anti-Rheumatic Treatment in Sweden Register; bDMARDs, biologic disease-modifying antirheumatic drugs; BSRBR, British Society of Rheumatology Biologics Register; CORRONA, Consortium of Rheumatology Researchers of North America; CZP, certolizumab pegol; ETA, etanercept; GOL, golimumab; IFX, infliximab; NR, not reported; RA, rheumatoid arthritis; RECORD, RECord-linkage On Rheumatic Diseases (administrative dataset); RTX, rituximab; TCZ, tocilizumab; TNFi, tumour necrosis factor inhibitor; TOFA, tofacitinib; tsDMARD, target synthetic disease-modifying antirheumatic drugs.

Malignancies

Three studies reported no increased risk of malignancies (excluding non-melanoma skin cancer (NMSC)) with bDMARDs compared with the general population.[28 31 32] Similarly, the risk of cancer was not increased in patients treated with bDMARDs compared with those on csDMARDs (aHR range 0.4–1.4; five studies, four at low RoB) (table 2),[26 29–32] including also patients with a history of cancer.[30] In two studies, both at low RoB, the risk of cancer was not different comparing TNFi with non-TNFi.[16 31] A signal, however, was found for an increased risk of NMSC with methotrexate in one study at moderate RoB (standardised incidence rate (SIR) 2.52 (95% CI 2.01; 3.11))[27]; and another study with bDMARDs (except tocilizumab) both compared with the general population.[31] The latter also reported an increased risk of NMSC with abatacept compared with csDMARDs (aHR 2.15 (95% CI 1.31; 3.52)) and TNFi (aHR 2.12 (95% CI 1.14; 3.95)) based on the occurrence of 17 events. Details on studies addressing malignancies are shown in online supplementary tables S32–S59.

Major cardiovascular events

Several studies addressing MACE could be included (10 studies, two at low RoB; details in online supplementary tables S60–S86). Three studies (one at low RoB) have shown no increased risk of MACE for bDMARDs compared with csDMARDs.[35 39 40] In four studies (one at low RoB), no differences between bDMARDs were found,[16 34 37 38] except in two studies, both at high RoB, in which a lower risk of myocardial infarction with abatacept compared with TNFi was reported (table 3).[36 41] Of note, no difference in risk of stroke or heart failure was found between abatacept and TNFi.[34 36 38] The risk of VTE was evaluated in two studies, both at high RoB.[33 36] One has shown no increase with tofacitinib (aHR 1.33 (95% CI 0.78; 2.24)) and another study showed no increase with abatacept (aHR 1.27 (95% CI 0.63; 2.57)), both compared with TNFi.

Lower intestinal perforations

Three studies addressed the risk of LIP (online supplementary tables S87–S92).[42–44] One study, at low RoB, compared the risk of LIP between various bDMARDs and csDMARDs and has shown that only patients on tocilizumab had an increased risk (aHR 4.48 (95% CI 2.01; 9.99)) (two patients had history of diverticulitis, one of them on tocilizumab).[43] Two other studies, at high RoB, compared the risk of LIP between non-TNFi and TNFi and both report again an increased risk for tocilizumab (IRR 4.0 (95% CI 1.1; 14.1)[42] and aHR 2.55 (95% CI 1.33; 4.88)).[44] All studies were adjusted for cotreatment with glucocorticoids and nonsteroidal anti-inflammatory drugs (NSAIDs), and the latter two studies also for history of diverticulitis. In addition, one of these studies has also shown an increased risk for tofacitinib compared with TNFi (aHR 3.24 (95% CI 1.05; 10.04)).[44]

Other adverse events

Studies addressing the risk of withdrawals due to adverse events and immunological reactions reported results in line with the known safety profile of bDMARDs (online supplementary tables S93–S103).[45–51]

Safety aspects from RCTs

In total, 21 studies evaluating bsDMARDs,[52–72] 18 studies evaluating boDMARDs[73–90] and 21 studies evaluating tsDMARDs[91–111] were included (online supplementary table S104). Overall, the incidence of major adverse events was low in all RCTs with mostly no differences between the active treatment and placebo or active comparator. Exceptions were a numerically higher number of deaths with sirukumab compared with placebo and adalimumab,[86 88] a numerically higher number of cases of NMSC with JAKi compared with placebo or active comparator,[91–93 95 98 111] and the additional safety signals detailed below. LTEs did not show new safety signals compared with the controlled phase of their respective trials (online supplementary tables S105–S118).

Herpes zoster

The cases of HZ was low but numerically higher with all JAKi compared with placebo in nine RCTs (five at low RoB; online supplementary table S115). In addition, the risk of infection by HZ with JAKi was reported in three head-to-head trials. In two studies, the risk was low and comparable between tofacitinib (1%–2%) or baricitinib (2%) and adalimumab (2%).[93 94] The risk was somewhat higher in another study comparing baricitinib (2%–3%) with methotrexate (1%).[95] Of note, in this study, HZ cases occurred mostly in Japanese patients (7/11; 73%). One LTE in Japanese patients treated with tofacitinib (5 or 10 mg) reported an HZ infection incidence rate of 7.4 cases per 100 patient years (PY).[108] The risk was much lower (1.72/100 PY) in another LTE with only Chinese patients on tofacitinib 5 mg (1.51/100 PY with 10 mg),[103] and in one multinational LTE (without Asian patients), in patients treated with baricitinib 4/8 mg (2.5/100 PY).[101]

Venous thromboembolism and pulmonary embolism

The risk of VTE/PE with JAKi was reported in three placebo-controlled trials and in two head-to-head trials (all at low RoB) (table 4). Although the number of events was low, in three of these trials, VTE occurred only in patients receiving tsDMARDs (in total six events, five were PE, one fatal).[92 94 96]

Table 2 Malignancies in patients on bDMARDs compared with patients on csDMARDs (observational studies)

Study ID	Registry	Intervention	Control	aHR (I vs C)	Risk of bias
All types of cancer					
Wadstrom 2017 JAMA Intern Med[31]	ARTIS	TCZ	csDMARDs	0.9 (0.7; 1.2)	Low
		ABA		0.9 (0.7; 1.1)	
		RTX		0.9 (0.7; 1.0)	
		TNFi		0.9 (0.9; 1.0)	
Patients with history of cancer					
Silva-Fernández 2016 Rheumatology (Oxford)[30]	BSRBR-RA	TNFi	csDMARDs	**0.6 (0.4; 0.9)**	Low
		RTX		0.4 (0.1; 1.8)	
Solid cancer (excluding NMSC)					
Wadström 2017 JAMA Intern Med[31]	ARTIS	TCZ	csDMARDs	1.0 (0.7; 1.3)	Low
		ABA		0.9 (0.7; 1.2)	
		RTX		0.9 (0.8; 1.1)	
		TNFi		0.9 (0.9; 1.0)	
Non-melanoma skin cancer					
Wadström 2017 JAMA Intern Med[31]	ARTIS	TCZ	csDMARDs	0.9 (0.4; 2.2)	Low
		ABA		**2.2 (1.3; 3.5)**	
		RTX		1.0 (0.7; 1.6)	
		TNFi		1.1 (0.8; 1.4)	
Melanoma					
Wadström 2017 JAMA Intern Med[31]	ARTIS	TCZ	csDMARD	<5 events	Low
		ABA		1.4 (0.7; 3.1)	
		RTX		0.7 (0.4; 1.4)	
		TNFi		0.8 (0.6; 1.2)	
Cervical cancer					
Kim 2016 Arthritis Rheumatol[26]	Claims database	bDMARDs	csDMARDs	1.3 (0.9; 2.0)	High
Wadström 2016 Ann Rheum Dis[32]	ARTIS	TNFi	csDMARDs	1.4 (0.6; 3.1)	Low
Haematological cancer					
Wadstrom 2017 JAMA Intern Med[31]	ARTIS	TCZ	csDMARDs	<5 events	Low
		ABA		1.0 (0.5; 2.0)	
		RTX		0.7 (0.5; 1.2)	
		TNFi		0.9 (0.7; 1.1)	
Lymphoma					
Mercer 2017 Ann Rheum Dis[29]	BSRBR-RA	IFX	csDMARDs	0.9 (0.4; 2.1)	Low
		ETA		1.0 (0.5; 2.3)	
		ADA		1.0 (0.5; 2.0)	
		All TNFi		1.0 (0.6; 1.8)	

Additional details in online supplementary tables S32–59.
ABA, abatacept; ADA, adalimumab; aHR, adjusted HR; ARSTIS, anti-Rheumatic Treatment in Sweden Register; bDMARDs, biologic disease-modifying antirheumatic drugs; BSRBR, British Society of Rheumatology Biologics Register; csDMARDs, conventional synthetic disease-modifying antirheumatic drugs; ETA, etanercept; IFX, infliximab; RA, rheumatoid arthritis; RTX, rituximab; TCZ, tocilizumab; TNFi, tumour necrosis factor inhibitor; TOFA, tofacitinib.

Lower intestinal perforations

Six trials reported the risk of intestinal perforations with interleukin (IL)-6 inhibitors (IL-6i) bDMARDs (including both IL-6R and IL-6 inhibitors) yet without observational data available (table 5). In two of these trials (both at low RoB), intestinal perforations occurred only in patients treated with IL-6i.[73 88] History of diverticulitis was an exclusion criteria in only one study,[73] and no association with other known risk factors, for example, treatment with glucocorticoids or NSAIDs, has been reported in any study. The risk of LIP was assessed in nine RCTs/LTEs in patients on tsDMARDs and all report no cases.[91 92 94 97 98 102 108 110 111]

DISCUSSION

New evidence from this SLR does not justify amending the previous statement that bDMARDs can be safely used to treat patients with RA.[3] In addition, it extends this conclusion to tsDMARDs, although data remain somewhat limited as yet. The risk of SIs was moderately increased with bDMARDs compared with csDMARDs and no difference was found across bDMARDs. The risk of tuberculosis is increased with TNFi, especially with monoclonal antibodies, but tuberculosis has occurred in trials of other b/tsDMARDs used in RA. The risk of HZ infection is not increased with bDMARDs, but is with JAKi, especially in certain ethnicities. The overall risk of malignancies (except NMSC) and MACE was not increased for bDMARDs or tsDMARDs. The known risk of LIP after IL-6i has been further confirmed. VTE/PE after JAKi is a valid concern and needs further evaluation.

Observational studies were defined as the main study type of interest in this SLR assessing safety of therapies in RA. With observational research, unselected patients from daily practice are studied including those with comorbidities usually ineligible for RCTs. As such, observational studies yield results that are easier to translate to what clinicians encounter in the 'real world' (external validity), and thus are more informative. Also, their long follow-up is ideal to study rare adverse events, which are too difficult to 'capture' in the shorter RCTs. However, observational studies are not without

Table 3 Major cardiovascular events, comparison between different bDMARDs/tsDMARDs (observational studies)

Study ID	Registry	Intervention	Control	aHR (I vs C)	Risk of bias
Major cardiovascular events					
Harrold 2018 Arthritis Res Ther[16]	CORRONA	CZP	Other TNFi	aIRR: 1.0 (0.5; 2.1)	Low
Jin 2018 J Rheumatol[36]	Claims database	ABA	TNFi	**0.8 (0.7; 0.9)**	High
Kim 2017 Arthritis Rheumatol[37]	Claims database	TCZ	TNFi	0.8 (0.6; 1.3)	High
Kim 2018 Semin Arthritis Rheum[38]		TCZ	ABA	0.8 (0.6; 1.2)	High
Myocardial infarction					
Jin 2018 J Rheumatol[36]	Claims database	ABA	TNFi	**0.6 (0.4; 0.9)**	High
Kim 2017 Arthritis Rheumatol[37]	Claims database	TCZ	TNFi	0.7 (0.4; 1.3)	High
Kim 2018 Semin Arthritis Rheum[38]		TCZ	ABA	1.1 (0.7; 1.9)	High
Zhang 2016 Ann Rheum Dis[41]	Claims database	ADA	ABA	1.2 (0.9; 1.6)	High
		CZP		1.2 (0.8; 2.0)	
		ETA		**1.3 (1.0; 1.8)**	
		GOL		1.1 (0.6; 2.1)	
		IFX		**1.3 (1.0; 1.7)**	
		RTX		1.1 (0.8; 1.4)	
		TCZ		0.9 (0.5; 1.5)	
		TNFi		**1.3 (1.0; 1.6)**	
Stroke					
Jin 2018 J Rheumatol[36]	Claims database	ABA	TNFi	1.1 (0.8; 1.5)	High
Kim 2017 Arthritis Rheumatol[37]	Claims database	TCZ	TNFi	0.9 (0.5; 1.6)	High
Kim 2018 Semin Arthritis Rheum[38]		TCZ	ABA	0.7 (0.4; 1.4)	High
Heart failure					
Generali 2019 Rheumatol Int[34]	Claims database	ABA	ETA	1.4 (0.6; 3.5)	High
Jin 2018 J Rheumatol[36]	Claims database	ABA	TNFi	0.8 (0.3; 1.9)	High
Kim 2018 Semin Arthritis Rheum[38]	Claims database	TCZ	ABA	1.2 (0.7; 2.0)	High
Venous thromboembolism					
Desai 2018 Arthritis Rheumatol[33]	Claims database	TOFA	TNFi	1.3 (0.8; 2.2)	High
Jin 2018 J Rheumatol[36]	Claims database	ABA	TNFi	1.3 (0.6; 2.6)	High

Additional details in online supplementary tables S60–86.
ABA, abatacept; ADA, adalimumab; aHR, adjusted HR; aIRR, adjusted incidence rate ratio; bDMARDs, biologic disease-modifying antirheumatic drugs; CORRONA, Consortium of Rheumatology Researchers of North America; CZP, certolizumab pegol; ETA, etanercept; GOL, golimumab; IFX, infliximab; RTX, rituximab; TCZ, tocilizumab; TNFi, tumour necrosis factor inhibitor; TOFA, tofacitinib; tsDMARDs, target synthetic disease-modifying antirheumatic drugs.

limitations. For instance, patients in different treatment groups may have prognostic dissimilarities (driven by non-random treatment allocation) that can blur treatment effects (confounding by indication).[4] Also, information bias, especially relevant in studies from administrative ('claims') databases, is a possible limitation. We assessed how researchers dealt with these and other issues by using a validated tool to estimate an overall RoB for each study, which should be considered when interpreting the results of this SLR.

Importantly, however, we have also evaluated safety data from RCTs and LTE for drugs as yet without much 'real-world' data available. Even if most RCTs are not powered to detect differences in adverse events between treatment groups, and LTEs have no comparator allowing a proper risk assessment, early safety signals can be detected and inform future research. Two examples are the assessment of VTE/PE with JAKi and the imbalance in mortality for sirukumab.[86 88 92 94 96]

New evidence from studies assessing the risk of infections with bDMARDs are mostly in line with the 2016 SLR. That is, an increased risk of SI with bDMARDs compared with csDMARDs was again noted, but without major differences across bDMARDs. New data also support an increased risk of tuberculosis with monoclonal TNFi, especially adalimumab, compared with etanercept (conflicting data in the previous SLR), but this is a quantitative and not a qualitative result and all patients undergoing TNFi (and most other bDMARD) therapy must be tested (and if positive treated) for latent tuberculosis.[13 17] In addition, all (old and new) studies are at high RoB (eg, by the lack of validation of the outcome), which hampers firm conclusions to be drawn. The risk of tuberculosis with non-TNFi has been less well studied. Although a lower risk of

Table 4 Venous thromboembolism in patients on tsDMARDs (randomised controlled trials)

Study ID (trial)	Follow-up	Intervention	N	VTE (%)	Risk of bias
Placebo-controlled trials					
Burmester 2018 Lancet (SELECT-NEXT)[91]	12	PBO	221	0 (0)	Low
		UPA 15 QD	221	0 (0)	
		UPA 30 QD	219	0 (0)	
Dougados 2017 Ann Rheum Dis (RA-BUILD)[92]	24	PBO	228	0 (0.0)	Low
		BAR 2 QD	229	0 (0.0)	
		BAR 4 QD	227	1 (0.4)*	
Genovese 2018 Lancet (SELECT-BEYOND)[96]	24	PBO	169	0 (0)	Low
		UPA 15 QD	164	3 (1.8)†	
		UPA 30 QD	165	1 (0.6)‡	
Head-to-head trials					
Fleischmann 2017 Arthritis Rheumatol (RA-BEGIN)[95]	52	MTX Q1W mono	210	1 (0.5)§	Low
		BAR 4 QD mono	159	0 (0.0)	
		BAR 4 QD+MTX Q1W	215	0 (0.0)	
Taylor 2017 N Engl J Med (RA-BEAM)[94]	52	BAR 4 QD	487	1 (0.2)¶	Low
		ADA 40 Q2W	330	0 (0.0)	

*Pulmonary embolism.
†One case of pulmonary embolism occurred during the 12-week PBO-controlled phase and two cases (one with concomitant deep venous thrombosis) between week 12 and week 24 in patients who switched from PBO to UPA15 (2/72=2.8%).
‡One case of pulmonary embolism in a patient who switched from PBO to UPA30 after week 12.
§Death by pulmonary thromboembolism.
¶Thrombophlebitis.
mono, monotherapy; QD, once daily; Q1W, once a week.

tuberculosis with rituximab compared with TNFi has been found, it remains unclear whether this finding reflects drugs' different modes of action or is better explained by residual confounding (eg, by treatment with glucocorticoids).[22]

The current SLR adds to the available literature by increasing the body of evidence showing no difference in the risk of HZ infection between TNFi and non-TNFi. On the contrary, one study from a claims database has shown an increased HZ risk with tofacitinib

Table 5 Intestinal perforations in patients on bDMARDs (IL-6 inhibitors) (randomised controlled trials)

Study ID (trial)	Follow-up	Intervention	N	N intestinal perforations (%)	Risk of bias
Placebo-controlled trials					
Aletaha 2017 Lancet (SIRROUND-T)[73]	24	PBO	294	0 (0.0)	Low
		SIR 50 Q4W	292	2 (0.7)	
		SIR 100 Q2W	292	3 (1.0)*	
Fleischmann 2017 Arthritis Rheumatol (TARGET)[79]	24	PBO	181	0 (0.0)	Low
		SAR 150 Q2W	181	0 (0.0)	
		SAR 200 Q2W	184	0 (0.0)	
Takeuchi 2016 Mod Rheumatol[85]	12	PBO	29	0 (0.0)	Unclear
		OKZ 60 Q4W	32	0 (0.0)	
		OKZ 120 Q4W	32	0 (0.0)	
		OKZ 240 Q4W	26	0 (0.0)	
Takeuchi 2017 Ann Rheum Dis (SIRROUND-D)[86]	52	PBO	556	1 (0.2)†	Unclear
		SIR 50 Q4W	663	1 (0.2)‡	
		SIR 100 Q2W	662	0 (0.0)	
Head-to-head trials					
Burmester 2017 Ann Rheum Dis (MONARCH)[74]	24	ADA 40 Q2W	184	0 (0.0)	Low
		SAR 200 Q2W	184	0 (0.0)	
Taylor 2018 Ann Rheum Dis (SIRROUND-H)[88]	68	ADA 40 Q2W	186	0 (0.0)	Low
		SIR 50 Q4W	186	1 (0.5)§	
		SIR 100 Q2W	187	1 (0.5)§	

*Two additional perforations occurred in patients switching from placebo to SIR 100 after week 24 up to week 52; thus, in total, seven perforations occurred (three upper gastrointestinal perforations and four lower intestinal perforations).
†Upper gastrointestinal perforation.
‡Lower intestinal perforation (patients randomised to PBO with early escape to SIR 50).
§Location not specified.
ADA, adalimumab; OKZ, olokizumab; PBO, placebo; Q2W, every 2 weeks; Q4W, every 4 weeks; SAR, sarilumab; SIR, sirukumab.

compared with abatacept.[14] RCTs and LTE were less informative due to small number of cases (mostly mild), but suggest a class effect for JAKis and that infection by HZ is especially relevant in Japanese[108] and Korean patients with RA.[112] The reason for this geographical distribution remains unknown, but a genetic predisposition could play a role. Live HZ vaccination has proven to be safe and effective in inducing immune responses,[113] but did not reduce the risk of infection in another (likely underpowered) study,[114] in patients with RA starting tofacitinib. A non-live, recombinant HZ vaccine is available but not yet tested in RA.[115] More data are needed to clarify the role of HZ vaccination in RA especially in patients starting on JAKi.[116]

The risk of LIP has been consistently found to be increased in patients on tocilizumab in three independent observational studies included in this SLR,[42–44] which is in line with the available evidence.[117] Thus far, 'real-world' data on IL-6Ri are available only for tocilizumab, but data from RCTs suggest a class effect. The risk of LIP with sarilumab will have to be re-evaluated once registry data become available. Screening for risk factors for LIP (eg, history of diverticulitis) is advised before initiating IL-6Ri.[117] More long-term observational studies (with a proper comparator) are needed to clarify the risk of LIP with JAKi seen in previous pooled analyses of trial data.[118–120]

Overall, the risk of MACE did not differ between bDMARDs and csDMARDs nor across different bDMARDs. Of note, most evidence stems from studies on 'claims databases' with a high risk of bias. One recent open-label RCT, not included in the SLR because it was accepted for publication after the search was done (8 March 2019), compared the risk of MACE between tocilizumab and etanercept over a mean of 3.2 years of follow-up in patients with ≥1 traditional cardiovascular (CV) risk factor and also found no difference in risk of MACE.[121] In contrast, RCT data suggest an imbalance in the number of deaths (also by MACE) between sirukumab and placebo/active comparator, which halted its further development in RA.[122]

While one observational study performed with 'claims' data showed no significant increased risk of VTE with tofacitinib compared with TNFi,[33] data from RCTs included in this SLR suggest an increased risk of VTE with JAKi. These data are in line with a recent pooled analysis of the baricitinib clinical trials programme, where VTE occurred exclusively among patients on baricitinib 4 mg, but not baricitinib 2 mg or placebo during the 24-week placebo-controlled period.[123] Additional events were observed in patients treated with baricitinib 2 and 4 mg after the first 24 weeks of exposure. An interim analysis of an ongoing open-label study (A3921133) reported an increased risk of blood clots in deep veins and in the lungs with both the 5 mg and, especially, with the 10 mg twice daily doses of tofacitinib as compared with patients taking TNFi in patients with ≥1 CV risk factor.[124 125] This interim analysis was published after the literature search (8 March 2019) and after the task force meeting for the EULAR recommendations on the management of RA had already taken place. These data suggest that JAKi increases the risk of VTE, above the underlying effect of RA itself,[126] especially in patients with CV risk factors, but the risk is low and with unclear pathogenic mechanisms. Nonetheless, in light of the currently available evidence, the European Medicine Agency (EMA) has issued warnings to use tofacitinib and baricitinib with caution in RA patients with risk factors for VTE.[124 127] In addition, the Food and Drug Administration did not approve the 4 mg dose of baricitinib.[128 129] Well-designed long-term observational studies will be key to clarify this issue in the near future.

Although this SLR aimed at including all safety outcomes, studies assessing the safety of using DMARDs during pregnancy could not be included. Also, controlled studies assessing the long-term safety of glucocorticoids are still lacking. Two studies (without comparator) have shown that treatment with glucocorticoids might associate with increased mortality, and in one of these studies, the risk was dose-dependent.[130 131] The reader is referred to the EULAR points to consider for the use of DMARDs in pregnancy and lactation and the EULAR recommendations on the management of glucocorticoid therapy in rheumatic diseases.[132 133] Recently, EMA alerted practitioners to the risk of severe liver failure with tocilizumab, based on yet unpublished data.[134]

Finally, although the first observational studies on tsDMARDs could have been included (all on tofacitinib), still most evidence included in this SLR pertains to bDMARDs. With more tsDMARDs expected to be approved in the coming years, more 'real-world' evidence will be generated to inform future updates of this SLR, following the usual periodic revisions of the RA management recommendations.

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