Safety of synthetic and biological DMARDs: a systematic literature review informing the 2022 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 antirheumatic drugs (DMARDs) to inform the 2022 update of the EULAR recommendations for the management of rheumatoid arthritis (RA).

Methods SLR of observational studies comparing safety outcomes of any DMARD with another intervention in RA. A comparator group was required for inclusion. For treatments yet without, or limited, registry data, randomised controlled trials (RCTs) were used.

Results Fifty-nine observational studies addressed the safety of DMARDs. Two studies (unclear risk of bias (RoB)) showed an increased risk of serious infections with bDMARDs compared with conventional synthetic (cs)DMARDs. Herpes zoster infections occurred more with JAKi than csDMARDs (adjusted HR (aHR): 3.66) and bDMARDs (aHR: 1.9–2.3) (four studies, two low RoB). The risk of malignancies was similar across bDMARDs (five studies) and with tofacitinib compared with bDMARDs (one study, low RoB). The risk of major adverse cardiovascular events (MACE) was similar with bDMARDs and tofacitinib (two studies, one low RoB). Thirty studies reported safety from RCTs, with one, designed to evaluate safety, showing that malignancies (HR (95% CI): 1.48 (1.04 to 2.09)) and MACE (HR (95% CI): 1.33 (0.91 to 1.94)) occurred numerically more frequently with tofacitinib (5 mg and 10 mg doses combined) than with TNFi in patients with cardiovascular risk factors. In this study, the risk of venous thromboembolism (VTE) was higher with tofacitinib 10 mg than with TNFi.

Conclusion The safety profile of bDMARDs was further demonstrated. Whether the difference in incidence of malignancies, MACE and VTE between tofacitinib and TNFi applies to other JAKi needs further evaluation.

WHAT IS ALREADY KNOWN ON THIS TOPIC

⇒ Since the 2019 EULAR recommendations for the management of rheumatoid arthritis (RA), new evidence has emerged on the safety of synthetic and biological disease-modifying antirheumatic drugs (bDMARDs) in RA.

WHAT THIS STUDY ADDS

⇒ The risk of malignancies and major adverse cardiovascular events (MACEs) is similar, or even decreased, with bDMARDs compared with conventional synthetic (cs)DMARDs.

⇒ Malignancies and MACE occurred more with tofacitinib than with TNFi in patients who had certain cardiovascular risk factors, especially in patients older than 65 years of age.

⇒ Herpes zoster is more common with JAKi than with csDMARDs or bDMARDs.

⇒ Lower intestinal perforations are rare but occur more often with tocilizumab than with other bDMARDs.

HOW THIS STUDY MIGHT AFFECT RESEARCH, PRACTICE OR POLICY

⇒ This review informed the 2022 EULAR recommendations for the management of RA, highlighting new evidence on safety of synthetic and bDMARDs.

INTRODUCTION

The main goals of the management of patients with rheumatoid arthritis (RA) include the relief of signs and symptoms, prevention of irreversible damage, improvement and normalisation of function, quality of life and social participation.[1–3] Achieving these goals has become increasingly easier, thanks to, among others, a growing number of treatment options at the disposal of clinicians taking care of patients with RA.

Interventions currently approved in RA include conventional synthetic disease-modifying antirheumatic dugs (csDMARDs), biological DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs).[4] These 'umbrella-terms' include drugs with diverse modes of action. Drugs targeting TNF (TNF inhibitors; TNFi) the IL-6-receptor (IL-6R inhibitors; IL-6Ri), T cell co-stimulation and B cells, are examples of bDMARDs. JAK inhibitors (JAKi) are, thus far, the only tsDMARDs approved

to treat RA. Despite their diverse mechanisms, these drugs have shown a remarkable overlap in efficacy.[5] Safety aspects can, however, differ and thus influence treatment decisions in clinical practice.[6]

Safety is a key component of the development programme of new drugs. However, randomised controlled trials (RCTs) are usually designed to evaluate efficacy. Their short follow-up and the inclusion of selected patients limit their ability to study safety thoroughly.[7] These challenges, among others, led to the development of patient registries. After regulatory approval, a new drug will be used in patients in clinical practice who subsequently can be enrolled in registries or other observational cohorts and databases. In the absence of RCTs designed to evaluate safety, observational studies stemming from real-world data sources in which drugs are directly compared in unselected patients over a long time, have regularly been used to inform management recommendations over the years.[1] Occasionally, large, long-term RCTs with a primary safety endpoint are designed, mostly on regulatory request,[2 3] providing information on specific safety aspects of certain drugs at the highest level of evidence.

In order to inform the task force responsible for the 2022 update of the EULAR RA management recommendations,[8] we performed a systematic literature review (SLR) to update the evidence for the safety of csDMARDs, bDMARDs and tsDMARDs in patients with RA. This SLR is an extension of the SLR performed previously for the corresponding 2019 update.[6] The results of this and two other SLRs, one focusing on efficacy,[9] and another one on glucocorticoids,[10] provided the task force with the current state of evidence.

METHODS

Literature search

The steering group of the EULAR task force for the 2022 update of the RA management recommendations outlined the scope of the literature search according to the Population, Intervention, Comparator, Outcomes format and defined the criteria for a study being eligible.[11] The search was performed in MEDLINE, Embase, Web of Science and The Cochrane CENTRAL Register of Controlled Trials (Central), without language restrictions, and comprised publications from 1 January 2019 to 14 January 2022, as an update of the previous SLR.[6] Details on complete search strategies are provided in online supplemental text 1. The literature search addressed the safety of DMARDs. Observational studies, namely cohort studies/registries with >50 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 (chloroquine, hydroxychloroquine, leflunomide, methotrexate, sulfasalazine, abatacept, anakinra, adalimumab, brodalumab, certolizumab pegol, etanercept, golimumab, guselkumab, infliximab, ixekizumab, mavrilimumab, ocrelizumab, ofatumumab, olokizumab, otilimab, rituximab, sarilumab, sirukumab, tabalumab, tocilizumab, ustekinumab, apremilast, baricitinib, decernotinib, evobrutinib, fenebrutinib, filgotinib, fostamatinib, peficitinib, ruxolitinib, tofacitinib, upadacitinib), formulations and duration. Studies were only eligible if they included a comparator group (either another DMARD, combination therapy, or the general population). Studies on glucocorticoids were excluded, as they were dealt with in a separate SLR.[10] The following safety outcomes were considered: infections (including serious infections, opportunistic infections such as tuberculosis (TB) and herpes zoster (HZ)), malignancies, mortality, major adverse cardiovascular events (MACEs), venous thromboembolism (VTE) including pulmonary embolism/deep venous thrombosis, changes in lipid levels, elevations of creatine phosphokinase, impairments in renal function, elevations of liver enzymes, haematological abnormalities, gastrointestinal side effects, demyelinating disease, induction of autoimmune disease, teratogenicity, fertility and pregnancy outcomes. For the risk of infection by SARS-CoV-2, only studies published after 31 May 2021 (the limit date of an SLR informing EULAR recommendations focusing on the topic) were considered.[12 13] RCTs with a primary safety outcome were included. In addition, RCTs and long-term extensions (LTEs), selected in the accompanying SLR addressing efficacy,[9] were also included to assess the safety of drugs without, or with limited real-world data available.

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

Two reviewers (AS and AK) independently screened 10% of all titles and abstracts, and if necessary, the full-text for eligibility. An agreement of 96% between the two reviewers was achieved for the decision to include a study and therefore the remaining screening was done only by one reviewer (AS). 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 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.[14 15] Decisions on study selection, extraction and RoB assessment were discussed with a third reviewer (RBML) whenever necessary.

RESULTS

From a total of 2961 references (after de-duplication), 226 were selected for a full-text review and 59 observational studies fulfilled the inclusion criteria.[16–74] In addition, 2 RCTs with a primary safety outcome,[2 3] and 28 RCTs/LTEs from the efficacy SLR,[75–102] were included (flow chart in online supplemental figure S1). Studies were heterogeneous, precluding data pooling, and results are presented descriptively.

Overview of observational studies

Of 59 observational studies, 51 assessed only 1 outcome,[16–66] and 8 addressed ≥2 outcomes (online supplemental table S1–137).[67–74] Of 27 studies evaluating the risk of infections,[27–47 67 69 71–74] 23 included patients on bDMARDs,[27–29 31–33 35–37 39–47 69 71–74] 9 of which also patients on JAKi,[27 28 30 31 42 45 69 71 72] 3 only patients on csDMARDs[34 38 67] and 1 patients either on tofacitinib or on csDMARDs.[30] Nine studies evaluated the risk of malignancies with bDMARDs,[48–53 71 73 74] and one of these also with tofacitinib.[71] Thirteen studies assessed the risk of MACE,[17–24 67–71] with 11 including patients on bDMARDs,[17–21 23 24 67 69–71] 6 of which included patients on JAKi[20 21 24 67 69 71] and 2 had patients only on csDMARDs.[22 68] Intestinal perforations[25 26] and neuroinflammatory events[60 61] were assessed in two studies, each in patients on bDMARDs. All-cause mortality with bDMARDs was assessed in seven studies.[58 59 68–72] Seven studies addressed withdrawals due to adverse events with bDMARDs[54–56 63–66] and one with JAKi.[57] One study assessed any serious adverse events,[67] another any adverse event,[16] both in patients with bDMARDs, and one evaluated pregnancy outcomes in patients on bDMARDs.[62]

Overview of RCTs

Eleven studies evaluating bDMARDs,[2 75 76 78 79 84 87 90 92 96 100] and 19 evaluating tsDMARDs were included (online supplemental tables S138–152).[3 77 80–83 85 86 88 89 91 93–95 97–99 101 102] 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. The exception was the ORAL-Surveillance study,[3] a non-inferiority trial in which patients ≥50 years old who failed methotrexate and had ≥1 cardiovascular risk factor were randomised to tofacitinib 5 mg two times per day, tofacitinib 10 mg two times per day, or TNFi (adalimumab or etanercept). The trial was designed to test whether the upper limit of the 95% CI around the risk ratio of MACE or malignancies for tofacitinib (5 mg and 10 mg two times per day combined) compared with TNFi, was below 1.8 (the non-inferiority question). In addition, the ENTRACTE trial, which had a similar design and non-inferiority margin, compared the risk of MACE (primary endpoint) between tocilizumab and etanercept.[2]

Infections

Observational studies

Of 27 studies addressing the risk of infections, 3 compared bDMARDs/JAKi to the general population,[27 44 47] 8 compared bDMARDs/JAKi to csDMARDs,[28 30–32 35 36 46 72] 3 compared the risk across csDMARDs[34 38 67] and 13 across bDMARDs/JAKi[29 33 35 37 39–43 45 69 71 74] (table 1 and online supplemental tables S2–S43).

The risk of serious infections was increased with bDMARDs compared with the general population in one study (adjusted HR (aHR): 4.1 (95% CI 3.6 to 4.7)),[44] and compared with csDMARDs in two studies, all at unclear RoB.[35 36] The risk was similar across csDMARDs in two studies comparing different csDMARDs (one at low RoB).[38 67] Seven studies reported a similar risk of serious infections across bDMARDs and two a lower risk with abatacept.[29 32] Of note, the latter result was not seen in five other studies, including one at low RoB from the Danish registry (table 1).[39] Serious infections were not more common with tofacitinib than with bDMARDs in three studies, including one, at low RoB, from the CORRONA registry (aHR: 0.99 (95% CI 0.75 to 1.30)).[42 45 71]

The risk of any opportunistic infection was not increased with TNFi plus methotrexate compared with triple csDMARD therapy,[46] and across bDMARDs (two studies at high and 1 at unclear RoB).[33 74] In one study at low RoB from the German RABBIT registry, patients on monoclonal TNFi (aHR: 1.63 (95% CI 1.17 to 2.28)) and on rituximab (aHR: 1.57 (95% CI 1.03 to 2.40)), but not on other bDMARDs, were more likely to be infected by HZ than patients on csDMARDs.[31] In the same cohort, the risk of HZ was also higher with JAKi (tofacitinib, baricitinib and upadacitinib) than with csDMARDs (aHR: 3.66 (95% CI 2.38 to 5.63)). Moreover, in three studies (one at low RoB) infections by HZ were more frequent with tofacitinib than with bDMARDs (table 1).[40 45 69 71]

The risk of TB was not increased with bDMARDs compared with the general population in a study from Slovenia, where strict procedures for screening and treatment of latent TB were in place (one study at high RoB).[47] Another study at high RoB found a similar risk of TB with abatacept compared with other b/tsDMARDs.[74] The risk of pneumonia due to *Pneumocystis jirovecii* was increased with methotrexate combined with other csDMARDs, compared with methotrexate alone (aHR: 5.98 (95% CI 1.91 to 18.74)) (one study at high Rob).[34]

Hospitalisation due to infection by SARS-CoV-2 was more likely with non-TNFi (analysed together) compared with csDMARDs and TNFi in one study,[27] and with rituximab compared with TNFi in another (both at high RoB).[28] However, in one study, at low RoB, the risk of hospitalisation due to infection by SARS-CoV-2 was similar with b/tsDMARDs and csDMARDs.[72] Reactivation of the hepatitis B virus was more common with abatacept and rituximab (but not tocilizumab) than with TNFi in one study at unclear RoB.[29]

Randomised controlled trials

In ORAL-Surveillance, the risk of serious infections was increased only with tofacitinib 10 mg two times per day compared with TNFi, while the risk of infections by HZ was increased both with tofacitinib 10 mg and 5 mg (figure 1). In two RCTs, infections by HZ were more common with filgotinib and upadacitinib than with placebo (table 2).[86 89] Whereas, in five active-controlled RCTs the number of infections caused by HZ was higher with the JAKi upadacitinib (range: 0.8%–3%) than with an active comparator (0.3%–1.3%),[80 94 101] but similar with the JAKi filgotinib (0.4%–1.0%) vs an active comparator (0.6%–1%).[77 102]

Malignancies

Observational studies

The risk of malignancies was not increased with bDMARD use compared with the general population in two studies.[50 53] In one of these, at low RoB, from the Swedish Rheumatology Quality Register,[53] there was a higher risk of lymphomas both in bDMARDs-naïve (aHR: 1.56 (95% CI 1.37 to 1.78) and in bDMARD-treated (aHR: 1.65 (95% CI 1.31 to 2.08)) patients compared with the general population. In this study, the risk was lower with bDMARDs (TNFi and non-TNFi analysed together) than with methotrexate (aHR: 0.52 (95% CI 0.32 to 0.83)). One study at high RoB, found no difference in the risk of malignancies between TNFi and csDMARDs and another, at low RoB, found no difference between tofacitinib and bDMARDs.[51 71] The risk of malignancies was, in general, similar across bDMARDs in five studies, with conflicting data for abatacept (table 3). Details on studies addressing malignancies are shown in online supplemental tables S44–S67.

Randomised controlled trials

Compared with TNFi, tofacitinib was associated with an increased risk of malignancies (HR: 1.48 (95% CI 1.04 to 2.09)) over 5.5 years in ORAL-Surveillance. Non-inferiority of tofacitinib could not be claimed for malignancies. In subgroup analyses, the incidence of malignancies was higher across all arms for patients aged ≥65 compared with patients aged <65 (range: 1.1–1.9/100 PY vs 0.6–0.9/100 PY). In two LTEs up to 52 weeks, the incidence of malignancies was similar with JAKi (filgotinib and upadacitinib) and adalimumab in patients who, by design, did not had to have malignancy risk factors.[77 83]

Major cardiovascular events

Observational studies

Thirteen studies evaluated the risk of MACE (table 4 and online supplemental tables S68–S100). In one study, at unclear RoB, patients on infliximab, etanercept and abatacept, but not on other bDMARDs or tofacitinib, had a lower risk of MACE compared with patients on csDMARDs.[20] In another study, the risk of MACE was lower if a bDMARD was combined with methotrexate than with a bDMARD alone.[19] The risk of MACE was similar with tofacitinib and bDMARDs in one study, at low

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			
Chen *et al*[40] 2020	Claims dataset	ABA	TNFi	**0.78 (0.64; 0.95)**	High
Chen *et al*[42] 2021	Claims dataset	ETA	ABA	1.52 (0.45; 5.14)	High
		ADA		2.15 (0.63; 7.26)	
		GOL		1.24 (0.27; 5.58)	
		TCZ		1.90 (0.38; 9.61)	
		TOFA		NE	
Grøn *et al*[39] 2019	DANBIO	ABA	RTX	0.95 (0.83; 1.10)	Low
		TCZ		0.98 (0.86; 1.12)	
		ABA	TCZ	0.98 (0.86; 1.10)	
Jeon *et al*[41] 2021	Claims dataset	TCZ	TNFi	1.00 (0.90; 1.11)	High
Kremer *et al*[71] 2021	CORRONA	TOFA	bDMARD	0.99 (0.75; 1.30)	Low
Montastruc *et al*[37] 2019	Claims dataset	ABA	Other bDMARD	1.04 (0.89; 1.21)	High
Ozen *et al*[73] 2019	FORWARD	ABA	other bDMARD	0.37 (0.18; 0.75)	Unclear
Pawar *et al*[45] 2020	Claims dataset	TOFA	ABA	1.20 (0.97; 1.49)	High
			ADA	1.06 (0.87; 1.30)	
			CZP	1.02 (0.80; 1.29)	
			ETA	**1.41 (1.15; 1.73)**	
			GOL	1.23 (0.94; 1.62)	
			INF	0.81 (0.65; 1.00)	
			TCZ	1.17 (0.89; 1.53)	
Patel *et al*[43] 2021	Claims dataset	TNFi	ABA	**1.48 (1.26; 1.75)**	High
		Non-TNFi		**1.46 (1.28; 1.66)**	
Simon *et al*[74] 2019	Claims dataset	ABA	Other bDMARD	0.96 (0.84; 1.09)	High
		Opportunistic infections			
Leon *et al*[33] 2019	HC San Carlos	Non-TNFi	TNFi	1.11 (0.46; 2.69)	Unclear
Simon *et al*[74] 2019	Claims dataset	ABA	other bDMARD	1.06 (0.96; 1.17)	High
		Herpes Zoster			
Chen *et al*[40] 2020	Claims dataset	ABA	TNFi	1.00 (0.73; 1.37)	High
Khosrow-Khavar *et al*[69] 2022	Claims dataset	TOFA	TNFi	**1.98 (1.78; 2.19)**	High
Kremer *et al*[71] 2021	Corrona-RA	TOFA	bDMARD	**2.32 (1.43–3.75)**	Low
Pawar *et al*[45] 2020	Claims dataset	TOFA	ABA	**1.94 (1.53; 2.44)**	High
			ADA	**1.99 (1.63; 2.43)**	
			CZP	**2.24 (1.68; 2.99)**	
			ETA	**2.12 (1.73; 2.58)**	
			GOL	**1.84 (1.35; 2.50)**	
			INF	**1.94 (1.51; 2.50)**	
			TCZ	**2.14 (1.53; 2.99)**	
		Tuberculosis			
Simon *et al*[74] 2019	Claims dataset	ABA	Other bDMARD	1.93 (0.45; 8.32)	High
		Hospitalisation due to COVID-19			
Curtis *et al*[27] 2021	Claims dataset	TOFA	non-TNFi	0.52 (0.25; 1.07)	High
		JAKi		0.60 (0.32; 1.10)	
		TNFi		**0.32 (0.20; 0.53)**	
Raiker *et al*[28] 2021	Claims dataset	RTX	TNFi	**1.78 (1.24; 2.54)**	High
		IL6i		1.50 (1.00; 2.25)	
		JAKi		1.27 (0.95; 1.71)	
		ABA		0.84 (0.55; 1.29)	
		Reactivation of hepatitis B			
Chen *et al*[29] 2021	Taipei Veterans GH	TCZ	TNFi	NE	Unclear
		ABA		**15.4 (3.1; 77.0)**	
		RTX		**35.6 (8.2; 155.8)**	

Values in bold highlight statistically significant effect sizes. Additional details in online supplemental tables S2–S43.
ABA, abatacept; ADA, adalimumab; aHR, adjusted HR; bDMARD, biological disease-modifying antirheumatic drug; c, control; CORRONA, Consortium of Rheumatology Researchers of North America; CZP, certolizumab pegol; DANBIO, Danish nationwide quality registry; ETA, etanercept; FORWARD, National Databank for Rheumatic Diseases longitudinal prospective observational study; GH, general hospital; GOL, golimumab; HC, hospital clínico; i, intervention; IL6i, interleukin 6 inhibitor; INF, infliximab; JAKi, JAK inhibitor; NE, not possible to estimate (no cases of infections); RTX, rituximab; TCZ, tocilizumab; TNFi, TNF inhibitor; TOFA, tofacitinib; tsDMARD, targeted synthetic DMARD.

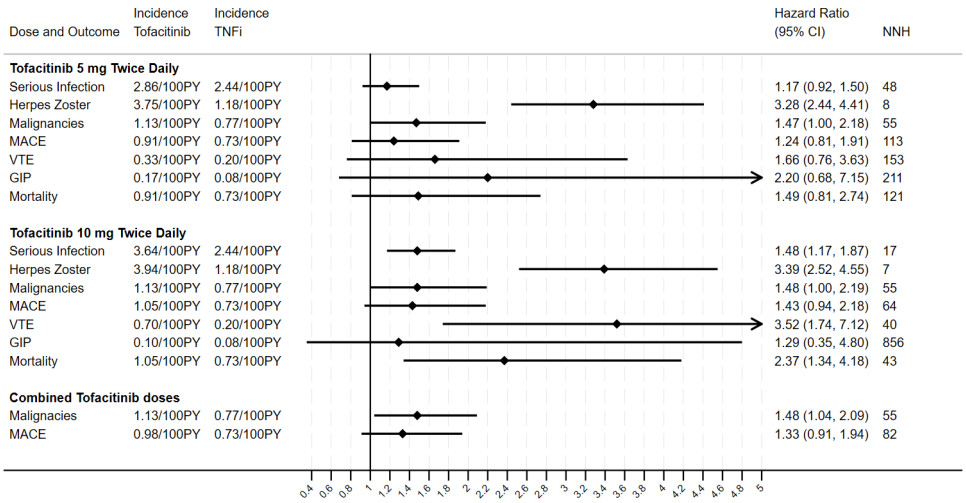

Figure 1 Incidence of major adverse events in patients with RA treated with tofacitinib compared with patients treated with a TNFi in the ORAL-Surveillance trial.[3] If the HR is >1 there is an increased risk with tofacitinib compared with TNFi (statistically significant if the 95% CI does not include 1). Non-inferiority was not demonstrated for the two coprimary endpoints (malignancies and MACE), because the upper limit of the 95% CI for the comparison between tofacitinib (combined doses) and TNFi was above 1.8 (predefined non-inferiority margin). NNH formula: (1/(cases/PY in TOFA – cases/PY in TNFi))/5. NNH interpretation: number of patients who would need to be treated over 5 years with tofacitinib rather than with TNFi to result in one additional event. GIP, gastrointestinal perforations; MACE, major adverse cardiovascular event; NNH, number needed to harm; PY, patient-years; RA, rheumatoid arthritis; TNFi, TNF inhibitor; VTE, venous thromboembolism.

RoB (aHR: 0.61 (95% CI 0.34 to 1.06)).[71] In another study, at high RoB, the risk of MACE was also similar with tofacitinib and TNFi both in a population representing 'real-world' patients (aHR: 1.01 (95% CI 0.83 to 1.23)), and in patients ≥50 years old and ≥1 cardiovascular risk factor (aHR: 1.24 (95% CI 0.90 to 1.69)).[69]

Four studies, at high RoB, evaluated the risk of VTE with csDMARDs and b/tsDMARDs.[21–24] There was no difference in the risk of VTE between bDMARDs and csDMARDs in two studies.[21 23] In one of these, there was an increased risk only in patients who switched to a second b/tsDMARD compared with patients on csDMARDs.[21] An increase in risk of VTE was found with methotrexate compared with hydroxychloroquine in another study at high RoB.[22] Finally, in one study, the risk of VTE was similar with tofacitinib and TNFi (aHR: 1.13 (95% CI 0.77 to 1.65).[24]

Table 2 Infections by Herpes Zoster (HZ) in patients on tsDMARDs (randomised controlled trials)

Study ID (trial)	Follow-up (weeks)	Treatment arm	N patients	HZ n (%)	Risk of bias
PBO-controlled trials					
Genovese *et al*[86] 2019	24	FIL 200 + csDMARD	147	2 (1.4)	Low
		FIL 100 + csDMARD	153	2 (1.3)	
		PBO + csDMARD	148	0 (0.0)	
Kameda *et al*[89] 2020	12	UPA 7.5$^{+\ csDMARD}$	49	1 (2.0)	Low
		UPA 15$^{+\ csDMARD}$	49	0 (0.0)	
		UPA 30$^{+\ csDMARD}$	50	3 (6.0)	
		PBO$^{+\ csDMARD}$	49	1 (2.0)	
Active-comparator trials					
Combe *et al*[77] 2021	24	FIL 200+MTX	475	2 (0.4)	Low
		FIL 100+MTX	480	2 (0.4)	
		ADA+MTX	325	2 (0.6)	
		PBO+MTX	475	2 (0.4)	
Fleischmann *et al*[90] 2019	26	UPA+MTX	650	5 (0.8)	Low
		ADA+MTX	327	1 (0.3)	
		PBO+MTX	652	3 (0.5)	
Rubbert-Roth *et al*[93] 2020	24	UPA 15+csDMARD	303	4 (1.3)	Low
		ABA+csDMARD	309	4 (1.3)	
Smolen *et al*[94] 2019	14	UPA 15	217	3 (1.0)	Low
		UPA 30	215	6 (3.0)	
		MTX	216	1 (<1)	
van Vollenhoven *et al*[101] 2020	24	UPA 15	317	7 (2.2)	Low
		UPA 30	314	7 (2.2)	
		MTX	314	1 (0.3)	
Westhovens *et al*[102] 2021	52	FIL 200+MTX	416	6 (1.0)	Low
		FIL 100+MTX	207	3 (1.0)	
		FIL 200	210	4 (2.0)	
		MTX	416	4 (1.0)	

ABA, abatacept; ADA, adalimumab; csDMARD, conventional synthetic disease-modifying antirheumatic drug; FIL, filgotinib; HZ, herpes zoster; MTX, methotrexate; PBO, placebo; tsDMARD, targeted synthetic DMARD; UPA, upadacitinib.

Randomised controlled trials

Compared with TNFi, tofacitinib was associated with an increased risk of MACE (HR: 1.33 (95% CI 0.91 to 1.94)) over 5.5 years in ORAL-Surveillance (not statistically significant). Non-inferiority of tofacitinib could not be claimed for MACE. In subgroup analyses, the incidence of MACE was higher across all arms for patients aged ≥65 compared with patients aged<65 (0.9–1.9/100 PY vs 0.7/100 PY). In ENTRACTE, the non-inferiority of tocilizumab compared with etanercept for the risk of MACE was demonstrated over a mean follow-up of 3.2 years (HR: 1.05 (95% CI 0.77 to 1.43)). In ORAL-Surveillance, the risk of VTE was increased only with tofacitinib 10 mg compared with TNFi. In two LTEs up to 52 weeks, the incidence of MACE was similar with JAKi (filgotinib and upadacitinib) and adalimumab in patients who, by design, did not had to have cardiovascular risk factors.[77 83]

Other adverse events

Observational studies

Studies evaluating other major outcomes are summarised in table 5 and reported in detail in online supplemental tables S101–S137). In a large study, at low RoB, lower intestinal perforations were uncommon but more frequent with tocilizumab (0.45/100 patient years (PY)) than with TNFi (0.18/100 PY) (aHR: 2.61 (95% CI 1.61; 4.24)). In another study, also

Table 3 Malignancies, comparison between different bDMARDs/tsDMARDs (observational studies)

Study ID	Registry	Intervention	Control	aHR (i vs C)	Risk of bias
		All types of cancer			
De Germay *et al*[48] 2020	Pharmacov. database	ABA	Other bDMARD	0.98 (0.91; 1.05)	High
Kim *et al*[49] 2019	Claims dataset	TCZ	TNFi	0.98 (0.80; 1.19)	High
Montastruc *et al*[52] 2019	Claims dataset	ABA	Other bDMARD	**1.17 (1.06; 1.30)**	High
Ozen *et al*[73] 2019	FORWARD	ABA	Other bDMARD	1.89 (0.93; 3.84)	Unclear
Kremer *et al*[71] 2021	CORRONA	TOFA	bDMARD	1.04 (0.68; 1.61)	Low
Simon *et al*[74] 2019	Claims dataset	ABA	other bDMARD	**1.09 (1.02; 1.16)**	High
		Non-melanoma skin cancer			
Kremer *et al*[71] 2021	CORRONA	TOFA	bDMARD	1.02 (0.69; 1.50)	Low
Montastruc *et al*[52] 2019	Claims dataset	ABA	Other bDMARD	**1.45 (1.03; 1.39)**	High
Ozen *et al*[73] 2019	FORWARD	ABA	Other bDMARD	1.10 (0.57; 2.11)	Unclear
		Melanoma			
De Germay *et al*[48] 2020	Pharmacov. database	ABA	Other bDMARD	**1.56 (1.17; 2.08)**	High
Kim *et al*[49] 2019	Claims dataset	TCZ	TNFi	0.71 (0.36; 1.40)	High
Montastruc *et al*[52] 2019	Claims dataset	ABA	Other bDMARD	0.86 (0.38; 1.59)	High
		Lymphoma			
De Germay *et al*[48] 2020	Pharmacov. database	ABA	Other bDMARD	0.76 (0.60; 0.97)	High
Hellgren *et al*[53] 2021	SRQ	ADA	ETA	1.02 (0.52; 1.99)	Low
		INF		0.64 (0.27; 1.56)	
		CZP		<5 lymphomas	
		GOL		<5 lymphomas	
		ABA		1.61 (0.50; 5.22)	
		RTX		<5 lymphomas	
		TCZ		<5 lymphomas	
		ANA		<5 lymphomas	
Kim *et al*[49] 2019	Claims dataset	TCZ	TNFi	1.31 (0.60; 2.88)	High
Simon *et al*[74] 2019	Claims dataset	ABA	Other bDMARD	1.27 (0.94; 1.72)	High

Values in bold highlight statistically significant effect sizes. Additional details in online supplemental tables S44-S67).
ABA, abatacept; ADA, adalimumab; aHR, adjusted HR; ANA, anakinra; bDMARD, biological disease-modifying antirheumatic drug; c, control; CORRONA, Consortium of Rheumatology Researchers of North America; CZP, certolizumab pegol; ETA, etanercept; FORWARD, National Databank for Rheumatic Diseases longitudinal prospective observational study; GOL, golimumab; i, intervention; INF, infliximab; Pharmacov, pharmacovigilance; RTX, rituximab; SRQ, Swedish Rheumatology Quality Register; TCZ, tocilizumab; TNFi, TNF inhibitor; TOFA, tofacitinib; tsDMARD, targeted synthetic DMARD.

at low RoB, diverticular perforations (but not of other aetiologies) occurred more often with tocilizumab than with rituximab/abatacept (HR: 3.8 (95% CI 1.1 to 13.6)).[26] No studies evaluating the risk of intestinal perforations with other IL-6Ri could be included.

Neuroinflammatory events were not more common with TNFi compared with the general population[61] and with csDMARDs.[60] The standardised mortality rate was similarly high for bDMARD users (1.8 (95% CI 1.7 to 2.0)) and non-users (1.5 (95% CI 1.4 to 1.5)) in one study at high RoB.[59] Another study, at low RoB, found a lower risk of death with bDMARDs than with csDMARDs,[72] and two studies (one at low RoB) found no difference between tofacitinib and bDMARDs.[69 71] Studies addressing the risk of withdrawals due to adverse events and any (serious) adverse events reported results in line with the known safety profile of b/tsDMARDs. (online supplemental tables S123-S137).

Randomised controlled trials

In ORAL-Surveillance, intestinal perforations were uncommon (tofacitinib 5 mg: 0.17/100 PY; tofacitinib 10 mg: 0.10/100 PY; TNFi: 0.08/100 PY) and did not occur significantly more frequently with tofacitinib 5 mg (HR: 2.20 (95% CI 0.68 to 7.15)) nor with tofacitinib 10 mg (HR: 1.29 (95% CI 0.35 to 4.80)) than with TNFi. No cases of intestinal perforation occurred in two other RCTs on IL-6Ri (sarilumab and olokizumab; online supplemental table S141),[90 92] and in five out of eight trials on JAKi (online supplemental table S148).[77 86 89 93 94] In ORAL-Surveillance, the risk of mortality was increased only with tofacitinib 10 mg compared with TNFi.

DISCUSSION

This SLR demonstrates that bDMARDs are relatively safe drugs in RA and also increases our knowledge of the safety of tsDMARDs, again showing they are relatively safe, although with some exceptions. The risk of malignancies and MACE is similar, or even decreased, with bDMARDs compared with csDMARDs. However, these adverse outcomes occurred more frequently with tofacitinib than with TNFi in patients who had certain cardiovascular risk factors. The risk of serious infections is increased with bDMARDs compared with csDMARDs and is similar across bDMARDs and tofacitinib. Of note, HZ is more common with JAKi than with csDMARDs or bDMARDs, with the possible exception of filgotinib. Lower intestinal perforations are rare but occur more often with tocilizumab than with other bDMARDs. Whether the overall safety profile differs across JAKi and across IL-6Ri remains unknown.

Randomisation is the main reason why RCTs are the 'gold standard' to test whether an outcome differs between two or more treatment groups. Randomisation ensures equal distribution of measured and unmeasured confounders between the different comparators. In most RCTs the primary outcome is an efficacy measure. Formal comparisons of safety outcomes

Table 4 MACE, comparison between different bDMARDs/tsDMARDs (observational studies)

Study ID	Registry	Intervention	Control	aHR (i vs c)	Risk of bias
		MACE			
Hsieh *et al*[70] 2020	Claims dataset	TCZ	RTX	**0.41 (0.23; 0.72)**	High
		ABA		**0.25 (0.11; 0.55)**	
Khosrow-Khavar *et al*[69] 2022	Claims dataset	TOFA	TNFi	1.01 (0.83; 1.23)	High
Kremer *et al*[71] 2021	CORRONA	TOFA	bDMARD	0.61 (0.34; 1.06)	Low
Xie *et al*[18]	Claims dataset	TNFi	TCZ	1.27 (1.02, 1.59)	High
		ADA		1.33 (0.99, 1.80)	
		ETA		1.10 (0.80, 1.51)	
		INF		**1.61 (1.22, 2.12)**	
		ABA		1.01 (0.79, 1.28)	
		RTX		1.16 (0.89, 1.53)	
		Heart failure			
Hsieh *et al*[70] 2020	Claims dataset	TCZ	RTX	0.48 (0.18; 1.31)	High
		ABA		**0.20 (0.05; 0.83)**	
Khosrow-Khavar *et al*[69] 2022	Claims dataset	TOFA	TNFi	1.07 (0.79; 1.46)	High
		Myocardial infarction			
Hsieh *et al*[70] 2020	Claims dataset	TCZ	RTX	**0.12 (0.02; 0.56)**	High
		ABA		0.26 (0.06; 1.12)	
Khosrow-Khavar *et al*[69] 2022	Claims dataset	TOFA	TNFi	1.04 (0.82; 1.33)	High
Xie *et al*[18] 2019	Claims dataset	TNFi	TCZ	1.20 (0.88; 1.62)	High
		ADA		1.24 (0.83; 1.87)	
		ETA		1.08 (0.71; 1.65)	
		INF		**1.55 (1.05; 2.28)**	
		ABA		1.01 (0.73; 1.40)	
		RTX		1.05 (0.72; 1.54)	
		Stroke			
Hsieh *et al*[70] 2020	Claims dataset	TCZ	RTX	0.54 (0.26; 1.12)	High
		ABA		**0.18 (0.05; 0.64)**	
Khosrow-Khavar *et al*[69] 2022	Claims dataset	TOFA	TNFi	0.93 (0.66; 1.31)	High
Xie *et al*[18] 2019	Claims dataset	TNFi	TCZ	1.25 (0.90; 1.73)	High
		ADA		1.26 (0.80; 1.99)	
		ETA		1.09 (0.68; 1.75)	
		INF		**1.49 (1.01; 2.21)**	
		ABA		0.99 (0.70; 1.40)	
		RTX		1.10 (0.74; 1.63)	
		Venous thromboembolism			
Desai *et al*[24] 2021	Claims dataset	TOFA	TNFi	1.13 (0.77; 1.65)	High

Values in bold highlight statistically significant effect sizes. Additional details in online supplemental tables S68–S100.
i; intervention; ABA, abatacept; ADA, adalimumab; aHR, adjusted HR; bDMARD, biological disease-modifying antirheumatic drug; c, control; CORRONA, Consortium of Rheumatology Researchers of North America; ETA, etanercept; INF, infliximab; RTX, rituximab; TCZ, tocilizumab; TNFi, TNF inhibitor; TOFA, tofacitinib; tsDMARD, targeted synthetic DMARD.

are limited by lack of power. In addition, RCTs usually exclude patients at risk of adverse events and are too short to capture outcomes with long latency periods (eg, malignancies). This is why observational studies comparing the safety of drugs in unselected patients followed over long periods are the main study type of this SLR. Except for rare outcomes, for which studies are frequently underpowered, safety comparisons in real-world settings are most informative. In observational studies, however, treatment allocation is not at random. Therefore, the groups may have differences in their baseline risk of adverse outcomes (confounding by indication).[7] The ideal study, combines the strengths of observational and experimental research. This SLR includes two of such studies, the ORAL-Surveillance and ENTRACTE trials.[2 3]

The ORAL-Surveillance study shows that malignancies and MACE occur more often with tofacitinib than with TNFi in patients with RA and cardiovascular risk factors (not statistically significant for MACE), especially in patients older than 65 years of age. In this population, one additional malignancy is expected to occur for each 55 patients who receive tofacitinib 5 mg two times per day instead of a TNFi over 5 years (NNH any time: 276). The 5-year number needed to harm is 113 for MACE (NNH any time: 567). These results led the European Medicines Agency (EMA) to caution against the use of tofacitinib in patients older than 65 years of age, current or past smokers or with other cardiovascular or malignancy risk factors (unless there is no alternative).[103–106] EMA is conducting a safety review procedure to ascertain whether the risks identified for tofacitinib apply to all JAKi.[107] The Food and Drug Administration, on the other hand, considers the use of all JAKi only after failure of a TNFi and after a careful evaluation of the benefit–risk ratio.[108–110]

Table 5 Intestinal perforations, neuroinflammatory events and mortality (observational studies)

Study ID	Registry	Intervention	Control	aHR (i vs C)	Risk of bias
		Lower intestinal perforations			
Barbulescu *et al*[25] 2020	ARTIS	ABA	TNFi	1.07 (0.55; 2.10)	Low
		RTX		0.89 (0.50; 1.58)	
		TCZ		**2.20 (1.28; 3.79)**	
Rempenault *et al*[26] 2021	FSR*	TCZ	RTX/ABA	**3.80 (1.10; 13.6)**	Low
		Neuroinflammatory events			
Kopp *et al*[60] 2020	ARTIS & DANBIO	TNFi	csDMARDs	0.76 (0.44; 1.33)	Low
Taylor *et al*[61] 2021	BSRBR-RA	TNFi	General pop	SIR: 1.10 (0.71; 1.63)	Unclear
		All-cause mortality			
Akhlaghi *et al*[58] 2019	Mashhad	INF/ETA+MTX	MTX	0.97 (0.86; 1.09)	Unclear
Bower *et al*[72] 2021	ARTIS	TNFi	csDMARDs	**0.57 (0.41; 0.79)**	Low
		ABA		0.69 (0.39; 1.21)	
		TCZ		0.57 (0.27; 1.18)	
		RTX		1.04 (0.67; 1.63)	
		JAKi		0.80 (0.44; 1.45)	
		All b/tsDMARD		**0.64 (0.48; 0.86)**	
Faselis *et al*[68] 2021	Claims dataset	HCQ	Other csDMARD	1.06 (0.84; 1.34)	High
Hsieh *et al*[70] 2020	Claims dataset	TCZ	RTX	**0.57 (0.34; 0.95)**	High
		ABA		**0.32 (0.15; 0.66)**	
Khosrow-Khavar *et al*[69] 2022	Claims dataset	TOFA	TNFi	1.20 (0.98; 1.46)	High
Kremer *et al*[71] 2021	CORRONA	TOFA	bDMARD	0.91 (0.59; 1.42)	Low
Lee *et al*[59] 2022	Claims dataset	bDMARDs	General pop	SMR: 1.82 (1.69; 1.96)	High

Values in bold highlight statistically significant effect sizes. Additional details in online supplemental tables S101–S117.
ABA, abatacept; ADA, adalimumab; aHR, adjusted HR; ARTIS, anti-Rheumatic Treatment in Sweden Register; bDMARD, biological disease-modifying antirheumatic drug; BSRBR, British Society of Rheumatology Biologics Register; c, control; CORRONA, Consortium of Rheumatology Researchers of North America; csDMARD, conventional synthetic DMARD; DANBIO, Danish nationwide quality registry; ETA, etanercept; FSR, French Society of Rheumatology; HCQ, hydroxychloroquine; i, intervention; INF, infliximab; JAKi, JAK inhibitor; RTX, rituximab; TCZ, tocilizumab; TNFi, TNF inhibitor; TOFA, tofacitinib; tsDMARD, targeted synthetic DMARD.

A proper explanation for the results of ORAL-Surveillance is not immediately at hand. Patients with RA have a higher risk of MACE and malignancies than the general population, at least in part due to chronic inflammation.[111–113] One study included in this SLR suggests, in line with others,[114 115] that bDMARDs reduce the excess risk of MACE in RA more than csDMARDs.[20] Another study included in this SLR,[53] in contrast to a previous one,[116] found a reduction of the excess risk of lymphoma with bDMARDs. It is reasonable to presume that these effects are mediated by the suppression of inflammation, however, that has not yet been proved. Besides, tofacitinib also suppresses inflammation, thus a similar effect would in principle be expected. Due to the lack of a csDMARD control group, the ORAL-Surveillance does not provide resolution. Thus, whether tofacitinib increases or, alternatively, is less efficacious than TNFi in suppressing the risk of MACE and cancer, remains unclear for now.

Of note, the results of ORAL-Surveillance differ from those of at least one observational study reporting no difference in the risk of MACE or malignancies between tofacitinib and bDMARDs.[71] This study is however challenged by the possibility of residual confounding. With that being said, it should be noted that there was no age restriction for inclusion and patients did not have to have cardiovascular risk factors as in ORAL-Surveillance. These results together with the observation of a higher incidence of MACE and malignancies in ORAL-Surveillance in patients older than 65 years, and not in younger patients, suggests there could be a threshold effect. The higher the background risk, the more likely for the drug-attributable risk to become apparent. Obviously, this finding needs confirmation from a second independent RCT.

One important safety signal identified in the 2019 SLR was the risk of VTE with JAKi. In ORAL-Surveillance, there was a clear dose–response effect. Patients on tofacitinib 10 mg two times per day had a threefold increase in the risk of VTE compared with TNFi (especially PE), while the risk was lower and non-significant for the 5 mg two times per day dose. Of note, all patients randomised to tofacitinib 10 mg were considered in their original group, including those who switched to tofacitinib 5 mg in February 2019. These data led the regulators to warn that all JAKi should be used with caution in patients with risk factors for VTE.[103–106] Available evidence is mostly limited to tofacitinib and more data, especially from studies in 'real-world' settings, are needed to clarify the risk of VTE in RA with other JAKi and the impact of (the type of) JAK inhibition as such on this risk.

In accordance with the 2019 SLR, the risk of serious infections was higher in patients on bDMARDs compared with patients on csDMARDs. Previous studies have demonstrated that the incidence of serious infections does not differ across bDMARDs and now new evidence extends this observation also to tofacitinib. The previous finding of a higher risk of TB with monoclonal TNFi than with etanercept and the lower risk with rituximab was not further studied. Data indicating that rituximab might increase the risk of severe infection by SARS-CoV-2 is aligned with a previous SLR informing the EULAR recommendation for the management of RMDs in the context to COVID-19.[12 13]

The increased risk of infection by HZ with JAKi was again demonstrated. Patients on upadacitinib, baricitinib and tofacitinib (analysed together) were three times more likely to

be infected with HZ than patients on csDMARDs.[31] In addition, infections were more common with tofacitinib than with bDMARDs in observational studies. RCTs included in this SLR, suggest an increased risk with upadacitinib, but not with filgotinib, compared with an active comparator. This finding is in line with pooled analyses of RCTs which report a similar incidence of infection by HZ with tofacitinib,[117] baricitinib,[118] and upadacitinib,[119] (3.0–5.3/100 PY), but a lower incidence with filgotinib (1.1–1.8/100 PY).[120] This is, however, an indirect comparison of selected patients included in RCTs. Observational studies comparing JAKi are needed to evaluate if the risks differ across JAKi.

New data have shown again the increased risk of lower intestinal perforations with tocilizumab. The underlying mechanism remains unclear. In one study, both the risk of diverticulitis and diverticular perforation was increased with tocilizumab, but not the risk of other perforations.[26] This suggests that suppressing IL-6 predisposes to diverticulitis that, because of atypical clinical presentation (eg, low levels of C reactive protein), is more difficult to detect and perhaps more susceptible to perforation because of diagnostic delay. Even though IL-6 pathway inhibition is one of the effects of JAKi, in ORAL-Surveillance, the risk of perforation did not differ between tofacitinib and TNFi. It should be noted, however, that ORAL-Surveillance was likely underpowered to detect this difference. No observational studies on other IL-6Ri or JAKi could be included to clarify whether this is a class effect common to all drugs targeting IL-6.

Studies included in this SLR have shed new light on the safety aspects of drugs used in RA. Important questions that remain unanswered are expected to be addressed in the future as more studies, especially those on JAKi other than tofacitinib and IL-6Ri other than tocilizumab become available. This new evidence will inform future updates of the recommendations for the management of RA.

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