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Original Article

Systematic review and meta-analysis for the 2024 update of the Japan College of Rheumatology clinical practice guidelines for the management of rheumatoid arthritis

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ABSTRACT

Objectives: The aim of this article is to update evidence on the efficacy and safety of disease-modifying antirheumatic drugs (DMARDs) and provide information to the taskforce for the 2024 update of the Japan College of Rheumatology clinical practice guidelines for the management of rheumatoid arthritis (RA).

Methods: We searched various databases for randomised controlled trials on RA published until June 2022, with no language restriction. For each of the 15 clinical questions, two independent reviewers screened the articles, evaluated the core outcomes, and performed meta-analyses.

Results: Subcutaneous injection of methotrexate (MTX) showed similar efficacy to oral MTX in MTX-naïve RA patients. Ozoralizumab combined with MTX improved drug efficacy compared to the placebo in RA patients with inadequate response (IR) to conventional synthetic DMARD

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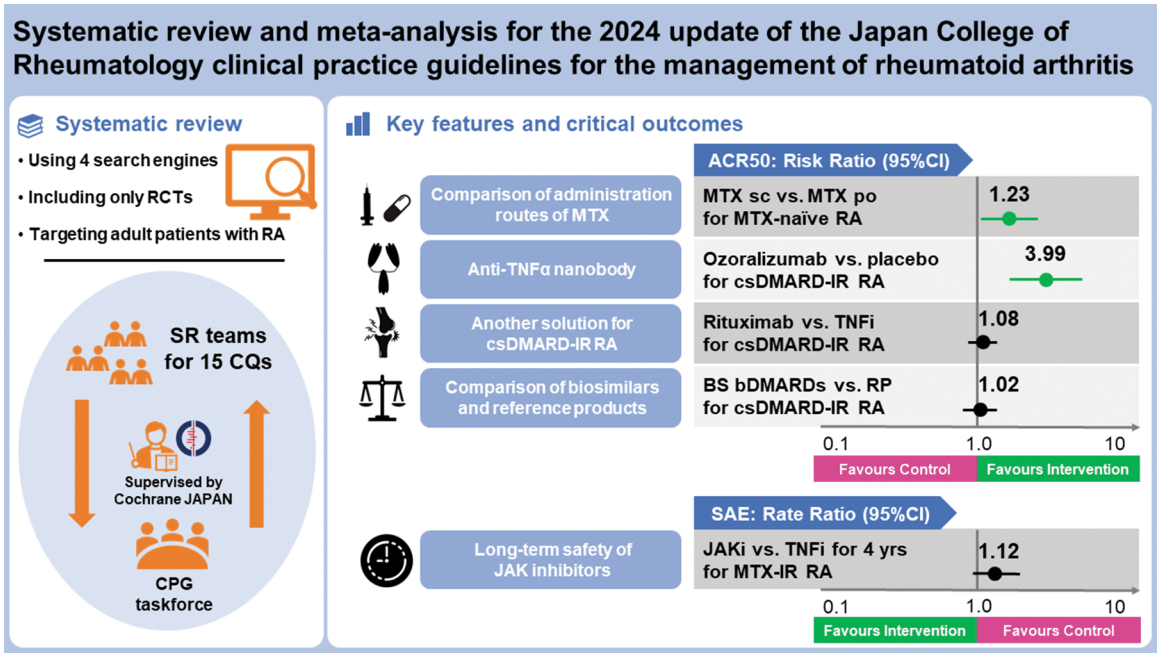
(csDMARD). Rituximab with and without concomitant csDMARDs showed similar efficacy to other biological DMARDs (bDMARDs) in bDMARD-IR RA patients. Combined Janus kinase inhibitors and MTX achieved similar clinical responses and equal safety during a 4-year period compared to tumour necrosis factor inhibitors in MTX-IR RA patients. Biosimilars showed efficacy equivalent to that of the original bDMARDs in csDMARD-IR and bDMARD-IR RA patients.

Conclusions: This systematic review provides latest evidence for the 2024 update of the Japan College of Rheumatology clinical practice guidelines for RA management.

KEYWORDS: Clinical practice guidelines; meta-analysis; ozoralizumab; rheumatoid arthritis; systematic review

Graphical Abstract



Introduction

Rheumatoid arthritis (RA) is a chronic systemic inflammatory autoimmune disease that significantly affects quality of life, daily living, and social participation owing to the deterioration of bone and joint structures [1, 2]. Developments in biologic disease-modifying antirheumatic drugs (DMARDs) and the advent of Janus kinase inhibitors (JAKi) have led to significant advances in the treatment of RA, with clinical and functional remission achieved in more patients with RA than previously [3]. Many clinical trials are ongoing to build evidence for the efficacy of pharmacological interventions with these biologic or targeted synthetic DMARDs (b/tsDAMRDs), which are commercially available worldwide. Guidelines or recommendations have been published by the American College of Rheumatology (ACR) and European Alliance of Associations for Rheumatology to optimise the applications of these therapies. Japan has a unique health care system in terms of the types of drugs covered by insurance and public insurance systems, different from those in Europe and the USA, and a super-aged population; therefore, appropriate clinical practice guidelines (CPGs) that reflect the health care environment are required. The Japan College of Rheumatology (JCR) introduced the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system earlier than did Western countries to establish high-quality CPGs for the management of RA [4], publishing the guidelines in 2014 and 2020 (2014 and 2020 JCR guidelines, respectively). Following the publication of the 2020 JCR guidelines, new RA medications have been introduced and new evidence on the existing RA therapies has accumulated, leading to the need for the revision of the 2020 JCR guidelines.

This systematic review (SR), therefore, aimed to provide a comprehensive overview of the currently available evidence on RA therapies and a quantitative summary to the taskforce responsible for the update of the 2020 JCR guidelines.

Materials and methods

Teams involved

The steering committee (Supplementary Table S1 presents the list of team members) supervised the project, prepared the scope of the guidelines, and drafted the clinical questions (CQs) to be addressed by the 2024 update of the JCR CPG for the management of RA (designated the 2024 JCR guidelines). The task force (CPG panel members), including two patient representatives, discussed and determined the recommendations. Twenty-two rheumatologists from across Japan were invited to join the SR team. They underwent four web-based training sessions by the SR support team and Cochrane Japan during the SR. The SR support team and CPG panel members provided consultation and feedback to the SR team throughout the project.

Table 1. The patient population, intervention, and comparator of each CQ and the studies employed.

CQ no.	Drug	Patient population	Intervention	Comparator	References
4	MTX	MTX naïve RA	MTX sc	MTX po	[8–10]
9	OZR	csDMARD-IR RA	OZR + MTX	PBO + MTX	[11]
19	RTX	csDMARD-IR RA	RTX	PBO	[12–16]
20	RTX	csDMARD-IR RA	RTX monotherapy	PBO or csDMARDs	[13, 17]
21	RTX	csDMARD-IR RA	csDMARDs + RTX	csDMARDs + TNFi	[18]
22	RTX	bDMARD-IR RA	RTX ± csDMARDs	PBO ± csDMARDs	[19]
23	RTX	bDMARD-IR RA	RTX ± csDMARDs	other bDMARD ± csDMARDs	[20–22]
24	JAKi	MTX-IR RA	JAKi	PBO	[23–28]
25	JAKi	MTX-IR RA	MTX + JAKi	MTX + PBO	[29–42]
26	JAKi	MTX-IR RA	MTX + JAKi	MTX + TNFi	[29, 34, 38, 43, 44]
27	JAKi	MTX-IR RA (long term)	MTX + JAKi	MTX + TNFi	[45]
28	JAKi	bDMARD-IR RA	MTX + JAKi	MTX + PBO	[46–50]
29	JAKi	bDMARD-IR/	JAKi	bDMARDs	[51]
32-1	BS	csDMARD-IR RA	BS excluding RTX	RP	[37, 52–84]
32-2	BS	csDMARD-IR RA	BS for RTX	RP	
32-3	BS	bDMARD-IR RA	BS for RTX	RP	
33-1	BS	RA	RP/BS	RP/RP	[61, 72, 85–95]
33-2	BS	RA	RP/BS	BS/BS	

Disclosures of conflicts of interest

All team members who were intellectually involved in the project and considered for guideline authorship disclosed their academic and economic conflicts of interest (COIs). These are available on the website (https://www.shindan.co.jp/). In addition, the COIs of Y.K., E.T., Y.K., and M.H. were deliberated by the committee on COIs of the JCR.

CQs for the 2024 JCR CPG update

CQs were drafted by the steering committee, and 15 CQs were prepared in the population, intervention, comparator, and outcomes format by the SR support team and approved by the CPG panel members to develop the 2024 JCR guidelines (Table 1). This SR was conducted as part of an update of the 2020 JCR guidelines. Therefore, the current CQ numbers were appended to the previous CQ numbers specified in the 2020 JCR guidelines.

Criteria for study inclusion in this review

Only randomised controlled trials (RCTs) were included. The inclusion criteria for participants were adult patients with RA. The same critical outcomes as those in the 2020 JCR guidelines were used, and beneficial and adverse critical outcomes were approved at a panel meeting (Table 2). Serious adverse events (SAEs) and serious infectious events (SIEs) were adopted as critical outcomes in this SR. In cases where the original study used the terms 'severe' adverse events and 'severe' infection/infectious events, they were deemed SAEs or SIEs, respectively.

Search strategy

Patient characteristics, interventions, comparisons, and outcomes derived from each CQ were extracted to provide search terms for the SR. PubMed, CENTRAL, EMBASE, and Japan Medical Abstracts Society (Igaku Chuo Zasshi) databases were used. We included papers written in any language. We searched for articles published up to June 2022 for the CQs.

Table 2. The beneficial and adverse critical outcomes for each CQ.

CQ no.	Beneficial outcome	Adverse outcome
4	ACR50 (3M-6M), ΔHAQ-DI (3M), retention rate (3M)	SAE (3M), SIE (3M)
9	ACR50 (6M)	SAE (6M), SIE (6M)
19	DAS28-ESR (6M), ACR50 (6M), ΔHAQ-DI (6M)	SAE (6M), SIE (6M)
20	ACR50 (6M), ΔHAQ-DI (6M,12M)	SAE (6M,12M), SIE (6M)
21	DAS28-ESR (3M), ACR50 (12M), ΔHAQ-DI (12M)	SAE (3M), SIE (3M)
22	DAS28-ESR (6M), ACR50 (3M, 6M), ΔHAQ-DI (6M), ΔmTSS (6M)	SAE (6M), SIE (6M)
23	DAS28-ESR (3M, 6M), ACR50 (3M, 6M), ΔHAQ-DI (6M, 12M), ΔmTSS (4M)	SAE (12M), SIE (12M)
24	DAS28-CRP (3M), ACR50 (3M), ΔHAQ-DI (3M)	SAE (3M), SIE (3M)
25	DAS28-CRP (3M), ACR50 (3M), ΔHAQ-DI (3M)	SAE (3M), SIE (3M)
26	ACR20, 50, 70 (6M), DAS28-ESR, CRP (6M), ΔHAQ-DI (6M), ΔmTSS (6M)	SAE (6M,12M), SIE (6M,12M)
27	ACR50 (4Y), ΔHAQ-DI (4Y)	SAE (4Y), SIE (4Y)
28	ACR50 (3M), DAS28-CRP (3M), ΔHAQ-DI (3M)	SAE (3M), SIE (3M)
29	DAS28-ESR (6M), ACR50 (6M), ΔHAQ-DI (6M)	SAE (6M), SIE (6M)
32-1	ACR50 (6M)	SAE (6M), SIE (6M)
32-2	ACR50 (6M)	SAE (6M), SIE(6M)
32-3	ACR50 (6M)	SAE (6M), SIE (6M)
33-1	ACR50 (6M)	SAE (6M), SIE (6M)
33-2	ACR50 (6M)	SAE (6M), SIE (6M)

The search formulas for each database are listed in Supplementary Tables S2–S6. Moreover, the Cochrane Review and previously published SRs on RA were used to identify relevant articles. Twenty-two members of the SR team were

divided into 10 pairs (some pairs included three members), and each pair screened the selected articles for each CQ by titles and abstracts, based on the criteria mentioned above, and excluded articles according to the Rayyan system (https://www.rayyan.ai). Subsequently, each member of the pair read the contents of the selected articles, independently affirmed their relevance, and determined the articles for data extraction after comparing the results and discussions. In cases of disagreement, adjudication was made by a third member.

Data extraction and assessment

Data extraction and assessment were conducted according to the Cochrane Japan guidelines. Two SR team members performed independent data extraction and evaluated the certainty of the evidence for each outcome from the adopted articles. In cases of disagreement regarding the certainty of evidence, an agreement was reached through a discussion. The SR team followed the methods proposed by the GRADE working group (https://gdt.guidelinedevelopment.org/app/handbook/handbook.html) and prepared 'evidence profiles' using GRADEpro GDT (McMaster University and Evidence Prime Inc., Ontario, Canada; http://gdt.guidelinedevelopment.org/). Five factors that possibly reduce the certainty of evidence, risk of bias (RoB), inconsistency, indirectness, imprecision, and publication bias were assessed for each outcome. Finally, the certainty of the evidence for each outcome was graded as high, moderate, low, or very low. We used the Cochrane Handbook for Systematic Reviews of Interventions [5] and the RoB 2 tool to analyse the RoB of the study results [6]. Relative risks (RRs) of 0.75 and 1.25 were arbitrarily used as clinical decision thresholds for the present SR [7].

Meta-analysis

Cochrane Review Manager (RevMan 5) software version 5.4 (http://tech.cochrane.org/revman) was used for the meta-analysis. The outcomes of the categorical (dichotomous) variables were integrated using a random-effects model, and the risk ratios and 95% confidence intervals were calculated. The outcomes of continuous variables were integrated using the random-effects model and inverse variance method, and the mean differences (MDs) between groups and SDs were calculated. Some figures were generated using R Statistical Software (v4.3.1; R Foundation for Statistical Computing, Vienna, Austria).

Results

Table 1 shows the patient population, interventions, and comparators for each CQ, and the studies included in the present SR. Table 2 summarises the beneficial and adverse outcomes of each CQ. Forest plots of ACR 50% response (ACR50) for CQs with two or more RCTs reviewed and CQ for ozoralizumab (OZR) (CQ4, CQ9, CQ19, CQ24, CQ25, CQ26, CQ28, CQ32, and CQ33) are shown in Figure 1 [8]. Forest plots of the SAEs and SIEs for CQ26 and CQ27 are shown in Figure 2 [8]. Forest plots for other outcomes, Preferred Reporting Items for Systematic Reviews and Meta-Analyses charts, and RoB results are listed in Supplementary Figures S1–S15 [8]. The search formulas and evidence profiles for each CQ are presented in Supplementary Tables S1–S6 and S7–S24, respectively [8]. The SR results for each CQ are presented below.

MTX

RA CQ4: subcutaneous injection of methotrexate compared to oral methotrexate for MTX-naïve patients with RA

Three RCTs [9–11] compared subcutaneous injection of methotrexate (MTX sc) (intervention) and oral methotrexate (MTX po) (comparator) in MTX-naïve patients with RA (Table 1). The proportion of patients who achieved ACR50 between 3 and 6 months was 56.1% (55/98) in the MTX sc group and 47.4% (45/95) in the MTX po group, resulting in an RR of 1.23 (1.01–1.50) (Figure 1(a)). MD in ΔHealth Assessment Questionnaire-Disability Index (HAQ-DI) at 3 months was 0 (−0.22 to 0.22) (Supplementary Figure S1c). SAE rates at 3 months were 0% (0/52) and 0% (0/50) in the MTX sc and po groups, respectively. SIE rates at 3 months were 0% (0/52) and 0% (0/50) in the MTX sc and po groups, respectively. The treatment retention rate at 3 months was 96.2% (50/52) in the MTX sc group and 96.0% (48/50) in the MTX po group, resulting in an RR of 1.00 (0.93–1.08).

Tumour necrosis factor inhibitor

RA CQ9: OZR + MTX versus placebo + MTX for csDMARD-IR RA

One RCT [12] compared OZR + MTX (intervention) and placebo (PBO) + MTX (comparator) in csDMARD-IR patients with RA (Table 1). The proportion of patients who achieved ACR50 at 6 months was 63.8% (97/152) in the OZR group and 16.0% (12/75) in the PBO group, resulting in an RR of 3.99 (2.34–6.79) (Figure 1(b)). SAE rate at 6 months was 2.0% (3/152) in the OZR group and 2.7% (2/75) in the PBO group, resulting in an RR of 0.74 (0.13–4.34) (Supplementary Figure S2c). SIE rate at 6 months was 4.6% (7/152) in the OZR group and 2.7% (2/75) in the PBO group, resulting in an RR of 1.73 (0.37–8.11).

Rituximab

RA CQ19: rituximab versus PBO for csDMARD-IR RA

Five RCTs [13–17] compared rituximab (RTX) (intervention) and PBO (comparator) in csDMARD-IR patients with RA (Table 1). The proportion of patients who achieved disease activity score (DAS)28-erythrocyte sedimentation rate (ESR) <2.6 at 6 months was 18.3% (59/323) in the RTX group and 5.3% (15/282) in the PBO group, resulting in an RR of 3.04 (1.76–5.24). The proportion of patients who achieved ACR50 at 6 months was 29.7% (144/485) in the RTX group and 11.5% (51/444) in the PBO group, resulting in an RR of 2.57 (1.92–3.44) (Figure 1(c)). MD in ΔHAQ-DI at 6 months was −0.15 (−0.31 to 0.01) (Supplementary Figure S3c). MD in Δmodified Total Sharp Score (mTSS) at 1 year was −1.08 (−1.69 to −0.47). SAE rate at 6 months was 7.9% (72/908) in the RTX group and 5.9% (28/471) in the PBO group, resulting in an RR of 1.35 (0.88–2.07).

RA CQ20: RTX monotherapy versus PBO or csDMARDs for csDMARD-IR RA

We have found two RCTs [14, 18] comparing RTX monotherapy (intervention) with PBO or csDMARDs (comparators) in

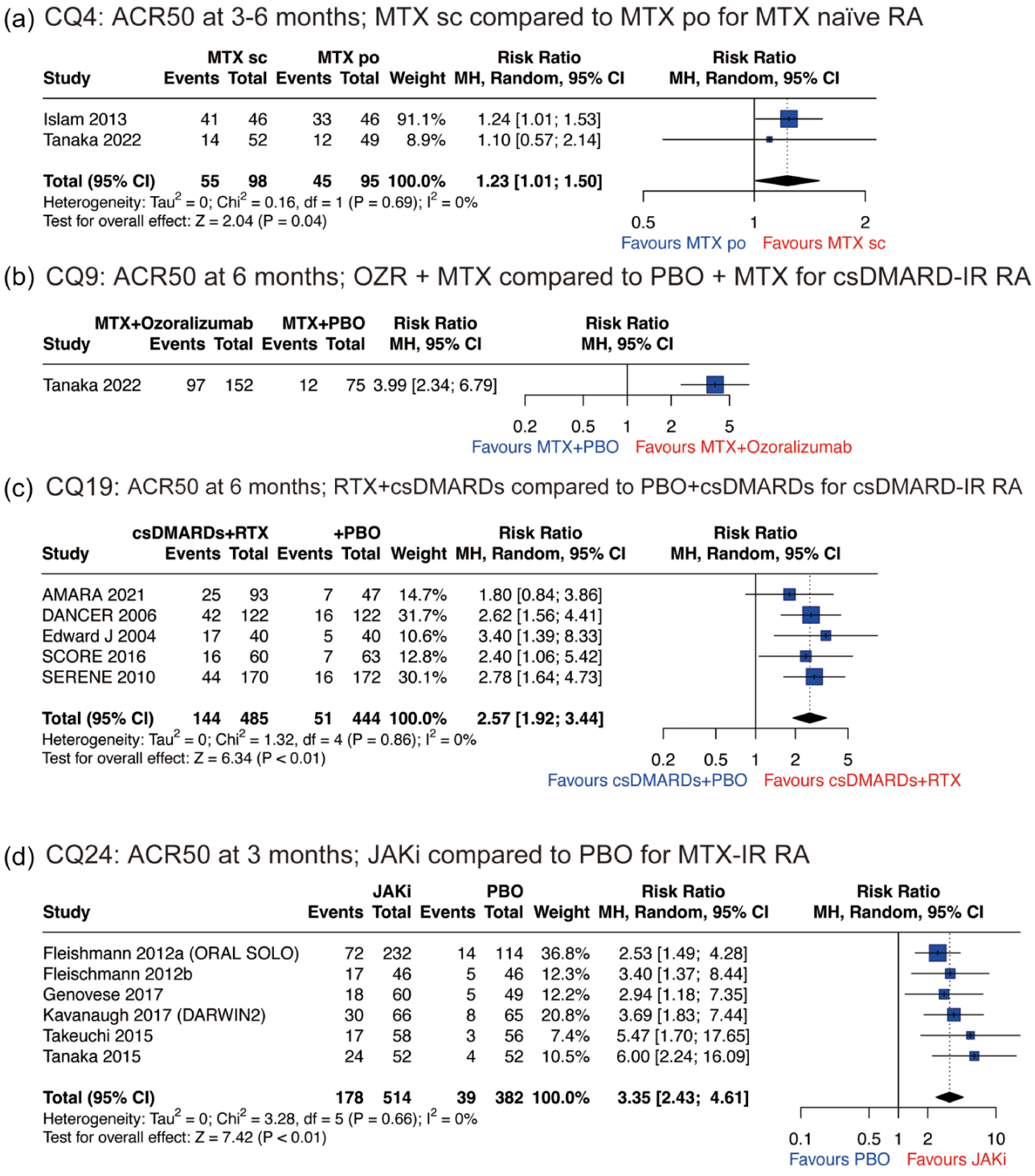
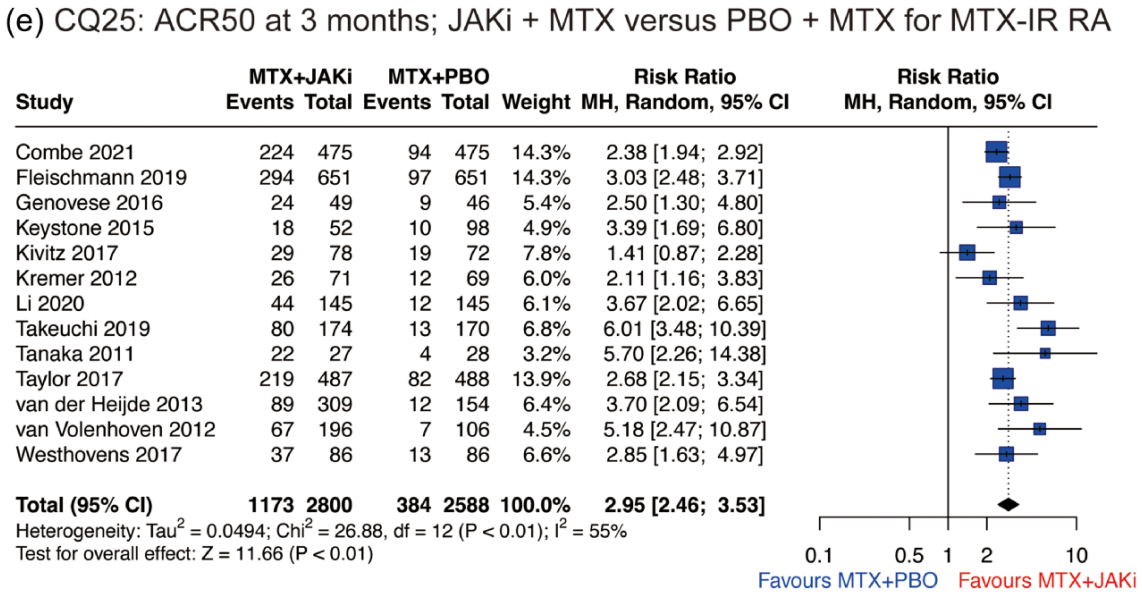
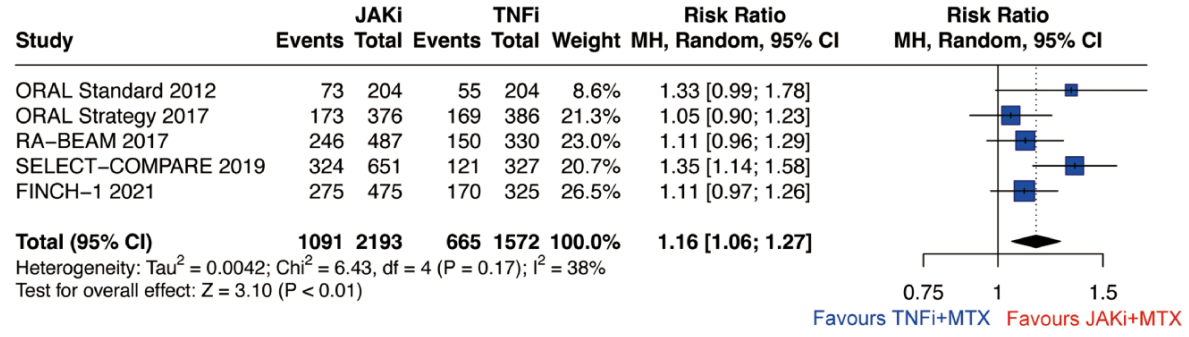


Figure 1. Forest plots of ACR50 (two or more randomised controlled trials and ozoralizumab), a common result among the data extracted from each CQ. (a) CQ4, (b) CQ9, (c) CQ19, (d) CQ24, (e) CQ25, (f) CQ26, (g) CQ28, (h) CQ32-1, (i) CQ32-2, (j) CQ32-3, (k) CQ33-1, and (l) CQ33-2. These figures were reprinted with permission from reference [8]. MH, Mantel–Haenszel test; ETN, etanercept; IFX, infliximab; ADA, adalimumab.

patients with csDMARD-IR patients with RA (Table 1). The proportion of patients who achieved ACR50 at 6 months was 32.5% (13/40) in the RTX group and 12.5% (5/40) in the comparator group, with an RR of 2.60 (1.02–6.61) (Supplementary Figure S4c). MD in ΔHAQ-DI at 6 months was −0.4 (−0.65 to −0.15). MD in ΔHAQ-DI at 12 months was −0.2 (−0.49 to 0.09). SAE rate at 6 months was 5.0% (2/40) in the RTX group and 7.5% (3/40) in the comparator group, resulting in a RR of 0.67 (0.12–3.78). SAE rate at 12 months was 10% (4/40) in the RTX group and 10% (4/40) in the comparator group, resulting in an RR of 1.0 (0.27–3.72). SIE rate at 6 months was 5.0% (2/40) in the RTX group and 2.5% (1/40) in the comparator group, resulting in an RR of 2.00 (0.19–21.18).





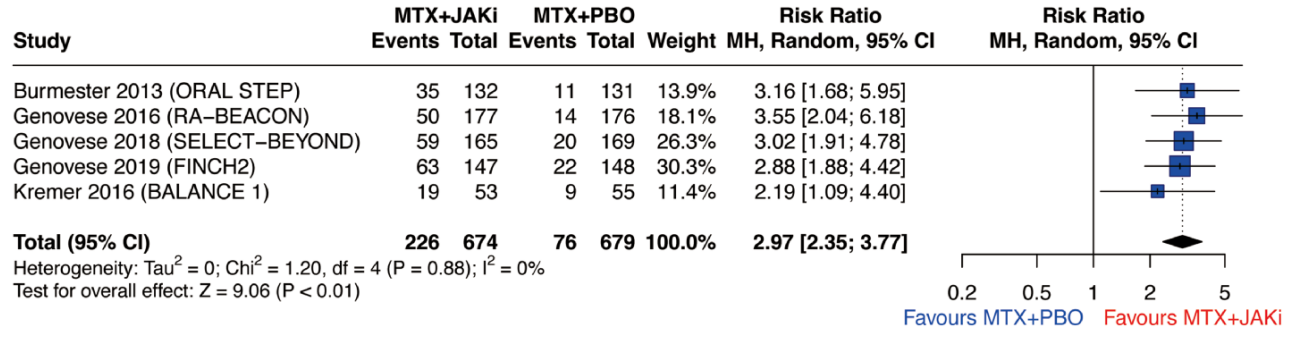


Figure 1. (Continued)

RA CQ21: RTX + csDMARDs versus tumour necrosis factor inhibitor + csDMARDs for csDMARD-IR RA

One RCT [19] compared RTX and csDMARDs (intervention) and tumour necrosis factor inhibitor (TNFi) + csDMARDs (comparator) in csDMARD-IR patients with RA (Table 1). The proportion of patients who achieved DAS28-ESR <2.6 at 3 months was 22.7% (30/132) in the RTX group and 20.9% (28/134) in the TNFi group, resulting in an RR of 1.09 (0.69–1.72). The proportion of patients who achieved ACR50 at 12 months was 48.9% (64/131) in the RTX group and 45.1% (60/133) in the TNFi group, resulting in an RR of 1.08 (0.84–1.40). MD in ΔHAQ-DI at 12 months was −0.11 (−0.24 to 0.02) (Supplementary Figure S5c). SAE rate at 3 months was 10.4% (15/144) in the RTX group and 7.9% (12/151) in the TNFi group, with an RR of 1.31 (0.64–2.70). SIE rate at 3 months was 5.6% (8/144) in the RTX group and 3.3% (5/151) in the TNFi group, resulting in an RR of 1.68 (0.56–5.01).

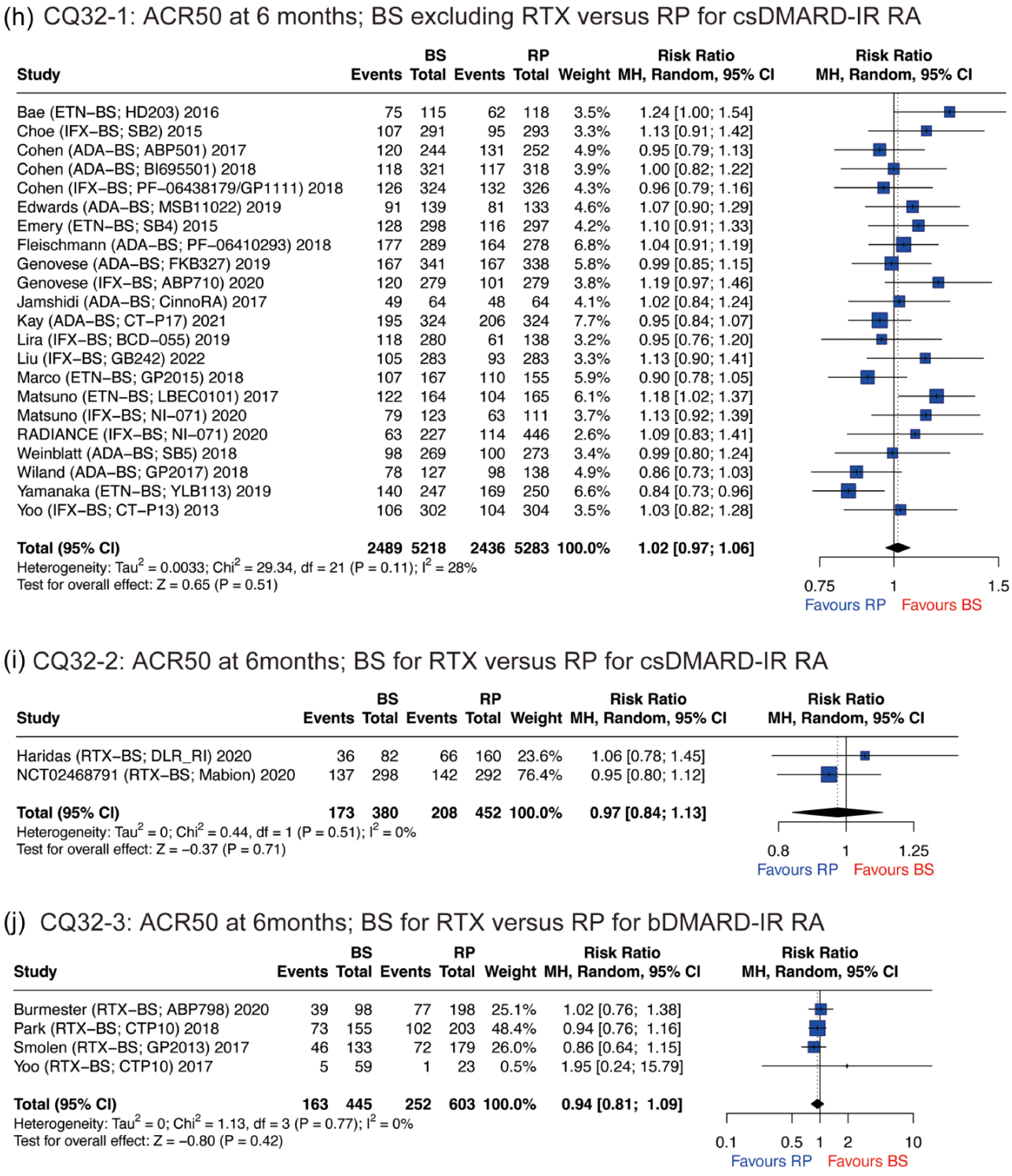
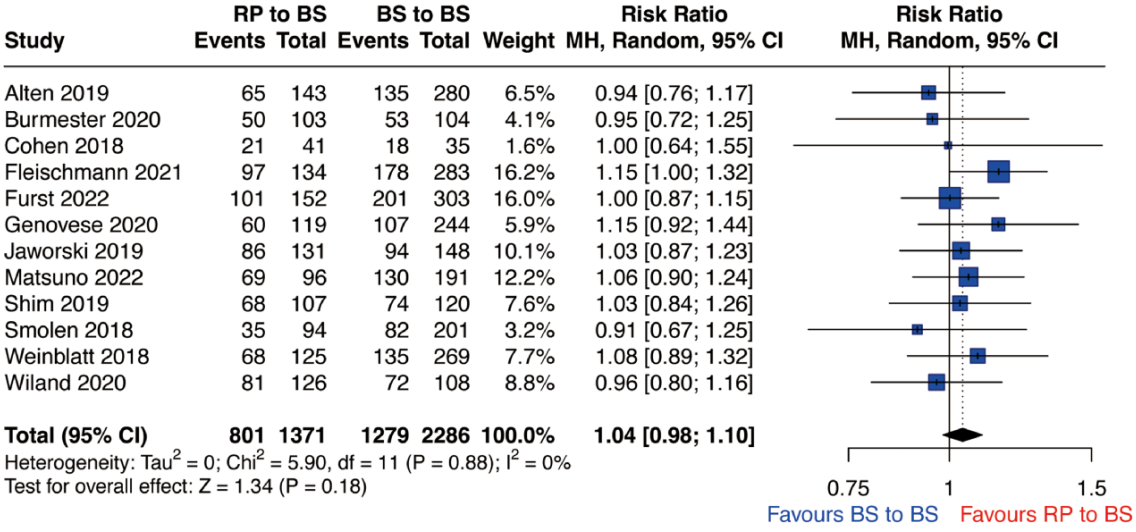


Figure 1. (Continued)

RA CQ22: RTX ± csDMARDs versus PBO ± csDMARDs for bDMARD-IR/intolerant RA

One RCT [20] compared RTX ± csDMARDs (intervention) and PBO ± csDMARDs (comparator) for patients with bDMARD-IR/intolerant RA (Table 1). The proportion of patients who achieved a DAS28-ESR of <2.6 at 6 months was 9.1% (27/298) in the RTX group and 0% (0/201) in the PBO group. The RR was 37.16 (2.28–605.68) after extrapolation of the proportion of patients who achieved DAS28-ESR remission from a study by Emery *et al.* [21]. The proportion of patients who achieved ACR50 at 3 months was 23.5% (70/298) in the RTX group and 7.5% (15/201) in the PBO group, resulting in an RR of 3.15 (1.86–5.34) (Supplementary Figure S6c). The proportion of patients who achieved ACR50 at 6 months was 26.8% (80/298) in the RTX group and 5.0% (10/201) in the PBO group, resulting in an RR of 5.40

(k) CQ33-1: ACR50 at 6months; RP to BS versus RP to RP in patients with MTX-IR RA



(l) CQ33-2: ACR50 at 6months; RP to BS versus BS to BS in patients with MTX-IR RA

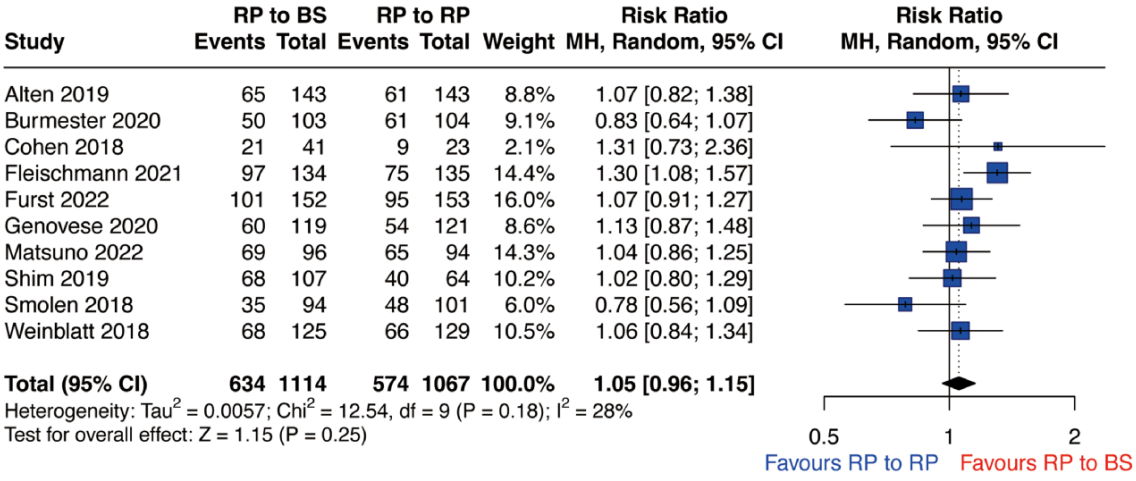


Figure 1. (Continued)

(2.87–10.16) (Supplementary Figure S6c). MD in ΔHAQ-DI at 6 months was −0.3 (−0.4 to −0.2). MD in ΔmTSS at 6 months was −0.6 (−1.14 to −0.06). SAE rate at 6 months was 17.9% (55/308) in the RTX group and 23.4% (49/209) in the PBO group, resulting in an RR of 0.76 (0.54–1.07). SIE rate at 6 months was 2.3% (7/308) in the RTX group and 1.4% (3/209) in the PBO group, resulting in an RR of 1.58 (0.41–6.05).

RA CQ23: RTX ± csDMARDs versus other bDMARD ± csDMARDs for bDMARD-IR RA

Three RCTs [22–24] compared RTX ± csDMARDs (intervention) and other bDMARD ±csDMARDs (comparator) in bDMARD-IR patients with RA (Table 1). The proportion of patients who achieved a DAS28-ESR of <2.6 at 3 months was 8.3% (13/157) in the RTX group and 17.4% (43/247) in the other bDMARD group, resulting in an RR of 0.40 (0.22–0.70). The proportion of patients who achieved a DAS28-ESR of <2.6 at 6 months was 14.0% (12/86) in the RTX group and 12.6% (22/175) in the other bDMARD groups, resulting in an RR of 1.11 (0.58–2.12). The proportion of patients who achieved ACR50 at 3 months was 7.5% (3/40) in the RTX group and 13.4% (11/82) in the other bDMARD group, resulting in a RR of 0.56 (0.17–1.89) (Supplementary Figure S7c). The proportion of patients who achieved ACR50 at 6 months was 7.5% (3/40) in the RTX group and 18.5% (15/81) in the other bDMARD group, resulting in an RR of 0.40 (0.12–1.32). MD in ΔHAQ-DI at 6 and 12 months was −0.1 (0.06–0.13) and −0.3 (−0.4 to −0.2), respectively. MD in ΔmTSS at 4 months was 0.08 (−0.11 to 0.27). SAE rate at 1 year was 7.7% (13/168) in the RTX group and 7.4% (18/243) in the other bDMARD group, resulting in an RR of 0.97 (0.43–2.19). SIE rate at 1 year was 2.5% (1/40) in the RTX group and 2.4% (2/82)

in the other bDMARD group, resulting in an RR of 1.02 (0.10–10.97).

JAK inhibitor

RA CQ24: JAKi versus PBO for MTX-IR RA

Six RCTs [25–30] compared JAKi (intervention) and PBO (comparator) in patients with MTX-IR RA (Table 1). The proportion of patients who achieved a DAS28-C-reactive protein (CRP) of <2.3 at 3 months was 21.3% (111/522) in the JAKi group and 6.2% (24/389) in the PBO group, resulting in an RR of 3.35 (2.19–5.15). The proportion of patients who achieved ACR50 at 3 months was 34.6% (178/514) in the JAKi group and 10.2% (39/382) in the PBO group, resulting in an RR of 3.35 (2.43–4.61) (Figure 1(d)). MD in ΔHAQ-DI at 3 months was −0.4 (−0.56 to −0.23) (Supplementary Figure S8c). SAE rate at 1 year was 1.5% (8/533) in the JAKi group and 3.4% (14/412) in the PBO group, resulting in an RR of 0.57 (0.18–1.81). SAE rate at 3 months was 17.9% (55/308) in the JAKi group and 23.4% (49/209) in the PBO group, with an RR of 0.76 (0.54–1.07). SIE rate at 3 months was 0.2% (1/535) in the JAKi group and 0.2% (1/412) in the PBO group, resulting in an RR of 1.12 (0.12–10.59).

RA CQ25: JAKi + MTX versus PBO + MTX for MTX-IR RA

Fourteen RCTs [31–44] compared JAKi + MTX (intervention) and PBO + MTX (comparator) in patients with MTX-IR RA (Table 1). The proportion of patients who achieved a DAS28-CRP of <2.3 at 3 months was 29.2% (549/1877) in the JAKi group and 7.9% (142/1789) in the PBO group, resulting in an RR of 3.62 (2.91–4.49). The proportion of patients who achieved ACR50 at 3 months was 41.9% (1173/2800) in the JAKi group and 14.8% (384/2588) in the PBO group, resulting in an RR of 2.95 (2.46–3.53) (Figure 1(e)). MD in ΔHAQ-DI at 3 months was −0.31 (−0.35 to −0.28) (Supplementary Figure S9c). SAE rate at 3 months was 3.0% (32/1075) in the JAKi group and 1.9% (17/880) in the PBO group, resulting in an RR of 1.28 (0.69–2.39). SIE rate at 3 months was 1.0% (11/1075) in the JAKi group and 0.1% (1/880) in the PBO group, resulting in an RR of 2.83 (0.80–10.06).

RA CQ26: JAKi + MTX versus TNFi + MTX for MTX-IR RA (short term)

Five RCTs [31, 36, 40, 45, 46] compared JAKi + MTX (intervention) and TNFi + MTX (comparator) in patients with MTX-IR RA in the short term (Table 1). The proportion of patients who achieved a DAS28-CRP of <2.3 at 6 months was 38.8% (771/1989) in the JAKi group and 30.3% (415/1368) in the TNFi group, resulting in an RR of 1.25 (1.07–1.47). The proportion of patients who achieved ACR50 at 6 months was 49.7% (1091/2193) in the JAKi group and 42.3% (665/1572) in the TNFi group, resulting in an RR of 1.16 (1.06–1.27) (Figure 1(f)). MD in ΔHAQ-DI at 6 months was −0.08 (−0.12 to −0.03) (Supplementary Figure S10c). MD in ΔmTSS at 6 months was 0.01 (−0.13 to 0.14). SAE at 6 months was 4.1% (55/1330) in the JAKi group and 4.0% (34/856) in the TNFi group, resulting in an RR of 1.04 (0.68–1.58) (Figure 2(a)). SAE rate at 1 year was 7.8% (120/1542) in the JAKi group and 5.8% (72/1245) in the TNFi group, resulting in an RR of 1.34 (1.01–1.79). SIE rate at 6 months was 1.7% (22/1330) in the JAKi group and 1.8% (15/856) in the TNFi group, resulting in an RR of 0.90 (0.46–1.76) (Figure 2(b)). SIE rate at 1 year was 4.0% (88/2193) in the JAKi group and 2.8% (44/1572) in the TNFi group, resulting in an RR of 1.25 (0.87–1.78).

RA CQ27: JAKi + MTX versus TNFi + MTX for MTX-IR RA (long term)

One RCT [47] compared JAKi + MTX (intervention) and TNFi + MTX (comparator) inpatients with MTX-IR RA in the long term (Table 1). The proportion of patients who achieved ACR50 at 4 years was 49.4% (422/854) in the JAKi group and 51.3% (424/826) in the TNFi group, resulting in an RR of 0.96 (0.88–1.06) (Supplementary Figure S11c). MD in ΔHAQ-DI at 4 years was −0.02 (−0.08 to 0.04). SAE rate at 4 years was 6.9% (351/5073) in the JAKi group and 6.2% (306/4941) in the TNFi group, resulting in an incidence rate ratio of 1.12 (0.95–1.31) (Figure 2(c)). SIE rate at 1 year was 2.9% (141/4931) in the JAKi group and 2.4% (119/4879) in the TNFi group, resulting in an incidence rate ratio of 1.17 (0.93–1.48) (Figure 2(d)).

RA CQ28: JAKi + MTX versus PBO + MTX for bDMARD-IR RA

Five RCTs [48–52] compared JAKi + MTX (intervention) and PBO + MTX (comparator) in patients with bDMARD-IR RA (Table 1). The proportion of patients who achieved a DAS28-CRP of <2.6 at 3 months was 22.1% (149/673) in the JAKi group and 7.1% (48/679) in the PBO group, resulting in an RR of 3.08 (2.26–4.18). The proportion of patients who achieved ACR50 at 3 months was 33.5% (226/674) in the JAKi group and 11.2% (76/629) in the PBO group, resulting in an RR of 2.97 (2.35–3.77) (Figure 1(g)). MD in ΔHAQ-DI at 3 months was −0.26 (−0.32 to −0.21) (Supplementary Figure S12c). SAE rate at 3 months was 4.0% (27/674) in the JAKi group and 2.8% (19/680) in the PBO group, with an RR of 1.19 (0.49–2.90). SIE rate at 3 months was 0.7% (5/676) in the JAKi group and 0.9% (6/681) in the PBO group, resulting in an RR of 0.86 (0.27–2.68).

RA CQ29: JAKi versus bDMARDs for bDMARD-IR/-intolerant RA

One RCT [53] compared JAKi (intervention) and bDMARDs (comparator) in patients with MTX-IR RA (Table 1). The proportion of patients who achieved a DAS28-CRP of <2.3 at 6 months was 45.9% (139/303) in the JAKi group and 31.4% (97/309) in the bDMARD group, with an RR of 1.46 (1.19–1.79) (Supplementary Figure S13c). The proportion of patients who achieved ACR50 at 6 months was 59.4% (180/303) in the JAKi group and 49.5% (153/309) in the bDMARD group, resulting in an RR of 1.20 (1.04–1.39). MD in ΔHAQ-DI at 6 months was −0.13 (−0.24 to −0.02). SAE rate at 6 months was 3.3% (10/303) in the JAKi group and 1.6% (5/309) in the bDMARD group, resulting in an RR of 2.04 (0.71–5.90). SIE rate at 6 months was 1.0% (3/303) in the JAKi group and 0.3% (1/309) in the bDMARD group, resulting in an RR of 3.06 (0.32–29.25).

Biosimilar

RA CQ32: biosimilar versus reference product for MTX-IR RA

Thirty-four RCTs [39, 54–85] compared biosimilar (BS), excluding RTX (intervention) and reference product (RP)

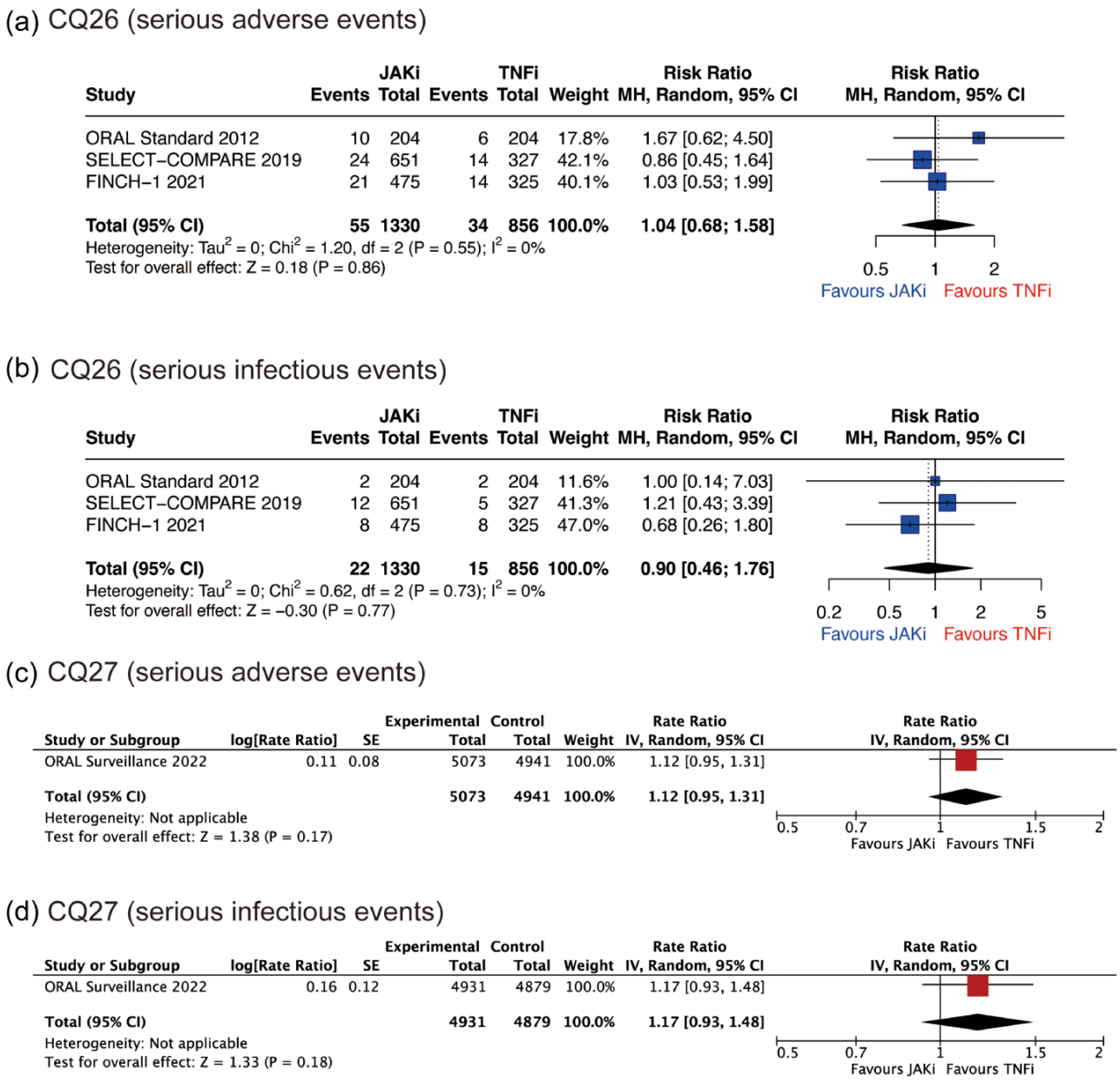


Figure 2. Forest plots of SAEs and SIEs in JAKi compared to TNFi (CQ26, short-term observations; CQ27, long-term observations). (a) CQ26, SAEs; (b) CQ26, SIEs; (c) CQ27, SAEs; and (d) CQ27, SIEs. These figures were reprinted with permission from reference [8]. MH, Mantel–Haenszel test.

(comparator), and RP in MTX-IR RA patients (Table 1). Evidence of BS, excluding RTX for csDMARD-IR RA (CQ32-1), RTX for csDMARD-IR RA (CQ32-2), and RTX for bDMARD-IR RA(CQ32-3), was separately analysed.

RA CQ32-1: BS excluding RTX versus RP for csDMARD-IR RA

The proportion of patients who achieved ACR50 at 6 months was 47.7% (2489/5218) in the BS group and 46.1% (2436/5283) in the RP group, resulting in an RR of 1.02 (0.97–1.06) (Figure 1(h)). SAE at 6 months was 4.1% (194/4762) in the BS group and 4.5% (213/4749) in the RP group, resulting in an RR of 0.92 (0.75–1.11) (Supplementary Figure S14c). SIE at 6 months was 1.3% (62/4759) in the BS group and 1.3% (64/4746) in the RP group, resulting in an RR of 1.01 (0.70–1.46).

RA CQ32-2: BS for RTX versus RP for csDMARD-IR RA

The proportion of patients who achieved ACR50 at 6 months was 45.5% (173/380) in the BS group and 46.0% (208/452) in the RP group, resulting in an RR of 0.97 (0.84–1.13) (Figure 1(i)). SAE rate at 6 months was 2.2% (9/410) in the BS group and 3.2% (16/494) in the RP group, resulting in an RR of 0.78 (0.29–2.05) (Supplementary Figure S14d). SIE rate at 6 months was 0.3% (1/319) in the BS group and 0.6% (2/309) in the RP group, resulting in an RR of 0.48 (0.04–5.31).

RA CQ32-3: BS for RTX versus RP for bDMARD-IR RA

The proportion of patients who achieved ACR50 at 6 months was 36.6% (163/445) in the BS group and 41.8% (252/603) in the RP group, resulting in an RR of 0.94 (0.81–1.09) (Figure 1(j)). SAE rate at 6 months was 5.5% (22/398) in the BS group and 6.2% (37/597) in the RP group, resulting in an RR of 0.87 (0.52–1.46) (Supplementary Figure S14e). SIE rate at 6 months was 1.5% (4/265) in the BS group and 1.7% (7/418) in the RP group, resulting in an RR of 0.95 (0.16–5.50).

RA CQ33: switching to BS versus unswitched in patients with MTX-IR RA

Thirteen RCTs [63, 74, 86–96] compared BS, excluding RTX (intervention), and RP (comparator) in patients with MTX-IR RA (Table 1). The effect of switching to BS (from RP to BS) in patients with RA on RP was analysed by dividing the comparator group (unswitched) into two subgroups: the group that received RP (from RP to RP) (CQ33-1) and the group that received BS (from BS to BS) (CQ33-2).

RA CQ33-1: switching to BS (from RP to BS) versus unswitched (from RP to RP) in patients with MTX-IR RA

The proportion of patients who achieved ACR50 at 6 months was 56.9% (634/1114) in the switched group and 53.8% (574/1067) in the unswitched group, resulting in an RR of 1.05 (0.96–1.15) (Figure 1(k)). SAE rate at 6 months was 2.8% (29/1024) in the switched group and 3.8% (38/993) in the unswitched group, resulting in an RR of 0.81 (0.48–1.36) (Supplementary Figure S15c). The rate of SIE at 6 months was 1.5% (11/729) in the switched group and 0.6% (4/697) in the unswitched group, resulting in an RR of 2.11 (0.72–6.17).

RA CQ33-2: switching to BS (from RP to BS) versus unswitched (BS to BS) in patients with MTX-IR RA

The proportion of patients who achieved ACR50 at 6 months was 58.4% (801/1371) in the switched group and 55.9% (1279/2286) in the unswitched group, resulting in an RR of 1.04 (0.98–1.10) (Figure 1(l)). The SAE rate at 6 months was 3.0% (39/1303) in the switched group and 3.7% (81/2210) in the unswitched group, resulting in an RR of 0.94 (0.61–1.47) (Supplementary Figure S15d). The rate of SIE at 6 months was 1.6% (11/676) in the switched group and 1.0% (13/1293) in the unswitched group, resulting in an RR of 1.60 (0.69–3.70).

Discussion

This SR was conducted to provide the most recent evidence for 15 CQs in the 2024 JCR guidelines. We conducted qualitative and quantitative analyses of RCTs to assess the efficacy and safety of various DMARDs.

For the SR of CQ4, we compared the clinical efficacy and safety of MTX sc and MTX po, including SAE and SIE. The proportion of patients who achieved ACR50 at 3 or 6 months was comparable between the two groups. No SAE or SIE were observed during 3-month follow-up. In this SR, we included a recent RCT conducted in Japan and the results were consistent with those of a previously published SR performed in 2016 [11, 97]. In Western countries, MTX sc has been used since the early 1990s, whereas in Japan, it was approved for clinical use in 2022. Due to this change in the accessibility of MTX sc, CQ4 was approved by CPG panel members, and this SR revealed that MTX sc was as efficacious and safe as MTX po.

In the 2020 JCR guidelines, the SR for CQ8 on TNFi was not updated because no additional new RCTs were performed after the publication of the 2014 JCR guidelines [98]. OZR is the latest TNFi approved in 2022 in Japan and the first NANOBODY® compound with anti-TNF multivalent ability. Therefore, we performed an SR for CQ9 to renew evidence on TNFi. In the present SR, we assessed the efficacy and safety of OZR; a single RCT comparing OZR + MTX and PBO + MTX IN csDMARD-IR patients reported that OZR + MTX was more efficacious than PBO + MTX [99]. As the certainty of evidence was very low for SAE and SIE and the directions of the effects were different among the critical outcomes, the overall certainty of evidence was very low. However, efficacy and safety data for TNFi in Japanese patients with RA are abundant, and the results of this SR agreed with those of a previous SR for other TNFi.

Although RTX was approved for RA more than a decade ago in Western countries, it has not been introduced into clinical practice in Japan [100]. In Japan, RTX has been approved for treating B-cell lymphoma and autoimmune diseases, including microscopic polyangiitis and granulomatosis with polyangiitis, scleroderma, and lupus nephritis. According to the 2021 ACR guidelines for RA, RTX is conditionally recommended for patients with RA who have a history of lymphoproliferative disorder (LPD) (for which RTX is an approved treatment) and moderate-to-high disease activity [101]. According to previous studies, the standardised incidence rate of lymphoma in Japanese patients with RA was 3–6, which is higher than that in Western countries [102–105]. A nationwide retrospective cohort study in Japan revealed that 80% of other iatrogenic immunodeficiency-associated LPD are of the B-cell type [106]. Due to the high incidence rate of other iatrogenic immunodeficiency-associated LPD and the increase in patients with RA and a history of LPD in Japan, these CQs were proposed and approved by the CPG panel members to add a new option to RA treatment. In comparison with the SR of the 2020 JCR guidelines, we added new CQs, CQ22 and CQ23. In these CQs, the efficacy and safety of RTX with or without csDMARDs were compared to those of PBO or bDMARDs with or without csDMARDs in patients with bDMARD-IR or bDMARD-intolerant RA. Compared with PBO with or without csDMARDs, RTX with or without csDMARDs was more efficacious and similarly safe to PBO for bDMARD-IR or bDMARD-intolerant patients. RTX with or without csDMARDs showed efficacy comparable to that of other bDMARDs, with or without csDMARDs.

The first JAKi, tofacitinib, was introduced for the clinical treatment of RA in Japan over a decade ago. Following the publication of the 2020 JCR guidelines, which included tofacitinib, baricitinib, and peficitinib, evidence for the use of two JAKi, upadacitinib and filgotinib, became available for SR. In the SR for CQ24 to CQ29, we assessed the latest evidence regarding the efficacy and safety of JAKi. Several RCTs were newly included in the SR of CQ24, CQ25, CQ26, and CQ28, of which the CQs in the 2020 RA CPG were CQ18, CQ19, CQ20, and CQ21, respectively [28, 31, 42, 46, 51, 52, 107]. The overall certainty of evidence for CQ24 was upgraded to high, whereas that for CQ25, CQ26, and CQ28 was downgraded to low, despite the increased number

of RCTs, because of the wide 95% confidence interval of the RR for SAE and/or SIE. Notably, in the 2024 JCR guidelines, the short- and long-term efficacy and safety of JAKi were assessed separately. In the SR of CQ26, the short-term efficacy and safety of JAKi + MTX and TNFi + MTX were compared in patients with MTX-IR RA. The efficacy and safety of both therapies were similar at 24 weeks. In the SR for CQ27, we reviewed the long-term outcomes of JAKi compared to TNFi with the concomitant use of MTX in patients with MTX-IR RA by employing a single RCT, the ORAL Surveillance study [47]. During a median follow-up of 4 years, using 'as observed' results, the efficacy of the two groups was comparable. Although the safety analysis revealed similar rates of SAE and SIE between the two groups, the incidence rates of major adverse cardiovascular events and malignancies were higher in the JAKi group than in the TNFi group. In a subanalysis of the ORAL Surveillance study, the risk of malignancy significantly increased in the JAKi with MTX group after 18 months of observation [108]. This evidence was based on one RCT; therefore, the results should be cautiously interpreted. The final results of postmarketing surveillance studies in Japan are required to determine whether JAKi has a class effect on adverse events. Further RCTs and cohort studies are required to clarify the long-term safety of JAKi.

In Japan, infliximab-BS, etanercept-BS, and adalimumab-BS were approved for the treatment of RA in 2014, 2018, and 2021, respectively. The cost of medical care in Japan has been increasing at a high rate, and dealing with this snowballing problem is of huge concern. Switching from the original bDMARDs (i.e. RP) to BS is cost-effective; however, the efficacy and safety of BS compared to RP should be considered. In the 2020 JCR guidelines, the SR for the same CQs as those in CQ31 and CQ32 were implemented. In the SR for CQ31, BS showed efficacy and safety equivalent to those of RP in csDMARD-IR patients with RA. In the SR for CQ32, switching from RP to BSs was equally efficacious and safe as continuing RP or BS. Most RCTs investigated short-term outcomes (a maximum of 52 weeks); therefore, the long-term efficacy and safety of BS need to be determined.

In the present SR, we comprehensively refined the methods used to identify and evaluate recent publications. First, the search terms for each CQ were drafted by the steering committee and refined by the SR support team, who are experts in SRs. Second, we searched for articles from PubMed, CENTRAL, the Japan Medical Abstracts Society (Igaku Chuo Zasshi), and EMBASE, with no language restrictions and no study type bias. Therefore, we performed an exhaustive review of recently published RCTs on DMARDs. Third, the risk of each RCT was assessed using the RoB 2 tool, which was released in August 2019 [6]. In Cochrane Reviews, RoB 2 tool is recommended for the assessment of the RoB in RCTs.

However, the present SR has some limitations. First, for most CQs, the number of included RCTs was insufficient to ensure certainty of the results of the analysis. In addition, owing to the limited number of RCTs, we could not assess publication bias. Second, we did not contact the authors of enrolled articles that lacked relevant data. Some studies, including those with unpublished data or those with negative results, may have been missed in the present SR.

In conclusion, we conducted an SR and meta-analysis of RCTs on DMARDs including MTX sc, OZR, RTX, JAKi, and BS. The results of this SR provide information to CPG panel members regarding the 2024 JCR guidelines.

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Supplementary data

Supplementary data is available at *Modern Rheumatology* online.

Conflict of interest

None declared.

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Author's contribution

S.F., Y.F., Y.H., M.U., Y.N., W.N., K.O., S.S., Y.T., Y.N., S.S., H.I., K.K., Y.T., S.H., G.D., R.M., T.H., K.M., K.M., R.M., and S.N. conducted the SR as SR team members. N.Y., R.Y., T.K., H.N., S.S., N.N., T.W., A.O., K.N., and R.W. supported the SR process as SR support team members. Y.N., W.N., and Y.T. drafted the manuscript. Y.K., E.T., Y.K., and M.H. supervised the SR. Y.N., W.N., and Y.T. wrote the manuscript. All the authors reviewed the draft manuscript and critically revised it for intellectual content. All authors approved the final version of the manuscript for publication and agreed to be accountable for any part of this work.

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