Efficacy and safety of various anti-rheumatic treatments for patients with rheumatoid arthritis: a network meta-analysis

Kexun Ma[1], Ling Li[2], Chunhui Liu[1], Lingling Zhou[3], Xueping Zhou[1]

[1]The First Clinical College, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China
[2]Department of Rheumatology, Taizhou Hospital of TCM, Taizhou, Jiangsu, China
[3]College of Pharmacy, Nanjing University of Chinese Medicine, Nanjing, Jiangsu, China

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Corresponding author:
Xueping Zhou
The First Clinical College
Nanjing University of Chinese Medicine
No. 138 Xianlin Avenue
Qixia District, Nanjing 210023
Jiangsu, China
Phone: +86 025 85811642
E-mail: yuhuali05@163.com

Abstract

Introduction: Biologics and traditional disease-modifying anti-rheumatic drugs (DMARDs) are generally used in treating patients with rheumatoid arthritis (RA). Previous studies have presented abundant data and information about the efficacy of such treatments, but the results were incomplete and inconclusive. This network meta-analysis was conducted to compare and assess the efficacy and safety of 15 therapies employing biologics and DMARDs for RA patients.

Material and methods: Six outcomes (American College of Rheumatology 20% response rate (ACR20), ACR50, ACR70, remission, adverse events (AEs) and serious adverse events (SAEs)) were used to evaluate the efficacy and safety of different treatments. The node-splitting method was used to assess the inconsistency, and the rank probabilities of the therapies were estimated by surface under the cumulative ranking curve. Besides, Jadad scale was used to evaluate the methodological quality of eligible studies.

Results: A total of 67 randomized controlled trials with 20,898 patients met the inclusion criteria. Most of the therapies presented better performance than conventional DMARDs (cDMARDs) and placebo in ACR20, ACR50 and ACR70. Conversely, the safety of cDMARDs and placebo seemed to be superior in AEs and SAEs. Also, tocilizumab (TCZ) and TCZ + methotrexate (MTX) showed better remission in pain compared to other treatments. Overall, certolizumab pegol (CZP) + MTX and TCZ + MTX had higher probability than the other treatments in efficacy outcomes.

Conclusions: We recommend CZP + MTX as the optimal drug therapy because it has the highest ranking in efficacy outcomes and relatively low risk of adverse events. TCZ + MTX is recommended as an alternative. Abatacept (ABT) and cDMARDs are not recommended due to their low efficacy.

Key words: rheumatoid arthritis, biologics, disease-modifying anti-rheumatic drugs, network meta-analysis.

Introduction

Rheumatoid arthritis (RA), a chronic systemic autoimmune disease distributed in all racial and ethnic groups, leads to joint stiffness, deformity and damage [1]. It is characterized by irreversible, alternating episodes, swelling, pain and tenderness, which results in worsening

of physical condition, a reduction of life quality, a decline in employment and increasing direct or indirect expenses [2]. Based on recent statistics, the morbidity of patients with RA in developed countries was approximately 1% in the adult population [3]. Generally, the prevalence of RA in Asian countries was less than that in North America (1.1–1.6%) or in Northern Europe (0.4–0.8%) [4].

A number of drugs which were used in treating the patients with RA separately or together responded well. Among them, infliximab, etanercept, adalimumab, golimumab, tocilizumab, abatacept, certolizumab pegol, methotrexate, and conventional disease-modifying anti-rheumatic drugs (cDMARDs) were the most common choices [5]. A report showed that the difference between certolizumab pegol and placebo in the American College of Rheumatology 20% response rate (ACR20) was statistically significant from 1 week to 24 weeks. For example, the ACR20 was 45.5% for certolizumab pegol (400 mg every 4 weeks) compared to 9.3% for placebo at week 24 [6]. However, in order to minimize the risk of neutralizing antibodies and to enhance efficacy, biologic agents are combined with cDMARDs most of the time, though several biologic agents were applied as single therapy [7]. According to the studies, patients with RA treated with placebo plus methotrexate, golimumab (100 mg) plus placebo, golimumab (50 mg) plus methotrexate and golimumab (100 mg) plus methotrexate had ACR20 response rates of 33.1%, 44.4%, 55.1% and 56.2% respectively. Apparently, the therapy combining golimumab with methotrexate can significantly relieve the disease and improve the physical condition [8].

Up to now, there have been dozens of pair-wise meta-analyses (MA) and network meta-analyses (NMA) which evaluate the efficacy and safety of different drug therapies for patients with RA. Nevertheless, most of the trials only focused on two interventions or just a few kinds of drugs, and some of the initial MAs were contradicted by subsequent studies. For instance, a 55% increase in risk of serious infection for patients who were treated with biologics was reported by a Cochrane review [9], while another trial evaluating malignancy risk in RA patients concluded that there was no significant evidence of an increased risk of malignancy using biologics [10]. In contrast, Bongartz *et al.* reported that RA patients who were treated by anti-TNF therapies had an increased risk of serious infections and malignancies [11]. Therefore, although previous studies have shown abundant data and information, they just verified the efficacy or safety of various therapies for patients with RA. However, the lack of head-to-head comparisons and the absence of systematical comparison made the results incomplete and inconclusive.

An NMA seeks to infer the relative efficacy of two treatments by direct and indirect comparisons. Simultaneously, it extracts and analyzes data from all randomized control trials (RCTs) to select the best therapy [12]. Four efficacy outcomes and two safety outcomes were chosen to systematically assess 15 therapies from 56 RCTs with a sample size of 20,898 patients. The objective of the current study is to better characterize the efficacy and safety of each treatment for patients with RA and then make the best choice in clinical practice.

Material and methods

Search strategy

We performed a systematic literature search in electronic databases, including PubMed, Embase and Cochrane Library, to retrieve eligible RCTs from 1997 to 2016. Key words and subject terms included "rheumatoid arthritis", "biological factors", "anti-TNF agents", "infliximab", "etanercept", "adalimumab", "golimumab", "certolizumab pegol", and "rituximab". Two reviewers performed the initial search, and all references were reviewed to identify additional studies that were not included in the retrieval. After that, they screened the titles and abstracts to make sure that the studies met predefined selection criteria individually.

Inclusion and exclusion criteria

Studies included should meet the following criteria: (1) the study design should be RCT; (2) the trials included at least one pairwise comparison between two interventions, which should be used to treat patients with RA; (3) detailed data of at least one relevant outcome were provided. In addition, we excluded duplicate data, reviews, meeting or conference abstracts and case reports from the current analysis.

Outcome measurement and data extraction

The information as follows was extracted from each eligible study: study code, first author, year of publication, country in which the study was conducted, length of follow-up, interventions, sample size of each therapy and respective outcomes for efficacy and safety. There were 6 outcome indicators to assess the efficacy and safety. American College of Rheumatology 20%, 50%, and 70% response rate (ACR20, ACR50 and ACR70, defined as a 20%, 50% and 70% improvement in patients) at 12–54 weeks and remission were the efficacy outcomes. Among them, the primary efficacy endpoints were ACR20 and ACR50, and the

secondary endpoints were ACR70 and remission. Meanwhile, adverse events (AEs) and serious adverse events (SAEs) were safety outcomes.

Statistical analysis

The indirect and direct evidence from a wide range of data was analyzed through a Bayesian NMA. After each pair-wise comparison was conducted, the network diagrams of ACR20, ACR50, ACR70, remission, AEs and SAEs were plotted with different interventions. The size of circles indicated the quantity of specific interventions and the boldness of arms showed the number of included studies. The results of these binary variables were presented as odds ratios (ORs) with corresponding 95% credible intervals (CrIs). In addition, net heat plots and node-splitting test were used to analyze the inconsistency level between indirect and direct evidence. The rank probabilities of efficacy and safety of 15 therapies were assessed using surface under the cumulative ranking curve (SUCRA), and the Jadad scale was used to evaluate the methodological quality of eligible studies. All statistical analyses were implemented by STATA version 12.0.

Results

Studies included in the network meta-analysis

According to a systematic literature search in electronic databases, a total of 8,104 records were identified. Among them, 1,465 duplicate publications and 6,394 articles were excluded due to their irrelevant titles and abstracts. The remaining 245 articles were selected for full-text review and 178 articles assessed as ineligible were excluded. Eventually, 67 RCTs dating from 1997 to 2016 met the inclusion criteria with 20,898 patients [13–79]. The searching and selection steps are shown in Figure 1.

Characteristics of included studies

The characteristics of included trials are shown in Table I. In detail, 33 of 56 different trials covered patients around the world and 15 trials included patients predominantly from Asia. The rest of the trials were reported to include patients from Europe (5 studies) and America (3 studies). The length of follow-up ranged from 12 to 54 weeks. Most of the trials included a comparison between two interventions. Only 5 trials mentioned comparisons among three interventions. All trials involved 10 drugs as follows: infliximab (INF), etanercept (ETN), adalimumab (ADA), golimumab (GOL), tocilizumab (TCZ), abatacept (ABT), certolizumab pegol (CZP), methotrexate (MTX), conventional disease-modifying anti-rheumatic drugs (cDMARDs) and placebo (PBO). The full network of comparisons categorized in different outcomes was shown in Figure 2.

American College of Rheumatology 20% response rate (ACR20)

ACR20 was normally defined as a 20% improvement for patients with rheumatoid arthritis. The estimated ORs with 95% CrIs of ACR20 for each comparison are shown in the lower panel of Table II. Among these 15 therapies, ABT + MTX (OR = 5.42, 95% CrI: 2.12–14.0), ADA (OR = 4.31, 95% CrI: 2.53–7.39), ADA + MTX (OR = 5.81, 95% CrI: 2.39–14.7), CZP (OR = 11.3, 95% CrI: 4.48–28.8), CZP + MTX (OR = 9.68, 95% CrI: 3.86–24.5), ETN (OR = 4.22, 95% CrI: 2.23–8.17), ETN + MTX (OR = 6.31, 95% CrI: 3.10–14.0), GOL + MTX (OR = 6.23, 95% CrI: 2.46–15.6), INF + MTX (OR = 5.75, 95% CrI: 2.39–14.1), TCZ (OR = 5.64, 95% CrI: 2.8–11.47) and TCZ + MTX (OR = 7.10, 95% CrI: 3.16–16.1) revealed superior efficacy under the endpoint of ACR20 compared with PBO. In addition, CZP + MTX was more efficacious than ETN when comparing ACR20 (OR = 2.29, 95% CrI: 1.03–5.10).

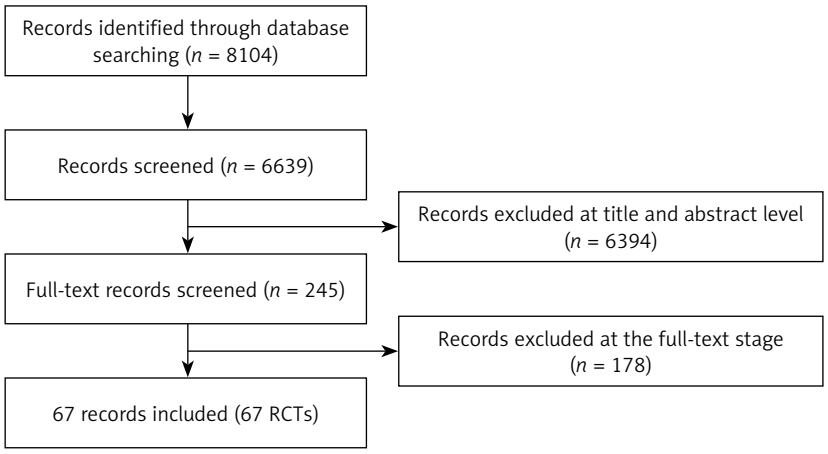


Figure 1. Flow diagram of study inclusion

Table I. Patient characteristics in the studies included in the mixed-treatment comparison (MTC) analysis

No.	Study	Author (year)	Country	Follow-up [weeks]	Sizes	Intervention 1		Intervention 2		Outcomes
						Drugs	Cases	Drugs	Cases	
1	Abe06	Abe (2006)	Japan	14	137	cDMARDs	47	IFX + MTX	90	①②③⑤⑥
2	APPEAL	Bae (2013) and Kim (2012)	Asia	16	300	ETN + MTX	197	cDMARDs	103	①②③④⑤⑥
3	Combe06&09	Combe (2009) and Combe (2006)	Finland	24	254	cDMARDs	50	ETN	103	①②③⑤⑥
								ETN + MTX	101	
4	ACT-RAY	Dougados (2013)	UK	24	553	TCZ + MTX	277	TCZ	276	①②③④⑤⑥
5	JESMR	Kameda (2010)	Japan	24	142	ETN	69	ETN + MTX	73	①②③④⑤⑥
6	RED-SEA	Jobanputra (2012)	UK	52	120	ADA	60	ETN	60	⑥
7	Kay08	Kay (2008)	Global	16	171	cDMARDs	35	GOL + MTX	136	①②③④⑤⑥
8	Kim07	Kim (2007)	Korean	24	128	cDMARDs	63	ADA + MTX	65	①②③⑤⑥
9	LITHE	Kremer (2011)	Global	52	1190	cDMARDs	393	TCZ + MTX	797	①②③④
10	AIM	Kremer (2006)	Global	26	652	ABT + MTX	433	cDMARDs	219	①②③④⑤⑥
11	Lan04	Lan (2004)	Taiwan	12	58	ETN + MTX	29	cDMARDs	29	①②③⑤
12	Mathias00& Moreland99	Mathias (2000) and Moreland (1999)	North-America	26	234	PBO	80	ETN	154	①②③
13	CHANGE	Miyasaka (2008)	Japan	24	352	PBO	87	ADA	265	①②③⑤⑥
14	SAMURAI	Nishimoto (2007)	Japan	52	302	cDMARDs	145	TCZ	157	①②③④⑤⑥
15	O'Dell2013	O'Dell (2013) and O'Dell (2012)	Global	48	353	cDMARDs	178	ETN + MTX	175	①②③④⑤⑥
16	SATORI	Nishimoto (2009)	Japan	24	125	TCZ + MTX	61	cDMARDs	64	①②③④⑤⑥
17	GO-FORTH	Tanaka (2012)	Japan	24	261	cDMARDs	88	GOL + MTX	173	①②③④⑤⑥
18	ATTEST	Schiff (2008)	Global	27	321	ABT + MTX	156	IFX + MTX	165	①②③④⑤⑥
19	ADORE	VanRiel (2006) and VanRiel (2008)	Europe	16	314	ETN	159	ETN + MTX	155	①②③④⑤⑥
20	AUGUSTII	Van Vollenhoven (2011)	Global	26	311	PBO	76	ADA	79	①②③⑤⑥
								ABT	156	

Table I. Cont.

No.	Study	Author (year)	Country	Follow-up [weeks]	Sizes	Intervention 1		Intervention 2		Outcomes
						Drugs	Cases	Drugs	Cases	
21	ARMADA	Weinblatt (2003) and Weinblatt (2006)	North-America	24	271	cDMARDs	62	ADA + MTX	209	①②③
22	START	Westhovens (2006)	Global	22	1084	cDMARDs	363	IFX + MTX	721	①②③④⑤⑥
23	Zhang2006	Zhang (2006)	China	18	173	IFX + MTX	87	cDMARDs	86	①②③⑤
24	CREATEIIB	Keystone (2012)	Global	26	129	cDMARDs	65	ETN + MTX	64	①②③⑤⑥
25	CERTAIN	Smolen (2011)	Global	24	194	cDMARDs	98	CZP + MTX	96	①②③⑤⑥
26	ADACTA	Gabay (2013)	Global	24	325	TCZ	163	ADA	162	①②③④
27	TOWARD	Genovese (2008)	Global	24	1216	TCZ + MTX	803	cDMARDs	413	①②③④⑤⑥
28	HIKARI	Yamamoto (2014)	Japan	24	230	PBO	114	CZP	116	①②③④⑤⑥
29	AMPLE	Schiff (2014) and Weinblatt (2014)	Global	52	646	ABT + MTX	318	ADA + MTX	328	①②③④⑤⑥
30	GO-FURTHER	Weinblatt (2013)	Global	24	592	cDMARDs	197	GOL + MTX	395	①②③⑤⑥
31	Fleischmann 2012	Fleischmann (2012)	Global	24	112	PBO	59	ADA	53	①②③⑤⑥
32	Choy 2012	Choy (2012)	Global	24	247	CZP + MTX	126	cDMARDs	121	①②③⑤⑥
33	RAPID-II	Smolen (2009) and Strand (2011)	Global	24	619	cDMARDs	127	CZP + MTX	492	①②③⑤⑥
34	GO-FORWARD	Keystone (2009)	Global	14	444	cDMARDs	133	GOL	133	①②③④⑤⑥
								GOL + MTX	178	
35	Chen 2009	Chen (2009)	Taiwan	14	47	ADA + MTX	35	cDMARDs	12	①②③⑤⑥
36	FAST4WARD	Fleischmann (2009)	Global	24	220	PBO	109	CZP	111	①②③⑤⑥
37	Moreland 1997	Moreland (1997)	Global	12	180	PBO	44	ETN	136	①②
38	OPTION	Smolen (2008)	Global	16	622	TCZ + MTX	418	cDMARDs	204	①②③④⑤⑥
39	RAPIDI	Keystone (2008)	Global	52	982	cDMARDs	199	CZP + MTX	783	①②③
40	CHARISMA	Maini (2006)	Europe	20	359	TCZ	159	TCZ + MTX	151	①②③⑤⑥
						cDMARDs	49			
41	VandePutte 2004	VandePutte (2004)	Global	26	544	ADA	434	PBO	110	①②③⑤⑥

Table I. Cont.

No.	Study	Author (year)	Country	Follow-up [weeks]	Sizes	Intervention 1		Intervention 2		Outcomes
						Drugs	Cases	Drugs	Cases	
42	TEMPO	Klareskog (2004)	Global	52	682	cDMARDs	228	ETN	223	①②③⑤⑥
								ETN + MTX	231	
43	VandePutte 2003	VandePutte (2003)	Global	12	284	PBO	70	ADA	214	①②③⑥
44	ATTRACT	Lipsky (2000) and Maini (1999)	Global	54	428	cDMARDs	88	IFX + MTX	340	①②③⑥
45	Kremer 2003	Kremer (2003)	Global	26	339	cDMARDs	119	ABT + MTX	220	①②③⑥
46	Chen 2016	Chen (2016)	China	12	358	ETN + MTX	239	cDMARDs	119	①②③⑤⑥
47	J-RAPID	Yamamoto (2014)	Japan	24	316	cDMARDs	77	CZP + MTX	239	①②③⑤⑥
48	LatinRA	Machado (2014) and Fleischmann (2014)	Latin America	24	423	ETN + MTX	281	cDMARDs	142	①②③④⑤⑥
49	BREVACTA	Kivitz (2014) and Kivitz (2013)	Global	24	656	TCZ	437	PBO	219	①②③⑤⑥
50	Hobbs 2015	Hobbs (2015)	Global	12	210	PBO	104	ETN	106	①②③⑤⑥
51	Li 2015	Li (2015)	China	14	264	cDMARDs	132	GOL + MTX	132	①②③④⑤⑥
52	ASSET	Conaghan (2013)	Global	16	50	ABT + MTX	27	cDMARDs	23	④⑤⑥
53	Keystone 2004	Keystone (2004)	Global	24	619	ADA + MTX	419	cDMARDs	200	①②③⑤
54	deFilippis 2006	DeFilippis (2006)	Global	22	30	ETN + MTX	15	IFX + MTX	15	①②③
55	Weinblatt 1999	Weinbaltt (1999)	Global	24	89	cDMARDs	30	ETN + MTX	59	①②③
56	STAR	Furst (2003)	Global	24	636	ADA + MTX	318	cDMARDs	318	③⑤⑥

PBO – placebo, MTX – methotrexate, IFX – infliximab, ETN – etanercept, ADA – adalimumab, GOL – golimumab, TCZ – tocilizumab, ABT – abatacept, CZP – clonazepam, cDMARDs – traditional synthetic disease modifying antirheumatic drugs, ACR – American College of Rheumatology, AEs – adverse events, SAEs – serious adverse events.
Outcomes: ① – ACR20 20% response rate, ② – ACR50 50% response rate, ③ – ACR70 70% response rate, ④ – Remission, ⑤ – AEs, ⑥ – SAEs.

American College of Rheumatology 50% response rate (ACR50)

Base on the upper panel of Table II, PBO showed the worst performance for ACR50 compared with all therapies except cDMARDs (OR = 1.86, 95% CrI: 0.94–3.71). As for cDMARDs, it revealed worse efficacy than the other treatments except ABT, GOL and PBO. In addition, ETN + MTX, CZP + MTX and TCZ + MTX were superior to ETN for the efficacy of ACR50 (ETN + MTX: OR = 1.59, 95% CrI: 1.01–2.56; CZP + MTX: OR = 2.27, 95% CrI: 1.07–4.76; TCZ + MTX: OR = 2.10, 95% CrI: 1.06–4.01.

American College of Rheumatology 70% response rate (ACR70)

As shown in the lower panel of Table III, only cDMARDs (OR = 2.41, 95% CrI: 0.91–7.10) demonstrated no statistically significant difference from PBO. Similarly, all the therapies appeared superior to cDMARDs when comparing ACR70, except for ABT (OR = 1.60, 95% CrI: 0.32–7.54), ADA (OR = 2.77, 95% CrI: 0.93–8.08) and GOL (OR = 2.69, 95% CrI: 0.37–10.3) Additionally, CZP enjoyed obvious superiority to ABT (OR = 0.05, 95% CrI: 0.01–0.62) and ADA (OR = 0.09, 95% CrI: 0.01–0.84).

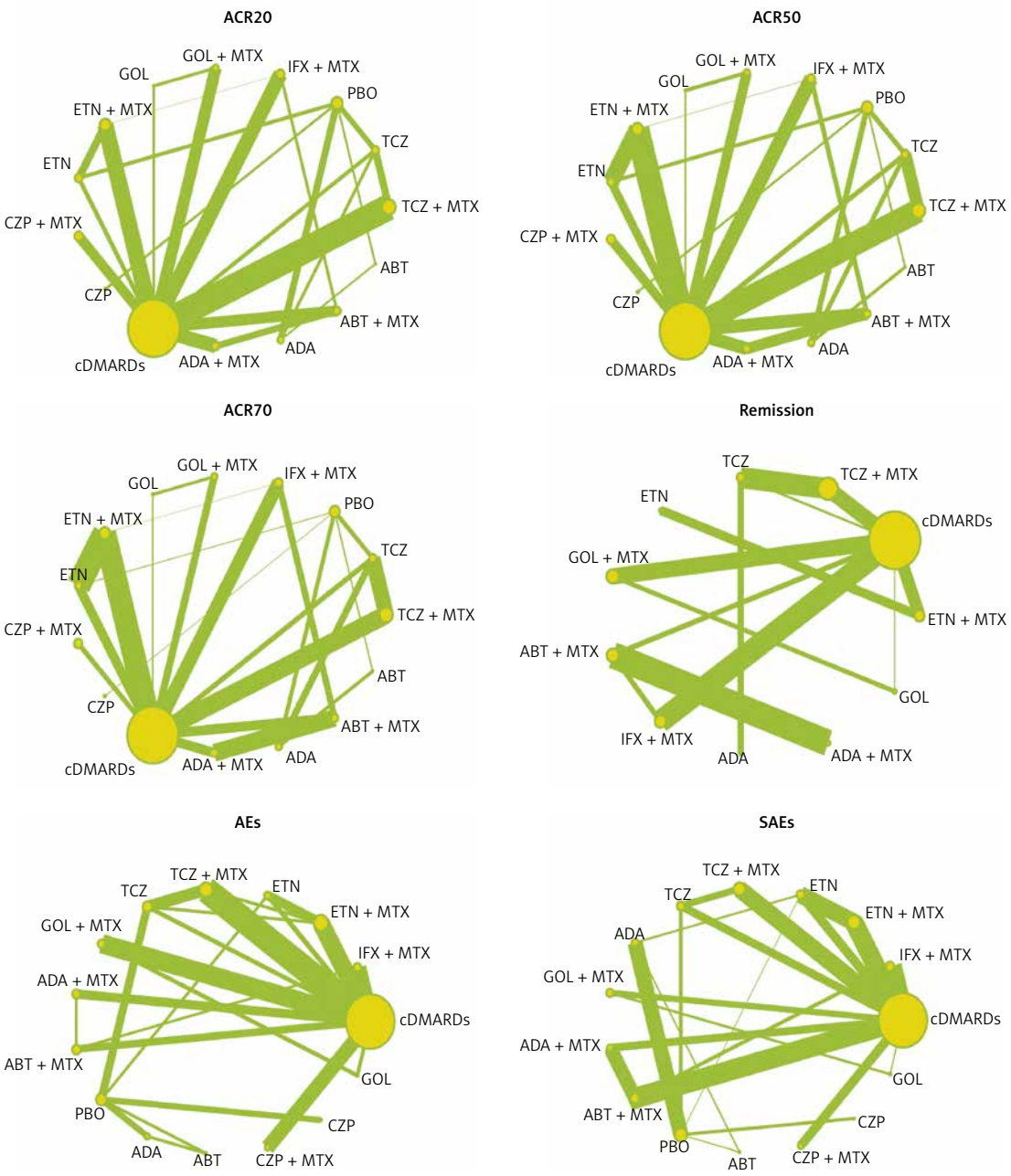


Figure 2. Full network of comparisons categorized in different outcomes. The width of the lines is proportional to the number of trials comparing each pair of treatments; the area of circles represents the cumulative number of patients for each intervention

Table II. Odds ratio estimates with 95% credible intervals of ACR20 and ACR50 for each comparison

Endpoint		ACR50														
ACR20	ABT	ABT	0.47 (0.13, 1.72)	0.66 (0.24, 1.73)	0.38 (0.11, 1.36)	1.79 (0.55, 5.81)	0.30 (0.07, 1.21)	0.31 (0.09, 1.14)	0.70 (0.22, 2.27)	0.44 (0.13, 1.45)	0.76 (0.16, 3.63)	0.41 (0.11, 1.52)	0.48 (0.13, 1.72)	3.35 (1.22, 9.21)	0.44 (0.14, 1.39)	0.34 (0.10, 1.14)
	ABT + MTX	0.28 (0.07, 1.13)	ABT + MTX	1.40 (0.54, 3.53)	0.82 (0.44, 1.52)	3.82 (2.29, 6.42)	0.64 (0.18, 2.32)	0.66 (0.32, 1.40)	1.52 (0.72, 3.13)	0.94 (0.49, 1.77)	1.63 (0.52, 5.05)	0.89 (0.41, 1.88)	1.03 (0.53, 1.93)	7.17 (3.06, 17.0)	0.95 (0.44, 2.03)	0.73 (0.36, 1.45)
	ADA	0.35 (0.12, 1.03)	1.27 (0.45, 3.53)	ADA	0.58 (0.23, 1.48)	2.72 (1.26, 6.11)	0.46 (0.15, 1.36)	0.48 (0.18, 1.25)	1.08 (0.50, 2.32)	0.68 (0.30, 1.49)	1.16 (0.32, 4.22)	0.63 (0.24, 1.67)	0.73 (0.30, 1.86)	5.10 (3.03, 8.85)	0.68 (0.34, 1.39)	0.52 (0.23, 1.20)
	ADA + MTX	0.26 (0.06, 1.02)	0.93 (0.47, 1.86)	0.73 (0.27, 1.97)	ADA + MTX	4.71 (2.89, 7.69)	0.79 (0.22, 2.83)	0.82 (0.39, 1.70)	1.86 (0.90, 3.78)	1.16 (0.62, 2.14)	1.99 (0.65, 6.17)	1.08 (0.52, 2.25)	1.26 (0.64, 2.46)	8.85 (3.78, 20.7)	1.16 (0.55, 2.46)	0.89 (0.45, 1.75)
	cDMARDs	0.89 (0.24, 3.22)	3.22 (1.80, 5.75)	2.53 (1.09, 5.87)	3.46 (2.05, 5.87)	cDMARDs	0.17 (0.05, 0.54)	0.17 (0.10, 0.30)	0.39 (0.23, 0.66)	0.25 (0.17, 0.35)	0.43 (0.15, 1.16)	0.23 (0.13, 0.39)	0.27 (0.16, 0.43)	1.86 (0.94, 3.71)	0.25 (0.14, 0.44)	0.19 (0.12, 0.30)
	CZP	0.13 (0.03, 0.55)	0.49 (0.13, 1.82)	0.38 (0.13, 1.12)	0.52 (0.14, 1.88)	0.15 (0.05, 0.49)	CZP	1.04 (0.28, 3.82)	2.36 (0.74, 7.39)	1.48 (0.45, 4.85)	2.53 (0.53, 12.2)	1.38 (0.38, 5.05)	1.60 (0.45, 5.70)	11.1 (4.35, 29.7)	1.48 (0.47, 4.76)	1.13 (0.34, 3.86)
	CZP + MTX	0.15 (0.04, 0.63)	0.56 (0.25, 1.25)	0.44 (0.16, 1.21)	0.60 (0.28, 1.30)	0.17 (0.10, 0.30)	1.16 (0.32, 4.26)	CZP + MTX	2.27 (1.07, 4.76)	1.42 (0.73, 2.72)	2.46 (0.76, 7.77)	1.34 (0.61, 2.86)	1.54 (0.75, 3.16)	10.8 (4.53, 26.1)	1.42 (0.66, 3.13)	1.08 (0.54, 2.23)
	ETN	0.35 (0.10, 1.23)	1.28 (0.57, 2.92)	1.02 (0.45, 2.25)	1.38 (0.63, 3.03)	0.40 (0.22, 0.71)	2.66 (0.86, 8.25)	2.29 (1.03, 5.10)	ETN	0.63 (0.39, 0.99)	1.07 (0.34, 3.39)	0.58 (0.28, 1.25)	0.68 (0.34, 1.38)	4.71 (2.56, 9.12)	0.63 (0.32, 1.25)	0.48 (0.25, 0.94)
	ETN + MTX	0.23 (0.06, 0.84)	0.84 (0.41, 1.68)	0.66 (0.28, 1.55)	0.90 (0.46, 1.73)	0.26 (0.17, 0.39)	1.73 (0.52, 5.70)	1.49 (0.75, 2.94)	0.65 (0.37, 1.13)	ETN + MTX	1.73 (0.59, 5.16)	0.93 (0.49, 1.82)	1.08 (0.61, 1.97)	7.54 (3.82, 15.6)	1.00 (0.54, 1.95)	0.76 (0.44, 1.39)
	GOL	0.46 (0.09, 2.41)	1.67 (0.48, 5.58)	1.31 (0.33, 5.16)	1.79 (0.54, 5.87)	0.51 (0.18, 1.51)	3.42 (0.69, 17.1)	2.94 (0.89, 9.87)	1.28 (0.38, 4.39)	1.97 (0.63, 6.36)	GOL	0.54 (0.20, 1.45)	0.63 (0.20, 1.93)	4.39 (1.31, 15.2)	0.58 (0.19, 1.86)	0.44 (0.15, 1.36)
	GOL + MTX	0.24 (0.06, 0.98)	0.88 (0.39, 1.95)	0.69 (0.25, 1.90)	0.94 (0.44, 2.03)	0.27 (0.16, 0.47)	1.82 (0.50, 6.69)	1.57 (0.72, 3.42)	0.68 (0.31, 1.54)	1.05 (0.53, 2.10)	0.53 (0.18, 1.55)	GOL + MTX	1.16 (0.57, 2.39)	8.08 (3.39, 19.7)	1.07 (0.50, 2.36)	0.82 (0.41, 1.70)
	IFX + MTX	0.26 (0.07, 1.02)	0.94 (0.46, 1.93)	0.75 (0.28, 1.97)	1.01 (0.49, 2.10)	0.29 (0.18, 0.49)	1.95 (0.55, 7.03)	1.68 (0.79, 3.56)	0.73 (0.34, 1.58)	1.13 (0.60, 2.14)	0.57 (0.17, 1.90)	1.07 (0.51, 2.29)	IFX + MTX	7.03 (3.06, 16.1)	0.92 (0.44, 1.95)	0.70 (0.37, 1.38)
	PBO	1.49 (0.51, 4.44)	5.42 (2.12, 14.0)	4.31 (2.53, 7.39)	5.81 (2.39, 14.7)	1.68 (0.81, 3.56)	11.3 (4.48, 28.8)	9.68 (3.86, 24.5)	4.22 (2.23, 8.17)	6.49 (3.10, 14.0)	3.29 (0.89, 12.3)	6.23 (2.46, 15.6)	5.75 (2.39, 14.1)	PBO	0.13 (0.07, 0.25)	0.10 (0.05, 0.21)
	TCZ	0.26 (0.08, 0.93)	0.97 (0.41, 2.27)	0.76 (0.35, 1.63)	1.04 (0.46, 2.36)	0.30 (0.16, 0.56)	1.99 (0.63, 6.42)	1.73 (0.76, 3.97)	0.75 (0.36, 1.57)	1.15 (0.58, 2.34)	0.58 (0.17, 2.01)	1.11 (0.48, 2.51)	1.03 (0.46, 2.29)	0.18 (0.09, 0.36)	TCZ	0.76 (0.43, 1.35)
	TCZ + MTX	0.21 (0.06, 0.79)	0.76 (0.35, 1.65)	0.61 (0.24, 1.48)	0.82 (0.40, 1.72)	0.24 (0.14, 0.39)	1.58 (0.46, 5.42)	1.36 (0.64, 2.89)	0.59 (0.29, 1.25)	0.91 (0.49, 1.73)	0.46 (0.14, 1.51)	0.88 (0.41, 1.84)	0.81 (0.39, 1.67)	0.14 (0.06, 0.32)	0.79 (0.41, 1.52)	TCZ + MTX

PBO – placebo, MTX – methotrexate, IFX – infliximab, ETN – etanercept, ADA – adalimumab, GOL – golimumab, TCZ – tocilizumab, ABT – abatacept, CZP – clonazepam, cDMARDs – traditional synthetic disease modifying antirheumatic drugs, ACR – American College of Rheumatology, AEs – adverse events, SAEs – serious adverse events.

Table III. Odds ratio estimates with 95% credible intervals of ACR70 and remission for each comparison

Endpoint																
									Remission							
ACR70	ABT + MTX	0.30 (0.05, 1.60)	ABT + MTX	0.34 (0.02, 6.11)	0.90 (0.12, 6.75)	4.06 (1.03, 16.3)	–	–	2.10 (0.20, 23.8)	1.19 (0.18, 7.61)	1.17 (0.09, 13.2)	0.71 (0.12, 4.06)	1.06 (0.20, 5.58)	–	0.06 (0.01, 0.45)	0.15 (0.03, 0.87)
	ADA	0.58 (0.17, 1.93)	1.90 (0.55, 6.96)	ADA	2.69 (0.08, 107)	12.1 (0.92, 185)	–	–	6.17 (0.26, 183)	3.53 (0.21, 70.1)	3.49 (0.12, 104)	2.14 (0.13, 38.1)	3.16 (0.17, 68.7)	–	0.17 (0.02, 1.39)	0.46 (0.03, 6.42)
	ADA + MTX	0.30 (0.05, 1.55)	0.97 (0.45, 2.12)	0.51 (0.14, 1.73)	ADA + MTX	4.53 (0.39, 52.5)	–	–	2.34 (0.10, 54.1)	1.32 (0.08, 20.5)	1.32 (0.05, 30.0)	0.80 (0.05, 11.3)	1.20 (0.09, 16.4)	–	0.06 (0.01, 1.12)	0.17 (0.01, 2.41)
	cDMARDs	1.60 (0.32, 7.54)	5.26 (2.77, 10.4)	2.77 (0.93, 8.08)	5.42 (2.92, 10.5)	cDMARDs	–	–	0.52 (0.08, 3.63)	0.29 (0.08, 0.98)	0.29 (0.03, 2.10)	0.18 (0.06, 0.50)	0.26 (0.06, 1.09)	–	0.02 (0.01, 0.07)	0.04 (0.01, 0.11)
	CZP	0.05 (0.01, 0.62)	0.18 (0.01, 1.97)	0.09 (0.01, 0.84)	0.18 (0.01, 2.05)	0.03 (0.01, 0.34)	CZP	–	–	–	–	–	–	–	–	–
	CZP + MTX	0.21 (0.04, 1.23)	0.70 (0.25, 2.05)	0.37 (0.10, 1.43)	0.73 (0.26, 2.08)	0.13 (0.06, 0.30)	3.97 (0.34, 133)	CZP + MTX	–	–	–	–	–	–	–	–
	ETN	0.49 (0.09, 2.34)	1.62 (0.61, 4.06)	0.85 (0.25, 2.53)	1.65 (0.63, 4.06)	0.31 (0.15, 0.58)	9.03 (0.86, 276)	2.29 (0.75, 6.36)	ETN	0.57 (0.12, 2.53)	0.57 (0.03, 9.03)	0.34 (0.04, 3.00)	0.51 (0.04, 5.53)	–	0.03 (0.01, 0.32)	0.07 (0.01, 0.64)
	ETN + MTX	0.31 (0.06, 1.49)	1.03 (0.44, 2.32)	0.54 (0.16, 1.63)	1.06 (0.46, 2.32)	0.20 (0.11, 0.31)	5.75 (0.55, 179)	1.46 (0.53, 3.71)	0.64 (0.36, 1.15)	ETN + MTX	1.00 (0.09, 10.2)	0.61 (0.11, 3.06)	0.90 (0.13, 5.87)	–	0.05 (0.01, 0.34)	0.13 (0.02, 0.65)
	GOL	0.59 (0.07, 4.71)	1.97 (0.44, 8.94)	1.04 (0.18, 5.81)	2.01 (0.47, 9.03)	0.37 (0.10, 1.42)	11.4 (0.75, 424)	2.80 (0.57, 13.3)	1.22 (0.28, 5.75)	1.90 (0.47, 8.41)	GOL	0.61 (0.09, 4.48)	0.90 (0.08, 11.7)	–	0.05 (0.01, 0.66)	0.13 (0.01, 1.36)
	GOL + MTX	0.33 (0.05, 1.82)	1.08 (0.40, 2.97)	0.57 (0.15, 2.10)	1.12 (0.41, 2.97)	0.21 (0.09, 0.43)	6.17 (0.52, 198)	1.54 (0.50, 4.57)	0.68 (0.25, 1.92)	1.05 (0.43, 2.66)	0.55 (0.15, 1.93)	GOL + MTX	1.48 (0.25, 9.30)	–	0.08 (0.01, 0.55)	0.22 (0.05, 0.98)
	IFX + MTX	0.36 (0.06, 1.86)	1.19 (0.52, 2.66)	0.62 (0.17, 2.12)	1.21 (0.51, 2.86)	0.22 (0.12, 0.41)	6.69 (0.59, 211)	1.67 (0.58, 4.66)	0.73 (0.30, 1.86)	1.14 (0.53, 2.59)	0.60 (0.13, 2.56)	1.08 (0.41, 2.86)	IFX + MTX	–	0.05 (0.01, 0.44)	0.15 (0.02, 0.86)
	PBO	3.86 (1.07, 14.6)	12.8 (4.01, 46.5)	6.69 (3.35, 14.7)	13.1 (4.14, 47.0)	2.41 (0.91, 7.10)	70.8 (9.49, 1900)	18.0 (5.10, 69.4)	7.92 (2.94, 26.1)	12.3 (4.53, 40.4)	6.49 (1.23, 37.3)	11.7 (3.46, 45.6)	10.8 (3.46, 38.8)	PBO		
	TCZ	0.39 (0.09, 1.70)	1.30 (0.50, 3.67)	0.68 (0.28, 1.75)	1.32 (0.52, 3.71)	0.24 (0.12, 0.53)	7.32 (0.77, 217)	1.82 (0.64, 5.64)	0.80 (0.34, 2.27)	1.25 (0.56, 3.25)	0.65 (0.15, 3.16)	1.19 (0.43, 3.63)	1.09 (0.44, 3.03)	0.10 (0.04, 0.24)	TCZ	2.66 (0.57, 13.5)
	TCZ + MTX	0.26 (0.05, 1.26)	0.86 (0.36, 2.12)	0.45 (0.15, 1.36)	0.88 (0.38, 2.14)	0.16 (0.09, 0.29)	4.85 (0.48, 148)	1.22 (0.45, 3.32)	0.53 (0.23, 1.35)	0.84 (0.41, 1.90)	0.44 (0.10, 1.92)	0.79 (0.31, 2.12)	0.73 (0.32, 1.79)	0.07 (0.02, 0.19)	0.67 (0.32, 1.32)	TCZ + MTX

PBO – placebo, MTX – methotrexate, IFX – infliximab, ETN – etanercept, ADA – adalimumab, GOL – golimumab, TCZ – tocilizumab, ABT – abatacept, CZP – clonazepam, cDMARDs – traditional synthetic disease modifying antirheumatic drugs, ACR – American College of Rheumatology, AEs – adverse events, SAEs – serious adverse events.

Table IV. Odds ratio estimates with 95% credible intervals of AEs and SAEs for each comparison

Endpoint		SAEs														
AEs	ABT	ABT	3.71 (0.88, 16.9)	2.39 (0.73, 8.67)	2.94 (0.66, 13.5)	2.94 (0.73, 12.3)	0.60 (0.12, 3.03)	1.82 (0.41, 8.76)	1.88 (0.45, 7.92)	2.29 (0.54, 9.49)	2.61 (0.38, 17.6)	1.31 (0.25, 6.55)	2.69 (0.63, 12.2)	2.36 (0.73, 8.41)	1.84 (0.46, 7.92)	2.12 (0.50, 9.49)
	ABT + MTX	1.77 (0.76, 4.26)	ABT + MTX	0.64 (0.24, 1.70)	0.80 (0.45, 1.28)	0.80 (0.51, 1.17)	0.16 (0.04, 0.66)	0.51 (0.24, 0.99)	0.51 (0.25, 0.92)	0.62 (0.32, 1.07)	0.68 (0.17, 2.64)	0.35 (0.14, 0.78)	0.73 (0.41, 1.25)	0.64 (0.25, 1.62)	0.50 (0.24, 0.96)	0.57 (0.30, 1.02)
	ADA	0.89 (0.48, 1.63)	0.50 (0.23, 1.05)	ADA	1.23 (0.44, 3.42)	1.25 (0.51, 2.94)	0.26 (0.08, 0.74)	0.78 (0.27, 2.25)	0.79 (0.32, 1.79)	0.96 (0.38, 2.27)	1.07 (0.23, 5.00)	0.55 (0.18, 1.67)	1.13 (0.41, 2.97)	0.99 (0.63, 1.60)	0.76 (0.32, 1.80)	0.88 (0.34, 2.25)
	ADA + MTX	1.86 (0.82, 4.48)	1.05 (0.68, 1.65)	2.10 (1.02, 4.48)	ADA + MTX	1 (0.6, 1.68)	0.21 (0.05, 0.86)	0.63 (0.29, 1.38)	0.64 (0.31, 1.27)	0.78 (0.39, 1.46)	0.87 (0.21, 3.49)	0.44 (0.17, 1.06)	0.91 (0.48, 1.77)	0.81 (0.31, 2.14)	0.62 (0.30, 1.32)	0.71 (0.36, 1.42)
	cDMARDs	2.29 (1.08, 5.10)	1.28 (0.90, 1.90)	2.59 (1.35, 5.00)	1.23 (0.85, 1.75)	cDMARDs	0.21 (0.05, 0.78)	0.63 (0.35, 1.12)	0.64 (0.38, 1.02)	0.78 (0.50, 1.14)	0.86 (0.22, 3.13)	0.44 (0.20, 0.89)	0.91 (0.59, 1.39)	0.80 (0.35, 1.88)	0.63 (0.36, 1.06)	0.71 (0.45, 1.12)
	CZP	0.92 (0.42, 1.99)	0.52 (0.24, 1.13)	1.05 (0.53, 1.97)	0.50 (0.22, 1.05)	0.40 (0.20, 0.79)	CZP	3.03 (0.72, 13.9)	3.13 (0.81, 12.4)	3.78 (0.97, 14.2)	4.31 (0.66, 25.5)	2.14 (0.45, 9.58)	4.44 (1.09, 18.2)	3.86 (1.48, 11.5)	3.03 (0.82, 10.9)	3.49 (0.89, 13.6)
	CZP + MTX	1.84 (0.81, 4.35)	1.04 (0.64, 1.68)	2.08 (1.01, 4.31)	1.00 (0.61, 1.58)	0.81 (0.58, 1.11)	1.99 (0.93, 4.39)	CZP + MTX	1.01 (0.46, 2.14)	1.22 (0.59, 2.46)	1.38 (0.34, 5.53)	0.70 (0.27, 1.75)	1.45 (0.71, 3.00)	1.28 (0.45, 3.49)	0.98 (0.45, 2.20)	1.13 (0.54, 2.39)
	ETN	1.42 (0.65, 3.16)	0.80 (0.47, 1.30)	1.60 (0.82, 3.10)	0.76 (0.45, 1.23)	0.62 (0.43, 0.87)	1.54 (0.76, 3.06)	0.77 (0.47, 1.21)	ETN	1.21 (0.76, 1.92)	1.36 (0.33, 5.31)	0.69 (0.28, 1.63)	1.43 (0.75, 2.83)	1.26 (0.57, 2.92)	0.98 (0.49, 1.97)	1.13 (0.58, 2.23)
	ETN + MTX	1.86 (0.86, 4.18)	1.05 (0.68, 1.63)	2.10 (1.08, 4.14)	1.00 (0.64, 1.54)	0.81 (0.64, 1.04)	2.01 (1.01, 4.10)	1.00 (0.68, 1.52)	1.31 (0.96, 1.86)	ETN + MTX	1.13 (0.27, 4.35)	0.57 (0.23, 1.32)	1.19 (0.66, 2.20)	1.03 (0.45, 2.51)	0.80 (0.42, 1.57)	0.92 (0.52, 1.73)
	GOL	2.23 (0.86, 5.81)	1.26 (0.64, 2.46)	2.51 (1.04, 5.99)	1.20 (0.61, 2.27)	0.97 (0.55, 1.68)	2.44 (1.00, 5.81)	1.21 (0.63, 2.27)	1.57 (0.82, 3.03)	1.20 (0.65, 2.18)	GOL	0.51 (0.15, 1.55)	1.06 (0.27, 3.90)	0.91 (0.21, 4.48)	0.72 (0.18, 2.83)	0.83 (0.21, 3.22)
	GOL + MTX	1.79 (0.79, 4.18)	1.00 (0.63, 1.62)	2.01 (0.99, 4.18)	0.96 (0.59, 1.51)	0.78 (0.58, 1.05)	1.93 (0.92, 4.10)	0.96 (0.63, 1.51)	1.26 (0.80, 2.03)	0.96 (0.66, 1.40)	0.80 (0.47, 1.40)	GOL + MTX	2.08 (0.93, 4.95)	1.80 (0.63, 5.58)	1.42 (0.58, 3.53)	1.63 (0.70, 3.86)

Table IV. Cont.

Endpoint														
SAEs														
	IFX + MTX	1.65 (0.73, 3.94)	0.94 (0.59, 1.45)	1.86 (0.90, 3.90)	0.90 (0.54, 1.39)	0.73 (0.52, 0.98)	1.79 (0.84, 3.82)	0.90 (0.57, 1.40)	1.17 (0.74, 1.88)	0.90 (0.59, 1.31)	0.75 (0.39, 1.40)	0.93 (0.59, 1.40)	IFX + MTX	0.88 (0.35, 2.25)	0.68 (0.34, 1.34)	0.78 (0.43, 1.45)
	PBO	1.86 (1.03, 3.42)	1.04 (0.57, 1.90)	2.10 (1.32, 3.25)	1.01 (0.54, 1.79)	0.81 (0.50, 1.31)	2.01 (1.25, 3.29)	1.00 (0.56, 1.80)	1.31 (0.80, 2.16)	1.00 (0.60, 1.63)	0.83 (0.40, 1.75)	1.04 (0.58, 1.82)	1.12 (0.63, 1.99)	PBO	0.77 (0.34, 1.70)	0.89 (0.36, 2.12)
	TCZ	1.51 (0.73, 3.32)	0.84 (0.52, 1.40)	1.70 (0.91, 3.19)	0.81 (0.50, 1.31)	0.65 (0.47, 0.92)	1.62 (0.86, 3.16)	0.81 (0.52, 1.31)	1.05 (0.70, 1.68)	0.80 (0.57, 1.17)	0.68 (0.36, 1.31)	0.84 (0.54, 1.32)	0.90 (0.58, 1.46)	0.81 (0.53, 1.27)	TCZ	1.15 (0.66, 2.03)
	TCZ + MTX	1.58 (0.74, 3.60)	0.89 (0.58, 1.42)	1.80 (0.91, 3.53)	0.85 (0.54, 1.32)	0.69 (0.53, 0.90)	1.72 (0.87, 3.49)	0.85 (0.58, 1.31)	1.12 (0.76, 1.73)	0.85 (0.61, 1.19)	0.71 (0.39, 1.34)	0.90 (0.60, 1.32)	0.95 (0.64, 1.46)	0.85 (0.53, 1.43)	1.06 (0.76, 1.48)	TCZ + MTX

PBO – placebo, MTX – methotrexate, IFX – infliximab, ETN – etanercept, ADA – adalimumab, GOL – golimumab, TCZ – tocilizumab, ABT – abatacept, CZP – clonazepam, cDMARDs – traditional synthetic disease modifying antirheumatic drugs, ACR – American College of Rheumatology, AEs – adverse events, SAEs – serious adverse events.

Remission

The efficacy endpoint of remission was evaluated among 11 treatments as displayed in the upper panel of Table III. It could be observed that TCZ and TCZ + MTX were significantly better than ABT + MTX (OR = 0.06, 95% CrI: 0.01–0.45; OR = 0.15, 95% CrI: 0.03–0.87), cDMARDs (OR = 0.01, 95% CrI: 0.01–0.07; OR = 0.04, 95% CrI: 0.01–0.11), ETN (OR = 0.03, 95% CrI: 0.01–0.32; OR = 0.07, 95% CrI: 0.01–0.64), ETN + MTX (OR = 0.05, 95% CrI: 0.01–0.34; OR = 0.13, 95% CrI: 0.02–0.65), GOL + MTX (OR = 0.08, 95% CrI: 0.01–0.55; OR = 0.22, 95% CrI: 0.05–0.98) and IFX + MTX (OR = 0.05, 95% CrI: 0.01–0.44; OR = 0.15, 95% CrI: 0.02–0.86) in disease remission. However, there was no particular evidence to confirm which one of TCZ and TCZ + MTX was better. ABT + MTX (OR = 0.25, 95% CrI: 0.06–0.97), ETN + MTX (OR = 0.29, 95% CrI: 0.08–0.98) and GOL + MTX (OR = 0.18, 95% CrI: 0.06–0.50) also presented greater remission of pain compared to cDMARDs. Additionally, GOL (OR = 0.05, 95% CrI: 0.01–0.66) was less efficacious than TCZ.

Adverse events (AEs)

The safety outcomes are shown in Table IV. Statistically, ABT (OR = 1.86, 95% CrI: 1.03–3.42), ADA (OR = 2.10, 95% CrI: 1.32–3.25) and CZP (OR = 2.01, 95% CrI: 1.25–3.29) presented a higher risk of AEs than PBO. ADA was more likely to cause adverse events than ADA + MTX (OR = 2.10, 95% CrI: 1.02–4.48), cDMARDs (OR = 2.59, 95% CrI: 1.35–5.00), CZP + MTX (OR = 2.08, 95% CrI: 1.01–4.31), ETN + MTX (OR = 2.10, 95% CrI: 1.08–4.14), GOL (OR = 2.51, 95% CrI: 1.04–5.99) and PBO (OR = 2.10, 95% CrI: 1.32–3.25). In comparison with ETN + MTX (OR = 2.01, 95% CrI: 1.01–4.10) and GOL (OR = 2.44, 95% CrI: 1.00–5.81) more patients taking CZP dropped out due to AEs. Moreover, the safety of cDMARDs for adverse events was superior to CZP (OR = 0.40, 95% CrI: 0.20–0.79), ETN (OR = 0.62, 95% CrI: 0.43–0.87), IFX + MTX (OR = 0.73, 95% CrI: 0.52–0.98), TCZ (OR = 0.65, 95% CrI: 0.47–0.92) and TCZ + MTX (OR = 0.69, 95% CrI: 0.53–0.90).

Serious adverse events (SAEs)

The comparison of SAEs for all the treatments is displayed in the upper panel of Table IV. CZP (OR = 3.86, 95% CrI: 1.48–11.5) presented a worse performance than PBO (OR = 0.26, 95% CrI: 0.09–0.68), INF + MTX (OR = 0.23, 95% CrI: 0.06–0.91), cDMARDs (OR = 0.21, 95% CrI: 0.05–0.78), ADA + MTX (OR = 0.21, 95% CrI: 0.05–0.86), ADA (OR = 0.26, 95% CrI: 0.08–0.74) and ABT + MTX (OR = 0.16, 95% CrI: 0.04–0.66). In contrast, ABT + MTX was more efficacious in reducing the SAEs in comparison with CZP + MTX (OR = 0.51, 95% CrI: 0.24–

0.99), ETN (OR = 0.51, 95% CrI: 0.25–0.92), GOL + MTX (OR = 0.35, 95% CrI: 0.14–0.78) and TCZ (OR = 0.50, 95% CrI: 0.24–0.96). Furthermore, cDMARDs (OR = 0.44, 95% CrI: 0.20–0.89) worked better than GOL + MTX in withdrawal due to SAEs.

Relative ranking analysis

Relative ranking of the treatments is assessed by SUCRA in Table V. Since CZP + MTX not only had high efficacy in ACR20 (83.3%), ACR50 (84.2%) and ACR70 (75.1%) but also performed well in AEs and SAEs, we recommend CZP + MTX as the optimal drug therapy. Another alternative was TCZ + MTX for the same reason. By contrast, ABT was regarded as the worst choice in treating RA because of its low probability in efficacy outcomes (ACR20: 10.8%, ACR50 = 2.4%, ACR70 = 20.0%) and safety outcomes (AEs = 14.8%, SAEs = 17.2%). Also, cDMARDs are not recommended due to their low efficacy, though their safety seemed to be superior.

Consistency test

The node-splitting method was used to evaluate the consistency level between direct and indirect evidence. *P*-values < 0.05 implied the existence of a significant inconsistency. As listed in Table VI, a significant inconsistency did exist in the analysis of remission and AEs. As for remission, obvious inconsistency was found in the comparisons between TCZ and cDMARDs ($p = 0.013$), TCZ + MTX and cDMARDs ($p = 0.015$), as well as TCZ + MTX and TCZ ($p = 0.019$). On the other hand, no consistency between ETN + MTX and cDMARDs ($p < 0.001$), TCZ and ETN + MTX ($p = 0.034$), TCZ + MTX and ETN + MTX ($p = 0.025$) was demonstrated when comparing them with AEs. The results of the consistency test are also visually presented in Figure 3 with net heat plots, which indicated the same results as in Table VI.

Publication bias

The estimate of publication bias was performed by the symmetry characteristics of the dots representing included trials with different colors in the funnel plots. According to Figure 4, all of the funnel plots were focused in the triangle funnel areas in left and right directions, which suggested that the distribution of dots verified no significant publication bias or small study effect among the trials in ACR20, ACR50, ACR70, AEs, SAEs and remission.

Evaluation of the methodological quality of eligible studies

The Jadad scale was used to appraise the methodological quality of included studies, and the scores of the Jadad scale of each individual study

Table V. Relative ranking of the treatments assessed by surface under cumulative ranking curve area

Treatments	ACR20	ACR50	ACR70	Remission	AEs	SAEs
ABT	0.108	0.239	0.200	–	0.148	0.172
ABT + MTX	0.510	0.564	0.605	0.402	0.549	0.852
ADA	0.392	0.375	0.326	0.617	0.077	0.551
ADA + MTX	0.554	0.722	0.620	0.428	0.606	0.693
cDMARDs	0.108	0.084	0.089	0.050	0.862	0.727
CZP	0.818	0.796	0.882	–	0.099	0.051
CZP + MTX	0.833	0.842	0.751	–	0.602	0.365
ETN	0.359	0.307	0.358	0.220	0.295	0.356
ETN + MTX	0.634	0.611	0.597	0.364	0.556	0.506
GOL	0.303	0.332	0.332	0.360	0.747	0.567
GOL + MTX	0.594	0.660	0.561	0.501	0.555	0.186
IFX + MTX	0.547	0.546	0.511	0.385	0.466	0.637
PBO	0.023	0.004	0.005	–	0.613	0.545
TCZ	0.532	0.609	0.470	0.890	0.352	0.346
TCZ + MTX	0.685	0.809	0.693	0.784	0.407	0.445

PBO – placebo, MTX – methotrexate, IFX – infliximab, ETN – etanercept, ADA – adalimumab, GOL – golimumab, TCZ – tocilizumab, ABT – abatacept, CZP – clonazepam, cDMARDs – traditional synthetic disease modifying antirheumatic drugs, ACR – American College of Rheumatology, AEs – adverse events, SAEs – serious adverse events.

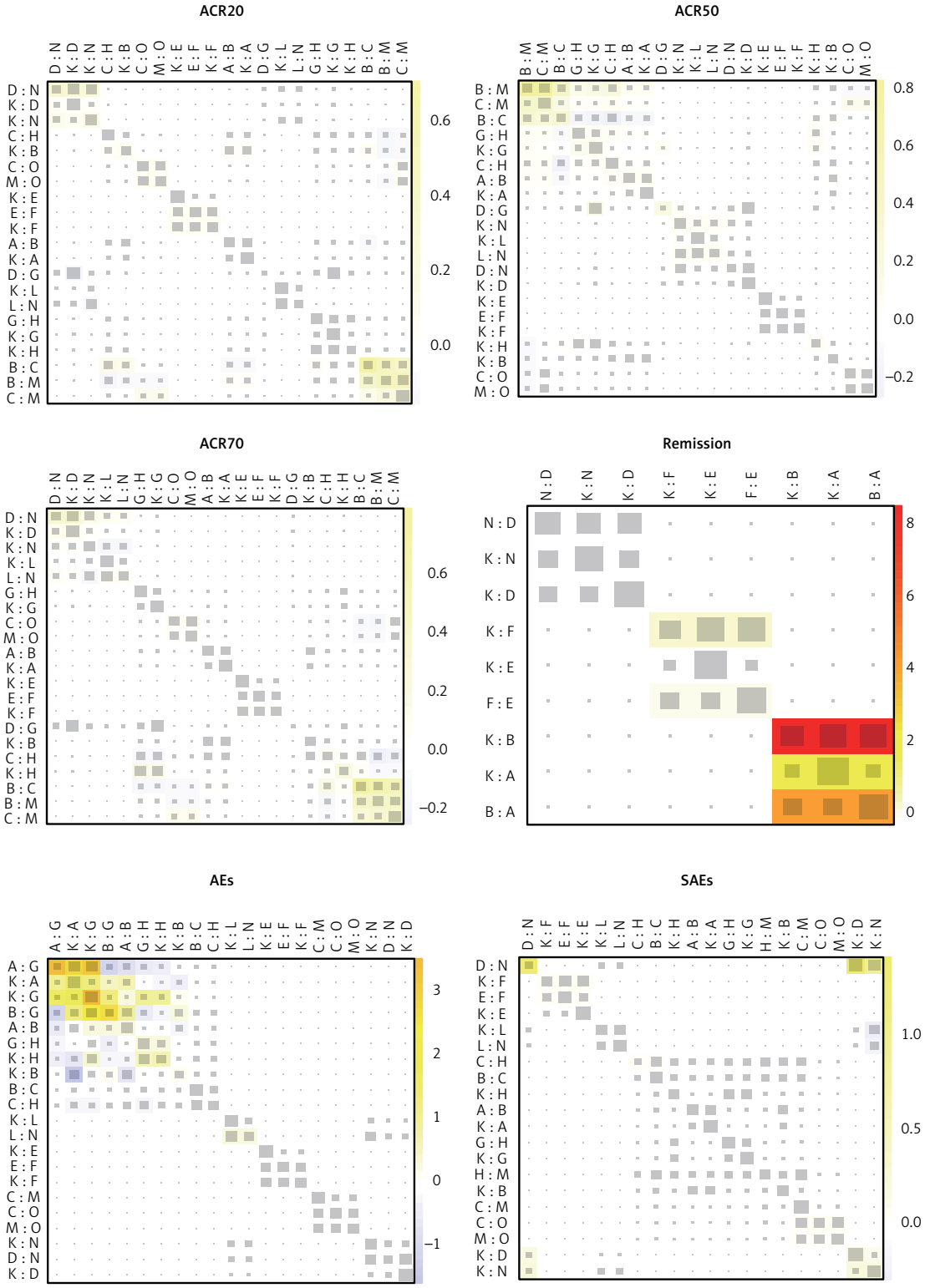


Figure 3. Results of consistency analysis by heat plot. Inconsistency between direct and indirect evidence was assessed using the net heat plots, which visually displayed the inconsistency level with different colors. The more vibrant the color was, the more serious was the indicated inconsistency

A – TCZ + MTX, B – TCZ, C – PBO, D – IFX + MTX, E – GOL + MTX, F – GOL, G – ETN + MTX, H – ETN, I – CZP + MTX, J – CZP, K – cDMARDs, L – ADA + MTX, M – ADA, N – ABT + MTX, O – ABT.

Table VI. Results of consistency analysis by node-splitting plot

Endpoint	Comparison	Direct OR (95% CI)	Indirect OR (95% CrI)	Network OR (95% CrI)	*P*-value
ACR20	ADA + MTX vs. ABT + MTX	1.10 (0.35, 3.50)	1.10 (0.48, 2.70)	1.10 (0.53, 2.10)	0.899
	cDMARDs vs. ABT + MTX	0.34 (0.17, 0.68)	0.29 (0.07, 1.10)	0.31 (0.17, 0.56)	0.819
	cDMARDs vs. ADA + MTX	0.29 (0.16, 0.52)	0.31 (0.08, 1.10)	0.29 (0.17, 0.49)	0.928
	ETN vs. cDMARDs	2.50 (1.00, 6.10)	2.40 (1.00, 5.90)	2.50 (1.40, 4.60)	0.963
	ETN + MTX vs. cDMARDs	3.80 (2.50, 5.70)	4.70 (1.30, 15.0)	3.80 (2.60, 5.70)	0.723
	ETN + MTX vs. ETN	1.50 (0.86, 2.90)	1.20 (0.27, 4.90)	1.50 (0.89, 2.70)	0.751
	IFX + MTX vs. ABT + MTX	0.72 (0.22, 2.40)	1.30 (0.53, 3.20)	1.10 (0.51, 2.30)	0.425
	IFX + MTX vs. cDMARDs	3.50 (2.00, 5.80)	3.90 (0.52, 26.0)	3.50 (2.00, 5.60)	0.933
	IFX + MTX vs. ETN + MTX	1.00 (0.15, 7.30)	0.88 (0.46, 1.70)	0.90 (0.47, 1.70)	0.871
	PBO vs. ADA	0.22 (0.12, 0.38)	0.41 (0.10, 1.70)	0.23 (0.13, 0.40)	0.423
	PBO vs. ETN	0.22 (0.10, 0.48)	0.29 (0.08, 1.10)	0.23 (0.13, 0.45)	0.691
	TCZ vs. ADA	1.90 (0.53, 6.20)	1.00 (0.34, 2.70)	1.30 (0.62, 2.90)	0.413
	TCZ vs. cDMARDs	3.40 (1.40, 8.50)	3.30 (1.30, 8.40)	3.30 (1.80, 6.40)	0.950
	TCZ vs. PBO	3.50 (1.10, 11.0)	7.70 (3.10, 18.0)	5.60 (2.80, 12.0)	0.274
	TCZ + MTX vs. cDMARDs	4.00 (2.40, 7.00)	4.80 (1.10, 21.0)	4.20 (2.50, 6.90)	0.818
	TCZ + MTX vs. TCZ	1.40 (0.60, 3.20)	0.94 (0.35, 2.90)	1.30 (0.65, 2.50)	0.574
ACR50	ADA + MTX vs. ABT + MTX	1.10 (0.42, 2.80)	1.40 (0.59, 3.00)	1.20 (0.63, 2.30)	0.741
	cDMARDs vs. ABT + MTX	0.29 (0.16, 0.56)	0.22 (0.07, 0.74)	0.26 (0.15, 0.45)	0.679
	cDMARDs vs. ADA + MTX	0.21 (0.12, 0.35)	0.24 (0.08, 0.82)	0.21 (0.13, 0.36)	0.789
	ETN vs. cDMARDs	2.20 (0.96, 4.80)	3.00 (1.40, 6.80)	2.50 (1.50, 4.50)	0.565
	ETN + MTX vs. cDMARDs	4.30 (2.90, 6.50)	2.90 (0.92, 9.20)	4.10 (2.80, 6.20)	0.520
	ETN + MTX vs. ETN	1.50 (0.89, 2.60)	1.80 (0.45, 7.00)	1.60 (0.97, 2.60)	0.834
	IFX + MTX vs. ABT + MTX	0.88 (0.30, 2.50)	1.10 (0.45, 2.40)	0.98 (0.51, 1.90)	0.776
	IFX + MTX vs. cDMARDs	3.60 (2.10, 6.00)	5.80 (0.84, 41.0)	3.80 (2.40, 6.00)	0.630
	IFX + MTX vs. ETN + MTX	1.40 (0.24, 9.40)	0.87 (0.47, 1.60)	0.93 (0.52, 1.60)	0.606
	PBO vs. ADA	0.17 (0.09, 0.30)	0.41 (0.10, 1.40)	0.19 (0.11, 0.32)	0.223
	PBO vs. ETN	0.21 (0.10, 0.47)	0.20 (0.06, 0.64)	0.21 (0.10, 0.40)	0.920
	TCZ vs. ADA	2.40 (0.83, 6.90)	0.98 (0.37, 2.60)	1.50 (0.71, 3.00)	0.199
	TCZ vs. cDMARDs	3.50 (1.50, 8.30)	4.40 (1.90, 9.80)	4.10 (2.30, 7.40)	0.710
	TCZ vs. PBO	5.00 (1.90, 14.0)	9.80 (4.40, 22.0)	7.70 (4.00, 15.0)	0.299
	TCZ + MTX vs. cDMARDs	4.60 (3.00, 7.20)	9.10 (2.70, 33.0)	5.30 (3.40, 8.30)	0.299
	TCZ + MTX vs. TCZ	1.60 (0.84, 2.90)	0.73 (0.29, 1.90)	1.30 (0.71, 2.30)	0.166
ACR70	ADA + MTX vs. ABT + MTX	0.95 (0.27, 2.90)	1.10 (0.39, 3.20)	1.00 (0.46, 2.20)	0.800
	cDMARDs vs. ABT + MTX	0.19 (0.08, 0.42)	0.16 (0.04, 0.69)	0.19 (0.09, 0.37)	0.809
	cDMARDs vs. ADA + MTX	0.18 (0.08, 0.36)	0.22 (0.05, 0.92)	0.18 (0.09, 0.35)	0.755
	ETN vs. cDMARDs	2.60 (1.00, 8.00)	4.40 (1.70, 13.0)	3.30 (1.70, 6.60)	0.463
	ETN + MTX vs. cDMARDs	5.20 (3.20, 9.50)	6.80 (1.10, 46.0)	5.00 (3.20, 8.90)	0.770
	ETN + MTX vs. ETN	1.60 (0.83, 2.80)	0.79 (0.07, 6.90)	1.60 (0.88, 2.70)	0.548
	IFX + MTX vs. ABT + MTX	1.20 (0.32, 4.30)	0.58 (0.21, 1.60)	0.85 (0.38, 1.90)	0.355
	IFX + MTX vs. cDMARDs	3.90 (2.10, 7.70)	5.30 (0.13, 230)	4.50 (2.40, 8.70)	0.856
	IFX + MTX vs. ETN + MTX	1.0 0(0.02, 33.0)	0.86 (0.38, 2.00)	0.89 (0.40, 1.80)	0.901
	PBO vs. ADA	0.12 (0.05, 0.27)	0.31 (0.07, 1.40)	0.15 (0.08, 0.29)	0.238

Table VI. Cont.

Endpoint	Comparison	Direct OR (95% CI)	Indirect OR (95% CrI)	Network OR (95% CrI)	*P*-value
	PBO vs. ETN	0.08 (0.01, 0.38)	0.17 (0.04, 0.64)	0.13 (0.04, 0.34)	0.478
	TCZ vs. ADA	2.20 (0.70, 7.10)	0.85 (0.22, 3.60)	1.50 (0.58, 3.60)	0.299
	TCZ vs. cDMARDs	3.20 (1.10, 8.80)	5.40 (1.50, 18.0)	4.10 (1.90, 8.40)	0.494
	TCZ vs. PBO	4.80 (1.50, 15.0)	18.0 (6.30, 59.0)	10.0 (4.10, 25.0)	0.085
	TCZ + MTX vs. cDMARDs	5.60 (3.30, 9.60)	7.70 (1.70, 30.0)	6.10 (3.50, 11.0)	0.661
	TCZ + MTX vs. TCZ	1.60 (0.83, 3.50)	0.90 (0.30, 3.00)	1.50 (0.73, 3.20)	0.396
Remission	IFX + MTX vs. ABT + MTX	1.10 (0.10, 11.0)	0.66 (0.04, 13.0)	0.94 (0.16, 5.00)	0.749
	TCZ vs. cDMARDs	360 (73.0,1800)	12.0 (2.60, 71.0)	70.0 (13.0,380)	0.013
	TCZ + MTX vs. cDMARDs	15.0 (7.10, 37.0)	430 (47.0, 3500)	26.0 (9.10, 78.0)	0.015
	TCZ + MTX vs. TCZ	1.30 (0.34, 4.60)	0.04 (0.01, 0.29)	0.38 (0.07, 1.70)	0.019
AEs	ADA + MTX vs. ABT + MTX	0.84 (0.41, 1.60)	1.00 (0.57, 1.80)	0.95 (0.60, 1.50)	0.628
	cDMARDs vs. ABT + MTX	0.83 (0.53, 1.30)	0.65 (0.30, 1.50)	0.77 (0.53, 1.10)	0.611
	cDMARDs vs. ADA + MTX	0.78 (0.50, 1.20)	0.96 (0.42, 2.20)	0.81 (0.57, 1.20)	0.635
	ETN vs. cDMARDs	2.00 (1.20, 3.50)	1.30 (0.85, 2.20)	1.60 (1.20, 2.40)	0.236
	ETN + MTX vs. cDMARDs	1.00 (0.79, 1.30)	2.70 (1.70, 4.30)	1.20 (0.97, 1.60)	< 0.001
	ETN + MTX vs. ETN	0.86 (0.55, 1.20)	0.47 (0.24, 0.93)	0.77 (0.53, 1.10)	0.154
	IFX + MTX vs. ABT + MTX	1.20 (0.58, 2.30)	0.99 (0.56, 1.80)	1.10 (0.67, 1.70)	0.679
	PBO vs. ETN	0.76 (0.37, 1.50)	0.76 (0.35, 1.50)	0.77 (0.45, 1.20)	0.996
	TCZ vs. cDMARDs	1.60 (0.92, 2.70)	1.40 (0.83, 2.20)	1.50 (1.10, 2.10)	0.708
	TCZ vs. ETN + MTX	0.68 (0.36, 1.30)	1.50 (0.97, 2.40)	1.20 (0.85, 1.80)	0.034
	TCZ vs. PBO	1.20 (0.75, 2.20)	1.20 (0.51, 2.80)	1.20 (0.79, 2.00)	0.996
	TCZ + MTX vs. cDMARDs	1.60 (1.20, 2.10)	0.94 (0.54, 1.60)	1.40 (1.10, 1.80)	0.093
	TCZ + MTX vs. ETN + MTX	0.61 (0.30, 1.10)	1.40 (0.99, 2.00)	1.20 (0.84, 1.60)	0.025
	TCZ + MTX vs. TCZ	0.86 (0.58, 1.30)	1.00 (0.53, 1.90)	0.95 (0.68, 1.30)	0.619
SAEs	ADA + MTX vs. ABT + MTX	1.20 (0.58, 2.40)	1.30 (0.61, 3.70)	1.20 (0.77, 2.20)	0.919
	cDMARDs vs. ABT + MTX	1.30 (0.80, 2.30)	1.20 (0.42, 3.00)	1.20 (0.83, 1.90)	0.885
	cDMARDs vs. ADA + MTX	0.97 (0.45, 1.90)	1.00 (0.45, 2.60)	0.99 (0.59, 1.70)	0.936
	ETN vs. ADA	1.30 (0.32, 4.30)	1.40 (0.43, 4.70)	1.30 (0.53, 3.40)	0.904
	ETN vs. cDMARDs	1.70 (0.92, 3.60)	1.40 (0.55, 4.00)	1.60 (0.97, 2.7)	0.760
	ETN + MTX vs. cDMARDs	1.30 (0.88, 2.20)	1.70 (0.26,11.0)	1.30 (0.88,2.10)	0.829
	ETN + MTX vs. ETN	0.81 (0.52, 1.30)	0.82 (0.18, 4.60)	0.82 (0.50, 1.30)	1.000
	IFX + MTX vs. ABT + MTX	2.40 (0.96, 6.60)	1.00 (0.56, 2.00)	1.30 (0.82, 2.40)	0.145
	IFX + MTX vs. ETN + MTX	1.30 (0.50, 3.80)	1.30 (0.34, 4.90)	1.30 (0.61, 3.30)	0.989
	PBO vs. ADA	1.00 (0.62, 1.70)	0.90 (0.16, 5.00)	1.00 (0.61, 1.50)	0.875
	PBO vs. ETN	0.61 (0.07, 4.30)	0.82 (0.31, 2.10)	0.76 (0.28, 1.70)	0.780
	TCZ vs. cDMARDs	1.70 (0.81,3.50)	1.40 (0.55,4.40)	1.60 (0.93,2.80)	0.839
	TCZ vs. PBO	0.85 (0.39, 1.80)	0.91 (0.37, 2.30)	0.88 (0.48, 1.50)	0.910
	TCZ + MTX vs. cDMARDs	1.40 (0.87, 2.40)	1.50 (0.35, 6.30)	1.40 (0.90, 2.20)	0.934

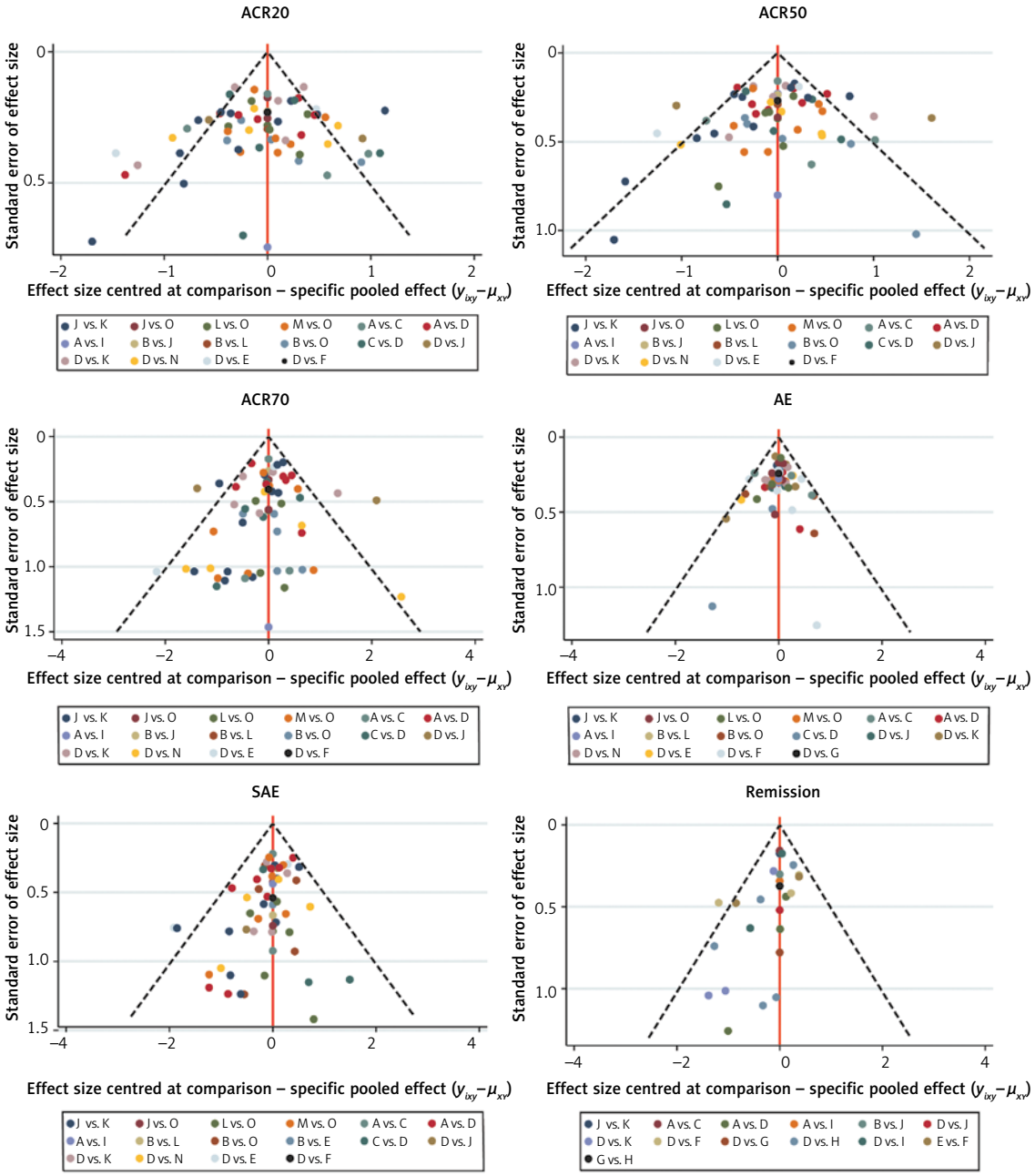
PBO – placebo, MTX – methotrexate, IFX – infliximab, ETN – etanercept, ADA – adalimumab, GOL – golimumab, TCZ – tocilizumab, ABT – abatacept, CZP – clonazepam, cDMARDs – traditional synthetic disease modifying antirheumatic drugs, ACR – American College of Rheumatology, AEs: adverse events, SAEs – serious adverse events.

are shown in Table VII. As shown in Table VII, most scores are greater than 4, which indicates that those included studies are of high quality.

Discussion

Based on the data and information of included RCTs, our study aims to evaluate the efficacy and safety of 15 drug therapies for RA patients. All available direct and indirect evidence of various treatment options was analyzed and compared simultaneously by NMA, which has a great advantage over traditional MA and makes up for the lack of head-to-head comparisons [80]. Therefore, our studies are much more reliable than the other MAs or NMAs. Moreover, it is more reasonable to select 4 efficacy and 2 safety endpoints as the evaluation indexes. Although there are also some NMA studies on this topic, they mostly include two or three outcomes to be compared. For example, some researchers only select ACR20 as the efficacy outcome and AEs as the safety outcome [1], which is not comprehensive enough.

After a systematic analysis of 15 therapies for patients with RA from 56 RCTs, we prefer to rec-



A – ABT–MTX, B – ADA, C – ADA–MTX, D – cDMARDs, E – ETN, F – ETN–MTX, G – GOL, H – GOL + MTX, I – IFX–MTX, J – TCZ, K – TCZ–MTX, L – ABT, M – CZP, N – CZP–MTX, O – PBO

Figure 4. Publication bias of different outcomes

Table VII. Jadad scale of 67 included studies

Author, year	Randomized	Blinded	Withdrawal
Abe *et al.*, 2006	2	2	0
Bae *et al.*, 2013	2	0	0
Kim *et al.*, 2012	2	0	1
Combe *et al.*, 2006	2	2	1
Combe *et al.*, 2016	2	2	1
Dougados *et al.*, 2013	2	2	1
Kameda *et al.*, 2014	2	0	0
Jobanputra *et al.*, 2012	2	0	1
Kay *et al.*, 2008	2	2	0
Kim *et al.*, 2007	2	2	1
Kremer *et al.*, 2011	2	2	1
Kremer *et al.*, 2006	2	2	0
Lan *et al.*, 2004	2	2	0
Mathias *et al.*, 2000	2	2	0
Moreland *et al.*, 1999	2	2	1
Miyasaka *et al.*, 2008	2	2	1
Nishimoto *et al.*, 2009	2	2	1
O'Dell *et al.*, 2013	2	2	1
O'Dell *et al.*, 2012	2	2	1
Nishimoto *et al.*, 2007	2	1	1
Tanake *et al.*, 2016	2	2	0
Schiff *et al.*, 2008	2	2	0
Van Riel *et al.*, 2006	2	0	0
Van Riel *et al.*, 2008	2	0	1
Van Vollenhoven *et al.*, 2011	2	2	0
Weinblatt *et al.*, 2003	2	2	1
Weinblatt *et al.*, 2006	2	2	1
Westhovens *et al.*, 2006	2	1	0
Zhang *et al.*, 2006	2	2	1
Keystone *et al.*, 2012	2	2	1
Smolen *et al.*, 2009	2	2	1
Smolen *et al.*, 2008	2	2	1
Gabay *et al.*, 2012	2	2	0
Genovese *et al.*, 2008	2	2	1
Yamamoto *et al.*, 2014	2	2	1
Schiff *et al.*, 2014	2	1	0
Weinblatt *et al.*, 2012	2	2	1
Weinblatt *et al.*, 2003	2	2	1
Fleischmann *et al.*, 2012	2	2	1
Feischmann *et al.*, 2009	2	2	1
Choy *et al.*, 2012	2	2	1

Table VII. Cont.

Author, year	Randomized	Blinded	Withdrawal
Keystone *et al.*, 2009	2	2	0
Chen *et al.*, 2009	2	2	0
Keystone *et al.*, 2008	2	2	1
Maini *et al.*, 2006	2	2	1
Maini *et al.*, 1999	2	2	1
Vandeputte *et al.*, 2004	2	2	1
Vandeputte *et al.*, 2003	2	2	1
Klareskog *et al.*, 2004	2	2	0
Lipsky *et al.*, 2000	2	0	0
Kremer *et al.*, 2003	2	2	0
Chen *et al.*, 2016	2	2	1
Fleischmann *et al.*, 2014	2	2	0
Machado *et al.*, 2014	2	0	0
Kivitz *et al.*, 2014	2	2	1
Kivitz *et al.*, 2013	2	2	1
Hobbs *et al.*, 2015	2	2	0
Li *et al.*, 2015	2	2	1
Conaghan *et al.*, 2013	2	2	1
Keystome *et al.*, 2004	2	2	1
Defilippis *et al.*, 2006	2	2	0
Weinbaltt *et al.*, 2003	2	2	1
Weinbaltt *et al.*, 1999	2	2	1
Smolen *et al.*, 2011	2	2	1
Strand *et al.*, 2011	2	2	1
Moreland *et al.*, 1997	2	2	1
Furst *et al.*, 2003	2	2	1

Each question was to be answered with either a yes or a no. Each yes would score a single point, each no zero points. Additional points were given if: The method of randomization was described in the paper, and that method was appropriate (1 extra point in the randomization part); the method of blinding was described, and it was appropriate (1 extra point in the blinding part).

ommend CZP + MTX as the best treatment due to it having the highest rankings in ACR20 (83.3%) and ACR50 (84.2%) response rates and relatively low risk of adverse events. TCZ + MTX is recommended as an alternative treatment due to its good performance in all efficacy and safety outcomes. ABT is considered as the worst therapy, and cDMARDs is also not recommended though its safety seemed to be superior.

Interestingly, among these 15 drug therapies, six are biologics and another six are different combinations of MTX and biologics, including comparisons between ABT and ABT + MTX, ADA and ADA + MTX, CZP and CZP + MTX, ETN and ETN + MTX, GOL and GOL + MTX as well as TCZ and TCZ + MTX. It is easy to find that in most cases the efficacy and safety of a biological agent plus MTX are superior to the corresponding biologic agent alone. For example, the SUCRAs of efficacy and safety outcomes for ABT are as follows: 10.8% (ACR20), 23.9% (ACR50), 20% (ACR70), 14.8% (AEs) and 17.2% (SAEs). By contrast, ABT + MTX is more efficacious and safer with corresponding SUCRAs of 51%, 56.4%, 60.5%, 54.9% and 85.2%. Previous researchers have also conducted direct comparisons between biologic monotherapy and a biological agent combined with MTX. For instance, Klareskog *et al.* demonstrated that the proportions of RA patients achieving ACR20, ACR50 and ACR70 were higher under the treatment of ETN + MTX than the

ETN monotherapy. At week 52, about 85%, 69%, 43% and 35% of patients in the ETN + MTX group achieved ACR20, ACR50, ACR70 and remission compared with 76%, 48%, 24% and 16% in the ETN groups [81], which is in line with our results.

However, a closer observation reveals that there is an exception. GOL + MTX performs better in all efficacy outcomes than GOL as the other treatments of a biologic agent plus MTX, while it performed worse in AEs and SAEs. There are also studies which presented a different conclusion. Some studies published before presented no difference between two kinds of treatment groups. Patients with RA treated with ETN and those treated with ETN + MTX were similar in ACR20, ACR50 and ACR70 (71.0% vs. 67.1%, 41.9% vs. 40.1% and 17.4% vs. 18.4%, respectively). The rates of adverse events and serious adverse events were also similar [82]. Maini *et al.* arrived at the same conclusion in the comparison between TCZ + MTX and TCZ [83]. Thus, further research should be conducted to estimate whether MTX benefits biologic monotherapy or not.

Although we have made the study as comprehensive as possible, there are still some limitations. Firstly, despite the fact that the inclusion trials were all RCTs, the results of efficacy and safety comparisons among 15 drug therapies still showed some statistical inconsistency. Perhaps the RCTs with contradictions between direct and indirect evidence should be reconsidered. Secondly, though disease durations of these interventions ranged from 14 weeks to 54 weeks, 16 of them only had a follow-up time of less than 20 weeks. A short duration is not enough to judge the safety of treatment [1]. Thirdly, medication dose, treatment cost, patient compliance and other influential factors also affected trial homogeneity. To some extent, the improvement in patients with RA is related to the dose of drugs, which was neglected in this study [83]. Last but not least, different RCTs included in our research had different definitions of safety outcomes. There is still a shortage of clear definition of AEs and SAEs.

In conclusion, we regard CZP + MTX as the optimal choice for RA patients in clinical practice and TCZ + MTX as an alternative treatment. Conversely, both ABT and cDMARDs are not recommended. It is necessary to conduct long-term studies on patients with RA in order to provide a more complete assessment of diverse treatments and make a more judicious choice in clinical practice. In other words, we ought not only take into account clinical parameters such as ACR response rates and safety outcomes, but should also consider medication dose, treatment cost, patient compliance and so on. All efforts should be made to improve the life quality and health standard for patients with RA.

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Conflict of interest

The authors declare no conflict of interest.

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