A comparison of discontinuation rates of tofacitinib and biologic disease-modifying anti-rheumatic drugs in rheumatoid arthritis: a systematic review and Bayesian network meta-analysis regression

J.S.-K. Park[1], M.-Y. Lee[1], E.-J. Jang[2], H.-L Kim[3], D.-M. Ha[1], E.-K. Lee[1]

[1]School of Pharmacy, Sungkyunkwan University, Suwon, Gyeonggi-do, South Korea;
[2]Department of Information Statistics, Andong National University, Gyeongsangbuk-do, South Korea;
[3]College of Pharmacy, Sahmyook University, Seoul, South Korea.

Sun-Kyeong Park, BA
Min-Young Lee, PhD
Eun Jin Jang, PhD
Hye-Lin Kim, PhD
Dong Mun Ha, PhD
Eui-Kyung Lee, PhD

Please address correspondence and reprint requests to:
Dr Eui-Kyung Lee,
School of Pharmacy,
Sungkyunkwan University,
300 Cheonchoen-dong,
Jangan-gu, Suwon,
Gyeonggi-do 440-746, South Korea.
E-mail: ekyung@skku.edu

Received on August 31, 2016; accepted in revised form on November 21, 2016.

Clin Exp Rheumatol 2017; 35: 689-699.

Key words: rheumatoid arthritis, discontinuation, Bayesian network meta-analysis, tofacitinib

Funding: this research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors.

Competing interests: none declared.

ABSTRACT

Objective. *The purpose of this study was to compare the discontinuation rates of tofacitinib and biologics (tumour necrosis factor inhibitors (TNFi), abatacept, rituximab, and tocilizumab) in rheumatoid arthritis (RA) patients considering inadequate responses (IRs) to previous treatment(s).*

Methods. *Randomised controlled trials of tofacitinib and biologics – reporting at least one total discontinuation, discontinuation due to lack of efficacy (LOE), and discontinuation due to adverse events (AEs) – were identified through systematic review. The analyses were conducted for patients with IRs to conventional synthetic disease-modifying anti-rheumatic drugs (cDMARDs) and for patients with biologics-IR, separately. Bayesian network meta-analysis was used to estimate rate ratio (RR) of a biologic relative to tofacitinib with 95% credible interval (CrI), and probability of RR being <1 (P[RR<1]).*

Results. *The analyses of 34 studies showed no significant differences in discontinuation rates between tofacitinib and biologics in the cDMARDs-IR group. In the biologics-IR group, however, TNFi (RR 0.17, 95% CrI 0.01–3.61, P[RR<1] 92.0%) and rituximab (RR 0.20, 95% CrI 0.01–2.91, P[RR<1] 92.3%) showed significantly lower total discontinuation rates than tofacitinib did. Despite the difference, discontinuation cases owing to LOE and AEs revealed that tofacitinib was comparable to the biologics.*

Conclusion. *The comparability of discontinuation rate between tofacitinib and biologics was different based on previous treatments and discontinuation reasons: LOE, AEs, and total (due to other reasons). Therefore, those factors need to be considered to decide the optimal treatment strategy.*

Introduction

The primary aim of rheumatoid arthritis (RA) treatment is to maximise long-term life with health quality through control of symptoms and prevention of disease progression or structural damage (1). Considering the chronic nature of RA, long-term use of treatment is important without discontinuation (2). Nonetheless, most treatments including biologics are generally discontinued due to lack of efficacy (LOE) and/or adverse events (AEs), even though the proportions are somewhat different among them (3). Therefore, the drug discontinuation rate can be an appropriate measurement of efficacy, safety, and tolerability in RA (4).

Generally, patients who are diagnosed as RA commence treatment with conventional synthetic disease-modifying anti-rheumatic drugs (cDMARDs) and who experience inadequate responses (IRs) to cDMARDs can be treated with biologics including tumour necrosis factor inhibitor (TNFi) biologics and non-TNFi biologics (abatacept, rituximab, and tocilizumab). Lately, tofacitinib, which had been restricted to patients with biologics-IR (5), can be now considered as the first treatment for patients with cDMARDs-IR as the American College of Rheumatology (ACR) guideline was revised in 2015 (6). Rheumatologists and patients face a variety of alternatives with the introduction of tofacitinib – oral, synthetic DMARD designed to target Janus kinases. However, there are no head-to-head trials or studies comparing the

discontinuation rates of tofacitinib relative to comparable biologics.

Bayesian network meta-analysis (NMA) can be a feasible alternative to simultaneous comparison of interesting treatments without head-to-head trials (7, 8). NMA is a method of estimating the effects of multiple interventions including both indirect and direct comparisons (7), and the Bayesian approach allows for calculation of the probability that a given treatment is the most efficient; this metric could be useful for clinicians and decision makers (8).

This study aimed to compare the discontinuation rates of tofacitinib with biologics using Bayesian NMA based on randomised controlled trials (RCTs) identified in a systematic review. Tofacitinib and biologics are available to both patients with cDMARDs-IR and biologics-IR, nonetheless patients with failed biologics should not be pooled with biologic-naïve patients when comparing treatments by meta-analysis due to the comparability problem (9, 10). Accordingly, we separated the patients by previous treatment(s): cDMARDs and biologics.

Methods

The literature search strategy

We carried out a systematic review to identify relevant published RCTs, which evaluated tofacitinib or biologics to treat RA patients with IRs to cDMARDs or biologics. MEDLINE and the Cochrane Library were accessed on 24 December 2015. The strategy involved the use of keywords or medical subject headings (MeSHs) relevant to the disease term with the drug name; tofacitinib, TNFi biologics (including adalimumab, certolizumab, etanercept, golimumab, infliximab), abatacept, rituximab, and tocilizumab. The search was limited to human RCTs published in English.

Study selection and quality assessment

Two independent investigators assessed the found articles for compatibility, and inconsistencies were resolved by a third investigator. Inclusion/exclusion through titles and abstracts was performed, and the remaining studies were further screened using the full-text articles whether they met the following inclusion criteria: full published RCTs with (1) minimum duration of 12 weeks in adults with RA; (2) tofacitinib or biologics in comparison with each other or a placebo in combination with cDMARDs (10); (3) RA patients showing failure with cDMARDs or biologics; (4) at least one of the outcomes of interest: total discontinuation, discontinuation due to LOE, discontinuation due to AEs; (5) the use of maintenance doses (treatment agent, dose, and cycle) recommended by ACR (http://www.rheumatology.org/I-Am-A/Patient-Caregiver/Treatments). In case of abatacept and certolizumab, the licensed dose was applied due to the absence of a recommendation: adalimumab, 40 mg, 2 weeks; certolizumab, 200 mg, 2 weeks or 400 mg, 4 weeks; etanercept, 25 mg, twice a week or 50 mg, 1 week; golimumab, 50 mg, 4 weeks; infliximab, 3 mg/kg, week 0/2/6 and then every 8 weeks; abatacept, 10 mg/kg, 4 weeks; rituximab, 2 × 1000 mg, 2 weeks; and tocilizumab, 8 mg/kg, 4 weeks. Studies that combined the trial population with a failure history of cDMARDs and biologics were excluded.

Quality assessment was performed for each identified study using Cochrane's Risk of Bias by two independent reviewers and a third investigator for discrepancies.

Data extraction

In this study, discontinuation was explored by reason (LOE and AEs) and by total score, which was the main parameter of interest. The discontinuation rate and rate ratio (RR) for each biologic relative to tofacitinib were measured for the three parameters. The outcomes of interest were extracted on the number of discontinuation events by reason with the follow-up period for use of the discontinuation rate per 100 patient-months because of the differences in follow-up periods between trials. In some tofacitinib trials (11-13), the number of patients with discontinuation events was hard to extract exactly due to study design (all patients in the placebo group changed treatment to tofacitinib at 6 months and the outcomes were presented at the time point of 12 months). Therefore, we supposed that all of events for a placebo occurred before 6 months, the period of placebo administration. Discontinuation due to AEs for a placebo was extracted at 3 months using published available safety data. Additionally, details for ascertaining the similarity between studies were extracted on study population characteristics such as age, concomitant drug(s), and baseline health assessment questionnaire (HAQ).

We pooled TNFi biologics into one treatment group (14), based on the assumption that the efficacy of TNFi biologics is similar. This method was on the basis of several studies that demonstrated similar efficacy of adalimumab, etanercept, and infliximab (15, 16), and nonsignificant differences in ACR 50/70 between certolizumab and other TNFi biologics (17). As a result, we determined the comparative discontinuation rate of tofacitinib, TNFi biologics, abatacept, rituximab, and tocilizumab.

Statistical analysis: Bayesian NMA

The Bayesian NMA was conducted to simultaneously compare tofacitinib and biologics for each outcome. The Bayesian approach estimates a posterior probability distribution through a combination of a prior distribution with likelihood distribution from the observed data. For Bayesian NMA, a Poisson likelihood and a log link were used, due to data on counts over a certain varying time period between each trial (18). To account for the heterogeneity between RCTs, the Bayesian random effects model was used (8). All models were fitted in WinBUGs 1.4.3 (Medical Research Council Biostatistics Unit, Cambridge, UK) using Markov Chain Monte Carlo (MCMC) algorithms. Two chains were employed for evaluating MCMC convergence, which was verified using the Gelman-Rubin statistics. Fifty thousand iterations were performed for each chain. The first 20,000 iterations were discarded to eliminate the initial value effect, and the remaining 80,000 values were used to estimate the posterior distribution. When the assumption of autocorrelation of MCMC samples was not satisfied, the proper thinning intervals were used.

Due to a skewed posterior probabil-

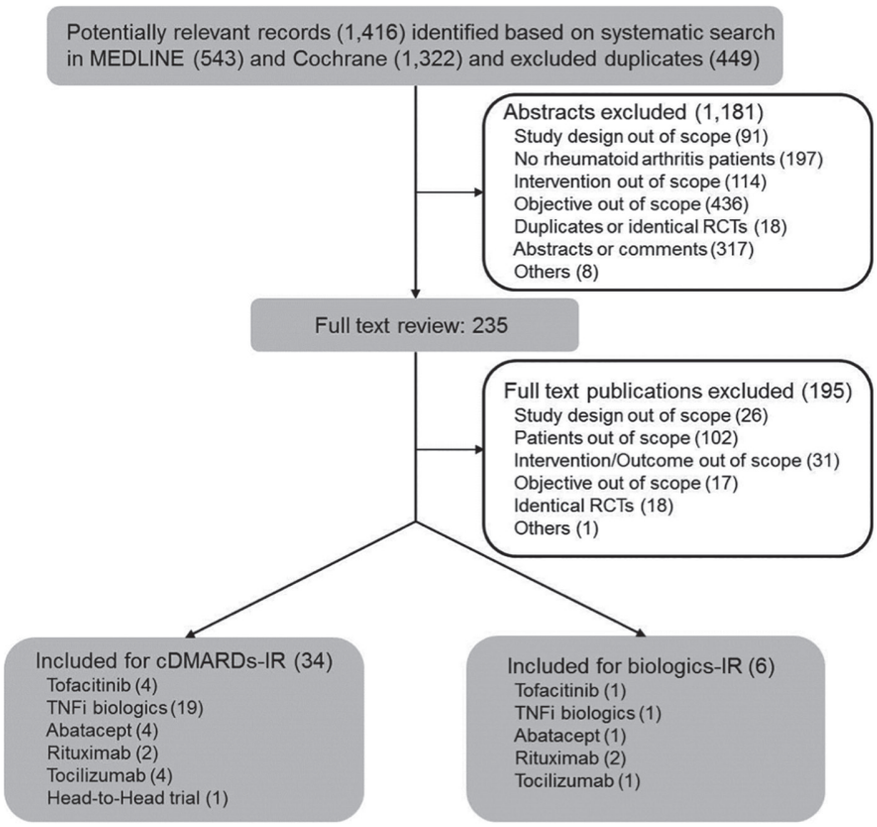

Fig. 1. Selection of randomised controlled trials included in the Bayesian network meta-analysis.

ity distribution, the posterior median discontinuation rate per 100 patient-months (hereafter referred to as discontinuation rate per 100 patient-months) was reported with corresponding 95% credible interval (CrI). This parameter for tofacitinib and biologics was based on the baseline discontinuation rate of a placebo, which was a common comparator for the included studies except one head-to-head trial. We applied informative prior distribution using the baseline rate of placebo, which was defined as a normal distribution with an average and inverse of variance of the absolute log-rate for a placebo (18). Except for the discontinuation rate, non-informative prior distributions were used for other parameters. The probability of the best (P[best]), which means the probability of being the lowest discontinuation rate among six interventions, was calculated for each treatment. RR for each biologic relative to tofacitinib with corresponding 95% CrI was also estimated. In this study, we wanted to confirm whether the discontinuation rate of biologics is lower than that of tofacitinib with a conservative approach; thus, the probabilities were calculated as the probability of RR being <1 (P[RR<1]). P[RR<1] >90% indicates a lower discontinuation rate of a biologic than that of tofacitinib, 50% indicates a null effect between a biologic and tofacitinib, and <10% suggests that a biologic had a higher discontinuation rate than tofacitinib did (19).

For identifying the heterogeneity between trials, we calculated the standard deviation (SD) between trials. An SD close to 0 indicated small heterogeneity, whereas SD >1 was assumed to indicate substantial heterogeneity (19).

Sensitivity analysis

We conducted two sensitivity analyses on total discontinuation. Sensitivity analysis 1 was to identify the impact of clinical data. In the base case analysis, we assumed the influence of study design of tofacitinib – all patients in the placebo group changed treatment to tofacitinib at 6 months – to be equivalent; however, we considered the influence of that in the sensitivity analysis 1. Accordingly, NMA was conducted with studies excluding 3 tofacitinib trials (11-13). Secondary sensitivity analysis was performed to ascertain robustness of the methodology through setting with different priors for variances between trials. In the base case, we set uniform priors on SD between zero to two. Nonetheless, we used an alternative approach with vague Gamma prior on the precision (inverse variance) in group cDMARDs-IR. For group biologics-IR, we simply changed the SD range between zero to ten. This is because the absence of large numbers of large trials (due to the scarcity of studies in group biologics-IR) could yield a poorly identified posterior distribution of SD when the alternative approach was used (18).

Results

Systematic review results

The search identified 1,416 potentially relevant studies. Of these, 235 studies remained after 1,181 studies were excluded due to non-compliance with the inclusion criteria based on a review of titles and abstracts. After review of the remaining studies with full manuscripts, the systematic review yielded 34 studies for group cDMARDs-IR (11-13, 20-50), and six studies for group biologics-IR (51-56) (Fig. 1). Most of the selected studies utilised a combination with MTX. The average age across trials was 52.2 and 53.8, and the duration of disease was 8 and 12 years in groups cDMARDs-IR and biologics-IR, respectively (Table I). The result of quality assessment is presented in Table II. Structures for the NMA of total discontinuation are shown by group in a network diagram (Fig. 2). Five studies (25, 31, 41, 47, 49) and 1 study (31) did not report discontinuation due to LOE and AEs in group cDMARDs-IR, respectively, and 1 study (52) did not report discontinuation due to LOE in group biologics-IR.

Total discontinuation

• *Group cDMARDs-IR*

Thirty-four trials with 11,257 patients were included, with 107,990 patient-months of follow-up (Table I). The

Table I. Baseline characteristics and clinical outcomes of the included studies.

Study	Treatment	Age (years)	Disease duration (years)	Baseline HAQ score	Concomitant drug	Patients (n)	Follow-up duration (weeks)	Number of discontinuations		
								Total	LOE	AE
cDMARDs-IR										
Tofacitinib										
van der Heijde 2013 (11)	Tofacitinib	53.7	8.9	1.4	MTX	321	52 weeks	71	7	36
	Placebo	52.7	9.1	1.3	MTX	160	24 weeks	32	4	5[§]
Kremer 2012 (12)	Tofacitinib	52.0	9.0	1.4	MTX	71	24 weeks	15	1	1
	Placebo	53.0	9.2	1.2	MTX	69	24 weeks	15	5	3
Tanaka 2011 (45)	Tofacitinib	50.0	8.3	1.2	cDMARDs	27	12 weeks	4	0	4
	Placebo	50.6	8.4	1.3	cDMARDs	28	12 weeks	5	1	2
TNFi biologics										
Furst 2003 (24)	Adalimumab	55.0	9.3	1.4	cDMARDs	318	24 weeks	28	5	9
	Placebo	55.8	11.5	1.4	cDMARDs	318	24 weeks	30	14	8
Keystone 2004 (29)	Adalimumab	56.1	11.0	1.5	MTX	207	52 weeks	48	6	26
	Placebo	56.1	10.9	1.5	MTX	200	52 weeks	60	23	13
Kim 2007 (30)	Adalimumab	48.5	6.8	1.4	MTX	65	18 weeks	6	0	4
	Placebo	49.8	6.9	1.3	MTX	63	18 weeks	4	0	4
Choy 2012 (21)	Certolizumab	53.0	9.4	1.4	MTX	124	24 weeks	28	16	7
	Placebo	55.6	9.9	1.5	MTX	119	24 weeks	56	45	6
Keystone 2008 (27)	Certolizumab	51.4	6.1	1.7	MTX	393	52 weeks	138	83[§]	17
	Placebo	52.2	6.2	1.7	MTX	199	52 weeks	156	125[§]	3
Smolen 2009 (40)	Certolizumab	52.2	6.1	1.6	MTX	246	24 weeks	72	54	11
	Placebo	51.5	5.6	1.6	MTX	127	24 weeks	110	107	2
Yamamoto 2014 (48)	Certolizumab	50.6	5.6	1.7	MTX	82	24 weeks	16	12	3
	Placebo	51.9	5.8	1.8	MTX	77	24 weeks	52	47	2
Combe 2006 (22)	Etanercept	50.6	6.5	1.6	SSZ	101	104 weeks	24	6	10
	Placebo	53.3	5.6	1.6	SSZ	50	104 weeks	34	26	4
Klareskog 2004 (32)	Etanercept	52.5	6.8	NR	MTX	231	52 weeks	38	6	24
	Placebo	53.0	6.8	NR	MTX	228	52 weeks	69	21	32
Weinblatt 1999 (46)	Etanercept	48.0	13.0	1.5	MTX	59	24 weeks	2	0	2
	Placebo	53.0	13.0	1.5	MTX	30	24 weeks	6	4	1
Kay 2008 (26)	Golimumab	57.0	8.2	1.7	MTX	35	52 weeks	6	3	2
	Placebo	52.0	5.6	1.3	MTX	35	16 weeks	6	3	3
Keystone 2009 (28)	Golimumab	52.0	4.5	1.4	MTX	89	16 weeks	2	0	2
	Placebo	52.0	6.5	1.3	MTX	133	16 weeks	6	0	4
Tanaka 2012 (44)	Golimumab	50.4	8.8	1.0	MTX	86	16 weeks	5	1	4
	Placebo	51.1	8.7	1.0	MTX	88	16 weeks	4	2	1
Abe 2006 (20)	Infliximab	55.2	9.1	NR	MTX	49	14 weeks	1	0	1
	Placebo	55.1	7.5	NR	MTX	47	14 weeks	5	3	1
Kim 2013 (31)	Infliximab	49.3	7.4	1.4	MTX	69	30 weeks	12	NR	NR
	Placebo	51.4	9.8	1.4	MTX	69	30 weeks	9	NR	NR
Lipsky 2000 (35)	Infliximab	54.0	10.0	1.8	MTX	86	54 weeks	23	17	5
	Placebo	51.0	11.0	1.7	MTX	88	54 weeks	44	32	7
Maini 1998 (37)	Infliximab	58.9	12.1	2.0	MTX	15	14 weeks	0	0	0
	Placebo	48.8	7.6	2.0	MTX	14	14 weeks	8	8	0
Westhovens 2006 (47)	Infliximab	53.0	7.8	1.5	MTX	360	22 weeks	26	NR	18
	Placebo	52.0	8.4	1.5	MTX	361	22 weeks	23	NR	8
Zhang 2006 (49)	Infliximab	47.9	7.1	NR	MTX	87	18 weeks	9	NR	6
	Placebo	48.9	8.0	NR	MTX	86	18 weeks	15	NR	4
Abatacept										
Kremer 2005 (33)	Abatacept	55.8	9.7	1.0	MTX	115	52 weeks	25	13	5
	Placebo	54.7	8.9	1.0	MTX	119	52 weeks	48	30	11
Kremer 2006 (34)	Abatacept	51.5	8.5	1.7	MTX	433	52 weeks	48	13	18
	Placebo	50.4	8.9	1.7	MTX	219	52 weeks	57	40	4
Takeuchi 2013 (43)	Abatacept	53.4	7.4	1.3	MTX	61	24 weeks	1	0	0
	Placebo	53.4	7.3	1.5	MTX	66	24 weeks	9	3	2
Rituximab										
Emery 2010 (23)	Rituximab	51.3	6.6	NR	MTX	170	48 weeks	15	0	7
	Placebo	52.2	7.5	NR	MTX	172	24 weeks	13	7	2
Strand 2006 (42)	Rituximab	53.5	11.5	1.8	MTX	40	104 weeks	22	4	1
	Placebo	53.7	11.0	2.0	MTX	40	104 weeks	34	17	4

Study	Treatment	Age (years)	Disease duration (years)	Baseline HAQ score	Concomitant drug	Patients (n)	Follow-up duration (weeks)	Number of discontinuations		
								Total	LOE	AE
Tocilizumab										
Fleischmann 2013 (50)	Tocilizumab	53.4	9.3	1.5	MTX	399	52 weeks	88[§]	2	33
	Placebo	51.3	9.0	1.5	MTX	392	52 weeks	66	12	11
Genovese 2008 (25)	Tocilizumab	53.0	9.8	1.5	cDMARDs	805	16 weeks	53	NR	32
	Placebo	54.0	9.8	1.5	cDMARDs	415	16 weeks	43	NR	8
Maini 2006 (36)	Tocilizumab	50.1	10.6	NR	MTX	50	16 weeks	7	1	6
	Placebo	50.9	11.2	NR	MTX	49	16 weeks	9	6	4
Smolen 2008 (41)	Tocilizumab	50.8	7.5	1.6	MTX	205	24 weeks	14	NR	12
	Placebo	50.6	7.8	1.5	MTX	204	24 weeks	15	NR	6[§]
Tofacitnib & TNFi biologics										
van Vollenhoven 2012 (13)	Tofacitinib	53.0	7.6	1.5	MTX	204	52 weeks	54	6	24
	Adalimumab	52.5	8.1	1.5	MTX	204	52 weeks	42	6	22
	Placebo	55.5	6.9	1.5	MTX	108	24 weeks	22	6	3[§]
TNFi biologics & abatacept										
Schiff 2008 (38)	Infliximab	49.1	7.3	1.7	MTX	165	52 weeks	24	6	12
	Abatacept	49.0	7.9	1.8	MTX	156	52 weeks	17	4	5
	Placebo	49.4	8.4	1.8	MTX	110	24 weeks	3	1	1
Schiff 2014 (39)	Adalimumab	51.0	1.7	1.5	MTX	328	104 weeks	83	16	30
	Abatacept	51.4	1.9	1.5	MTX	318	104 weeks	66	19	11
Number of included patients in analysis by discontinuation reason (n)								11,257	8,596	11,119
Total patients-months by discontinuation reason								107,990	86,225	101,091
Biologics-IR										
Tofacitinib										
Burmester 2013 (51)	Tofacitinib	55.4	13.0	1.6	MTX	133	24 weeks	26	2	12
	Placebo	54.4	11.3	1.6	MTX	132	12 weeks	6	2	2
TNFi biologics										
Smolen 2009 (56)	Golimumab	55.0	9.6	1.6	cDMARDs	152	24 weeks	12	6	4
	Placebo	54.0	9.8	1.8	cDMARDs	155	24 weeks	31	11	10
Abatacept										
Genovese 2005 (54)	Abatacept	53.4	12.2	1.8	cDMARDs	258	24 weeks	35	14	9
	Placebo	52.7	11.4	1.8	cDMARDs	133	24 weeks	34	27	5
Rituximab										
Cohen 2006 (52)	Rituximab	52.2	12.1	1.9	MTX	309	24 weeks	55	NR	8
	Placebo	52.8	11.7	1.9	MTX	208	24 weeks	96	NR	2
Mease 2010 (55)	Rituximab	54	12.0	1.5	MTX	318	48 weeks	27	15[¶]	7
	Placebo	54	11.0	1.5	MTX	157	48 weeks	23	16[¶]	7
Tocilizumab										
Emery 2008 (53)	Tocilizumab	53.9	12.6	1.7	MTX	175	24 weeks	23	4	11
	Placebo	53.4	11.4	1.7	MTX	159	24 weeks	33	19	10
Number of included patients in analysis by discontinuation reason (n)								2,289	1,772	2,289
Total patient-months by discontinuation reason								14,861	12,013	14,861

HAQ: Health Assessment Questionnaire; LOE: lack of efficacy; AE: adverse event; cDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; IR: inadequate responses; MTX: methotrexate; TNF: tumour necrosis factor; SSZ: sulfasalazine; NR: not reported.
[¶]Discontinuation due to a physician and patients' decision. [§]The follow-up period is different (the following values were applied in this order: 12, 16, 16, 104, 16 and 12 weeks).

total discontinuation rate was the highest for placebo (2.75 events per 100 patient-months; 95% CrI 0.68–11.12) and lowest for abatacept (1.24 events per 100 patient-months; 95% CrI 0.29–5.24) with the highest probability of the best: 65.5% (Table III).

The estimated RR relative to tofacitinib was 0.71 for abatacept (95% CrI 0.40–1.26; P[RR<1] 88.7%). Although the result was not significant due to a lower P[RR<1] than 90%, the result marginally suggested that abatacept had a lower total discontinuation rate than tofacitinib did. The RR for rituximab was 0.99 (95% CrI 0.45–2.16) and the P[RR<1] marginally showed a null effect with tofacitinib: 51.6% of P [RR < 1].

• *Group biologics-IR*

Six randomised trials with 2,289 patients were included, with 14,861 patient-months of follow-up (Table I). The total discontinuation rate was the lowest for TNFi biologics (1.03 events per 100 patient-months; 95% CrI 0.10–10.35) with the highest P[best]: 42.9% (Table III).

The estimated RRs relative to tofacitinib were <1.0 for biologics. Especially, TNFi biologics (RR 0.17; 95% CrI 0.01-3.61; P[RR<1] 92.0%) and rituximab (RR 0.20; 95% CrI 0.01–2.91; P[RR<1] 92.3%) showed significantly lower total discontinuation rates than tofacitinib did, based on the probability (RR <1) values higher than threshold (90%).

Discontinuation due to LOE

• *Group cDMARDs-IR*

Twenty-nine randomised trials with 8,596 patients were included, with 86,225 patient-months of follow-up (Table I). The median discontinuation rate was the lowest for rituximab (0.19 events per 100 patient-months; 95% CrI 0.02–1.73; P[best] 55.6%) (Table III). Tocilizumab showed the second highest value of P[best] (0.23 events per 100 patient-months; 95% CrI 0.02-2.27; P[best] 38.9%) and the other treatments – tofacitinib, TNFi and abatacept – had similar median discontinuation rates.

The estimated RRs relative to tofacitinib were <1.0 for rituximab (RR 0.43; 95% CrI 0.09-1.66; P[RR<1] 88.5%) and tocilizumab (RR 0.53; 95% CrI 0.09–2.33; P[RR<1] 79.8%), nonetheless, no significant differences in discontinuation rates due to LOE were identified between biologics and tofacitinib according to the P[RR<1] of <90%. Moreover, TNFi biologics (RR 1.00; 95% CrI 0.45–2.28; P[RR<1], 50.3%) and abatacept (RR 1.01; 95% CrI 0.40–2.62; P[RR<1] 49.4%) showed a null effect relative to tofacitinib: P[RR<1] of ~50%.

• *Group biologics-IR*

Five randomised trials with 1,772 patients were included, with 12,013 patient-months of follow-up (Table I). The discontinuation rate due to LOE was the lowest for tocilizumab (0.25 events per 100 patient-months; 95% CrI 0.01–4.63; P[best] 42.2%) (Table III).

The estimated RRs relative to tofacitinib were <1.0 for biologics except TNFi biologics. On the basis of the P[RR<1], no significant differences in discontinuation rates due to LOE were identified between biologics and tofacitinib. Moreover, TNFi biologics (RR 1.06;

Table II. Quality assessment of included studies.

Study	Sequence generation	Allocation Concealment	Blinding	Incomplete Outcome Data	Selective Outcome Reporting	Other bias
cDMARDs-IR						
Tofacitinib						
van der Heijde 2013 (11)	Unclear	Yes	Yes	Yes	Yes	Unclear
Kremer 2012 (12)	Unclear	Unclear	Yes	Yes	Yes	Unclear
Tanaka 2011 (45)	Unclear	Unclear	Yes	Yes	Yes	Yes
TNF-α inhibitors						
Adalimumab						
Furst 2003 (24)	Unclear	Yes	Yes	Yes	Yes	Yes
Keystone 2004 (29)	Unclear	Unclear	Yes	Yes	Yes	Yes
Kim 2007 (30)	Unclear	Unclear	Yes	Yes	Yes	Yes
Certolizumab						
Choy 2012 (21)	Unclear	Unclear	Yes	Yes	Yes	Yes
Keystone 2008 (27)	Unclear	Unclear	Yes	Yes	Yes	Yes
Smolen 2009 (40)	Unclear	Unclear	Yes	Yes	Yes	Yes
Yamamoto 2014 (48)	Yes	Yes	Yes	Yes	Yes	Yes
Etanercept						
Combe 2006 (22)	Yes	Yes	Yes	Yes	Yes	Yes
Klareskog 2004 (32)	Yes	Yes	Yes	Yes	Yes	Yes
Weinblatt 1999 (46)	Unclear	Unclear	Yes	Yes	Yes	Yes
Golimumab						
Kay 2008 (26)	Unclear	Unclear	Yes	Yes	Yes	Yes
Keystone 2009 (28)	Yes	Yes	Yes	Unclear	Yes	Yes
Tanaka 2012 (44)	Unclear	Unclear	Yes	Yes	Yes	Yes
Infliximab						
Abe 2006 (20)	Unclear	Unclear	Yes	Yes	Yes	Yes
Kim 2013 (31)	Unclear	Unclear	Yes	Yes	Yes	Yes
Lipsky 2000 (35)	Yes	Yes	Yes	Yes	Yes	Yes
Maini 1998 (37)	Yes	Yes	Unclear	Yes	Yes	Yes
Westhovens 2006 (47)	Unclear	Unclear	Yes	Yes	Yes	Yes
Zhang 2006 (49)	Unclear	Unclear	Yes	Unclear	Yes	Yes
Abatacept						
Kremer 2005 (33)	Yes	Yes	Yes	Yes	Yes	Yes
Kremer 2006 (34)	Yes	Unclear	Yes	Yes	Yes	Yes
Takeuchi 2013 (43)	Unclear	Unclear	Yes	Yes	Yes	Yes
Rituximab						
Emery 2010 (23)	Unclear	Unclear	Yes	Yes	Yes	Yes
Strand 2006 (42)	Unclear	Unclear	Yes	Yes	Yes	Yes
Tocilizumab						
Fleischmann 2013 (50)	Unclear	Unclear	Yes	Yes	Yes	Yes
Genovese 2008 (25)	Unclear	Unclear	Yes	Yes	Yes	Yes
Maini 2006 (36)	Unclear	Yes	Yes	Yes	Yes	Yes
Smolen 2008 (41)	Yes	Unclear	Yes	Yes	Yes	Yes
Tofacitnib & TNF-α inhibitors						
van Vollenhoven 2012 (13)	Unclear	Yes	Yes	Yes	Yes	Unclear
TNF-αinhibitors & Abatacept						
Schiff 2008 (38)	Unclear	Unclear	Yes	Yes	Yes	Yes
Schiff 2014 (39)	Unclear	Unclear	No	Yes	Yes	Yes
Biologics-IR						
Tofacitinib						
Bernerster 2013 (51)	Yes	Yes	Yes	Yes	Yes	Yes
TNF-α inhibitors						
Smolen 2009 (56)	Yes	Yes	Yes	Yes	Yes	Unclear
Abatacept						
Genovese 2005 (54)	Yes	Yes	Yes	Yes	Yes	Unclear
Rituximab						
Cohen 2006 (52)	Unclear	Unclear	Yes	Yes	Yes	Unclear
Mease 2010 (55)	Unclear	Unclear	Yes	Yes	Yes	Unclear
Tocilizumab						
Emery 2008 (53)	Unclear	Unclear	Yes	Yes	Yes	Unclear

95% CrI 0.02-70.33; P[RR<1] 48.7%) and rituximab (RR 0.92; 95% CrI 0.01–61.86; P[RR<1] 51.8%) showed an approximate null effect relative to tofacitinib: P[RR<1] of ~50%.

Discontinuation due to AEs

• *Group cDMARDs-IR*

Thirty-three randomised trials with 11,119 patients were included, with 101,091 patient-months of follow-up (Table I). All results, except those on abatacept and rituximab, for the median discontinuation rate were higher than those for a placebo. The median discontinuation rate was the lowest for abatacept (0.47 events per 100 patient-months; 95% CrI 0.10–2.17; P[best] 54.9%) (Table III).

The estimated RRs relative to tofacitinib were <1.0 for abatacept (RR 0.61; 95% CrI 0.27-1.43; P[RR<1] 88.0%) and rituximab (RR 0.75; 95% CrI 0.19–3.03; P[RR<1] 66.2%) with P[RR<1]s lower than threshold. Contrast to that, the 8% of P[RR<1] was suggestive of a significantly higher rate of discontinuation due to AEs for tocilizumab compared to tofacitinib.

• *Group biologics-IR*

Six randomised trials with 2,289 patients were included, with 14,861 patient-months of follow-up (Table I). The discontinuation rate due to AEs was the lowest for TNFi biologics (0.28 events per 100 patient-months; 95% CrI 0.02–4.88; P[best] 53.0%), followed by abatacept, tocilizumab, a placebo, rituximab and tofacitinib (Table III).

The estimated RRs of biologics relative to tofacitinib were <1.0. Although the results of RR were not significant on the basis of the P[RR <1], the results of TNFi biologics could suggest a marginally lower discontinuation rate than tofacitinib did: P[RR<1] of ~90%.

Sensitivity analyses

In sensitivity analysis 1, tofacitinib showed the highest probability of yielding the lowest discontinuation rate (52.1%) in group cDMARDs-IR (Table IV). Overall, the tendency of RR changed to >1.0, which means that the discontinuation rate for biologics were higher than those of tofacitinib in contrast to the base case. In group biologics-IR, sensitivity analysis was not conducted due to the absence of tofacitinib trial that meets the including criteria.

In sensitivity analysis 2, the result of sensitivity analysis was consistent with the results on the base case in group cDMARDs-IR, nonetheless, the P[RR<1] was lower than in the base case in group biologics-IR (Table IV).

Discussion

We found that tofacitinib is comparable to biologics for RA patients with cDMARDs-IR. The sensitivity analyses clinically and statistically confirmed robustness of the finding. In the biologics-IR group, the respective results on discontinuation due to LOE and AEs suggested that tofacitinib yields a discontinuation rate comparable to that of biologics. Nonetheless, the total discontinuation rate for tofacitinib was significantly higher than for biologics. This result may be caused by the higher proportion of reasons other than LOE or AEs for tofacitinib relative to a placebo in the trial of tofacitinib (51). 26 patients treated with tofacitinib discontinued at 6 months, and a half of the patients discontinued treatment for reasons other than AEs or LOE (12 for AEs, 2 for LOE, 9 were no longer willing to continue the treatment, 1 was lost to follow-up, and 2 for other reasons). In the placebo group, however, 2 patients discontinued for other reasons among the total of 6 discontinuing patients at 3 months (2 for AEs, 2 for LOE, and 2 for other reasons).

There are studies that are consistent with the present study on patients with cDMARDs-IR. One is a meta-analysis with biologics and synthesised odds ratios (ORs) of discontinuation by reason (57). The results on OR for abatacept due to AEs were under 1.0 relative to each TNFi biologic with the exception of etanercept. This result is consistent with the present study: the discontinuation rate due to AEs for abatacept was lower than that for TNFi biologics. Additionally, two meta-analyses suggested that tofacitinib is comparable to biologics according to OR of ACR response criteria and the risk ratio of serious infections (14, 58), just as we estimated a comparable discontinuation rate due to LOE and AEs, respectively. There is a study that compared abatacept, rituximab, tocilizumab, and tofacitinib used for patients with biologics-IR by Lee *et al*. (59). This analysis uncovered a tendency (in ORs of ACR 20 responses between treatments) and that is similar to the present study's results on RR for discontinuation due to LOE. On the other hand, ORs of discontinuation due to AEs between treatments were different from those in our analyses. This apparent discrepancy may be the result of different time points (Lee *et al*. extracted data of tofacinib 5mg during months 3–6) of data extraction and analytical techniques (a fixed *vs*. random approach).

According to the results from registries – one for identifying discontinuation

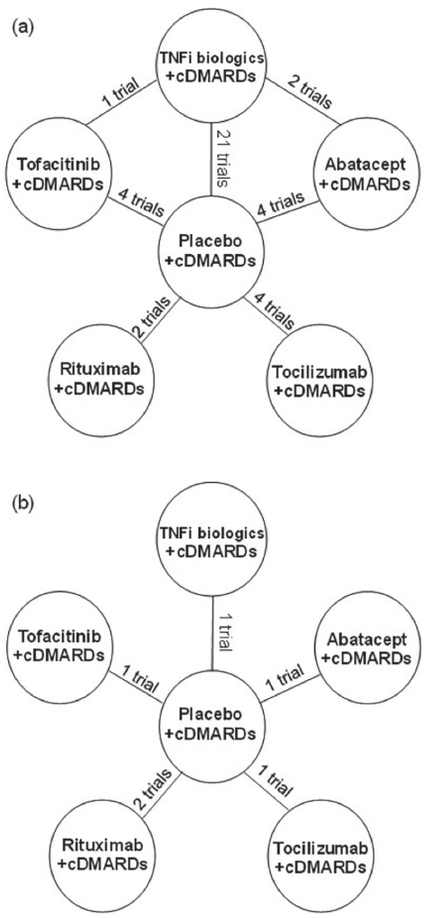

Fig. 2. A network diagram of evidence for total discontinuation in the cDMARDs-IR group (a) and in the biologics-IR group (b).
TNFi: tumour necrosis factor inhibitor; cDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs.

of MTX in the UK and the other for comparing patients' characteristics and outcomes between the US and Europe – 34% of patients who have received MTX and 11–25% of patients treated with TNFi biologics (adalimumab, etanercept, or infliximab) have discontinued each treatment (60, 61). This result could be interpreted as follows: there are unmet needs in terms of the evidence for the relative comparison between treatments for patients with IR to a previous treatment. Our study can help rheumatologists or patients to decide on the treatment strategy in clinical practice by providing evidences of comparative discontinuation rate – a meaningful parameter involving the comprehensive meaning of efficacy and safety – of biologics and tofacitinib. Also, the result of study could suggests that previous treatments and discontinuation reasons need to be considered when determining the treatment strategy; because the comparability between tofacitinib and biologics differs by a history of failure of a previous treatment and discontinuation reason; LOE, AEs, and total (due to other reasons).

The results of present Bayesian NMA should be interpreted with caution considering some limitations. First, the comparability would be influenced by the value of threshold. For instance, the result of abatacept in cDMARDs-IR group, which showed non-significant RR (0.71) due to 88.7% of P[RR<1], could be differently interpreted; abatacept had a significantly lower total discontinuation rate than that of tofacitinib, if the lower threshold (*e.g.* 85%) was applied. Although, the value of threshold was based on the previous studies (19, 62), the interpretation for the results showing the marginal value of P[RR<1] should be done with caution. The other limitations are associated with heterogeneity. Heterogeneity among the included trials could introduce a bias into the results of NMA. Therefore, we included trials with a combination therapy and synthesised outcomes considering a previous treatment and various follow-up periods in accordance with the recommendation (10). Nonetheless, there are some risk factors related to heterogeneity. In this study, we included only evidence from RCTs, but RCTs were conducted under controlled conditions. Discontinuation could occur for a greater variety of reasons in clinical practice, and the results extracted from registries with a large population or open-label studies may be more appropriate. However, combining various study designs could raise uncertainty of analysis, and data for analysing the discontinuation of tofacitinib might be insufficient due to short period of tofacitinib use. Additionally, we included trials involving a combination therapy with cDMARDs, but we did not set a limit on the type of concomitant treatments or dosing. This approach may have had an influence on the observed effect of a placebo and treatments, as in the present analysis.

There are additional limitations for biologics-IR group. In the biologics-IR group, the results on SD – which was interpreted as heterogeneity between RCTs – showed substantial heterogeneity with SD >1.0 for discontinuation due to LOE and AEs, contrast to cDMARDs-IR group. Heterogeneity could be induced by the following factors. Despite the comprehensive nature of systematic review, only one RCT was included for each treatment except

Table III. Results of Bayesian network meta-analyses of discontinuation rates.

Drug	Total			Lack of efficacy			Adverse event		
cDMARDs-IR									
	Rate†	95% CrI	P [best]	Rate†	95% CrI	P [best]	Rate†	95% CrI	P [best]
PBO	2.75	0.68-11.12	0.0%	1.62	0.24-10.58	0.0%	0.67	0.16-2.77	2.6%
TOF	1.73	0.40-7.44	6.6%	0.45	0.06-3.45	3.7%	0.76	0.16-3.67	6.3%
TNFi	1.48	0.36-6.03	9.4%	0.45	0.07-2.98	0.5%	0.89	0.20-3.86	0%
ABT	1.24	0.29-5.24	65.5%	0.45	0.06-3.13	1.3%	0.47	0.10-2.17	54.9%
RTX	1.71	0.36-7.95	15.9%	0.19	0.02-1.73	55.6%	0.57	0.09-3.74	36.1%
TCZ	1.93	0.44-8.34	2.6%	0.23	0.02-2.27	38.9%	1.39	0.29-6.51	0.1%
	RR‡	95% CrI	P [RR<1]	RR‡	95% CrI	P [RR<1]	RR‡	95% CrI	P [RR<1]
TNFi	0.85	0.54-1.35	76.3%	1.00	0.45-2.28	50.3%	1.17	0.62-2.28	30.7%
ABT	0.71	0.40-1.26	88.7%	1.01	0.40-2.62	49.4%	0.61	0.27-1.43	88.0%
RTX	0.99	0.45-2.16	51.6%	0.43	0.09-1.66	88.5%	0.75	0.19-3.03	66.2%
TCZ	1.12	0.61-2.08	35.4%	0.53	0.09-2.33	79.8%	1.83	0.78-4.33	7.9%
SD		0.31			0.28			0.31	
Biologics-IR									
	Rate†	95% CrI	P [best]	Rate†	95% CrI	P [best]	Rate†	95% CrI	P [best]
PBO	2.69	1.02-7.15	0.2%	1.39	0.38-5.06	0.1%	0.73	0.33-1.64	2.1%
TOF	6.19	0.59-66.57	1.8%	0.70	0.02-23.28	16.0%	2.77	0.14-71.53	3.4%
TNFi	1.03	0.10-10.35	42.9%	0.74	0.04-13.54	9.1%	0.28	0.02-4.88	53.0%
ABT	1.43	0.15-13.91	19.2%	0.36	0.02-6.14	23.1%	0.70	0.04-12.65	17.1%
RTX	1.24	0.23-7.02	22.4%	0.65	0.04-11.04	9.5%	0.78	0.10-7.35	9.5%
TCZ	1.69	0.18-16.35	13.7%	0.25	0.01-4.63	42.2%	0.72	0.05-11.74	14.9%
	RR‡	95% CrI	P [RR<1]	RR‡	95% CrI	P [RR<1]	RR‡	95% CrI	P [RR<1]
TNFi	0.17	0.01-3.61	92.0%	1.06	0.02-70.33	48.7%	0.10	0.00-5.37	89.6%
ABT	0.23	0.01-4.79	89.3%	0.53	0.01-33.98	65.0%	0.25	0.00-13.88	78.8%
RTX	0.20	0.01-2.91	92.3%	0.92	0.01-61.86	51.8%	0.28	0.01-10.04	79.0%
TCZ	0.27	0.01-5.73	87.4%	0.35	0.00-24.20	71.7%	0.26	0.00-13.27	79.0%
SD		0.75			1.00			1.06	

cDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; IR: inadequate responses; CrI: credible interval; P [best]: probability of the best; PBO: placebo; TOF: tofacitinib; TNFi: tumour necrosis factor α inhibitors; ABT: abatacept; RTX: rituximab; TCZ: tocilizumab; RR: rate ratio; P [RR<1]: probability of RR under 1; SD: standard deviation.
†Median discontinuation rate (events per 100 patient-months). ‡Rate ratio for each biologic relative to tofacitinib.

Table IV. Results of sensitivity analyses of the total discontinuation.

Drug	Sensitivity analysis 1			Sensitivity analysis 2		
cDMARDs-IR	Rate†	95% CrI	P [best]	Rate†	95% CrI	P [best]
PBO	2.75	0.68-11.25	0.0%	2.77	0.68-11.31	0.0%
TOF	1.11	0.13-8.81	52.1%	1.73	0.40-7.50	6.1%
TNFi	1.50	0.36-6.21	4.4%	1.48	0.36-6.11	9.0%
ABT	1.23	0.29-5.31	32.5%	1.24	0.29-5.31	67.4%
RTX	1.70	0.36-8.21	9.4%	1.71	0.37-7.89	15.2%
TCZ	1.95	0.44-8.59	1.7%	1.93	0.45-8.35	2.3%
	RR‡	95% CrI	P [RR<1]	RR‡	95% CrI	P [RR<1]
TNFi	1.35	0.29-7.00	35.2%	0.85	0.56-1.32	77.8%
ABT	1.11	0.22-6.02	44.9%	0.72	0.41-1.23	89.5%
RTX	1.55	0.28-9.23	30.5%	0.98	0.47-2.05	51.8%
TCZ	1.76	0.35-9.68	24.3%	1.11	0.63-2.01	35.2%
SD		0.36			0.28	
Biologics-IR	Rate†	95% CrI	P [best]	Rate†	95% CrI	P [best]
PBO		Not available		2.69	1.02-7.12	0.9%
TOF				6.10	0.00-22600.0	6.6%
TNFi				1.03	0.03-3316.00	35.3%
ABT				1.43	0.04-5456.00	20.4%
RTX				1.24	0.00-427.70	20.3%
TCZ				1.70	0.05-6813.00	16.5%
	RR‡	95% CrI	P [RR<1]	RR‡	95% CrI	P [RR<1]
TNFi		Not available		0.17	0.00-15250.0	79.5%
ABT				0.24	0.00-24410.0	77.0%
RTX				0.20	0.00-4716.0	79.8%
TCZ				0.28	0.00-32120.0	75.4%
SD		-			2.50	

cDMARDs: conventional synthetic disease-modifying anti-rheumatic drugs; IR: inadequate responses; CrI, credible interval; P [best]: probability of the best; PBO: placebo; TOF: tofacitinib; TNFi: tumour necrosis factor α inhibitors; ABT, abatacept; RTX, rituximab; TCZ, tocilizumab; RR, rate ratio; P [RR<1]: probability of RR under 1; SD: standard deviation.
†Median discontinuation rate (events per 100 patient-months). ‡Rate ratio for each biologic relative to tofacitinib.

rituximab (52, 55) Even the RCT of golimumab represented the efficacy of TNFi biologics. Furthermore, different baseline characteristics such as shorter duration of disease for TNFi biologics than for other treatments may introduce the bias. In addition, the treatment effect may be influenced by the type and number of previously used biologics, but we did not consider these data. According to the clinical guidelines (5, 6), tofacitinib is indicated ideally after a failure of two biologics; therefore, the number and type of previous biologics could be a point to consider. The relative discontinuation rate of tofacitinib and biologics in this group still needs to be determined to obtain more reliable evidence for decision making during RA treatment. More research – such as head-to-head trials and studies taking into account the influence of the number and type of previously used biologics – needs to be conducted.

References

1. SMOLEN JS, ALETAHA D, BIJLSMA JW *et al*.: Treating rheumatoid arthritis to target: recommendations of an international task force. *Ann Rheum Dis* 2010; 69: 631-7.
2. MAETZEL A, WONG A, STRAND V, TUGWELL P, WELLS G, BOMBARDIER C: Meta-analysis of treatment termination rates among rheumatoid arthritis patients receiving disease-modifying anti-rheumatic drugs. *Rheumatology* (Oxford) 2000; 39: 975-81.
3. MATSUBARA H, KOJIMA T, KANEKO A *et al*. Longterm retention rate and risk factor for discontinuation due to insufficient efficacy and adverse events in Japanese patients with rheumatoid arthritis receiving etanercept therapy. *J Rheumatol* 2014; 41: 1583-9.
4. SOLIMAN MM, ASHCROFT DM, WATSON KD *et al*.: Impact of concomitant use of DMARDs on the persistence with anti-TNF therapies in patients with rheumatoid arthritis: results from the British Society for Rheumatology Biologics Register. *Ann Rheum Dis* 2011; 70: 583-9.
5. SMOLEN JS, LANDEWÉ R, BREEDVELD FC *et al*.: EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. *Ann Rheum Dis* 2014; 73: 492-509.
6. SINGH JA, SAAG KG, BRIDGES SL, JR. *et al*.: 2015 American College of Rheumatology Guideline for the Treatment of Rheumatoid Arthritis. *Arthritis Care Res* (Hoboken) 2016; 68: 1-25.
7. LEE AW: Review of mixed treatment comparisons in published systematic reviews shows marked increase since 2009. *J Clin Epidemiol* 2014; 67: 138-43.
8. JANSEN JP, CRAWFORD B, BERGMAN G, STAM W: Bayesian meta-analysis of multiple treatment comparisons: an introduction to mixed treatment comparisons. *Value Health* 2008; 11: 956-64.
9. LEON L, RODRIGUEZ-RODRIGUEZ L, ROSALES Z *et al*.: Long-term drug survival of biological agents in patients with rheumatoid arthritis in clinical practice. *Scand J Rheumatol* 2016: 1-5.
10. THORLUND K, DRUYTS E, AVINA-ZUBIETA JA, WU P, MILLS EJ: Why the findings of published multiple treatment comparison meta-analyses of biologic treatments for rheumatoid arthritis are different: an overview of recurrent methodological shortcomings. *Ann Rheum Dis* 2013; 72: 1524-35.
11. HEIJDE D, TANAKA Y, FLEISCHMANN R *et al*.: Tofacitinib (CP-690,550) in patients with rheumatoid arthritis receiving methotrexate: twelve-month data from a twenty-four-month phase III randomized radiographic study. *Arthritis Rheum* 2013; 65: 559-70.
12. KREMER JM, COHEN S, WILKINSON BE *et al*.:A phase IIb dose-ranging study of the oral JAK inhibitor tofacitinib (CP-690,550) versus placebo in combination with background methotrexate in patients with active rheumatoid arthritis and an inadequate response to methotrexate alone. *Arthritis Rheum* 2012; 64: 970-81.
13. VAN VOLLENHOVEN RF, FLEISCHMANN R, COHEN S *et al*.: Tofacitinib or adalimumab versus placebo in rheumatoid arthritis. *N Engl J Med* 2012; 367: 508-19.
14. BUCKLEY F, FINCKH A, HUIZINGA TW, DEJONCKHEERE F, JANSEN JP: Comparative efficacy of novel DMARDs as monotherapy and in combination with methotrexate in rheumatoid arthritis patients with inadequate response to conventional DMARDs: a net-

work meta-analysis. *J Manag Care Spec Pharm* 2015; 21: 409-23.
15. HOCHBERG MC, TRACY JK, HAWKINS-HOLT M, FLORES RH: Comparison of the efficacy of the tumour necrosis factor alpha blocking agents adlimumab, etanercept, and infliximab when added to methotrexate in patients with active rheumatoid arthritis. *Ann Rheum Dis* 2003; 62 (Suppl. II): ii13-6.
16. GARTLEHNER G, HANSEN RA, JONAS BL, THIEDA P, LOHR KN: The comparative efficacy and safety of biologics for the treatment of rheumatoid arthritis: A systematic review and metaanalysis. *J Rheumatol* 2006; 33: 2398-408.
17. PARK SK, KIM HL, LEE MY, KIM A, LEE EK: Comparative Effectiveness of Biologic DMARDs in Rheumatoid Arthritis Patients with Inadequate Response to conventional DMARDs: Using a Bayesian Network Meta-analysis. *Korean J Clin Pharm* 2015; 25: 9-17.
18. DIAS S, WELTON NJ, SUTTON AJ, ADES AE: NICE DSU Technical Support Document 2: A Generalised Linear Modelling Framework for Pairwise and Network Meta-Analysis of Randomised Controlled Trials. 2011; last updated April 2014; available from http://www.nicedsu.org.uk
19. PETER JV, JOHN P, GRAHAM PL, MORAN JL, GEORGE IA, BERSTEN A: Corticosteroids in the prevention and treatment of acute respiratory distress syndrome (ARDS) in adults: meta-analysis. *BMJ* 2008; 336: 1006-9.
20. ABE T, TAKEUCHI T, MIYASAKA N *et al*.: A multicenter, double-blind, randomized, placebo controlled trial of infliximab combined with low dose methotrexate in Japanese patients with rheumatoid arthritis. *J Rheumatol* 2006; 33: 37-44.
21. CHOY E, MCKENNA F, VENCOVSKY J *et al*.: Certolizumab pegol plus MTX administered every 4 weeks is effective in patients with RA who are partial responders to MTX. *Rheumatology* 2012; 51: 1226-34.
22. COMBE B, CODREANU C, FIOCCO U *et al*.: Etanercept and sulfasalazine, alone and combined, in patients with active rheumatoid arthritis despite receiving sulfasalazine: a double-blind comparison. *Ann Rheum Dis* 2006; 65: 1357-62.
23. EMERY P, DEODHAR A, RIGBY WF *et al*.: Efficacy and safety of different doses and retreatment of rituximab: a randomised, placebo-controlled trial in patients who are biological naive with active rheumatoid arthritis and an inadequate response to methotrexate (Study Evaluating Rituximab's Efficacy in MTX iNadequate rEsponders (SERENE)). *Ann Rheum Dis* 2010; 69: 1629-35.
24. FURST DE, SCHIFF MH, FLEISCHMANN RM *et al*.: Adalimumab, a fully human anti tumor necrosis factor-alpha monoclonal antibody, and concomitant standard antirheumatic therapy for the treatment of rheumatoid arthritis: results of STAR (Safety Trial of Adalimumab in Rheumatoid Arthritis). *J Rheumatol* 2003; 30: 2563-71.
25. GENOVESE MC, MCKAY JD, NASONOV EL *et al*.: Interleukin-6 receptor inhibition with tocilizumab reduces disease activity in rheumatoid arthritis with inadequate response to disease-modifying antirheumatic drugs: the tocilizumab in combination with traditional disease-modifying antirheumatic drug therapy study. *Arthritis Rheum* 2008; 58: 2968-80.
26. KAY J, MATTESON EL, DASGUPTA B *et al*.: Golimumab in patients with active rheumatoid arthritis despite treatment with methotrexate: a randomized, double-blind, placebo-controlled, dose-ranging study. *Arthritis Rheum* 2008; 58: 964-75.
27. KEYSTONE E, HEIJDE D, MASON D, JR. *et al*.: Certolizumab pegol plus methotrexate is significantly more effective than placebo plus methotrexate in active rheumatoid arthritis: findings of a fifty-two-week, phase III, multicenter, randomized, double-blind, placebo-controlled, parallel-group study. *Arthritis Rheum* 2008; 58: 3319-29.
28. KEYSTONE EC, GENOVESE MC, KLARESKOG L *et al*.: Golimumab, a human antibody to tumour necrosis factor α given by monthly subcutaneous injections, in active rheumatoid arthritis despite methotrexate therapy: the GO-FORWARD Study. *Ann Rheum Dis* 2009; 68: 789-96.
29. KEYSTONE EC, KAVANAUGH AF, SHARP JT *et al*.: Radiographic, clinical, and functional outcomes of treatment with adalimumab (a human anti-tumor necrosis factor monoclonal antibody) in patients with active rheumatoid arthritis receiving concomitant methotrexate therapy: a randomized, placebo-controlled, 52-week trial. *Arthritis Rheum* 2004; 50: 1400-11.
30. KIM HY, LEE SK, SONG YW *et al*.: A randomized, double-blind, placebo-controlled, phase III study of the human anti-tumor necrosis factor antibody adalimumab administered as subcutaneous injections in Korean rheumatoid arthritis patients treated with methotrexate. *APLAR J Rheumatol* 2007; 10: 9-16.
31. KIM JH, RYU HJ, YOO DH *et al*.: A clinical trial and extension study of infliximab in Korean patients with active rheumatoid arthritis despite methotrexate treatment. *J Korean Med Sci* 2013: 1716-22.
32. KLARESKOG L, VAN DER HEIJDE D, DE JAGER JP *et al*.: Therapeutic effect of the combination of etanercept and methotrexate compared with each treatment alone in patients with rheumatoid arthritis: double-blind randomised controlled trial. *Lancet* 2004; 363: 675-81.
33. KREMER JM, DOUGADOS M, EMERY P *et al*.: Treatment of rheumatoid arthritis with the selective costimulation modulator abatacept: twelve-month results of a phase iib, double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005; 52: 2263-71.
34. KREMER JM, GENANT HK, MORELAND LW *et al*.: Effects of abatacept in patients with methotrexate-resistant active rheumatoid arthritis: a randomized trial. *Ann Intern Med* 2006; 144: 865-76.
35. LIPSKY PE, VAN DER HEIJDE DM, ST CLAIR EW *et al*.: Infliximab and methotrexate in the treatment of rheumatoid arthritis. *N Engl J Med* 2000; 343: 1594-602.
36. MAINI RN, TAYLOR PC, SZECHINSKI J *et al*.: Double-blind randomized controlled clinical trial of the interleukin-6 receptor antagonist, tocilizumab, in European patients with rheumatoid arthritis who had an incomplete response to methotrexate. *Arthritis Rheum* 2006; 54: 2817-29.
37. MAINI RN, BREEDVELD FC, KALDEN JR *et al*.: Therapeutic efficacy of multiple intravenous infusions of anti-tumor necrosis factor α monoclonal antibody combined with low-dose weekly methotrexate in rheumatoid arthritis. *Arthritis Rheum* 1998; 41: 1552-63.
38. SCHIFF M, KEISERMAN M, CODDING C *et al*.: Efficacy and safety of abatacept or infliximab vs placebo in ATTEST: a phase III, multicentre, randomised, double-blind, placebo-controlled study in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Ann Rheum Dis* 2008; 67: 1096-103.
39. SCHIFF M, WEINBLATT ME, VALENTE R *et al*.: Head-to-head comparison of subcutaneous abatacept versus adalimumab for rheumatoid arthritis: two-year efficacy and safety findings from AMPLE trial. *Ann Rheum Dis* 2014; 73: 86-94.
40. SMOLEN J, LANDEWÉ RB, MEASE P *et al*.: Efficacy and safety of certolizumab pegol plus methotrexate in active rheumatoid arthritis: the RAPID 2 study. A randomised controlled trial. *Ann Rheum Dis* 2009; 68: 797-804.
41. SMOLEN JS, BEAULIEU A, RUBBERT-ROTH A *et al*.: Effect of interleukin-6 receptor inhibition with tocilizumab in patients with rheumatoid arthritis (OPTION study): a double-blind, placebo-controlled, randomised trial. *Lancet* 2008; 371: 987-97.
42. STRAND V, BALBIR-GURMAN A, PAVELKA K *et al*.: Sustained benefit in rheumatoid arthritis following one course of rituximab: improvements in physical function over 2 years. *Rheumatology* 2006; 45: 1505-13.
43. TAKEUCHI T, MATSUBARA T, NITOBE T *et al*.: Phase II dose-response study of abatacept in Japanese patients with active rheumatoid arthritis with an inadequate response to methotrexate. *Mod Rheumatol* 2013; 23: 226-35.
44. TANAKA Y, HARIGAI M, TAKEUCHI T *et al*.: Golimumab in combination with methotrexate in Japanese patients with active rheumatoid arthritis: results of the GO-FORTH study. *Ann Rheum Dis* 2012; 71: 817-24.
45. TANAKA Y, SUZUKI M, NAKAMURA H, TOYOIZUMI S, ZWILLICH SH, THE TOFACITINIB STUDY INVESTIGATORS: Phase II study of tofacitinib (CP-690,550) combined with methotrexate in patients with rheumatoid arthritis and an inadequate response to methotrexate. *Arthritis Care Res* (Hoboken) 2011; 63: 1150-8.
46. WEINBLATT ME, KREMER JM, BANKHURST AD *et al*.: A trial of etanercept, a recombinant tumor necrosis factor receptor:Fc fusion protein, in patients with rheumatoid arthritis receiving methotrexate. *N Engl J Med* 1999; 340: 253-9.
47. WESTHOVENS R, YOCUM D, HAN J *et al*.: The safety of infliximab, combined with background treatments, among patients with rheumatoid arthritis and various comorbidities: a large, randomized, placebo-controlled trial. *Arthritis Rheum* 2006; 54: 1075-86.
48. YAMAMOTO K, TAKEUCHI T, YAMANAKA

H *et al*.: Efficacy and safety of certolizumab pegol plus methotrexate in Japanese rheumatoid arthritis patients with an inadequate response to methotrexate: the J-RAPID randomized, placebo-controlled trial. *Mod Rheumatol* 2014; 24: 715-24.
49. ZHANG FC, HOU Y, HUANG F *et al*.: Infliximab versus placebo in rheumatoid arthritis patients receiving concomitant methotrexate: a preliminary study from China. *APLAR J Rheumatol* 2006; 9: 127-30.
50. FLEISCHMANN RM, HALLAND AM, BRZOSKO M *et al*.: Tocilizumab inhibits structural joint damage and improves physical function in patients with rheumatoid arthritis and inadequate responses to methotrexate: LITHE study 2-year results. *J Rheumatol* 2013; 40: 113-26.
51. BURMESTER GR, BLANCO R, CHARLES-SCHOEMAN C *et al*.: Tofacitinib (CP-690,550) in combination with methotrexate in patients with active rheumatoid arthritis with an inadequate response to tumour necrosis factor inhibitors: a randomised phase 3 trial. *Lancet* 2013; 381: 451-60.
52. COHEN SB, EMERY P, GREENWALD MW *et al*.: Rituximab for rheumatoid arthritis refractory to anti-tumor necrosis factor therapy: Results of a multicenter, randomized, double-blind, placebo-controlled, phase III trial evaluating primary efficacy and safety at twenty-four weeks. *Arthritis Rheum* 2006; 54: 2793-806.
53. EMERY P, KEYSTONE E, TONY HP *et al*.: IL-6 receptor inhibition with tocilizumab improves treatment outcomes in patients with rheumatoid arthritis refractory to anti-tumour necrosis factor biologicals: results from a 24-week multicentre randomised placebo-controlled trial. *Ann Rheum Dis* 2008; 67: 1516-23.
54. GENOVESE MC, BECKER JC, SCHIFF M *et al*.: Abatacept for rheumatoid arthritis refractory to tumor necrosis factor alpha inhibition. *N Engl J Med* 2005; 353: 1114-23.
55. MEASE PJ, COHEN S, GAYLIS NB *et al*.: Efficacy and safety of retreatment in patients with rheumatoid arthritis with previous inadequate response to tumor necrosis factor inhibitors: results from the SUNRISE trial. *J Rheumatol* 2010; 37: 917-27.
56. SMOLEN JS, KAY J, DOYLE MK *et al*.: Golimumab in patients with active rheumatoid arthritis after treatment with tumour necrosis factor alpha inhibitors (GO-AFTER study): a multicentre, randomised, double-blind, placebo-controlled, phase III trial. *Lancet* 2009; 374: 210-21.
57. DESAI RJ, HANSEN RA, RAO JK *et al*.: Mixed treatment comparison of the treatment discontinuations of biologic disease-modifying antirheumatic drugs in adults with rheumatoid arthritis. *Ann Pharmacother* 2012; 46: 1491-505.
58. STRAND V, AHADIEH S, FRENCH J *et al*.: Systematic review and meta-analysis of serious infections with tofacitinib and biologic disease-modifying antirheumatic drug treatment in rheumatoid arthritis clinical trials. *Arthritis Res Ther* 2015; 17: 362.
59. LEE YH, BAE SC: Comparative efficacy and safety of tocilizumab, rituximab, abatacept and tofacitinib in patients with active rheumatoid arthritis that inadequately responds to tumor necrosis factor inhibitors: a Bayesian network meta-analysis of randomized controlled trials. *Int J Rheum Dis* 2015.
60. CURTIS JR, JAIN A, ASKLING J *et al*.: A comparison of patient characteristics and outcomes in selected European and U.S. rheumatoid arthritis registries. *Semin Arthritis Rheum* 2010; 40: 2-14.
61. NIKIPHOROU E, NEGOESCU A, FITZPATRICK JD *et al*.: Indispensable or intolerable? Methotrexate in patients with rheumatoid and psoriatic arthritis: a retrospective review of discontinuation rates from a large UK cohort. *Clin Rheumatol* 2014; 33: 609-14.
62. MORAN J, GRAHAM P, ROCKLIFF S, BERSTEN A: Updating the evidence for the role of corticosteroids in severe sepsis and septic shock: a Bayesian meta-analytic perspective. *Critical Care* 2010; 14: R134.