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The European Journal of Health Economics
Health Economics in Prevention and Care

ISSN 1618-7598

Eur J Health Econ
DOI 10.1007/s10198-014-0594-4

Springer

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ORIGINAL PAPER

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Received: 4 February 2014 / Accepted: 31 March 2014

Abstract
Objective The aim of this meta-analysis was to compare the efficacy and safety of infliximab-biosimilar and other available biologicals for the treatment of rheumatoid arthritis (RA), namely abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab and tocilizumab.
Methods A systematic literature review of MEDLINE database until August 2013 was carried out to identify relevant randomized controlled trials (RCTs). Bayesian mixed treatment comparison method was applied for the pairwise comparison of treatments. Improvement rates by the American College of Rheumatology criteria (ACR20 and ACR50) at week 24 were used as efficacy endpoints, and the occurrence of serious adverse events was considered to assess the safety of the biologicals.
Results Thirty-six RCTs were included in the meta-analysis. All the biological agents proved to be superior to placebo. For ACR20 response, certolizumab pegol showed the highest odds ratio (OR) compared to placebo, OR 7.69 [95 % CI 3.69–14.26], followed by abatacept OR 3.7 [95 % CI 2.17–6.06], tocilizumab OR 3.69 [95 % CI 1.87–6.62] and infliximab-biosimilar OR 3.47 [95 % CI 0.85–9.7]. For ACR50 response, certolizumab pegol showed the highest OR compared to placebo OR 8.46 [3.74–16.82], followed by tocilizumab OR 5.57 [95 % CI 2.77–10.09], and infliximab-biosimilar OR 4.06 [95 % CI 1.01–11.54]. Regarding the occurrence of serious adverse events, the results show no statistically significant difference between infliximab-biosimilar and placebo, OR 1.87 [95 % CI 0.74–3.84]. No significant difference regarding efficacy and safety was found between infliximab-biosimilar and the other biological treatments.
Conclusion This is the first indirect meta-analysis in RA that compares the efficacy and safety of biosimilar-infliximab to the other biologicals indicated in RA. We found no significant difference between infliximab-biosimilar and other biological agents in terms of clinical efficacy and safety.

Keywords Arthritis · Rheumatoid · Biosimilar pharmaceuticals · Meta-analysis · Mixed treatment comparison

JEL Classification I10 · I19

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Introduction

Currently eight biological medicines—namely, abatacept, adalimumab, certolizumab pegol, etanercept, golimumab,

Published online: 16 May 2014

infliximab, rituximab and tocilizumab—are registered by the European Medicines Agency (EMA) for the treatment of rheumatoid arthritis (RA). These biologicals are indicated for the treatment of adult patients with active disease when "the response to disease-modifying antirheumatic drugs (DMARDs), including methotrexate (MTX), has been inadequate." Adalimumab, etanercept, golimumab, infliximab are also indicated for "adult patients with severe, active and progressive disease not previously treated with MTX or other DMARDs" as a 'first-line therapy'.[1,2]

In September 2013, infliximab-biosimilar therapy (CT-P13, Trade names: Remsima and Inflectra) was also licensed in the EU for the treatment of RA. According to the EMA, Remsima and Inflectra are 'biosimilar'[3] medicines of infliximab.

The results of the randomized controlled trial (RCT) with biosimilar-infliximab treatment in RA were published in May 2013 [1]. PLANETRA was a double-blind, non-inferiority study, and aimed to prove the similar efficacy and safety of infliximab-biosimilar in combination with MTX and the originator infliximab combined with MTX. The primary endpoint of the trial was the therapeutic equivalence of clinical response according to ACR20 criteria at week 30 (See the definition of ACR20 in the "Methods" section). The study was performed between November 2010 and November 2011 at 100 centers across 19 countries in Europe, Asia, Latin America and the Middle East. Altogether, 606 patients with active RA despite MTX treatment were enrolled in the study. According to the results, at week 30, ACR20 and ACR50 responses were 60.9 and 35.1 %, respectively, on the infliximab-biosimilar arm, and 58.6 and 34.2 % on the originator infliximab arm in the intention-to-treat population. The difference not statistically significant at these two efficacy endpoints. Nor was a significant difference found in other efficacy and safety endpoints.

The aim of this study is to compare the efficacy and safety of the new infliximab-biosimilar treatment to the available originator biological drugs. We carry out systematic literature review and meta-analysis of published RCTs with infliximab-biosimilar and other biological treatments in the recommended doses defined by EMA's product characteristic information in RA, applying mixed treatment comparison (MTC). This method allows us to carry out pairwise comparison of treatments with different comparators. In our case, infliximab-biosimilar is only compared to the originator infliximab, while other biologicals are compared to placebo in most of the studies. According to our knowledge, no indirect meta-analyses have yet been published that involve the infliximab-biosimilar treatment in the comparison.

Methods

Treatments

The analysis compared the recommended doses of biological DMARDs indicated in RA:[4] abatacept (10 mg/kg at days at weeks 0, 2 and 4, and every 4 weeks thereafter, or by patient groups based on patient weight <60 kg, 500 mg; 60–100 kg, 750 mg; >100 kg, 1,000 mg, administered as a 30-min intravenous infusion); adalimumab (40 mg every other week as subcutaneous injection); certolizumab pegol (400 mg at 0, 2, 4 weeks and then 200 mg at every 2 weeks or 400 mg at every 4 weeks as subcutaneous injection); etanercept (25 mg twice weekly or 50 mg once weekly as subcutaneous injection); golimumab (50 mg once a month as subcutaneous injection); infliximab (3 mg/kg at 0, 2, 6 weeks and then every 8 weeks as intravenous infusions over a 2-h period) rituximab (1,000 mg on weeks 0, 2 as intravenous infusions); tocilizumab (8 mg/kg every 4 weeks as intravenous infusions) and infliximab-biosimilar (CT-P13) (3 mg/kg at 0, 2, 6 weeks and then every 8 weeks as intravenous infusions over a 2-h period).

In RA, infliximab-biosimilar (as well as the originator infliximab) must be administered concomitantly with MTX. Thus, we only included studies evaluating combination therapy with biologicals and conventional synthetic DMARD (csDMARD)[5] In this way, we expected to increase the comparability of the results.

Endpoints

The rates of patients who achieved ACR20 and ACR50 response at week 24 were used as efficacy endpoints in the meta-analysis of RA trials. The American College of Rheumatology (ACR) response core set consists of a tender

[1] The product information details can be found at http://www.ema.europa.eu/ema/.

[2] Also when the patient is intolerant to previous therapy with tumour-necrosis-factor (TNF) antagonists.

[3] According to the definition of EMA, "A biosimilar medicine is a medicine which is similar to a biological medicine that has already been authorized (the 'biological reference medicine'). The active substance of a biosimilar medicine is similar to that of the biological reference medicine. Biosimilar and biological reference medicines are used in general at the same dose to treat the same disease."

[4] Anakinra is also registered for the treatment of RA by the EMA; however, its utilization has not spread in the clinical practice of CEE countries where infliximab-biosimilar is marketed. Thus, anakinra was not included in the meta-analysis.

[5] Adalimuab, certolizumab, etanercept and tocilizumab can be administered as monotherapy, in the case of intolerance to methotrexate.

joint count, swollen joint count, patient's assessment of pain, patient's and physician's global assessments of disease activity, patient's assessment of physical function (HAQ), and laboratory evaluation of one acute-phase reactant [2]. ACR criteria are indicated as ACR20, ACR50, and ACR70, reflecting 20, 50, or 70 % relative improvement compared to baseline. Most of the RA clinical trials with biologicals use ACR20 as primary endpoint, but also report the percentage of study participants who achieve ACR50 response as a secondary endpoint.

The safety of biological therapies was also evaluated. The occurrence of serious adverse events at week 24 of the treatment was used as safety endpoint in the analysis.

Search strategy

Electronic databases (MEDLINE and Cochrane Library) as well as references of retrieved articles were searched. The Cochrane Highly Sensitive Search Strategy [3] was applied to identify randomized controlled publications and was combined with the disease MeSH terms 'arthritis, rheumatoid' and the drug names.[6]

The search dates were 1 November 2009 to 20 August 2013. References of RCTs from earlier time periods were taken from our previous systematic review [4].

A separate search was carried out to identify RCTs with a biosimilar agent with the generic name (CT-P13), without any restrictions.

Exclusion and inclusion criteria

We have applied the following inclusion criteria:

- Double-blind, parallel RCTs with full paper obtainable (studies with only abstracts available were excluded). Non-randomized or uncontrolled studies, observational studies, case series, letters to the editor, studies with no abstracts or with conference abstracts only were not included.
- The patients of interest are adults with moderate-to-severe RA. (Trials in diseases other than RA were not included.)
- Head-to-head trials of combined biological therapies or studies with MTX or other csDMARD therapy control.
- RA patients in at least one arm of the trial must receive one of the following treatments: abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, rituximab, tocilizumab or infliximab-biosimilar treatment in the licensed dose combined with csDMARDs.

We have applied the following exclusion criteria:

- Off-label doses.
- Monotherapy in RA (infliximab-biosimilar can be administered only in combination with MTX; therefore, only combination therapies were compared).
- Studies reporting solely on laboratory measures aimed at investigating disease, or treatment mechanisms and which do not report relevant clinical outcomes.
- Studies involving patients with age <18 years.
- Pilot studies.
- Studies shorter than 20 weeks, or studies that do not report ACR50 response at month 6.
- Studies where all the patients enrolled previously failed biological therapy.

RA trials range widely in design regarding patient population. Some of them include patients not responding to csDMARD therapy, while others involve csDMARD-naïve patients. The authorization of infliximab-biosimilar also allows the application of the drug for RA patients previously not treated with MTX or other csDMARDs, in the case of severe, active and progressive disease. Thus, we included studies with MTX-naïve (or csDMARD-naïve) patients in the analysis as well.

However, we excluded studies that only involved patients who failed previous biological therapy.

Data extraction and quality assessment

Data were extracted by two independent researchers and checked by a third reviewer. Any disagreement was resolved through discussion until consensus was reached. For each selected study, details regarding study design, patients' demographic and morbidity characteristics, treatment interventions, end-points and duration of follow-up were subtracted.

The quality of selected studies was evaluated using the Jadad score [5]. This is the most frequently used scale in quality assessment of clinical trials [6]. The Jadad scale assesses the quality of published clinical trials through methods of random assignment, double blinding, and the withdrawals and dropout of patients. Jadad score ranges from zero to five.

Meta-analysis: mixed treatment comparison

We have conducted a meta-analysis to compare the efficacy and safety of the biologicals included in the studies. An indirect comparison of study outcomes for biological therapies was carried out. In this paper, we examine the

[6] (arthritis. rheumatoid"[MeSH Terms]) AND (abatacept OR adalimumab OR certolizumab pegol OR golimumab OR infliximab OR etanercept OR rituximab OR tocilizumab) AND ((randomized controlled trial[pt] OR controlled clinical trial[pt] OR randomized[tiab] OR placebo[tiab] OR "clinical trials as topic"[MeSH Terms:noexp] OR randomly[tiab] OR trial[ti]) NOT ("animals"[MeSH Terms] NOT "humans"[MeSH Terms])) AND ("2009/11/01"[PDAT]: "2013/08/20"[PDAT]).

relative effectiveness of each individual treatment using the Lu method for combining direct and indirect evidence in mixed treatment comparisons (MTC), a Bayesian approach [7, 8]. Statistical models developed by NICE Decision Support Unit (DSU) were used. We estimated the posterior densities for all unknown parameters using MCMC (Markov chain Monte Carlo) for each model in WinBUGS version 1.4.3 (MRC Biostatistics Unit, Cambridge, UK). Each outcome measure was analyzed using random effects models.

All MTC models used the odds ratio (OR) as the measure of relative treatment effect, and assumed that treatment effects on the odds-ratio scale were multiplicative and exchangeable between trials. We also present the 95 % credibility intervals (CI) containing the true value of OR with 95 % probability.

Results

Literature review

The search in MEDLINE yielded 354 potential citations for RCTs examining the biological treatment of RA (search period: 01.11.2009–20.08.2013). In RA, 15 RCTs identified by our search met our inclusion criteria. Furthermore, out of 32 RCTs identified by Brodszky et al. [4], 21 were taken and included in our analysis. The rest were not included because they were either monotherapy studies, or examined biologicals after previous failure with biologicals [9–12].

The search for infliximab-biosimilar did not identify RCTs other than the PLANETRA trial [1].

Altogether, we included 36 RCTs (RA patients with combination therapy of MTX or other DMARDs). Most of the studies compared biologicals with placebo: five abatacept [13–17], seven adalimumab [18–24], three certolizumab pegol [25–27], four etanercept [28–31],[7] four golimumab [32–35], three infliximab [36–38], four rituximab [39–42] and three tocilizumab [43–45]. One study compared abatacept versus adalimumab [46], one infliximab versus abatacept versus placebo [47] and one infliximab versus infliximab-biosimilar [1]. The number of trials in given comparisons might be different (e.g., on efficacy or safety endpoints) because of the specific inclusion criteria for each comparison and the distinct endpoints reporting across trials.

The main characteristics of the trials, i.e., number of patients, treatment arms, and JADAD score, are presented in Table 1.

Out of the 36 RA trials included in this analysis, eight studies applied study drugs to MTX-naïve patients [16, 21, 24, 30, 31, 33, 37, 42], and one study on csDMARD-naïve patients [23]. The rest of the studies involved patients with prior inadequate response to csDMARDs.

In some abatacept, rituximab, tocilizumab and golimumab studies [13, 15, 34, 40, 45], patients were not excluded if previously treated with biologicals prior to the study. Since the share of patients who were treated with biologicals before was relatively low in these studies, we included them in the meta-analysis. However, studies where all patients were previously treated with biologicals [12] or all patients gave prior inadequate response to biologicals [9–11] were not included in our meta-analysis.

Most of the RCTs reported ACR20 and ACR50 response at week 24. In contrast, the infliximab-biosimilar RCT reported results at week 30. However, patients in the infliximab-biosimilar study received the same number of infusions as patients in the infliximab trials.

Mixed treatment comparison: efficacy and safety

Efficacy

Out of the 36 RA trials identified by our search, 34 reported results for ACR20 response at week 24, and 35 reported ACR50 response at week 24. Weinblatt et al. [15] reported study results only on safety and Westhovens et al. [16] did not report ACR20 response. Data for 15,044 patients for ACR20 response and 14,535 for ACR50 response were included in the analysis.

All biological drugs were found to be superior to placebo regarding ACR20 and ACR50 responses. The results are presented in Table 2. On the ACR20 endpoint, certolizumab pegol showed the highest odds ratio compared to placebo, OR 7.69 [95 % CI 3.69–14.26], followed by abatacept OR 3.7 [95 % CI 2.17–6.06], tocilizumab OR 3.69 [1.87–6.62], and infliximab-biosimilar OR 3.47 [95 % CI 0.85–9.7].

For ACR50 response, certolizumab pegol showed the highest OR compared to placebo OR 8.46 [3.74–16.82], followed by tocilizumab OR 5.57 [95 % CI 2.77–10.09], and infliximab-biosimilar OR 4.06 [95 % CI 1.01–11.54].

The results of pairwise comparison did not show significant differences between the efficacy of infliximab-biosimilar and the other biologicals in terms of ACR20 or ACR50 response at week 24 (see Fig. 1).

[7] Moreland et al. [31] was a 2-year, randomized, double-blind trial with four treatment arms: immediate treatment with MTX plus etanercept, immediate oral triple therapy (MTX plus sulfasalazine plus hydroxychloroquine), or step-up from MTX monotherapy to one of the combination therapies (MTX plus etanercept or MTX plus sulfasalazine plus hydroxychloroquine) at week 24. Since before week 24, treatment arms with MTX + etanercept and MTX alone were selected to be included in this meta-analysis.

Table 1 Characteristics of the RCTs in RA included in the analysis

Study	Treatment arms	Study duration (weeks)	N (ITT)	Age, years	HAQ score	Disease duration, years	JADAD score
Kremer [13]	ABT(2 mg/kg) + MTX	26	105	54.4	1	9.7	5
	ABT(10 mg/kg) + MTX		115	55.8	1	9.7	
	Placebo + MTX		119	54.7	1	8.9	
Kremer [14]	**ABT(10 mg/kg) + MTX**	26	433	51.5	1.7	8.5	5
AIM	**Placebo + MTX**		219	50.4	1.7	8.9	
Weinblatt [15]	**ABT(10 mg/kg) + DMARD**	52	959	52.5	1.5	10.4	5
ASSURE	**Placebo + DMARD**		482	52.1	1.6	10.4	
Westhovens [16]*	**ABT(10 mg/kg) + MTX**	104	256	NR	1.7	0.56	5
	Placebo + MTX		253		1.7	0.56	
Takeutchi [17]	**ABA(10 mg/kg) + MTX**		61	53.4	1.33	7.4	5
	ABA(2 mg/kg) + MTX		67	52.5	1.24	8.5	
	Placebo + MTX		66	53.4	1.5	7.3	
Furst [18]	**ADL(40 mg/eow) + DMARD**	24	318	55	1.4	9.3	3
STAR	**Placebo + DMARD**		318	55.8	1.4	11.5	
Keystone [19]	ADL(20 mg/ew) + MTX	24	212	57.3	1.4	11	3
	ADL(40 mg/eow) + MTX		207	56.1	1.5	11	
	Placebo + MTX		200	56.1	1.5	10.9	
Weinblatt [20]	ADL(20 mg/eow) +MTX	24	69	53.5	1.52	13.1	3
ARMADA	**ADL(40 mg/eow) + MTX**		67	57.2	1.55	12.2	
	ADL(80 mg/eow) + MTX		73	55.5	1.55	12.8	
	Placebo + MTX		62	56	1.64	11.1	
Breedveld [21]	ADL(40 mg/eow)	52	274	52.1	0.7	1.6	5
PREMIER*	**ADL(40 mg/eow) + MTX**		268	51.9	0.7	1.5	
	Placebo + MTX		257	52	0.7	1.5	
Kim [22]	**ADL(40 mg/eow) + MTX**	24	65	48.5	1.4	6.8	1
	Placebo + MTX		63	49.8	1.3	6.9	
Detert [23]	**ADL(40 mg/eow) + MTX**	24	87	47.2	1.4	1.8	5
HIT HARD*	**Placebo + MTX**		85	52.5	1.3	1.6	
Kavanaugh [24]	**ADL(40 mg/eow) + MTX**	26	515	50.7	1.61	0.3	4
OPTIMA*	**Placebo + MTX**		517	50.4	1.6	0.4	
Keystone [25]	**CRT(200 mg) + MTX**	52	393	51.4	1.7	6.1	5
RAPID1	CRT(400 mg) + MTX		390	52.4	1.7	6.2	
	Placebo + MTX		199	52.2	1.7	6.2	
Smolen [26]	**CRT(200 mg) + MTX**	24	246	51.9	1.6	6.1	3
RAPID2	CRT(400 mg) + MTX		246	52.2	1.6	6.5	
	Placebo + MTX		127	51.5	1.6	5.6	
Choy [27]	**CRT(400meg/4 week) + MTX**	24	126	53	1.4	9.4	5
	Placebo + MTX		121	55.6	1.5	9.9	
Weinblatt [28]	**ETN(2 × 25 mg/ew) + MTX**	24	59	48	1.5	13	3
	Placebo + MTX		30	53	1.5	13	
Emery [30]	**ETN(50 mg/ew) + MTX**	52	274	50.5	1.7	0.7	5
COMET*	**Placebo + MTX**		268	52.3	1.6	0.8	
Klareskog [29]	ETN(2 × 25 mg/ew)	24	223	53.2	1.7	6.3	5
TEMPO	**ETN(2 × 25 mg/ew) + MTX**		231	52.5	1.8	6.8	
	Placebo + MTX		228	53	1.7	6.8	
Moreland [31] (till week 24)*	ETN**(50 mg/ew) + MTX**	102	244	50.7	NR	3.5	5
	Placebo + MTX		379	48.8		3.4	

Table 1 continued

Study	Treatment arms	Study duration (weeks)	N (ITT)	Age, years	HAQ score	Disease duration, years	JADAD score
Keystone [32]	GOL(100 mg) + placebo	24	133	51	1.4	5.9	5
GO-FORWARD	**GOL(50 mg) + MTX**		89	52	1.4	4.5	
	GOL(100 mg) + MTX		89	50	1.4	6.7	
	Placebo + MTX		133	52	1.3	6.5	
Emery [33]*	GOL(100 mg) + PLACEBO	24	159	48.2	1.6	4.1	5
	GOL(50 mg) + MTX		159	50.9	1.5	3.5	
	GOL(100 mg) + MTX		159	50.2	1.5	3.6	
	Placebo + MTX		160	48.6	1.5	2.9	
Kremer [34]	GOL(50 mg)	24	128	NR	1.6	7.4	5
	GOL(50 mg) + MTX		129		1.5	8.1	
	GOL(100 mg)		129		1.5	8.4	
	GOL(100 mg) + MTX		128		1.5	9.4	
	Placebo + MTX		129		1.5	7.4	
Tanaka [35]	**GOL(50 mg) + MTX**		86	50.4	1	8.8	5
	GOL(100 mg) + MTX		87	50	0.9	8.1	
	Placebo + MTX		88	51.1	1	8.7	
Maini [36]	**INF(3 mg/kg/4 weeks) + MTX**	30	86	56	1.8	8.4	5
ATTRACT	INF(3 mg/kg/4 weeks) + MTX		86	51	1.8	7.2	
	INF(10 mg/kg/8 weeks) + MTX		81	55	1.8	9	
	INF(10 mg/kg/4 weeks) + MTX		81	52	1.5	8.7	
	Placebo + MTX		88	51	1.8	8.9	
Clair [37]	**INF(3 mg/kg) + MTX**	54	373	51	1.5	0.8	3
ASPIRE*	INF(6 mg/kg) + MTX		378	50	1.5	0.9	
	Placebo + MTX		298	50	1.5	0.9	
Westhovens [38]	**INF(3 mg/kg) + MTX**	22	361	53	1.5	7.8	5
START	INF(10 mg/kg) + MTX		360	52	1.5	6.3	
	Placebo + MTX		363	52	1.5	8.4	
Edwards [39]	RTX(2 × 500 mg)	24	40	54	1.8	12	3
	RTX(2 × 500 mg) + cyclo.		41	53		9	
	RTX(2 × 500 mg) + MTX		40	54		10	
	Placebo + MTX		40	54		11	
Emery [40]	**RTX(2 × 500 mg) + MTX**	24	123	51.4	1.7	11.1	5
DANCER	RTX(2 × 1,000 mg) + MTX		122	51.1	1.8	10.8	
	Placebo + MTX		123	51.1	1.7	9.3	
Emery [41]	**RTX(2 × 500 mg) + MTX**		168	NR	NR	7.1	3
SERRENE	RTX(2 × 1,000 mg) + MTX		172			6.61	
	Placebo + MTX		172			7.48	
Tak [42]	**RTX(2 × 500 mg) + MTX**		249	NR	NR	0.99	5
IMAGE*	RTX(2 × 1,000 mg) + MTX		250			0.92	
	Placebo + MTX		249			0.91	
Smolen [43]	**TCL(8 mg/kg) + MTX**	24	205	50.8	1.6	7.5	5
OPTION	TCL(4 mg/kg) +MTX		214	51.4	1.6	7.4	
	Placebo + MTX		204	50.6	1.5	7.8	
Genovese [44]	**TCL(8 mg/kg) + DMARD**	24	805	53	1.5	9.8	5
TOWARD	**Placebo + DMARD**		415	54	1.5	9.8	
Yazici [45]	**TCL(8 mg/kg) + DMARD**		409	55.2	NA	8.62	3
ROSE	**Placebo + DMARD**		207	55.8	NA	8.52	

Table 1 continued

Study	Treatment arms	Study duration (weeks)	N (ITT)	Age, years	HAQ score	Disease duration, years	JADAD score
Weinblatt [46]	**ABT(10 mg/kg) + MTX**		318	51.4	1.5	1.9	5
	ADL + MTX		328	51	1.5	1.7	
Schiff [47]	**ABT(10 mg/kg) + MTX**	52	156	49	1.8	7.9	5
ATTEST	**INF (3 mg/kg) + MTX**		165	49.1	1.7	7.3	
	Placebo + MTX		110	49.4	1.8	8.4	
Yoo [1]	**INF-biosimilar(3 mg) + MTX**	30	304	50	1.6	NR	
PLANETRA	**INF(3 mg) + MTX**		302	50	1.6		

ABT abatacept, *ADA* adalimumab, *CRT* certolizumab pegol, *ETN* etanercept, *GOL* golimumab, *INF* infliximab, *RTX* rituximab, *TCL* tocilizumab. Bold letters indicate the treatment arms included in the meta-analysis. * Studies with MTX-naïve or csDMARD-naïve patients

Table 2 The efficacy and safety of biological and biosimilar treatment of RA compared to placebo, the results of the mixed treatment comparison

Treatment	ACR20 at week 24 OR [95 % CI]	ACR50 at week 24 OR [95 % CI]	Serious AEs OR [95 % CI]
Abatacept vs placebo	3.7 [2.17–6.06]	3.64 [2.25–5.76]	0.91 [0.64–1.18]
Adalimumab vs placebo	2.92 [1.9–4.36]	3.48 [2.27–5.22]	0.85 [0.57–1.19]
Certolizumab pegol vs placebo	7.69 [3.69–14.26]	8.46 [3.74–16.82]	2.02 [1.16–3.3]
Etanercept vs placebo	2.72 [1.47–4.71]	3.07 [1.68–5.38]	0.84 [0.48–1.34]
Golimumab vs placebo	2.8 [1.5–4.83]	2.83 [1.48–4.98]	1.63 [0.74–3.14]
Infliximab vs placebo	2.71 [1.51–4.54]	3.3 [1.82–5.66]	1.15 [0.77–1.64]
Rituximab vs placebo	2.81 [1.5–4.86]	3.19 [1.66–5.62]	1.18 [0.7–1.87]
Tocilizumab vs placebo	3.69 [1.87–6.62]	5.57 [2.77–10.09]	1.46 [0.89–2.27]
Infliximab-biosimilar vs placebo	3.47 [0.85–9.7]	4.06 [1.01–11.54]	1.87 [0.74–3.84]

Safety and tolerability

Thirty studies reported the occurrence of serious adverse events at week 24. Data for 14,708 patients were included in the analysis.

Etanercept had the lowest OR 0.84 [95 % CI 0.48–1.34], followed by adalimumab OR 0.85 [95 % CI 0.57–1.19] and abatacept 0.91 [95 % CI 0.64–1.18]. For infliximab-biosimilar the OR was 1.87 [95 % CI 0.74–3.84], while for the originator infliximab the OR was 1.15 [0.77–1.64]. In this endpoint, the lower ORs are in favor of biologicals, as the lower OR, the lower the chance of the occurrence of serious adverse events (AEs) compared to placebo. Certoluzimab pegol was found to have significantly worse safety profile than placebo OR 2.02 [1.16–3.3]. For the rest of the treatments, the difference between placebo and biological treatments was not significant.

Regarding the pairwise comparison of the treatments, we found no significant difference in the safety of infliximab-biosimilar and other biological treatments (see Fig. 2).

Discussion

The efficacy and safety of infliximab-biosimilar was compared only to infliximab in a non-inferiority RCT. This study was aimed to carry out an indirect meta-analysis and compare the efficacy and safety of infliximab-biosimilar to each biological available for the treatment of RA. We used mixed-treatment comparison, which in contrast to traditional methods allows the pairwise comparison of the treatments with different comparators. This was necessary, as infliximab-biosimilar was only compared to the originator infliximab treatment, while the other biologicals were usually compared to placebo, and moreover, head-to-head comparisons were rare.

Our study, involving altogether 15,044 RA patients, has demonstrated that there is no significant difference in the efficacy and safety of infliximab-biosimilar and other biological drugs in RA.

Thus far, several reviews have been published synthesizing the findings on direct comparisons of a single biological agent combined with sDMARDs and sDMARDs

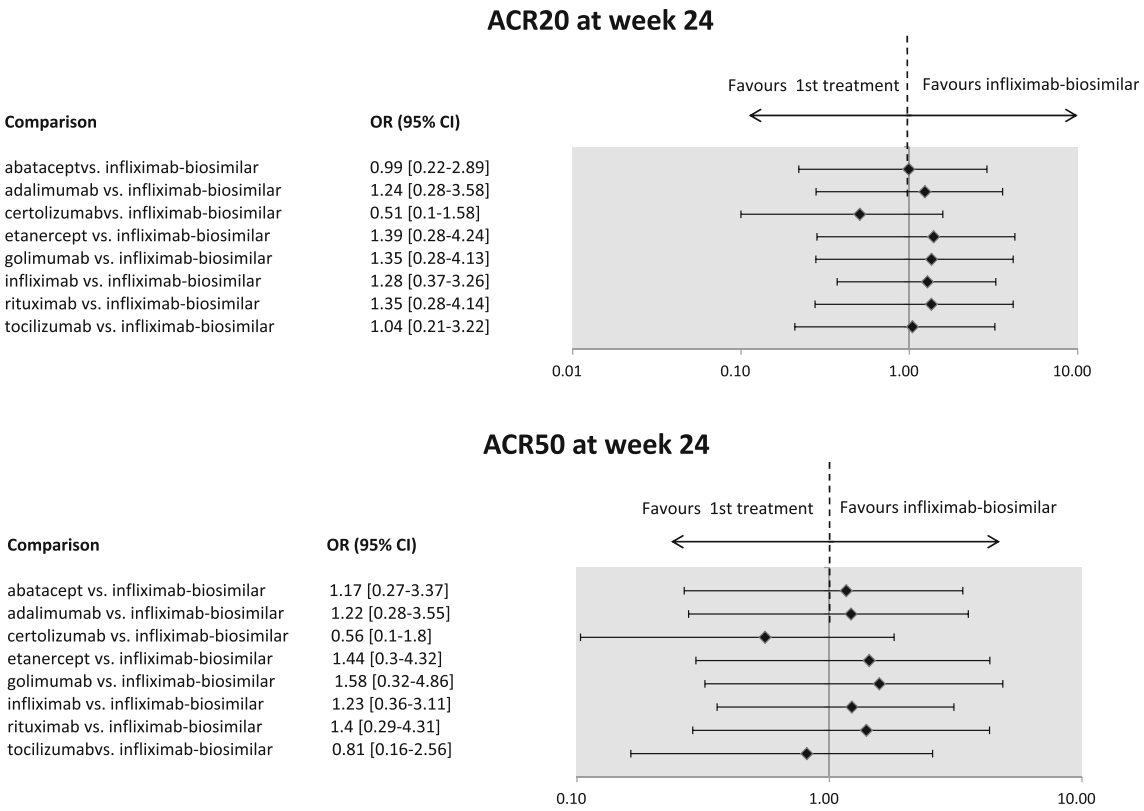

Fig. 1 Efficacy results of the mixed treatment comparison of infliximab-biosimilar versus other biologicals in RA–ACR20 and ACR50 response at week 24. The infliximab-biosimilar study presented results for week 30. The figure presents odds ratios (OR) between treatments. If the point estimate is greater than 1, then the biosimilar treatment is more effective (although not necessarily statistically significantly more effective) compared to the originator biologicals. Credibility intervals provide information on whether the difference between treatments is statistically significant. If the CI contains the value 1, the difference is not statistically significant

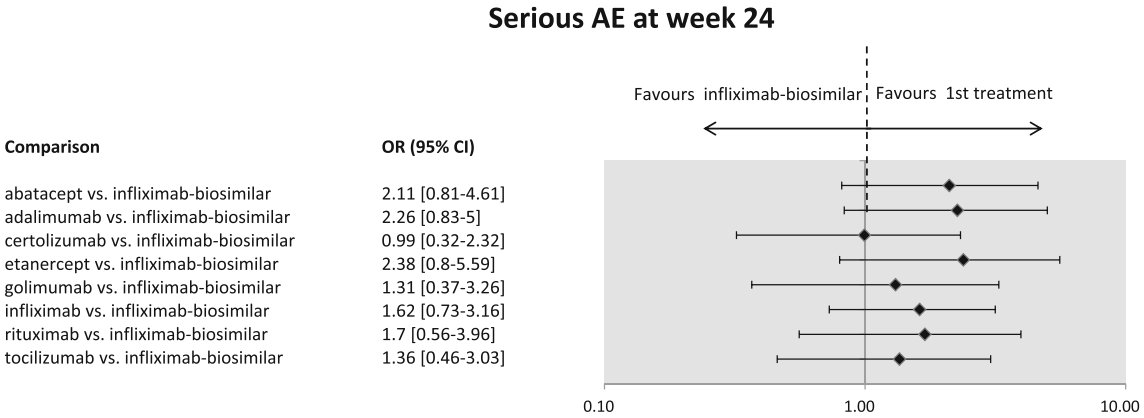

Fig. 2 Safety: Serious adverse events (AEs) in RA infliximab-biosimilar versus other biologicals at week 24. The infliximab-biosimilar study presented results for week 30. The figure presents odds ratios (OR) between treatments. If the point estimate is lower than 1, then the biosimilar treatment is safer (although not necessarily statistically significantly safer). Credibility intervals provide information on whether the difference between treatments is statistically significant. If the CI contains the value 1, the difference is not statistically significant

alone [48–57]. These studies come to the same conclusion as ours, that biologicals (including the originator infliximab) are significantly more efficient treatments compared to csDMARDs. Only the latest by Nam et al. [48] involved infliximab-biosimilar in the review; however, its efficacy and safety was not compared to other biologicals [48].

Indirect comparisons published previously have not considered infliximab-biosimilar, but the originator infliximab.

Some studies that carried out indirect comparison of the efficacy of different biologicals in RA found that the difference between infliximab and other biologicals were not statistically significant [4, 58–61], which supports our results for infliximab and infliximab-biosimilar.

However, some studies found significant differences between infliximab and certolizumab pegol in favor of certolizumab pegol [62–64]. Schmitz et al.'s study [63] involving 16 RCTs with patients who produced an inadequate response to MTX, and Turkstra et al.'s study [64] involving 27 RCTs with patients who produced an inadequate response to MTX found certolizumab pegol to be superior to infliximab in ACR20 and ACR50 responses at month 6. In our study, we also found that certolizumab pegol gave the highest ORs in terms of ACR20 and ACR50 response, but the difference between cetrolizumab pegol and infliximab and infliximab-biosimilar therapies were not statistically significant. In contrast to our study, the meta-analyses of Turkstra et al. [64] and Schmitz et al. [63] did not include the results of a recently published RCT with certolizumab pegol [27]. Furthermore, they also involved studies where patients were enrolled after MTX or other csDMARD failure, and studies where biologicals were administered in monotherapy. Turkstra et al. [64] included only two RCTs for infliximab (one small and one large), while we included five. These differences might partly explain the contradictory results.

Nevertheless, the outstanding result of certolizumab pegol deserves further considerations. In two of the certolizumab pegol RCTs (RAPID 1 and RAPID 2), patients who did not show an ACR20 response at both weeks 12 and 14 were to be withdrawn from the study [25, 26]. This design differs from the first biological RCTs in RA, and the early evaluation of efficacy reflects the EMA guideline (2003), which suggests to consider the principle as follows: "since it would be unethical to retain a patient with rheumatoid arthritis on placebo treatment indefinitely, the duration of placebo control must necessarily be limited. Depending on the severity and the activity of the disease, 3–6 months is acceptable" [65]. As a consequence, we observe an extremely high rate of early withdrawal in the placebo group in these certolizumab pegol trials [66]. The high withdrawal rates resulted in the high OR rate of certolizumab pegol compared to placebo.

Launois et al. [66] also doubt the comparability of the certolizumab pegol studies, due to the low ACR responses to placebo mentioned as a limitation in their study. However, they do not discuss that the low placebo response rate (as well as high ORs) and the extremely high rate of early withdrawal in the placebo group are in correlation.

Regarding safety and tolerability, some of the studies found significant differences between treatments, e.g., in favor of etanercept [58] or in favor of abatacept compared to a combined group of biologicals [61]. However, these studies examined a tolerability endpoint, namely the withdrawal of therapy due to adverse events, while we examined safety in terms of the occurrence of serious adverse events. The unfavorable safety results for certolizumab pegol can be also explained by the different study design and the extremely high withdrawal rates in the placebo group (see above).

We have to acknowledge some limitations of our study. Due to the diversity of study designs regarding patient population, we pooled the evidence from studies with DMARD-naïve patients (i.e., early aggressive treatment) and patients with inadequate response to DMARDs. Yet, Brodszky et al. [4] found a significant positive association with the disease duration efficacy of the drug. Our reasons to pool evidence from studies with different study populations were twofold: (1) some of the biologicals are also indicated for patients not previously treated with MTX or other csDMARDs, in the case of severe, active and progressive disease; (2) excluding studies with DMARD-naïve patients would have resulted in the exclusion of studies with high number of patients, which would result in biased results. For example, three of the four etanercept studies involved DMARD-naïve patients ($N = 1{,}624$), while only one with low sample population studied the efficacy of etanercept on patients who did not respond to previous treatments with csDMARD ($N = 89$).

Also, only combination therapy with csDMARDs was examined in this study. Furthermore, it is to be highlighted that the infliximab-biosimilar study reports efficacy and safety results at week 30, 6 weeks later than most of the studies included in the analysis, which report the results at week 24. However, patients in the infliximab-biosimilar study received the same number of injections as patients in the infliximab studies.

We acknowledge that estimated ORs might vary depending on the designs of the mixed treatment comparison (e.g., whether monotherapy studies, or studies with DMARD-naïve patients, are included); however, we found that the main conclusions, i.e., the similar efficacy and safety of biologicals, did not change. Also, the analysis was limited to the endpoints selected; however, the examination of other safety and efficacy endpoints may be of interest as well.

To conclude, according to our knowledge, this is the first study in RA that includes infliximab-biosimilar in a meta-analysis, and compares it to the originator biologicals that are approved for use in European clinical practice. Our study, involving data for 15,044 RA patients, has demonstrated the similar efficacy and safety profile of infliximab-biosimilar treatment compared to other biologicals. The

results might support clinical as well as financial decision making, providing evidence on the similar efficacy and safety of infliximab-biosimilar and other biologicals indicated in RA.

Acknowledgments The study was supported by an unrestricted grant from EGIS Pharmaceuticals and the Center for Public Affairs Studies Foundation.

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