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ABSTRACT

Introduction: Early biological treatment of rheumatoid arthritis (RA) may reverse the autoimmune response in some patients resulting in favorable long-term outcomes. Although the cost-effectiveness of this strategy has been questioned, biosimilar entries warrant the revision of clinical and pharmaco-economic evidence.

Areas covered: We conducted a systematic review of randomized controlled trials (RCTs) published up to 24 May 2018 in Pubmed, EMBASE and Cochrane CENTRAL, comparing infliximab with non-biological therapy in patients with RA naïve to methotrexate. We performed meta-analyses for efficacy outcomes at month 6 and years 1 and 2. Six RCTs were identified, involving 1832 patients. At month 6 ACR70 response and remission, and at year 1 ACR20/ACR70 responses and remission were improved significantly with first-line infliximab versus control. The differences were not significant at year 2. We reviewed cost-utility studies, up to 31 October 2018 in PubMed, Cochrane CENTRAL and the CRD HTA databases. Four studies indicated that first-line use of originator infliximab calculated at 2005–2008 prices was not cost-effective.

Expert opinion: We demonstrated the efficacy benefits of first-line infliximab therapy up to 1 year in methotrexate-naïve RA. We highlighted the need for standardized reporting of outcomes and conducting cost-effectiveness analyses of first-line biosimilar therapy in RA.

1. Introduction

Rheumatoid arthritis (RA) affects the synovial joints, causing inflammation and pain. Without treatment, progressive destruction of the joints can lead to considerable disability [1–3]. Patients with early or 'recent-onset' RA can be defined as individuals with a disease duration of 2 years or less [1,2]. Of late, there has been increasing emphasis on the prompt referral of patients with suspected early RA to rheumatologists in order to prevent irreversible joint damage [1,2]. Effective early treatment within the therapeutic 'window of opportunity' for RA may reverse the autoimmune response in some patients, leading to more favorable long-term outcomes compared with patients who are treated later in the disease course [4,5]. Moreover, achievement of early response may allow eventual tapering of RA treatment and potential drug-free remission in some patients [6].

Tumor necrosis factor inhibitors (TNFis) and other biological disease-modifying antirheumatic drugs (bDMARDs) have traditionally been used to treat patients with long-standing RA who have experienced inadequate response to previous conventional synthetic DMARDs (csDMARDs) such as methotrexate (MTX) or leflunomide. However, a number of studies have demonstrated that TNFi treatment is also effective in patients with early RA [7–15]. Indeed, several bDMARDs, including infliximab and other TNFis, have now been approved for the first-line treatment of patients with severe, active and progressive disease that has not been treated with MTX or other csDMARDs [16]. Recent meta-analyses have demonstrated the short-term benefits of biologic agents over csDMARDs in early, MTX/csDMARD-naïve RA, suggesting that more patients may achieve remission with first-line biological therapy than with csDMARDs [3,17–19]. However, the selection of studies in these meta-analyses were diverse and sometimes incomplete [3,17,18].

At the current time, bDMARDs such as infliximab are not widely used in first-line treatment of patients with early RA [16,20]. This fact is likely to be at least partly related to the most recent (2016) guidance on this topic issued by the European League Against Rheumatism (EULAR) [21] and National Institute for Health and Care Excellence (NICE) [16], both of which do not recommend first-line treatment with bDMARDs in patients with RA. The EULAR recommendations note that the early use, and potential for subsequent withdrawal, of bDMARDs was discussed, but was not supported by the majority of members of the recommendations task force

Article highlights

- We performed a systematic search of the literature for RCTs of infliximab in early methotrexate-naïve rheumatoid arthritis, up to 24 May 2018
- We identified six RCTs with diverse designs, involving 1,832 patients. The sample size ranged between 20-1,049, and follow-up times between 1-10 years.
- The reporting of results was heterogenous: in 26 journal articles we identified 57 endpoints for 19 time-points, allowing 244 time-point outcome combinations. 77% of outcomes were reported by a single study, 16% by at least two studies and only 7% by more than two studies. These results highlight the need for standardized reporting of outcomes.
- The meta-analysis demonstrated that first-line infliximab was more effective than delayed biological therapy at month 6 (ACR70, remission) and at year 1 (ACR20, ACR70, remission). At year 2 the difference was not significant.
- Economic evaluations using originator prices from years 2005–2008 did not demonstrate the cost-effectiveness of first-line infliximab therapy in early RA. The cost-effectiveness of this strategy at biosimilar prices is yet to be determined.

[21]. One reason for this was the lack of evidence for superiority of bDMARDs compared with the combination of MTX plus glucocorticoid. Furthermore, the task force commented that in the context of a treat-to-target strategy, initial use of csDMARDs has equivalent long-term efficacy. The cost-effectiveness of first-line bDMARD therapy was also questioned and considered to be poor given the lack of evidence supporting its superior long-term efficacy [21]. EULAR therefore recommend the use of MTX in combination with short-term glucocorticoid as a first-line strategy for the treatment of RA. Following treatment failure with initial csDMARD therapy, additional csDMARDs or bDMARDs/targeted synthetic DMARDs may be initiated, depending on the prognostic status of each patient. The EULAR recommendations further state that tapering of bDMARDs should be considered if the patient is in sustained remission [21]. NICE recommend the use of bDMARDs in combination with MTX for patients with severe RA (disease activity score [DAS] 28 > 5.1) following csDMARD therapy [16].

The lack of uptake of biologic agents for the first-line treatment of RA may also be due to high drug costs [20]. However, the introduction of biosimilar versions of RA-approved drugs may help to reduce treatment costs, with the availability of biosimilar infliximab since 2013 already leading to considerable price discounts in some regions [22]. Budget impact analyses have predicted large healthcare savings following the uptake of biosimilar infliximab in RA across multiple markets [23–25]. There is, however, a need for more recent cost-effectiveness analyses that take into account recent reductions in the cost of some bDMARDs following the introduction of biosimilars. Because of its comparable efficacy and lower cost versus originator infliximab, biosimilar infliximab may be an ideal candidate with which to reassess the available medical and economic evidence for first-line biological therapy in MTX-naïve, early RA. The aims of our study, therefore, were to systematically review the literature and analyze the outcomes of first-line infliximab treatment versus other treatment strategies in patients with MTX-naïve RA, with a special focus on long-term efficacy outcomes. We also reviewed available health economic literature for infliximab cost-utility studies in this patient population.

2. Methods

2.1. Search strategy for clinical studies

We conducted a systematic literature search in PubMed, EMBASE and the Cochrane Central Register of Controlled Trials (CENTRAL) up to 24 May 2018. Our search included the Cochrane filter for clinical trials [26], all known development codes of infliximab [27–29], and the MeSH term for RA. Full details of the PubMed, Embase and CENTRAL search criteria are shown in Supplementary Tables S1, S2 and S3, respectively. To identify papers not yet indexed by MeSH terms, we conducted another search in PubMed without including RA as a keyword for the period of January 1 to 24 May 2018 (Supplementary Table S1).

2.2. Selection of clinical studies

Eligible studies included published randomized controlled trials (RCTs) involving patients with RA who were MTX-naïve at randomization. The treatment intervention of interest was infliximab. Control treatments could include any pharmacological treatment (i.e. placebo, csDMARDs and/or steroids) with or without concomitant MTX that did not involve any biological therapy at study initiation, although biological treatment could be included per protocol in a later phase of the study. Multiple publications from the same RCT were retained, including RCT extension studies. We did not impose any language restrictions on our search, but we excluded case studies, pooled analyses, review articles and conference abstracts.

For mapping available evidence, outcomes of interest included any physician- or patient-reported clinical efficacy, economic or radiological outcome, as well as any key safety outcomes such as occurrence of adverse events (AEs), discontinuations due to AEs, deaths, infusion reactions, severe infections, tuberculosis, malignancy, cardiovascular events and immunogenicity (i.e. the presence of anti-drug antibodies [ADAs]). For quantitative syntheses, we included studies reporting American College of Rheumatology (ACR) response criteria (ACR20/ACR70) or clinical remission (see 'Data extraction' section below for definitions) measured at month 6, year 1 and year 2. The abstract of each potential publication was reviewed by two independent researchers to confirm relevance and, if needed, a third independent researcher resolved any differences.

2.3. Data extraction from clinical studies

All reported outcomes (detailed above) and corresponding time points for all relevant primary and secondary publications of the selected studies were recorded. For quantitative synthesis, a Microsoft Excel spreadsheet was developed to capture the following details of relevant studies by treatment arm: study name; reference; treatment and dosing; number of randomized patients, risk of bias assessment; ACR20, ACR70 and

remission based on any criteria (ACR, EULAR, DAS in 28 or 44 joints [DAS28/DAS44], Simple Disease Activity Index [SDAI] or Clinical Disease Activity Index [CDAI]) at month 6, year 1 and year 2. If multiple remission measures were reported, we used DAS28-erythrocyte sedimentation rate (ESR) if available, or the measure with highest number of patients in remission in the treatment arms combined.

2.4. Risk of bias assessment of clinical studies

The Cochrane Risk of Bias Tool [26] was applied to all studies. In short, based on the overall assessment of available information on randomization, treatment allocation concealment, blinding of participants, personnel and outcome assessments, the attrition of participants as well as the reporting of outcomes and other potential sources, we categorized studies as having a low, high or unknown risk of bias. Due to the transitions between double-blind and open-label observation strategies at various time points, risk of bias was assessed separately at month 6, year 1 and year 2.

2.5. Meta-analysis of clinical endpoints

All endpoints were included on an intent-to-treat basis, using the number of patients initially randomized. Calculations were performed using the Stata14 statistical software package (StataCorp LLC., College Station, Texas, USA). Due to the heterogenous design of studies, we chose different quantitative synthesis methods for pre-defined short- and long-term outcomes. For month 6 outcomes, a network meta-analysis using the Stata network meta package was performed comparing the infliximab plus MTX combination, multiple DMARD combinations with corticosteroid with or without infliximab, steroid and MTX combinations, and MTX monotherapy, using MTX monotherapy as control [30]. There was no source of loop-inconsistency (i.e. incomparable results from direct and indirect comparisons) within the network, therefore we applied the consistency network meta-analysis model (assuming random effects for study heterogeneity but no inconsistency between direct- and indirect comparisons). Due to the changes in applied treatments and observation strategies from month 6, treatment arms used in the network meta-analysis were not feasible for later outcomes. Rather, treatments were dichotomized according to a first-line infliximab treatment versus other strategies (control) at randomization, and, – considering the heterogeneity of studies – outcomes at year 1 and 2 were assessed using a random effects meta-analysis according to the method of DerSimonian and Laird [31]. Month 18 outcomes were included in the meta-analysis at year 2, if no year 2 outcomes were available from the same study. For ACR20, ACR70 and remission, log odds ratios (ORs) with 95% confidence intervals were applied for the comparisons. The significance threshold was set at p < 0.05.

We also investigated how the results of our analysis at year 2 would have changed if the ASPIRE trial [15], a 1-year parallel design study of first-line infliximab versus placebo in combination with MTX, had included a long-term extension study. We projected hypothetical year 2 ACR70 results in the ASPIRE study using published year 1 ACR70 data and included the simulated results in our meta-analysis.

2.6. Search for cost-utility studies

We also searched for cost-utility studies of first-line infliximab in PubMed, Cochrane CENTRAL and the Centre for Reviews and Dissemination (CRD) Health Technology Assessment (HTA) database of the University of York up to 31 October 2018. The search-terms included keywords for economic analyses, infliximab and the MeSH terms for rheumatoid arthritis. Full details of the PubMed, CENTRAL and CRD search criteria are shown in Supplementary Tables S4, S5 and S6, respectively. Eligible studies included those that reported incremental cost-effectiveness ratio (ICER) values for infliximab in patients with MTX-naïve RA. Full text manuscripts were considered. Data extraction for main characteristics of the evaluations (publication year, country, type of model, time horizon applied, data sources used, study sample, applied treatments and comparators, year of costs, study perspective, ICER) was performed.

3. Results

3.1. Literature search of clinical studies

A PRISMA flow diagram for our systematic review is shown in Figure 1 and includes the number of citations found and screened. We identified six RCTs (reported in 26 full text publications) of first-line infliximab in RA: ASPIRE (3 publications) [15,32,33], BeSt (15 publications) [34–48], Durez 2007 (1 publication) [49], IDEA (1 publication) [12], NEO-RACo (3 publication) [50–52] and Quinn 2005 (3 publications) [53–55]. The sample size of these RCTs ranged from 20 to 1,049 patients; follow-up times were between 1 and 10 years. Key details of the studies are shown in Table 1. Data from six studies (reported in eight publications [12,15,34,35,38,49,51,53]) were included in the quantitative synthesis. The studies included 1,832 patients at baseline, of whom 1,009 (55%) received first-line infliximab. Inclusion criteria for RA diagnosis was based on ACR criteria in all six RCTs. Disease activity criteria was defined in most studies as having ≥6 tender and swollen joints. Disease duration was limited to between 3 months and 3 years.

Results were reported for 19 different time points and for 57 relevant endpoints, allowing 244 different time point–outcome combinations (Supplementary Tables S7 and S8). Of these, 188 (77%) were reported only by a single study, 39 (16%) by at least two studies and 17 (7%) by more than two studies. Results of ACR response and remission rates by any criteria were reported at month 6 by three [12,34,49] and four [12,34,49,51] studies, respectively, and at year 1 by five and four studies, respectively [12,15,34,49,51,53]. ACR20 and ACR70 at year 1 were reported by four studies; all other measures were reported by no more than three studies at the same time point. Apart from three studies reporting ACR70 outcomes at year 2 [35,51,53], longer-term results (>1 year) for each measure were reported by a maximum of two studies at the same time point (Supplementary Tables S7 and S8). Although the presence of ADAs was included among the pre-defined outcomes, none of the studies reported ADA results.
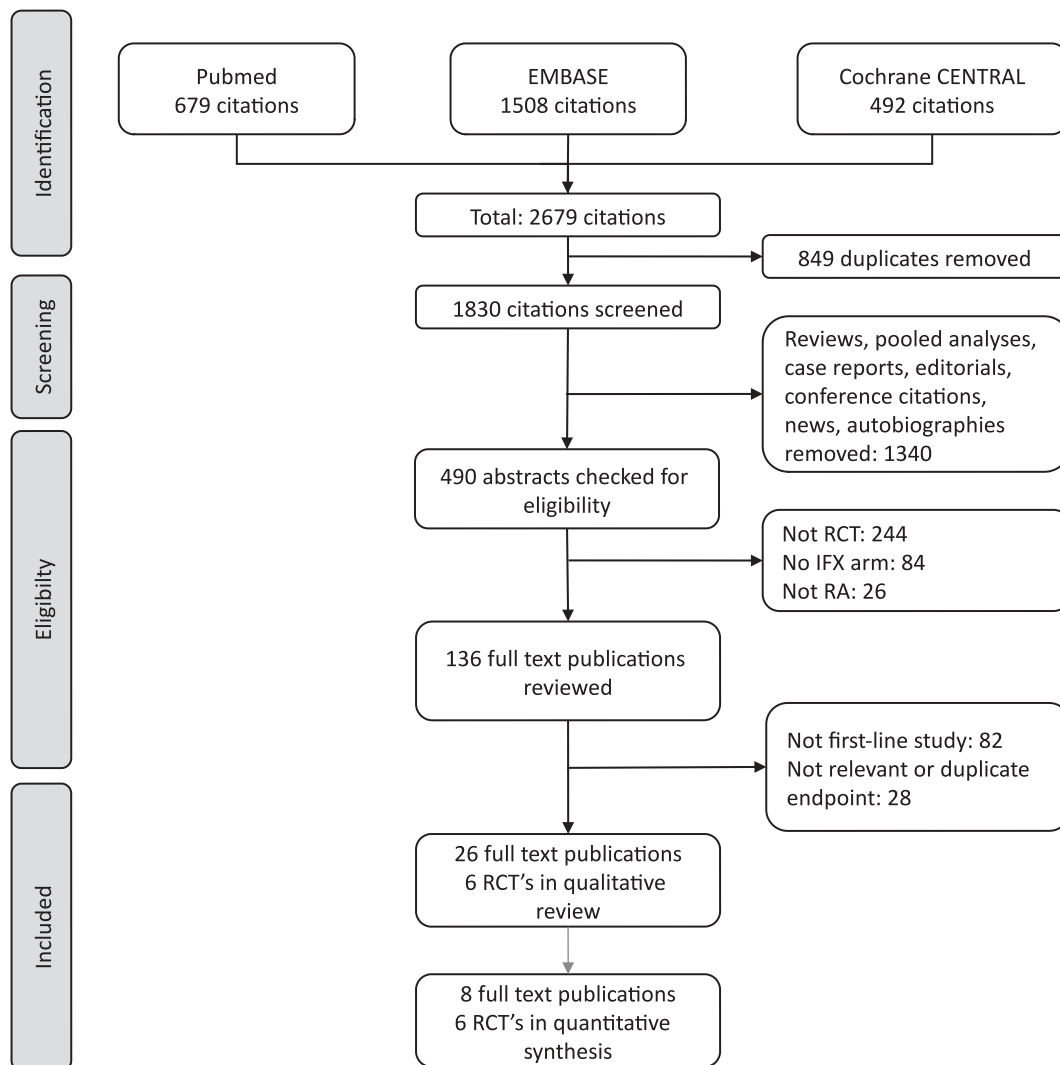
Pubmed 679 citations	EMBASE 1508 citations	Cochrane CENTRAL 492 citations

Total: 2679 citations

849 duplicates removed

1830 citations screened

Reviews, pooled analyses, case reports, editorials, conference citations, news, autobiographies removed: 1340

490 abstracts checked for eligibility

Not RCT: 244
No IFX arm: 84
Not RA: 26

136 full text publications reviewed

Not first-line study: 82
Not relevant or duplicate endpoint: 28

26 full text publications 6 RCT's in qualitative review

8 full text publications 6 RCT's in quantitative synthesis

Figure 1. PRISMA flow diagram of the systematic review.

CENTRAL Cochrane Central Register of Controlled Trials; *IFX* infliximab, *RA* rheumatoid arthritis, *RCT* randomized controlled trial.

3.2. Methodological heterogeneity of clinical studies

The study designs showed great heterogeneity. The methodological heterogeneity of studies and the treatment arms are summarized in Figure 2 and Supplementary Table S9, respectively. Patients were naïve to any DMARDs in three studies [12,51,53], and were exposed to csDMARDs other than MTX in two studies [34,49]. In ASPIRE [15], minimal exposure to MTX was allowed. All patients were naïve to bDMARDs. Two studies had a duration of 1 year [15,49] and four studies had patient follow-up beyond 1 year [12,34,51,53]. Randomized treatments changed substantially between month 6 and year 2 in all studies. The BeSt [34] study was an open-label, strategic, treat-to-target study from the onset. In the NEO-RACo [51] and IDEA [12] studies, patients continued an open-label, treat-to-target protocol following 6 months of double-blind treatment. Patients in the Quinn 2005 et al. [53] study could continue open-label MTX treatment after cessation of infliximab at 1 year. Infliximab was also discontinued in the NEO-RACo study after 6 months [51].

3.3. Risk of bias analysis of clinical studies

At month 6 relevant outcomes were reported from four studies. One study was a randomized, open-label, strategic trial and was assessed as having a high risk of bias due to the lack of blinding [34]. Three double-blind, randomized controlled studies had a low risk of bias [12,49,51]. At year 1, three studies were categorized as high risk of bias due to their open-label design [12,34,51], while outcomes were measured during the double-blind randomized phase of three studies categorized as having a low risk of bias [15,49,53]. At year 2, all studies were open-label and were assessed as having a high risk of bias [12,34,51,53].

3.4. Meta-analyses of clinical studies

We performed network meta-analysis for efficacy outcomes at month 6. The network map for 6-month ACR and remission outcomes are displayed in Supplementary Figure S10. There was no source of inconsistency in the network structure of the included treatments, therefore we performed the network meta-analysis using the consistency model assuming no

Table 1. RCTs of first-line infliximab treatment in patients with RA.

Study	Reference	Patients	Randomized arms	N	Arm in network meta-analysis	Arm in random effects meta-analysis	Double-blind phase	Open-label phase
ASPIRE	[15,32,33]	RA (ACR 1987) Age 18–75 years Disease duration ≥3 months, ≤3 years Active disease: ≥10 SJC; ≥12 TJC and at least one of: RF-positive or bone erosion on hand/feet or CRP ≥20 mg/L Exclusion: prior MTX (≤3 doses were allowed), any sDMARD in 4 weeks prior to baseline (LEF in 6 months), prior TNFi treatment	3 mg/kg IFX (at week 0, 2, 6 and q8w) + MTX	373	IFX + MTX	FL-IFX	54 weeks Randomization at BL: 3 groups, 5:5:4 Baseline steroids and NSAIDs were allowed	No open-label phase
			6mg/kg IFX (at week 0, 2, 6 and q8w) + MTX	378				
			PLA + MTX	298	MTX	Control		
BeSt	[34–47]	Early RA (ACR 1987) Disease duration ≤ 24 months Age ≥18 years Active disease: ≥6/66 SJC; ≥6/68 TJC; ESR ≥28 mm/hour; or a global health score ≥20 mm (best = 0, worst = 100 mm) Exclusion: previous treatment with sDMARDs other than anti-malarials	Initial IFX combination: MTX + IFX (3->10 mg/kg) -> pre-defined sDMARD mono/combination sequence	128	IFX + MTX	FL-IFX	No double-blind phase	10-year strategic trial Randomization at BL: 4 groups Treatment adjustments every 3 months: if DAS44 ≥ 2.4, -> next step in the allocated treatment. If DAS44 ≤ 2.4 for 6 months, medication was tapered ->1 drug at maintenance dose. PRD and IFX were always tapered first. If DAS44 ≥ 2.4 after tapering, the last effective dose was reintroduced
			Sequential monotherapy: MTX -> pre-defined sDMARD sequence	126	MTX	Control		
			Step-up combination: MTX -> MTX + pre-defined sDMARD combination sequence	121	MTX	Control		
			Initial PRD combination: MTX + SSZ + PRD (60 -> 7.5 mg/week) -> pre-defined sDMARD mono/combination sequence	133	Co	Control		
Durez 2007	[49]	RA (ACR 1987) Disease duration <1 year Age not specified Active disease: SJC ≥6; TJC ≥8 Exclusion: previous MTX, corticosteroids ≥3 months or 4 weeks prior to BL, >2 sDMARDs or iv MPD	IFX 3 mg/kg iv (week 0, 2, 6, then q8w) + MTX	15	IFX + MTX	FL-IFX	52 weeks Randomization at BL: 3 groups	After week 52 iv MPD and IFX was discontinued. No report available about extension study
			iv MPD (1 g) + MTX	15	CS	Control		
			MTX	14	MTX	Control		
IDEA	[12]	RA (based on ACR 1987 criteria) Symptom duration: 3–12 months Age 18–80 years Active disease (DAS44 > 2.4) DMARD-naïve Exclusion: any prior csDMARD, corticosteroid use within 1 month prior to baseline	IFX (3 mg/kg) + MTX	55	IFX + MTX	FL-IFX	26 weeks Randomization at BL: 2 groups If DAS44 > 2.4, treat-to-target: MPD 120 mg iv/sc at week 6, 14, 22, 38, 50	52 weeks Pragmatic escalation protocol: sDMARD change or escalation, if DAS >5.2 and two sDMARDs failed -> other biologic, if DAS44 < 1.6 for 6 months: IFX withdrawal
			MPD (250 mg iv at week 2, 6, 14, 22) + MTX	57	CS	Control		
NEO-RACo	[50,51]	RA (ACR 1987) Symptom duration: ≤12 months Age 18–60 years Not permanently work disabled or retired Active disease: ≥6 SJC and ≥6 TJC and at least one from: morning stiffness ≥45 min; ESR ≥30 mm/hr; CRP ≥20 mg/L; or DMARD-naïve Exclusion: oral glucocorticoids in previous 6 months; iv glucocorticoids in 1 month	IFX (3 mg/kg at week 4, 6, 10, 18, 16) + open intensified FIN-RACo (MTX + SSZ + HCQ + PRD) -> pre-defined schedule of sDMARDs	50	IFX + Co	FL-IFX	26 weeks Double-blind infusion induction added to the open-label FIN-RACo protocol. Treatment targeted to remission during the entire study	5 years Strategic treatment targeted to remission. Mandatory switches if ACR remission not achieved, always using a combination of three sDMARDs + PRD. If <ACR50 response after week 26 at consecutive visits, unrestricted treatment including switch to other TNFi
			PLA (at wk 4, 6, 10, 18, 16) + open intensified FIN-RACo (MTX + SSZ + HCQ + PRD) -> pre-defined schedule of sDMARDs	49	Co	Control		

(Continued)

treatment effect variation between designs [30]. ACR70 and remission outcomes at 6 months were improved significantly with first-line infliximab plus MTX compared with MTX control (Table 2). ACR20 at 6 months was not significantly different between the infliximab and control groups (Table 2).

At year 1 and year 2, first-line infliximab was compared with other strategies via random effects meta-analysis. Heterogeneity between studies was low and was not significant in the year 1 models. Our analyses showed that ACR20, ACR70 and remission at year 1, significantly favored the infliximab group compared with the control group (Table 2); ACR70 response at year 1 is also shown in Figure 3(a). At year 2, there were no significant differences in outcomes (ACR20, ACR70 and remission) between the infliximab and control groups (Table 2; Figure 3(b)). Heterogeneity was significant in the year 2 ACR70 (I^2 = 79.2%; p = 0.002) and remission models (I^2 = 75.8%; p = 0.006).

In studies with TNFis that had at least 1 year of a double-blind, parallel phase and reported year 2 results (etanercept: COMET [9], Ebrel ERA [56]; golimumab: GO-BEFORE [57,58]; adalimumab: PREMIER [8]; infliximab: Quinn 2005 [53]), there was an additional 8.9% and 9.3% of patients with an ACR70 response at year 2 versus year 1 in the control group and TNFi group, respectively. We assumed that ACR70 response rates of the MTX alone and infliximab plus MTX combination arms in ASPIRE would change from 21% and 38% in year 1 to 21% and 35.8% by year 2, respectively. Based on these results, projected hypothetical year 2 ACR70 outcomes from the 1-year parallel design ASPIRE study were included in our meta-analysis of ACR70 response at year 2 (Figure 3(b)). Although projected year 2 ACR70 data from ASPIRE increased the between-group difference in favor of infliximab, the difference remained non-significant (Figure 3(b)).

3.5. Summary of cost-effectiveness studies

Our searches yielded 96 abstracts in PubMed, 37 abstracts in the Cochrane CENTRAL database and 123 abstracts in the CRD HTA database. We removed 27 duplicates, 171 records based on their title and two conference posters. From the remaining 56 records we identified four full text journal publications reporting cost-utility studies of infliximab as first-line treatment in patients with RA (Table 3). Two studies were conducted in the United States, and the other studies were conducted in the United Kingdom and the Netherlands. ICERs ranged between €22,000/quality-adjusted life-year (QALY) and £650,000/QALY (Table 3). The cost effectiveness of first-line infliximab treatment was above the usually acceptable financial threshold of the respective countries in most models. All models were calculated with prices prior to the registration of biosimilar infliximab by the European Medicines Agency in 2013.

4. Conclusions

In summary, our systematic review and meta-analysis has demonstrated that 1-year efficacy outcomes (ACR20, ACR70 and remission) were improved significantly with first-line infliximab versus control strategies in patients with csDMARD-naïve RA. These efficacy differences were not significant in
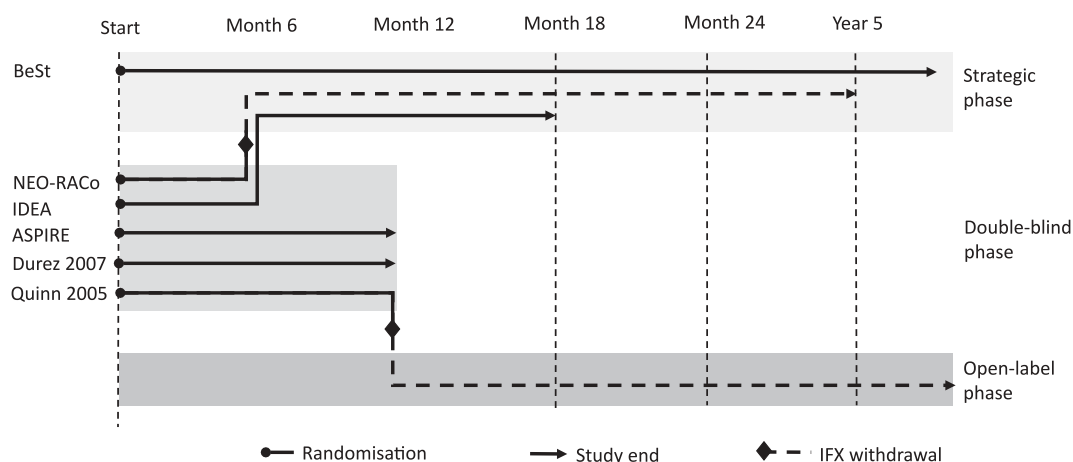
Table 1. (Continued).

Study	Reference	Patients	Randomized arms	N	Arm in network meta-analysis	Arm in random effects meta-analysis	Double-blind phase	Open-label phase
Quinn 2005	[53]	RA (ACR 1987) Symptom duration: <12 months Poor prognosis by PISA scoring system (PISA score ≥3) No previous sDMARDs or oral corticosteroids, MCP joint involvement, stable on NSAID ≥2 weeks prior to screening Exclusion: inflammatory condition that might confound the diagnosis; previous TNFi; CPA; nitrogen mustard; chlorambucil; or other alkylating agents	IFX (3 mg/kg) + MTX PLA + MTX	10 10	IFX + MTX MTX	FL-IFX Control	54 weeks Randomization at BL: 2 groups	8 years IFX was discontinued at week 54, non-responders received step-up combination therapy (+ SSZ -> + HCQ)

ACR American College of Rheumatology, BL baseline, Co multiple DMARD combination with corticosteroid, CPA cyclophosphamide, CRP C-reactive protein, CS steroid and methotrexate combination, DAS Disease Activity Score, ESR erythrocyte sedimentation rate, FL first-line, HCQ hydroxychloroquine, IFX infliximab, iv intravenous, LEF leflunomide, MCP metacarpophalangeal, MPD methylprednisolone, MTX methotrexate, NSAID non-steroidal anti-inflammatory drug, PISA Persistent Inflammatory Symmetrical Arthritis, PLA placebo, PRD prednisolone, q8w every 8 weeks, RA rheumatoid arthritis, RCT randomized controlled trials, RF rheumatoid factor, sc subcutaneous, (s)DMARD (synthetic) disease-modifying antirheumatic drug, SJC swollen joint count, SSZ sulfasalazine, TJC tender joint count, TNFi tumor necrosis factor inhibitor

Figure 2. Heterogeneity of studies.
IFX infliximab.

a longer follow-up of 2 years. The diminished effect size and precision of long-term estimates may partly be explained by the highly diverse methodology of studies. The long-term effects of first-line biological therapy on disease progression should be further analyzed using all TNFi agents.

Analysis of cost-utility studies performed before the availability of lower cost infliximab biosimilars revealed that first-line use of originator infliximab was not cost effective. New cost-effectiveness analyses are needed in early RA that consider the sizable potential savings resulting from the uptake of biosimilar infliximab.

Given the potentially considerable savings due to biosimilar infliximab, the evident short-term efficacy benefits, the availability of prognostic factors for progressive disease and the potential for biological-free remission if administered early, the cost-effectiveness of first-line infliximab in early, treatment-naïve RA should be re-assessed using biosimilar prices.

5. Expert opinion

The results of this systematic review and network meta-analysis show that ACR70 and remission outcomes at 6 months in patients with MTX-naïve RA were significantly improved with infliximab versus MTX control. At year 1, ACR20, ACR70 and remission outcomes were also significantly improved with infliximab versus control strategies. However, at year 2, no statistically significant differences in ACR20, ACR70 or remission outcomes were observed between treatment groups. Long-term (>2 years) results on clinical remission were available only from two RCTs (BeSt [34], NEO-RACo [51]) and patient-reported outcome data were presented only from the BeSt [34] and Quinn 2005 [53] studies.

We have demonstrated the need for improved standardized reporting of studies. Despite the 244 reported time point-outcome combinations, neither ACR response nor remission rates were reported by all studies at 6 months and 1 year, and apart from ACR70, only two studies reported these efficacy outcomes at the same time point after 1 year. For a given time point only two outcomes were reported in four studies and 13 outcomes were reported in three studies. The diverse

reporting of results is a major barrier for effective evidence synthesis.

The included studies showed increasingly heterogenous designs over time, which partly explains the smaller effect sizes and increasing variance at year 2 compared with year 1 outcomes. However, due to the small number of studies, the decomposition of study heterogeneity via meta-regression was not feasible [26]. The randomized treatments were modified substantially beyond month 6 in all studies. In NEO-RACo [51], infliximab treatment was discontinued after 6 months, and in Quinn 2005 [53], after 12 months. In the BeSt study [34,35] at year 2 nearly three quarters of initially randomized patients received infliximab plus MTX combination therapy, while in the DMARD monotherapy arm more than one quarter of patients received infliximab. In IDEA [12] two thirds of patients in the control arm received dose escalation, while DMARDs were adjusted in more than half of the patients in the infliximab arm, and infliximab was discontinued in every fourth patient due to sustained low disease activity.

While five of the six studies measured endpoints in a double-blind setting at month 6, year 2 efficacy outcomes were available only from open-label studies. We hypothesize that longer-term benefits of biologic combinations and MTX monotherapy would be demonstrated in studies that remain blinded for longer periods. Therefore, using ACR70 data, we investigated how the results of our analyses at year 2 might have changed if the 1-year long ASPIRE study [15] had included a long-term extension study. The absolute risk difference in ACR70 response at year 2 between the treatment and control arms in the PREMIER [8] and COMET [9] studies were 26% and 25%, respectively. However, in our analysis of hypothetical year 2 ASPIRE results, we assumed a conservative 15% difference between infliximab plus MTX and MTX monotherapy. Although the projected year 2 ACR70 data from ASPIRE increased the between-group difference in favor of infliximab, the difference remained non-significant. Although loss of sustained clinical response due to immunogenicity [63] may be an alternative explanation for the moderate long-term effect size, we found no reports of anti-drug-antibody levels in the included studies (Supplementary Table S7).

Table 2. Results of meta-analysis for efficacy outcomes at month 6, year 1 and year 2.

	Network meta-analysis of month 6 results First-line IFX + MTX vs MTX monotherapy				Random effects meta-analysis of year 1 results First-line IFX vs control				Random effects meta-analysis of year 2 results First-line IFX vs control			
	Studies	Ref.	log OR [95% CI]	p value	Studies	Ref.	log OR [95% CI]	p value	Studies	Ref.	log OR [95% CI]	p value
ACR20	BeSt Durez 2007 IDEA	[12,34,49]	0.854 [−0.337, 2.045]	0.160	ASPIRE BeSt Durez 2007 Quinn 2005	[15,34,49,53]	0.459 [0.424, 0.495]	<0.0001	BeSt IDEA Quinn 2005	[12,35,53]	−0.002 [−0.108, 0.104]	0.602
ACR70	BeSt Durez 2007 IDEA	[12,34,49]	1.046 [0.526, 1.567]	<0.0001	ASPIRE BeSt, Durez 2007 Quinn 2005	[15,34,49,53]	0.716 [0.598, 0.835]	<0.0001	BeSt IDEA NEO-RACo Quinn 2005	[12,35,51,53]	0.103 [−0.285, 0.491]	0.603
Remission	BeSt Durez 2007 IDEA NEO-RACo	[12,34,49,51]	1.058 [0.556, 1.561]	<0.0001	BeSt IDEA NEO-RACo Durez 2007	[12,34,49,51]	0.256 [0.171, 0.341]	<0.0001	BeSt IDEA NEO-RACo Quinn 2005	[12,38,51,53]	−0.070 [−0.445, 0.304]	0.713

ACR American College of Rheumatology, CI confidence interval, IFX infliximab, MTX methotrexate; OR odds ratio; Ref. reference.

A key strength of our study is that we provide a comprehensive evaluation of efficacy endpoints that are relevant for pharmacoeconomic analyses – ACR20, ACR70 and remission – at different time points from 6 months up to long-term outcomes at 2 years. While the benefit of immediate infliximab in preventing joint damage has been shown over other treatment strategies [15,34], radiographic progression was out of the scope of this review. Several other recent meta-analyses have compared the combination of biologic agents plus MTX over csDMARDs in early MTX-naïve RA [3,17–19,64]. The Cochrane report from Singh et al. [3] included analyses of ACR50, Health Assessment Questionnaire (HAQ) scores and remission rates at <6 months, 6–12 month and >12 month time points. From the included 19 RCTs seven were infliximab studies; however, in one of them all patients received MTX at baseline [3]. Cai et al. [17] included 20 RCTs in the analysis of ACR20, ACR50 and ACR70 endpoints. In one of the five included infliximab studies, all patients received three months of MTX induction therapy before randomization [17]. Stevenson et al. [64] in a comprehensive HTA report commissioned by NICE, synthesized month 6 ACR and EULAR response outcomes for seven biological drugs, including two infliximab trials. Albert et al. [18] included one infliximab study in an indirect pairwise meta-analysis of year 1 ACR20, ACR50 and ACR70 endpoints from six RCTs of biologics + DMARD therapy. Donahue et al. [19] reported less radiological progression and higher ACR50 response rates at year 1 with four TNFis in combination with MTX versus MTX monotherapy. Three of the 13 trials included infliximab. Taken together, data from these studies support the results of our own analysis that, in the short-term, biologics combined with MTX are superior to MTX monotherapy in terms of ACR and remission endpoints in early RA. To date, no consistent evidence supports the superiority of one biologic therapy over another.

In all the six RCTs, RA diagnosis was based on the 1987 ACR diagnostic criteria for RA [65], which have been criticized for their lack of sensitivity in early disease [66]. The new ACR/EULAR classification system introduced in 2010, focuses on symptoms at earlier stages of the disease rather than establishing the diagnosis by its late-stage features [66]. Further studies using the new ACR/EULAR classification system may contribute to a better understanding of the effectiveness of first-line infliximab treatment in early-stage RA. Moreover, we believe that there is a need for new outcomes to detect the long-term effects of deteriorated health patients may suffer due to the lack of early elimination of symptoms. These may include measures to assess the impact on internalization and legitimization of societal stereotypes of RA, subjective expectations regarding future health and treatment goals, acceptability of symptoms, uncertainty about the future, work capacity, long-term life planning and wellbeing in terms of the ability to do things that are important in patients' lives [67–71].

In our cost-utility analysis, the cost-effectiveness of originator infliximab was deemed unacceptable in the published economic analyses we reviewed, with ICERs of between €22,000/QALY and £650,000/QALY reported. Due to the broad variety of modelling assumptions of long-term
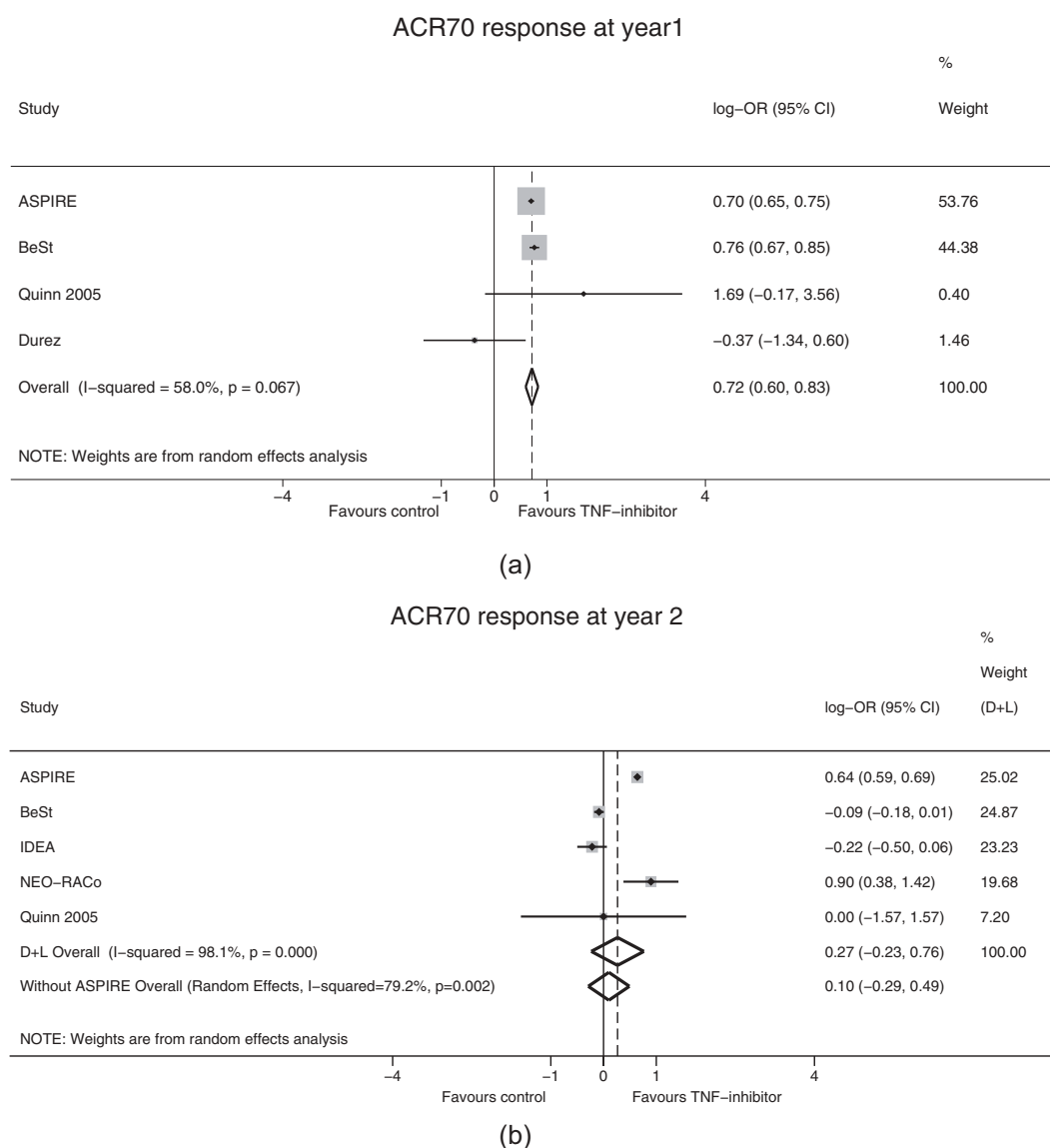
Figure 3. Random effects meta-analysis ACR70 response (a) at year 1 and (b) at year 2 with and without simulated ASPIRE results*.

*ASPIRE 2-year ACR70 response was projected from 1 year-long double-blind, parallel-group RCTs*ACR* American College of Rheumatology, *CI* confidence interval, *D + L* DerSimonian & Laird random effects meta-analysis, *OR* odds ratio, *RCT* randomized controlled trial

outcomes, the results of cost-effectiveness analyses need to be interpreted with caution. Although systematic reviews did not demonstrate a substantial difference between branded TNFi drugs in terms of efficacy, ICERs between individual drugs differed considerably. In a review of six cost-utility analyses by Stevenson et al. [64], ICERs were >US$100,000/QALY in three of four infliximab studies, two of five adalimumab studies, and five of six etanercept studies. Treating biological agents as a homogenous group, Stevenson et al. estimated that the ICER for a first-line biological strategy versus MTX monotherapy in MTX-naïve, early RA was £58,300/QALY, still above the acceptable cost-effectiveness threshold.

However, the available cost-effectiveness studies with infliximab in MTX-naïve RA were performed before the market entry of biosimilar competitors. The most recent economic evaluation of MTX-naïve, early RA reported base case results using 2013 innovator etanercept prices [72]. Reductions in the price of infliximab therapy due to the entry of biosimilar products in the RA market could improve the cost-effectiveness of first-line infliximab therapy for patients with RA. The considerable cost saving achievable with biosimilar infliximab along with the potential to improve access to RA has been demonstrated in several budget impact analyses [23–25,73]. We hypothesize that given the considerable price reductions driven by biosimilar competition, the cost-effectiveness of first-line infliximab therapy may fall under the financing threshold in many countries and allow use of this agent in the first-line setting for the treatment of patients with early RA. If proven to be cost effective, first-line therapy with biologic agents could provide a valuable opportunity to test the window of

Table 3. Cost-utility studies of infliximab as first-line treatment in patients with RA.

Publication	Reference	Country	Model	Time horizon	Data source, sample	Treatment cost	Comparator	Perspective	ICER
Spalding & Hay 2006	[59]	USA	HAQ based Markov model	Life-time	Hypothetical cohort of US females aged 55–60 years with RA	2005 US$	IFX + MTX, (ADA, ETN) vs MTX	Payer	US$409,523/QALY
Chen et al 2006	[60]	UK	HAQ based individual sampling model (BRAM)	Life-time	Literature review	2004 £	IFX + MTX (ADA, ETN) vs cDMARD	Payer	£650,000/QALY
Davies et al 2009	[61]	USA	ACR response and HAQ based individual sampling model	Life-time	Simulation based on trial data	2007 US$	IFX + MTX (ADA, ETN) vs cDMARD	Societal	US$53,607/QALY
van den Hout et al. 2009	[62]	The Netherlands	Trial based analysis	2 years	Trial	2008 €	IFX + MTX vs cDMARD + corticosteroid combination	Societal	€130,000/QALY (friction cost method) €22,000/QALY (human capital approach)

ACR American College of Rheumatology, ADA adalimumab, BRAM Birmingham Rheumatoid Arthritis Model, csDMARD conventional synthetic disease-modifying antirheumatic drug, ETN etanercept, HAQ health assessment questionnaire, IFX infliximab, MTX methotrexate, QALY quality-adjusted life year, RA rheumatoid arthritis, UK United Kingdom, US United States, USA United States of America

opportunity hypothesis in a real-world setting and increase the possibility for drug-free remission in some patients with RA.

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