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ORIGINAL RESEARCH

Long-Term Efficacy of Tumor Necrosis Factor Inhibitors for the Treatment of Methotrexate-Naïve Rheumatoid Arthritis: Systematic Literature Review and Meta-Analysis

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ABSTRACT

Introduction: Synthesis of evidence on the long-term use of first-line biologic therapy in patients with early rheumatoid arthritis (RA) is required. We compared the efficacy of up to 5 years' treatment with first-line tumor necrosis factor inhibitors (TNFis) versus other treatment strategies in this population.

Methods: Previous systematic reviews, PubMed and the Cochrane Central Register of Controlled Trials were searched for randomized controlled trials (RCTs) involving treatment of methotrexate-naïve RA patients with first-line TNFis. Literature was synthesized qualitatively, and a meta-analysis conducted to evaluate American College of Rheumatology (ACR) responses, clinical remission defined by any standard measure, and Health Assessment Questionnaire Disability Index (HAQ) at Years 2 and/or 5.

Results: Ten RCTs involving 4306 patients [first-line TNFi, $n = 2234$; other treatment strategies (control), $n = 2072$] were included in the meta-analysis. Three studies were double-blind for the first 2 years, while seven were partly/completely open label during this period. Five studies reported data at Year 5; all were open label at this time point. At Year 2, ACR50

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response, ACR70 response and remission rates were significantly improved with first-line TNFi versus control in double-blind RCTs [log-odds ratio (OR) 0.32 [95% confidence interval (CI) 0.02, 0.62; $p = 0.035$], log-OR 0.48 (95% CI 0.20, 0.77; $p = 0.001$), and log-OR 0.44 (95% CI 0.13, 0.74; $p = 0.005$), respectively], but not in open-label studies. No significant between-group differences were observed in mean HAQ at Year 2 in double-blind or open-label RCTs or in ACR response or remission outcomes at Year 5.

Conclusion: In double-blind studies, 2-year efficacy outcomes were significantly improved with first-line TNFi versus other treatment strategies in patients with MTX-naïve RA. No significant differences in these outcomes were observed when data from open-label RCTs were considered on their own. Further data on the efficacy of TNFi therapy over ≥ 2 years in patients with methotrexate-naïve RA are required.

Plain Language Summary: Plain language summary available for this article.

Keywords: Biologic; Disease-modifying antirheumatic drug; Early; Efficacy; First line; Meta-analysis; Methotrexate-naïve; Systematic review; Tumor necrosis factor inhibitor

PLAIN LANGUAGE SUMMARY

Rheumatoid arthritis (RA) is a disease of the joints and surrounding tissue, which often becomes worse over time. It causes inflammation, pain, stiffness and swelling that can destroy the joints and lead to disability. Biologics are a type of disease-modifying antirheumatic drug (DMARD) that suppress the immune system and reduce inflammation in the joints, thereby preventing joint damage.

Messenger proteins such as tumor necrosis factor (TNF) play an important role in inflammation. Tumor necrosis factor inhibitors (TNFis) are biologic drugs that block TNF and can reduce or stop inflammation in patients with RA. Currently, TNFis are not often used as the first treatment for patients with RA. Patients usually receive other drugs (conventional synthetic DMARDs) first.

Doctors face the challenge of identifying which type of DMARD to use first in patients with RA. Although previous studies have demonstrated the short-term benefits of using biologics as the first treatment, the longer-term effects of doing this have yet to be proven.

We conducted this analysis to find out if patients with RA who were first treated with TNFis in clinical trials had long-term improvements in their disease compared with patients receiving other treatments. We conducted a thorough review of the literature and used a meta-analysis approach to combine data from relevant randomized controlled trials. We found that, in certain types of tightly controlled trials, using TNFis as the first treatment can improve disease in the long term (up to 2 years at least). However, further studies are required to confirm this finding.

INTRODUCTION

Rheumatoid arthritis (RA) is a chronic inflammatory disease affecting 0.5–1% of the general population [1]. The disease is characterized by persistent joint inflammation, pain, stiffness and swelling that can lead to irreversible damage and disability if not adequately treated [2]. Twenty years ago, authorization of the first biologic drugs for use in RA, which act by inhibiting the activity of tumor necrosis factor (TNF), initiated a new age of treatment [2, 3]. Since then, biologic drugs possessing different mechanisms of action (e.g., B-lymphocyte depletion, T-cell co-stimulation modulation and interleukin receptor antagonism) have also become part of the therapeutic landscape [2]. Today, RA is undoubtedly one of the most studied diseases in rheumatology, for which the highest number of biologic drugs are approved, with TNF inhibitors (TNFis) the largest group.

Since their introduction into clinical practice, biologic drugs have proven to be effective in patients with RA who have had inadequate response to previous conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) such as methotrexate (MTX). Initially, biologics were used to treat patients with long-standing disease who had failed multiple

prior csDMARDs. Data from the British Society for Rheumatology Biologics Register published in 2005 showed that mean disease duration at first initiation of TNFi therapy was 14 years. Patients beginning on TNFis had previously received a mean of four different DMARDs [4]. However, with the emergence of new diagnostic tools (e.g., immunological markers and imaging techniques) and new therapeutic goals (e.g., reaching clinical and radiological remission, and maintaining productivity and quality of life), the global understanding of RA has begun to shift. In particular, recognition of the importance of preventing radiological progression and joint damage has led to prioritization of early diagnosis and treatment [5]. As a consequence, the time between RA diagnosis and administration of first biologic treatment has gradually decreased [6]. In line with this trend, randomized controlled trials (RCTs) have been conducted to formally assess the efficacy of biologic drugs in the first-line treatment of RA [7–9].

Today, of the ten available biologic DMARDs (bDMARDs) approved by the European Medicines Agency for use in RA, seven (abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, infliximab, and tocilizumab) are indicated for the treatment of adult patients with severe, active, and progressive disease not previously treated with MTX or any other csDMARD. However, due to both economic constraints associated with the use of biologic therapy and the concerns of some expert healthcare professionals, the use of biologic drugs in MTX-naïve RA has not yet become a widespread component of everyday practice [10, 11]. European League Against Rheumatism (EULAR) recommendations for the management of RA with synthetic and biological disease-modifying drugs (2016) state that "Therapy with DMARDs should be started as soon as the diagnosis of RA is made" and that "MTX should be part of the first treatment strategy" [12]. Use of early bDMARD treatment, including an induction regimen with subsequent withdrawal of bDMARDs, was debated during the development of the recommendations but no consensus was achieved. Members of the recommendations task force noted that there was a "lack of evidence for superiority of such therapy compared with the use of MTX plus glucocorticoid" and "when placed in the context of a treat-to-target strategy, [initial use of csDMARDs] yields equal results in the long-term". The recommendations also state that "the cost-effectiveness of first-line bDMARD therapy, especially in light of the reasons just mentioned, is very poor" [12]. Thus, while there is great interest in the long-term benefits of using biologics in MTX-naïve RA, there is a discrepancy between already available (and approved) treatment options and current professional recommendations.

The high price of biologic drugs has been a barrier to their widespread use in many countries [13, 14]. However, the introduction of biosimilar versions of RA-approved drugs from 2013 onwards has enabled biologic therapy to be offered at considerably reduced cost [15, 16]. Currently, biosimilars of three of the five 'originator' TNFis (adalimumab, etanercept, infliximab) are approved for use in RA in Europe. The availability of biosimilars has also led to a reduction in the price of originator biologics [17]. Currently, there is a shortage of up-to-date economic evaluations of biologics (originators and/or biosimilars) in MTX-naïve RA that incorporate these recent reductions in costs. Before such cost-effectiveness analyses can be properly performed, good-quality input data on the relative long-term effectiveness of biologics and csDMARDs, based on the meta-analysis of RCTs, are needed.

The benefits of biologic therapy given first line over delayed therapy (i.e., biologics given later in the treatment line after MTX failure/intolerance) have been demonstrated for up to 1 year in recent systematic reviews/meta-analyses [7–9]; however, longer-term comparisons have not been performed. The aims of our study were, therefore, to systematically review the literature then qualitatively review and quantitatively synthesize available evidence on the long-term efficacy of first-line treatment with TNFi (adalimumab, certolizumab pegol, etanercept, golimumab, or infliximab) versus other treatment strategies in MTX-naïve RA.

METHODS

Systematic Literature Search

To identify evidence in the literature published before January 2015, we used two systematic reviews and meta-analyses on the first-line biologic treatment of RA: the Cochrane review of Singh et al. published in 2017 [7] and the 2018 work of Cai et al. [8]. Both included and excluded studies reported by Singh et al. were reviewed, as were lists of ongoing RCTs from that publication. A detailed list of excluded studies was not reported by Cai et al.

For the period from January 2015 to July 2018, we conducted a systematic search in PubMed and the Cochrane Central Register of Controlled Trials (CENTRAL). Our search included the Medical Subject Headings term for RA, the Cochrane filter for RCTs, and the international non-proprietary name of any biologic drug indicated for the treatment of RA (abatacept, adalimumab, anakinra, certolizumab, etanercept, golimumab, infliximab, rituximab, sarilumab and tocilizumab). As we focus on bDMARDs in this review, targeted synthetic DMARDs, such as baricitinib and tofacitinib, were not included. We added a selection of keywords to narrow our search to studies involving treatment-naïve patients with RA. The keywords most frequently used to identify treatment-naïve patients with RA in the RCT publications retrieved by Singh et al. [7] and Cai et al. [8] were 'naïve' and 'early'; therefore, we used these two keywords in our search, alongside some less commonly used ones (e.g., 'untreated'). In addition, the acronyms of RCTs identified by Singh et al. and Cai et al. were included in our search strategy so that publications reporting long-term extension studies of these RCTs were identified. Full details of our PubMed and CENTRAL search strategies are shown in Supplementary Tables S1 and S2, respectively. Additional searches using trial identifiers and RCT acronyms in PubMed and Google Scholar [18] were conducted.

Selection of Studies

We considered studies as the unit of our analysis; therefore, multiple publications of the same study or its extensions were only retained if these reported new data on outcomes of interest from the initially randomized patient populations. Peer-reviewed journals were included without language restrictions. Review articles, pooled analyses, case studies and conference abstracts were excluded.

Eligible studies involved patients with a diagnosis of RA who were naïve to MTX therapy. Patients very recently (< 4 weeks) initiated on MTX were considered MTX-naïve. Treatment interventions could include any pharmacological therapeutic strategy for RA that started with TNFi treatment (adalimumab, certolizumab pegol, etanercept, golimumab or infliximab) with or without concomitant MTX (hereinafter 'first-line TNFi treatment'; FL-TNFi). No distinction was made between originator and biosimilar TNFis. Control treatments could include any synthetic pharmacological therapeutic strategy for RA (i.e., placebo, csDMARDs and/or steroids), with or without concomitant MTX, that did not involve any biologic therapy at study initiation [although TNFi could be applied per protocol in a later phase of the study (hereinafter 'delayed TNFi treatment')]. Outcomes could include responses based on American College of Rheumatology (ACR)20, ACR50 or ACR70 criteria, clinical remission [defined by any standard measure (see "Data extraction")], or the Health Assessment Questionnaire Disability Index (HAQ-DI, hereinafter 'HAQ'), measured at Year 2 or Year 5 [19]. This article does not contain any new studies with human or animal subjects performed by any of the authors.

Data Extraction

A Microsoft Excel spreadsheet was developed to capture the following details of each considered study by treatment arm: study name; reference; start year; treatment and dosing; duration of double-blind, open-label or strategic-treatment phase; funding (with one of two categories:

'sponsored by pharmaceutical company' and 'no pharmaceutical company sponsor') to be selected based on the information provided); baseline characteristics {number of randomized patients and patient gender, age, disease activity score [DAS, based on erythrocyte sedimentation rate ($DAS28_{ESR}$) or C-reactive protein ($DAS28_{CRP}$)], HAQ and duration of disease}; risk of bias assessment; number of patients at Year 2 and Year 5; and ACR20, ACR50, ACR70, HAQ and remission [based on ACR criteria, DAS in 28 or 44 joints (DAS28/DAS44), the Simple Disease Activity Index or Clinical Disease Activity Index] at Years 2 and 5. Missing DAS28 scores were calculated from DAS using the formula $DAS28 = 1.072 \times DAS + 0.938$ [20]. If outcomes on multiple remission criteria were reported, we preferred $DAS28_{ESR}$ if available, otherwise the measure with the highest number of patients achieving remission in the entire study population was selected.

Risk of Bias Assessment

The Cochrane Risk of Bias Tool [21] was applied to all studies. Based on the overall assessment, studies were categorized as having a low, high or unknown risk of bias.

Data Synthesis

All outcomes were included on an intent-to-treat (ITT) basis, using the number of patients initially randomized. If not provided directly, the nearest even number of patients achieving the desired outcome was calculated from the percentages provided in tables or graphs. GraphClick 3.0.3 was used to retrieve data from graphs (Arizona Software, AZ, USA).

In the case of multiple-arm studies, arms were pooled into one of two groups: FL-TNFi or 'other strategy' (control group). For complex study designs, one of the two following criteria must have been met for study arms to be included: (1) treatment changes (dose escalations or reductions, switches or additions of drugs) were applied according to predefined criteria based on the clinical status of patients (e.g., in strategic treat-to-target trials), or (2) possible changes (e.g., discontinuation of therapy) were applied to all randomized patients with equal probability. When the placebo (with or without csDMARD) arm of a double-blind study subsequently received open-label biologic therapy, this was considered delayed TNFi treatment and the arm was included in the control group. Multiple TNFi doses, as well as TNFi with or without concomitant MTX, were pooled in the FL-TNFi arm. Data reported for Month 18 were included in Year 2 analyses.

Using ACR70 data, we also investigated how the results of our analyses at Year 2 might have changed if the ASPIRE study, a 1-year double-blind RCT of first-line infliximab versus placebo in combination with MTX [22], had included a long-term extension study. Sensitivity analyses were also performed to determine how the analysis of Year 2 remission rates would change if patients from C-OPERA were excluded and how analyses for ACR70 and Year 2 remission rates would change if OPTIMA and COMET patients were excluded.

Statistical Analysis

All calculations were performed in the Stata14 statistical software package (StataCorp, TX, USA). Baseline characteristics of study populations were compared via one-way analysis of variance (ANOVA) and Chi-squared tests. Predefined outcomes were combined by random-effects meta-analysis according to the method of DerSimonian and Laird [23]. The significance threshold was set at $p < 0.05$.

Sources of between-study heterogeneity were explored by random-effects meta-regression of the following study-level variables: percentage of total study time used by the double-blind period, risk of bias (low/high or uncertain), funding category (pharmaceutical company/non-pharmaceutical company sponsor), type of TNFi, and percentage of patients who dropped out (treatment and control arms combined).

RESULTS

A PRISMA flow diagram for our systematic review is presented in Fig. 1. We identified 18

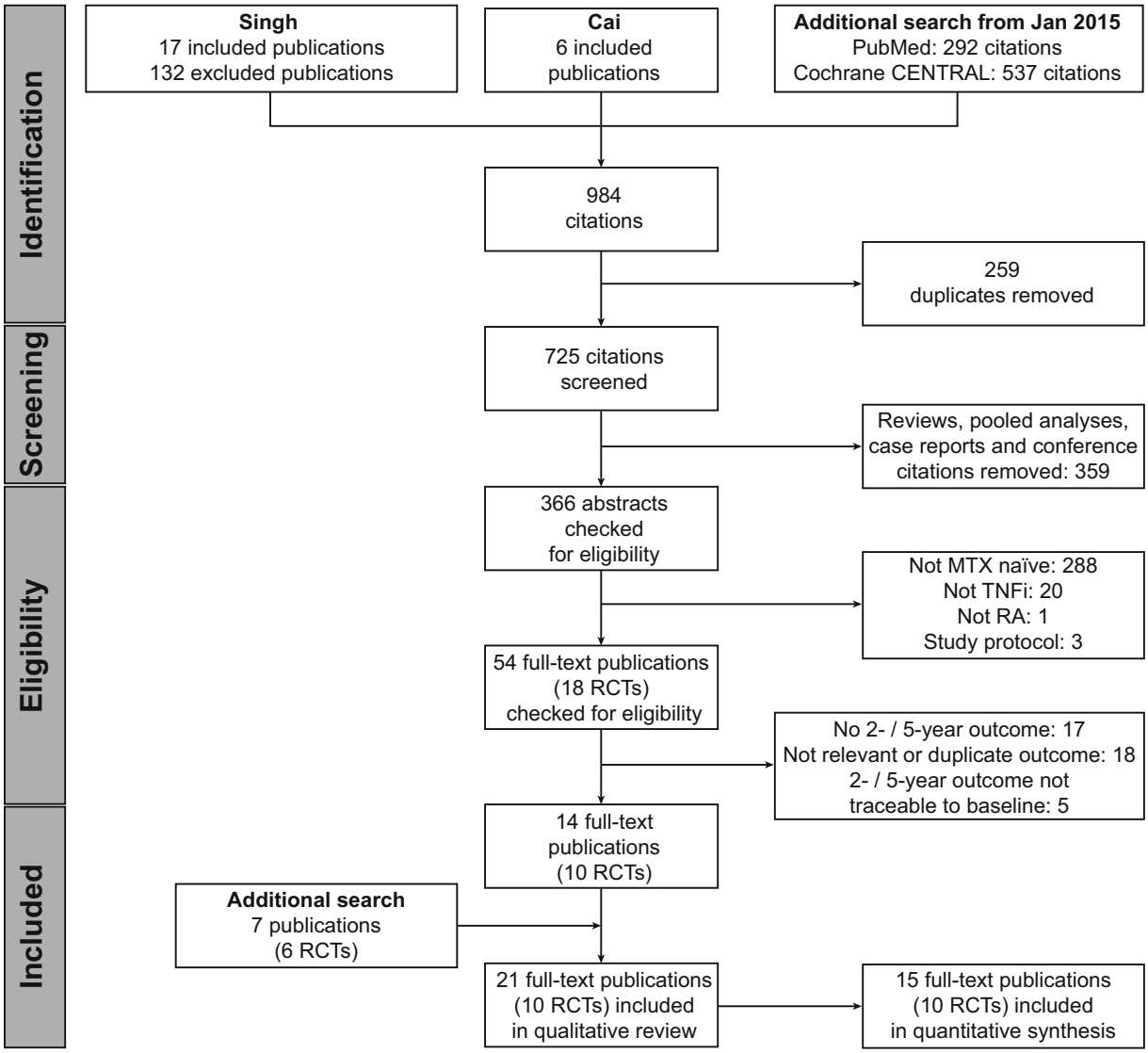

Fig. 1 Search results. *MTX* methotrexate, *RA* rheumatoid arthritis, *RCT* randomized controlled trial, *TNFi* tumor necrosis factor inhibitor

RCTs (reported in 61 publications) involving TNFi treatment of MTX-naïve patients with RA: Bejarano 2008 [24], BeSt [25–32], C-EARLY [33, 34], C-OPERA [35, 36], COMET [37, 38], Durez 2007 [39], Enbrel ERA [40–42], GO-BEFORE [43–47], GUEPARD [48], HIT HARD [49], HOPEFUL [50–52], IDEA [53, 54], Marcora 2006 [55], NEO-RACo [56–62], OPERA [63–74], OPTIMA [75–77], PREMIER [78–83] and Quinn 2005 [84]. None of these 18 RCTs involved biosimilar TNFi treatment.

Twelve of the 18 identified RCTs reported outcomes beyond Year 1. In two of these RCTs (C-EARLY and HOPEFUL), long-term results for the initially randomized populations could not be unambiguously determined. Therefore, we included 10 RCTs (BeSt, C-OPERA, COMET, Enbrel ERA, GO-BEFORE, IDEA, NEO-RACo, OPTIMA, PREMIER and Quinn 2005) in our qualitative review (see Table 1 for study details and citations for the 21 included publications and Supplementary Table S3 for excluded publications and reasons for exclusion).

Table 1 RCTs of first-line TNF inhibitor treatment in RA

Study	Patients	Randomized arms	Arm in meta-analysis	*n* in meta-analysis	Double-blind phase	Open-label phase
BeSt [25, 26, 28]	Early RA (ACR 1987) Disease duration ≤ 24 months Age ≥ 18 years Active disease with ≥ 6/66 SJC, ≥ 6/68 TJC, ESR ≥ 28 mm/h or a global health score ≥ 20 mm (best = 0, worst = 100 mm) Exclusion: previous treatment with sDMARDs other than antimalarials	Initial IFX combination: MTX + IFX (3 → 10 mg/kg) → predefined sDMARD mono/combination sequence	FL-TNFi	128	No DB phase	10-year strategic trial Randomization at BL: four 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 → one 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 → predefined sDMARD sequence	Control	380		
		Step-up combination: MTX → MTX + predefined sDMARD combination sequence	Control			
		Initial PRD combination: MTX + SSZ + PRD (60 → 7.5 mg/week) → predefined sDMARD mono/combination sequence	Control			
COMET [37, 38]	Adult-onset RA Disease duration 3–24 months Age ≥ 18 years DAS28 ≥ 3.2; ESR ≥ 28 mm/h or CRP ≥ 20 mg/L Exclusion: previous treatment with MTX, ETN or another TNFi any time, sDMARDs or corticosteroid injections in the 4 weeks before BL	ETN (1 × 50 mg/week sc) + MTX → ETN (1 × 50 mg/week sc) + MTX	FL-TNFi	137	104 weeks Randomization at BL: four groups The two treatment groups in Year 1 (ETN vs. PLA) were split to four groups in Year 2 according to initial randomization.	
		ETN (1 × 50 mg/week sc) + MTX → ETN (1 × 50 mg/week sc) monotherapy	Excluded	–		
		PLA + MTX → ETN (1 × 50 mg/week sc) + MTX	Control	268		
		PLA + MTX → PLA + MTX	Control			
C-OPERA [35, 36]	RA (based on ACR/EULAR 2010 criteria) Symptom duration: ≤ 12 months Age: 20–64 years DAS28 ESR ≥ 3.2, poor prognostic factors: ACCP ≥ 3× upper limit of normal and RF+ or BE hands/feet Exclusion: previous exposure to MTX, LEF or biologic DMARDs	CZP + MTX → MTX	FL-TNFi	159	52 weeks Randomization at BL: two groups Non-responders (DAS28 > 3.2) after Week 24 continued on rescue open-label CZP in both arms.	52 weeks CZP was discontinued after Week 52, completers of the DB phase continued on MTX monotherapy in both arms.
		PLA + MTX → MTX	Control	157		

Table 1 continued

Study	Patients	Randomized arms	Arm in meta-analysis	*n* in meta-analysis	Double-blind phase	Open-label phase
Enbrel ERA [40, 42]	RA Disease duration ≤ 36 months Age ≥ 18 years RF+, ≥ 3 BEs on hands, wrists or feet, ≥ 10 SJC, ≥ 12 TJC, ESR ≥ 28 mm/hr, CRP ≥ 20 mg/L, morning stiffness ≥ 45 min MTX naïve, previous sDMARDs (HCQ, SSZ, LEF), ANA, experimental drugs were allowed with washout Exclusion: previous treatment with IFX, RTX, ETN, ADA, NAT, cytotoxic agents	ETN (2 × 10 mg/w sc) + PLA oral → ETN (2 × 10 mg/week sc) → ETN (2 × 25 mg/week sc) ETN (2 × 25 mg/w sc) + PLA oral → ETN (2 × 25 mg/week sc) PLA sc + MTX oral → MTX oral → ETN (2 × 25 mg/week sc)	FL-TNFi FL-TNFi Control	415 217	52 weeks Randomization at BL: three arms Gradual transition to open-label phase, mean length of DB phase: 18.4 months (range: 13.8–23.6 months)	10 years PLA was discontinued at Week 52, randomized treatment continued until Week 104. From Week 104, all pts received ETN monotherapy (including Year 2 completers and Year 1 dropouts). After 3 months in LTE, NSAIDs, sDMARDs and PRD could be added/withdrawn or adjusted.
GO-BEFORE [43, 44, 46]	RA (based on ACR 1987 criteria) Symptom duration: ≥ 3 months Age ≥ 18 years Active RA ≥ 4 SJC, ≥ 4 TJC, at least two from: CRP ≥ 15 mg/L or ESR ≥ 28 mm/hr or morning stiffness ≥ 30 min, or ≥ 1 bone erosion or ACCP+ or RF+) ≤ 3 weeks of oral MTX	GOL 100 mg/month sc + PLA oral (if EE: GOL 100 mg/month + MTX) GOL 50 mg/month sc + MTX oral (if EE: GOL 100 mg/month + MTX) GOL 100 mg/month sc + MTX oral PLA sc + MTX oral (if EE: GOL 50 mg/month + MTX)	FL-TNFi FL-TNFi FL-TNFi Control	477 160	52 weeks Randomization at BL: four groups After Week 24 EE, if ≤ 20% improvement from BL in SJC and TJC	4 years If no EE at Week 24, then PLA + MTX group with ≥ 1 TJC or ≥ 1 SJC → GOL 50 mg/month + MTX. In open LTE, MTX and corticosteroids could be adjusted, GOL could be escalated by 50 mg/month.
IDEA [53]	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 sDMARD, corticosteroid use within 1 month prior to BL	IFX (3 mg/kg) + MTX MPD (250 mg iv at Week 2, 6, 14, 22) + MTX	FL-TNFi Control	55 57	26 weeks Randomization at BL: two groups If DAS44 > 2.4, treat-to-target: MPD 120 mg ia/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

Table 1 continued

Study	Patients	Randomized arms	Arm in meta-analysis	*n* in meta-analysis	Double-blind phase	Open-label phase
NEO-RACo [56, 57]	RA (based on ACR 1987 criteria) 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 DMARD naïve Exclusion: oral glucocorticoids in previous 6 months, ia glucocorticoids in previous 1 month	IFX (3 mg/kg at Week 4, 6, 10, 18, 26) + open intensified FIN-RACo (MTX + SSZ + HCQ + PRD) → predefined schedule of sDMARDs PLA (at Week 4, 6, 10, 18, 26) + open intensified FIN-RACo (MTX + SSZ + HCQ + PRD) → predefined schedule of sDMARDs	FL-TNFi Control	50 49	26 weeks DB 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.
PREMIER [78–80]	RA (based on ACR 1987 criteria) Disease duration of 3 years Age ≥ 18 years ≥ 8 SJC, ≥ 10 TJC, ESR ≥ 28 mm/h or CRP ≥ 15 mg/L, and either RF+ or ≥ 1 joint erosion Exclusion: previous MTX, CSA, AZA, CPA, two sDMARDs	ADA (40 mg/2 weeks sc) + MTX ADA (40 mg/2 weeks sc) + PLA PLA + MTX	FL-TNFi FL-TNFi Control	542 257	104 weeks Randomization at BL: three arms	10 years From Week 104, all pts received ADA monotherapy (40 mg/2 weeks sc). MTX could be added any time.

Table 1 continued

Study	Patients	Randomized arms			Arm in meta-analysis	*n* in meta-analysis	Double-blind phase	Open-label phase
OPTIMA [75, 76]	RA (based on ACR 1987 criteria) Disease duration < 1 year Age ≥ 18 years Active RA Exclusion: previous TNFi, MTX or > 2 sDMARDs	ADA + MTX	If stable LDA (1:1)	→ PLA + MTX (ADA withdrawal, 49.3%)	Excluded	–	78 weeks Period 1 (26 weeks): 1:1 randomization at BL: two groups (ADA + MTX vs. PLA + MTX) Period 2 (Weeks 26–78); treatment changes depending on LDA (DAS28 < 3.2 in Weeks 22 and 26) status: ADA pts in stable LDA, 1:1 randomization: ADA withdrawal vs. ADA continuation MTX pts in stable LDA, MTX monotherapy continued ADA pts not in LDA → ADA carry-on MTX pts not in LDA → ADA rescue	–
				→ ADA + MTX (ADA continue)	FL-TNFi weight: 50.7%	261		
			If LDA not achieved → ADA + MTX (ADA carry-on, weight = 50.7%)		FL-TNFi			
		PLA + MTX	If stable LDA → PLA + MTX (MTX mono)		Control	517		
			If LDA not achieved → ADA + MTX (ADA rescue)		Control			

Table 1 continued

Study	Patients	Randomized arms	Arm in meta-analysis	*n* in meta-analysis	Double-blind phase	Open-label phase
Quinn 2005 [84]	RA (based on ACR 1987 criteria) Symptom duration ≥ 12 months No previous sDMARDs or oral corticosteroids, MCP joint involvement, stable on NSAID ≥ 2 weeks prior to screening, poor prognosis by PISA scoring system 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	FL-TNFi Control	10 10	54 weeks Randomization at BL: two groups	8 years IFX was discontinued at Week 54. Non-responders received step-up combination therapy (+ SSZ → + HCQ).

ACCP antibodies against cyclic citrullinated peptides, *ACR* American College of Rheumatology, *ADA* adalimumab, *ANA* anakinra, *AZA* azathioprine, *BE* bone erosion, *BL* baseline, *CPA* cyclophosphamide, *CRP* C-reactive protein, *CSA* cyclosporine A, *CZP* certolizumab pegol, *DAS* disease activity score, *DAS28* DAS in 28 joints, *DAS44* DAS in 44 joints, *DB* double-blind, *EE* early escape, *ESR* erythrocyte sedimentation rate, *ETN* etanercept, *EULAR* European League Against Rheumatism, *FL* first-line, *GOL* golimumab, *HCQ* hydroxychloroquine, *ia* intra-articular, *IFX* infliximab, *iv* intravenous, *LDA* low disease activity, *LEF* leflunomide, *LTE* long-term extension, *MCP* metacarpophalangeal, *MPD* methylprednisolone, *MTX* methotrexate, *NAT* natalizumab, *NSAID* non-steroidal anti-inflammatory drug, *PISA* Persistent Inflammatory Symmetrical Arthritis, *PLA* placebo, *PRD* prednisolone, *RA* rheumatoid arthritis, *RCT* randomized controlled trial, *RF* rheumatoid factor, *RTX* rituximab, *sc* subcutaneous, *(s)DMARD* (synthetic) disease-modifying antirheumatic drug, *SJC* swollen joint count, *SSZ* sulfasalazine, *TJC* tender joint count, *TNF* tumor necrosis factor, *TNFi* TNF inhibitor

The total number of patients in the 10 RCTs was 4697 (FL-TNFi: n = 2625; control: n = 2072). The RCTs comprised four studies of infliximab, two of etanercept, two of adalimumab, one of certolizumab pegol and one of golimumab. Patients withdrawn from treatment during the blinded study phases of the OPTIMA and COMET studies were excluded from the meta-analysis. In the withdrawn patient groups, treatment discontinuations were not mirrored in the control arms and treatment withdrawals were neither linked to remission nor performed during the open-label phase; therefore, patients could have received sub-optimal treatment. In OPTIMA, adalimumab was withdrawn after 1:1 re-randomization of responders receiving adalimumab plus MTX treatment. The adalimumab non-responder group was weighted correspondingly by 50.7% in order to preserve response rates in the ITT population. From the randomized population of OPTIMA [75], a total of 254 patients were excluded from the meta-analysis. In COMET, MTX was withdrawn in one of the four randomized study groups after 52 weeks of combination treatment with etanercept plus MTX (n = 137) [38]. After excluding OPTIMA and COMET patients withdrawn from treatment, 4306 patients (FL-TNFi: n = 2234; control: n = 2072) were included in the meta-analysis. Data included in the meta-analysis were from 15 publications on the 10 RCTs [26, 28, 36, 38, 42, 44, 46, 53, 56, 57, 75, 78–80, 84].

In addition to ongoing long-term extension studies of previously published RCTs, we identified 14 studies involving treatment of MTX-naïve RA patients with biologic agents (n = 3459) that were listed in clinical trial registries but had yet to be published in peer-reviewed journals [85–98]. Two of these studies [85, 89] started after August 1, 2017 and therefore were not included in the review of Singh et al. [7]. Among the 14 non-fully reported studies, the estimated completion date was not available for 2 [92, 97], 1 was published as a conference poster [93], another was stopped early due to issues with participant recruitment [98], and the results of 2 had not yet been published [87, 88]; the remaining 8 studies were still ongoing. Most of the 14 studies were sponsored by academic or clinical institutions; 2 were funded by industry [86, 95] and 2 by government [97, 98]. Seven of the studies were blinded RCTs [86, 88–90, 92, 93, 98], 5 were open-label randomized trials [85, 87, 91, 95, 96] and 2 were non-randomized open-label studies [94, 97]. Ten of the studies investigated the clinical efficacy of biologic agents in various settings [86, 88–93, 96–98], 2 investigated the pathophysiology of inflammatory processes [85, 95] and 2 evaluated radiological techniques [87, 94]. TNFis were investigated in 9 of the 14 studies (N = 1828) [87–92, 96–98].

Risk of Bias Analysis

Two RCTs (COMET and PREMIER) were double-blind at the end of Year 2 and therefore their risk of bias at this time point was categorized as low. All other studies except OPTIMA had an open-label arm at Year 2 and were considered high risk. Risk of bias at Year 2 for OPTIMA was categorized as unknown due to the partial unblinding of treatment for study non-responders. At Year 5, all studies were open label and therefore had a high risk of bias.

Methodological Heterogeneity of Studies

The methodology of included studies was diverse. Most were double-blind RCTs that varied in duration between 6 and 24 months, were followed by open-label or strategic-treatment extension phases of varying durations ($\leq$ 10 years) and involved changes in treatment at different time points. One included study employed an open-label, treat-to-target strategy from randomization (BeSt). The longest double-blind period without treatment changes was 24 months (PREMIER). By Year 5, all studies were in open-label phases that featured modifications of originally assigned treatment. The methodological heterogeneity of studies is summarized in Fig. 2.

Characteristics of Patients with RA at Baseline

Baseline study populations were clinically homogenous and comprised MTX-naïve adult

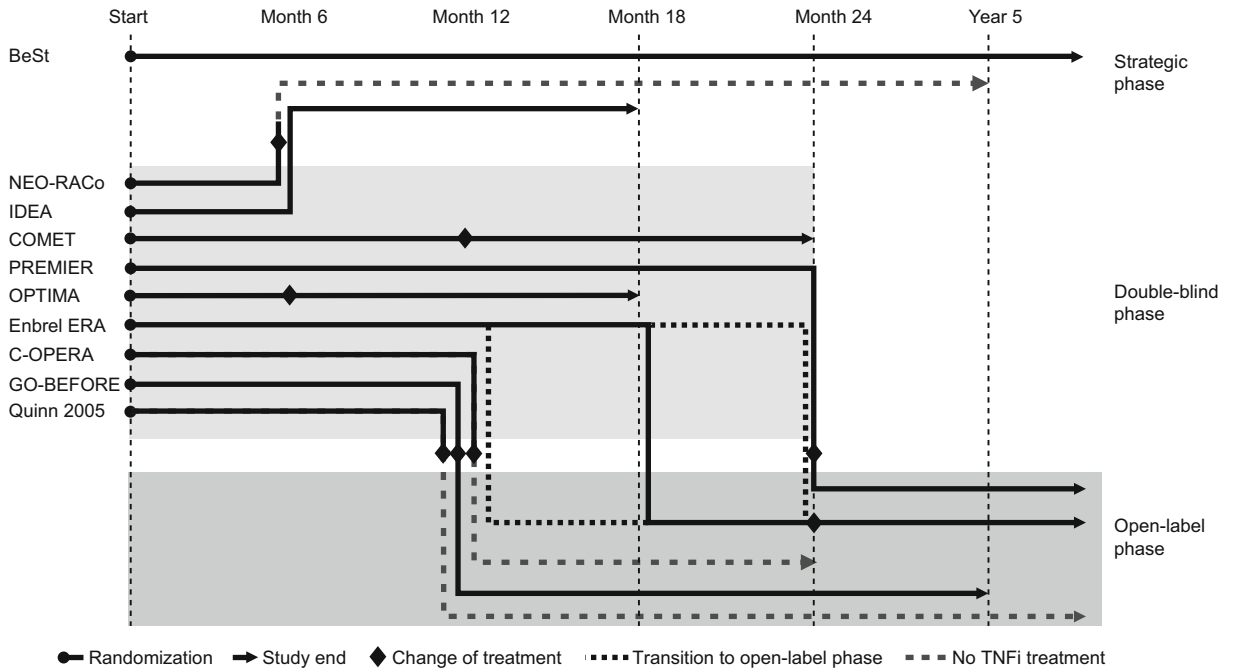

Fig. 2 Methodological heterogeneity of studies. *TNFi* tumor necrosis factor inhibitor

patients with RA, most of whom had active early disease. However, previous treatment exposure varied among studies. In IDEA, NEO-RACo and Quinn 2005, patients were naïve to all csDMARDs, whereas in BeSt, COMET, C-OPERA, PREMIER and OPTIMA, previous treatment with some csDMARDs (but not MTX) was permitted. In Enbrel ERA and GO-BEFORE, only previous treatment with MTX led to exclusion. Although comparisons of baseline age, disease duration, HAQ and DAS28 (with ANOVA) and gender distribution (with Chi-squared tests) revealed statistically significant differences between randomized study arms, these baseline characteristics were considered clinically comparable. Mean age was 51.0 years [range 47 (NEO-RACo) to 55 (BeSt) years; $F_{(26,\ 4279)} = 3.17$, $p < 0.001$]. Mean disease duration was 12.4 months [range 3.9 (OPTIMA) to 49.2 (GO-BEFORE) months; $F_{(26,\ 4279)} = 39.27$, $p < 0.001$]. Mean HAQ was 1.47 [range 0.9 (NEO-RACo) to 1.7 (COMET); $F_{(26,\ 4279)} = 10.04$, $p < 0.001$]. Mean DAS28 was 5.85 [range 4.75 (IDEA) to 6.95 (Quinn 2005); $F_{(26,\ 4279)} = 26.10$, $p < 0.001$]. Females comprised 74.7% of study participants [range 63.27% (NEO-RACo) to 100% (Quinn 2005); $\chi^2_{(26)} = 63.8$, $p < 0.001$]. In four trials that reported anti-citrullinated protein antibody (ACPA) status, 81% of patients were ACPA positive at baseline [range 67% (COMET) to 100% (C-OPERA)].

Results of the Meta-Analysis

For each outcome, and where possible, we performed meta-analysis for the subgroup of RCTs that were double blind for the first 2 years (COMET, OPTIMA and/or PREMIER), for the other subgroup of studies that were partly or completely open label during either time period (seven open-label RCT extensions of double-blind RCTs or open-label strategic-treatment RCTs) and for both types of study overall. Data were not available from all 10 studies for any of the assessed outcomes at either time point. At Year 2, ACR70 and at least one of the predefined remission outcomes were available for nine studies, ACR50 and ACR20 outcomes for eight studies and HAQ results for five studies. At Year 5, remission outcomes were available for four studies, ACR70 for three studies and ACR20 or ACR50 outcomes for two studies.

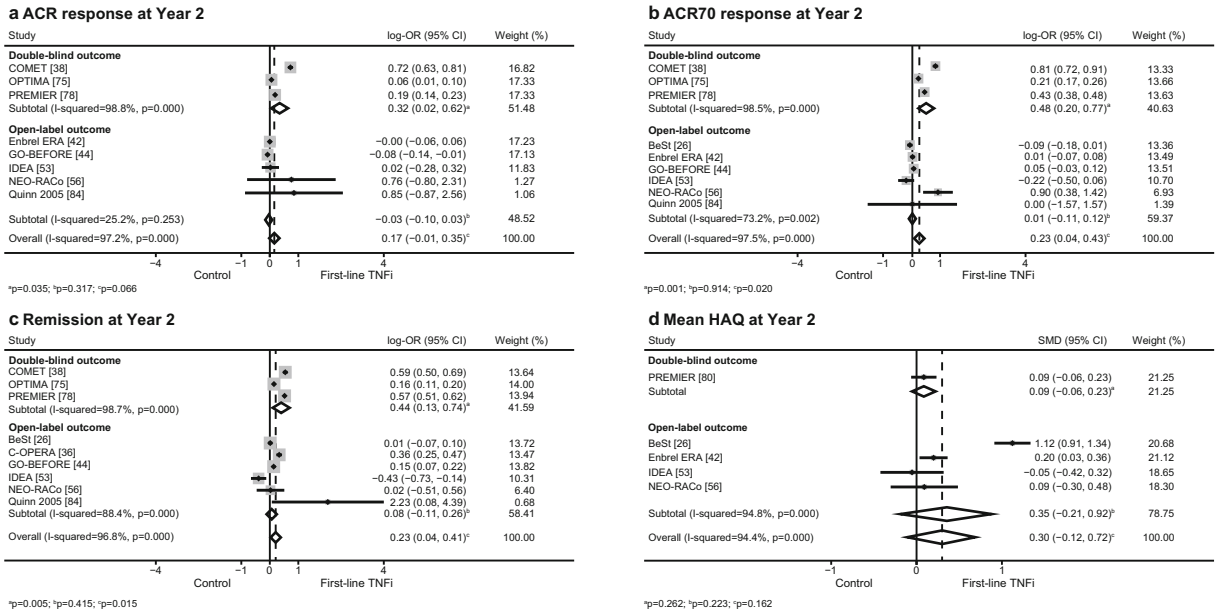

Fig. 3 Meta-analyses of double-blind and open-label studies of first-line TNFi versus control at Year 2*. **a** ACR50 response at Year 2. **b** ACR70 response at Year 2. **c** Remission at Year 2. **d** Mean HAQ at Year 2. Weights are from random-effects analysis. *Double-blind RCTs with open-label extension at Year 2 were considered in the open-label subgroup. Data presented for Month 18 in the OPTIMA trial were considered among the double-blind results at Year 2. *ACR* American College of Rheumatology, *CI* confidence interval, *HAQ* Health Assessment Questionnaire Disability Index, *OR* odds ratio, *RCT* randomized controlled trial, *SMD* standardized mean difference, *TNFi* tumor necrosis factor inhibitor

Year 2

Our analyses showed that for ACR20 at Year 2, FL-TNFi was not significantly different from the control group in either the double-blind RCT or open-label study subgroups, or overall (Supplementary Figure S1). For ACR50, ACR70 and remission outcomes, differences were significant in favor of FL-TNFi in the double-blind RCTs; no significant differences in these outcomes were revealed in analysis of open-label studies (Fig. 3a–c). In overall analyses including both double-blind RCTs and open-label studies, differences between the two groups were significant for ACR70 [log-OR 0.23 (95% CI 0.04, 0.43); $p = 0.020$; Fig. 3b] and remission outcomes [log-OR 0.23 (95% CI 0.04, 0.41); $p = 0.015$; Fig. 3c].

For HAQ outcomes, standard deviations (SDs) were not reported for the Enbrel ERA and IDEA trials; therefore, the pooled SD of BeSt, GO-BEFORE, NEO-RACo, OPTIMA and PREMIER was used. In the IDEA trial, HAQ change versus baseline was used to calculate mean HAQ score. Meta-analysis revealed no significant difference between the TNFi and control groups in terms of mean HAQ (Fig. 3d).

Following our observation that the benefits of FL-TNFi in terms of response and remission could be demonstrated in the double-blind RCTs but that differences between FL-TNFi and control groups were not apparent in analyses of open-label studies, we investigated how the results might have changed if the ASPIRE study had included a long-term extension study. We projected Year 2 results for ASPIRE based on available Year 2 and Year 1 ACR70 results of studies with at least a 1-year-long double-blind randomized phase (COMET, Enbrel ERA, GO-BEFORE, PREMIER, Quinn 2005). Inclusion of projected ACR70 data for Year 2 of ASPIRE in the overall meta-analysis for this outcome further increased the between-group difference in favor of FL-TNFi (Supplementary Figure S2).

Table 2 Summary results of meta-regression, explaining between-study heterogeneity

Number of studies	ACR20 Year 2		ACR50 Year 2		ACR70 Year 2		Remission Year 2	
	n = 8		*n* = 8		*n* = 9		*n* = 8	
	Coeff	*p*	Coeff	*p*	Coeff	*p*	Coeff	*p*
Study								
Funded by industry	0.212	0.472	− 0.028	0.936	0.182	0.542	0.453	0.075
Low risk of bias	0.405	0.128	0.427	0.053	0.537	0.046	0.487	0.047
Percentage of double-blind period within the 2 years, %	0.401	0.259	0.417	0.367	0.429	0.251	0.549	0.099
Dropout rate, %	1.746	0.126	1.353	0.409	0.814	0.525	0.902	0.285
Study joint Wald test		0.734		0.687		0.532		0.214
TNFi								
CZP vs. ADA	–	–	–	–	–	–	− 0.003	0.995
ETN vs. ADA	0.511	0.082	0.238	0.539	0.086	0.856	0.231	0.624
GOL vs. ADA	− 0.122	0.677	− 0.200	0.669	− 0.276	0.638	− 0.216	0.646
IFX vs. ADA	− 0.053	0.830	0.107	0.809	− 0.189	0.667	− 0.439	0.268
TNFi joint Wald test		0.159		0.778		0.871		0.579

Coefficients and *p* values for individual variables are reported from univariate meta-regression. *p* values are also reported for joint Wald tests of study-related and treatment-related variables

ACR American College of Rheumatology, *ADA* adalimumab, *coeff* coefficient, *CZP* certolizumab pegol, *ETN* etanercept, *GOL* golimumab, *IFX* infliximab, *TNFi* tumor necrosis factor inhibitor

Year 5

At Year 5, five of the ten studies reported data on at least one relevant outcome (BeSt, Enbrel RA, GO-BEFORE, NEO-RACo and PREMIER); however, these trials were no longer double-blind at this time point. Therefore, data available at Year 5 were taken from the open-label extension periods of these studies. Meta-analyses determined that between-group differences were not significant for ACR20, ACR50, ACR70 or remission outcomes (Supplementary Fig. S3–S6). SD values for mean HAQ were not reported by any study at Year 5; therefore, meta-analysis of HAQ data at this time point was not performed.

Meta-Regression of Study-Level Variables

Very high heterogeneity was observed in all models, with I^2 ranging from 87.9 to 99.7%. Random-effects meta-regression analysis revealed that low risk of bias was associated with significantly greater effect size in ACR70 ($p = 0.046$) and remission ($p = 0.047$) outcomes at Year 2 (Table 2). Other study-related variables (funding source, percentage of double-blind period within the 2-year observation, dropout rate) did not explain the heterogeneity of the effect size for any of the 2-year efficacy outcomes. No significant differences between different TNFi agents for any of the response or remission outcomes at Year 2 were observed.

Sensitivity Analyses

Although the approach to certolizumab pegol discontinuation in C-OPERA was very similar to that in the excluded arm in OPTIMA, patients in C-OPERA were followed up in an open-label

phase, potentially allowing physicians to optimize patient response; therefore, C-OPERA patients were not excluded from our main analyses. We did, however, conduct a sensitivity analysis to determine how our results would differ if we had excluded C-OPERA patients. Only Year 2 remission rates were reported in C-OPERA. Although treatment withdrawal in the certolizumab pegol arm would indicate a diminished difference between the FL-TNFi and control groups suggesting a positive effect on the overall effect size after removal of C-OPERA data, the effect size of Year 2 remission rates decreased and became non-significant [log-OR 0.20 (95% CI – 0.002, 0.41); $p = 0.067$]. We also conducted a sensitivity analysis to establish how the inclusion of all patients from OPTIMA and COMET would influence our results. Following inclusion of these patients, differences between the FL-TNFi and control groups for ACR70 [log-OR: 0.18 (95% CI – 0.003, 0.37); $p = 0.064$] and remission outcomes [log-OR: 0.19 (95% CI – 0.014, 0.39); $p = 0.068$] became non-significant.

DISCUSSION

This systematic review and meta-analysis has demonstrated the long-term (2-year) benefits of FL-TNFi treatment versus other treatment strategies in MTX-naïve patients with RA participating in RCTs with a double-blind, randomized, parallel-group design. In contrast, no statistically significant benefits were observed at this time point in open-label studies (randomized strategic-treatment studies or RCT extensions). At Year 2, ACR50, ACR70 and remission outcomes were significantly improved in FL-TNFi versus control groups in double-blind RCTs but not in open-label studies. In terms of mean HAQ, no significant differences between TNFi and control groups were observed at Year 2. At Year 5, data collected during open-label treatment in three studies did not show any significant between-group differences in response and remission outcomes. Meta-regression analysis of Year 2 outcomes did not reveal significant differences between individual TNFi agents. Our sensitivity analyses demonstrated that decisions about the inclusion or exclusion of individual studies could influence conclusions regarding the long-term efficacy advantage of FL-TNFi treatment.

To our knowledge, our study is the first meta-analysis focusing on the long-term efficacy outcomes of FL-TNFi treatment in MTX-naïve RA. Other meta-analyses have established the short-term efficacy benefits of using first-line biologic therapy in MTX/csDMARD-naïve RA [7, 8, 99]. In a small, indirect, pairwise meta-analysis of six RCTs for up to 1 year, all included biologic regimens demonstrated a significantly higher likelihood of achieving an ACR20 response than MTX alone. Furthermore, all but one biologic drug showed significant differences in ACR50 and ACR70 responses versus MTX monotherapy [99]. In a systematic review and network meta-analysis including 19 trials, Singh et al. demonstrated that biologic agents in combination with MTX were associated with clinically meaningful benefits in terms of ACR50, remission and HAQ outcomes versus MTX alone for up to 1 year [7]. In a network meta-analysis including 20 trials, Cai et al. showed that biologics used in combination with MTX were associated with significant improvements in ACR20, ACR50, ACR70 and remission outcomes compared with csDMARDs alone [8]. In that analysis, the majority of included studies had follow-up periods of less than 1 year, with the exception of COMET and PREMIER, which lasted 104 weeks. More recently, a comprehensive network meta-analysis by Donahue et al. demonstrated the 1-year benefit of immediate TNFi treatment when compared with MTX in studies with double-blind randomized designs in terms of clinical efficacy (ACR50), joint damage (Sharp van der Heijde Score) and safety profile [9]. Our results demonstrated that the benefits of FL-TNFi therapy are retained over 2 years, at least in double-blind randomized studies. Data at Year 5 were insufficient to draw well-founded conclusions at that time point. Despite the similar objectives and conclusions of previous meta-analyses, they included a substantially different and incomplete range of studies.

We aimed to include a broad range of studies of heterogeneous design, as healthcare

professionals may adopt different TNFi treatment strategies (e.g., early or non-first line/delayed) depending on local therapeutically and/or economically focused guidelines, as well as the individual preferences of patients [100]. A potential strength of our work is that we applied a thorough search for secondary publications to identify relevant long-term outcomes. Of the 13 study publications included in the meta-analysis, only 3 were primary publications, while 10 studies were secondary publications of the studies of interest. However, the heterogeneity of treatment strategies and designs, as well as insufficient reporting of outcomes in long-term studies represented a key methodological challenge for the quantitative synthesis of the results; therefore, caution is required when interpreting the results of our analysis. A possible limitation of our search strategy is that we relied on the systematic reviews of Singh et al. [7] and Cai et al. [8] for identifying studies involving MTX-naïve patients from the period before 2015. Therefore, potentially eligible studies that were not listed among the included or excluded trials in these two systematic reviews may have been missed in our study.

Although the benefits of FL-TNFi treatment versus other treatment strategies for most Year 2 efficacy outcomes were demonstrated in RCTs with a double-blind design, meta-regression analysis did not reveal an association between the percentage of the 2-year period that was double-blind and the effect size of efficacy outcomes. However, low risk of bias was associated with a greater effect size for several efficacy outcomes. The risk of bias and the percentage of total study time that was double-blind in the included studies were closely, but not fully, related. At Year 2, only two studies (COMET and PREMIER) were considered at low risk of bias. In both of these studies, 100% of the 2-year study period was double-blind. Although the same applied to OPTIMA, this study was categorized as having an unknown risk of bias due to partial unblinding of treatment for non-responders. For the remaining studies (categorized as low or unknown risk), the percentage of total study time that was double-blind varied from 0 to 77%. Although the number of studies included in the meta-regression was too low to detect statistically significant results, the consistently positive coefficients of characteristic features of double-blind parallel studies were concordant with our hypothesis that double-blind parallel designs have a greater ability to demonstrate the long-term benefits of starting immediate TNFi treatment versus other treatment strategies.

Data from open-label studies and extensions of double-blind RCTs suggest that first-line non-biologic treatment can be as effective as FL-TNFi treatment over a 2-year period. The initial benefit of first-line biological therapy can be offset by strategic treat-to-target protocols (as employed in BeSt, NEO-RACo, and IDEA) if both patients and rheumatologists adhere to tight disease management controls. However, adoption of treat-to-target recommendations in RA care is far from universal in Europe. A multi-country study (performed in France, Germany, Italy, Spain, and the UK in 2014) revealed that a treat-to-target approach was not adopted in almost half of patients with RA, and if applied it was mostly used in patients at $\geq$ 2 years since RA diagnosis and thus not in early RA [101]. For three RCTs (GO-BEFORE, C-OPERA and Quinn 2005), initial treatment differences between randomized arms were equalized during subsequent open-label extension phases. In the GO-BEFORE study, initiation of biological therapy was allowed in the control arm in the event of suboptimal response, while in C-OPERA and Quinn 2005, TNFi treatment was discontinued in all patients after the double-blind period. While pragmatic treatment escalations reflect clinical practice, the discontinuation of biologics in the absence of sustained clinical remission is unlikely in a real-life setting. In C-OPERA, non-responders moved to rescue treatment during the double-blind phase, and in the open-label extension phase of Quinn 2005, treatment escalation with csDMARD combinations was possible. In the COMET and OPTIMA studies, treatment de-escalation occurred during the double-blind phase in the FL-TNFi arms without symmetrical changes in the control groups. To mitigate the potential negative bias due to these treatment changes, the MTX withdrawal arm of COMET and patients in OPTIMA who were randomized to adalimumab withdrawal after

responding to adalimumab were removed from our main analysis. Sensitivity analysis demonstrated that these changes significantly affected ACR70 and remission results at Year 2. Overall, these findings suggest that, in early RA, the choice of first-line treatment alone does not guarantee optimal long-term outcomes unless a proper disease management strategy is also employed.

In accordance with approved TNFi labels, we included patients with established RA in our analysis. However, recent research suggests that prevention of RA is possible in the earliest phase of this inflammatory disease, before a diagnosis can be established. Early treatment with effective DMARD therapy and subsequent achievement of remission in the early phase of RA (i.e., within the 'window of opportunity') may reverse the autoimmune response in some patients and lead to improved long-term outcomes [5, 102]. Two recent studies (EMPIRE and DINORA) have evaluated immediate TNFi treatment in early inflammatory arthritis. In both studies, biologic induction treatment was given until sustained remission was achieved, but for no longer than 1 year. Although the EMPIRE trial could not demonstrate a statistically significant difference between etanercept plus MTX and MTX monotherapy at Week 78 [103], the 2-year DINORA study provided encouraging evidence that even a short course of infliximab plus MTX was more effective than MTX alone or placebo in achieving sustained disease reversal [104]. Because we excluded patients with early inflammatory arthritis not fulfilling the criteria for RA diagnosis from our study, the patient population included in our analysis may not be the right population to demonstrate the preventive effects of early biologic therapy. It should be noted, however, that early inflammatory arthritis may resolve spontaneously in some patients, remain undifferentiated or may develop into an arthropathy other than RA. Although several prognostic factors of progressive erosive disease have been identified (e.g., number of swollen joints, acute-phase reactants, rheumatoid factor, ACPAs, or imaging signs) and should inform treatment decisions, the search is ongoing for better predictive models of optimal therapeutic strategies [105].

We hope that the results of ongoing studies will provide the necessary additional evidence to draw firmer conclusions regarding the optimal treatment strategy for patients with MTX-naïve early RA. As of July 2018, we identified 14 clinical trials involving treatment of 3459 such patients with biologic drugs that had not had results published in peer-reviewed journals [85–98]. Hence, this area is undoubtedly one in which the volume of research is rapidly growing. Eight of the 13 identified ongoing or completed studies (one study was stopped [98]) involve treatment with TNFi drugs, with seven assessing clinical efficacy; of these, six are focusing on induction of remission. These new studies may add valuable knowledge about identifying relevant target patient populations, and the optimal timing of biologic therapy, for RA prevention.

The apparently poor cost-effectiveness of originator TNFis has been noted by EULAR and in cost-effectiveness analyses performed by the National Institute for Health and Clinical Excellence and others, contributing to the limited use of biologic therapy in MTX-naïve early RA [11, 12, 106]. However, these analyses utilized biologic drug prices before approval of biosimilar TNFis. The introduction of biosimilar drugs offers hope that cost barriers for use in first-line settings will be overcome in the near future [16, 107]. Reliable data from new meta-analyses such as this one can be used to inform new cost-effectiveness analyses that accurately reflect recent changes to the current treatment landscape, including the introduction of biosimilars. The availability of up-to-date clinical and pharmacoecomic evidence may also ultimately lead to changes in treatment guidelines.

CONCLUSIONS

To our knowledge, this is the first systematic review and meta-analysis to provide evidence on the efficacy of biologic treatment over 1 year in MTX-naïve early RA. In double-blind studies, 2-year ACR50/ACR70 responses and remission

rate outcomes were significantly improved with first-line TNFis compared with other treatment strategies. However, no significant differences in these outcomes were observed in open-label studies, including those with strict treatment protocols. Heterogeneity of studies and lack of publication standards hampered the analyses, and a possible limitation of our search strategy was that we relied on previous systematic reviews to identify studies published before 2015. Further good-quality evidence is needed if the efficacy of biologic therapy over 2 years is to be established in patients with early RA, and especially in those with inflammatory arthritis, who were not included in this analysis. The economic value of long-term TNFi in this setting also remains to be determined, although cost-effectiveness analyses based on the findings reported here are already underway. Due to the considerable price reduction in biologic therapy following the introduction of biosimilars, immediate TNFi treatment may become an attractive treatment option in early RA, due to its short-term efficacy benefits and the promise of offering disease reversal and sustained remission for a considerable proportion of patients.

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Data Availability. All data used in this systematic review and meta-analysis are available in the published sources.

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