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TNF inhibitor monotherapy versus combination with methotrexate in the treatment of psoriatic arthritis: a systematic review of the literature

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Running title: TNF inhibitors with or without MTX in PsA

Abstract

Objective. To review the available evidence on TNF inhibitor monotherapy versus add-on therapy to ongoing methotrexate (MTX) in psoriatic arthritis (PsA).

Methods. A literature search was conducted up to and including October 2013 for randomized controlled trials (RCTs) and observational studies comparing TNF inhibitor monotherapy versus combination therapy with MTX in patients with PsA. Key information was extracted from the abstracts and/or full text of articles retrieved.

Results. Eleven published articles and three conference abstracts were retrieved, reporting on six RCTs of four TNF inhibitors. Most RCTs found no differences in efficacy for peripheral arthritis between patients treated with or without MTX. However, the studies were not powered to answer this question. Some data suggest that concomitant MTX may reduce progression of structural damage. No significant differences in other outcomes have been reported. Data on TNF inhibitor monotherapy versus MTX combination therapy was reported from six registries. Three registries reported that use of concomitant MTX did not affect the efficacy of TNF inhibitor therapy. Data from three EU registries suggest that TNF inhibitor (especially monoclonal antibody) drug survival is superior in patients taking concomitant MTX, while one Canadian registry reported no difference.

Conclusions. Available evidence on the efficacy and safety of TNF inhibitor monotherapy versus add-on to MTX shows little or no improvement with combination therapy, although use of concomitant MTX appears to prolong TNF inhibitor drug survival of monoclonal antibody TNF inhibitors. Registries and observational studies have the potential to fill some of the knowledge gaps in this area.

Key words: Adalimumab, Certolizumab pegol, Etanercept, Golimumab, Infliximab, Methotrexate, Psoriatic arthritis, TNF inhibitors.

Introduction

Tumour necrosis factor (TNF) inhibitors have been shown to be effective in the treatment of both skin and joint symptoms of psoriatic arthritis (PsA) [1], with remission being an achievable target [2]. The European League Against Rheumatism (EULAR) and Group for Research and Assessment of Psoriasis and Psoriatic Arthritis (GRAPPA) recommend TNF inhibitor therapy in PsA patients with an inadequate response to at least one disease-modifying anti-rheumatic drug (DMARD), or those with predominantly axial disease, dactylitis or enthesitis. Methotrexate (MTX) is the suggested first-line DMARD in PsA; however, neither EULAR nor GRAPPA currently recommend the use of MTX in combination with TNF inhibitor therapy owing to the availability of insufficient data [3, 4].

Despite this, the use of MTX in combination with TNF inhibitors in PsA is not uncommon; there could be several reasons for this. Firstly, rheumatologists are accustomed to using concomitant MTX with TNF inhibitor therapy in rheumatoid arthritis (RA). Combination therapy with MTX has demonstrated superior efficacy compared with biologic monotherapy for the treatment of RA and this approach is recommended by EULAR [5]. MTX is also an effective therapy in psoriasis, but combination use with TNF inhibitors has been less well studied than in RA [6]. In two small clinical trials, the combination of etanercept and MTX showed greater efficacy than monotherapy for skin outcomes in psoriasis patients [6, 7]. There is also some evidence from a small observational study that the addition of MTX may improve treatment efficacy in psoriasis patients with an inadequate response to adalimumab [8]. Conversely, a small observational study did not find any difference in efficacy between infliximab monotherapy and combination therapy with MTX in psoriasis patients [9]. Concomitant MTX may reduce the risk of infusion reactions in psoriasis patients

treated with infliximab [10]. The addition of MTX to infliximab reversed the anti-drug antibody (ADA) status and achieved sustained clinical efficacy in ADA-positive psoriasis patients in a small pilot study [11].

The potential effect of MTX on the formation of ADAs, especially in the case of monoclonal antibody (mAb) TNF inhibitors, could also support the concomitant use of MTX in PsA. The development of ADAs against mAb TNF inhibitors in PsA patients is associated with low serum drug levels and diminished clinical response [12]. Concomitant MTX has been shown to reduce immunogenicity in a dose-dependent manner in adalimumab-treated RA patients [13]. MTX also reduced immunogenicity of infliximab in a study of 94 patients with spondyloarthritis (including 22 patients with PsA) [14]. Recently, the use of concomitant MTX was shown to reduce immunogenicity of adalimumab and infliximab in an Israeli cohort of 93 PsA patients [15].

In this review, we address the role of concomitant MTX in PsA patients (excluding those with psoriasis only) by examining the available evidence for TNF inhibitor combination therapy with MTX, especially with regards to TNF inhibitor monotherapy, and help to identify knowledge gaps around this topic.

Methods

A search of PubMed was conducted up to and including October 2013 for randomized controlled trials (RCTs) and observational studies comparing TNF inhibitor monotherapy versus add-on therapy to ongoing MTX in patients with PsA. The search terms used were: “Psoriatic arthritis” AND (“TNF” OR “adalimumab” OR “certolizumab” OR “etanercept” OR “golimumab” OR “infliximab”). Relevance to the topic was determined by scanning the title

and abstract of the retrieved articles. Full text articles were obtained if the abstract did not contain sufficient information to determine relevance. Articles were included in the review only if they reported data for PsA patients treated with a TNF inhibitor alone versus those receiving a TNF inhibitor in combination with MTX. In addition, titles of abstracts from appropriate sessions of EULAR Congresses in 2011–13 and American College of Rheumatology/Association of Rheumatology Health Professionals (ACR/ARHC) Annual Meetings in 2011–13 were scanned for relevant new data not fully published at the time of the search.

Information extracted from reports of RCTs included inclusion criteria, baseline disease and treatment data, MTX dose, efficacy outcomes for joint and skin symptoms, safety outcomes and ADA formation. Information extracted from observational studies included PsA severity and duration, concomitant treatment, and efficacy, safety and drug survival data.

Results

Figure 1 illustrated the process of publication selection. The searches using the names of individual TNF inhibitors returned 1610 articles (372 for adalimumab, 23 for certolizumab, 601 for etanercept, 65 for golimumab and 549 for infliximab). After assessment of relevance and exclusion of duplicates, 36 potential articles remained for inclusion. The search replacing individual drug names with “TNF” returned one additional relevant article. Searches of conference abstracts found four relevant abstracts.

Randomized controlled trials

Eleven published articles and three conference abstracts were retrieved, reporting on six RCTs of four TNF inhibitors. Two articles reported on the ADEPT trial of adalimumab [16, 17]. Two articles reported on two RCTs of etanercept [18, 19], and a conference abstract reported a post-hoc analysis of pooled data from these trials [20]. Two articles and two conference abstracts reported on the GO-REVEAL trial of golimumab [21-24]. Five articles reported on two trials (IMPACT and IMPACT 2) of infliximab [25-29].

In addition, one article reported on the RAPID-PsA trial of certolizumab pegol, but only data for monotherapy versus any concomitant DMARD therapy (not specifically MTX) were available [30].

Some key inclusion criteria and baseline characteristics of the included RCTs are shown in Table 1.

Efficacy data in RCTs

ACR response rates

All RCTs found no or minor differences in efficacy for peripheral arthritis, as assessed by ACR response rates, between patients treated with or without MTX (Table 2). No statistical analyses comparing monotherapy and combination therapy were performed in any of the trials; comparisons were based solely on numerical values.

The ADEPT adalimumab trial found no differences for ACR20, ACR50 or ACR70 at weeks 12 and 48 [16, 17]. Similarly, the GO-REVEAL golimumab trial reported no effect of concomitant MTX on ACR20, 50 or 70 at 14 weeks [21], 2 years [22] or 5 years [23, 24].

No differences in response to etanercept with or without MTX at week 12 were reported by Mease *et al.* or for the PRESTA trial [18, 19]. A post-hoc analysis of pooled data from Mease *et al.* and PRESTA found no differences between etanercept (n=322) and etanercept plus MTX (n=153) arms in ACR20 at 24 weeks (71% vs. 70%); numerically, a higher proportion of patients in the monotherapy arm achieved ACR50 (55% vs. 48%) and ACR70 (35% vs. 27%) responses [20].

In the IMPACT trial of infliximab, concomitant use of MTX had no effect on ACR20 response at week 16 [25]. In IMPACT 2, numerically fewer MTX users achieved an ACR50 and ACR70 response at week 14 than MTX non-users (see Table 2), although the number of patients included in these analyses was small [26]. There was no difference between the two groups in ACR20 response at week 14 or in any ACR response at week 24 [26]. The ACR response at week 54 was consistent, regardless of baseline MTX use [28].

In addition, the RAPID-PsA trial of certolizumab pegol found no difference in ACR20 at 12 weeks between groups with and without concomitant DMARDs for either certolizumab dose investigated [30].

Structural outcomes

Three RCTs reported structural outcomes in patients with and without MTX (Table 2). ADEPT found no effect of MTX on radiographic progression in adalimumab-treated patients at week 24, although there was some suggestion of a difference at week 48 (mean mTSS change -0.1 with MTX vs. 0.4 without MTX) [17]. In GO-REVEAL, patients receiving MTX at baseline demonstrated numerically less progression at week 104 than patients not receiving MTX despite having more radiographic damage at baseline (mean change from baseline in

modified Sharp/van der Heijde score [SHS] -0.78 vs. 0.03 for golimumab 50 mg every 4 weeks and -0.65 vs. 0.00 for 100 mg) [22]. A similar pattern was seen at week 256 [23, 24].

In IMPACT 2, the difference in radiographic progression at 1 year between infliximab and placebo groups was greater in patients with baseline MTX use (median difference between treatment groups in change from baseline in total modified SHS 0.5 vs. 0.0) [29].

Other arthritis outcomes

In IMPACT 2, significant improvements in Health Assessment Questionnaire Disability Index (HAQ-DI) scores were seen in the infliximab group compared with the placebo group, regardless of MTX use at baseline [27]. Mean percentage improvement from baseline in HAQ at week 14 was 34% in patients receiving infliximab and MTX (versus 3.7% for placebo) and 61% (versus -36% [i.e. worsening] for placebo) in those receiving infliximab monotherapy. A similar pattern was seen at week 24 [27].

The pooled analysis of etanercept trials found little numerical difference between etanercept alone and etanercept plus MTX arms for DAS28 (change from baseline -1.9 vs. -1.8), Psoriatic Arthritis Response Criteria (PsARC) response (80% vs. 83%) or HAQ-DI (change from baseline -0.5 vs. -0.6) at week 24 [20].

Skin outcomes in PsA patients

In ADEPT, Psoriasis Area Severity Index (PASI) 50, 75, 90 and 100 response rates were numerically greater in the adalimumab plus MTX sub-group at week 48 (83% vs. 55%, 72%

vs. 48%, 59% vs. 38% and 41% vs. 28%, respectively), but the difference was only significant for PASI 50 ($p < 0.05$) [17].

PRESTA found some benefit of MTX for skin symptoms at week 12 in patients with severe skin disease (mean baseline PASI of 20) receiving etanercept 50 mg twice weekly but not those receiving 50 mg once weekly [19]. The pooled analysis of etanercept trials found little numerical difference in PASI improvement from baseline to week 24 between etanercept only and etanercept plus MTX arms (change from baseline -14 vs. -12) [20].

In GO-REVEAL, in the 217/292 (74%) patients with at least 3% body surface area affected, benefit of golimumab on PASI at week 14 was observed irrespective of MTX use ($P=0.32$) [21]. At week 104, similar PASI 50, 75 and 90 responses were seen irrespective of baseline MTX use (monotherapy 81% vs. MTX 88%, 64% vs. 62% and 44% vs. 38%, respectively, for golimumab 50 mg; 83% vs. 89%, 73% vs. 71% and 51% vs. 42%, respectively, for 100 mg) [22]. At week 256, PASI responses were similar in patients treated with and without MTX [23, 24].

In IMPACT 2, compared with patients not receiving MTX at baseline, those receiving MTX in combination with infliximab had similar PASI 75 responses at week 54 (48% vs. 53%, respectively) [28].

QoL outcomes

In IMPACT 2, significant benefits, as measured by SF-36 scores, were seen in the infliximab group compared with placebo, regardless of baseline MTX use [27]. For MTX users, the mean improvement from baseline at week 14 was 7.9 in the infliximab group versus 2.9 in the placebo group for the physical component summary (PCS) score and 2.0 versus -3.4

(worsening) for the mental component summary (MCS) score. For non-MTX users, the corresponding improvement was 10.1 in the infliximab group versus -0.5 (worsening) in the placebo group for the PCS score, and 5.3 versus 0.6 for the MCS score. A similar pattern was found when the data were analysed at week 24 [27].

Safety data in RCTs

In ADEPT, nine patients had serum transaminase values three times the upper limit of normal; five of these patients were receiving MTX [17]. In GO-REVEAL, concomitant MTX did not appear to affect transaminase levels at week 14 [21].

In IMPACT 2, five patients on infliximab had markedly abnormal alanine transaminase (ALT) or aspartate transaminase (AST) levels at week 24; one of these patients was on MTX [26].

At week 54, the incidence of adverse events was generally similar between patients receiving MTX and those not receiving MTX at baseline (88% vs. 83%) [28]. Slightly more infliximab-treated patients not receiving MTX had an ALT or AST value that rose from normal to high compared with those receiving MTX (47% vs. 40% and 31% vs. 22%, respectively). The rate of infusion reactions was lower in patients receiving MTX at baseline (0.9% vs. 3.2%) [28].

Immunogenicity data in RCTs

In GO-REVEAL, the incidence of antibodies to golimumab at week 14 was low (4.6%), and no patients receiving MTX at baseline developed antibodies [21]. By week 104, 5.4% of

golimumab-treated patients had developed antibodies; this appeared to be less common in patients receiving (1.6%) than those not receiving MTX at baseline (9.1%) [22].

In IMPACT 2, only 3.6% of patients receiving MTX at baseline were positive for antibodies to infliximab through week 66 compared with 26.1% of those not receiving MTX [28]. ACR improvement at week 54 was lower (22% vs. 33%) and mild-to-moderate infusion reactions were 3.5-fold more common in patients with ADAs [28].

Observational studies/registries

Seven published articles and one conference abstract reported TNF inhibitor monotherapy versus MTX combination therapy data from six registries [31-38]. Characteristics of the registries and PsA patients included are shown in Table 3. In addition, one article and one abstract reported data on TNF inhibitor therapy with and without concomitant DMARDs (not specifically MTX) [39, 40]. Three reports of relevant observational studies were also retrieved [41-43].

In three registries (BSRBR, NOR-DMARD, ROB-FIN) that reported efficacy data, use of concomitant MTX did not affect the efficacy of TNF inhibitor therapy [34, 35, 38].

Registries – drug survival data

Drug survival data were reported for four registries. In the Norwegian DMARD registry (NOR-DMARD), concomitant MTX was associated with better 1-year TNF inhibitor drug survival in PsA patients ($p=0.02$) [31]. Reasons for discontinuing treatment were: lack of efficacy (18%), adverse events (69%), patient request (5%) and other reason/unknown (8%).

Discontinuation rates in the monotherapy versus combination therapy groups were not reported; however, no combination treatment courses were discontinued due to lack of efficacy, whereas lack of efficacy was the reason for about 40% of monotherapy discontinuations [31].

In another analysis of NOR-DMARD data, the difference in TNF inhibitor drug survival with concomitant MTX was most prominent for patients receiving infliximab [32]. The groups of patients receiving TNF inhibitor as monotherapy (n=170) and those receiving concomitant MTX (n=270) had similar baseline characteristics, except for a higher swollen joint count in the concomitant MTX group. Drug survival analyses showed a borderline significant difference in favour of patients receiving MTX (p=0.07); this was most prominent for patients receiving infliximab (p=0.01). A similar trend was seen for patients treated with adalimumab (p=0.12); the group difference in the etanercept group was negligible (p=0.79). In a Cox regression analysis, lack of concomitant MTX and current smoking were independent predictors of TNF inhibitor discontinuation. Reasons for discontinuation were loss/lack of efficacy (monotherapy 20% versus concomitant MTX 14%), adverse events (21% vs. 14%) and other (13% vs. 18%). Patients receiving infliximab as monotherapy had markedly higher discontinuation rates due to adverse events (p<0.001) [32].

The South Swedish Arthritis Treatment Group (SSATG) noted no baseline differences between 100 patients receiving TNF inhibitor monotherapy and 161 receiving concomitant MTX, other than greater NSAID use in the MTX group (61% [98/161] vs. 48% [48/100]; p=0.04) [33]. Concomitant MTX (hazard ratio 0.64, 95% CI 0.39–0.95; p=0.03), use of etanercept (0.49, 0.28–0.86; p=0.01) and high C-reactive protein levels (0.77, 0.61–0.97; p=0.03) at treatment initiation were associated with better overall drug survival over 7

years. The improved drug survival with concomitant MTX appeared to be related to significantly fewer dropouts because of adverse events (hazard ratio 0.24, 0.11–0.52; $p < 0.01$) [33].

In the Danish biologics registry (DANBIO), 54% of 410 PsA patients were receiving concomitant MTX at baseline [36]. Baseline MTX use was more prevalent among patients receiving infliximab (70%) than adalimumab (49%) or etanercept (39%) ($p < 0.001$). After 3 months, 329 (80%) patients continued to receive concomitant MTX, 44 patients (11%) had stopped MTX but continued TNF inhibitor therapy, and 37 patients (9%) had stopped receiving a TNF inhibitor. In a Cox regression analysis, male gender, CRP level >10 mg/L, concomitant MTX use, and low patient health visual analogue scale score at baseline were associated with longer drug survival. The adjusted hazard ratio for discontinuation of TNF inhibitor associated with lack of MTX use was 1.37 (95% CI 1.07–1.75). Lack of MTX use was associated with discontinuation due to adverse events but not due to lack of efficacy [36].

In contrast to the above findings, the Canadian Rhumadata clinical database and registry found that concomitant MTX did not demonstrate improved 5-year retention with adalimumab or etanercept (52% for combination therapy versus 67% for monotherapy; $p = 0.74$) [37].

In addition, there were two reports of TNF inhibitor drug survival with and without concomitant DMARDs (not specifically MTX). The British Society of Rheumatology Biologics Register (BSRBR) reported that, for TNF inhibitor discontinuation due to inefficacy, there was a trend towards better survival in patients receiving concomitant DMARD therapy [39]. The particular DMARDs used were not specified. Finally, in the US CORRONA registry, patients initiated on biologic–DMARD combination therapy had slightly higher disease

severity at baseline and were at higher risk of changing therapy compared with those receiving biologic monotherapy [40].

Other observational studies

A non-interventional study of 95 PsA patients treated with TNF inhibitors found that concomitant MTX did not predict response (defined as an improvement of $\geq 40\%$ in active and swollen joint count and $\geq 50\%$ improvement in PASI score) in the logistic regression models used [41]. An Italian multicenter longitudinal pilot study found no difference in efficacy between TNF inhibitors with or without concomitant MTX in PsA patients, but the number of patients was very small (n=29) [42].

Finally, a prospective observational study of 82 PsA patients treated with etanercept with or without concomitant MTX in one Italian center found that the main demographic and clinical features, including rates of withdrawal due to inefficacy or toxicity, were not significantly different in patients with PsA treated with etanercept alone or in combination with MTX; concomitant MTX treatment did not appear to be a positive predictor of drug survival [43].

Discussion

Among six RCTs of TNF inhibitors in PsA, most found no effect of concomitant MTX on efficacy outcomes, and one study of infliximab (IMPACT 2) actually found numerically lower ACR50 and ACR70 responses at week 14 in patients taking concomitant MTX [26]. It should be noted that these studies were not sufficiently powered to answer this question and no

statistically tests were conducted. Some data suggest that concomitant MTX may reduce structural progression, with numerically less progression at weeks 104 and 256 in patient receiving MTX and golimumab in GO-REVEAL [22-24] and a greater difference in radiographic progression at 1 year between infliximab and placebo groups with concomitant MTX in IMPACT 2 [29]. No significant differences in other outcomes have been reported, other than some benefit of MTX for skin symptoms at week 12 in patients with severe skin symptoms receiving etanercept 50 mg twice weekly (but not 50 mg once weekly) in PRESTA [19]. No randomized trials designed to compare TNF inhibitor monotherapy versus concomitant MTX have been performed to date; the comparisons reported are based on stratification rather than randomization, and baseline differences need to be taken into account.

It has been suggested that the lack of improvement in efficacy with MTX and TNF inhibitor combination therapy may be due to differences in the efficacy of MTX in PsA versus RA [16]. A study of MTX in PsA found no evidence for improvement of synovitis [44]. Alternatively, the efficacy of TNF inhibitors at the studied doses in PsA RCTs is already maximal and therefore not subject to improvement via the mechanisms that MTX might have in RA (e.g. an additive immunomodulatory effect or a direct effect on TNF inhibitor clearance mechanisms) [16].

There is little data from RCTs comparing the safety of TNF inhibitors with and without concomitant MTX. However, in the IMPACT 2 trial, infusion reactions with infliximab were slightly less frequent in patients receiving MTX [28]. In this trial, the low number of patients on concomitant MTX who had increased transaminase levels may be due in part to the 3

months of MTX exposure at baseline, and hence there may have been some selection bias towards patients who were less prone to development of abnormal liver enzymes [28].

Formation of ADAs against infliximab and golimumab also appears to be lower in patients receiving concomitant MTX [21, 22, 28]. A small study recently demonstrated a significant correlation between the use of MTX and the absence of ADAs in PsA patients treated with infliximab and adalimumab [15], but more data is needed before the use of MTX can be recommended to reduce immunogenicity in PsA patients.

Data from three EU registries (BSRBR, ROB-FIN, NOR-DMARD) showed no difference in the efficacy of TNF inhibitors with and without concomitant MTX [34, 35, 38]. However, data from three EU registries (NOR-DMARD, SSATG, DANBIO) suggest that TNF inhibitor drug survival is better in patients taking concomitant MTX [31-33, 36]. Only one of these registries separated the data by TNF inhibitor agent [32]. There was no difference in drug survival for etanercept with or without MTX, whereas patients receiving infliximab as monotherapy had markedly higher discontinuation rates due to adverse events ($p < 0.001$). The authors suggested that the difference in drug survival could be explained by mechanisms related to the potential for MTX to prevent ADA formation [32]. The other two registries reported that lack of MTX appeared to be associated with discontinuation due to adverse events rather than lack of efficacy [33, 36]. A Canadian registry found no difference in drug survival with or without MTX [37].

Confounding by indication is a concern in observational studies. A higher degree of drug intolerance and treatment resistance may be present in patients on TNF inhibitor monotherapy. Absence of concomitant MTX might be associated with the presence of a co-

morbidity relevant to drug continuation. MTX use seems to be higher in patients on infliximab compared with other TNF inhibitors.

Overall, there is little evidence to guide physicians treating patients with PsA as to whether TNF inhibitors should be used as monotherapy or in combination with MTX. A recent study of treatment patterns with adalimumab and etanercept in patients with psoriasis or PsA in the setting of a US claims database found that 46.3% of adalimumab-treated and 36.8% of etanercept-treated PsA patients were also receiving MTX, compared with 14.4% and 10.4%, respectively, of psoriasis patients [45].

One possible treatment strategy in PsA might be to add a TNF inhibitor in patients with an inadequate response to MTX. Following a good response, MTX could be tapered and then possibly withdrawn, although drug survival data suggest this may not be advisable with mAb agents. An alternative strategy could be to initiate TNF inhibitor monotherapy and add MTX if a partial response is seen. Although RCTs could be designed to answer this question, large numbers of patients would be required to identify the most appropriate strategy in a controlled environment. Observational studies and analyses of registry data may offer a more practical approach.

Conclusions

Available evidence on the efficacy and safety of TNF inhibitor monotherapy versus concomitant MTX shows little or no improvement with combination therapy, although use of MTX appears to prolong TNF inhibitor drug survival, especially with mAb TNF inhibitors. Information on the use of different treatment strategies in PsA, such as starting with combination therapy and then withdrawing MTX or starting with TNF inhibitor monotherapy

and then adding MTX, is lacking. Registries and observational studies have the potential to address such questions and fill some of the knowledge gaps in this area.

Key messages

- Combination with MTX does not improve the efficacy or safety of TNF inhibitors in PsA
- Use of concomitant MTX appears to prolong TNF inhibitor drug survival, especially with mAbs
- Information on the use of different treatment strategies in PsA is lacking

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Figure 1. Flow chart of publication selection

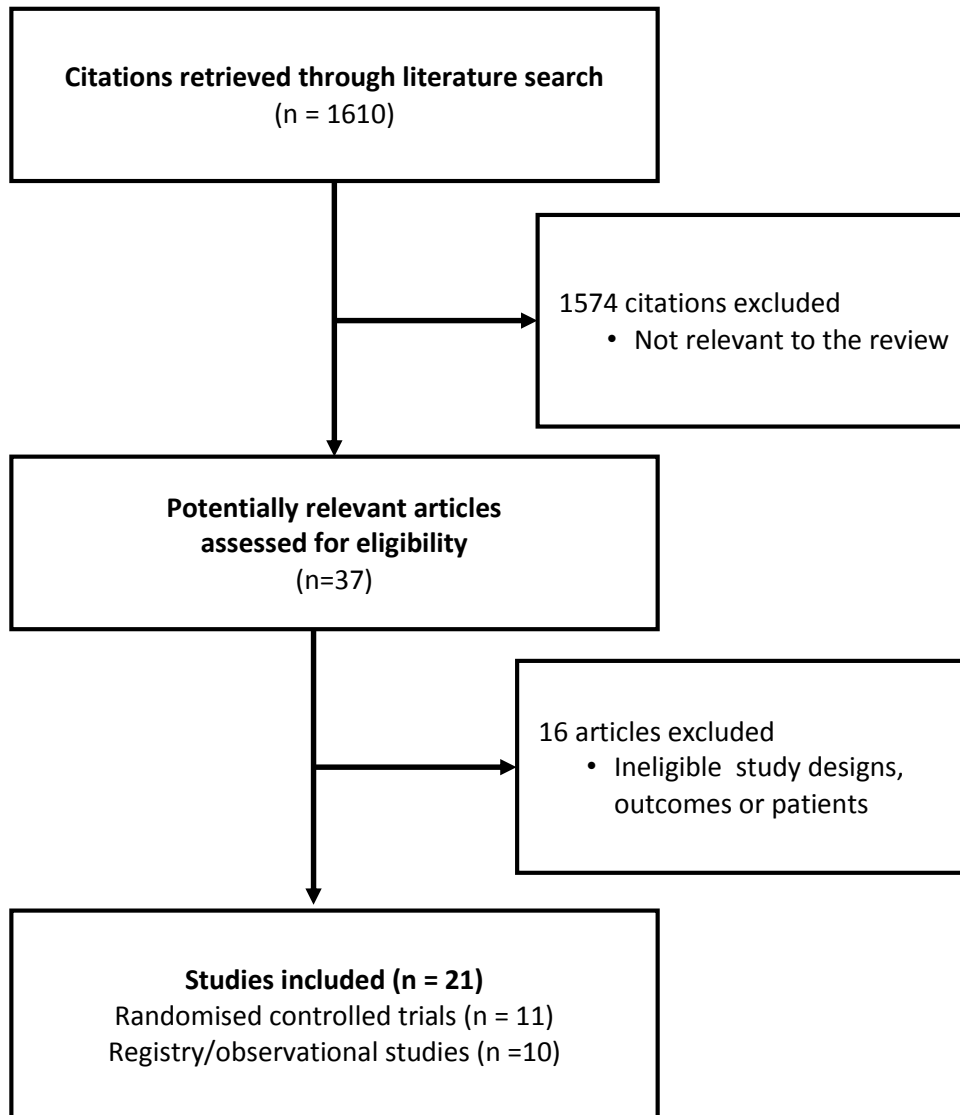


Table 1. Characteristics of patients in TNF inhibitor arms of RCTs

Drug / trial	Patient population	TNFi dose / duration	PsA duration (years)	PsA type	Skin involvement	Disease severity		Concomitant treatment	MTX at baseline	Stratified by MTX use?
						Joints	Skin			
Adalimumab										
ADEPT [16]	Mod-severe PsA; NSAID-IR	40 mg EOW for 24 weeks (n=151) + OLE	Mean 9.8 ± 8.3	64% symmetric polyarthritis 25% asymmetric polyarthritis 15% DIA 1% arthritis mutilans 1% spondylitis	46% ≥3% BSA	TJC (0-78): 23.9 ± 17.3 SJC (0-76): 14.3 ± 12.2 HAQ-DI: 1.0 ± 0.6	Mean PASI: 7.4 ± 6.0	NSAIDs, prednisolone allowed	51%	Yes
Etanercept										
Mease et al [18]	Active PsA; NSAID-IR	25 mg BIW for 24 weeks (n=101) + OLE	Mean 9.0	86% polyarthritis 51% DIA 41% asymmetric peripheral arthritis 1% arthritis mutilans 3% AS-like arthritis	Mean BSA: 10.9%			CS 19% NSAIDs 88%	42% (n=42; mean dose 16.3 mg/wk)	Yes
PRESTA [19]	Mod-severe psoriasis and PsA	50 mg BIW/QW (n=379); 12/12 weeks	Mean 7 ± 7			TJC: 19 ± 18 SJC: 12 ± 15	Mean BSA: 31% PASI: 20 ± 11	Stable CS, NSAIDs allowed	25% (mean dose 12.7 mg/wk)	No
		50 mg QW/QW (n=373); 12/12 weeks	Mean 7 ± 7			TJC: 19 ± 18 SJC: 13 ± 15	Mean BSA: 30% PASI: 19 ± 10			
Golimumab										
GO-REVEAL [21]	Active PsA despite NSAIDs	50 mg Q4W (n=146) for 20 weeks + OLE	Mean 7.2 ± 6.8	16% DIA 30% asymmetric peripheral arthritis 43% polyarthritis 1% arthritis mutilans 10% spondylitis + peripheral arthritis	75% ≥3% BSA	TJC: (0-68) 24.0 ± 17.1 SJC: (0-66) 14.1 ± 11.4 DAS28-CRP: 4.4 ± 1.1	Mean PASI: 9.8 ± 8.6 Mean BSA: 16.2%	CS 13% NSAIDs 75%	49% (n=71; mean dose 14.8 mg/wk)	Yes

		100 mg Q4W (n=146) for 20 weeks + OLE	Mean 7.7 ± 7.8	15% DIA 34% asymmetric peripheral arthritis 38% polyarthritis 1% arthritis mutilans 12% spondylitis + peripheral arthritis	74% ≥3% BSA	TJC (0–68): 22.5 ± 15.7 SJC (0–66): 12.0 ± 8.4 DAS28-CRP: 4.3 ± 1.0	Mean PASI: 11.1 ± 9.5 Mean BSA: 17.7%	CS 18% NSAIDs 75%	47% (n=67; mean dose 15.5 mg/wk)	
Infliximab										
IMPACT [25]	Active PsA ≥6 months; failed ≥1 DMARD	5 mg/kg for 16 weeks (n=52) + OLE	Mean 11.7 ± 9.8	100% peripheral polyarticular arthritis	42% PASI ≥2.5	TJC (0–68): 23.7 ± 13.7 SJC (0–66): 14.6 ± 7.5 DAS28: 5.5 ± 1.1	Mean PASI: 5.1 ± 5.9	Stable CS and NSAIDs allowed	DMARD 63% MTX 46% (n=24; mean dose 15.9 mg/wk)	No
IMPACT 2 [26]	Active PsA ≥6 months; failed ≥1 DMARD or NSAID	5 mg/kg for 24 weeks (n=100) + OLE	Mean 8.4 ± 7.2	26% DIA 18% asymmetric peripheral arthritis 53% polyarthritis 1% arthritis mutilans 2% spondylitis + peripheral arthritis	83% ≥3% BSA	TJC (0–68): 24.6 ± 14.1 SJC (0–66): 13.9 ± 7.9 HAQ-DI: 1.1 ± 0.6	Mean PASI: 11.4 ± 12.7	CS 15% NSAIDs 71%	47% (n=47; mean dose 16 mg/wk)	Yes

AS: ankylosing spondylitis; DIA: distal interphalangeal arthropathy; BIW: twice weekly; BSA: body surface area; CRP: C-reactive protein; CS: corticosteroid; DAS: disease activity score; DMARD: disease-modifying anti-rheumatic drug; EOW: every other week; HAQ-DI: Health Assessment Questionnaire Disability Index; IR: inadequate response; MTX: methotrexate; NSAID: non-steroidal anti-inflammatory drug; OLE: open-label extension; PASI: Psoriasis Area Severity Index; PsA: psoriatic arthritis; Q4W: every 4 weeks; QW: once weekly; SJC: swollen joint count; TJC: tender joint count

Table 2. ACR response rates and radiographic changes in RCTs

Drug / trial	Time point / TNFi dose		No of patients		Mean MTX dose	ACR20		ACR50		ACR70		Mean (\pm SD) change from baseline in mTSS	
			Mono	+ MTX		Mono	+ MTX	Mono	+ MTX	Mono	+ MTX	Mono	+ MTX
Adalimumab													
ADEPT [16, 17]	Week 12		76	75		61%*	55%*	36%	36%	23%	17%		
	Week 24											-0.2 \pm 1.17	-0.2 \pm 1.59
	Week 48		66	72		50%	63%	38%	49%	29%	31%	0.4	-0.1
Etanercept													
Mease et al [18]	Week 12*		288	143	16.3 mg/wk	71%	70%	55%	48%	35%	27%		
PRESTA [19]	Week 12*				12.7 mg/wk								
Golimumab													
GO-REVEAL [21-24]	Week 14*		292			Benefit seen irrespective of MTX use (P=0.66)							
	Week 104	50 mg & 50/100 mg	55	63	14.8 mg/wk	64%	70%	44%	49%	24%	34%	0.03 \pm 2.25	-0.78 \pm 2.04
		100 mg	61	68	15.5 mg/wk	72%	68%	52%	51%	37%	51%	0.00 \pm 1.51	-0.65 \pm 2.15
	Week 256		204			ACR responses were similar in patients treated with and without MTX						Changes were minimal and numerically less in patients on MTX	
Infliximab													
IMPACT [25]	Week 16*		52		15.9 mg/wk	74%	63%	-	-	-	-		
IMPACT 2 [26, 28]	Week 14*				16 mg/wk	57%	60%	43%	28%	21%	9%		
	Week 24		53	47		51%	57%	40%	43%	32%	21%	0.0** (p=0.108)	0.5** (p<0.001)
	Week 54		90			61%	57%	-	-	-	-		

*Primary endpoint

**Median difference between treatment groups

Note: Differences between monotherapy and combination therapy were not tested for statistical significance

Table 3. Characteristics of registries

Registry	Region	Indication	No of TNFi-treated PsA patients	PsA disease duration (years)	Disease severity (joints)	Concomitant MTX	
						No; %	Dose
NOR-DMARD [31]	Norway	RA, PsA, AS	172 (48 IFX, 96 ETA, 28 ADA)	Mean 12.1 ± 9.3	Global VAS: 43.9 ± 19.3	68%	
NOR-DMARD [32]			440	Median 5.2 (IQR 1.5–12.5)	SJC (0–32): 3 (IQR 1–6) Physician global: 37.4 ± 17.9 Patient global: 54.6 ± 23.7 MHAQ 0.70 ± 0.46	270; 61%	Mean 14.7 ± 5.1 mg/wk
NOR-DMARD [38]			146 (44 IFX, 83 ETA, 19 ADA)	Mean 11.6 ± 9.3	SJC (0–28) 4.9 ± 4.8 TJC (0–28) 7.5 ± 7.0 Physician global 44.8 ± 19.6 Patient global 58.1 ± 21.3 DAS-28 4.8 ± 1.4 MHAQ 1.83 ± 0.47	75% IFX, 60% ETA, 79% ADA	Mean 12.5 ± 4.7 mg/wk
SSTAG [33]	South Sweden	IA	261 (MTX: 17 ADA, 70 ETA, 74 IFX; no MTX: 11, 49, 40)	Median 7.9 (IQR 3.7–15.0) MTX; 9.4 (4.2–17.8) no MTX	HAQ: 1.0 (IQR 0.6–1.4) MTX; 1.0 (0.5–1.5) no MTX DAS28: 4.9 (3.9–5.7) MTX; 4.8 (3.8–5.5) no MTX	161; 62%	Median 15.0 (IQR 10–20) mg/wk
ROB-FIN [35]	Finland	IA	127 (IFX, ETA)	Median 11 (IQR 6–18)	SJC (0–54): 6 (IQR 3–11) TJC (0–53): 7 (4–13) HAQ: 1.0 (0.63–1.5) Patient global: 59 (42–75) Physician global: 50 (45–75)	51% (IFX 71%; ETA 44%)	Median 13.75 (IQR 5–25) mg/wk IFX; 15 (8.75–25) ETA
DANBIO [36]	Denmark	IA	764 (320 ADA, 260 IFX, 184 ETA)	Median 5 (IQR 2–11)	SJC: 3 (IQR 1–7) TJC: 7 (3–13) HAQ: 1.0 (0.6–1.5) DAS28: 4.8 (3.9–5.5) VAS global: 69 (50–81)	410; 54% (IFX 70%, ADA 49%, ETA 39%)	Not reported
BSRBR [34]	UK	Primarily RA	596 (333 ETA, 171 IFX, 92 ADA)	Mean 12.4 ± 8.7	TJC (0–28) 13.4 ± 7.7 SJC (0–28) 8.9 ± 6.1 DAS28 6.4 ± 5.6 HAQ 1.9 (1.4–2.3)	Not reported	Not reported

ADA: adalimumab; AS: ankylosing spondylitis; DAS: disease activity score; DMARD: disease-modifying anti-rheumatic drug; ETA: etanercept; HAQ: Health Assessment Questionnaire; IA: inflammatory arthritis; IFX: infliximab; IQR: interquartile range; MTX: methotrexate; PsA: psoriatic arthritis; SJC: swollen joint count; RA: rheumatoid arthritis; TJC: tender joint count; TNFi: tumour necrosis factor inhibitor; VAS: visual analogue scale

