

EXTENDED REPORT

Pharmacological treatment of psoriatic arthritis: a systematic literature review for the 2015 update of the EULAR recommendations for the management of psoriatic arthritis

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ABSTRACT

Objective To update the evidence on the efficacy and safety of pharmacological agents in psoriatic arthritis (PsA).

Methods Systematic literature review of randomised controlled trials comparing pharmacological interventions in PsA: non-steroidal anti-inflammatory drugs, glucocorticoid, synthetic disease modifying antirheumatic drugs (sDMARDs) either conventional or targeted, biologicals (bDMARDs), placebo or any combination. Main outcomes were American College of Rheumatology (ACR)20–50, Psoriasis Area Severity Index 75, radiographic progression, and withdrawals due to adverse events (AEs). Multiple studies of the same intervention were meta-analysed using random effects.

Results In total, 25 papers and 12 abstracts were included. The efficacy of tumour necrosis factor inhibitors (including the recently added golimumab and certolizumab pegol) was confirmed and 16 articles/abstracts focused on 3 drugs with new modes of action: ustekinumab (UST), secukinumab (SEC) and apremilast (APR). All were placebo-compared trials and met their primary end point, ACR20. In 2 studies with UST ACR20 was met by 50% and 44% of patients with UST 90 mg, 42% and 44% with UST 45 mg vs 23% and 20% with placebo, respectively. In two studies with SEC ACR20 ranged 54% (SEC 300 mg), 50–51% (SEC 150 mg), 29–51% (SEC 75 mg) and 15–17% (placebo). In four studies with APR, ACR20 ranged 32–43% (APR 30 mg), 29–38% (APR 20 mg) and 17–20% (placebo). For all three drugs, no more withdrawals due to AEs than placebo were seen and, in general, safety appeared satisfactory. A strategy trial, Tight Control of Psoriatic Arthritis (TICOPA), showed better ACR responses with treatment adaptations upon tight control compared with standard care.

Conclusions UST, SEC and APR are new drugs with efficacy demonstrated for the treatment of PsA. No major safety signals arise, but long-term studies are needed. This review informed about the European League Against Rheumatism recommendations for management of PsA.

INTRODUCTION

Pharmacological management of psoriatic arthritis (PsA) is an area that has witnessed an important

expansion in the last few years. Initially the management of the disease was based on knowledge that was borrowed from the experience in rheumatoid arthritis (RA). Later on, and mainly since the advent of the biological therapies, trials started to be conducted specifically in patients with PsA, mostly after the same drugs had demonstrated efficacy in RA. However, this situation has recently changed, with randomised controlled trials (RCTs) demonstrating efficacy of new compounds that are not used for the treatment of RA.^{1–5} This provides rheumatologists with new options for the treatment of PsA, which, in turn, calls for the need of updating treatment recommendations.⁶ The European League against Rheumatism (EULAR) developed management recommendations in 2011⁶ and an initiative took place in 2014–2015 to update these recommendations.⁷

The objective of the present work was to update the evidence on efficacy and safety of pharmacological agents for the management of patients with PsA through a systematic literature review (SLR) with meta-analysis if possible to inform the task force on the update of the EULAR recommendations for the management of PsA.

METHODS

The present SLR was performed as an update of the 2011 EULAR SLR,⁸ thus only pharmacological non-topical treatments were dealt with, and only data published after 2010 were included.

Search methodology

The questions were reformulated according to the PICO format (Patients, Interventions, Comparisons and Outcomes)⁹ and the eligible study types were defined. Patients were defined as adults (≥18 years old) with a clinical diagnosis of PsA. The intervention was defined as any disease modifying antirheumatic drug (DMARD), either biological (bDMARD) or synthetic (sDMARD), the latter in turn including conventional (csDMARD) and targeted (tsDMARD) sDMARDs;¹⁰ systemic glucocorticoids; non-steroidal anti-inflammatory drugs (NSAIDs) or any combination of them. The following bDMARDs were included: anakinra, infliximab, etanercept, adalimumab, rituximab, abatacept, tocilizumab, golimumab,

certolizumab pegol, ustekinumab (UST), secukinumab (SEC), brodalumab, ixekizumab, in all formulations, and duration, as well as biosimilars if data were available. Similarly, all sDMARDs were considered, including csDMARDs previously analysed in PsA: methotrexate (MTX), leflunomide, hydroxychloroquine, sulfasalazine, gold/auranofin, azathioprine, chlorambucil, chloroquine, cyclosporine, cyclophosphamide, mycophenolate, minocycline or penicillamine, but also the tsDMARDs apremilast (APR) and tofacitinib. The comparator was any bDMARD, sDMARD, glucocorticoid, NSAID, combination of any of these or placebo (PBO).

The outcomes were divided into efficacy and safety. For efficacy, we report on the primary outcomes of the respective trials, but focus on the American College of Rheumatology 20% improvement (ACR20), as this was frequently the primary end point in trials. For safety, the primary outcome was withdrawals due to adverse events (AEs). Secondary efficacy outcomes collected were ACR50, ACR70, Psoriasis Area Severity Index (PASI)50–70–90, PsA response criteria (PsARC), EULAR good or moderate response, improvement in the 28-joint count Disease Activity Score or its components (swollen joint count (SJC), tender joint count, patient's global assessment of disease activity, and erythrocyte sedimentation rate or C reactive protein), minimum disease activity state,¹¹ improvement in functional disability, improvement in enthesitis, dactylitis and nail involvement, absenteeism, work productivity, cost-efficacy and structural damage. Secondary safety outcomes were serious AEs (SAEs), serious infections, tuberculosis, candidiasis, malignancies, skin exacerbation and demyelinating disease. Only RCTs published after 2010, either phase III or IV (including long-term extensions) as well as strategy trials were included.

The search was performed in Medline, Embase and The Cochrane Central Register of Controlled Trials (Central), on 17 December 2014, without language restrictions. Abstracts were also obtained from the 2013–2014 EULAR and ACR conferences. If an abstract used for the SLR was published in a manuscript before the present paper was submitted in its final format (5 October 2015), then the data from the manuscript were used. Also, some papers were made available by the authors once in press and this was also taken into account in the references. Details on the complete search strategy are provided in online supplementary text 1.

Study selection, data collection and assessment of risk of bias

One reviewer (SR) assessed titles and abstracts for suitability for inclusion in the SLR, according to predetermined inclusion criteria, followed by full-text review, where necessary. Data were extracted on study characteristics, interventions and all the above-mentioned outcomes. Risk of bias (RoB) was assessed according to the Risk of Bias Cochrane tool.¹²

Data analysis

For all interventions and patient populations for which more than one relevant RCT was identified, a meta-analysis was performed for the following main efficacy outcome measures: ACR20–50–70, PASI75–90 and EULAR response. Only studies that were judged as clinically homogeneous were pooled together. A random-effects model was used to be conservative, independently of the statistical heterogeneity, and analysis was conducted using RevMan.¹³ Risk ratios (RRs) with corresponding 95% CIs were calculated. Numbers needed to treat (NNT) were calculated for the main efficacy outcomes at the time point of the primary end point of the initial RCT.

RESULTS

The search yielded 2278 articles, of which 113 were selected for detailed review, and 387 conference abstracts. In the end, 25 full papers and 12 conference abstracts met inclusion criteria (see online supplementary figure S1). Of these, three studies investigated the effect of csDMARDs.^{14–16} In total, 15 papers and 2 abstracts focused on tumour necrosis factor inhibitors (TNFis), mainly the ones for which no data were previously available in PsA⁸—golimumab and certolizumab pegol,^{17–27} one study on the combination of infliximab with MTX versus MTX in MTX-naïve patients,²⁸ one post hoc analysis with adalimumab²⁹ and one study compared two etanercept regimens.^{30–33} A substantial part of the new evidence (6 papers and 10 abstracts) addressed the new compounds: UST (bDMARD anti-IL-12/23), SEC (bDMARD, anti-IL-17A) and APR (tsDMARD, inhibitor of phosphodiesterase 4).^{1–5 34–43} One strategy trial was included.⁴⁴ No studies were found on biosimilars, glucocorticoids or NSAIDs (table 1). Details on several efficacy and safety outcomes from each study can be found in the online supplementary tables S1–S8.

Conventional synthetic disease modifying antirheumatic drugs

The Methotrexate In Psoriatic Arthritis (MIPA) trial,¹⁴ at low RoB, compared MTX 15 mg/week to PBO in DMARD-naïve patients. The primary end point, PsARC at 24 weeks, was 1.77 times more likely to be achieved by patients on MTX compared with PBO (no individual responses per treatment arm reported); however, this difference did not reach statistical significance. ACR responses were not significantly different either; improvements in patients' and physicians' global assessments were higher in the MTX arm (see online supplementary tables S2 and S4).

Tumour necrosis factor inhibitors

RCTs with golimumab and certolizumab pegol have demonstrated their efficacy and safety with respect to all outcomes in the treatment of PsA, as had already been shown for other TNFis.^{17–27} Interestingly, unlike in other trials of TNFi the certolizumab pegol trial, RAPID-PsA, included patients who were TNFi inadequate responders (TNFi-IR, stratified randomisation), allowing a proper subgroup comparison. ACR responses were similar in TNFi-naïve and TNFi-IR patients (see online supplementary table S3), however, only about 20% of the patients were TNFi-IRs.

There was no trial comparing the start of a TNFi as monotherapy versus the start of a TNFi with MTX. The RESPOND,²⁸ at high RoB (not blinded, with recruitment stopping prematurely), comparing the combination of infliximab and MTX with MTX did not provide useful information.

The Psoriasis Randomized Etanercept Study in Subjects with Psoriatic Arthritis (PRESTA) trial,^{30–33} comparing two regimens of etanercept (50 mg twice a week vs 50 mg once a week) revealed no differences in joint responses (similar ACR responses), nor in the effect on the entheses, dactylitis or on functional disability, but a higher skin response for the higher dose (PASI75 of 55% for etanercept twice a week vs 36% for etanercept once a week).

Therapies against new targets: UST, SEC and APR

Efficacy and safety aspects of the three new compounds (UST, SEC and APR) are summarised in tables 1 and 2, figures 1–3, online supplementary tables S1–S9 and figures S2 and S3.

Table 1 Characteristics of the RCTs of pharmacological drugs in PsA published in 2010–2015†

Drug and trial acronym	Number of publications (abstracts)	Interventions compared	Type of patients included	Timing of primary end point	Primary end point	Risk of bias assessment
MTX (MIPA) ¹⁴	1 (0)	MTX 15 m/week, PBO	DMARD or NSAIDs failure, but MTX naive	24W	PsARC	Low
MTX vs Ciclosporine ¹⁵	1 (0)	ETA+MTX, ETA+CYC	DMARD failure	24W	NA	Unclear
Leflunomide ¹⁶	1 (0)	LEF, MTX	NA	24W	PsARC	High
Golimumab (GO-REVEAL) ^{17–21}	5 (0)	GOL 100 mg, GOL 50 mg, PBO	DMARD or NSAIDs failure	14W+24W (coprimary end point)	ACR20+change in radiographic score	Low
Certolizumab pegol (RAPID-PsA) ^{22–27}	4 (2)	CZP 400 mg, CZP 200 mg, PBO	DMARD or TNFi failure	12W	ACR20	Low
Infliximab (RESPOND) ²⁸	1 (0)	IFX 5 mg/kg+MTX 15 mg, MTX 15mg	DMARD or NSAIDs failure, but MTX naive	16W	ACR20	High
Adalimumab (ADEPT) ²⁹	1 (0)	ADA 40 mg, PBO	NSAIDs failure	12W+24W (coprimary end point)	ACR20+change in radiographic score	Unclear
Etanercept (PRESTA) ^{30 31 32 33}	4 (0)	ETA 50 mg 2×week, ETA 50 mg 1×week	DMARD or NSAIDs failure	12W	Physician's global assessment of psoriasis	Low
UST						
—PSUMMIT 1 ^{1 45}	1 (1)	UST 90 mg, UST 45 mg, PBO	DMARD or NSAIDs failure	24W	ACR20	Low
—PSUMMIT 2 ^{2 34}	2 (0)		DMARD or NSAIDs or TNFi failure	24W	ACR20	Low
SEC						
—FUTURE 1 ⁵	1 (0)	SEC 150 mg, SEC 75 mg, PBO	DMARD or NSAIDs or TNFi failure	24W	ACR20	Low
—FUTURE 2 ⁴	1 (0)	SEC 300 mg, SEC 150 mg, SEC 75 mg, PBO	DMARD or NSAIDs or TNFi failure	24W	ACR20	Low
APR						
—PALACE 1 ^{3 35–37}	1 (3)	APR 30 mg, APR 20 mg, PBO	DMARD or TNFi failure (<10%)	16W	ACR20	Unclear
—PALACE 2 ³⁸	0 (1)		DMARD or TNFi failure	16W	ACR20	NA*
—PALACE 3 ³⁹	0 (1)		DMARD or TNFi failure	16W	ACR20	NA*
—PALACE 4 ^{40–43}	0 (4)		DMARD or TNFi failure	16W	ACR20	NA*
Strategy trial (TICOPA) ⁴⁴	1 (0)	Tight control, standard care	DMARD naive	48W	ACR20	Low

No trials were available for glucocorticoids or non-steroidal anti-inflammatory drugs (NSAIDs).

†25 publications and 12 abstracts have been included.

ACR20, American College of Rheumatology 20% improvement; ADA, adalimumab; ADEPT, adalimumab effectiveness in psoriatic arthritis trial; APR, apremilast; CYC, ciclosporine; CZP, certolizumab pegol; DMARD, disease-modifying antirheumatic drug; ETA, etanercept; GOL, golimumab; IFX, infliximab; LEF, leflunomide; MIPA, methotrexate in psoriatic arthritis; MTX, methotrexate; NA*, not assessed, risk of bias assessment not possible as only abstract data; NA, not available; NSAID, non-steroidal anti-inflammatory drug; PALACE, psoriatic arthritis long-term assessment of clinical efficacy; PBO, placebo; PRESTA, psoriasis randomized etanercept study in subjects with psoriatic arthritis; PsA, psoriatic arthritis; PsARC, PsA response criteria; RCTs, randomised controlled trials; SEC, secukinumab; TICOPA, tight control of psoriatic arthritis; TNFi, tumour necrosis factor inhibitor; UST, ustekinumab.

UST RCTs (PSUMMIT-1 and PSUMMIT-2),^{1 2 34} at low RoB, met their primary end point, ACR20 at 24 weeks. Main efficacy and safety outcomes can be found in [table 2](#), including the NNT. For ACR50, the NNT compared with PBO was 5.2 for UST90 mg and 6.2 for UST45 mg in PSUMMIT-1. PSUMMIT-2 included 58% of TNFi-IR, and NNTs for ACR50 were 6.2 for UST90 mg and 9.3 for UST45 mg. UST also showed good skin responses, improvement in functional disability and structural damage inhibition. Treatment responses were independent of comedication with MTX and occurred in TNFi-naive and TNFi-experienced patients, but with a numerically better response in the former group. Pooling both studies together, the RRs for ACR20 versus PBO were 2.17 (95% CI 1.71 to 2.76) and 1.95 (95% CI 1.52 to 2.50) for UST90 mg

and UST45 mg, respectively ([figure 1](#)). Less patients on UST had enthesitis or dactylitis at 24 weeks when compared with PBO. There were not more withdrawals due to AEs or serious infections with UST compared with PBO.

For SEC, two trials have been conducted (FUTURE-1 and FUTURE-2),^{4 5} both meeting their primary end points, ACR20 at 24 weeks, and both at low RoB. The NNT for ACR50 was 3.6 for SEC300 mg in FUTURE-2 and ranged 3.6–3.7 for SEC150 mg and 4.3–9.0 for SEC75 mg ([table 2](#)). Treatment responses to SEC were independent of comedication with MTX and were confirmed in TNFi-naive and TNFi-experienced patients, but with a numerically lower response in the latter group. SEC also showed good responses regarding the skin as well as on resolution of enthesitis and dactylitis, improvement

Table 2 Main efficacy and safety outcomes for the new drugs for the treatment of PsA, at time point of the trial's primary end point

Trial, time point	Treatment arm	ACR20 (%) (NNT)	ACR50 (%) (NNT)	PASI75 (%) (NNT)	Delta HAQ mean (95%CI or SD)	Delta mSvdH mean (SD)	Withdrawals due to AEs (%)
PSUMMIT 1 24W ¹	UST 90 mg (N=204)	49.5 (3.7)	27.9 (5.2)	62.4 (1.9)	−0.25 (−0.75 to 0.00)	0.4 (2.4)*	1.5
	UST 45 mg (N=205)	42.4 (5.1)	24.9 (6.2)	57.2 (2.2)	−0.25 (−0.63 to 0.00)	0.4 (2.1)*	1.5
	PBO (N=206)	22.8	8.7	11.0	0.00 (−0.38 to 0.00)	1.0 (3.9)*	3.4
PSUMMIT 2 24W ^{2, 34}	UST 90 mg (N=105)	43.8 (4.2)	22.9 (6.2)	55.6 (2.0)	−0.25 (−0.50 to 0.00)	†	2.9
	UST 45 mg (N=103)	43.7 (4.3)	17.5 (9.3)	51.3 (2.2)	−0.13 (−0.38 to 0.00)	†	1.9
	PBO (N=104)	20.2	6.7	5.0	0.00 (−0.13 to 0.13)	†	10.6
PALACE 1 16W ³	APR30 mg (N=168)	38.1 (5.2)	NA	NA	−0.24 (0.04)	NA	NA
	APR20 mg (N=168)	30.4 (8.8)	NA	NA	−0.20 (0.04)	NA	NA
	PBO (N=168)	19.0	NA	NA	−0.09 (0.04)	NA	NA
PALACE 2 16W ³⁸	APR30 mg (N=162)	34.4 (6.7)	NA	NA	NA	NA	NA
	APR20 mg (N=163)	38.4 (5.3)	NA	NA	NA	NA	NA
	PBO (N=159)	19.5	NA	NA	NA	NA	NA
PALACE 3 16W ³⁹	APR30 mg (N=159)	42.8 (4.2)	NA	NA	NA	NA	NA
	APR20 mg (N=163)	29.4 (9.5)	NA	NA	NA	NA	NA
	PBO (N=164)	18.9	NA	NA	NA	NA	NA
PALACE 4 16W ^{40–43}	APR30 mg (N=175)	32.3 (6.5)	NA	NA	NA	NA	NA
	APR20 mg (N=175)	29.2 (8.1)	NA	NA	NA	NA	NA
	PBO (N=176)	16.9	NA	NA	NA	NA	NA
FUTURE 1 24 W ⁵	SEC 150 mg (N=202)	50.0 (3.1)	34.7 (3.7)	61.1 (1.9)	−0.40 (0.04)	0.13 (0.09)	1.5
	SEC 75 mg (N=202)	50.5 (3.0)	30.7 (4.3)	64.8 (1.8)	−0.41 (0.04)	0.02 (0.12)	2.0
	PBO (N=202)	17.3	7.4	8.3	−0.17 (0.05)	0.57 (0.19)	2.5
FUTURE 2 24 W ⁴	SEC 300 mg (N=100)	54.0 (2.6)	35.0 (3.6)	63.0 (2.1)	−0.56 (0.05)	NA	2.0
	SEC 150 mg (N=100)	51.0 (2.8)	35.0 (3.6)	48.0 (3.1)	−0.48 (0.05)	NA	0.0
	SEC 75 mg (N=99)	29.0 (7.1)	18.0 (9.0)	28.0 (7.9)	−0.32 (0.05)	NA	2.0
	PBO (N=98)	15.0	7.0	16.0	−0.31 (0.06)	NA	3.0

*Results reflect a pooled analysis of PSUMMIT 1 and 2, as a priori predefined.

†See results for PSUMMIT 1 which reflect a pooled analysis of PSUMMIT 1 and 2, as a priori predefined.

ACR20: American College of Rheumatology 20% improvement; AE, adverse event; APR, apremilast; HAQ, health assessment questionnaire; mSvdH, modified Sharp-van der Heijde score; NA, not available; NNT, number needed to treat; PALACE, psoriatic arthritis long-term assessment of clinical efficacy; PASI, psoriatic arthritis skin index; PBO, placebo; SEC, secukinumab; UST, ustekinumab.

of functional impairment and structural damage inhibition. Meta-analysis across trials resulted in RRs for ACR20 vs PBO of 3.31 (2.04 to 5.36) for SEC300 mg, 5.82 (1.56 to 21.71) for SEC150 mg and 4.47 (0.66 to 30.26) for SEC75 mg (figure 2). Regarding safety, there were no differences in withdrawals due to AEs or serious AEs (SAEs) in SEC compared with PBO. Of note, there were some cases of candidiasis with SEC (2% in FUTURE-1 and 5% in FUTURE-2, both with SEC 150 mg), though not leading to more withdrawals, and no case was observed with PBO.

Four trials have been conducted with APR (PALACE 1–4),^{3 35–43} but only one had been published as a full paper at the time of the present review (psoriatic arthritis long-term assessment of clinical efficacy; PALACE-1).³ In PALACE-1, RoB was considered 'unclear' (due to presenting per protocol analyses and no intention-to-treat analysis, unclear sequence generation and allocation concealment). This trial met its primary end point, ACR20 at 16 weeks. For ACR20 NNTs from the four trials ranged 4.2–6.7 for APR30 mg and 5.3–9.5 for APR20 mg, both versus PBO (table 2). Meta-analysis resulted in RRs for APR30 mg and APR20 mg versus PBO of 1.98 (1.64 to 2.38) and 1.70 (1.40 to 2.06), respectively (figure 3). APR showed skin response, improvement in functional disability and reduction of enthesitis, compared with PBO, but no significant effect on dactylitis. None of the four trials has included data on

structural damage. Regarding safety, there were numerically slightly more withdrawals due to AEs (eg, 7.1% with APR30 mg, 6% with APR20 mg vs 4.8% PBO in PALACE-1), but there were no differences in SAEs. Up to 19% of the patients on APR developed diarrhoea, which occurred early after treatment start and was usually self-limited.

For the three new compounds, no signals on higher malignancy rates compared with PBO were identified.

Treatment strategies

Tight Control of Psoriatic Arthritis (TICOPA) is the first strategy trial in PsA.⁴⁴ A tight control strategy was compared with standard care. In the tight control arm, patients were started on MTX with rapid escalation to 25 mg and, when the target minimum disease activity was not achieved, treatment was escalated to combination DMARDs and later TNFi, if necessary. The primary end point, ACR20 at 48 weeks, was met showing superiority of tight control (62% vs 45%). The same was true for ACR50–70 responses and PASI75. There were no differences in radiographic progression between the groups, with overall low damage progression in both groups. Patients under tight control had a higher incidence of SAEs (14% patients with SAEs in tight control and 6% in standard care), but no unexpected AEs were observed (half of these events were infections). By week 48, 26% of the patients in the tight control arm were still on MTX monotherapy (which was

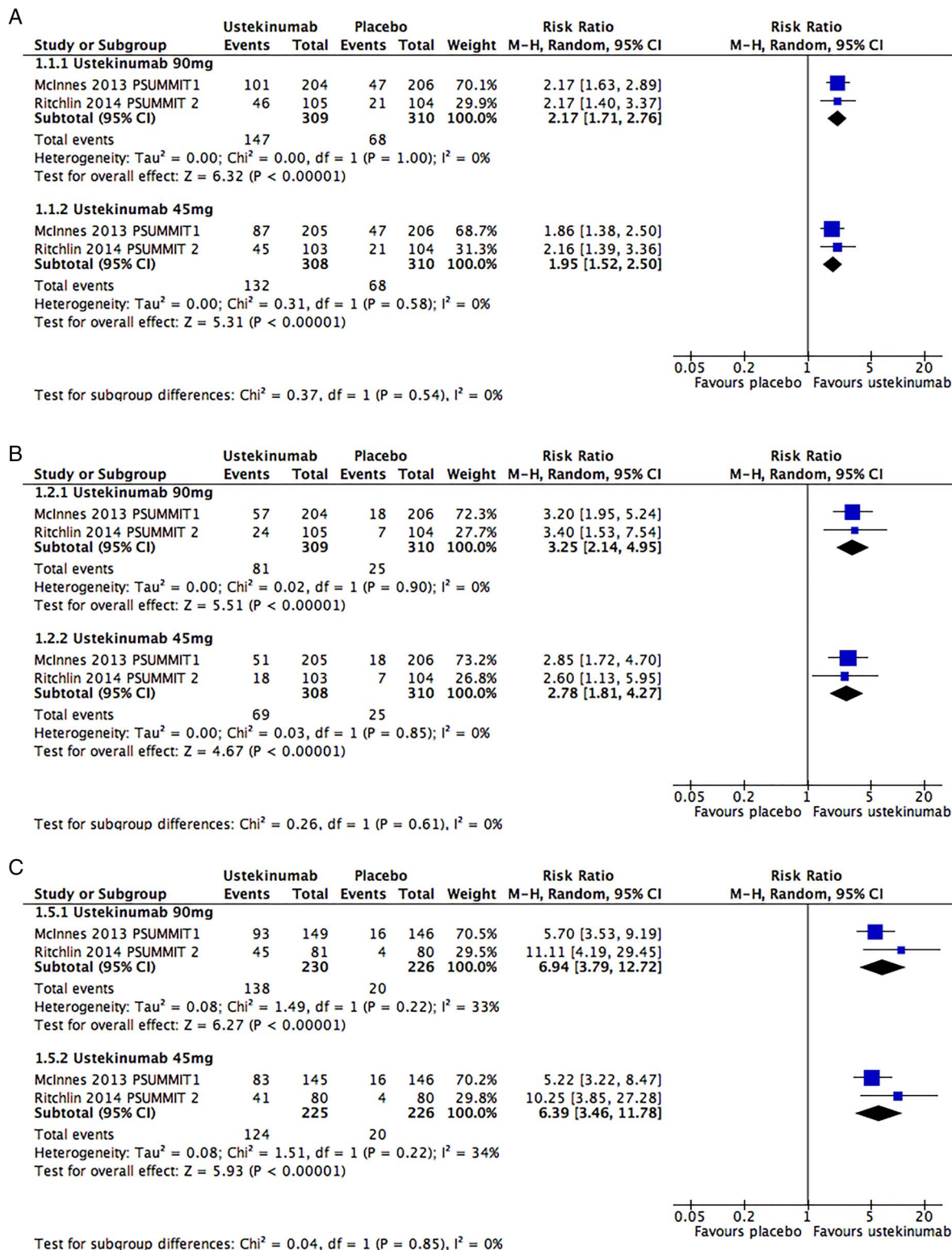


Figure 1 Main efficacy outcomes of ustekinumab at 24 weeks: (A) American College of Rheumatology 20% improvement (ACR 20); (B) ACR 50; (C) Psoriasis Area Severity Index (PASI) 75.

the first step of the treatment algorithm), compared with 49% in the standard care arm.

DISCUSSION

This SLR summarises current data from RCTs for DMARDs in PsA. It reveals that two bDMARDs against new therapeutic

targets, UST and SEC, and one new tsDMARD, APR, are efficacious for the treatment of PsA and have no major safety signals. Moreover, studies with new TNFis (golimumab and certolizumab pegol) confirm the efficacy of this class of drugs. Finally, one strategy trial indicates that treatment set to a therapeutic target achieves better outcome than non-targeted therapy in

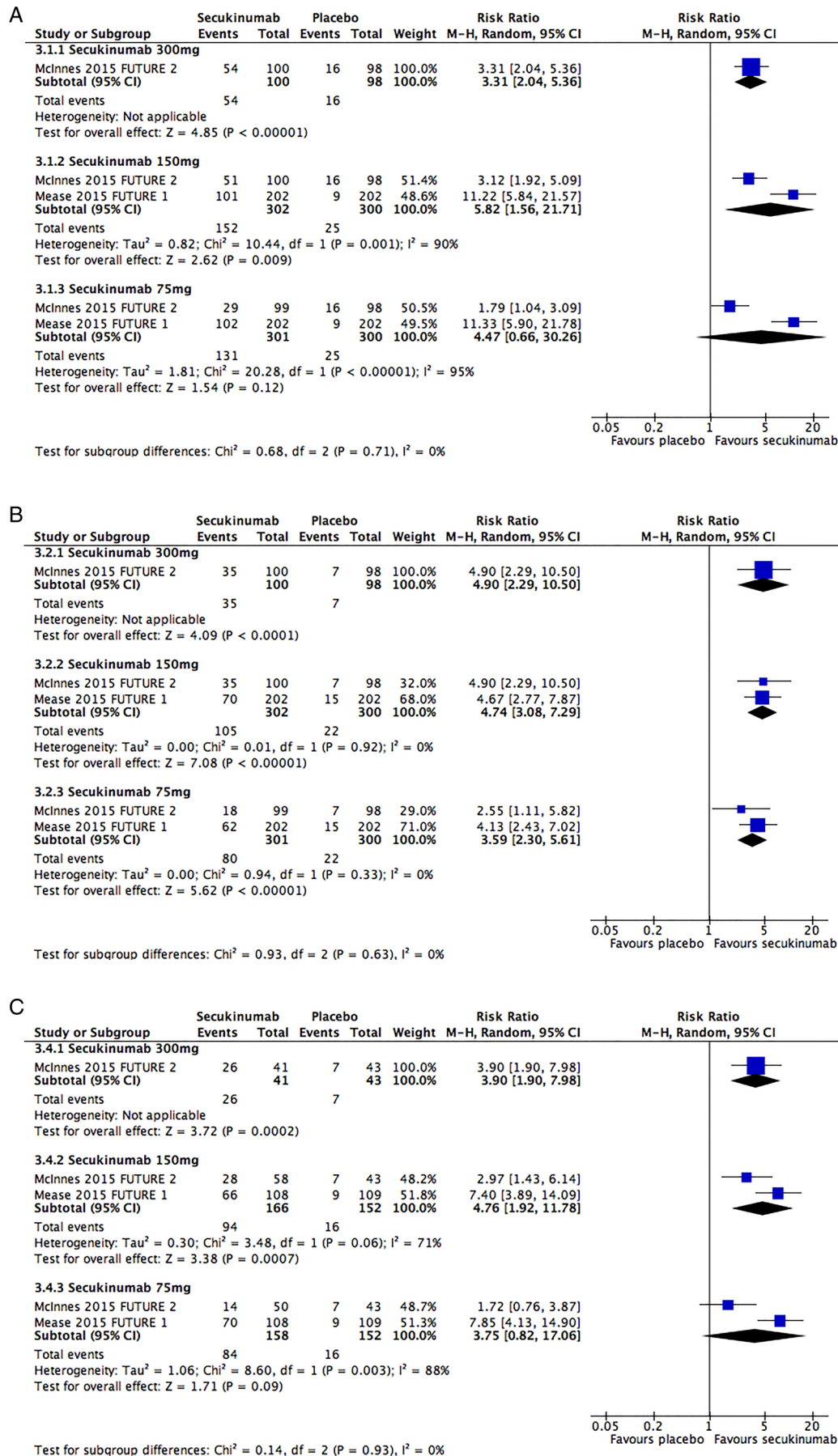


Figure 2 Main efficacy outcomes of secukinumab at 24 weeks: (A) American College of Rheumatology 20% improvement (ACR 20); (B) ACR 50; (C) Psoriasis Area Severity Index (PASI) 75.

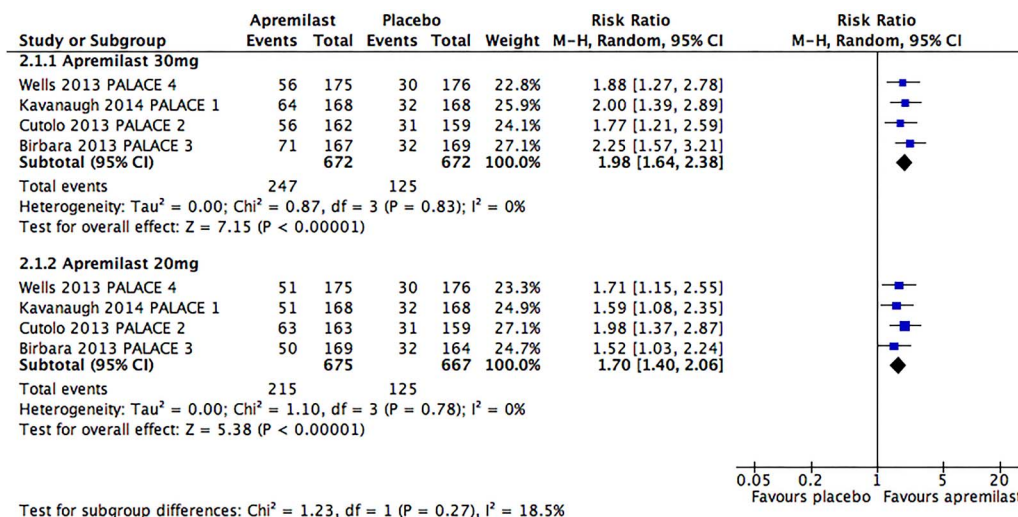


Figure 3 Main efficacy outcomes of apremilast available at 16 weeks: American College of Rheumatology 20% improvement (ACR 20). Most of these data were obtained from abstracts, were percentage of outcome achievement are reported, so the absolute figures had to be calculated for this review.

PsA, and indirectly shows efficacy of MTX in a high dose as this was the first step in the treatment algorithm.

UST, APR and SEC reflect the innovation in the treatment armamentarium of PsA. PBO-controlled trials have demonstrated their efficacy. However, in the absence of head-to-head studies, it is challenging to make accurate comparisons between the drugs, or between these agents and the already existing ones (eg, TNFi). The trial populations are different, for instance some of them included no TNFi-IR patients, others <10% and others >50%, and these trials have also shown that patients who are TNFi-IR, though also responding to these drugs, have a numerically lower response. This and other aspects jeopardise comparison across the studies. Still suffering from these limitations, the calculation of NNT allows us to judge outcome achievement with one intervention taking the PBO response into account. We have found that responses from UST and SEC were numerically higher when compared with APR, and both on joint and especially on skin outcomes, as well as on dactylitis. Additionally, data on structural damage are currently lacking for APR; such data will be essential to learn about its potential disease modifying action. Regarding safety, these new compounds have also demonstrated safety on a short/medium term and no major safety issues have arisen. Some signals have been found, such as the occurrence of (mainly oral) candidiasis with SEC and diarrhoea with APR; while these did not lead to a higher proportion of withdrawals due to AEs in the active treatment arm, they warrant further information. Long-term safety data and data from daily clinical practice are needed, and with the licensing of these drugs, they are expected to be gathered during the upcoming years. Meanwhile, we can gain more insights into the safety of these new agents with the experience acquired in psoriasis, which is reassuring.⁴⁶

This SLR also highlighted a known problem in trials with PsA: there is a lack of uniformity of outcomes reported and, especially, of the instruments chosen to address some of the outcomes.⁴⁷ The PsA Working Group within Outcome Measures in Rheumatology (OMERACT) group has selected a core set of domains to be reported in trials.⁴⁸ This core set does recommend specific instruments to be used to address each domain^{47–48} but an update is ongoing and will hopefully provide clear guidance on the choice of instruments.⁴⁹

Furthermore, in trials, the core set is not always assessed.⁴⁷ In PsA, possibly due to additional lack of standardisation of instruments to address each of the outcomes, trials report several different outcome measures in particular for enthesitis and dactylitis (see online supplementary table S5). Harmonisation of outcomes assessments and instruments included in RCTs would be expected to improve the assessment of new treatment agents, and is therefore desirable.

An aspect that is common to almost all interventions evaluated is the lack of data on PsA patients with axial involvement. Trials have not specifically addressed this particular group of patients. This remains an unmet need, for which, until further resolution, likely the best alternative is to rely on data from patients with axial spondyloarthritis.⁵⁰

The new studies with TNFi (golimumab and certolizumab pegol) have mainly been confirmatory for the class they belong to. One new aspect is that we now have data on the response to TNFi among TNFi-IR patients. These patients still respond to TNFi, namely certolizumab pegol, and in a similar proportion to TNFi-naïve patients; while this appears to be different from respective observations in RA⁵¹ and may support switching within the same mechanism of action, namely between TNFis.²² However these results are based on only one trial in which this population only constituted a subset of patients studied; thus, more data are needed in this respect.

An important trial aiming at clarifying the role of MTX in PsA, the methotrexate in psoriatic arthritis (MIPA) trial, has been conducted.¹⁴ This was a low RoB trial, which could have shed more light on this question. MIPA, however, failed to reach its primary end point, which casts doubt on the role of MTX in PsA. But two important aspects cannot be ignored: (1) dosages of MTX used were lower (15 mg/week) than what is commonly used in clinical practice or was applied in the TICOPA trial (25 mg/week); (2) patients with ≥ 1 SJC were included (actually the study population had a SJC ranging from 2 onwards), and the primary end point, PsARC, is based on a change in $\geq 30\%$ in SJC, which may be difficult to achieve in patients with few swollen joints. Because of these methodological pitfalls, the interpretation of the MIPA results is difficult.

Lastly, TICOPA indicated that a more target-driven approach to treatment improves patient outcomes.⁴⁴ This underlines the

importance of treating patients towards a predefined therapeutic target. Given the fact that MTX at a dose of 25 mg was the first step in the treatment algorithm used, this trial indirectly provides evidence that MTX is efficacious in PsA. At 48 weeks, a quarter of the patients were still on MTX monotherapy, which confirms its efficacy in this group of patients. This proportion is to be compared with half of the patients on MTX monotherapy in the standard care arm, in which rheumatologists were free to choose their patient's treatment. This challenges the findings from MIPA, pointing towards an efficacy of MTX in PsA (in appropriate doses) and emphasises the need for another trial to clarify the precise role of MTX in the treatment of PsA.

This systematic review has some limitations that need to be taken into account. The study selection and data extraction were performed by one reviewer only, whereas ideally this work should be undertaken by two people independently. In what concerns safety outcomes, where the long term is of particular importance, RCTs are not the best study type to provide the necessary answers. However, observational studies are only truly informative when they include sufficient patient numbers and the follow-up is of high quality; as such studies are currently very scarce in the PsA literature they were not analysed here. The risk of bias could not be assessed for all included studies when only the abstract was available. Strengths of this SLR are the methodological rigour with which it was conducted and the useful information it provides, for clinicians as well as for the task force responsible for updating the PsA treatment recommendations.

In conclusion, we have updated the evidence on efficacy and safety of pharmacological treatment of PsA. This review informs the update of the EULAR recommendations for the management of PsA.

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UCB, Vertex. Director of Imaging Rheumatology bv. MD: Abbvie, Novartis, Pfizer, Lilly, UCB. PE Abbvie, BMS, MSD, Novartis-Sandoz, Pfizer, Roche-Chugai, Samsung, UCB. MdW: AbbVie, BMS, Eli-Lilly, Roche, MCC, Celltrion, BMS, Abbvie, Actelion, Mundipharma, Horizon, Pfizer, Novartis, Boehringer, SO: AbbVie, Hospira, MSD. LG: Abbvie, Celgene, Chugai, Janssen, MSD, Novartis, Pfizer, Roche, Sanofi-Aventis, UCB.

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**Pharmacological treatment of psoriatic arthritis: a systematic literature review
for the 2015 update of the EULAR Recommendations for the management of
psoriatic arthritis**

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Note: all abbreviations that appear throughout the document are listed in chapter 6 of this document, page 28.

1. Online Supplementary Text Section 1 - Search Strategy

MEDLINE

1. psoriatic arthritis/
2. (psoria\$ adj (arthriti\$ or arthropath\$)).tw.
3. ((arthriti\$ or arthropath\$) adj psoria\$).tw.
4. oligoarthriti\$.tw.
5. or/1-4
6. randomized controlled trial.pt.
7. controlled clinical trial.pt.
8. randomized.ab.
9. placebo.ab.
10. drug therapy.fs.
11. randomly.ab.
12. trial.ab.
13. groups.ab.
14. or/6-13
15. exp animals/ not humans.sh.
16. 14 not 15
17. 5 and 16
18. limit 17 to yr="2010 -Current"

EMBASE

- #21. AND (2010:py OR 2011:py OR 2012:py OR 2013:py OR 2014:py)
- #20. #3 AND #19
- #19. #5 OR #6 OR #7 OR #8 OR #9 OR #10 OR #11 OR #12 OR #13 OR #14 OR #15 OR #16 OR #17 OR #18
- #18. volunteer*:ab,ti
- #17. allocat*:ab,ti
- #16. assign*:ab,ti
- #15. (singl* NEXT blind*):ab,ti
- #14. (doubl* NEXT blind*):ab,ti
- #13. placebo*:ab,ti
- #12. 'cross over':ab,ti OR 'cross overs':ab,ti
- #11. crossover*:ab,ti
- #10. factorial*:ab,ti
- #9. random*:ab,ti
- #8. 'single blind procedure'/de
- #7. 'randomized controlled trial'/de
- #6. 'double blind procedure'/de
- #5. 'crossover procedure'/de
- #4. #1 OR #2 OR #3
- #3. oligoarthriti*:ab,ti
- #2. (psoria* NEAR/2 (arthriti* OR arthropath*)):ab,ti
- #1. 'psoriatic arthritis'/de

The Cochane Library

- #1 MeSH descriptor: [Arthritis, Psoriatic] this term only
 #2 (psoria* next (arthriti* or arthropath*)):ti,ab
 #3 ((arthriti* or arthropath*) next psoria*):ti,ab
 #4 oligoarthritis*:ti,ab
 #5 #1 or #2 or #3 or #4 Publication Year from 2010 to 2014
 colour referring to source of information

2. Results of the search and flowchart

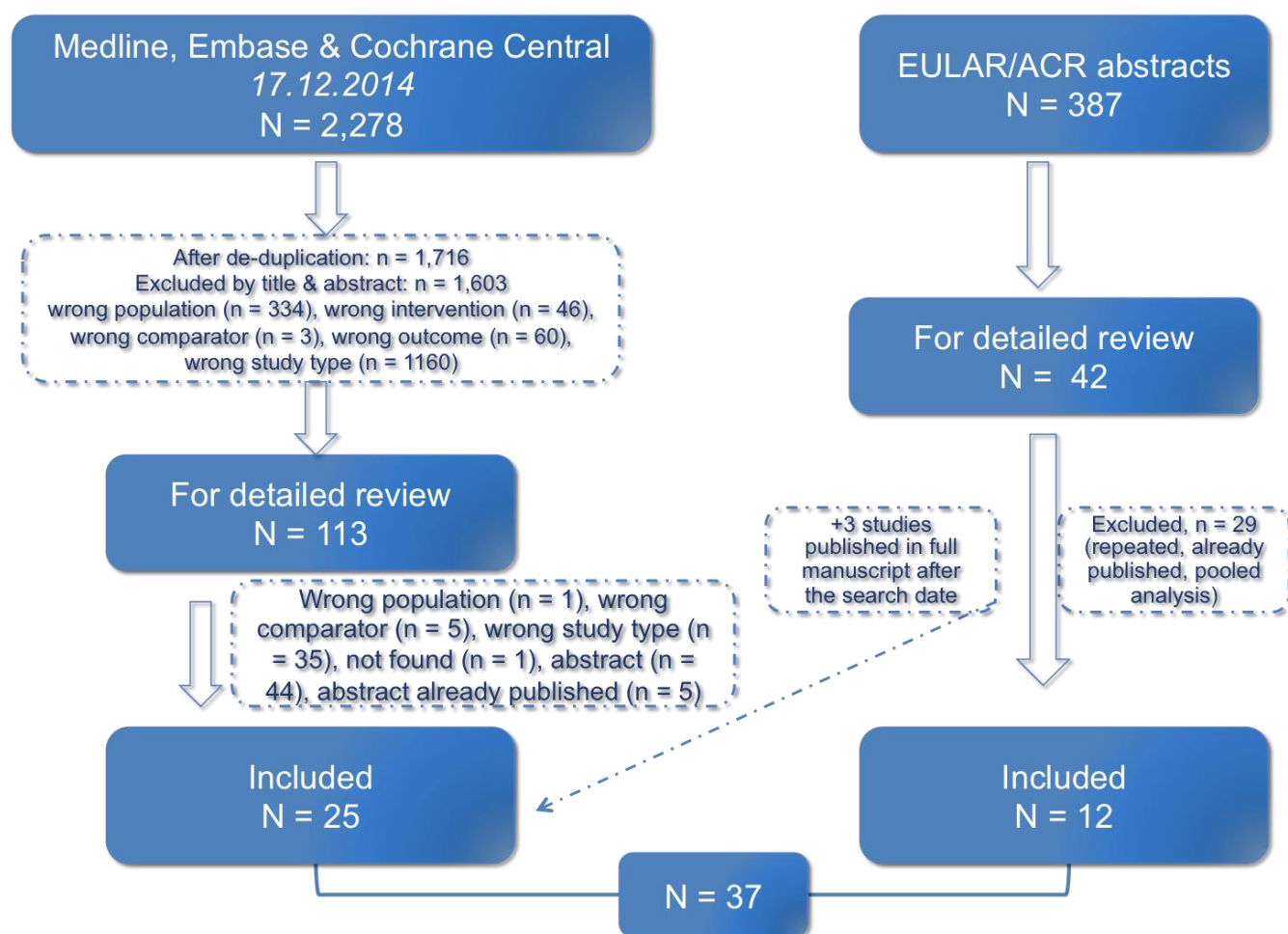


Figure S1 - Flowchart for the Systematic Literature Review

3. Details of the included studies

Details of the included studies with respect to several outcomes are shown in the series of tables below.

Frequently more than one publication addressed the same study. The corresponding publication is indicated in the column on the left hand side. When there are multiple publications addressing the same study and the same time point, the publication names are written in different colours. The colour in which the outcome extracted is written refers to the publication from which it has been extracted, whose name is in the same colour.

Online Supplementary Table S1 - Characteristics of the population of the included studies

Study ID (Trial acronym)	Treatment group	N of patients	Age	% Males	Disease duration (years)	Mean baseline DAS28	Mean baseline HAQ	Pts with dactylitis	Pts with enthesitis	Pts with psoriasis≥3% BSA	Previous TNFi use (%)
Kingsley 2012 Rheumatology (MIPA)	MTX	109	46 (13)	51	1 (1 - 5)		0.88 (0.38 - 1.50)				0.0
	PBO	112	51 (11)	61	1 (1 - 6)		1.13 (0.63 - 1.63)				0.0
Atzeni 2011 ARD	MTX	22	50 (13)	41	9.6 (7.2)	6.07 (0.8)					
	CYC	19	55 (11)	53	9.1 (6.4)	6.2 (0.60)					
Asaduzzaman 2014 J Pakistan Association of Dermatologists	LEF	16	42 (13)	88	3.2 (2.4)		0.88 (0.20)				
	MTX	14	38 (9)	93	2.8 (2.2)		0.87 (0.16)				
Kavanaugh 2012 A&R (GO-REVEAL) Kavanaugh 2012 JRheum (GO-REVEAL) Kavanaugh 2013 AC&R (GO-REVEAL)	GOL 100mg	146	48 (11)	59	7.7 (7.8)	4.9 (1.1)	1.1 (0.6)	34.0	79.0	74.0	
	GOL 50mg	146	46 (11)	61	7.2 (6.8)	5.0 (1.1)	1.0 (0.7)	34.0	75.0	75.0	
	PBO	113	47 (11)	61	7.6 (7.9)	4.9 (1.0)	1.0 (0.6)	34.0	78.0	70.0	
Mease 2014 ARD (RAPID-PsA) Gladman 2014 AC&R (RAPID-PsA) van der Heijde 2014 ARD (RAPID-PsA)	CZP 400mg	135	47 (11)	46	8.1 (8.3)		1.3 (0.6)	28.1	62.2	56.3	17.0
	CZP 200mg	138	48 (12)	46	9.6 (8.5)		1.3 (0.7)	25.4	63.8	65.2	22.5
	PBO	136	47 (11)	42	7.9 (7.7)		1.3 (0.7)	25.7	66.9	63.2	19.0
Mease 2013 J Rheum (ADEPT)	ADA	67	50 (14)	57			1.1 (0.6)				
	PBO	69	48 (12)	57			1.1 (0.7)				
Sterry 2010 BMJ (PRESTA) Prinz 2010 JEADV (PRESTA) Gniadecki 2011 JEADV (PRESTA) Boggs 2014 BMC_Derm (PRESTA)	ETA 50mg 2xweek	379	46 (11)	64	7 (7)		0.90 (0.69)	41.7	40.4		
	ETA 50mg 1xweek	373	47 (11)	62	7 (7)		0.93 (0.70)	42.9	35.9		
Baranauskaite 2012 ARD (RESPOND)	IFX + MTX	56	40 (12)	48	2.8 (2.6)	5.16 (1.1)	1.54 (0.62)				
	MTX	54	42 (11)	61	3.7 (2.7)	5.07 (1.2)	1.49 (0.66)				
McInnes 2013 Lancet (PSUMMIT 1)	UST 90mg	204	47 (38.5;54)	57	4.9 (1.7;8.3)	5.2 (4.6;5.8)	1.3 (0.8;1.6)	48.5	75.5	73.0	0.0
	UST 45mg	205	48 (39;55)	52	3.4 (1.2;9.2)	5.2 (4.6;5.7)	1.3 (0.8;1.8)	49.3	69.3	70.7	0.0
	PBO	206	48 (39;57)	52	3.6 (1.0;9.7)	5.2 (4.4;6.0)	1.3 (0.8;1.8)	46.6	70.4	70.9	0.0
Ritchlin 2014 ARD (PSUMMIT 2)	UST 90mg	105	48 (41;57)	44	4.5 (1.7;10.3)	5.3 (4.7;6.0)	1.3 (0.8;1.9)	39.0	72.4	77.1	55.0*
	UST 45mg	103	49 (49;56)	45	5.3 (2.3;12.2)	5.6 (4.9;6.3)	1.4 (0.8;1.9)	46.6	69.9	77.7	58.0*
	PBO	104	48 (38;56)	47	5.5 (2.3;12.2)	5.2 (4.4; 5.9)	1.3 (0.8; 1.8)	36.5	70.2	76.9	60.0*
Mease 2015 NEJM (FUTURE-1)	SEC 150mg	202	50 (12)	57		4.8 (1.1)	1.2 (0.7)	51.5	62.4	53.5	29.2
	SEC 75mg	202	49 (12)	42		4.9 (1.2)	1.3 (0.7)	51.5	63.9	53.5	29.7
	PBO	202	49 (11)	47		4.9 (1.1)	1.2 (0.6)	57.4	57.9	54.0	29.2
McInnes 2015 Lancet (FUTURE-2)	SEC 300mg	100	47 (13)	51		4.8 (1.0)	1.3 (0.6)	46.0	56.0		35.0

	SEC 150mg	100	47 (12)	55		4.9 (1.1)	1.2 (0.6)	32.0	64.0		
	SEC 75mg	99	49 (11)	47		4.7 (1.0)	1.2 (0.6)	33.0	69.0		
	PBO	98	50 (13)	40		4.7 (1.0)	1.2 (0.7)	28.0	66.0		
Kavanaugh 2014 ARD (PALACE 1)	APR 30mg	168	51 (12)	45	8.1 (8.1)	4.9 (1.0)	1.2 (0.6)	40.5	67.9	48.8	24.4
	APR 20mg	168	49 (11)	51	7.2 (6.8)	4.8 (1.1)	1.2 (0.6)	35.1	61.3	45.8	22.0
	PBO	168	51 (12)	52	7.3 (7.1)	4.9 (1.0)	1.2 (0.6)	40.5	58.3	40.5	24.4
Cutolo 2013 ACR (PALACE 2)	APR 30mg	162									
	APR 20mg	163									
	PBO	159									
Birbara 2013 EULAR (PALACE 3) Edwards 2013 ACR (PALACE 3)	APR 30mg	167									
	APR 20mg	169									
	PBO	169									
Wells 2013 ACR (PALACE 4) Wells 2014 ACR (PALACE 4) Adebajo 2014 EULAR (PALACE 4) Wells 2014 ACR (PALACE 4)	APR 30mg	175									
	APR 20mg	175									
	PBO	176									
Coates 2015 Lancet (TICOPA)	Tight control	101	46 (38-55)	53	0.9 (0.5-2.1) months			35	81	80	0.0
	Standard Care	105	45 (36-51)	52	0.7 (0.4-1.8) months			26	76	89	0.0

Values indicate n (%) for categorical variables or mean (SD), mean (95%CI (x;y)) or median (IQR (x-y)) for continuous variables

* Percentages calculated for this review based on absolute figures presented in the manuscript

Online Supplementary Table S2 - ACR, PsARC and cutaneous outcomes

Study ID (Trial acronym)	Treatment group	Time point for outcomes	ACR20	ACR20 (p)	ACR50	ACR50 (p)	ACR70	ACR70 (p)	PsARC (%)	PsARC (p)	PASI 50 (%)	PASI 50 (p)	PASI 75 (%)	PASI 75 (p)	PASI 90 (%)	PASI 90 (p)	% PASI change	Physician's assessment of psoriasis
Kingsley 2012 Rheumatology (MIPA)	MTX	24W	2.0	0.23					1.77	0.06			1.26					
	PBO		(0.65 - 6.22)*	REF					(0.97 - 3.23)*	REF			(0.58 - 2.72)*					
Atzeni 2011 ARD	MTX	12W									33.4		4.5					
	CYC										44.5		33.3					
	MTX	24W									73.0	<0.05	32.0	<0.05				
	CYC										88.0	REF	53.0	REF				
Asaduzzaman 2014 J Pakistan Association of Dermatologists	LEF	24W	100.0		81.3	0.342	31.3	0.004	100.0		86.8	0.455	31.7	0.646				
	MTX		100.0		85.7	REF	14.2	REF	100.0		64.3	REF	28.6	REF				
Kavanaugh 2012 A&R (GO-REVEAL) Kavanaugh 2012 JRheum (GO-REVEAL) Kavanaugh 2013 AC&R (GO-REVEAL)	GOL 100mg	52W	71.2		50.7		30.1						68.5					
	GOL 50mg		67.1		48.6		35.6						62.4					
	PBO		65.5		38.9		19.5						48.1					
Kavanaugh 2013 ARD (GO-REVEAL) Kavanaugh 2013 AC&R (GO-REVEAL)	GOL 100mg	104W	69.9		51.4		35.6				85.2		72.2		47.2			
	GOL 50mg		67.1		46.6		28.8				84.4		63.3		41.3			
	PBO		62.8		46.0		31.0				72.2		55.7		39.2			
Kavanaugh 2014 ARD (GO-REVEAL)	GOL 100mg	5Y	69.9		50.7		35.6				88.0		72.2		56.5			
	GOL 50mg		65.8		47.9		30.8				78.9		61.5		42.2			
	PBO		62.8		43.4		32.7				79.7		60.8		39.2			
Mease 2014 ARD (RAPID-PsA) Gladman 2014 AC&R (RAPID-PsA) van der Heijde 2014 ARD (RAPID-PsA) Kavanaugh 2015 ARD (RAPID-PsA) Kavanaugh 2013 ACR (RAPID-PsA) Kavanaugh 2014 ACR (RAPID-PsA)	CZP 400mg	12W	51.9	<0.001	32.6	<0.001	12.6	0.016			63.2	NA	47.4	<0.005	19.7	<0.005		
	CZP 200mg		58.0	<0.001	36.2	<0.001	24.6	<0.001			68.9	NA	46.7	<0.005	22.2	<0.005		
	PBO		24.3	REF	11.0	REF	2.9	REF			26.7	NA	14.0	REF	4.7	REF		
	CZP 400mg	24W	56.3	<0.001	40.0	<0.001	23.7		78.3	<0.001	72.4	NA	60.5	<0.005	35.5	<0.005		
	CZP 200mg		63.8	<0.001	44.2	<0.001	28.3	<0.001	77.0	<0.001	74.4	NA	62.2	<0.005	46.7	<0.005		
	PBO		23.5	REF	12.5	REF	4.4	REF	33.1	REF	27.9	NA	15.1	REF	5.8	REF		
Sterry 2010 BMJ (PRESTA) Prinz 2010 JEADV (PRESTA) Gniadecki 2011 JEADV (PRESTA) Boggs 2014 BMC_Derm (PRESTA)	ETA 50mg 2xweek	12W	66.4		44.7	0.287	20.3		76.6				54.9	<0.001			77.0	52.0
	ETA 50mg 1xweek		60.8		40.6	REF	21.9		76.0				36.4	REF			76.0	45.0

	ETA 50mg 2xweek	24W	69.0	0.379	51.8	0.594	34.6	0.53	81.5				70.3	0.026			82.0	57.0
	ETA 50mg 1xweek		71.7	REF	53.6	REF	36.7	REF	80.4				62.3	REF			80.0	55.0
Baranauskaite 2012 ARD (RESPOND)	IFX + MTX	16W	86.3	0.021	72.5	0.0009	49.0	0.0015					97.1	<0.0001	70.6		93.3	
	MTX		66.7	REF	39.6	REF	18.8	REF					54.3	REF	28.6		67.4	
McInnes 2013 Lancet (PSUMMIT 1)	UST 90mg	24W	49.5	<0.0001	27.9	<0.0001	14.2	<0.0001					62.4	<0.0001				
	UST 45mg		42.4	<0.0001	24.9	<0.0001	12.2	0.0001					57.2	<0.0001				
	PBO		22.8	REF	8.7	REF	2.4	REF					11.0	REF				
	UST 90mg	52W	60.3		37.0		21.2						68.1					
	UST 45mg		55.7		31.4		18.0						70.1					
	PBO		65.2		38.0		16.3						67.7					
Kavanaugh 2013 ACR (PSUMMIT 1)	UST 90mg	100W	63.6		46.0		22.2						71.3					
	UST 45mg		56.7		38.8		24.7						72.5					
	PBO		62.7		37.3		18.6						63.9					
Ritchlin 2014 ARD (PSUMMIT 2)	UST 90mg	24W	43.8	<0.001	22.9	<0.01	8.6	NS					55.6	<0.001	44.4	<0.001		
	UST 45mg		43.7	<0.001	17.5	<0.05	6.8	NS					51.3	<0.001	30.0	<0.001		
	PBO		20.2	REF	6.7	REF	2.9						5.0	REF	3.8	REF		
	UST 90mg	52W	48.4		26.3		17.9						64.4		49.3			
	UST 45mg		46.8		27.7		12.8						56.5		37.7			
	PBO		55.8		28.6		15.6						56.1		36.8			
Mease 2015 NEJM (FUTURE-1)	SEC 150mg	24W	50.0	<0.0001	34.7	<0.0001	18.8	<0.0001					61.1	<0.0001	45.4	<0.0001		
	SEC 75mg		50.5	<0.0001	30.7	<0.0001	16.8	<0.0001					64.8	<0.0001	49.1	<0.0001		
	PBO		17.3	REF	7.4	REF	2.0	REF					8.3	REF	3.7	REF		
	SEC 150mg	52W	59.9		43.1		24.3						76.9		59.3			
	SEC 75mg		56.9		32.7		21.8						65.7		48.1			
McInnes 2015 Lancet (FUTURE-2)	SEC 300mg	24W	54.0	<0.0001	35.0	0.004	20.0						63.0	<0.0001	49.0	0.0005		
	SEC 150mg		51.0	<0.0001	35.0	0.0555	21.0						48.0	0.0017	33.0	0.0057		
	SEC 75mg		29.0	0.0399	18.0	0.9195	6.1						28.0	0.165	12.0	0.6421		
	PBO		15.0	REF	7.0	REF	1.0						16.0	REF	9.0	REF		
	SEC 300mg	52W	64.0		44.0								73.2		56.1			
	SEC 150mg		64.0		39.0								56.9		43.1			
	SEC 75mg		50.5		30.3								48.0		24.0			
Kavanaugh 2014 ARD (PALACE 1)	APR 30mg	16W	38.1	0.0001														

Zhang 2014 ACR (PALACE 1) Kavanaugh 2014 ACR (PALACE 1) Mease 2014 ACR (PALACE 1)	APR 20mg		30.4	0.0166													
	PBO		19.0	REF													
	APR 30mg	24W	36.6	<0.0001	19.9	<0.0001	10.6	0.0001			50.6	0.0001	21.0	0.004			
	APR 20mg		26.4	0.0032	14.7	0.0013	5.5	0.0102			33.8	0.0439	17.6	0.018			
	PBO		13.3	REF	4.2	REF	0.6	REF			18.5	REF	4.6	REF			
	APR 30mg	52W	54.6		24.6		13.8				60.3		36.8				
	APR 20mg		63.0		24.8		15.4				52.8		24.5				
	APR 30mg	104W	66.3		35.6		19.8				54.7		30.2				
	APR 20mg		61.3		29.8		16.0				53.7		36.6				
Cutolo 2013 ACR (PALACE 2)	APR 30mg	16W	34.4	0.024													
	APR 20mg		38.4	0.0002													
	PBO		19.5	REF													
	APR 30mg	52W	52.6								58.9		39.3				
	APR 20mg		52.9								49.2		27.1				
Birbara 2013 EULAR (PALACE 3) Edwards 2013 ACR (PALACE 3)	APR 30mg	16W	42.8	<0.0001													
	APR 20mg		29.4	0.02													
	PBO		18.9	REF													
	APR 30mg	24W	42.0								46.0	<0.05	27.0	<0.05			
	APR 20mg		40.0								36.0	NS	23.0	NS			
	PBO		NA								26.0	REF	12.0	REF			
	APR 30mg	52W	63.0								54.7		39.1				
	APR 20mg		56.0								49.2		28.6				
Wells 2013 ACR (PALACE 4) Wells 2014 ACR (PALACE 4) Adebajo 2014 EULAR (PALACE 4) Wells 2014 ACR (PALACE 4)	APR 30mg	16W	32.3	0.0076													
	APR 20mg		29.2	0.011													
	PBO		16.9	REF													
	APR 30mg	24W															
	APR 20mg																
	PBO																
	APR 30mg	52W	59.0		32.0		18.0				56.0		31.9				-60.0
	APR 20mg		53.0		27.0		14.0				61.5		41.0				-61.0
	APR 30mg	104W	57.3		37.3		18.9				61.1		38.9				
	APR 20mg		64.8		40.0		27.9				60.9		46.9				

Coates 2015 Lancet (TICOPA)	Tight control	48W	62	0.0194	51	0.0004	38	0.0026					59	0.0015	42.7			
	Standard Care		44	REF	25	REF	17	REF					33	REF	23.5			

* Values reflect Odds Ratio and 95% Confidence Intervals

Online Supplementary Table S3 - ACR and PASI responses stratified by co-medication with MTX and by previous TNFi exposure

Study ID (Trial acronym)	Treatment group	Time point for out-comes	ACR20 in MTX+	ACR20 in MTX-	ACR50 in MTX+	ACR50 in MTX-	ACR70 in MTX+	ACR70 in MTX-	PASI50 in MTX+	PASI50 in MTX-	PASI75 in MTX+	PASI75 in MTX-	ACR20 in TNFi naive	ACR20 in TNFi exper.	ACR50 in TNFi naive	ACR50 in TNFi exper.	ACR70 in TNFi naive	ACR70 in TNFi exper.	PASI75 in TNFi naive	PASI75 in TNFi exper.
Kavanaugh 2013 ARD (GO-REVEAL)	GOL 100mg	104W	67.6	72	50.7	52.0	33.8	37.3	88.9	82.5	71.1	73.0								
	GOL 50mg		70.4	64.0	49.3	44.0	33.8	24.0	88.0	81.4	62.0	64.4								
	PBO		67.3	58.6	49.1	43.1	29.1	32.8	74.3	70.5	68.6	45.5								
Kavanaugh 2014 ARD (GO-REVEAL)	GOL 100mg	5Y	67.6	72.0	50.7	50.7	32.4	38.7	91.1	85.7	68.9	74.6								
	GOL 50mg		73.2	58.7	49.3	46.7	33.8	28.0	76.0	81.4	60.0	62.7								
	PBO		72.7	53.4	38.2	48.3	29.1	36.2	82.9	77.3	68.6	54.5								
Mease 2014 ARD (RAPID-PsA) Gladman 2014 AC&R van der Heijde 2014 ARD Kavanaugh 2015 ARD Kavanaugh 2013 ACR Kavanaugh 2014 ACR	CZP 400mg	12W	55.0	42.9																
	CZP 200mg		58.6	56.4																
	PBO		28.4	16.7																
	CZP 400mg	24W											60.3	59.3	41.6	44.4	26.0	25.9		
	CZP 200mg																			
	PBO												26.4	11.5	14.5	3.8	4.5	3.8		
McInnes 2013 Lancet (PSUMMIT 1)	UST 90mg	24W	45.5	53.4							55.1	68.8								
	UST 45mg		43.4	41.5							48.5	64.6								
	PBO		26.0	20.0							15.2	7.5								
Ritchlin 2014 ARD (PSUMMIT 2)	UST 90mg	24W	40.4	47							56.4	54.8	55.3	34.5					62.5	48.8
	UST 45mg		50.0	36.7							48.7	53.7	53.5	36.7					58.3	45.5
	PBO		28.6	12.7							10.3	2.0	28.6	14.5					10.0	2.0
	UST 90mg	52W									63.9	64.9	58.5	40.7	34.1	20.4	31.7	7.4	81.8	50.0
	UST 45mg										60.0	52.9	60.0	37.0	40.0	18.5	22.5	5.6	78.8	36.1
	PBO										62.5	51.5	73.0	40.0	40.5	17.5	18.9	12.5	70.4	43.3
Mease 2015 NEJM (FUTURE-1)	SEC 150mg	24W	52.1	46.9									54.5	39.0	39.9	22.0	22.4	10.2		
	SEC 75mg		49.2	52.5									55.6	38.3	36.6	16.7	19.0	11.7		
	PBO		19.2	14.3									17.5	16.9	8.4	5.1	2.8	0.0		
McInnes 2015 Lancet (FUTURE-2)	SEC 300mg	24W	54.5	53.6	38.6	32.1	27.3	14.3					58.0	45.0	39.0	27.0	22.0	15.0	63.0	64.0
	SEC 150mg		47.7	53.6	31.8	37.5	15.9	25.0					63.0	30.0	44.0	19.0	27.0	11.0	56.0	36.0
	SEC 75mg		44.7	15.4	27.7	9.6	10.6	1.9					37.0	15.0	25.0	6.0	6.0	6.0	30.0	24.0
	PBO		20.0	10.4	8.0	6.3	2.0	0.0					16.0	14.0	6.0	9.0	2.0	0.0	19.0	8.0

Online Supplementary Table S4 - Disease activity and functional disability outcomes

Study ID (Trial acronym)	Treatment group	Time point for outcomes	DAS28 remission (<2.6)	DAS28 remission (p)	EULAR good or moderate response	EULAR good or moderate response (p)	delta DAS28 (mean)	delta DAS28 (p)	MDA (%)	MDA (p)	delta HAQ-DI (mean)	delta HAQ-DI (p)	HAQ-DI response (%)	HAQ-DI response (p)
Kingsley 2012 Rheumatology (MIPA)	MTX	24W			1.70 (0.90 - 3.17)	0.1					-0.2 (0.1 - 0.4)	0.1		
	PBO					REF					-0.1 (0.0 - 0.3)	REF		
Atzeni 2011 ARD	MTX	12W	0.0				-1.58 (0.82)	0.56						
	CYC		0.0				-1.70 (0.52)	REF						
	MTX	24W	5.5				-2.32 (0.74)	0.22						
	CYC		11.8				-2.64 (0.66)	REF						
Kavanaugh 2012 A&R (GO-REVEAL) Kavanaugh 2012 JRheum (GO-REVEAL) Kavanaugh 2013 AC&R (GO-REVEAL)	GOL 100mg	24W									-0.39 (0.50)			
	GOL 50mg										-0.33 (0.55)			
	PBO										0.01 (0.49)			
	GOL 100mg	52W			82.9		-1.20 (1.21)				-0.43 (0.53)		55.5	
	GOL 50mg				81.5		-2.02 (1.34)				-0.41 (0.53)		50.0	
	PBO				80.5		-1.67 (1.19)				-0.37 (0.56)		51.3	
Kavanaugh 2013 ARD (GO-REVEAL) Kavanaugh 2013 AC&R (GO-REVEAL)	GOL 100mg	104W			85.6						-0.45 (0.55)		58.9	
	GOL 50mg				86.3						-0.43 (0.56)		52.7	
	PBO				77.0						-0.36 (0.58)		54.0	
Kavanaugh 2014 ARD (GO-REVEAL)	GOL 100mg	5Y			84.9								58.2	
	GOL 50mg				83.6								54.1	
	PBO				75.2								52.2	
Mease 2014 ARD (RAPID-PsA) Gladman 2014 AC&R (RAPID-PsA) van der Heijde 2014 ARD (RAPID-PsA) Kavanaugh 2015 ARD (RAPID-PsA) Kavanaugh 2013 ACR (RAPID-PsA) Kavanaugh 2014 ACR (RAPID-PsA)	CZP 400mg	12W									-0.39 (0.47)	<0.001		
	CZP 200mg										-0.45 (0.56)	<0.001		
	PBO										-0.16 (0.36)	REF		
	CZP 400mg	24W							34.1	<0.001	-0.43 (0.54)	<0.001	48.1	
	CZP 200mg								33.3	<0.001	-0.52 (0.66)	<0.001	49.3	
	PBO								5.9	REF	-0.17 (0.43)	REF	15.4	
Mease 2013 J Rheum (ADEPT)	ADA	12W							33.3	<0.001				

	PBO	24W							3.2	REF				
	ADA								38.7	<0.001				
	PBO								6.7	REF				
Baranauskaite 2012 ARD (RESPOND)	IFX + MTX	16W	68.6		98,0	<0.0001	-2.95 (1.05)	<0.0001	58.9	<0.05	-0.99 (0.72)	0.0041		
	MTX		29.2		72.9	REF	-1.51 (1.31)	REF	24.1	REF	-0.56 (0.72)	REF		
McInnes 2013 Lancet (PSUMMIT 1)	UST 90mg	24W	19.6	0.0009	67.6	<0.0001					-0.25 (-0.75;0.00)	<0.0001	47.5	<0.0001
	UST 45mg		20.5	0.0004	65.9	<0.0001					-0.25 (-0.63;0.00)	<0.0001	47.8	<0.0001
	PBO		8.3	REF	34.5	REF					0.00 (-0.38;0.00)	REF	28.2	REF
	UST 90mg	52W			74.6						-0.4 (-0.8;0.0)		51.3	
	UST 45mg				72.7						-0.3 (-0.6;0.0)		47.4	
	PBO				74.5						-0.4 (-0.6;0.0)		53.8	
Kavanaugh 2013 ACR (PSUMMIT 1)	UST 90mg	100W									-0.45 (0.60)		51.7	
	UST 45mg										-0.36 (0.56)		47.8	
	PBO										-0.36 (0.51)		50.3	
Ritchlin 2014 ARD (PSUMMIT 2)	UST 90mg	24W	15.2	<0.01	53.3	<0.001					-0.25 (-0.50;0.00)	<0.001	38.1	<0.001
	UST 45mg		10.7	NS	54.4	<0.001					-0.13 (-0.38;0.00)	<0.01	34.0	<0.01
	PBO		3.8	REF	29.8	REF					0.00 (-0.13;0.13)	REF	16.3	REF
	UST 90mg	52W			62.1						-0.3 (-0.5;0.0)		44.2	
	UST 45mg				59.6						-0.3 (-0.5;0.0)		35.1	
	PBO				68.8						-0.1 (-0.5;0.0)		37.7	
Mease 2015 NEJM (FUTURE-1)	SEC 150mg	24W					-1.62 (0.08)	<0.0001			-0.40 (0.04)	<0.0001		
	SEC 75mg						-1.67 (0.09)	<0.0001			-0.41 (0.04)	<0.0001		
	PBO						-0.77 (0.12)	REF			-0.17 (0.05)	REF		
	SEC 150mg	52W					-1.77 (0.08)				-0.41 (0.04)			
	SEC 75mg						-1.77 (0.08)				-0.39 (0.04)			
McInnes 2015 Lancet (FUTURE-2)	SEC 300mg	24W					-1.61 (0.11)	0.0013			-0.56 (0.05)	0.004		
	SEC 150mg						-1.58 (0.11)	0.0057			-0.48 (0.05)	0.0555		
	SEC 75mg						-1.12 (0.11)	0.6421			-0.32 (0.05)	0.9195		
	PBO						-0.96 (0.15)	REF			-0.31 (0.06)	REF		
	SEC 300mg	52W					-1.78 (0.12)				0.56 (0.05)			
	SEC 150mg						-1.69 (0.12)				-0.47 (0.05)			
	SEC 75mg						-1.42 (0.12)				-0.31 (0.05)			
Kavanaugh 2014 ARD (PALACE 1)	APR 30mg	16W									-0.24 (0.04)	0.0017	39.8	0.0149
	APR 20mg										-0.20 (0.04)	0.0252	33.7	NA

Zhang 2014 ACR (PALACE 1) Kavanaugh 2014 ACR (PALACE 1) Mease 2014 ACR (PALACE 1)	PBO										-0.09 (0.04)	REF	27.3	REF
	APR 30mg	24W	18.6	<0.0001	44.1	<0.0001	-0.91 (0.09)	<0.0001			-0.26 (0.04)	0.0004		
	APR 20mg		11.7	0.0011	31.3	0.0016	-0.66 (0.09)	0.0002			-0.21 (0.04)	0.0092		
	PBO		2.4	REF	16.4	REF	-0.20 (0.09)	REF			-0.08 (0.04)	REF		
	APR 30mg	52W	23.3				-1.31				-0.32		44.7	
	APR 20mg		32.5				-1.4				-0.37		45.8	
	APR 30mg	104W	38.6				-1.83				-0.43		54.5	
	APR 20mg		35.1				-1.61				-0.33		51.5	
Cutolo 2013 ACR (PALACE 2)	APR 30mg	52W									-0.330 (0.509)			
	APR 20mg										-0.192 (0.573)			
Birbara 2013 EULAR (PALACE 3) Edwards 2013 ACR (PALACE 3)	APR 30mg	24W	21.0	<0.05										
	APR 20mg		22.0	<0.05										
	PBO		12.0	REF										
	APR 30mg	52W									-0.350 (0.505)			
	APR 20mg										-0.332 (0.505)			
Wells 2013 ACR (PALACE 4) Wells 2014 ACR (PALACE 4) Adebajo 2014 EULAR (PALACE 4) Wells 2014 ACR (PALACE 4)	APR 30mg	16W									-0.21	<0.0001		
	APR 20mg										-0.17	0.0008		
	PBO										0.03	REF		
	APR 30mg	52W									-0.39		48.9	
	APR 20mg										-0.32		48.5	
	APR 30mg	104W									-0.4		50.0	
	APR 20mg										-0.37		52.8	
Coates 2015 Lancet (TICOPA)	Tight control	48W									0.5 (0.1 - 0.9)			
	Standard Care										0.1 (0.0 - 0.5)			

Online Supplementary Table S5 - Dactylitis, enthesitis and nail involvement

Study ID (Trial acronym)	Treatment group	Time point for outcomes	delta dactylitis (mean)	delta dactylitis (p)	% change dactylitis score	Pts with dactylitis (%)	Pts with dactylitis (p)	Resolution dactylitis	Resolution dactylitis (p)	delta enthesitis (mean)	delta enthesitis (p)	% change enthesitis score	Pts with enthesitis (%)	Pts with enthesitis (p)	Resolution enthesitis	Resolution enthesitis (p)	delta NAPS I (mean)	% change NAPS I score	delta NAPS I (p)
Kavanaugh 2012 A&R (GO-REVEAL) Kavanaugh 2012 JRheum (GO-REVEAL)*	GOL 100mg	24W		<0.001	-82.1						<0.001	-52.4							
	GOL 50mg			0.09	-65.5						<0.001	-46.1							
	PBO			REF	-27.7						REF	12.9							
	GOL 100mg	52W	-4.6 (6.6)		-83.0					-3.4 (4.0)		-51.9					-3.3 (2.5)	-65.8	
	GOL 50mg		-4.2 (4.8)		-70.4					-3.0 (3.6)		-56.3					-2.2 (2.2)	-51.6	
	PBO		-1.7 (2.8)		-57.2					-2.1 (3.1)		-39.1					-2.7 (2.3)	-56.2	
Kavanaugh 2013 ARD (GO-REVEAL)	GOL 100mg	104W			-85.3							-56.0						-69.7	
	GOL 50mg				-83.0							-59.5						-60.6	
	PBO				-67.4							-40.4						-61.8	
Mease 2014 ARD (RAPID-PsA) Gladman 2014 AC&R §	CZP 400mg	12W																	
	CZP 200mg																		
	PBO																		
	CZP 400mg	24W	-53.5 (69.1)	<0.001						-1.8 (1.9)	≤0.003						-2.0		<0.001
	CZP 200mg		-40.7 (34.6)	≤0.003						-2.0 (1.8)	<0.001						-1.6		0.003
	PBO		-22.0 (46.9)	REF						-1.1 (1.8)	REF						-1.1		REF
Sterry 2010 BMJ (PRESTA) Prinz 2010 JEADV (PRESTA) ±	ETA 50mg 2xweek	12W			-74.3							-73.7							
	ETA 50mg 1xweek				-78.4							-70.0							
	ETA 50mg 2xweek	24W			-84.5							-80.9							
	ETA 50mg 1xweek				-84.8							-81.3							
McInnes 2013 Lancet (PSUMMIT 1)*	UST 90mg	24W				55.8	0.0038						60.8	0.0002					
	UST 45mg					56.6	0.005						68.6	0.0179					
	PBO					76.1	REF						81.0	REF					
	UST 90mg	52W				46.2							54.2						
	UST 45mg					39.2							55.6						
	PBO					40.7							51.6						
Kavanaugh 2013	UST 90mg	100W			-57.7							-58.2							

ACR (PSUMMIT 1)	UST 45mg				-71.3							-46.3						
	PBO				-65.1							-38.9						
Ritchlin 2014 ARD (PSUMMIT 2) *	UST 90mg	24W			-64.6	57.9	NS					-48.33	70.0	<0.05				
	UST 45mg				0.0	65.2	NS					-33.33	75.7	<0.01				
	PBO				0.0	75.8	REF					0.0	88.2	REF				
	UST 90mg	52W			-90.9							-60.0						
	UST 45mg				-95.0							-36.7						
	PBO				-100.0							-33.3						
Mease 2015 NEJM (FUTURE-1)	SEC 150mg	24W						52.4	<0.05						47.5	<0.05		
	SEC 75mg																	
	PBO							15.5	REF						12.8	REF		
	SEC 150mg	52W				30.8							34.1					
	SEC 75mg					26.9							41.1					
McInnes 2015 Lancet (FUTURE-2) §	SEC 300mg	24W	-2.3 (4.0)					57.0	0.0021	-1.7 (1.8)					48.0	0.0025		
	SEC 150mg		-3.1 (4.5)					50.0	0.0056	-1.5 (2.0)					42.0	0.0108		
	SEC 75mg		-1.0 (1.6)					30.0	0.3149	-1.4 (1.7)					32.0	0.1678		
	PBO		-0.6 (2.4)					15.0	REF	-0.9 (2.1)					22.0	REF		
	SEC 300mg	52W				30.4							46.4					
	SEC 150mg					34.4							51.6					
	SEC 75mg					36.4							54.4					
Kavanaugh 2014 ARD (PALACE 1)*	APR 30mg	24W	-1.8 (0.27)	0.1753				47.7	NS	-1.7 (0.29)	0.0334				33.6	0.013		
	APR 20mg		-2.0 (0.30)	0.071				50.9	NS	-1.6 (0.30)	0.0678				32.0	0.037		
	PBO		-1.3 (0.27)	REF				40.9	REF	-0.8 (0.31)	REF				14.4	REF		
Wells 2013 ACR (PALACE 4) Wells 2014 ACR (PALACE 4)	APR 30mg	52W			-100.0			68.8							45.9			
	APR 20mg				-100.0			68.6							39.6			
	APR 30mg	104W						84.0							58.7			
	APR 20mg							82.5							59.7			
Coates 2015 Lancet (TICOPA)	Tight control	48W	38 (20.0 - 72.0)							2 0.0 - 4.0)							3.0 (-1.0 - 9.0)	
	Standard Care		58.5 (30.0 - 50.0)							1.0 (-1.0 - 4.0)							2.0 (1.0 - 8.0)	

*Enthesitis score used was the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES); § Enthesitis score used was the Leeds Enthesitis Index (LEI); ± Enthesitis score refers to the % of patients with improvement of enthesitis. Values indicate n (%) for categorical variables or mean (SD), mean (95%CI (x;y)) or median (IQR (x-y)) for continuous variables

Online Supplementary Table S6 - Structural damage

Study ID (Trial acronym)	Treatment group	Time point for outcomes	delta vdHS (mean)	delta vdHS (p)	delta vdHS =0 (%)	delta vdHS =0 (p)	delta vdHS ≤SDC (%)	delta vdHS ≤SDC (p)	delta vdHS in MTX+	delta vdHS in MTX-	delta vdHS =0 in MTX+ (%)	delta vdHS =0 in MTX- (%)	delta vdHS in TNFi naïve	delta vdHS in TNFi experienced
Kavanaugh 2012 A&R (GO-REVEAL) Kavanaugh 2012 JRheum (GO-REVEAL) Kavanaugh 2013 AC&R (GO-REVEAL)	GOL 100mg	24W	-0.02 (1.32)	0.086	76.6	0.02	5.8*	0.146	-0.16 (1.36)	0.11 (1.28)	77.6	75.7		
	GOL 50mg		-0.16 (1.31)	0.011	78.8	0.007	3.8*	0.03	-0.34 (1.10)	0.01 (1.47)	84.6	73.1		
	PBO		0.27 (1.26)	REF	62.7	REF	10.8*	REF	0.22 (1.25)	0.31 (1.28)	60.4	65.3		
	GOL 100mg	52W	-0.14 (1.53)						-0.38 (1.82)	0.09 (1.16)				
	GOL 50mg		-0.22 (1.64)						-0.52 (1.46)	0.05 (1.76)				
	PBO		0.22 (1.38)						0.06 (1.23)	0.37 (1.51)				
Kavanaugh 2013 ARD (GO-REVEAL) Kavanaugh 2013 AC&R (GO-REVEAL)	GOL 100mg	104W	-0.32 (1.87)		76.8		4.0*		-0.65 (2.15)	0 (1.51)				
	GOL 50mg		-0.39 (2.04)		77.2		4.4*		-0.78 (1.76)	0.03 (2.25)				
	PBO		0.08 (3.19)		72.9		8.2*		-0.24 (2.09)	0.53 (4.30)				
Kavanaugh 2014 ARD (GO-REVEAL)	GOL 100mg	5Y	0.1 (2.7)		65.3				-0.3 (3.4)	0.4 (1.8)				
	GOL 50mg		0.3 (4.2)		62.4				-0.3 (4.8)	0.9 (3.3)				
	PBO		0.3 (3.8)		63.0				0 (2.2)	0.7 (5.4)				
Mease 2014 ARD (RAPID-PsA) Gladman 2014 AC&R (RAPID-PsA) van der Heijde 2014 ARD (RAPID-PsA)	CZP 400mg	24W	0.11 (0.08)	0.072	87.8	NS								
	CZP 200mg		0.01 (0.07)	0.004	91.7	<0.05								
	PBO		0.28 (0.07)	REF	81.9	REF								
McInnes 2013 Lancet (PSUMMIT 1)	UST 90mg	24W	0.2 (1.4)	<0.001										
	UST 45mg		0.3 (1.9)	0.001										
	PBO		1.2 (4.5)	REF										
Kavanaugh 2013 ACR (PSUMMIT 1)	UST 90mg	100W	1.18 (5.52)											
	UST 45mg		0.95 (3.82)											
	PBO		2.26 (12.58)											
Ritchlin 2014 ARD (PSUMMIT 2)	UST 90mg	24W	0.8 (3.6)	0.965										
	UST 45mg		0.7 (2.4)	0.605										
	PBO		0.5 (1.9)	REF										
	UST 90mg	52W												
	UST 45mg													
	PBO													
Kavanaugh 2014 ARD (PSUMMIT 1 &	UST 90mg	24W	0.4 (2.4)	<0.001	69.0	0.026	91.9§	0.004	0.5 (2.2)	0.3 (2.6)				
	UST 45mg		0.4 (2.1)	0.017	64.0	0.317	91.7§	0.005	0.6 (2.3)	0.3 (1.9)				
	PBO		1.0 (3.9)	REF	59.8	REF	83.8§	REF	0.8 (1.8)	1.1 (5.0)				

2)	UST 90mg	52W	0.7 (3.7)											
	UST 45mg		0.6 (2.6)											
	PBO		1.2 (5.4)											
Mease 2015 NEJM (FUTURE-1)	SEC 150mg	24W	0.13 (0.09)	<0.05										
	SEC 75mg		0.02 (0.12)	<0.05										
	PBO		0.57 (0.19)	REF										
	SEC 150mg	52W	0.37											
	SEC 75mg		0.22											
Coates 2015 Lancet (TICOPA)	Tight control	48W	0.0 (-2.0; 0.5)											
	Standard Care		0.0 (-2.0; 0.0)											

*SDC=1.56; % refers to delta vdHS ≥ SDC; SDC=2.01

Online Supplementary Table S7 - Safety outcomes

Study ID (Trial acronym)	Treatment group	Time point for outcomes	N SAEs	% SAEs	SAEs (p)	N withdrawals due to AEs	% withdrawals due to AEs	Withdrawals AEs (p)	N Serious infections	% serious infections	Serious infections (p)	N malignancies	% malignancies
Kingsley 2012 Rheumatology (MIPA)	MTX	24W				9	8.3*						
	PBO					7	6.3*						
Kavanaugh 2012 A&R (GO-REVEAL) Kavanaugh 2012 JRheum (GO-REVEAL) Kavanaugh 2013 AC&R (GO-REVEAL)	GOL 100mg	52W	5	3.4		7	4.8		1	0.7		3	2.1
	GOL 50mg		9	6.2		5	3.4		2	1.4		1	0.7
	PBO		2	3.9		2	3.9		0	0.0		1	2.0
Kavanaugh 2013 ARD (GO-REVEAL) Kavanaugh 2013 AC&R (GO-REVEAL)	GOL 100mg	104W	18	7.9		12	5.3						1.51 (0.49 - 3.52)
	GOL 50mg		16	6.5		11	4.4						0.84 (0.17 - 2.45)
	PBO			NA			NA						NA
Kavanaugh 2014 ARD (GO-REVEAL)	GOL 100mg	5Y	25	22.9		19	17.4		6	5.5		8	1.77 (0.77 - 3.49)
	GOL 50mg		29	20.9		21	15.1		5	3.6		8	1.58 (0.68 - 3.12)
	PBO			NA			NA			NA		NA	NA
Mease 2014 ARD (RAPID-PsA) Gladman 2014 AC&R (RAPID-PsA)	CZP 400mg	24W	13	9.6		6	4.4		2	1.5			
	CZP 200mg		8	5.8		4	2.9		2	1.4			
	PBO		6	4.4		2	1.5		1	0.7			
Serry 2010 BMJ (PRESTA) Prinz 2010 JADV (PRESTA)	ETA 50mg 2xweek	12W	15	4.0	0.55				2	0.5	0.684	3	0.8
	ETA 50mg 1xweek		11	2.9	REF				3	0.8	REF	1	0.3
Baranauskaite 2012 ARD (RESPOND)	IFX + MTX	16W	2	3.5		7	12.3						
	MTX		0	0.0		2	3.7						
McInnes 2013 Lancet (PSUMMIT 1)	UST 90mg	24W	3	1.5		3	1.5		0	0.0		0	0.0
	UST 45mg		6	2.9		3	1.5		0	0.0		0	0.0
	PBO		5	2.4		7	3.4		0	0.0		0	0.0
	UST 90mg	52W	7	3.4		7	3.4					0	0.0
	UST 45mg		12	5.9		5	2.4					0	0.0
	PBO		10	5.3		3	1.6					0	0.0
Ritchlin 2014 ARD (PSUMMIT 2)	UST 90mg	24W	2	1.9		3	2.9						
	UST 45mg		0	0.0		2	1.9						
	PBO		5	4.8		11	10.6						

	UST 90mg	52W	6	5.8		11	3.8						
	UST 45mg		6	5.8		4	5.8						
	PBO		3	3.8		1	1.3						
Mease 2015 NEJM (FUTURE-1)	SEC 150mg	16W	9	4.5		3	1.5						
	SEC 75mg		5	2.5		4	2.0						
	PBO		10	5.0		5	2.5						1.4/100PY
	SEC 150mg	52W	38	11.5		10	3.4						0.3/100PY
	SEC 75mg		25	7.4		13	4.5						0.9/100PY
McInnes 2015 Lancet (FUTURE-2)	SEC 300mg	24W	5	5.0		2	2.0					0	0.0
	SEC 150mg		1	1.0		0	0.0					1	1.0
	SEC 75mg		4	4.0		2	2.0					2	2.0
	PBO		2	2.0		3	3.0					0	0.0
Kavanaugh 2014 ARD (PALACE 1) Zhang 2014 ACR (PALACE 1) Kavanaugh 2014 ACR (PALACE 1) Mease 2014 ACR (PALACE 1)	APR 30mg	24W	9	5.4		12	7.1		2			1	
	APR 20mg		8	4.8		10	6.0		0			0	
	PBO		7	4.2		8	4.8		2			1	
	APR 30mg	52W	21	8.6		23	9.4		3	1.2			
	APR 20mg		14	5.7		17	6.9		2	0.8			
	APR 30mg	104W	8	4.7		3	1.8		1	0.6			
	APR 20mg		11	6.4		2	1.2		2	1.2			
Cutolo 2013 ACR (PALACE 2)	APR 30mg	52W		5.1									
	APR 20mg			4.7									
Birbara 2013 EULAR (PALACE 3) Edwards 2013 ACR (PALACE 3)	APR 30mg	24W	6										
	APR 20mg		3										
	PBO		9										
	APR 30mg	52W		4.1									
	APR 20mg			5.4									
Wells 2013 ACR (PALACE 4) Wells 2014 ACR (PALACE 4) Adebajo 2014 EULAR (PALACE 4) Wells 2014 ACR (PALACE 4)	APR 30mg	24W	1	0.6		6	3.4		1	0.6			
	APR 20mg		3	1.7		4	2.3		1	0.6			
	PBO		5	2.8		4	2.3		1	0.6			
	APR 30mg	52W	6	2.4		12	4.8		2	0.8			
	APR 20mg		16	6.3		14	5.6		1	0.4			
	APR 30mg	104W	5	5.0		7	3.5						
	APR 20mg		10	5.6		3	1.7						
Coates 2015 Lancet (TICOPA)	Tight	48W	14	14									

	control												
	Standard Care		6	6									

*% were calculated for this review

Online Supplementary Table S8 - Risk of bias assessment

Study ID (Trial acronym)	Sequence generation	Allocation concealment	Blinding participants and personnel	Blinding outcome assessment	Incomplete outcome data	Selective reporting	Other bias	Overall assessment	Comments concerning the assessment
Kingsley 2012 Rheumatology (MIPA)	Low	Low	Low	Low	Low	Low	Unclear	Low	Primary outcome based on change in $\geq 30\%$ SJC and pts were included with only 1 swollen joint; low MTX dosage
Atzeni 2011 ARD	Unclear	Unclear	High	High	Unclear	Unclear	Unclear	Unclear	Open-label study; only letter to the editor available (restricted information to assess RoB)
Asaduzzaman 2014 J Pakistan Association of Dermatologists	Low	Unclear	High	High	Unclear	Low	High	High	Open-label. Per-protocol analysis only. No sample size calculation. Likely no power to detect any difference. Very strange results with 100% of outcome fulfillment
Kavanaugh 2012 A&R (GO-REVEAL)	Low	Low	Low	Low	Low	Low	Low	Low	
Mease 2014 ARD (RAPID-PsA)	Low	Low	Unclear	Unclear	Low	Low	Low	Low	
Mease 2013 J Rheum (ADEPT)	Unclear	Unclear	Unclear	Unclear	Low	Low	Low	Unclear	Information on sequence generation, allocation concealment and blinding missing (even in the main publication, original trial)
Sterry 2010 BMJ (PRESTA)	Unclear	Unclear	Low	Low	Low	Low	Low	Low	
Baranauskaite 2012 ARD (RESPOND)	Unclear	Unclear	High	High	High	Low	High	High	Recruitment stopped earlier, no new power calculation, not blinded
McInnes 2013 Lancet (PSUMMIT 1)	Low	Low	Low	Low	Low	Low	Low	Low	
Ritchlin 2014 ARD (PSUMMIT 2)	Low	Low	Low	Low	Low	Low	Low	Low	
Mease 2015 NEJM (FUTURE-1)	Low	Low	Low	Low	Low	Low	Low	Low	
McInnes 2015 Lancet (FUTURE-2)	Low	Low	Low	Low	Low	Low	Low	Low	
Kavanaugh 2014 ARD (PALACE 1)	Unclear	Unclear	Low	Low	Low	Low	High	Unclear	Analyses are not presented as intention-to-treat. but as per protocol. Primary endpoint at 16W and only 2 outcomes are presented for that timepoint.
Cutolo 2013 ACR (PALACE 2)	NA	NA	NA	NA	NA	NA	NA	NA	
Edwards 2013 ACR (PALACE 3)	NA	NA	NA	NA	NA	NA	NA	NA	
Wells 2013 ACR (PALACE 4)	NA	NA	NA	NA	NA	NA	NA	NA	
Coates 2015 Lancet (TICOPA)	Low	Low	High	Low	Low	Low	Low	Low	

NA: not available; risk of bias could not be assessed as only abstract data are available

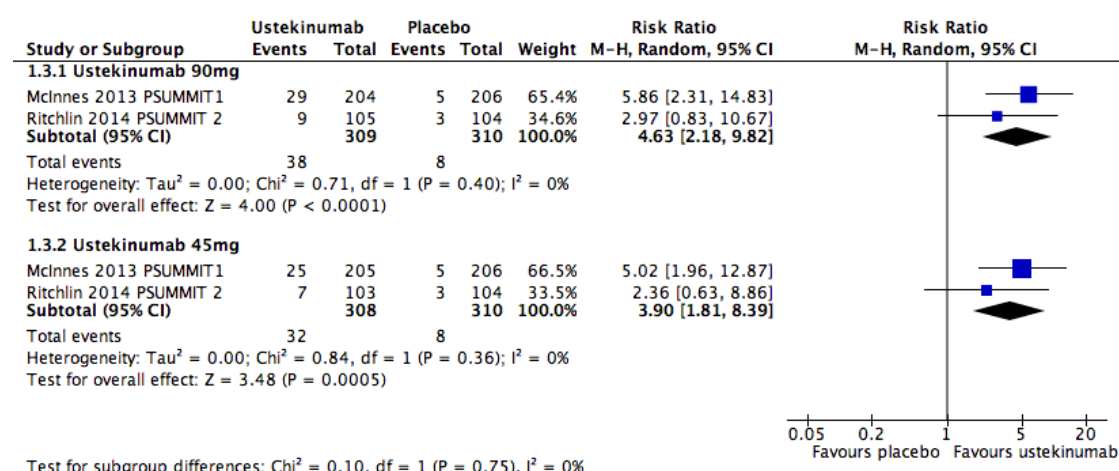
4. Meta-analysis of the efficacy outcomes for the new compounds

Online Supplementary Table S9 - Meta-analysis of treatment responses across the different drugs at the time point of the primary endpoint*

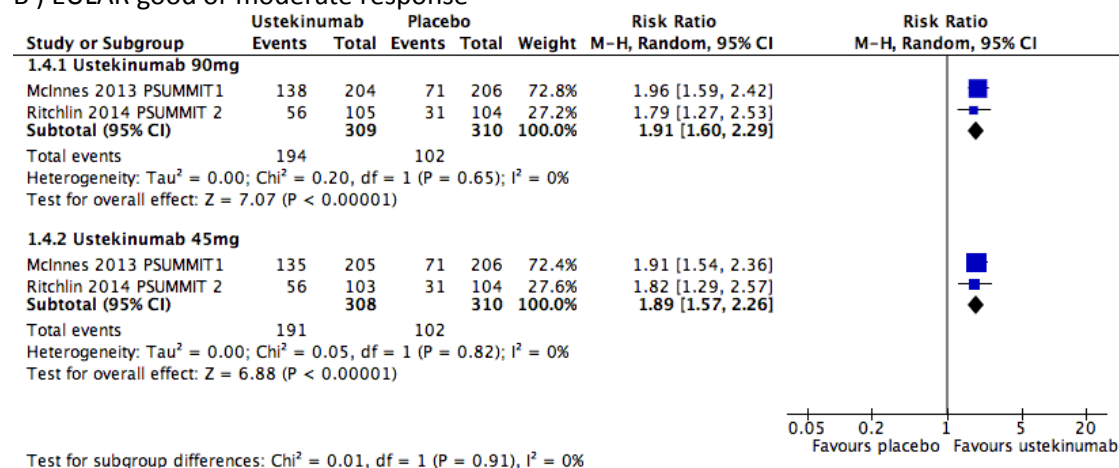
Treatment arm vs PBO	ACR20 RR (95% CI)	ACR50 RR (95% CI)	ACR70 RR (95% CI)	PAIS75 RR (95% CI)	PASI90 RR (95% CI)
UST 90mg	2.17 (1.71; 2.76)	3.25 (2.14; 4.95)	4.63 (2.18; 9.82)	6.94 (3.79; 12.72)	11.85 (3.80; 36.93)
UST 45mg	1.95 (1.52; 2.50)	2.78 (1.81; 4.27)	3.90 (1.81; 8.39)	6.39 (3.46; 11.78)	8.00 (2.51; 25.51)
SEC 300mg	3.31 (2.04; 5.36)	4.90 (2.29; 10.50)	19.60 (2.68; 143.23)	3.90 (1.90; 7.98)	5.24 (1.96; 14.04)
SEC 150mg	5.82 (1.56; 21.71)	4.74 (3.08; 7.29)	11.14 (4.52; 27.44)	4.76 (1.92; 11.78)	6.62 (1.88; 23.30)
SEC 75mg	4.47 (0.66; 30.26)	3.59 (2.30; 5.61)	7.94 (3.18; 19.83)	3.75 (0.82; 17.06)	4.26 (0.40; 45.59)
APR 30mg	1.98 (1.64; 2.38)	NA	NA	NA	NA
APR 20mg	1.70 (1.40; 2.06)	NA	NA	NA	NA

* Time point of the primary endpoint: for UST and SEC 24 weeks, for APR 16 weeks

A) ACR70



B) EULAR good or moderate response



C) PASI 90

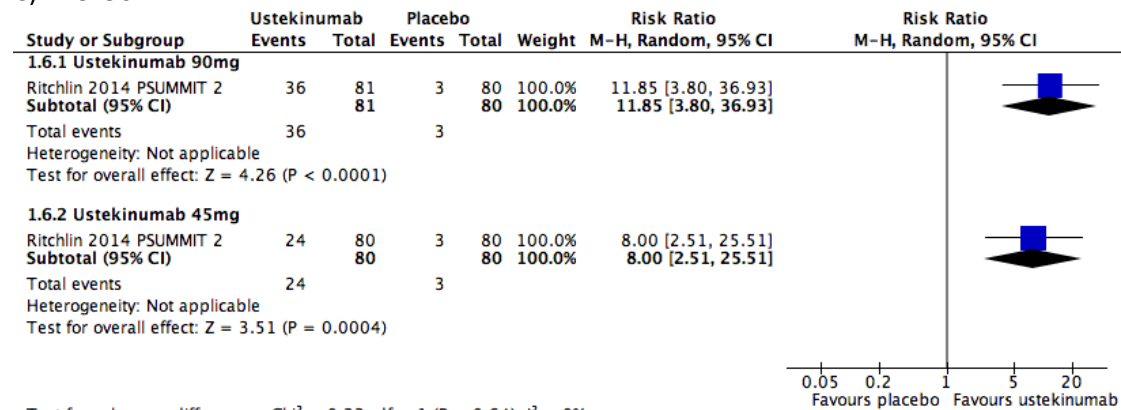
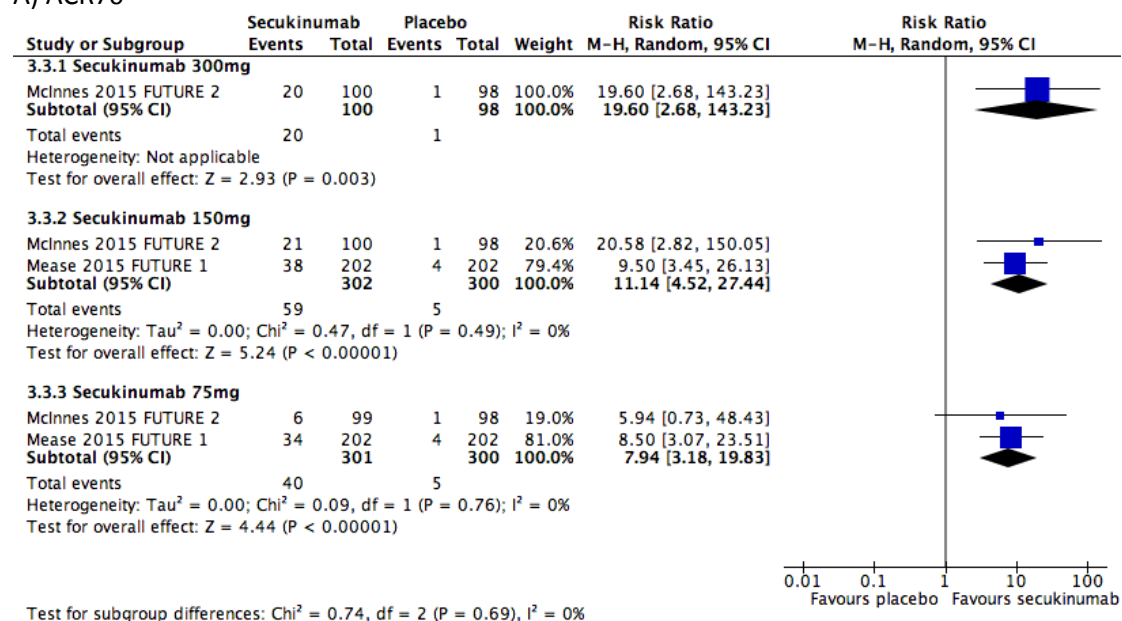


Figure S2 - Additional efficacy outcomes of ustekinumab at 24 weeks: A) ACR 70; B) EULAR good or moderate response; C) PASI 90

A) ACR70



B) PASI90

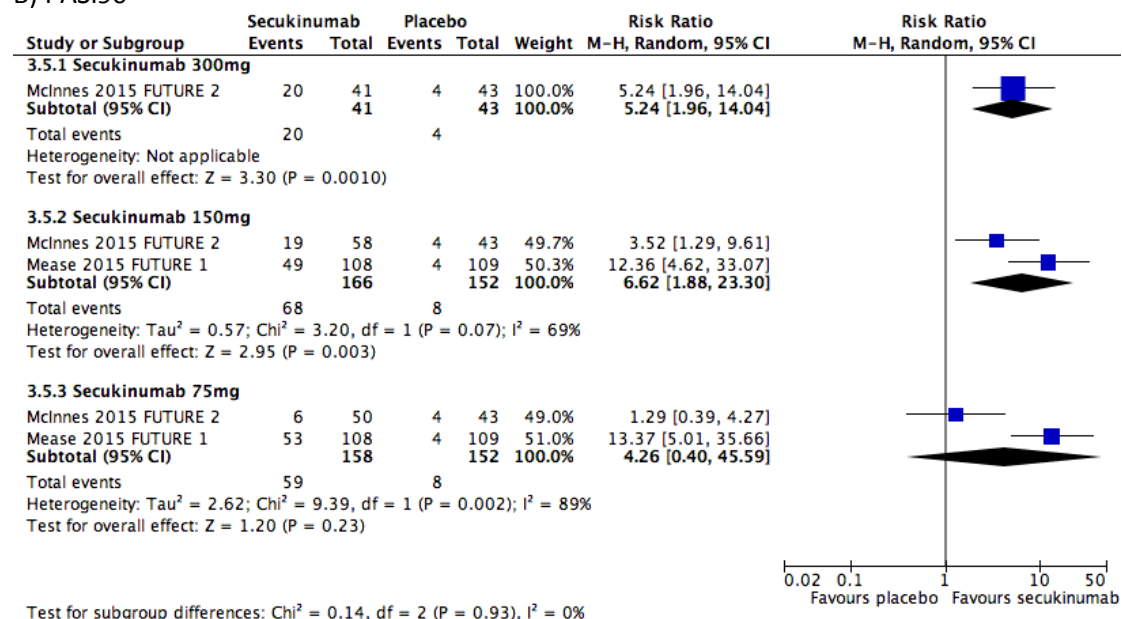


Figure S3 - Additional efficacy outcomes of secukinumab at 24 weeks: A) ACR 70; B) PASI 90

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6. List of abbreviations

ACR	American College of Rheumatology
ADA	adalimumab
AEs	adverse events
APR	apremilast
BSA	body surface area
CYC	cyclosporine
CZP	certolizumab pegol
DAS28	28-joint disease activity assessment
ETA	etanercept
EULAR	European League Against Rheumatism
GOL	golimumab
HAQ	Health Assessment Questionnaire
IFX	infliximab
LEF	leflunomide
MDA	minimum disease activity
MTX	methotrexate
NA	not available
NAPSI	nail psoriasis severity index
PASI	Psoriasis Area Severity Index
PBO	placebo
PsARC	Psoriatic arthritis response criteria
PY	person-years
SAEs	serious adverse events
SDC	smallest detectable change
SEC	secukinumab
TNFi	tumor necrosis factor inhibitor
UST	ustekinumab
vdHS	van der Heijde Sharp score