Biological DMARD efficacy in psoriatic arthritis:
a systematic literature review and meta-analysis on articular,
enthesitis, dactylitis, skin and functional outcomes

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Abstract

Objective

There is no hierarchy in the use of biotherapies (bDMARDs) in psoriatic arthritis (PsA) and no published head-to-head
comparative studies. Our purpose is to evaluate the respective efficacy of TNF inhibitors, IL12/23 inhibitors (ustekinumab),
IL17 inhibitors (secukinumab, ixekizumab) and CTLA4Ig (abatacept) on articular, enthesitis, dactylitis, skin and
functional outcomes in PsA.

Methods

Randomised controlled trials assessing bDMARDs in PsA were selected through the MedLine, Cochrane
and Embase databases. ACR20/50/70 and PASI75/90 response rates, enthesitis and dactylitis reduction rates
and HAQ-DI mean reductions were collected. Pooled meta-analyses were performed to assess relative risks
(RR) with their 95% confidence interval (95%CI) for each class of bDMARDs in comparison with placebo.

Results

17 RCTs were analysed. Compared to placebo, all bDMARDs showed higher ACR20 response rates, with RR ranging
from 1.77 (1.31, 2.39) to 3.21 (2.52, 4.08), and a greater HAQ-DI mean reduction. TNF inhibitors, secukinumab and
IL17 inhibitors showed higher ACR50/70 and PASI75/90 response rates. TNF inhibitors, secukinumab and IL17 inhibitors
showed higher enthesitis resolution rates and only TNF inhibitors and IL17 inhibitors showed higher dactylitis resolution
rates, with RRs ranging from 1.41 (1.02, 1.95) to 2.31 (1.60, 3.34) and from 2.07 (1.38, 3.12) to 2.65 (1.79, 3.94),
respectively.

Conclusion

All bDMARDs showed higher ACR20 response rates and better HAQ-DI mean reduction compared to placebo.
This meta-analysis highlights the variability of bDMARD efficacy on ACR50/70, PASI75/90 and enthesitis or dactylitis
response rates. Head-to-head studies are needed to draw definitive conclusions on potential efficacy-related differences
between bDMARDs in PsA.

Key words

psoriatic arthritis, DMARD, meta-analysis
Introduction
Psoriatic arthritis (PsA) is an inflammatory disease which associates arthritis and psoriasis. Up to 30% of patients affected by psoriasis will develop PsA, based on the CASPAR criteria (1). The disease is strongly associated with a reduced quality of life, its burden being similar to rheumatoid arthritis and axial spondyloarthritis (2). Nearly half of patients will present with bone erosions within two years of disease onset (3). The treatment of PsA is complex and there is still no universal consensus regarding remission criteria even though treatment guidelines are available from the EULAR and GRAPPA study groups (4, 5). First-line treatments include NSAIDs and local glucocorticoid injections. Second-line therapies include conventional synthetic disease-modifying anti-rheumatic drugs (csDMARDs) such as methotrexate, leflunomide and sulfasalazine. Third-line treatments include biological DMARDs (bDMARDs) and targeted synthetic DMARDs (tsDMARDs), such as JAK inhibitors and phosphodiesterase-4 (PDE4) inhibitors. PsA management also covers patient education, weight reduction, smoking cessation, exercising, joint protection and stress management (7).

bDMARDs have been allowed as third-line treatments in PsA since the early 2000s. TNF inhibitors include monoclonal antibodies targeting TNF (adalimumab, certolizumab pegol, infliximab and golimumab) and soluble TNF receptors (etanercept). Ustekinumab targets the p40 subunit of IL-12/23. Ixekizumab and secukinumab target IL-17. Abatacept targets CTLA4 and blocks T-cell co-stimulation signals. New targets are currently investigated, such as the p19 subunit of IL-23 (guselkumab, risankizumab and tildrakizumab), or IL-6 (clazakizumab) (8, 9).

bDMARDs are an expensive treatment option and their prescription does not always trigger an adequate clinical response: results from the DANBIO registry show that only 54% of patients treated with anti-TNF agents satisfy the EULAR good response criteria (10). Meta-analyses have been performed on ACR20, PASI and HAQ outcomes in PsA, but these meta-analyses do not include all available bDMARDs (11), do not systematically assess their impact on enthesitis, dactylitis, skin and functional outcomes (12–19) or do not analyse separately novel biologics, which does not account for their different mechanisms of action (11).

The purpose of our meta-analysis is to assess the relative efficacy of the four currently marketed bDMARD classes (TNF inhibitors, IL12/23 inhibitors, IL17 inhibitors and CTLA4-Ig) in terms of both articular and extra-articular outcomes, in order to guide the clinical prescription of third-line drugs according to the clinical presentation of the disease.

Methods
This meta-analysis has been performed in accordance with the Preferred reporting items for systematic review and meta-analysis protocols (PRISMA) (20).

Search strategy
The search was conducted on 15 March 2017 and updated on 5 February 2018. It was conducted through the MedLine, Cochrane and Embase databases, using the following keywords: “(TNF OR abatacept OR adalimumab OR certolizumab OR etanercept OR golimumab OR infliximab OR secukinumab OR ustekinumab OR ixekizumab) AND psoriatic arthritis”, with a filter to restrict the results to randomised controlled trials. Manual research was also conducted through the 2016 and 2017 ACR and EULAR Congress abstracts.

Study selection
We focused on original randomised controlled trials evaluating one or more marketed bDMARDs versus placebo in adults suffering from PsA. No restriction was applied to prior bDMARD use, duration of study or primary or secondary endpoints. Patients in the study treatment arm received a bDMARD at a dosage approved for the treatment of PsA by either the European Medicines Agency (EMA) or the Food and Drugs Administration (FDA). No restriction was placed on the fulfilment of classification criteria since the first RCTs pre-date the CASPAR criteria (21).
Data extraction

The following data were extracted by NS using a pre-defined grid: reference and year of the trial, duration of study, primary endpoints, secondary endpoints, intervention design, number of patients enrolled, inclusion criteria, prior bDMARD use and baseline characteristics of the study population (age, sex ratio, length of time since disease onset, number of swollen joints, number of tender joints, disease activity VAS as stated by the patient, CRP levels, presence of enthesitis or dactylitis). For the meta-analysis, the following criteria were recorded: number of

Table I. Detail of included studies.

<table>
<thead>
<tr>
<th>Study</th>
<th>Year</th>
<th>Duration</th>
<th>Primary endpoint</th>
<th>Treatment</th>
<th>Prior bDMARD use</th>
<th>Patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mease et al. <em>Lancet</em></td>
<td>2000</td>
<td>12 weeks</td>
<td>PsARC</td>
<td>Etanercept</td>
<td>No</td>
<td>TRT: 30</td>
</tr>
<tr>
<td>Mease et al. <em>Arthritis Rheum</em></td>
<td>2004</td>
<td>24 weeks</td>
<td>ACR20</td>
<td>Etanercept</td>
<td>No</td>
<td>TRT: 101</td>
</tr>
<tr>
<td>IMPACT</td>
<td>2005</td>
<td>16 weeks</td>
<td>ACR20</td>
<td>Infliximab</td>
<td>No</td>
<td>TRT: 52</td>
</tr>
<tr>
<td>IMPACT2</td>
<td>2005</td>
<td>24 weeks</td>
<td>ACR20</td>
<td>Infliximab</td>
<td>No</td>
<td>TRT: 100</td>
</tr>
<tr>
<td>ADEPT</td>
<td>2005</td>
<td>12 weeks</td>
<td>ACR20</td>
<td>Adalimumab</td>
<td>No</td>
<td>TRT: 151</td>
</tr>
<tr>
<td>Genovese et al. <em>J Rheumatol</em></td>
<td>2007</td>
<td>12 weeks</td>
<td>Sharp score</td>
<td>Adalimumab</td>
<td>No</td>
<td>TRT: 51</td>
</tr>
<tr>
<td>GO-REVEAL</td>
<td>2009</td>
<td>24 weeks</td>
<td>ACR20</td>
<td>Golimumab</td>
<td>No</td>
<td>TRT: 146</td>
</tr>
<tr>
<td>RAPID-PSA</td>
<td>2014</td>
<td>24 weeks</td>
<td>ACR20</td>
<td>Certolizumab pegol</td>
<td>Yes (20%)</td>
<td>Q2W: 138</td>
</tr>
<tr>
<td>GO-VIBRANT</td>
<td>2017</td>
<td>24 weeks</td>
<td>ACR20</td>
<td>Golimumab</td>
<td>No</td>
<td>TRT: 241</td>
</tr>
<tr>
<td>OPAL BROADEN</td>
<td>2017</td>
<td>12 weeks</td>
<td>ACR20</td>
<td>Tofacitinib</td>
<td>Adalimumab</td>
<td>PBO: 105</td>
</tr>
<tr>
<td>PSUMMIT1</td>
<td>2013</td>
<td>24 weeks</td>
<td>ACR20</td>
<td>Ustekinumab</td>
<td>No</td>
<td>U45: 205</td>
</tr>
<tr>
<td>PSUMMIT2</td>
<td>2014</td>
<td>24 weeks</td>
<td>ACR20</td>
<td>Ustekinumab</td>
<td>Yes (58%)</td>
<td>U45: 103</td>
</tr>
<tr>
<td>FUTURE1</td>
<td>2015</td>
<td>24 weeks</td>
<td>ACR20</td>
<td>Secukinumab</td>
<td>Yes (28%)</td>
<td>S150: 202</td>
</tr>
<tr>
<td>FUTURE2</td>
<td>2015</td>
<td>24 weeks</td>
<td>ACR20</td>
<td>Secukinumab</td>
<td>Yes (35%)</td>
<td>S150: 100</td>
</tr>
<tr>
<td>SPIRIT P1</td>
<td>2017</td>
<td>24 weeks</td>
<td>ACR20</td>
<td>Ixekizumab Adalimumab</td>
<td>No</td>
<td>Q4W: 107</td>
</tr>
<tr>
<td>SPIRIT P2</td>
<td>2017</td>
<td>24 weeks</td>
<td>ACR20</td>
<td>Ixekizumab Adalimumab</td>
<td>Yes (59%)</td>
<td>Q4W: 122</td>
</tr>
<tr>
<td>ASTRAEA</td>
<td>2017</td>
<td>24 weeks</td>
<td>ACR20</td>
<td>Abatacept</td>
<td>Yes (60%)</td>
<td>TRT: 213</td>
</tr>
</tbody>
</table>

ACR: American College of Rheumatology; PASI: psoriasis area severity index; bDMARD: biological disease-modifying anti-rheumatic drug; PsARC: psoriatic arthritis response criteria; HAQ-DI: health assessment questionnaire disability index; TRT: treatment; PBO: placebo.
patients fulfilling the ACR20 response criteria, ACR50 response criteria, and ACR70 response criteria, number of enthesitis-free patients and number of dactylitis-free patients, number of patients fulfilling the PASI75 response criteria and PAS90 response criteria at the time of primary criteria evaluation, which was ranging from 12 to 24 weeks and the HAQ-DI mean score variation from baseline. Enthesitis and dactylitis outcomes were assessed as difference from baseline. When not explicitly reported, enthesitis and dactylitis resolution was considered achieved if the evaluation criteria (Leeds Enthesitis Index, Maastricht Ankylosing Spondylitis Enthesitis Score, Leeds Dactylitis Index or Dactylitis Severity Score) was equal or superior to the baseline. When not explicitly reported, enthesitis and dactylitis resolution was considered achieved if the evaluation criteria was equal or superior to the baseline.

**Study quality evaluation**

Risk of bias was evaluated using the Cochrane Collaboration’s Assessment Tool (22).

**Statistical analysis**

The meta-analysis was restricted to treatment arms using the dosage approved by the EMA or the FDA for PsA. Analysis was performed on the total population at the end of the double-blind period. Only one intervention group was compared to the placebo in the analysis except when detailed data wasn’t available, in which case we used pooled numbers for treatment arms (23). Enthesitis and dactylitis outcomes were assessed using the number of enthesitis-free or dactylitis-free patients at the time of evaluation reported to the number of patients with enthesitis or dactylitis at baseline. Meta-analysis was performed to assess the relative risk (RR) with 95% confidence interval (95% CI) for each study and pooled for the 4 different bDMARD classes marketed for PsA.

Heterogeneity was assessed according to Cochran’s Q-test and I² values. Calculations were made with the Cochrane RevMan 5.3 software. p-values less than 0.05 were considered significant.

**Results**

**Study selection**

The search yielded 324 original results. 304 articles were excluded after title screening and 3 were excluded after full text screening because the dosage used was not the standard one (Fig. 1). The 17 remaining articles were included in the meta-analysis, after assessment by NS and ARC.

All of the randomised, placebo-controlled trials included in our meta-analysis were published between 2000 and 2017. Two RCTs studied etanercept (24, 25), 2 studied infliximab (26, 27), 3 studied adalimumab (28-30), 2 studied golimumab (31, 32), 1 studied certolizumab (33), 2 studied ustekinumab (34, 35), 2 studied secukinumab (23, 36), 2 studied ixekizumab (37, 38) and 1 studied abatacept (39) (Table I).

The double-blind period ranged between 12 and 24 weeks. Eight RCTs allowed prior bDMARD use. In total, 4303 patients (bDMARDs: n=2168; placebo: n=2135) were included in our primary analysis. The mean age at baseline ranged from 43.5 to 52.6 years. The percentage of female subjects ranged from 29 to 60%. The average duration of the disease ranged from 3.4 to 11.7 years.

**Risk of bias**

All of the studies were of good quality, as evaluated per the Cochrane Collaboration’s Assessment Tool (22) (Supplementary Fig. 1).

**Meta-analysis**

Higher ACR20 response rates were shown for all bDMARDs in comparison to placebo, with RR (95%CI) ranging from 3.21 (2.52, 4.08) for anti-TNF agents, 7.59 (3.32, 17.2) for anti-IL17 agents, 1.95 (1.52, 2.49) for ustekinumab to 1.77 (1.31, 2.39) for abatacept (Fig. 2). The same trends were observed for ACR50 response rates, with RR (95%CI) ranging from 6.47 (4.57, 9.17) for anti-TNF agents, 4.22 (2.83, 6.28) for anti-IL17 agents, 2.78 (1.81, 4.27) for ustekinumab to 1.56 (0.99, 2.46) for abatacept (not statistically sig-

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**Fig. 2.** Risk ratio (95%CI) for bDMARDs in terms of fulfilling the ACR20 response criteria compared to placebo, pooled per class (higher is better).
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response rates, with RRs (95%CI) of 8.89 (5.98, 13.21) for anti-TNF agents, 8.84 (3.65, 21.39) for anti-IL17 agents, 3.90 (1.81, 8.39) for ustekinumab and 1.56 (0.82, 2.96) for abatacept (not statistically significant) (Suppl. Fig. 3). Analysis focused on bDMARD naïve patients showed similar results concerning ACR20 response rates, with RR (95%CI) ranging from 3.14 (2.44, 4.05) for anti-TNF agents, 2.75 (1.80, 4.21) for anti-IL17 agents, 1.86 (1.43, 2.42) for ustekinumab, except for abatacept with RR (95%CI) of 1.23 (0.90, 1.68) (not statistically significant) (Suppl. Fig. 4). The RRs (95%CI) for dactylitis resolution versus placebo ranged from 2.65 (1.79, 3.94) for anti-IL17 agents, 2.07 (1.38, 3.12) for anti-TNF agents to 1.42 (0.97, 2.08) for ustekinumab (not statistically significant) (Fig. 3).

Higher PASI75 response rates were shown for most bDMARDs in comparison to placebo, with RRs (95%CI) ranging from 8.51 (4.56, 15.90) for anti-TNF agents, 5.14 (3.16, 8.56) for anti-IL17 agents, 6.36 (3.49, 11.60) for ustekinumab to 1.62 (0.89, 2.96) for abatacept (not statistically significant) (Fig. 5). PASI90 response rates followed the same trends, with RRs (95%CI) ranging from 8.76 (3.84, 19.89) for anti-TNF agents, 4.95 (2.85, 8.61) for anti-IL17 agents to 5.76 (2.46, 25.52) for ustekinumab (no data available for abatacept) (Suppl. Fig. 5).

Higher HAQ-DI reductions were shown for most bDMARDs compared to placebo, with mean differences (95%CI) of -0.31 (-0.42, -0.20) for anti-TNF agents, -0.26 (-0.33, -0.20) for anti-IL17 agents and -0.13 (-0.25, -0.01) for abatacept (no data available for ustekinumab) (Suppl. Fig. 6).

Discussion
In our meta-analysis, all bDMARDs proved superior to placebo in terms of the ACR20 response rates and HAQ-DI mean reductions. Not all bDMARDs showed statistically significant higher ACR50/70 response rates, higher rates of enthesitis or dactylitis resolution or higher PASI75/90 response rates in comparison to placebo.

This meta-analysis assessed the relative efficacy of the four currently marketed classes of bDMARDs in terms of both articular and extra-articular outcomes, in RCTs conducted in PsA. We selected 17 high-quality (22) RCTs comparing bDMARDs to placebo using the MedLine, Cochrane and Embase databases, and compiled the most relevant and frequently reported response criteria for arthritis, enthesitis and dactylitis, skin

![Fig. 3. Risk ratio (95%CI) for bDMARDs in terms of enthesitis reduction compared to placebo, pooled per class (higher is better).](image)

![Fig. 4. Risk ratio (95%CI) for dactylitis reduction compared to placebo, pooled per class (higher is better).](image)
involvement and quality of life. We focused this analysis on bDMARDs and did not include tsDMARDS such as apremilast or Jak inhibitors. RCTs that did not use the marketed treatment posology (40–42) were excluded in order to their use in clinical practice. The selected RCT publication date covers 2000 to 2017, and therefore displays disparities, such as the duration of the disease at inclusion, ranging from 3.5 years to 11.4 years, the severity of the disease or the duration of the double-blind period which spans 12 to 24 weeks. One limitation arises from the bDMARD-naive populations with better treatment response rates than previously exposed populations (4). In the RCTs evaluating TNF inhibitors, only the RAPID-PsA trial allowed 20% of its population to have prior exposure to anti-TNF agents. In those evaluating anti-IL17 agents, anti-IL12/23 agents and abatacept, four out of seven allowed some of the randomised patients (28% to 60%) to have had prior exposure to bDMARDs (Table I).

Concerning articular outcomes, our meta-analysis shows that all available bDMARDs have a strong relative risk of fulfilling the ACR20 response criteria compared to placebo. Only abatacept fails to display statistically significant superiority over placebo in terms of the ACR70 response criteria (40% to 50%) (12, 13). Those results are consistent with previously published analyses (11, 14–18). The ACR20 evaluation criteria is the form of a DAPSA evaluation of disease activity (39).

Concerning dactylitis outcomes, our meta-analysis shows a statistical difference compared to placebo for anti-TNF and anti-IL17 agents, but not for anti-IL12/23 agents. We encountered methodological issues on incorporating enthesitis and dactylitis outcomes in the present meta-analysis. Firstly, no data were reported on enthesitis and dactylitis outcomes in three studies evaluating anti-TNF agents (24, 25, 28). Secondly, three other studies reported those outcomes solely as composite index reduction and could not be analysed (29, 39, 43). Lastly, one study only reported pooled numbers for both treatment arms, which we chose to include in the analysis (23). We chose to focus on absolute enthesis or dactylitis reduction and not composite indexes in order to obtain analysable data. Concerning skin outcomes, our meta-analysis showed statistically significant, higher PASI75 and PASI90 response rates compared to placebo, except for abatacept which did not display statistically significant superiority to placebo in terms of the PASI75 response criteria (no data for the PASI90 response criteria). The authors attribute the lack of statistical significance to lower epidermal bioavailability (39). Recent network meta-analyses corroborate our results concerning skin outcomes compared to placebo (44, 45) and, in this respect, IL-17 inhibitors seem to be the most effective treatment. Moreover, head-to-head studies confirmed the superiority of ustekinumab (46), secukinumab (47) and ixekizumab (48) over etanercept, and of ixekizumab (49) and secukinumab (50) over ustekinumab. Concerning functional outcomes, all RCTs analysed showed a statistically significant mean reduction in HAQ versus placebo. The data provided for ustekinumab could not be analysed as it was a median reduction. Only one previous meta-analysis assessed HAQ improvement for PsARC responders and non-responders, with insufficient statistical evidence to demonstrate differences in effectiveness between anti-TNF agents (51).

To date, our meta-analysis is the first to assess the efficacy of all marketed bDMARDs in PsA in 2018 on both arthritic, enthesisis, dactylitis, skin, and functional outcomes. On the one hand, all bDMARDs showed higher ACR20 response rates and a better HAQ-DI mean reduction compared to placebo. On the other hand, this meta-analysis highlights the variability in terms of bDMARD efficacy on ACR50/70, enthesisis-free or dactylitis-free response rates and PASI75/90. The results of ongoing head-to-head studies are needed in order to draw definitive conclusions on differences in potential efficacy between bDMARDs in PsA.
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References


