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

N. Simons[1], Y. Degboé[1], T. Barnetche[2], A. Cantagrel[1], A. Ruyssen-Witrand[1], A. Constantin[1]

[1]Department of Rheumatology, Purpan Hospital, Toulouse III University, Toulouse, France; [2]Department of Rheumatology, FHU ACRONIM, Pellegrin Hospital, Bordeaux University, Bordeaux, France.

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 RRs 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

Numa Simons, MB
Yannick Degboé, MD, PhD
Thomas Barnetche, PhD
Alain Cantagrel, MD, PhD
Adeline Ruyssen-Witrand, MD, PhD
Arnaud Constantin, MD, PhD

Please address correspondence to:
Numa Simons,
Service de rhumatologie,
Hopital Pierre-Paul Riquet,
Place du Dr Baylac, TSA 40031,
31059 Toulouse Cedex 9, France.
E-mail: numa.simons@gmail.com

Received on May 16, 2019; accepted in revised form on July 15, 2019.

Competing interests: Y. Degboé received a Partner Fellowship supported by Celgene in 2018; A. Cantagrel has received speaker fees from Abbvie, Janssen, Lilly, MSD, Novartis, Pfizer, and UCB in the last three years, and research support from Abbvie, MSD, and Pfizer; A. Constantin has received honoraria for consultancies from Abbvie, BMS, Janssen, Lilly, MSD, Novartis, Pfizer, Roche-Chugai, Sanofi, and UCB. The other co-authors have declared no competing interests.

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, rizankizumab 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 predate the CASPAR criteria (21).

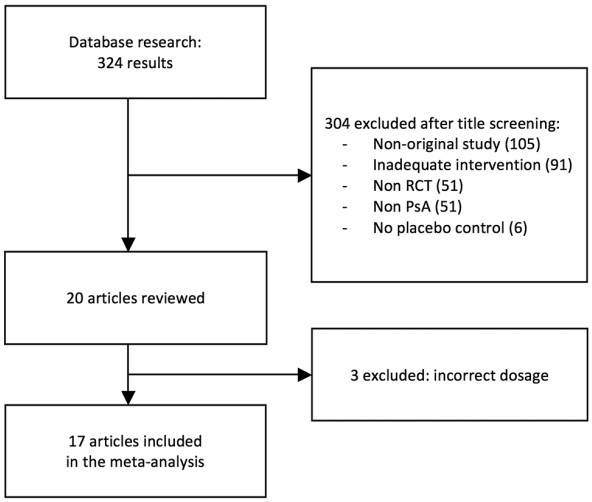

Fig. 1. Flow chart. RCT: randomised controlled trial, PsA: psoriatic arthritis.

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.

	Study	Year	Duration	Primary endpoint	Treatment	Prior bDMARD use	Patients
TNF inhibitors	Mease *et al.Lancet*	2000	12 weeks	PsARC	Etanercept	No	TRT: 30 PBO: 30
	Mease *et al. Arthritis Rheum*	2004	24 weeks	ACR20	Etanercept	No	TRT: 101 PBO: 104
	IMPACT Antoni *et al. Arthritis Rheum*	2005	16 weeks	ACR20	Infliximab	No	TRT: 52 PBO: 52
	IMPACT2 Antoni *et al. Ann Rheum Dis*	2005	24 weeks	ACR20	Infliximab	No	TRT: 100 PBO: 100
	ADEPT Mease *et al. Arthritis Rheum*	2005	12 weeks	ACR20 Sharp score	Adalimumab	No	TRT: 151 PBO: 162
	Genovese *et al. J Rheumatol*	2007	12 weeks	ACR20	Adalimumab	No	TRT: 51 PBO: 49
	GO-REVEAL Kavanaugh *et al. Arthritis Rheum*	2009	24 weeks	ACR20	Golimumab	No	TRT: 146 PBO: 113
	RAPID-PSA Mease *et al. Ann Rheum Dis*	2014	24 weeks	ACR20	Certolizumab pegol	Yes (20%)	Q2W: 138 PBO: 136
	GO-VIBRANT Kavanaugh *et al. Arthritis Rheum*	2017	24 weeks	ACR20	Golimumab	No	TRT: 241 PBO: 239
	OPAL BROADEN Mease *et al. NEJM*	2017	12 weeks	ACR20 HAQ-DI	*Tofacitinib* Adalimumab	No	PBO: 105 ADA: 106
anti IL12/23	PSUMMIT1 McInnes *et al. Lancet*	2013	24 weeks	ACR20	Ustekinumab	No	U45: 205 PBO: 206
	PSUMMIT2 Ritchlin *et al. Ann Rheum Dis*	2014	24 weeks	ACR20	Ustekinumab	Yes (58%)	U45: 103 PBO: 104
anti IL17	FUTURE1 Mease *et al. NEJM*	2015	24 weeks	ACR20	Secukinumab	Yes (28%)	S150: 202 PBO: 202
	FUTURE2 McInnes *et al. Lancet*	2015	24 weeks	ACR20	Secukinumab	Yes (35%)	S150: 100 PBO: 98
	SPIRIT P1 Mease *et al. Ann Rheum Dis*	2017	24 weeks	ACR20	Ixekizumab Adalimumab	No	Q4W: 107 PBO: 106
	SPIRIT P2 Nash *et al. Lan cet*	2017	24 weeks	ACR20	Ixekizumab	Yes (59%)	Q4W: 122 PBO: 118
CTLA4Ig	ASTRAEA Mease *et al. Ann Rheum Dis*	2017	24 weeks	ACR20	Abatacept	Yes (60%)	TRT: 213 PBO: 211

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 PASI90 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 to zero at evaluation, in patients with a dactylitis or enthesitis score superior to zero at baseline. For trials with an early drop-out option in the placebo group, we used data as presented at the end of the double-blind period. All results were obtained from an intent-to-treat population. When data were unavailable, we contacted the research team in order to obtain further information.

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.

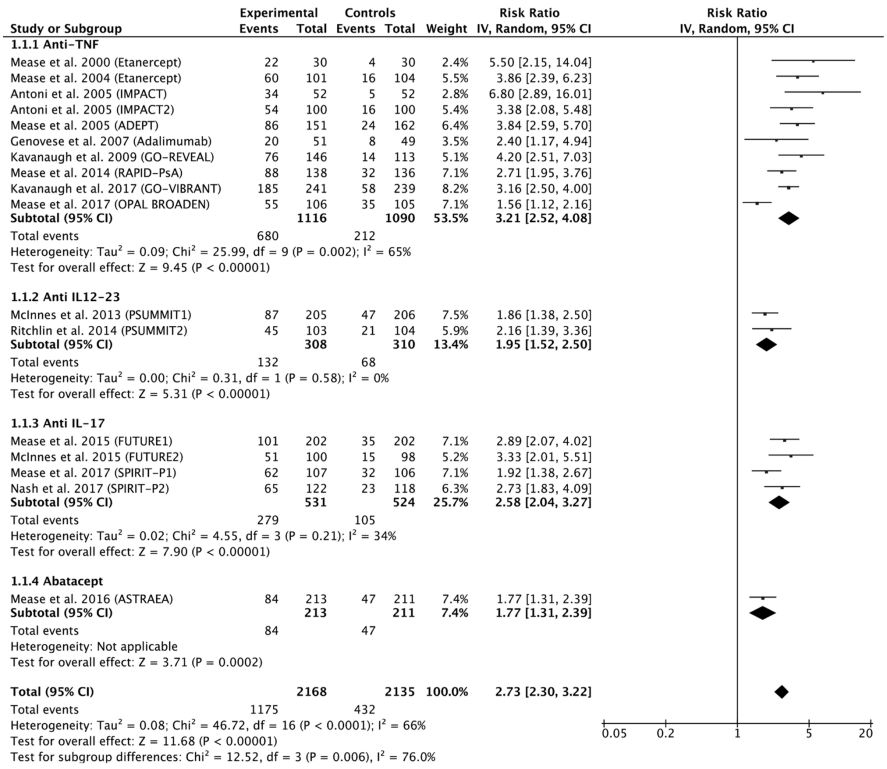

Fig. 2. Risk ratio (95%CI) for bDMARDs in terms of fulfilling the ACR20 response criteria compared to placebo, pooled per class (higher is better).

Heterogeneity was assessed according to Cochran's Q-test and I^2 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 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 RRs (95%CI) ranging from 3.21 (2.52, 4.08) for anti-TNF agents, 2.58 (2.04, 3.27) for anti-IL17 agents, 1.95 (1.52, 2.50) for ustekinumab to 1.77 (1.31, 2.39) for abatacept (Fig. 2). The same trends were observed for ACR50 response rates, with RRs (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-

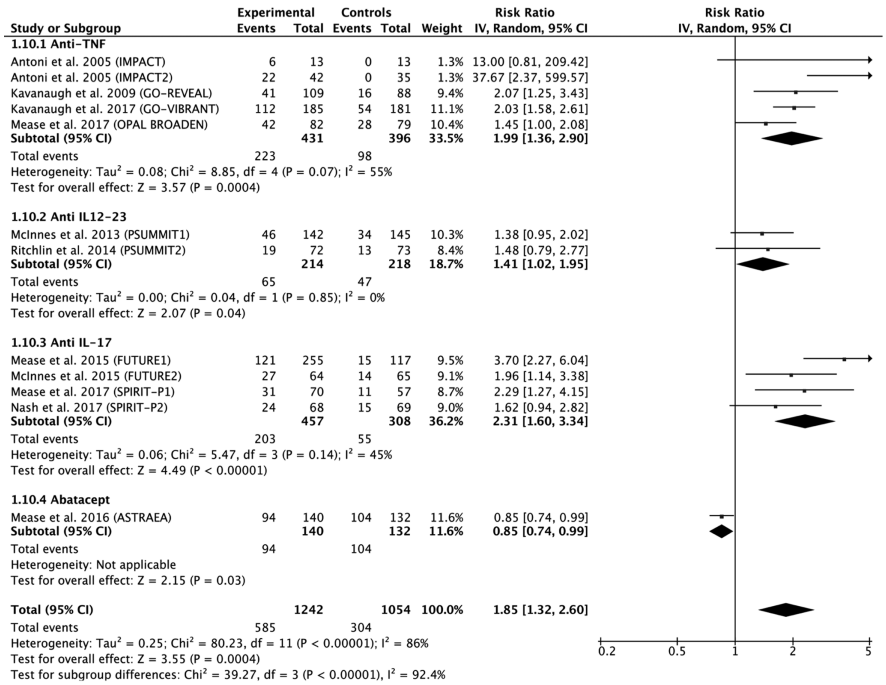

Fig. 3. Risk ratio (95%CI) for bDMARDs in terms of enthesitis reduction compared to placebo, pooled per class (higher is better).

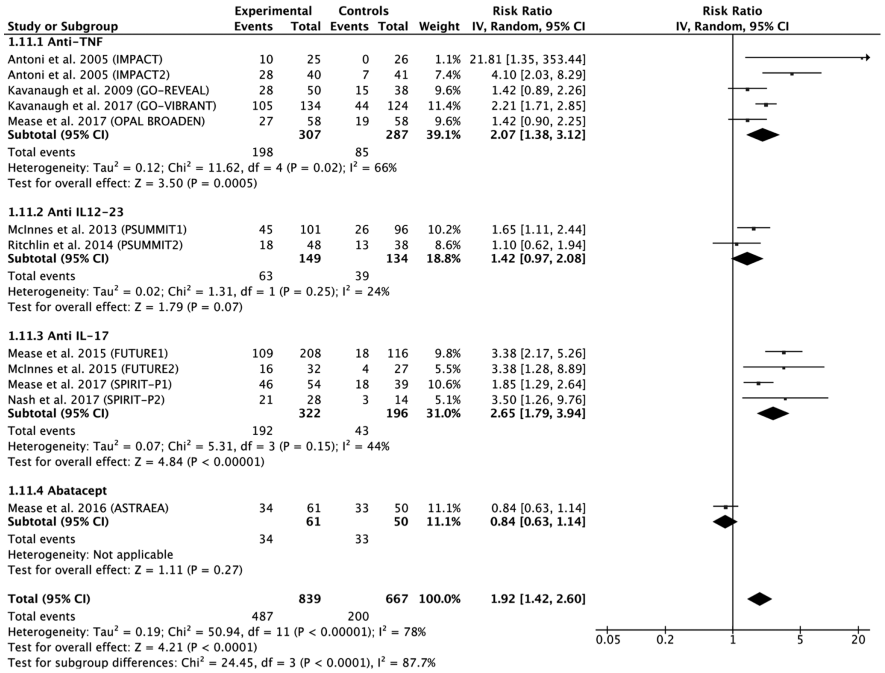

Fig. 4. Risk ratio (95%CI) for bDMARDs in terms of dactylitis reduction compared to placebo, pooled per class (higher is better).

nificant) (Suppl. Fig. 2), and for ACR70 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, to 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 (C95%CI) for enthesitis resolution in comparison to placebo ranged from 2.31 (1.60, 3.34) for anti-IL17 agents, 1.99 (1.36, 2.90) for anti-TNF agents to 1.41 (1.02, 1.95) for ustekinumab (Fig. 3).

The RRs (C95%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. 4).

Higher PASI75 response rates were shown for most bDMARDs in comparison to placebo, with RRs (CI95%) ranging from 8.51 (4.56, 15.90) for anti-TNF agents, 5.14 (3.16, 8.36) 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, 20.01) for anti-TNF agents, 4.95 (2.85, 8.61) for anti-IL17 agents to 11.57 (5.46, 24.52) 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

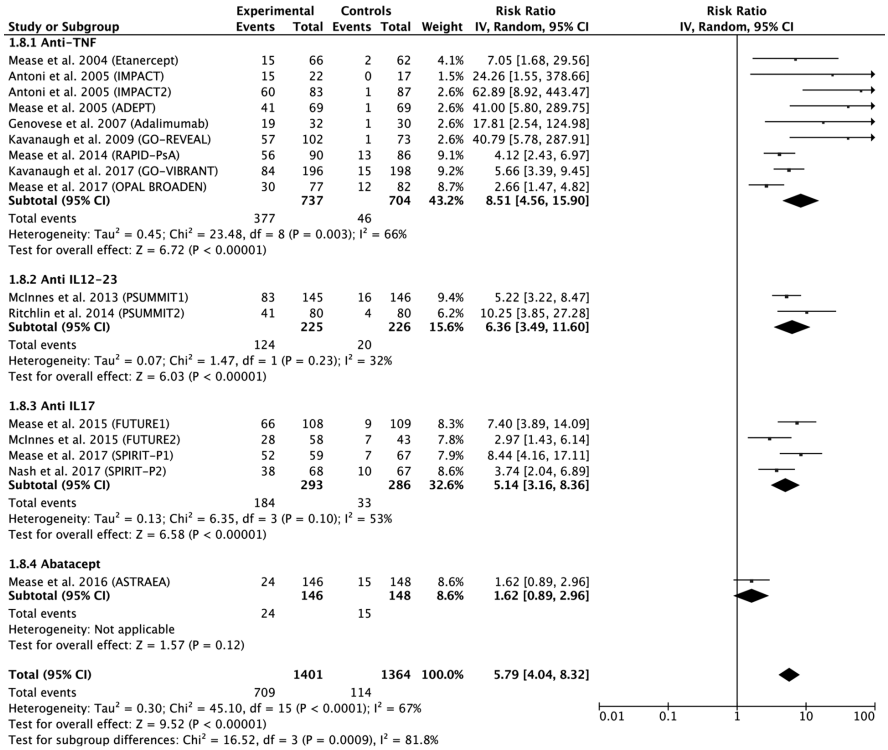

Fig. 5. Risk ratio (95%CI) for bDMARDs in terms of fulfilling the PASI75 response criteria compared to placebo, pooled per class (higher is better).

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 assess bDMARD efficacy according 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 fact that the first studies were performed on 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 superiority over placebo regarding the ACR50 and ACR70 response criteria, for which the authors involved the lower proportion of bDMARD-naive patients (40%) (39). Those results are consistent with previously published analyses (11, 14–18). The ACR20 evaluation criteria is not specific to psoriatic arthritis. Only one trial included specific evaluation in 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 enthesitis 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 articular, enthesitis, 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, enthesitis-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.

Acknowledgements

We are grateful to MSD, Pfizer, and Janssen laboratories, who responded to our request for additional data.

This meta-analysis was carried out with the institutional support of Abbvie, which sponsored the original meetings to discuss this publication.

References

1. VILLANI AP, ROUZAUD M, SEVRAIN M *et al*.: Prevalence of undiagnosed psoriatic arthritis among psoriasis patients: Systematic review and meta-analysis. *J Am Acad Dermatol* 2015; 73: 242-8.
2. MICHELSEN B, FIANE R, DIAMANTOPOULOS AP *et al*.: A Comparison of Disease Burden in Rheumatoid Arthritis, Psoriatic Arthritis and Axial Spondyloarthritis. *PLoS One* 2015; 10: 1-11.
3. MCHUGH NJ, BALACHRISHNAN C, JONES SM: Progression of peripheral joint disease in psoriatic arthritis: a 5-yr prospective study. *Rheumatology* 2003; 42: 778-83.
4. GOSSEC L, SMOLEN JS, RAMIRO S *et al*.: European League Against Rheumatism (EULAR) recommendations for the management of psoriatic arthritis with pharmacological therapies: 2015 update. *Ann Rheum Dis* 2016; 75: 499-510.
5. COATES LC, KAVANAUGH A, MEASE PJ *et al*.: Group for Research and Assessment of Psoriasis and Psoriatic Arthritis 2015 Treatment Recommendations for Psoriatic Arthritis. *Arthritis Rheumatol* 2016; 68: 1060.
6. KAVANAUGH A, MEASE PJ, GOMEZ-REINO JJ *et al*.: Treatment of psoriatic arthritis in a phase 3 randomised, placebo-controlled trial with apremilast, an oral phosphodiesterase 4 inhibitor. *Ann Rheum Dis* 2014 ; 73: 1020-6.
7. RITCHLIN CT, COLBERT RA, GLADMAN DD: Psoriatic arthritis. *N Engl J Med* 2017; 376: 2095-6.
8. DEODHAR AA, GOTTLIEB AB, BOEHNCKE WH *et al*.: Efficacy and safety results of guselkumab in patients with active psoriatic arthritis over 56 weeks from a phase 2a, randomized, double-blind, placebo-controlled study [Abstract]. *Arthritis Rheumatol* 2017 ; 69 (Suppl 10).
9. MEASE PJ, GOTTLIEB AB, BERMAN A *et al*.: The efficacy and safety of clazakizumab, an anti-interleukin-6 monoclonal antibody, in a phase IIb study of adults with active psoriatic arthritis. *Arthritis Rheumatol* 2016; 68: 2163-73.
10. GLINTBORG B, ØSTERGAARD M, DREYER L *et al*.: Treatment response, drug survival, and predictors thereof in 764 patients with psoriatic arthritis treated with anti-tumor necrosis factor α therapy: Results from the nationwide Danish DANBIO registry. *Arthritis Rheum* 2011; 63: 382-90.
11. MOURAD A, GNIADECKI R: Treatment of dactylitis and enthesitis in psoriatic arthritis with biologic agents: a systematic review and metaanalysis. *J Rheumatol* 2019 Mar 1 [Epub ahead of print].
12. LEMOS LLP, COSTA J DE O, ALMEIDA AM *et al*.: Treatment of psoriatic arthritis with anti-TNF agents: a systematic review and meta-analysis of efficacy, effectiveness and safety. *Rheumatol Int* 2014; 34: 1345-60.
13. FÉNIX-CABALLERO S, ALEGRE-DEL REY EJ, CASTAÑO-LARA R, PUIGVENTÓS-LATORRE F, BORRERO-RUBIO JM, LÓPEZ-VALLEJO JF: Direct and indirect comparison of the efficacy and safety of adalimumab, etanercept, infliximab and golimumab in psoriatic arthritis. *J Clin Pharm Ther* 2013; 38: 286-93.
14. UNGPRASERT P, THONGPRAYOON C, DAVIS JM: Indirect comparisons of the efficacy of biological agents in patients with psoriatic arthritis with an inadequate response to traditional disease-modifying anti-rheumatic drugs or to non-steroidal anti-inflammatory drugs: A meta-analysis. *Semin Arthritis Rheum* 2016; 45: 428-38.
15. WU D, YUE J, TAM L-S: Efficacy and safety of biologics targeting interleukin-6, -12/23 and -17 pathways for peripheral psoriatic arthritis: a network meta-analysis. *Rheumatology* 2018; 57: 563-71.
16. BILAL J, RIAZ IB, KAMAL MU, ELYAN M, SUDANO D, KHAN MA: A systematic review and meta-analysis of efficacy and safety of novel interleukin inhibitors in the management of psoriatic arthritis. *J Clin Rheumatol* 2018; 24: 6-13.
17. KAWALEC P, HOLKO P, MOĆKO P, PILC A: Comparative effectiveness of abatacept, apremilast, secukinumab and ustekinumab treatment of psoriatic arthritis: a systematic review and network meta-analysis. *Rheumatol Int* 2018; 38: 189-201.
18. NAIK GS, MING WK, MAGODORO IM *et al*.: Th17 inhibitors in active psoriatic arthritis: a systematic review and meta-analysis of randomized controlled clinical trials. *Dermatology* 2017; 233: 366-77.
19. DRUYTS E, PALMER JB, BALIJEPALLI C *et al*.: Treatment modifying factors of biologics for psoriatic arthritis: a systematic review and Bayesian meta-regression. *Clin Exp Rheumatol* 2017; 35: 681-88.
20. MOHER D, SHAMSEER L, CLARKE M *et al*.: Preferred reporting items for systematic review and meta-analysis protocols (PRISMA-P) 2015 statement. *Syst Rev* 2015; 4: 1.
21. TAYLOR W, GLADMAN D, HELLIWELL P, MARCHESONI A, MEASE P, MIELANTS H: Classification criteria for psoriatic arthritis: Development of new criteria from a large international study. *Arthritis Rheum* 2006; 54: 2665-73.
22. HIGGINS JPT, ALTMAN DG, GØTZSCHE PC *et al*.: The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ* 2011; 343: d5928.
23. MEASE PJ, MCINNES IB, KIRKHAM B *et al*.: Secukinumab inhibition of interleukin-17A in patients with psoriatic arthritis. *N Engl J Med* 2015; 373: 1329-39.
24. MEASE PJ, GOFFE BS, METZ J, VANDERSTOEP A, FINCK B, BURGE DJ: Etanercept in the treatment of psoriatic arthritis and psoriasis: a randomised trial. *Lancet* 2000; 356: 85.
25. MEASE PJ, KIVITZ AJ, BURCH FX *et al*.: Etanercept treatment of psoriatic arthritis: safety, efficacy, and effect on disease progression. *Arthritis Rheum* 2004; 50: 2264-72.
26. ANTONI CE, KAVANAUGH A, KIRKHAM B *et al*.: Sustained benefits of infliximab therapy for dermatologic and articular manifestations of psoriatic arthritis: results from the infliximab multinational psoriatic arthritis controlled trial (IMPACT). *Arthritis Rheum* 2005; 52: 1227-36.
27. ANTONI C, KRUEGER GG, DE VLAM K *et al*.: Infliximab improves signs and symptoms of psoriatic arthritis: results of the IMPACT 2 trial. *Ann Rheum Dis* 2005; 64: 1150-57.
28. MEASE PJ, GLADMAN DD, RITCHLIN CT *et al*.: Adalimumab for the treatment of patients with moderately to severely active psoriatic arthritis: results of a double-blind, randomized, placebo-controlled trial. *Arthritis Rheum* 2005; 52: 3279-89.
29. GENOVESE MC, MEASE PJ, THOMSON GTD *et al*.: Safety and efficacy of adalimumab in treatment of patients with psoriatic arthritis who had failed disease modifying antirheumatic drug therapy. *J Rheumatol* 2007; 34: 1040-50.
30. MEASE PJ, HALL S, FITZGERALD O *et al*.: Efficacy and safety of tofacitinib, an oral janus kinase inhibitor, or adalimumab in patients with active psoriatic arthritis and an inadequate response to conventional synthetic disease-modifying antirheumatic drugs (CSDMARDS): a randomised, placebo-controlled, phase 3 trial. *Ann Rheum Dis* 2017; 76 (Suppl. 2): 141-42.
31. KAVANAUGH A, MCINNES I, MEASE P *et al*.: Golimumab, a new human tumor necrosis factor alpha antibody, administered every four weeks as a subcutaneous injection in psoriatic arthritis: Twenty-four-week efficacy and safety results of a randomized, placebo-controlled study. *Arthritis Rheum* 2009; 60: 976-86.
32. KAVANAUGH A, HUSNI ME, HARRISON DD *et al*.: Safety and efficacy of intravenous golimumab in patients with active psoriatic arthritis. *Arthritis Rheumatol* 2017; 69: 2151-61.
33. MEASE PJ, FLEISCHMANN R, DEODHAR AA *et al*.: Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Ann Rheum Dis* 2014; 73: 48-55.
34. MCINNES IB, KAVANAUGH A, GOTTLIEB AB *et al*.: Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. *Lancet* 2013; 382: 780-9.
35. RITCHLIN C, RAHMAN P, KAVANAUGH A *et al*.: Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. *Ann Rheum Dis* 2014; 73: 990-9.
36. MCINNES IB, MEASE PJ, KIRKHAM B *et al*.: Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. *Lancet* 2015; 386: 1137-46.

37. MEASE PJ, HEIJDE D VAN DER, RITCHLIN CT *et al*.: Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. *Ann Rheum Dis* 2017; 76: 79-87.
38. NASH P, KIRKHAM B, OKADA M *et al*.: Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. *Lancet* 2017; 389: 2317-27.
39. MEASE PJ, GOTTLIEB AB, VAN DER HEIJDE D *et al*.: Efficacy and safety of abatacept, a T-cell modulator, in a randomised, double-blind, placebo-controlled, phase III study in psoriatic arthritis. *Ann Rheum Dis* 2017; 76: 1550-8.
40. GOTTLIEB A, MENTER A, MENDELSOHN A *et al*.: Ustekinumab, a human interleukin 12/23 monoclonal antibody, for psoriatic arthritis: randomised, double-blind, placebo-controlled, crossover trial. *Lancet* 2009; 373: 633-40.
41. MEASE P, GENOVESE MC, GLADSTEIN G *et al*.: Abatacept in the treatment of patients with psoriatic arthritis: results of a six-month, multicenter, randomized, double-blind, placebo-controlled, phase II trial. *Arthritis Rheum* 2011; 63: 939-48.
42. MCINNES IB, SIEPER J, BRAUN J *et al*.: Efficacy and safety of secukinumab, a fully human anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriatic arthritis: a 24-week, randomised, double-blind, placebo-controlled, phase II proof-of-concept trial. *Ann Rheum Dis* 2014; 73: 349-56.
43. MEASE PJ, FLEISCHMANN R, DEODHAR AA *et al*.: Effect of certolizumab pegol on signs and symptoms in patients with psoriatic arthritis: 24-week results of a Phase 3 double-blind randomised placebo-controlled study (RAPID-PsA). *Ann Rheum Dis* 2014; 73: 48-55.
44. LOOS AM, LIU S, SEGEL C, OLLENDORF DA, PEARSON SD, LINDER JA: Comparative effectiveness of targeted immunomodulators for the treatment of moderate-to-severe plaque psoriasis: A systematic review and network meta-analysis. *J Am Acad Dermatol* 2018; 79: 135-144.e7.
45. SIGNOROVITCH JE, BETTS KA, YAN YS *et al*.: Comparative efficacy of biological treatments for moderate-to-severe psoriasis: a network meta-analysis adjusting for cross-trial differences in reference arm response. *Br J Dermatol* 2015; 172: 504-12.
46. GRIFFITHS CEM, STROBER BE, VAN DE KERKHOF P *et al*.: Comparison of ustekinumab and etanercept for moderate-to-severe psoriasis. *N Engl J Med* 2010; 362: 118-28.
47. LANGLEY RG, ELEWSKI BE, LEBWOHL M *et al*.: Secukinumab in plaque psoriasis--results of two phase 3 trials. *N Engl J Med* 2014; 371: 326-38.
48. GRIFFITHS CEM, REICH K, LEBWOHL M *et al*.: Comparison of ixekizumab with etanercept or placebo in moderate-to-severe psoriasis (UNCOVER-2 and UNCOVER-3): results from two phase 3 randomised trials. *Lancet* 2015; 386: 541-51.
49. REICH K, PINTER A, LACOUR JP *et al*.: Comparison of ixekizumab with ustekinumab in moderate-to-severe psoriasis: 24-week results from IXORA-S, a phase III study. *Br J Dermatol* 2017; 177: 1014-23.
50. THACI D, MORITA A, BIRT J, LIN C-Y, SHULER CL, GOTTLIEB AB: Association of early skin improvement with ACR responses among biologic DMARD-naive psoriatic arthritic patients treated with Ixekizumab. *Arthritis Rheumatol* 2016; 68: 2106-8.
51. THORLUND K, DRUYTS E, AVIÑA-ZUBIETA JA, MILLS EJ: Anti-tumor necrosis factor (TNF) drugs for the treatment of psoriatic arthritis: an indirect comparison meta-analysis. *Biol Targets Ther* 2012; 6: 417-27.