

## ORIGINAL RESEARCH

## Targeted systemic therapies for psoriatic arthritis: a systematic review and comparative synthesis of short-term articular, dermatological, enthesitis and dactylitis outcomes

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## ABSTRACT

**Introduction** Randomised controlled trials (RCTs) have compared biological and targeted systemic disease-modifying antirheumatic drugs (DMARDs) against placebo in psoriatic arthritis (PsA); few have compared them head to head.

**Objectives** To compare the efficacy and safety of all evaluated DMARDs for active PsA, with a special focus on biological DMARDs (bDMARDs) licensed for PsA or psoriasis.

**Methods** A systematic review identified RCTs and Bayesian network meta-analysis (NMA) compared treatments on efficacy (American College of Rheumatology (ACR) response, Psoriasis Area and Severity Index (PASI) response, resolution of enthesitis and dactylitis) and safety (patients discontinuing due to adverse events (DAE)) outcomes. Subgroup analyses explored ACR response among patients with and without prior biological therapy exposure.

**Results** The NMA included 46 studies. Results indicate that some tumour necrosis factor inhibitors (anti-TNFs) may perform numerically, but not significantly, better than interleukin (IL) inhibitors on ACR response but perform worse on PASI response. Few significant differences between bDMARDs on ACR response were observed after subgrouping for prior bDMARD exposure. Guselkumab and IL-17A or IL-17RA inhibitors—brodalumab, ixekizumab, secukinumab—were best on PASI response. These IL-inhibitors and adalimumab were similarly efficacious on resolution of enthesitis and dactylitis. Infliximab with and without methotrexate, certolizumab 400 mg every 4 weeks and tildrakizumab showed the highest rates of DAE; abatacept, golimumab and the IL-inhibitors, the lowest.

**Conclusions** Despite similar efficacy for ACR response, IL-17A and IL-17RA inhibitors and guselkumab offered preferential efficacy to anti-TNFs in skin manifestations, and for enthesitis and dactylitis, thereby supporting drug selection based on predominant clinical phenotype.

## INTRODUCTION

Psoriatic arthritis (PsA) is a chronic inflammatory disease associated with psoriasis (PsO).<sup>1</sup> Up to 30% of patients with PsO may

## Key messages

## What is already known about this subject?

► Increasingly, choice of psoriatic arthritis (PsA) treatments are being tailored based on a patient's exposure to prior therapies, disease severity, comorbidities and individual manifestations of disease, including enthesitis, dactylitis and axial disease.

## What does this study add?

► This is a contemporary and comprehensive analysis of the efficacy and safety of systemic therapies for moderate to severe active PsA, with a focus on biological disease-modifying anti-rheumatic drugs licensed in PsA or psoriasis.  
► In addition to American College of Rheumatology and Psoriasis Area and Severity Index responses, we report resolution of enthesitis and dactylitis, both highly relevant and for which comparative evidence is limited.

## How might this impact on clinical practice or further developments?

► Faced with a multitude of therapeutic options, these study results could help clinicians tailor treatment choice according to different domains of disease and provides additional evidence for developing patient-centred treatment guidelines.

go on to develop PsA during their lifetime.<sup>2</sup> Annual incidence rates of PsA are estimated at approximately six per 100 000 (0.006%) in the general population, and in those with PsO, 2.7%. Affecting males and females equally, the majority of patients with PsA develop skin symptoms first, some develop skin and joint symptoms at the same time and in 10%–15% of patients, joint symptoms develop first.<sup>1</sup> PsA is a heterogeneous condition characterised by sore, painful

and stiff joints, involving both articular and dermatological manifestations.<sup>3,4</sup> Due to the different patterns of involvement, PsA can mimic different inflammatory arthritides.<sup>5</sup> Delayed diagnosis has been identified as a contributor to poorer quality of life and disease outcomes in the long term.<sup>6</sup>

Traditionally PsA was treated with non-steroidal anti-inflammatory drugs, corticosteroids and conventional systemic disease-modifying antirheumatic drugs (csDMARDs).<sup>2,7</sup> Therapy for PsA has advanced, with an improved understanding of the immunological processes underlying the pathogenesis of disease and the introduction of biological treatment (biological DMARDs, bDMARDs). Antitumour necrosis factor (TNF) agents have been shown to be successful in treating PsA across different domains of the disease.<sup>8</sup> Newer biological agents approved by the European Medicine Agency or the US Food and Drug Administration, or both, for the treatment of PsA include the interleukin (IL)-12/IL-23 inhibitor ustekinumab,<sup>9</sup> IL-17A inhibitors secukinumab<sup>10</sup> and ixekizumab,<sup>11</sup> IL-23 inhibitor guselkumab<sup>12</sup> and the selective T-cell costimulation modulator abatacept,<sup>13</sup> as well as non-biological treatments such as phosphodiesterase 4 inhibitor apremilast<sup>14</sup> and the Janus kinase (JAK) inhibitors tofacitinib<sup>15</sup> and upadacitinib.<sup>16</sup> Interleukin-23 inhibitors tildrakizumab and risankizumab, and IL-17RA inhibitor brodalumab, all currently licensed for the treatment of PsO, have been evaluated in the treatment of PsA and shown to be efficacious<sup>8,17–25</sup> as has the new JAK inhibitor filgotinib.<sup>26</sup>

Active PsA as defined by the American College of Rheumatology (ACR) and National Psoriasis Foundation (NPF), is disease causing symptoms at an unacceptably bothersome level as reported by the patient, and judged by the examining clinician to be due to PsA based on  $\geq 1$  of the following: swollen joints, tender joints, dactylitis, enthesitis, axial disease, active skin and/or nail involvement, and extraarticular inflammatory manifestations such as uveitis or inflammatory bowel disease.<sup>1</sup> Current pharmacological therapy options for treating long-term active PsA vary depending on prior treatments, disease severity and comorbidities. General recommendations involve treating with anti TNF agents first, followed by IL-17A and IL-12/23 inhibitor therapies. Oral small molecule therapies apremilast and tofacitinib may also be recommended. More recently, the ACR/NPF, EULAR and GRAPPA guidelines have put greater emphasis on tailoring treatments based on the individual manifestations of PsA, including enthesitis, dactylitis and axial disease, recognising that the efficacy of bDMARDs may vary across these different domains based on their mode of action.<sup>1,7,27</sup>

The aim of this systematic literature review (SLR) and network meta-analysis (NMA) was to identify the latest evidence and compare the efficacy and safety of all evaluated systemic therapies for the treatment of active PsA.

## MATERIALS AND METHODS

### Search strategy

An initial search was performed on 11 March 2020 and updated on 18 August 2020 in Embase, MEDLINE, MEDLINE In-Process via Ovid and the Cochrane Library (online supplemental table S1). These were supplemented by searching conference abstracts and clinical trial databases for ongoing or recently completed studies (online supplemental table S2). In addition, reference lists of included studies and any relevant SLRs or NMAs identified during the screening were searched to identify further studies.

### Study selection

Titles and abstracts were assessed for inclusion by one reviewer, with another reviewer performing a 40% check. Full-text articles were fully assessed by two independent reviewers. Randomised controlled trials (RCTs) in patients who were at least 16 years old with active PsA, with  $\geq 50$  patients randomised to at least one trial arm, were included in the review. Interventions of interest were limited to abatacept, apremilast, adalimumab, bimekizumab, brodalumab, certolizumab pegol, etanercept, filgotinib, golimumab, guselkumab, infliximab, ixekizumab, netakimab, risankizumab, secukinumab, tildrakizumab, tofacitinib, upadacitinib and ustekinumab. Treatments could be reported as monotherapy or in combination with another systemic therapy. Only articles published in English were considered eligible. A full set of inclusion and exclusion criteria can be found in online supplemental table S3.

### Data extraction and quality assessment

Details of the study design, baseline patient characteristics, interventions, outcomes and results were extracted by one reviewer and quality checked by another. The methodological quality of included studies was assessed by one reviewer using the Cochrane Risk of Bias tool<sup>28</sup> and checked by a second reviewer.

To reduce the risk of statistical heterogeneity in our analysis, we assessed clinical heterogeneity in our evidence by closely examining variability in the participants, interventions and outcomes studied. We also assessed methodological heterogeneity by looking for variability in study design and risk of bias. The aim of these assessments was to identify imbalances between trials in potential treatment effect modifiers and use this information to inform the statistical analysis plan.

### Network meta-analysis

Using recommended methods for evidence synthesis,<sup>29</sup> a Bayesian NMA compared the relative efficacy and safety of licensed and unlicensed systemic therapies for the treatment of active PsA. Efficacy endpoints included ACR response rates (ACR20, ACR50 and ACR70), Psoriasis Area and Severity Index (PASI) response rates (PASI75 and PASI90), and the resolution of enthesitis and dactylitis (measured by any scale that represents resolution with

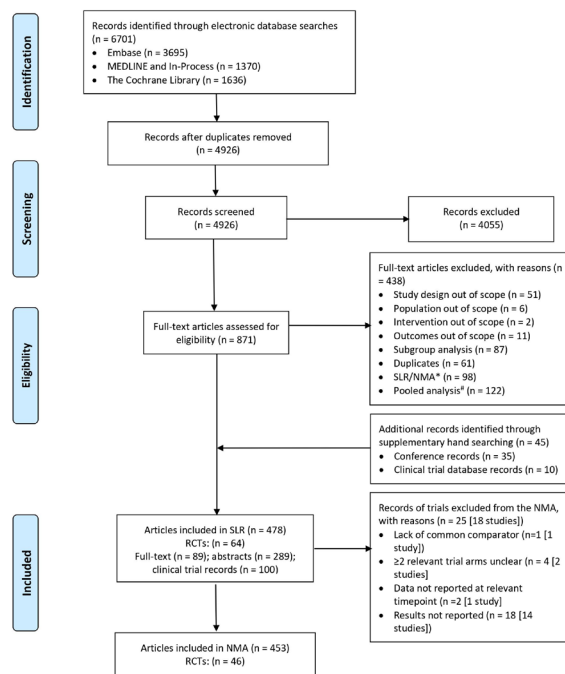
a score of zero); safety end points included the proportion patients discontinuing due to adverse events (DAE). Relative efficacy for all endpoints was based on results reported at 12–16 weeks, where available, or up to 26 weeks if the earlier time point was unavailable. Safety outcomes were evaluated at study endpoint. All outcomes were assessed in the overall population regardless of prior bDMARD exposure, while ACR response rates were also explored in bDMARD-naïve and bDMARD-experienced subgroups.

ACR and PASI responses were analysed using a multinomial likelihood model with a probit link. Resolution of enthesitis and dactylitis, and DAE were analysed using a binomial likelihood model with a logit link. Both random-effects and fixed-effects models were run, and the goodness of fit was assessed using the deviance information criterion. For efficacy outcomes, network meta-regressions to control for cross-trial variation in placebo-arm responses were also carried out on the model with the best fit.<sup>30</sup> Adjusted and unadjusted models were then compared for fit, informed by the statistical significance of the regression coefficient. The model with the best fit was used to draw conclusions.

Inconsistency between direct and indirect estimates of effect was assessed for any loops in the evidence the network using the two-stage Bucher method.<sup>31 32</sup> Across the networks for all outcomes, there were up to four closed loops, made up of placebo, adalimumab and either ixekizumab, secukinumab, tofacitinib or upadacitinib. No evidence of inconsistency was found.

WinBUGS V.1.4<sup>33</sup> was used to perform all statistical analyses, using non-informative priors. After an initial burn-in of at least 20 000 simulations, convergence was confirmed through visual inspection the Brook-Gelman-Rubin diagnostic and history plots. Sampled parameters were then estimated using 50 000 simulations on three chains. Results were calculated as the absolute probabilities of response for each treatment and as treatment effects for each pairwise comparison vs placebo for each endpoint. Point estimates reflecting the median value are presented, along with 95% credible intervals (95% CrI), reflecting the range of true effects with 95% probability. For results presented on a scale that requires a baseline for calculation, a meta-analysis estimate of the placebo arm effect across the placebo-controlled trials was used.<sup>34</sup> Significance between comparators was determined from the 95% CrI of the treatment effect. Where it excludes the line of null effect, we can describe the difference as statistically significant.

Results for key comparators—biological therapies at doses licensed for use in PsO or PsA—are presented below. Results for all comparators, including conventional and targeted oral systemic and unlicensed biological therapies or unlicensed doses of licensed biological therapies) are presented in online supplemental file 1 along with pairwise comparisons between key comparators and selected systemic therapies.



**Figure 1** PRISMA flow diagram. NMA, network meta-analysis; PRISMA, Preferred Reporting Items for Systematic Reviews and Meta-Analyses; RCTs, randomised controlled trial; SLR, systematic literature review.

\* Bibliographies of eligible SLR/ NMAs were reviewed to identify any RCTs that met the inclusion criteria and then excluded. # Bibliographies of eligible pooled analyses were reviewed to identify relevant RCTs that met the inclusion criteria and included only if data were not reported in the individual RCTs.

## RESULTS

### Identification of trials

Electronic database searches identified 6701 articles. After deduplication, 4926 titles and abstracts were screened for inclusion and a subsequent 871 publication assessed for their eligibility. A further 45 articles were identified and included through searching conferences and clinical trial databases. A total of 64 RCTs reported in 478 articles were included in the SLR. Seventeen trials were not included in the NMA either because they did not report results or did not report them at a time point of interest or because the dosing regimen during the randomised treatment phase was unclear. One further trial was considered for the NMA, but due to a lack of common comparator with other studies in the network it could not be included.<sup>35</sup> Data from 46 unique RCTs were included in at least one NMA. Details are shown in figure 1.

### Network meta-analysis

#### Study and patient characteristics

Key details of trials included in the NMA are summarised in table 1. Further details of baseline and patient

**Table 1** Studies included in the NMA

| Study                       | Treatment arms                          | No. patients (N) | Timepoint (weeks) | Outcomes included in NMA                       |
|-----------------------------|---|------------------|-------------------|--|
| ASTRAEA <sup>24</sup>       | Placebo                                 | 211              | 16                | ACR-20, 50, 70; PASI 75*; EnthR*; DactR*; DAE  |
|                             | Abatacept 125 mg                        | 213              |                   |  |
| ADEPT <sup>70</sup>         | Placebo                                 | 162              | 12                | ACR-20, 50, 70; PASI-75, 90; DAE               |
|                             | Adalimumab 40 mg                        | 153              |                   |  |
| Genovese 2007 <sup>71</sup> | Placebo                                 | 51               | 12                | ACR-20, 50, 70; DAE                            |
|                             | Adalimumab 40 mg                        | 51               |                   |  |
| Mease 2018 <sup>61</sup>    | Placebo                                 | 24               | 12                | ACR-20, 50, 70; PASI-75; 90; DAE               |
|                             | Adalimumab 40 mg                        | 72               |                   |  |
|                             | Remtolumab 120 mg                       | 71               |                   |  |
|                             | Remtolumab 240 mg                       | 73               |                   |  |
| ACTIVE <sup>62</sup>        | Placebo                                 | 109              | 16                | ACR-20, 50, 70; DAE                            |
|                             | Apremilast 30 mg twice daily            | 110              |                   |  |
| Schett 2012 <sup>36</sup>   | Placebo                                 | 68               | 12                | ACR-20, 50, 70; DAE                            |
|                             | Apremilast 20 mg twice daily            | 69               |                   |  |
|                             | Apremilast 40 mg once daily             | 67               |                   |  |
| PALACE 1 <sup>37</sup>      | Placebo                                 | 168              | 16                | ACR-20, 50, 70; PASI 75*; EnthR; DactR; DAE    |
|                             | Apremilast 20 mg twice daily            | 168              |                   |  |
|                             | Apremilast 30 mg twice daily            | 168              |                   |  |
| PALACE 2 <sup>38</sup>      | Placebo                                 | 159              | 16                | ACR-20, 50, 70; PASI 75; EnthR; DactR; DAE     |
|                             | Apremilast 20 mg twice daily            | 163              |                   |  |
|                             | Apremilast 30 mg twice daily            | 162              |                   |  |
| PALACE 3 <sup>39</sup>      | Placebo                                 | 169              | 16                | ACR-20, 50, 70; PASI 75; EnthR; DactR; DAE     |
|                             | Apremilast 20 mg twice daily            | 169              |                   |  |
|                             | Apremilast 30 mg twice daily            | 167              |                   |  |
| Mease 2014 <sup>22</sup>    | Placebo                                 | 55               | 12                | ACR-20, 50, 70; DAE                            |
|                             | Brodalumab 140 mg                       | 57               |                   |  |
|                             | Brodalumab 280 mg                       | 56               |                   |  |
| AMVISION 1 <sup>23</sup>    | Placebo                                 | 161              | 16                | ACR-20, 50, 70; PASI-75, 90; EnthR; DactR; DAE |
|                             | Brodalumab 140 mg                       | 158              |                   |  |
|                             | Brodalumab 210 mg                       | 159              |                   |  |
| AMVISION 2 <sup>23</sup>    | Placebo                                 | 161              | 16                | ACR-20, 50, 70; PASI-75, 90; EnthR; DactR; DAE |
|                             | Brodalumab 140 mg                       | 160              |                   |  |
|                             | Brodalumab 210 mg                       | 163              |                   |  |
| RAPID-PsA <sup>40</sup>     | Placebo                                 | 136              | 12                | ACR-20, 50, 70; PASI-75, 90; DAE               |
|                             | Certolizumab 200 mg every two weeks     | 138              |                   |  |
|                             | Certolizumab 400 mg every four weeks    | 135              |                   |  |
| Mease 2004 <sup>72</sup>    | Placebo                                 | 104              | 12                | ACR-20, 50, 70; PASI 75*; DAE                  |
|                             | Etanercept 25 mg twice weekly           | 101              |                   |  |
| PRESTA <sup>63</sup>        | Etanercept 50 mg once weekly            | 373              | 12                | ACR-20, 50, 70; PASI 75*; DAE                  |
|                             | Etanercept 50 mg twice weekly           | 379              |                   |  |
| SEAM-PsA <sup>66</sup>      | Placebo +MTX 20 mg once weekly          | 284              | 16                | ACR-20, 50, 70; DAE                            |
|                             | Placebo +Etanercept 50 mg once weekly   | 284              |                   |  |
|                             | Etanercept 50 mg +MTX 20 mg once weekly | 283              |                   |  |

Continued



**Table 1** Continued

| Study                      | Treatment arms                      | No. patients (N) | Timepoint (weeks) | Outcomes included in NMA                          |
|----------------------------|-------------------------------------|------------------|-------------------|---|
| EQUATOR <sup>26</sup>      | Placebo                             | 66               | 16                | ACR-20, 50, 70; PASI 75; EnthR; DactR; DAE        |
|                            | Filgotinib 200 mg                   | 65               |                   |   |
| GO-REVEAL <sup>41</sup>    | Placebo                             | 113              | 14                | ACR-20, 50, 70; PASI-75, 90; DAE                  |
|                            | Golimumab 50 mg                     | 146              |                   |   |
|                            | Golimumab 100 mg                    | 146              |                   |   |
| GO-VIBRANT <sup>42</sup>   | Placebo                             | 239              | 14                | ACR-20, 50, 70; PASI-75, 90; DAE                  |
|                            | Golimumab 2 mg/kg                   | 241              |                   |   |
| GO-DACT <sup>64</sup>      | Placebo +MTX 15–25 mg               | 23               | 12                | DactR   |
|                            | Golimumab 50 mg +MTX 15–25 mg       | 21               |                   |   |
| DISCOVER 1 <sup>17</sup>   | Placebo                             | 126              | 16                | ACR-20, 50, 70; PASI*-75, 90; EnthR*, DactR*; DAE |
|                            | Guselkumab 100 mg every eight weeks | 128              |                   |   |
|                            | Guselkumab 100 mg every four weeks  | 128              |                   |   |
| DISCOVER 2 <sup>18</sup>   | Placebo                             | 247              | 16                | ACR-20, 50, 70; PASI*-75, 90; EnthR*; DactR*; DAE |
|                            | Guselkumab 100 mg every eight weeks | 248              |                   |   |
|                            | Guselkumab 100 mg every four weeks  | 246              |                   |   |
| Deodhar 2018 <sup>19</sup> | Placebo                             | 49               | 16                | ACR-20, 50, 70; PASI*-75, 90; EnthR*; DactR*; DAE |
|                            | Guselkumab 100 mg every eight weeks | 100              |                   |   |
| IMPACT <sup>43</sup>       | Placebo                             | 52               | 16                | ACR-20, 50, 70; PASI-75, 90; DAE                  |
|                            | Infliximab 5 mg/kg                  | 52               |                   |   |
| IMPACT 2 <sup>44</sup>     | Placebo                             | 100              | 14                | ACR-20, 50, 70; PASI-75, 90; DAE                  |
|                            | Infliximab 5 mg/kg                  | 100              |                   |   |
| RESPOND <sup>65</sup>      | Infliximab 5 mg/kg+MTX 15 mg        | 57               | 16                | ACR-20, 50, 70; PASI-75, 90; DAE                  |
|                            | MTX 15 mg                           | 58               |                   |   |
| SPIRIT H2H <sup>45</sup>   | Adalimumab 40 mg                    | 283              | 16                | ACR-50; PASI*-75, 90; EnthR*; DactR*; DAE         |
|                            | Ixekizumab 80 mg                    | 283              |                   |   |
| SPIRIT P1 <sup>46</sup>    | Placebo                             | 106              | 12                | ACR-20, 50, 70; PASI-75, 90; EnthR†; DactR†; DAE  |
|                            | Adalimumab 40 mg                    | 101              |                   |   |
|                            | Ixekizumab 80 mg every four weeks   | 107              |                   |   |
|                            | Ixekizumab 80 mg every two weeks    | 103              |                   |   |
| SPIRIT P2 <sup>47</sup>    | Placebo                             | 118              | 12                | ACR†-20, 50, 70; PASI-75, 90; EnthR; DactR; DAE   |
|                            | Ixekizumab 80 mg every four weeks   | 122              |                   |   |
|                            | Ixekizumab 80 mg every two weeks    | 123              |                   |   |
| PATERA <sup>48</sup>       | Placebo                             | 97               | 24                | ACR-20, 50, 70                                    |
|                            | Netakimab 120 mg                    | 97               |                   |   |
| CHOICE <sup>49</sup>       | Placebo                             | 52               | 16                | ACR-20, 50, 70; PASI-75, 90; EnthR; DactR; DAE    |
|                            | Secukinumab 150 mg                  | 103              |                   |   |
|                            | Secukinumab 300 mg                  | 103              |                   |   |
| FUTURE 1 <sup>50</sup>     | Placebo                             | 202              | 16                | ACR-20, 50, 70; PASI*-75, 90; EnthR*; DactR*; DAE |
|                            | Secukinumab 75 mg (IV LD)           | 202              |                   |   |
|                            | Secukinumab 150 mg (IV LD)          | 202              |                   |   |

Continued

Table 1 Continued

| Study                       | Treatment arms                | No. patients (N) | Timepoint (weeks) | Outcomes included in NMA  |
|-----------------------------|-------------------------------|------------------|-------------------|---|
| FUTURE 2 <sup>51</sup>      | Placebo                       | 98               | 16                | ACR-20, 50, 70; PASI*-75, 90; EnthR*; DactR*; DAE                       |
|                             | Secukinumab 75 mg (SC LD)     | 99               |                   |   |
|                             | Secukinumab 150 mg            | 100              |                   |   |
|                             | Secukinumab 300 mg            | 100              |                   |   |
| FUTURE 3 <sup>67</sup>      | Placebo                       | 137              | 16                | ACR-20, 50; PASI*-75, 90; EnthR*; DactR*; DAE                           |
|                             | Secukinumab 150 mg            | 138              |                   |   |
|                             | Secukinumab 300 mg            | 139              |                   |   |
| FUTURE 4 <sup>68</sup>      | Placebo                       | 114              | 16                | ACR-20, 50, 70; PASI-75, 90; EnthR; DactR                               |
|                             | Secukinumab 150 mg (no LD)    | 113              |                   |   |
|                             | Secukinumab 150 mg            | 114              |                   |   |
| FUTURE 5 <sup>52</sup>      | Placebo                       | 332              | 16                | ACR-20, 50, 70; PASI-75, 90; EnthR; DactR; DAE                          |
|                             | Secukinumab 150 mg (no LD)    | 222              |                   |   |
|                             | Secukinumab 150 mg            | 220              |                   |   |
|                             | Secukinumab 300 mg            | 222              |                   |   |
| EXCEED <sup>53</sup>        | Adalimumab 40 mg              | 427              | 16                | ACR-20, 50, 70; PASI-75, 90; EnthR; DactR; DAE                          |
|                             | Secukinumab 300 mg            | 426              |                   |   |
| MAXIMISE <sup>69</sup>      | Placebo                       | 166              | 12                | ACR 20  |
|                             | Secukinumab 150 mg            | 165              |                   |   |
|                             | Secukinumab 300 mg            | 167              |                   |   |
| Gottlieb 2019 <sup>20</sup> | Placebo                       | 79               | 16                | ACR-20, 50, 70; PASI-75, 90; DAE  |
|                             | Tildrakizumab 20 mg           | 78               |                   |   |
|                             | Tildrakizumab 100 mg          | 77               |                   |   |
|                             | Tildrakizumab 200 mg          | 79               |                   |   |
| Opal Beyond <sup>54</sup>   | Placebo                       | 131              | 13                | ACR-20, 50, 70; PASI 75; EnthR; DactR; DAE                              |
|                             | Tofacitinib 5 mg twice daily  | 131              |                   |   |
|                             | Tofacitinib 10 mg twice daily | 132              |                   |   |
| Opal Broaden <sup>55</sup>  | Placebo                       | 105              | 13                | ACR-20, 50, 70; PASI 75; EnthR; DactR; DAE                              |
|                             | Adalimumab 40 mg              | 106              |                   |   |
|                             | Tofacitinib 5 mg twice daily  | 107              |                   |   |
|                             | Tofacitinib 10 mg twice daily | 104              |                   |   |
| SELECT-PsA 1 <sup>56</sup>  | Placebo                       | 423              | 16                | ACR±-20, 50, 70; PASI 75; EnthR <sup>1</sup> ; DactR <sup>1</sup> ; DAE |
|                             | Upadacitinib 15 mg once daily | 429              |                   |   |
|                             | Upadacitinib 30 mg once daily | 423              |                   |   |
|                             | Adalimumab 40 mg              | 429              |                   |   |
| SELECT-PsA 2 <sup>57</sup>  | Placebo                       | 212              | 16                | ACR±-20, 50, 70; PASI 75; EnthR; DactR; DAE                             |
|                             | Upadacitinib 15 mg once daily | 211              |                   |   |
|                             | Upadacitinib 30 mg once daily | 218              |                   |   |
| Gottlieb 2009 <sup>58</sup> | Placebo                       | 70               | 12                | ACR-20, 50, 70; PASI-75, 90; DAE  |
|                             | Ustekinumab 90 mg             | 76               |                   |   |
| PSUMMIT 1 <sup>59</sup>     | Placebo                       | 206              | 16                | ACR-20; PASI 75*; EnthR*; DactR*; DAE                                   |
|                             | Ustekinumab 45 mg             | 205              |                   |   |
|                             | Ustekinumab 90 mg             | 204              |                   |   |
| PSUMMIT 2 <sup>60</sup>     | Placebo                       | 104              | 16                | ACR-20; PASI 75*; EnthR*; DactR*; DAE                                   |
|                             | Ustekinumab 45 mg             | 103              |                   |   |
|                             | Ustekinumab 90 mg             | 105              |                   |   |

Continued

**Table 1** Continued

| Study | Treatment arms | No. patients (N) | Timepoint (weeks) | Outcomes included in NMA |
|-------|----------------|------------------|-------------------|--------------------------|
|-------|----------------|------------------|-------------------|--------------------------|

\*Data reported at week 24.

†Data reported at week 16.

‡Data reported at week 12.

ACR, American College of Rheumatology; DactR, resolution of dactylitis; DAE, withdrawal due to adverse events; EnthR, resolution of enthesitis; IV, intravenous; LD, loading dose; MTX, methotrexate; NMA, network meta-analysis; PASI, Psoriasis Area and Severity Index; SC, subcutaneous.

characteristics from studies included in the NMA are provided in online supplemental table S4.

Patient eligibility criteria across the included studies were largely consistent. Thirty-eight trials required patients to have been diagnosed with PsA for a minimum of 3 months,<sup>17–20 22 23 26 36–65</sup> and 36 trials used CASPAR as PsA diagnostic criteria.<sup>17–20 22 24 26 35 37–40 42 45–57 60–62 64 66–69</sup> All trials except for GO-DACT<sup>64</sup> and MAXIMISE<sup>69</sup> reported the number of swollen and tender joints required at baseline.

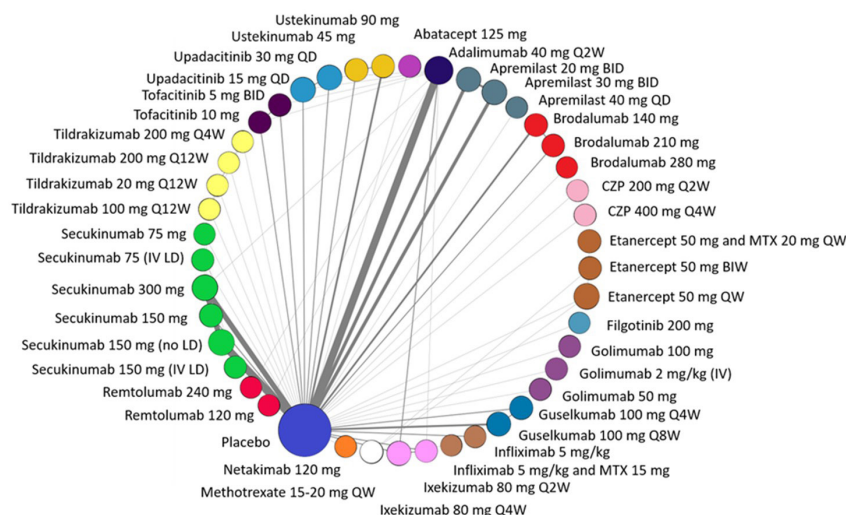
Patients mean age at baseline was reasonably consistent across the included studies, ranging from 41.2<sup>65</sup> to 53.4 years.<sup>57</sup> More variable characteristics were the duration of PsA (ranging from 3.2<sup>66</sup> to 11.4 years),<sup>43</sup> and the percentage of females (ranging from 37.1%<sup>63</sup> and 64.6%<sup>22</sup>). The number of patients with prior exposure to biological therapies varied across trials from 100% exposure in three trials,<sup>47 54 57</sup> to no exposure in twenty.<sup>18 35 41–46 49 53 59 62–66 69–72</sup> Twenty further RCTs reported the percentage of patients previously exposed to biologics, ranging from 3.2%<sup>55</sup> to 61.1%.<sup>24</sup> Ten trials included 100% of patients with prior exposure to csDMARDs.<sup>24 26 35 43 45 47 53 55 56 71</sup> Twelve further RCTs reported the percentage of patients previously exposed to csDMARDs, ranging from 13.1%<sup>66</sup> to 88.1%.<sup>19</sup>

A summary of the risk of bias of included studies, as measured by the Cochrane risk of bias tool, is presented in online supplemental figures S1 and S2. Statistics used to assess goodness of model fit for each network of evidence are presented in online supplemental table S5.

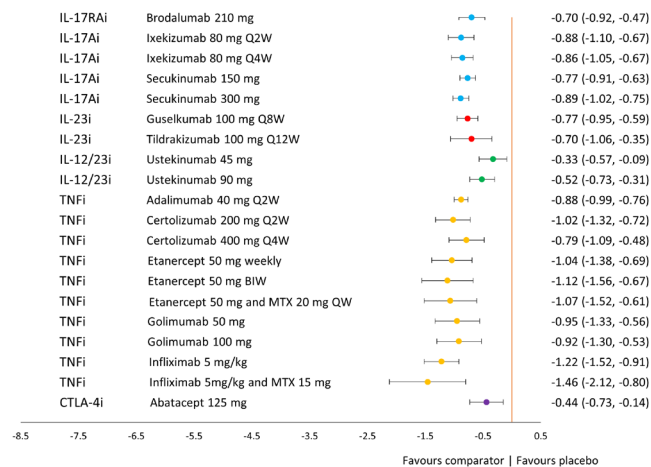
### ACR response

The ACR network for the overall population is presented in figure 2 and included 45 studies<sup>17–20 22–24 26 36–47 49–62 65–68 70 71</sup> of 19 treatments broken down across 44 unique treatment regimens. Figures for the evidence networks broken down by bDMARD-exposure subgroup are presented in online supplemental figures S3 and S4.

Figure 3 presents the ACR treatment effects of each key comparator vs placebo on the probit scale, where 0 represents no difference and negative values indicate higher response rates associated with treatment. All key comparators were more efficacious than placebo. Infliximab 5 mg in combination with or without methotrexate showed the greatest effect, followed by all regimens of etanercept: 50 mg QW, 50 mg two times in a week and 50 mg in combination with methotrexate. The poorest performing licensed biological therapies were ustekinumab (45 mg and 90 mg) and abatacept, which tended to be significantly less effective than TNFi therapies and



**Figure 2** Network diagram for ACR response note that the node size denotes total number of patients randomised to that treatment; edge line thickness denotes total number of studies informing that comparison. ACR, American College of Rheumatology; BID, twice daily; BIW, twice weekly; IV, intravenous; LD, loading dose; MTX, methotrexate; QD, once daily; QW, weekly; Q2W, every two weeks; Q4W, every four weeks; Q8W, every eight weeks; Q12W, every twelve weeks.



**Figure 3** Forest plot of treatment effects for key comparators versus placebo on ACR response. ACR overall treatment effect was based on a random-effects model with placebo adjustment. Median treatment effects and 95% credible intervals are plotted on the probit scale. Key comparators include bDMARDs at doses licensed for use in PSA or PSO. ACR, American College of Rheumatology; bDMARD, biological disease modifying anti-rheumatic drug; BIW, twice weekly; MTX, methotrexate; PSA, psoriatic arthritis; PSO, psoriasis; QD, once daily; QW, weekly; Q2W, every two weeks; Q4W, every four weeks; Q8W, every eight weeks; Q12W, every twelve weeks.

a subset of IL-17A and IL-23 inhibitor therapies (online supplemental table S6).

Treatment effects for other comparators included in the NMA are reported in online supplemental figure S5. Of these comparators, the licensed oral therapies—upadacitinib, tofacitinib and apremilast—performed similarly to golimumab, IL-23 inhibitors and ustekinumab, respectively. Unlicensed comparators, such as filgotinib and remtolumab showed a strong response, though the evidence for each come from small phase 2 studies.

Treatment effects from subgroup analyses of ACR response based on prior bDMARD exposure are presented in online supplemental figures S6 and S7. Expected probabilities of ACR 20, 50 and 70 response for the overall population as well as bDMARD-naïve and bDMARD-experienced patients are presented together in table 2 for key comparators and in online supplemental table S7 for all evaluated interventions.

Thirty-six studies<sup>17–19 23 24 26 37–46 49–53 55 59 60 62 63 65–72</sup> assessing 33 unique treatment regimens were included in the bDMARD-naïve network and findings were consistent with the overall analysis: all key comparators were more effective than placebo. Similarly, infliximab showed the greatest efficacy, followed by etanercept. Most key comparators performed the same or slightly better among bDMARD-naïve patients than in the overall analysis; only the efficacy of guselkumab appeared to decrease slightly. Ustekinumab, abatacept and apremilast remained the least efficacious licensed therapies in this subgroup.

For the subgroup of bDMARD-experienced patients, 20 studies<sup>17 19 22–24 26 37–40 47 50–52 54 57 60 67 68</sup> evaluating 25 unique treatment regimens were included. All key comparators, except ustekinumab, were more effective than placebo. Certolizumab performed best, followed by ixekizumab and secukinumab. The treatment effect of abatacept showed a slight improvement and brodalumab, a slight deterioration compared with the overall population analysis.

### PASI response

Twenty-two studies reported PASI 75 and/or PASI 90 at 12–16 weeks and a further 14 studies reported PASI outcomes at 24 weeks, allowing for the evaluation of 37 treatment regimens (see online supplementary figure S8 for network diagram).<sup>17–20 23 24 26 37–55 58–61 63 67 68 70 72</sup>

Figure 4 presents the PASI treatment effects of each key comparator versus placebo on the probit scale and table 3 presents the expected probabilities of PASI 75 and 90 response. Treatment effects for other comparators included in the NMA are reported in online supplementary figure S9 and online supplemental table S8.

All key comparators were more efficacious than placebo. Guselkumab 100 mg Q8W was associated with the largest treatment effect versus placebo, followed by brodalumab 210 mg, an IL-17RA inhibitor and the other IL-17A inhibitors—ixekizumab 80 mg (Q2W and Q4W) and secukinumab 300 mg—and infliximab. Differences between guselkumab, brodalumab and infliximab were not found to be statistically significantly different, nor were differences between brodalumab and infliximab and the other IL-17A inhibitors. Brodalumab and guselkumab were shown to be more efficacious than ustekinumab (45 and 90 mg); the 300 mg dose of secukinumab and the fortnightly dose of ixekizumab were also more efficacious than the 45 mg dose of ustekinumab. Brodalumab, ixekizumab and secukinumab 300 mg along with guselkumab, ustekinumab and infliximab were shown to be significantly more efficacious than adalimumab, certolizumab (200 mg and 400 mg), etanercept (50 mg weekly or two times in a week), golimumab 50 mg, abatacept, secukinumab 150 mg and tildrakizumab (online supplemental table S9).

Of the other comparators included in the NMA, the licensed oral therapies—tofacitinib and apremilast—were associated with smaller effect sizes than most biological therapies. Unlicensed comparators, such as filgotinib and remtolumab showed a similar level of PASI response to the licensed comparators, though the evidence for each come from small phase 2 studies.

### Resolution of enthesitis and dactylitis

Fourteen RCTs reported evidence on the resolution of enthesitis and 12 RCTs reported evidence on the resolution of dactylitis at 12–16 weeks and a further 10 RCTs reported evidence for both outcomes at 24 weeks, allowing for the evaluation of 22 treatment regimens





**Table 2** Expected probabilities of ACR response by bDMARD exposure subgroup for key comparators

| Probability of response, median (95% credible interval) |                    | bDMARD-naïve       |                    |                      |                      |                      |                      | bDMARD-exposed       |                      |                      |                      |                      |                      |                      |                      |
|---|--------------------|--------------------|--------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|----------------------|
|   |                    | ACR 20             | ACR 50             | ACR 70               | ACR 20               | ACR 50               | ACR 70               | ACR 20               | ACR 50               | ACR 70               | ACR 20               | ACR 50               | ACR 70               |                      |                      |
| <b>All patients</b>                                     |                    |                    |                    |                      |                      |                      |                      |                      |                      |                      |                      |                      |                      |                      |                      |
| <b>Intervention*</b>                                    | <b>ACR 20</b>      | <b>ACR 50</b>      | <b>ACR 70</b>      | <b>ACR 20</b>        | <b>ACR 50</b>        | <b>ACR 70</b>        | <b>ACR 20</b>        | <b>ACR 50</b>        | <b>ACR 70</b>        | <b>ACR 20</b>        | <b>ACR 50</b>        | <b>ACR 70</b>        | <b>ACR 20</b>        | <b>ACR 50</b>        | <b>ACR 70</b>        |
| Brodalumab 210 mg                                       | 48.6% (37.6, 59.7) | 24.6% (16.7, 34.3) | 9.8% (16.7, 34.3)  | 53.1% (40.4, 65.3)   | 28.5% (18.7, 40)     | 13% (18.7, 40)       | 32.3% (15.9, 53.1)   | 14.7% (5.6, 30.6)    | 13% (18.7, 40)       | 32.3% (15.9, 53.1)   | 14.7% (5.6, 30.6)    | 13% (18.7, 40)       | 32.3% (15.9, 53.1)   | 14.7% (5.6, 30.6)    | 5.4% (5.6, 30.6)     |
| Ixekizumab 80 mg every two weeks                        | 56% (44.5, 66.6)   | 30.9% (21.5, 41.3) | 13.4% (21.5, 41.3) | 60.2% (45.1, 74.2)   | 34.9% (22.1, 50.1)   | 17.3% (22.1, 50.1)   | 47.2% (28.1, 67)     | 25.5% (12.1, 44.1)   | 17.3% (22.1, 50.1)   | 47.2% (28.1, 67)     | 25.5% (12.1, 44.1)   | 17.3% (22.1, 50.1)   | 47.2% (28.1, 67)     | 25.5% (12.1, 44.1)   | 11.2% (12.1, 44.1)   |
| Ixekizumab 80 mg every four weeks                       | 55.1% (44.5, 64.8) | 30% (21.5, 39.3)   | 12.9% (21.5, 39.3) | 55.5% (43.1, 67.7)   | 30.6% (20.6, 42.5)   | 14.4% (20.6, 42.5)   | 49.4% (29.9, 69)     | 27.3% (13.2, 46.4)   | 14.4% (20.6, 42.5)   | 49.4% (29.9, 69)     | 27.3% (13.2, 46.4)   | 14.4% (20.6, 42.5)   | 49.4% (29.9, 69)     | 27.3% (13.2, 46.4)   | 12.2% (13.2, 46.4)   |
| Secukinumab 150 mg                                      | 51.5% (42.7, 60.4) | 27% (20.2, 35)     | 11.1% (20.2, 35)   | 54.2% (45.4, 63.3) † | 29.4% (22.2, 38) †   | 13.6% (22.2, 38) †   | 40.7% (23.7, 59.7) † | 20.5% (9.6, 36.6) †  | 13.6% (22.2, 38) †   | 40.7% (23.7, 59.7) † | 20.5% (9.6, 36.6) †  | 13.6% (22.2, 38) †   | 40.7% (23.7, 59.7) † | 20.5% (9.6, 36.6) †  | 8.3% (9.6, 36.6) †   |
| Secukinumab 300 mg                                      | 56.3% (47.4, 64.8) | 31.2% (23.7, 39.4) | 13.6% (23.7, 39.4) | 57.2% (48.2, 66.3) † | 32.1% (24.4, 41.1) † | 15.4% (24.4, 41.1) † | 51% (32.2, 69.4) †   | 28.6% (14.7, 46.9) † | 15.4% (24.4, 41.1) † | 51% (32.2, 69.4) †   | 28.6% (14.7, 46.9) † | 15.4% (24.4, 41.1) † | 51% (32.2, 69.4) †   | 28.6% (14.7, 46.9) † | 13.1% (14.7, 46.9) † |
| Guselkumab 100 mg every eight weeks                     | 51.6% (40.5, 61)   | 27.1% (18.6, 35.5) | 11.1% (18.6, 35.5) | 52.6% (41, 63.4) †   | 28.1% (19.1, 38.1) † | 12.8% (19.1, 38.1) † | 63% (36.2, 84.8) ‡   | 39.8% (17.3, 67) ‡   | 12.8% (19.1, 38.1) † | 63% (36.2, 84.8) ‡   | 39.8% (17.3, 67) ‡   | 12.8% (19.1, 38.1) † | 63% (36.2, 84.8) ‡   | 39.8% (17.3, 67) ‡   | 20.7% (17.3, 67) ‡   |
| Tildrakizumab 100 mg every twelve weeks                 | 48.9% (32.9, 64.3) | 24.9% (13.7, 38.8) | 9.9% (13.7, 38.8)  | -                    | -                    | -                    | -                    | -                    | -                    | -                    | -                    | -                    | -                    | -                    | -                    |
| Ustekinumab 45 mg                                       | 34.2% (24.6, 45.9) | 14.5% (9.1, 22.5)  | 4.8% (9.1, 22.5)   | 41.8% (29.7, 55.1)   | 19.6% (11.9, 30.2)   | 7.9% (11.9, 30.2)    | 32.9% (13.6, 59)     | 15.1% (4.6, 36)      | 7.9% (11.9, 30.2)    | 32.9% (13.6, 59)     | 15.1% (4.6, 36)      | 7.9% (11.9, 30.2)    | 32.9% (13.6, 59)     | 15.1% (4.6, 36)      | 5.6% (4.6, 36)       |
| Ustekinumab 90 mg                                       | 41.6% (32, 52.7)   | 19.4% (13.2, 28)   | 7.1% (13.2, 28)    | 46% (33.5, 59)       | 22.8% (14.1, 33.8)   | 9.6% (14.1, 33.8)    | 31.9% (13, 57.9)     | 14.5% (4.3, 34.9)    | 9.6% (14.1, 33.8)    | 31.9% (13, 57.9)     | 14.5% (4.3, 34.9)    | 9.6% (14.1, 33.8)    | 31.9% (13, 57.9)     | 14.5% (4.3, 34.9)    | 5.3% (4.3, 34.9)     |
| Adalimumab 40 mg every two weeks                        | 55.8% (46.5, 63.6) | 30.7% (23, 38.1)   | 13.3% (23, 38.1)   | 55.5% (46.3, 64.8)   | 30.6% (22.9, 39.4)   | 14.4% (22.9, 39.4)   | -                    | -                    | 14.4% (22.9, 39.4)   | -                    | -                    | 14.4% (22.9, 39.4)   | -                    | -                    | -                    |
| Certolizumab 200 mg every two weeks                     | 61.3% (47.1, 73.8) | 35.8% (23.5, 49.4) | 16.6% (23.5, 49.4) | 55.8% (41, 70.3)     | 30.9% (19.1, 45.4)   | 14.6% (19.1, 45.4)   | 65.3% (36.4, 88.1)   | 42.2% (17.5, 72.3)   | 14.6% (19.1, 45.4)   | 65.3% (36.4, 88.1)   | 42.2% (17.5, 72.3)   | 14.6% (19.1, 45.4)   | 65.3% (36.4, 88.1)   | 42.2% (17.5, 72.3)   | 22.5% (17.5, 72.3)   |
| Certolizumab 400 mg every four weeks                    | 52.2% (37.9, 65.7) | 27.6% (16.9, 40.3) | 11.5% (16.9, 40.3) | -                    | -                    | -                    | -                    | -                    | 11.5% (16.9, 40.3)   | -                    | -                    | 11.5% (16.9, 40.3)   | -                    | -                    | -                    |
| Etanercept 50 mg once weekly                            | 61.8% (47.2, 75.6) | 36.3% (23.6, 51.7) | 16.9% (23.6, 51.7) | 60.3% (42.8, 75.1)   | 35% (20.3, 51.3)     | 17.3% (20.3, 51.3)   | -                    | -                    | 17.3% (20.3, 51.3)   | -                    | -                    | 17.3% (20.3, 51.3)   | -                    | -                    | -                    |
| Etanercept 50 mg twice weekly                           | 64.8% (46.7, 80.4) | 39.4% (23.2, 58.1) | 19% (23.2, 58.1)   | 63.3% (40.8, 80.4)   | 38% (19, 58.3)       | 19.5% (19, 58.3)     | -                    | -                    | 19.5% (19, 58.3)     | -                    | -                    | 19.5% (19, 58.3)     | -                    | -                    | -                    |
| Etanercept 50 mg and Methotrexate 20 mg once weekly     | 63% (44.4, 79.4)   | 37.5% (21.5, 56.7) | 17.7% (21.5, 56.7) | 61.6% (38.7, 79.3)   | 36.2% (17.5, 56.7)   | 18.2% (17.5, 56.7)   | -                    | -                    | 18.2% (17.5, 56.7)   | -                    | -                    | 18.2% (17.5, 56.7)   | -                    | -                    | -                    |
| Golimumab 50 mg   | 58.4% (43.3, 73.9) | 33% (20.6, 49.6)   | 14.7% (20.6, 49.6) | 55.9% (35.3, 73.3)   | 30.9% (15.3, 48.9)   | 14.6% (15.3, 48.9)   | -                    | -                    | 14.6% (15.3, 48.9)   | -                    | -                    | 14.6% (15.3, 48.9)   | -                    | -                    | -                    |

Continued

**Table 2** Continued

**Probability of response, median (95% credible interval)**

| Intervention*                             | All patients          |                       |                       | bDMARD-naïve           |                       |                      | bDMARD-exposed        |                      |                     |
|---|-----------------------|-----------------------|-----------------------|------------------------|-----------------------|----------------------|-----------------------|----------------------|---------------------|
|   | ACR 20                | ACR 50                | ACR 70                | ACR 20                 | ACR 50                | ACR 70               | ACR 20                | ACR 50               | ACR 70              |
| Golimumab 100 mg                          | 57.2%<br>(42, 72.9)   | 32%<br>(19.7, 48.3)   | 14.1%<br>(19.7, 48.3) | 55%<br>(34.6, 72.5)    | 30.1%<br>(14.8, 48)   | 14.1%<br>(14.8, 48)  | -                     | -                    | -                   |
| Infliximab 5 mg/kg                        | 68.4%<br>(56.7, 79.9) | 43.2%<br>(31.5, 57.5) | 21.8%<br>(31.5, 57.5) | 66.6%<br>(51.6, 79.3)  | 41.4%<br>(27.2, 56.8) | 22%<br>(27.2, 56.8)  | -                     | -                    | -                   |
| Infliximab 5 mg/kg and methotrexate 15 mg | 76.5%<br>(52, 92.1)   | 52.9%<br>(27.4, 77.7) | 29.6%<br>(27.4, 77.7) | 75.3%<br>(45, 92.2)    | 51.5%<br>(22, 77.9)   | 30.2%<br>(22, 77.9)  | -                     | -                    | -                   |
| Abatacept 125 mg                          | 38.4%<br>(25.7, 51.6) | 17.2%<br>(9.6, 27.1)  | 6%<br>(9.6, 27.1)     | 45.9%<br>(29.1, 63.8)  | 22.7%<br>(11.5, 38.4) | 9.6%<br>(11.5, 38.4) | 26.4%<br>(12.6, 45.1) | 11.1%<br>(4.1, 23.9) | 3.8%<br>(4.1, 23.9) |
| Placebo                                   | 20.7%<br>(9.5, 37.3)  | 7.1%<br>(2.5, 16.5)   | 1.9%<br>(2.5, 16.5)   | 20.9%<br>(10.2, 36.4)† | 7.2%<br>(2.7, 16)†    | 2.2%<br>(2.7, 16)†   | 18.3%<br>(9.6, 30.7)† | 6.8%<br>(2.9, 13.8)† | 2%<br>(2.9, 13.8)†  |

\*Key comparators include bDMARDs at doses licensed for use in PsA or PsO.

†Based on a combination of studies reporting outcomes at week 12 or 16 and week 24.

‡Based on studies reporting outcomes at week 24 only.

ACR, American College of Rheumatology; bDMARD, biological disease-modifying antirheumatic drug; PsA, psoriatic arthritis; PsO, psoriasis.

in each network (online supplemental figures S10 and S11).<sup>17-19 23 24 26 37-39 45-47 50-55 59 60 62 67 68</sup>

Figure 5A,B presents the ORs for each key comparator vs placebo for resolution of enthesitis and dactylitis, respectively, and table 3 presents the expected probabilities of achieving each endpoint.

All treatments were more efficacious than placebo in terms of the proportion of patients achieving a resolution of enthesitis, though the effects were not statistically significant for ustekinumab 45 mg and abatacept. Among the key comparators, there was little differentiation between adalimumab, ustekinumab 90 mg, secukinumab (150 or 300 mg), ixekizumab every 2 weeks, brodalumab 210 mg or guselkumab 100 mg every 8 weeks (online supplemental table 9).

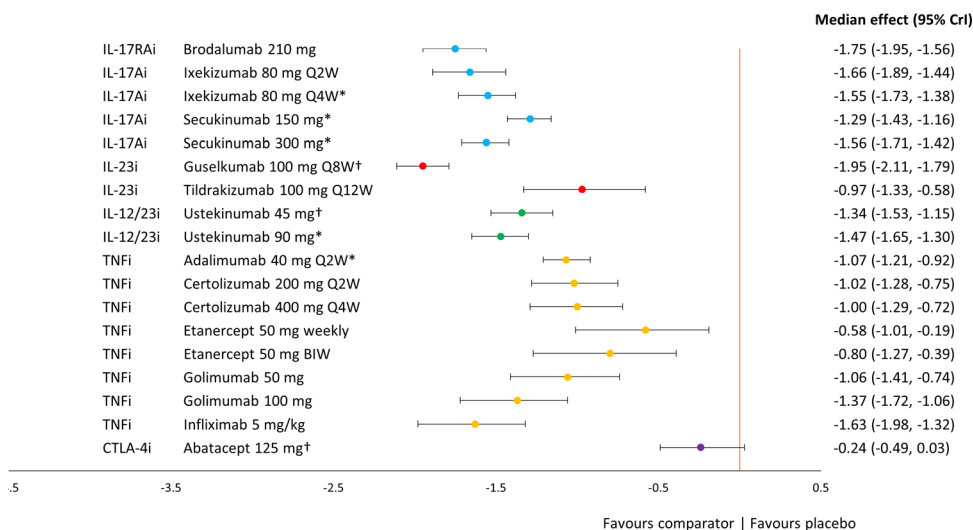
For the resolution of dactylitis, all key interventions except abatacept were statistically superior to placebo. Based on the median effects, the IL-17A, IL-17RA and IL-23 inhibitors ranked best followed by adalimumab and then ustekinumab. Statistically significant differences between key comparators were limited to secukinumab 300 mg, which was more efficacious than both ustekinumab and abatacept (online supplemental table 9).

Among the other licensed therapies included in the resolution of enthesitis and dactylitis analyses, tofacitinib 10 mg was significantly more effective than placebo on the outcome of dactylitis, but neither tofacitinib 5 mg nor apremilast were significantly more efficacious on either outcome (online supplemental figures 1213 and online supplemental table 9). Results showed filgotinib, an unlicensed therapy, to be significantly more efficacious than placebo on the outcome of enthesitis, but not dactylitis.

**Discontinuation due to adverse events**

Discontinuations due to AEs were reported in two ways: discontinuation from study drug, which was used in the analysis where available, or discontinuation from study. The analysis relied on DAE reported at the end of study follow-up, however defined by study authors. The DAE network included 43 studies<sup>17-20 23 24 26 36-47 49-63 65-68 70-72</sup> 2 of which were pooled<sup>23</sup> and 43 unique treatment regimens (online supplementary figure S14). Table 3 presents the probability of patient discontinuation due to AEs for key interventions.

Withdrawal was least likely for patients on abatacept 125 mg (0.6%) and ustekinumab 45 mg (0.6%) and 90 mg (0.7%). The analysis showed that patients receiving 50 mg or 100 mg golimumab or brodalumab 210 mg would have a low probability of DAE (0.8% and 1.4%, respectively). Treatments with the greatest risk of DAE were infliximab in combination with (12.4%) and without (8.2%) MTX, tildrakizumab 100 mg every 12 weeks (11.8%) and certolizumab 400 mg every 4 weeks (8.2%) and 200 mg every 2 weeks (5.2%). All other treatments were associated with a risk between 1.9% (guselkumab every 8 weeks and secukinumab 300 mg) to 4.2% (etanercept 100 mg two times weekly). Only the differences between ustekinumab and



**Figure 4** Forest plot of treatment effects for key comparators versus placebo on PASI response. \*Based on a combination of studies reporting outcomes at week 12 or 16 and week 24; †Based on studies reporting outcomes at week 24 only note that PASI treatment effect was based on a fixed-effects model with placebo adjustment. Median treatment effects and 95% credible intervals are plotted on the probit scale. Key comparators include bDMARDs at doses licensed for use in PSA or PSO. bDMARD, biological disease modifying antirheumatic drug; BIW, twice weekly; PASI, Psoriasis Area and Severity Index; PSA, psoriatic arthritis; PSO, psoriasis; Q2W, every two weeks; Q4W, every four weeks; Q8W, every eight weeks; Q12W, every twelve weeks.

placebo and adalimumab and placebo reached statistical significance.

Probabilities of DAE for other comparators included in the NMA are reported along with their relative effects versus placebo in online supplemental figures S15 and S16. Due to the low frequency of DAEs overall, there was substantial uncertainty. Although filgotinib and tildrakizumab were associated with relatively high absolute risks of DAE, there was insufficient evidence to conclude a difference. Only apremilast 30 mg and upadacitinib 30 mg were found to have a statistically significantly greater risk of DAE than placebo.

## DISCUSSION

Our SLR identified 46 RCTs for inclusion in an NMA evaluating the efficacy and safety of systemic therapies for the treatment of patients with active PsA. Data for at least one outcome of interest were available for a total of 19 638 patients receiving one of 19 treatments, divided out into up to 43 unique doses or dosing regimens. We compared these treatments on the outcomes of ACR response, PASI response and resolution of enthesitis and dactylitis as well as discontinuation due to AEs and showed that most therapies licensed for active PsA or moderate to severe PsO were better than placebo and similar to one another.

In the last several years, numerous NMAs have been published comparing the efficacy of various treatments in active PsA.<sup>73–83</sup> This largely reflects the rapid evolution of the treatment landscape, in terms of new treatments and new clinical trials and the demand for up-to-date, rigorous comparative analyses from health technology assessment agencies. That said, none of the currently

published NMAs include all evaluated treatments in this patient population. The results presented here are not dissimilar from those reported by other authors but extends the possible comparisons by taking a more inclusive approach to the available evidence.

To our knowledge, this NMA provides the most recent and comprehensive comparison of treatments evaluated for active PsA. Specifically, it is the first to include the recently published clinical trial data from EXCEED, AMVISION-1 and -2, SELECT-PsA 1 and 2 and GO-DACT.<sup>23 53 56 57 64</sup> Though several of the most recent clinical trials have included a head-to-head comparison of targeted therapies, such direct comparisons are still a rarity and many comparisons remain unobserved.<sup>45 46 53 55 56 61</sup>

In their absence, the network meta-analytical approach gives the most reliable estimate of comparative efficacy and safety. Indeed, where it is possible to compare the results from a head-to-head RCT with those generated in our NMA, they are in broad agreement. For example, EXCEED<sup>53</sup> directly compared secukinumab and adalimumab and reported a risk ratio of 1.05 (95% CI 0.89 to 1.26) for the outcome of ACR50. The risk ratio generated from the NMA for the same comparison was 1.02 (95% CrI: 0.85 to 1.21). Similarly, SPIRIT H2H<sup>45</sup> and SPIRIT P1<sup>46</sup> both compared ixekizumab and adalimumab and ACR 50 outcomes at week 16 result in risk ratios of 0.96 (95% CI 0.69 to 1.33) and 1.57 (0.88 to 2.8), respectively. Meta-analysing these results in a pairwise fashion gives rise to a pooled treatment effect of 1.05 (0.89 to 1.23) which is comparable to the effect of 1.01 (95% CrI 0.76 to 1.3) generated in the NMA.

**Table 3** Expected probabilities of response by outcome for key comparators

| Intervention*                           | Probability of response, median (95% credible interval) |                     |                          |                          |                            |
|---|---|---------------------|--------------------------|--------------------------|----------------------------|
|   | PASI 75   | PASI 90             | Resolution of enthesitis | Resolution of dactylitis | Discontinuation due to AEs |
| Brodalumab 210 mg                       | 70.3% (62.3, 77.4)                                      | 52.7% (44, 61.3)    | 38% (24.9, 52.6)         | 53.6% (38.5, 70.6)       | 1.4% (0.2, 7.2)            |
| Ixekizumab 80 mg every two weeks        | 67% (57.8, 75.5)  | 49% (39.4, 58.9)    | 40.5% (26.7, 56.3)       | 59.8% (36.3, 77.4)       | 3.9% (1, 14.5)             |
| Ixekizumab 80 mg every four weeks†      | 63.1% (55.4, 70.3)                                      | 44.9% (37.1, 52.7)  | 33.1% (21.5, 46.8)       | 63.2% (41.7, 78.2)       | 2.1% (0.6, 7.8)            |
| Secukinumab 150 mg†                     | 53.2% (45.7, 59.5)                                      | 35% (28.3, 41.1)    | 41.6% (29.6, 53.7)       | 50.5% (35.8, 67.2)       | 2.3% (0.6, 8.2)            |
| Secukinumab 300 mg†                     | 63.7% (56.3, 69.5)                                      | 45.4% (37.9, 51.9)  | 44.4% (32, 56.7)         | 62.4% (47.4, 77.1)       | 1.9% (0.6, 6.5)            |
| Guselkumab 100 mg every eight weeks‡    | 76.6% (68.5, 82.2)                                      | 60.3% (50.7, 67.5)  | 42.3% (28.1, 56.3)       | 60.4% (42.4, 73.8)       | 1.9% (0.4, 8.4)            |
| Tildrakizumab 100 mg every twelve weeks | 40.2% (25.5, 55.1)                                      | 23.7% (13, 36.8)    | –                        | –                        | 11.8% (0.4, 98.3)          |
| Ustekinumab 45 mg‡                      | 60% (52.8, 67.8)  | 41.6% (34.6, 49.9)  | 32.9% (21.1, 49.9)       | 43.9% (29.5, 62.2)       | 0.6% (0.1, 2.9)            |
| Ustekinumab 90 mg                       | 54.8% (46.6, 63)*                                       | 36.5% (29.1, 44.8)* | 40.4% (27.2, 57.9)†      | 46.8% (32, 65)†          | 0.7% (0.1, 3.2)            |
| Adalimumab 40 mg every two weeks†       | 44.2% (36.9, 50.7)                                      | 27% (21.2, 32.8)    | 39.7% (27.6, 52.6)       | 51.3% (33.3, 68.1)       | 3.8% (1.2, 11.8)           |
| Certolizumab 200 mg every two weeks     | 42.2% (31, 53)  | 25.4% (16.8, 34.8)  | –                        | –                        | 5.2% (0.7, 36.8)           |
| Certolizumab 400 mg every four weeks    | 41.5% (30, 53.3)  | 24.8% (16.1, 35.2)  | –                        | –                        | 8.2% (1.2, 47.4)           |
| Etanercept 50 mg once weekly            | 26.1% (15.4, 42.2)                                      | 13.5% (6.8, 25.4)   | –                        | –                        | 2.6% (0.1, 48.7)           |
| Etanercept 50 mg +MTX 20 mg once weekly | –   | –                   | –                        | –                        | 3.3% (0.1, 56.7)           |
| Etanercept 50 mg twice weekly           | 33.9% (20.1, 52.5)                                      | 18.9% (9.6, 34.3)   | –                        | –                        | 4.2% (0.1, 63.1)           |
| Golimumab 50 mg                         | 43.5% (32.1, 58.4)                                      | 26.5% (17.6, 40)    | –                        | –                        | 0.8% (0.1, 6.4)            |
| Golimumab 100 mg                        | 55.7% (44, 69.6)  | 37.4% (26.9, 52)    | –                        | –                        | 0.8% (0.1, 6.4)            |
| Infliximab 5 mg/kg                      | 65.8% (54.7, 78)  | 47.7% (36.4, 62)    | –                        | –                        | 8.2% (1.3, 47)             |
| Infliximab 5 mg/kg+MTX 15 mg            | –   | –                   | –                        | –                        | 12.4% (0.2, 89.9)          |
| Abatacept 125 mg‡                       | 16.3% (10.4, 23.9)                                      | 7.4% (4.2, 12)      | 33.9% (20, 51.8)         | 43.1% (25.2, 62.3)       | 0.6% (0, 7.2)              |
| Placebo†                                | 9.7% (3.4, 22)  | 3.9% (1.1, 10.8)    | 23% (12.7, 37.8)         | 31.1% (11, 62.3)         | 2.4% (0.8, 7.1)            |

\*Key comparators include bDMARDs at doses licensed for use in PsA or PsO.

†Based on a combination of studies reporting outcomes at week 12 or 16 and week 24.

‡Based on studies reporting outcomes at week 24 only bDMARD.

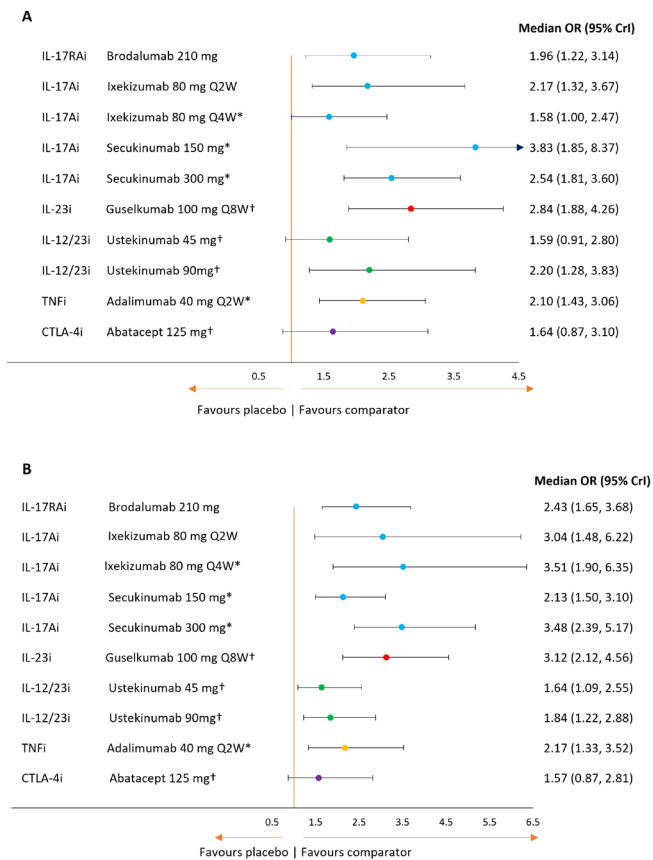
AE, adverse event; bDMARD, biological disease-modifying antirheumatic drug; MTX, methotrexate; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; PsO, psoriasis.

This NMA was based on a systematic review of RCTs evaluating a range of treatments, licensed and unlicensed. We followed a protocol designed for the systematic review; however, this was not registered online. English-language publications were searched, which has the potential to introduce bias; however, we believe this was unlikely to have had a substantial impact on our findings.

We intentionally took a broader approach to the comparators of interest than other recent NMAs, which restricted their inclusion criteria to licensed therapies only. We were interested in comparing any drug, at any dose, that has been evaluated in an RCT among patients

with active PsA. This approach meant we could include evidence for recently approved drugs or those in late-stage development, but not yet approved. It also meant that we could assess drugs or doses of drugs that are licensed for the treatment of PsO and see how they performed in patients with PsA, on both dermatological and rheumatological outcomes. Results from our analysis of PASI response among patients with PsA show a similar pattern to those from other NMAs among patients with PsO, which indicate the highest levels of response among IL-17A, IL-17RA and IL-23 inhibitor therapies.<sup>84–90</sup>





**Figure 5** Forest plot of treatment effects for key comparators versus placebo on resolution of enthesitis (A) and dactylitis (B). \*Based on a combination of studies reporting outcomes at week 12 or 16 and week 24; †Based on studies reporting outcomes at week 24 only. Note that treatment effect on resolution of enthesitis was based on a random-effects model with placebo adjustment. Treatment effect on resolution of dactylitis was based on a fixed-effects model with placebo adjustment. Key comparators include bDMARDs at doses licensed for use in PSA or PSO. bDMARD, biological disease modifying antirheumatic drug; CrI, credible interval; PSA, psoriatic arthritis; PSO, psoriasis; Q2W, every two weeks; Q4W, every four weeks; Q8W, every eight weeks.

We opted to evaluate unique doses and dosing regimens of different treatments rather than pooling across treatments in order to ensure the usefulness of the data to clinical decision-making. Although pooling all doses and dosing regimens for a given treatment would simplify the networks and streamline the analysis, the results could be misleading. Combining any evaluated dose of a drug included in phase 2 dose-finding studies with ultimately licensed doses could introduce bias by failing to take account of potential dose-response relationships and heterogeneity. The sheer volume of strategies evaluated in RCTs of PsA are reflected in our networks and are presented in full in online supplemental materials, but for the easier interpretation of results, we focused on a subset of 20 key comparators—biological therapies

licensed for the treatment of PsA or PsO—that would be most relevant to clinicians.

The SLR identified phase 2, dose-finding studies for risankizumab and bimekizumab, but their small sample size failed to meet the inclusion criteria for further consideration.<sup>21 91</sup> Results from the two KEEPSAKE phase 3 studies for risankizumab are anticipated, with preliminary results suggesting that risankizumab is associated with strong ACR and PASI responses. Phase 3 studies of bimekizumab in PsA are ongoing (NCT03895203, NCT03896581) however, completed studies in moderate to severe PsO suggest that bimekizumab will at least have a significant effect on PASI outcomes.<sup>92 93</sup> Future updates of these NMAs should include these studies and assess the comparative efficacy and safety of both new therapies.

We focused on commonly investigated outcomes in PsA, including ACR and PASI response rates for efficacy and DAE for safety and tolerability. In addition, we presented results for the resolution of enthesitis and dactylitis, symptoms experienced by more than half of people with PsA and which contribute to disability and quality of life impairment.<sup>94</sup> Both outcomes are highly relevant for PsA, for which comparisons in the literature are limited.<sup>79–82</sup> Looking at this suite of outcomes helps to contextualise the evidence across disease markers relevant to the patient, including intra-articular, extra-articular and dermatological manifestations of PsA as well as the tolerability of the drugs. Outcomes such as Psoriatic Arthritis Response Criteria (PsARC) and the Health Assessment Questionnaire (HAQ) are also well reported secondary endpoints across the RCT evidence base and have been compared in other NMAs.<sup>78 80 81 95</sup> One recent NMA also compared therapies in terms of their efficacy against structural damage using the van der Heijde-Sharp score.<sup>83</sup> Outcomes such as PsARC and HAQ have been associated with issues of reliability, in that the former is not fully validated and may be easily achieved, as evidenced by high placebo response rates<sup>96</sup> and the latter may be influenced by other factors, including co-morbidities and duration of disease.<sup>97</sup>

Wherever possible, outcomes reported at 12–16 weeks were synthesised. In the few cases where data were not available at this time point, outcomes reported at week 24 were extracted and included in the analysis. For the outcome of ACR response among the full study populations, all RCTs reported outcomes at the earlier time point; however, there was more diversity for the subgroup analyses on ACR response and for the secondary outcomes of PASI and resolution of enthesitis or dactylitis. For example, the DISCOVER studies<sup>17 18</sup> of guselkumab, the ASTRAEA study<sup>24</sup> of abatacept and the PSUMMIT studies<sup>59 60</sup> of ustekinumab reported PASI, dactylitis and enthesitis outcomes at week 24 only. Similarly, the only PASI response evidence for etanercept was reported at week 24.<sup>63 72</sup> For therapies such as adalimumab, ixekizumab and secukinumab, evidence was available for each from studies of varied follow-up, such that the effect sizes reflect a pooling of evidence at week 12 or 16 and week

24. These effects were synthesised with the evidence for drugs evaluated in studies reporting outcomes at week 12 or 16.<sup>22 23 26 40–44 54–58 65</sup>

Pooling across a narrower time range may have been more appropriate as relative efficacy, particularly for outcomes defined by larger percentage improvements from baseline, continues to increase between 4 and 6 months. This trend is particularly marked for PASI 75, PASI 90 and PASI 100 outcomes, as illustrated in the trends over time from studies such as RAPID-PsA, GO-REVEAL, SPIRIT P1, SPIRIT P2 and Gottlieb *et al.*<sup>20 40 41 46 47</sup> The pooling of evidence across time points has the potential to introduce an important source of heterogeneity leading to bias against drugs studied over a shorter period, such as brodalumab, tildrakizumab, certolizumab, golimumab, infliximab and tofacitinib. This limitation had to be weighed against the fact that excluding evidence beyond 16 weeks would have limited the ability to make comparisons between some of the most relevant comparators. Authors of a recent NMA chose to synthesise all outcomes reported at the study defined endpoint, anywhere from 12 to 26 weeks, regardless of the potential heterogeneity introduced.<sup>83</sup> Their results were broadly aligned with those presented here and not dissimilar from the results of evaluations in patients with moderate to severe PsO.<sup>84–88</sup>

Finally, the focus of these comparative analyses has been on outcomes reported between 3 and 6 months because this is the minimum duration of most RCTs in PsA. PsA is a chronic, lifelong condition, therefore, a better understanding of the biological drugs and targeted therapies beyond this short induction period would be worthwhile. Future work could explore the feasibility and appropriateness of comparisons of longer-term outcomes and possibly the synthesis of real-world registry studies. Indeed, an extension to other types of evidence, may be helpful to assess the durability of response and to detect rarer safety endpoints that may only emerge with long-term treatment.

## CONCLUSIONS

Results of this NMA confirm the efficacy and acceptability of bDMARDs in patients with active PsA. The anti-TNF therapies infliximab, etanercept, golimumab and certolizumab were among the most effective therapies for ACR response, though the differences between them and other key interventions in these networks including adalimumab, the interleukin-17 inhibitors and guselkumab were small and not statistically significant. Results were consistent across subgroups of patients with and without prior exposure to bDMARDs. Interleukin-17 inhibitors—brodalumab, ixekizumab and secukinumab—along with guselkumab, were the most effective therapies on the outcome of PASI response, followed closely by infliximab and then golimumab, ustekinumab and adalimumab. Although data on the outcomes of enthesitis and dactylitis resolution were comparatively sparse, the analysis showed that adalimumab, guselkumab and IL-17 inhibitors were

broadly similar. Tolerability was similar across drugs, though infliximab, certolizumab and tildrakizumab were associated with higher levels of discontinuation due to adverse events.

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