Treatment of Dactylitis and Enthesitis in Psoriatic Arthritis with Biologic Agents: A Systematic Review and Meta-Analysis

AHMED MOURAD (ORCID ID: 0000-0002-0575-1773)
ROBERT GNIADECKI (ORCID ID: 0000-0002-2310-8300)

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[1]Faculty of Medicine & Dentistry, University of Alberta [2]Division of Dermatology, Department of Medicine, University of Alberta

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Conflict of interest: Dr. Gniadecki has received speaker's honorarium from Mallinckrodt, Janssen, AbbVie, Novartis, and Leo Pharma, is on the advisory board for Mallinckrodt, Janssen, Amgen, AbbVie, Eli Lily, Sanofi, Novartis, and Leo Pharma. Dr. Gniadecki is an investigator in clinical trials for Janssen, Celgene, AbbVie, and Leo Pharma.

Ahmed Mourad[1] (A.M.) BSc: Medical Student, University of Alberta Faculty of Medicine & Dentistry

Robert Gniadecki[1,2] (R.G.) MD PhD DMSci: Professor, Divisional Director, Division of Dermatology, University of Alberta

Correspondence:

Ahmed Mourad, 2-166 Clinical Sciences Building,
Division of Dermatology, University of Alberta Faculty of Medicine & Dentistry,
Edmonton, Alberta, Canada

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ABSTRACT

Objective: Biologic agents with different mechanisms of actions (inhibitors of TNF-α, interleukin-12/23 and interleukin-17) showed efficacy in randomized controlled trials in the treatment of psoriatic arthritis. We aimed to conduct a pooled meta-analysis of those agents for dactylitis and enthesitis and compare those with the American College of Rheumatology 20 (ACR20) response, and Health Assessment Questionnaire Disability Index (HAQ-DI) scores.

Methods: A systematic literature search was performed and a pooled meta-analysis of randomized controlled trials with anti-TNF-α (infliximab, golimumab, adalimumab), anti-interleukin-12/23 (ustekinumab) and anti-interleukin-17 (secukinumab, ixekizumab) was conducted using the random-effects model. Bias was assessed using the Cochrane Risk Of Bias tool.

Results: Eighteen randomized controlled trials were included in the pooled analysis (n=6981). Both TNF-α inhibitors and novel biologics (ustekinumab, secukinumab, ixekizumab) demonstrated significant resolution of dactylitis at week 24 with pooled risk ratios (RRs) versus placebo of 2.57 (95% CI: 1.36-4.84) and 1.88 (95% CI: 1.33-2.65), respectively. For the resolution of enthesitis at week 24, RR for TNF-α inhibitors was 1.93 (95% CI: 1.33-2.79) vs 1.95 (95% CI: 1.60-2.38) for novel biologics. Both biologic categories showed overlapping ranges of ACR20 responses (TNF-α inhibitors: RR=2.23, 95% CI: 1.60-3.11, pooled interleukin-12/23 and -17: RR=2.30, 95% CI 1.94-2.72) and similar quality of life improvement scores with mean HAQ-DI score changes of -0.29 (95% CI: -0.39, -0.19) and -0.26 (95% CI: -0.31, -0.22), respectively.

Conclusion: The pooled analysis demonstrates that anti-TNF-α agents have the same efficacy as novel agents (ustekinumab, secukinumab, and ixekizumab) in dactylitis and enthesitis.

INTRODUCTION

Psoriatic arthritis (PsA) is chronic condition comprising inflammation within the joint (synovitis) and in the periarticular soft tissue (dactylitis and enthesitis) (1-5). Both dactylitis and enthesitis impair joint function and negatively impact patient's quality of life. Dactylitis (sausage digit) is thought to result from flexor tenosynovitis whereas enthesitis is defined by the inflammation of the attachment site of tendons, ligaments or joint capsules to bones (6-8). The presence of dactylitis correlates with PsA severity and increases risk of erosive damage of the joints (1, 9).

Both TNF-α and the cytokines of the T_H17 pathway (IL-23, IL-17A and IL-17F) have been identified as important elements in the pathogenesis of PsA, including dactylitis and enthesitis (10-13). However, the primary endpoint in randomized controlled trials in PsA was the American College of Rheumatology 20% (ACR20) response that mainly captures intra-articular joint manifestations. Extra-articular manifestations were included only as secondary endpoints and partially captured by various outcome measures and by Health Assessment Questionnaire Disability Index (HAQ-DI) scores (14). Thus, in spite of the widespread use of biologics to treat extra-articular manifestations of PsA, the supportive evidence is inferior to that for psoriatic synovitis (10, 12, 13, 15). Therefore, we decided to conduct a systematic literature review and meta-analysis on the evidence available on dactylitis and enthesitis using clinical disease resolution as an endpoint. Moreover, we created a pooled analysis for ACR20 and HAQ-DI to contextualize improvement in dactylitis and enthesitis in psoriatic arthritis and PsA-related disability.

MATERIALS AND METHODS

This study was conducted in accordance with the Preferred Items for the Reporting of Systematic reviews and Meta-analysis (PRISMA) guidelines (16).

Study Eligibility

This study included randomized controlled trials investigating biologic treatment outcomes of dactylitis resolution, enthesitis resolution, efficacy and health-related quality of life. The primary outcomes of interest that we included in this study were resolution of dactylitis and enthesitis, and secondary outcomes were ACR20 response rates and change in Health Assessment Questionnaire (HAQ) score from baseline at weeks 12-16 and week 24. Studies were excluded for the following reasons: unclear reporting of data, lack of randomization or control group, patient age <18, abstracts, conference proceedings, letters to the editor, review papers, and case reports. All included studies were published in English.

Search Strategy

A literature search was conducted by A.M using Medline (PubMed), the Cochrane Library, EMBASE (Ovid), Scopus, and Web of Science. The search string used in this systematic review (using MeSH terminology) was “psori* AND biologic AND arth* AND dactylitis AND enthesitis AND HAQ AND ACR”. The date of the last search was February 12, 2018. Additional studies were searched manually and identified from the reference lists of the included studies.

Study Screening

A.M. and R.G. screened the title and abstracts of the articles for inclusion using the inclusion criteria. Both authors reviewed full texts independently and in an un-blinded fashion.

Data extraction

Data was extracted from the included papers and presented in tables, which were triple-checked for accuracy. The extracted study characteristics were: Study Title (author and year), Treatment vs. Control, Patient Number (Treatment), Patient Number (Control), Study Duration (week), Study Week (week), Age (year), Dactylitis (n), Enthesitis (n), ACR20 response, and HAQ score change from baseline and week 24 of treatment and, where available, for week 12-16. Bias was assessed using the Cochrane Risk Of Bias Assessment Tool. We recorded the assessment for selection bias, detection bias, attrition bias, reporting bias and other bias.

Statistical Analysis

The numbers of patients with dactylitis and enthesitis resolution were calculated from the data reported on the number of patients with dactylitis and enthesitis at baseline and weeks 12-16 and week 24 follow up. A meta-analysis of the included studies was performed for dactylitis and enthesitis resolution, ACR20 response and change of HAQ from baseline for biologics vs. placebo. Supplementary meta-analyses were also generated for the biologics which performed ‘best-in-class’ and were directly compared.

A random effects model was used to generate the forest plots. Statistical analysis was completed using Review Manager 5.3 *(*Review Manager (RevMan) [Computer program]. Version 5.3. Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

RESULTS

Study Selection

The included studies were randomized controlled trials investigating the biologic treatment of dactylitis and enthesitis resolution, ACR20 response and quality of life measuring through HAQ. After removal of duplicates, the systematic search identified 625 studies. Of these studies, 39 were considered to be potentially relevant and were read as full texts. After this step we finally included 19 articles comprising of 7254 patients (Figure 1). All studies contained at least 24 week efficacy data for at least one efficacy endpoint; 8 studies for dactylitis resolution (treatment n=546, placebo n=138) (17-24), 8 studies for enthesitis resolution (treatment n=516, placebo n=123) (18-22, 24, 25), 11 studies for ACR20 response (treatment n=1402, placebo n=440) (17-19, 21, 22, 24, 26-29), and 9 studies for HAQ-DI response (treatment n=1826, placebo n=1388 (18, 20-22, 24, 25, 27, 29, 30) (Supplementary Table 1).

To increase the power of the analysis we stratified the treatment groups into TNF-α inhibitor group (adalimumab, etanercept, infliximab, certolizumab and golimumab) and the novel biologic group (ustekinumab, secukinumab, brodalumab, and ixekizumab) which all target cytokines from the T_H17 pathway (IL-23, IL-17A,F and IL-17 receptor).

Risk of Bias

The Cochrane risk of bias assessment was conducted and revealed a low overall risk of bias for selection bias, detection bias, attrition bias, reporting bias and other bias for the studies included (Supplementary Figure 1).

Dactylitis Resolution

At weeks 12-14 the dactylitis resolution pooled RR for TNF-α inhibitors was 1.53 (95% CI: 1.01-2.31), and the pooled RR for novel biologics was 1.39 (95% CI: 1.06-1.81). This corresponded to pooled RR for all biologics combined of 1.42 (95% CI: 1.13-1.80) (Supplementary Figure 2). At week 24, the pooled RR for all biologics combined was 2.07 (95% CI: 1.54-2.80) (Figure 2). Pooled RRs for TNF-α inhibitors and novel biologics were 2.57 (95% CI: 1.36-4.84) and 1.88 (95% CI: 1.33-2.65) respectively (Figure 2).

Enthesitis Resolution

At weeks 12-14 the enthesitis resolution pooled RR for TNF-α inhibitors was 1.75 (95% CI: 0.96-3.21), and the pooled RR for novel biologics was 1.87 (95% CI: 0.77-4.54). This corresponded to pooled RR for all biologics combined of 1.72 (95% CI: 1.14-2.59) (Supplementary Figure 3). Pooled RRs for enthesitis resolution for biologics combined was 1.95 (95% CI: 1.63-2.32). Enthesitis resolution yielded RRs of 1.93 (95% CI: 1.33-2.79) and 1.95 (95% CI: 1.60-2.38) for TNF-α inhibitors and novel biologics respectively (Figure 3).

ACR20 Response and Change in HAQ-DI Scores from Baseline

At week 12-16 the ACR20 response pooled RR for TNF-α inhibitors was 3.47 (95% CI: 2.45- 4.92), and the pooled RR for novel biologics was 2.04 (95% CI: 1.79-2.33). This corresponded to pooled RR for all biologics combined of 2.62 (95% CI: 2.17-3.18) (Supplementary Figure 4). The pooled RR for ACR20 response for all biologics at 24 weeks was 2.25 (95% CI: 1.86-2.73). TNF-α inhibitors and novel biologics showed pooled RRs of 2.23 (95% CI 1.60-3.11) and 2.30 (1.94-2.72), respectively (Figure 4). The pooled mean change in HAQ scores at weeks 12-14 was -0.24 (95% CI: -0.28, -0.20) for TNF- α inhibitors and -0.34 (-0.35, -0.33) for novel biologics, corresponding to a pooled mean change for all biologics of -0.27 (-0.35, -0.20) (Supplementary Figure 5). At week 24, the mean change in HAQ scores from baseline gave a pooled value of -0.27 (95% CI: -0.31, -0.23) for all biologics, -0.29 (95% CI: -0.39, -0.19) for TNF-α inhibitors and -0.26 (95% CI: -0.31, -0.22) for novel biologics (Figure 5).

Comparing Best in Class Biologics

A supplementary meta-analysis was conducted to compare the biologics which performed the best for each respective outcome. Secukinumab performed best in the four outcomes and was compared to the best TNF-α inhibitor in each outcome (Supplementary Figure 6). There was no difference between infliximab (RR: 4.10 (95% CI: 2.03=8.29) and secukinumab (pooled RR: 3.19 (95% CI: 2.16 – 4.72)) for dactylitis resolution. Golimumab (RR: 2.06 (95% CI: 1.28-3.31)) and secukinumab (pooled RR: 2.28

(95% CI: 1.55-3.36)) were the best in class for enthesitis resolution, and there was no significant statistical difference between each biologic in the meta-analysis. Moreover, there was no difference between infliximab (pooled RR: 3.38 (95% CI: 2.08 – 5.48) and secukinumab (pooled RR: 2.91 (95% CI: 2.23 – 3.79) regarding the ACR20 response. Meta-analysis for HAQ-DI improvement showed no difference between adalimumab (pooled mean difference: -0.25 (95% CI: -0.34, -0.16)) and secukinumab (pooled mean difference: -0.24 (95% CI: -0.25, -0.23)).

DISCUSSION

To our knowledge, this is the first study analyzing the pooled effect of biologics on dactylitis and enthesitis resolution in patients with psoriatic arthritis. The pooled random-effects analysis demonstrated significantly higher rates for resolution of dactylitis and enthesitis with biologic treatment compared to placebo at both weeks 12-14 and weeks 24. Interestingly, we did not detect an appreciable difference between the previous generation TNF-α inhibitors and novel biologics targeting IL-23 and IL-17.

A prior systematic review on dactylitis treatment showed that ustekinumab, certolizumab, infliximab, and golimumab were promising candidates for treating of dactylitis (7). A meta-analysis was not possible at that time due to limited data. The current pooled analysis showed that treatment with TNF-α inhibitors and novel biologics were respectively 2.57 times and 1.88 times more likely to cause resolution of dactylitis at week 24 than placebo, with no significant difference between these classes. Testing for subgroup differences at week 24 also showed no significant difference between TNF-α and novel biologics due to heterogeneity (Figure 2).

A systematic review completed by Orbai et al (2014) showed that the TNF-α inhibitors golimumab, certolizumab, and infliximab were effective in treating enthesitis (31). At the time, evidence for adalimumab and etanercept was inconclusive and remains sparse to date. One randomized controlled trial exists reporting enthesitis resolution for adalimumab and showed modest rates with a calculated ratio of 1.24 (95% CI: 0.76-

2.05) and 1.74 (95% CI: 1.33-2.79) at weeks 12 and 24 respectively (19). More robust evidence regarding enthesitis treatment is available for biologics that target the T_H17 pathway. Six randomized controlled trials were included in the current meta-analysis which showed ustekinumab, secukinumab, and ixekizumab effectively resolved enthesitis compared to placebo treatment, corresponding to an overall pooled risk ratio for these trials of 1.95 (95% CI: 1.60-2.38) (Figure 6). According to the pooled analysis, there is no significant difference in the enthesitis resolution rates for TNF-α inhibitors and the novel biologic groups. Moreover, testing for subgroup differences did not reveal a significant difference between the two biologic subgroups due to heterogeneity (Figure 6). Our data support the role of T_H17 pathway in the pathogenesis of enthesitis, which was initially proposed on the basis of the beneficial effect of IL-12/23 inhibitor ustekinumab (31, 32).

Analyses of ACR20 and HAQ responses for biologics in PsA were conducted previously but to our knowledge there is no meta-analysis comparing anti-TNF-α with novel biologics targeting T_H17 pathway (26). Analogously to the comparable efficacy in dactylitis and enthesitis, we did not see any significant differences between these two biologic classes for neither ACR20 responses (Figure 4 and Supplementary Figure 4) nor HAQ scores at week 24 (Figure 5 and Supplementary Figure 5). This result indicates that in contrast to efficacy in psoriatic skin lesions where novel biologics are vastly superior to TNF-α blockers, the level of clinical and functional improvement in relation to PsA is comparable with any class of biologic drugs.

Methodologies including head to head comparative studies between biologics, are important in demonstrating differences in effectiveness for the relative biologics. Previous matched comparison studies revealed discrepant results for the ACR comparison between secukinumab and adalimumab. The study conducted by Nash and Colleagues (2018) (33) demonstrated that patients treated with secukinumab had significantly higher proportions of ACR response compared to adalimumab whereas another study (34) showed that adalimumab was superior with respect to ACR response. Meta-analysis of the ACR20 data for secukinumab vs adalimumab in the current study demonstrated no difference in ACR20 response at weeks 12-16 (Supplementary Figure 7 A). At week 24, secukinumab had had a superior ACR20 response (pooled RR: 2.91 (95% CI: 2.23 – 3.79)) compared to adalimumab (pooled RR: 1.59 (95% CI: 1.22 – 2.08)) (Supplementary Figure 7 B). Moreover, a further meta-analysis was conducted with the biologics that performed best in class for the four outcomes of interest in the current study. Secukinumab was superior to the other biologics in its class, and as such was compared to the best TNF-α inhibitor. This supplementary meta-analysis revealed no statistically significant difference between the best TNF-α inhibitor versus secukinumab, with the limitation of a small sample size and a low number of studies included.

A key strength this study is the inclusion of randomized controlled trials with high-quality evidence and low risk of bias. One limitation of this study is that randomized controlled trial data was limited beyond 24 weeks and meta-analysis beyond this time frame was not possible. It is difficult to extrapolate week 24 data to long-term

outcomes, as biologics may lose efficacy at different rates during long-term treatment. Another limitation of this study includes the differences in the placebo groups between the different included RCTs, which contributed to an inherent source of heterogeneity for the pooled analysis. A further limitation of the studies included is the consideration of dosing of biologics in the studies. Studies where dose increases are allowed showed improvements in the efficacy of biologic with regards to the four parameters, thereby suggesting that these biologics may not be dose optimized. Further studies are required to clearly elucidate this. As the scope of the current study was to compare the two overall classes of biologics (anti-TNF vs novel biologics), a pairwise meta-analysis was conducted. A future direction of this study could be to conduct a network meta-analysis to estimate direct and indirect comparisons between the individual biologics.

In conclusion, the pooled analysis demonstrates that the drugs targeting both TNF-α and IL-17 and IL-12/23 effectively resolve dactylitis and enthesitis, with no significant difference between either class of biologic.

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FIGURE LEGEND

Figure 1: Study selection process in accordance with PRISMA guidelines.

Figure 2: Forest plot of dactylitis Resolution for TNF-α inhibitors and novel biologics at week 24.The square sizes represent the statistical weight for each study. The black horizontal bars represent 95% confidence intervals. The diamond values indicate the pooled effect estimates.

Figure 3: Forest plot of enthesitis resolution for TNF-α inhibitors and novel biologics at week 24. The square sizes represent the statistical weight for each study. The black horizontal bars represent 95% confidence intervals. The diamond values indicate the pooled effect estimates.

Figure 4: Forest plot of ACR20 responses for TNF-α inhibitors and novel biologics at 24 weeks. The square sizes represent the statistical weight for each study. The black horizontal bars represent 95% confidence intervals. The diamond values indicate the pooled effect estimates.

Figure 5: Forest plot of mean change in HAQ-DI scores at 24 weeks compared to baseline for TNF-α inhibitors and novel biologics. The square sizes represent the statistical weight for each study. The black horizontal bars represent 95% confidence intervals. The diamond values indicate the pooled effect estimates.

SUPPLEMENTARY DATA

Supplementary Table 1: Table of outcome measures for meta-analysis *denotes median age [a]Number of randomized patients with dactylitis at baseline, week 12-16, and week 24 [b]Number of randomized patients with enthesitis at baseline, week 12-16, and week 24 [c]Number of randomized patients achieving ACR20 criteria at week 12-16 and week 24 compared to baseline [d]Change of HAQ-DI scores (SD unless specified) of patients at weeks 12-16 and week 24 compared to HAQ-DI scores at baseline. [e]bracketed values denote HAQ-DI mean ranges. Values in bold were used in the meta-analyses.

Supplementary Figure 1: Cochrane risk of bias summary

Supplementary Figure 2: Forest plot of dactylitis Resolution for TNF-α inhibitors and novel biologics at week 12-14. The square sizes represent the statistical weight for each study. The black horizontal bars represent 95% confidence intervals. The diamond values indicate the pooled effect estimates.

Supplementary Figure 3: Enthesitis Resolution for TNF-α inhibitors and novel biologics at week 12-14. The square sizes represent the statistical weight for each study. The black horizontal bars represent 95% confidence intervals. The diamond values indicate the pooled effect estimates.

Supplementary Figure 4: Forest plot of ACR20 responses for TNF-α inhibitors and novel biologics at 12-16 weeks. The square sizes represent the statistical weight for each study. The black horizontal bars represent 95% confidence intervals. The diamond values indicate the pooled effect estimates.

Supplementary Figure 5: Forest plot of change in mean HAQ-DI scores at 12-14 weeks compared to baseline for TNF-α inhibitors and novel biologics. The square sizes represent the statistical weight for each study. The black horizontal bars represent 95% confidence intervals. The diamond values indicate the pooled effect estimates.

Supplementary Figure 6: Comparing the best in class biologics at week 24 for (A) Dactylitis Resolution, (B) Enthesitis resolution, (C) ACR20 response, and (D) change in HAQ-DI score from baseline. The square sizes represent the statistical weight for each study. The black horizontal bars represent 95% confidence intervals. The diamond values indicate the pooled effect estimates.

Supplementary Figure 7: Forest plot of ACR20 responses for adalimumab vs secukinumab at (A) 12-16 weeks and (B) 24 weeks. The square sizes represent the statistical weight for each study. The black horizontal bars represent 95% confidence intervals. The diamond values indicate the pooled effect estimates.

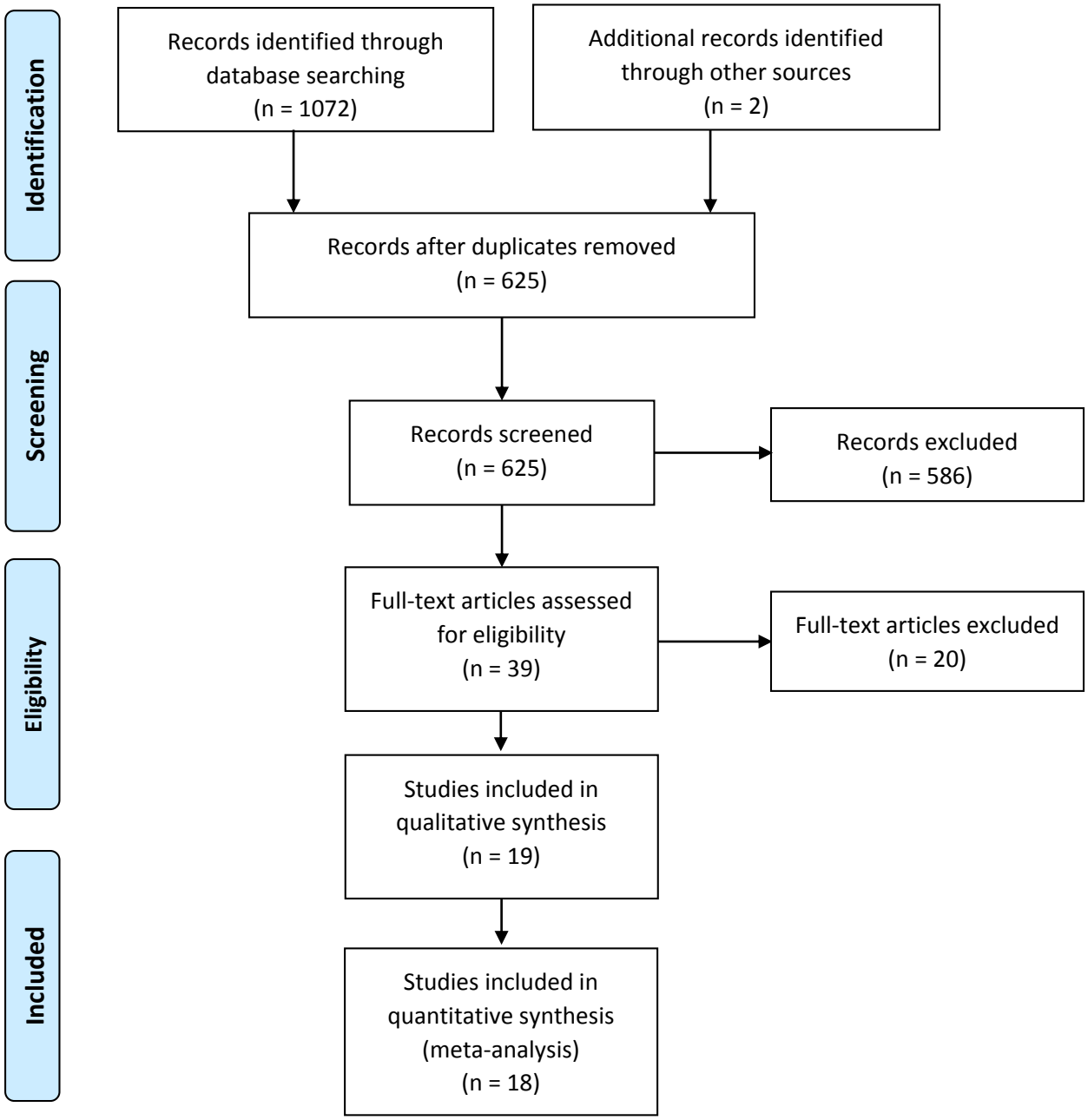

Figure 1: Study selection process in accordance with PRISMA guidelines

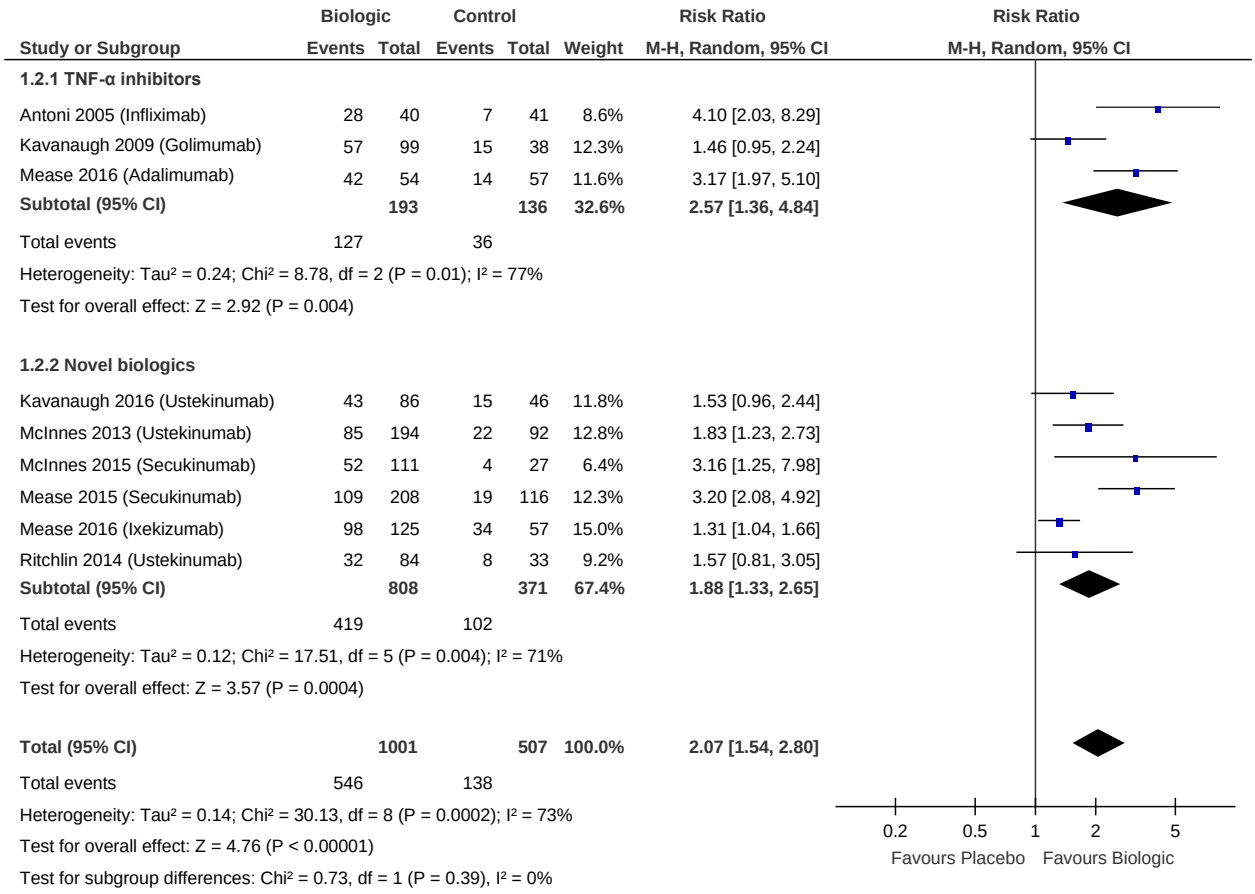

Figure 2: Forest plot of dactylitis Resolution for TNF-α inhibitors and novel biologics at week 24.The square sizes represent the statistical weight for each study. The black horizontal bars represent 95% confidence intervals. The diamond values indicate the pooled effect estimates.

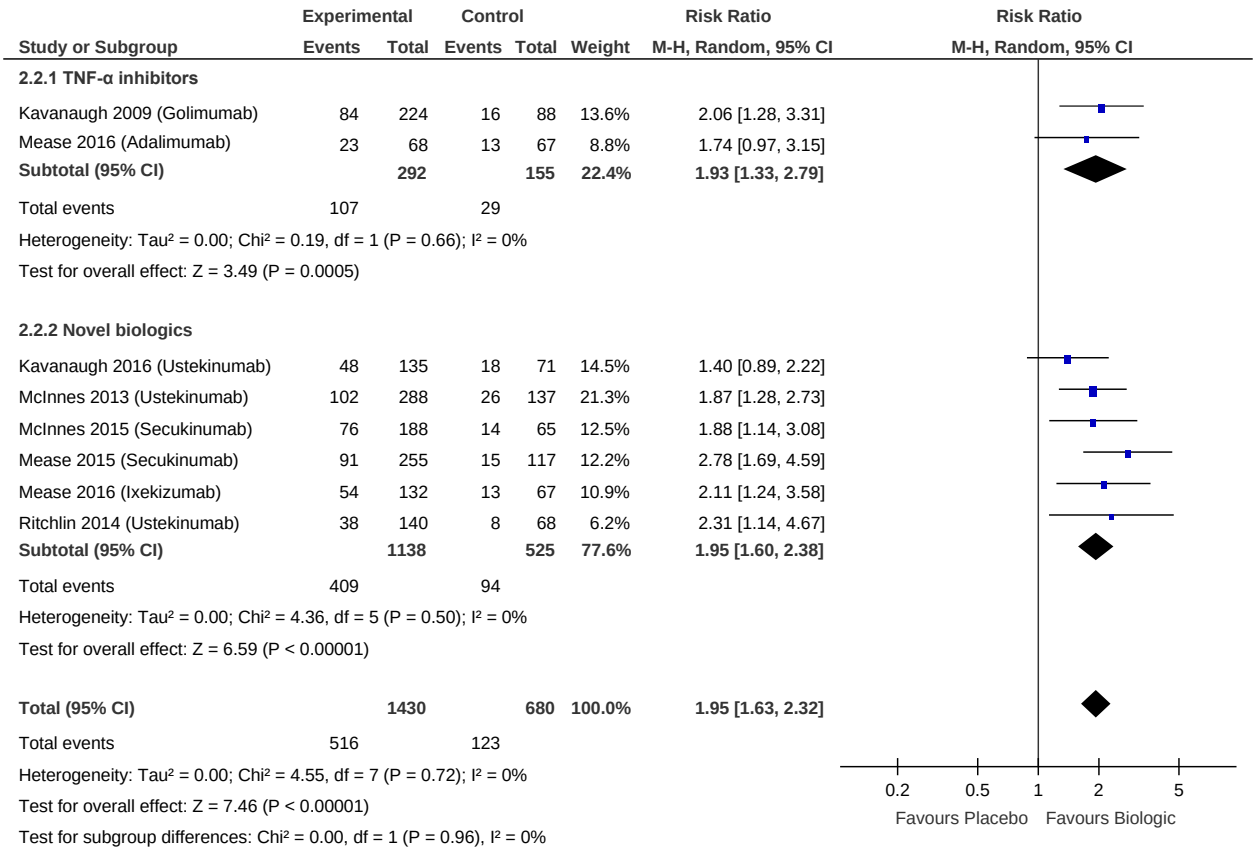

Figure 3: Forest plot of enthesitis resolution for TNF-α inhibitors and novel biologics at week 24. The square sizes represent the statistical weight for each study. The black horizontal bars represent 95% confidence intervals. The diamond values indicate the pooled effect estimates.

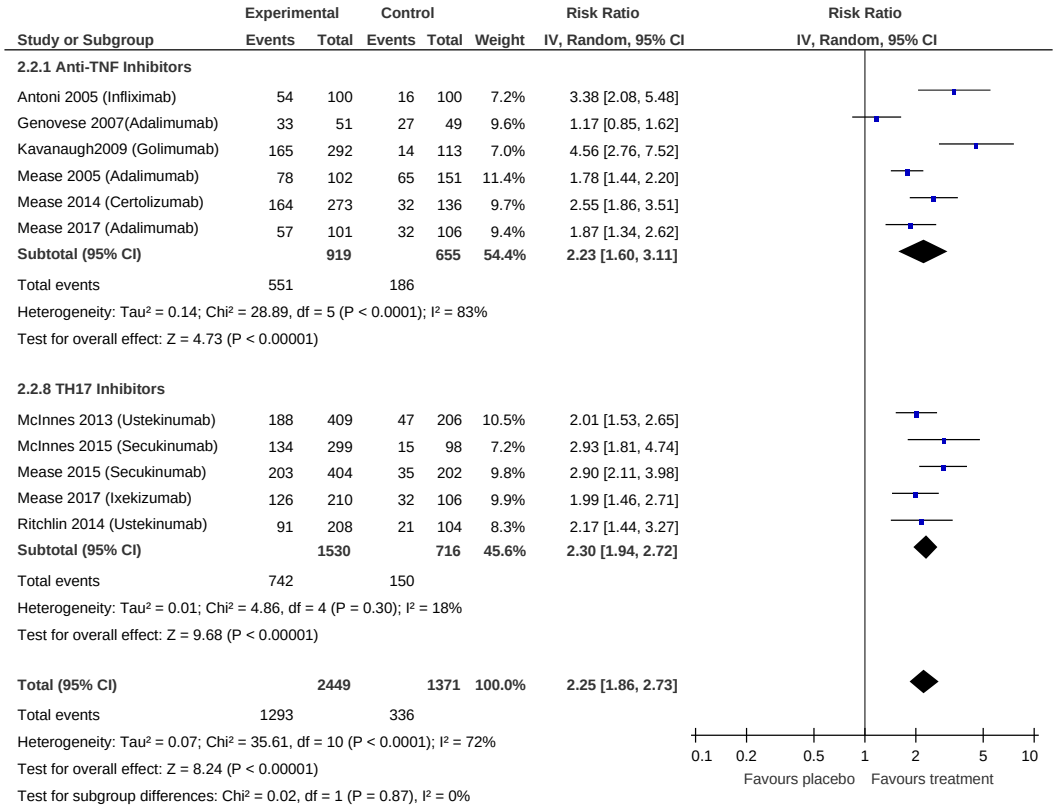

Figure 4: Forest plot of ACR20 responses for TNF-α inhibitors and novel biologics at 24 weeks. The square sizes represent the statistical weight for each study. The black horizontal bars represent 95% confidence intervals. The diamond values indicate the pooled effect estimates.

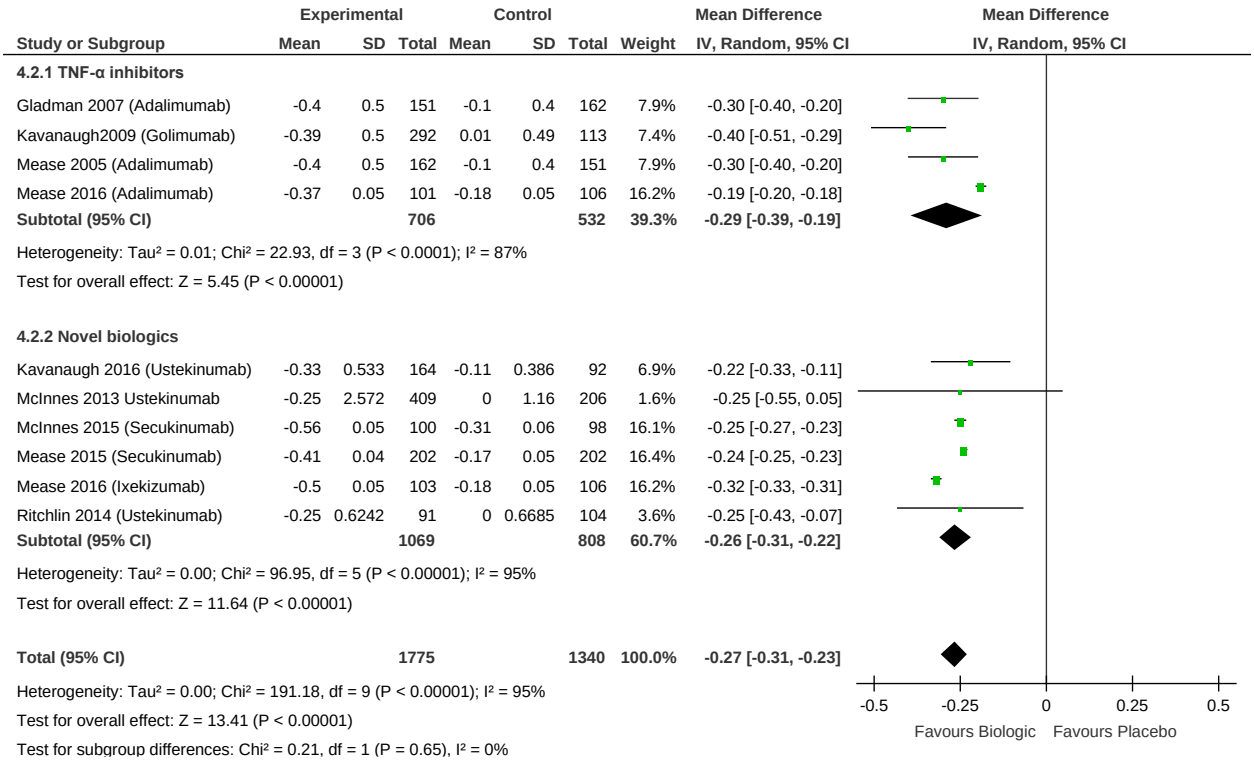

Figure 5: Forest plot of mean change in HAQ-DI scores at 24 weeks compared to baseline for TNF-α inhibitors and novel biologics. The square sizes represent the statistical weight for each study. The black horizontal bars represent 95% confidence intervals. The diamond values indicate the pooled effect estimates.