Pharmacological Treatment of Psoriatic Arthritis: A Systematic Literature Research for the 2019 Update of the EULAR Recommendations for the Management of Psoriatic Arthritis

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Pharmacological treatment of psoriatic arthritis: a systematic literature research for the 2019 update of the EULAR recommendations for the management of psoriatic arthritis.

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Abstract (words)

Objectives: To perform an update of a review of the efficacy and safety of disease-modifying drugs (DMARDs) in psoriatic arthritis (PsA).

Methods: Systematic literature research of 2015-2018 publications on all DMARDs in patients with PsA searching MEDLINE, Embase and the Cochrane Library. Efficacy was assessed in randomised controlled trials. For safety, cohort studies, case-control studies and long-term extensions (LTEs) were analysed.

Results: 56 (efficacy: n=33; safety n=23) were analysed. Articles on TNF inhibitors (n=6; golimumab, etanercept and biosimilars), IL-17A inhibitors (n=10; ixekizumab, secukinumab), IL-23-p19 inhibitors (n=2; guselkumab, risankizumab), clazakizumab (IL-6-inhibitor), abatacept (CD80/86 inhibitor), and ABT-122 (anti-TNF/IL-17A), respectively. One study compared ustekinumab (IL12/23i) to TNFi therapy in patients with entheseal disease. Three articles investigated DMARD tapering. Trials on tsDMARDs investigated apremilast (PDE4-inhibitor) and Janus kinase inhibitors (JAKi; tofacitinib, filgotinib). Biosimilar comparison with bio-originator showed non-inferiority. Safety was evaluated in 13 LTEs, 9 cohort studies and 1 case-control study investigating malignancies, infections, infusion reactions, multiple sclerosis and major cardiovascular events as well as efficacy and safety of vaccination. No new safety signals were identified, however warnings on the risk of venous thromboembolic events including pulmonary embolism when using JAKi were issued by regulators based on other studies.

Conclusion: Many drugs are available in PsA and have demonstrated efficacy against placebo. Efficacy varies across the PsA manifestations. Safety must also be taken into account. This review informed the development of the EULAR 2019 updated PsA management recommendations.

Introduction

Pharmacological treatment options for psoriatic arthritis (PsA) have significantly increased over the past years. Data from randomized controlled trials (RCTs) have provided evidence for efficacy of various novel agents, such as biological (b) or targeted synthetic (ts) Disease Modifying Antirheumatic Drugs (DMARDs). Among these are bDMARDs targeting IL-17A (ixekizumab, secukinumab) [1-5]; the p19 subunit of IL-23 (guselkumab, risankizumab),[6, 7]; the costimulation molecule CD80/86 (abatacept),[8]; the IL-6 cytokine (clazakizumab);[9] and a bispecific antibody inhibiting TNF and IL-17A (ABT-122).[10] Further, Janus kinase inhibitors (including tofacitinib and filgotinib) have recently been assessed in PsA.[11-13]

Safety evaluation of pharmacological interventions in PsA have to be derived beyond the controlled period of RCTs and need to account for long-term extension phases of RCTs and patients included in observational clinical cohorts, registries and post-marketing monitoring; these latter are especially relevant, since they also comprise routine care patients who are not suitable for inclusion into clinical trials, for example due to comorbidities.[14]

The objective of the present systematic literature research (SLR) was to inform the task force developing the 2019 update of the European League against Rheumatism (EULAR) recommendations for the management of PsA on the current state of evidence of efficacy and safety of non-topical pharmacological agents for the treatment of PsA. This SLR focused on studies published since the last SLRs which were performed in 2015.[15]

Methods

The review protocol for this SLR was developed by the steering group in accordance with the EULAR standardised operating procedures for EULAR recommendations.[16]

The eligibility criteria for inclusion were defined conform previous SLRs as studies in adult patients (≥18 years) with PsA, classified according to the CASPAR or Moll and Wright criteria.[15] Patient populations of interest were as follows: naïve for conventional synthetic (cs) DMARDs or insufficient responders (IR) to non-steroidal anti-inflammatory drugs (NSAIDs) who were eligible for csDMARD treatment; csDMARD-IR patients; bDMARD-IR patients; and cs+bDMARD-IR mixed populations.

Only studies on systemic PsA therapies were searched; these were defined as csDMARDs (including methotrexate, leflunomide, sulfasalazine, hydroxychloroquine, chloroquine, injectable gold/gold salts, azathioprine, cyclosporine, penicillamin, cyclophosphamide, mycophenolate, chlorambucil, minocyclin); bDMARDs (anakinra, infliximab, etanercept, adalimumab, rituximab, abatacept, tocilizumab, golimumab, certolizumab-pegol, alefacept, ustekinumab, secukinumab, brodalumab, ixekizumab, guselkumab, clazakizumab and bimekizumab and respective biosimilars); tsDMARDs (apremilast, tofacitinib, baricitinib, upadacitinib, filgotinib); systemic glucocorticoids or NSAIDs; and any combination of these treatments.

For efficacy evaluation, only randomized, controlled double-blind trials (RCTs) were included. Phase 2 trials were included if no phase 3 trials were available for a given compound. In the case of strategic, switching or dose-reduction trials, open-label designs were also eligible for inclusion. Placebo treatment or any of the agents listed above were eligible as comparator. Data on switching to a TNFi after failure of another TNFi, DMARD tapering and/or stopping treatment were expected to be scarce, therefore we expanded the eligibility criteria for study inclusion beyond RCTs to inform the taskforce with any data available, including open-label, cohort and case-control studies.

Outcomes of interest were signs and symptoms of PsA, defined as composite measures including the American College of Rheumatology (ACR) response criteria, the Disease Activity Index for Psoriatic Arthritis (DAPSA) or the Minimal Disease Activity (MDA) state. Core set measures of disease activity that were evaluated included swollen and tender joints; patient pain as well as patient and evaluator global assessments of disease activity; dactylitis; enthesitis; skin disease (evaluated through the Psoriasis Area Severity Index (PASI) or psoriasis affected body surface area (BSA)); and physical function (Health Assessment Questionnaire Disability Index, HAQ; Short-Form 36 Physical Component Score, SF-36 PCS).

Progression of structural damage was assessed as reported, which was by the PsA modified Sharp/van der Heijde Score (mTSS).

For safety, RCTs and their long-term extension periods were evaluated for safety signals. In addition, cross-sectional, cohort and case-control studies were analysed. Aside from laboratory abnormalities, the most important safety outcomes evaluated were infections (including candida and herpes zoster infections), malignancies, cardiovascular events, gastrointestinal adverse events, depression and suicide attempts and proportions of serious adverse events (for RCTs).

The initial literature search was conducted by a database expert (L.F.) in EMBASE, Medline and the Cochrane Library without language restriction. Based on the previous SLR, the search included all studies published between January 1st, 2015 and December 21, 2018 (last date searched). For completeness, data of full articles published after the last date searched of the literature search could be included in the SLR, if the abstract of the respective trial had been published within the time frame of our SLR. The search terms used are shown in the supplementary appendix (Table S1.1-S1.6). Title and abstract screening, as well as data extraction was conducted by one researcher (A.K.). Results of the title and abstract screening process were discussed with several experienced authors (J.S.S., L.G., X.B.).

Risk of bias (RoB) was assessed using the Cochrane Collaboration's Risk of Bias tool for RCTs, and each study was assigned as having low, unclear or high risk of bias. Cohort and case-control (i.e. safety) studies were assessed using the Newcastle-Ottawa Scale (details shown in Tables 4.2.1 and 4.2.2).[17, 18]

Results

Of 5528 studies screened, 181 were assessed for eligibility in detail and 56 publications (33 articles on efficacy and 23 on safety) were finally included in this SLR (for details see the flowchart in Figure 1 and Table 1). Figure 2 depicts a crude summary on the efficacy results of interventions by mode of action and disease domain. Most RCTs were regarded as having low RoB, while unclear RoB was most commonly due to insufficient reporting on random sequence generation. Open-label studies (n=3) and long-term extensions included (n=13) were considered as having a high RoB. Detailed RoB results (efficacy: Table S2.2; safety: Table S4.2.3 and Table S4.2.4), baseline characteristics (efficacy: Tables S2.3-S2.5; safety: Table S4.3) and detailed results (Tables S3.1-S3.2) are presented in the supplementary appendix.

Efficacy of conventional synthetic disease modifying anti-rheumatic drugs

No primary trial data were published from 2015-2018 on the efficacy of conventional synthetic DMARDs. Indirect evidence on the efficacy of methotrexate (MTX) was shown in the SEAM-PsA trial. Whilst a placebo arm was absent, MTX monotherapy showed good efficacy regarding arthritis measures (50.7%, 30.6% and 13.8% for ACR20, 50 and 70 responses, respectively) as well as good skin responses (66.3% clear or almost clear skin) and improvement of physical function (-0.41 Health Assessment Questionnaire Disability Index, HAQ-DI; change from baseline) at week 24. Radiographic progression in the MTX arm was very low with 0.08 mean change from baseline to week 48 and 89.4% of patients were not progressing in the PsA modified Sharp van der Heijde Score. However, baseline radiographic damage was low in this population, possibly contributing to a low amount of radiographic progression across all treatment arms.[19]

Efficacy of biological disease modifying anti-rheumatic drugs

TNFi

Two trials investigated the efficacy of TNF inhibition in csDMARD naïve (etanercept) and csDMARD insufficient responders (golimumab).*[19, 20]*

The SEAM-PsA study compared etanercept monotherapy or etanercept + methotrexate combination therapy to methotrexate monotherapy in csDMARD naïve patients. Etanercept monotherapy as well as combination therapy with methotrexate were superior to MTX and showed similar efficacy in both treatment groups (ACR20 response at week 24: 50.7% vs. 60.9% vs. 64% for MTX, etanercept

monotherapy and etanercept + MTX combination therapy, respectively); improvement in skin changes, swollen or tender joint counts and disability according to the HAQ did not differ between the etanercept groups and the MTX group. Intravenous golimumab was superior compared to placebo (ACR20 at week 14: 75.1% vs. 21.8%).[19] Detailed results are shown in Tables S3.1 and S3.2.

One cohort study (high RoB) investigated the feasibility of switching to a second or third TNFi after insufficient response to a first TNFi. Patients achieved moderate efficacy results in their second, but only weak responses in their third TNFi course. Median drug survival was 64 months (second TNFi) and 14 months (third TNFi).[21]

Biosimilar studies

Two non-inferiority studies demonstrated the bioequivalence of biooriginators and their respective biosimilars (infliximab vs. CT-P13, low RoB; etanercept vs. CHS-0214).[22, 23] Registry data (high RoB) of non-medical switching between infliximab (INF) and CT-P13 suggest similar clinical efficacy at 3 months post-switch and similar 1-year retention rates (INF: 86.2%; 95% CI 84%-88%; CT-P13 86%; 95% CI 80%-91%).[24]

bDMARDs targeting IL-17A

Ten reports of IL-17A-inhibiting agents (ixekizumab, secukinumab) were included with low RoB of all primary study reports; secukinumab has already been addressed in the previous SLR.[15]

Ixekizumab (IXE) was efficacious in csDMARD-IR as well as TNFi-IR patients. In csDMARD-IR (SPIRIT-P1) better efficacy was seen at week 24 compared to placebo with numerically similar ACR 20, 50 and 70 rates as adalimumab (ADA) (included as reference arm; study not powered to show non-inferiority). Further, structural progression was significantly lower compared to placebo and similar to ADA (Table 2); skin responses were also significantly better with ixekizumab (IXE) than placebo and appeared also better for IXE than ADA.[1, 25] Stratification by concomitant DMARD usage revealed similar results regarding clinical signs and symptoms and physical function and a trend towards an advantage of combination therapy as opposed to monotherapy in the Q4W group. Also in TNFi-IR patients (SPIRIT-P2), IXE showed superiority over placebo for IXE Q2W and Q4W at week 24 regarding signs and symptoms, physical disability, skin disease, and extra-articular manifestations (dactylitis, enthesitis) of PsA.[2, 26, 27]

Secukinumab (FUTURE 1-5) continued to show efficacy in reducing signs and symptoms of arthritis as well as skin disease and extraarticular musculoskeletal manifestations (enthesitis, dactyilitis) and inhibited radiographic progression when compared to placebo in NSAID-IR, csDMARD-IR and TNF-IR patients.[3-5, 28-30]

bDMARDs targeting IL-23-p19

Two trials, investigating molecules targeting the p19 subunit of IL-23, guselkumab (low RoB) and risankizumab (conference abstract), were included. Guselkumab was superior compared to placebo in reducing arthritis signs and symptoms as well as enthesitis and dactylitis.[6] Risankizumab improved arthritis and skin symptoms significantly more than placebo, but there was no clear difference between the different dosing intervals and no significant difference vs placebo in improving dactylitis, enthesitis or physical function.[7, 31]

Other bDMARDs

In an open-label RCT (high RoB) on patients with primary entheseal disease but unbalanced baseline characteristics ustekinumab (UST) was reported to be superior to TNFi therapy in resolving enthesitis (SPARCC=0 at week 24: UST 73.9% vs. TNFi 41.7%, p=0.018) and skin disease (PASI100 at week 24: UST 59% vs. TNFi 29%, p=0.039). No differences in resolving arthritis disease activity was observed between the groups.[32]

A study on abatacept (anti-CD80/86) in PsA patients with previous IR to csDMARDs or TNFis showed significant, but only modest efficacy compared to placebo for musculoskeletal (Table 2) and skin manifestations but was not effective regarding physical function. More patients in the abatacept arm showed radiographic non-progression at week 24 compared to placebo (42.7% vs. 32.7%, nominal p=0.034) while the mean change of structural damage appeared similar between the groups (0.30 vs. 0.35 at week 24 for abatacept and placebo, respectively).[8]

ABT-122 (a dual variable domain immunoglobulin directed against TNF and IL-17) was investigated in a 12-week phase 2 study in MTX-IR patients. ABT-122 was superior to placebo at both doses (120mg and 240mg) showing similar ACR20 responses compared to ADA (Table 2); the 240mg dose showed significantly higher efficacy compared to placebo and ADA in ACR 50 and 70 responses PASI75 and PASI90 responses were similar to ADA and significantly higher in ABT-122 groups compared to placebo.[10]

Interleukin-6 inhibition through clazakizumab showed only modest efficacy compared to placebo, with no clear dose-response and no difference in skin outcomes in a phase 2 trial.[9]

Detailed results of non-TNFi bDMARDs are shown in Table 2.

Efficacy of targeted synthetic disease modifying anti-rheumatic drugs

Three RCTs (all with low RoB) investigated JAKi in PsA (Table 3).

Tofacitinib was superior to placebo in csDMARD-IR patients and, although not formally tested, exhibited numerically similar results as adalimumab in OPAL Broaden.[12] OPAL Beyond investigated tofacitinib in TNFi-IR patients and met its co-primary efficacy endpoints (ACR20 and HAQ at week 12) for 5 and 10mg twice daily (BID), compared to placebo ($p<0.001$). Filgotinib, a selective JAK-1 inhibitor, also significantly reduced signs and symptoms of PsA compared to placebo in a phase 2 trial.[13]

Evidence regarding the clinical efficacy of PDE-4 inhibition using apremilast (APR) in csDMARD-IR patients was confirmed in two RCTs (1 low RoB, 1 unclear RoB).[33, 34] Furthermore, APRwas effective in reducing signs and symptoms of PsA in patients who were csDMARD naïve (PALACE-4, low RoB),[35] or bDMARD-naïve (ACTIVE), but the overall response rates were relatively low.[36]

Detailed results are summarized in Table 3 and Tables S3.1-S3.2.

Tapering/stopping treatment

A small pilot RCT (n=17, high RoB) on phased treatment tapering (of cs and bDMARDs) over a total time-period of 4 months was performed in patients with stable minimal disease activity (MDA) and on a stable treatment regimen for the past 6 months. While 5 of eleven patients in the withdrawal arm (45%) could be withdrawn from treatment without experiencing a flare (i.e. losing MDA at follow-up), six patients experienced a flare (54.6%, 4 on bDMARD+MTX, 2 on MTX monotherapy) compared to none in the continuation (control) arm.[37]

A small German cohort study (high RoB) investigated treatment stopping of any DMARD (without tapering) in 26 patients (14 receiving MTX monotherapy and 12 receiving TNFi therapy) with absence of any disease symptoms (arthritis, enthesitis, dactylitis, axial disease) and minimal skin disease (PASI<1). 76.9% of patients experienced a flare after a mean of 74.5 (±51.7) days, with no difference between previous treatments or any other variable predictive for flare.[38]

Safety

Cohort and case-control studies

bDMARD therapy was associated with an increased infection risk (odds ratio, OR 1.7 vs. no bDMARD; 95% confidence interval (CI) 1.33–2.18) while csDMARD therapy was not (OR vs. no csDMARD 1.15; 95% CI 0.91–1.47).[39] A study investigating the risk of herpes zoster found a significantly increased risk in patients treated with glucocorticoids (HR 1.08; 95%CI 1.04-1.13) and TNFi + csDMARD combination therapy (HR 2.37; 95% CI 1.32-4.22), but not with either csDMARD or TNFi monotherapy.[40] Influenza vaccination was safe and effective in inducing immune responses in PsA patients receiving TNFi and/or csDMARD treatment.[41]

A large cohort study from the UK utilizing a medical record database found a higher incidence of major adverse cardiac events (MACE) in PsA patients without DMARD prescription (HR 1.24, 95% CI 1.03–1.49), while PsA patients with DMARD prescription did not show a significantly higher incidence (HR 1.17, 95% CI 0.95–1.46) when compared to matched control patients (without the diagnosis of PsO, PsA or RA and without DMARD prescription).[42] Eder et al. investigated the incidence of cardiovascular events in a large PsA clinic and found no difference in MACE between TNFi vs. MTX vs. untreated PsA patients, and further no increased incidence in patients treated with glucocorticids or NSAIDs.[43] Another cohort study from a UK register found a significantly higher incidence rate of MACE in patients receiving glucocorticoids (IRR 4.95; 95% CI 2.04–12.01) as compared to patients receiving DMARDs (MTX, SZP, bDMARDs: IRR 1.31; 95% CI 0.99–1.73; LEF, AZA: IRR 0.71 95% CI 0.23–2.21) and PsA patients without drug prescription (reference group).[44]

No increased risk of cancer (risk ratio of TNFi treated vs. TNFi naïve: 0.9; 95%CI 0.7-1.1) was found in a study combining two large population based registries from Sweden (ARTIS) and Denmark (DANBIO).[45] A small Italian longitudinal cohort study investigated the incidence of malignancies and found no increased risk of malignancy occurrence in patients receiving TNFi therapy compared to csDMARD treated patients after adjusting for conventional risk factors.[46]

TNFi treatment did not lead to an increased risk for development of multiple sclerosis in an analysis of the Danish DANBIO registry (SIR: 1.45; 95%CI 0.20-10.3).[47] No new safety signals were found in a study investigating infusion reactions in a large cohort of patients receiving infliximab irrespective of the indication.[48]

Adverse events of special interest of randomized controlled trials and long-term extension studies

Ixekizumab showed increased rates of injection site reactions as compared to control arms (SPIRIT-P1: PLC 4.7% vs. IXEQ4W 24.3% vs. IXEQ2W 26.5% vs. ADA 5.9%; SPIRIT-P2: PLC 4% vs. IXEQ4W 11% vs. IXEQ2W 24%) at week 24. Candida infections were observed in patients treated with IXE (SPIRIT-P1: PLC and ADA 0 vs. 2 cases receiving IXE; SPIRIT-P2: PLC 0 vs. IXE 8 (3%) cases).[49, 50] During the placebo-controlled period no incident case of inflammatory bowel disease occurred.[1, 2] However, one event of inflammatory bowel disease (IBD) occurred after week 108 in SPIRIT-P2.[50] In a LTE of a phase 2 study investigating brodalumab (IL-17 receptor inhibitor) 11 cases of oral candidiasis, 1 report of suicidal ideation and 1 case of neutropenia was observed.[51]

No new safety signals were observed in studies investigating apremilast, with nausea and diarrhea more commonly occurring in treatment groups as compared to placebo.[33-36, 52] In ACTIVE two patients treated with apremilast experienced an AE of depression during the placebo-controlled period and another two during the extension apremilast-exposure period.[36]

IL-6 inhibition with clazakizumab did not show new safety signals compared to IL-6R inhibitors.[9]

During the treatment period of guselkumab (IL-23-p19i) most AEs were mild and similar compared to placebo.[6] One adjudicated major cardiovascular event (MACE) occurred in a patient receiving risankizumab (IL-23-p19i), and two cases of depression, with none on placebo.[31]

No new unexpected safety events were identified in LTEs of studies investigating ustekinumab and certolizumab-pegol.[53, 54]

JAK inhibition with tofacitinib showed higher rates of herpes zoster (IR 2.05; 95% CI 1.17-3.33) and MACE were reported in three patients (IR 0.38; 95% CI 0.08-1.11).[55] One case of herpes zoster and one MACE were observed in patients treated with filgotinib (vs. none in the placebo group).[13] While no venous thromboembolic events or pulmonary embolisms were observed in PsA patients treated with tofacitinib or filgotinib, [13, 55] such events were seen in other indications when tofacitinib, baricitinib and upadacitnib were used, especially in an ongoing study in RA patients with high cardiovascular risk (tofacitinib study A3921133); warnings in these regards were issued by regulators, especially with respect to patients with a high risk for venous thromboembolic events.[56, 57]

DISCUSSION

To inform the taskforce conducting the 2019 update of the EULAR recommendations for pharmacologic management of PsA, this SLR was conducted and included results of 56 publications from January 2015 to December 2018. The field is emerging quickly and several new compounds, not captured in the timeframe of this update are currently under investigation.[58, 59]

Efficacy of TNF inhibition across various disease domains was confirmed, as well as the bioequivalence of biosimilars compared to their biooriginators. IL-17A inhibition was effective across all disease domains, while bispecific inhibition of TNF and IL-17A (ABT-122) showed numerically better results compared to ADA. Agents targeting the subunit p19 of IL-23 had heterogenous results. Guselkumab had good efficacy in reducing arthritis, skin, enthesitis and dactylitis symptoms, while risankizumab was only efficacious in resolving arthritis and skin disease. Inhibition of Janus kinases appeared effective in PsA. Clinical efficacy of PDE4 inhibition was confirmed, however radiographic outcomes have still not been assessed.

Switching to a second TNFi after failure of a first course of TNFi therapy appears to be effective based on observational data. Studies on DMARD tapering in PsA are scarce - only one small pilot RCT studied treatment tapering with 20-45% of patients continuing to have controlled disease activity after treatment cessation for 3 months.

Evaluation of treatment safety across 9 cohort studies and 1 case-control study did not reveal new safety signals for TNFi and csDMARDs regarding infections, occurrence of cardiovascular events, malignancies, infusion reactions or incidence of multiple sclerosis in PsA patients. Safety data of RCTs and respective LTEs showed higher rates of injection site reactions and candida infections in patients receiving IXE, as well as one event of IBD after 108 weeks, in line with data on secukinumab. Herpes zoster rates were higher in patients receiving tofacitinib, and one herpes zoster event was seen in a patient receiving filgotinib. No venous thromboembolic events or pulmonary embolisms were reported in any of the RCTs or LTEs in JAKi treated PsA patients, but regulators issued warnings on the risk of venous thromboembolism (VTE) and pulmonary embolism (PE) based on data in other patient populations and indications, especially for patients at risk for VTE.

This SLR has several limitations: (1) abstract screening, report analysis, risk of bias analysis and data extraction were performed by one researcher only (A.K.); (2) due to the heterogeneity of the RCTs included, meta-analysis would not have led to representative results, therefore results were reported

narratively; (3) only little data on drug tapering and only few safety studies were available for analysis, limiting the conclusions on these topics; (4) no trial has been published that investigated the efficacy of treatments on axial spondylarthritis in PsA patients; we could therefore not address this aspect in our SLR.

This SLR informed the task force on the 2019 update of the EULAR management recommendations for pharmacologic treatment in PsA.

Contributors

All authors contributed and finally approved the current manuscript.

Patient and Public Involvement statement

The taskforce on this project involved a PPI representative (MdW), member of the EULAR Standing Committee of People with Arthritis/Rheumatism in Europe, who contributed during all task force meetings, especially to take patient perspectives into account and refine research questions.

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Competing interests

Andreas Kerschbaumer, MD: Bristol-Myers Squibb, Celgene, Eli-Lilly, Gilead, Merck Sharp and Dohme, Novartis and Pfizer

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REFERENCES

1. Mease PJ, van der Heijde D, Ritchlin CT, Okada M, Cuchacovich RS, Shuler CL, et al. Ixekizumab, an interleukin-17A specific monoclonal antibody, for the treatment of biologic-naive patients with active psoriatic arthritis: results from the 24-week randomised, double-blind, placebo-controlled and active (adalimumab)-controlled period of the phase III trial SPIRIT-P1. Annals of the Rheumatic Diseases. 2017 Jan; 76(1):79-87.
2. Nash P, Kirkham B, Okada M, Rahman P, Combe B, Burmester GR, et al. Ixekizumab for the treatment of patients with active psoriatic arthritis and an inadequate response to tumour necrosis factor inhibitors: results from the 24-week randomised, double-blind, placebo-controlled period of the SPIRIT-P2 phase 3 trial. Lancet. 2017 06 10; 389(10086):2317-2327.
3. Nash P, Mease PJ, McInnes IB, Rahman P, Ritchlin CT, Blanco R, et al. Efficacy and safety of secukinumab administration by autoinjector in patients with psoriatic arthritis: results from a randomized, placebo-controlled trial (FUTURE 3). Arthritis Res Ther. 2018 Mar 15; 20(1):47.
4. Kivitz A, Nash P, Tahir H, Everding A, Pellet P, Widmer A, et al. Arthritis: primary results through 52weeks from a phase-3 randomized placebo-controlled study (future 4). Journal of clinical rheumatology Conference: 20th pan-american league of associations of rheumatology congress, PANLAR 2018 Argentina. 2018; 24(3 Supplement 1):S1-S2.
5. Mease P, van der Heijde D, Landewe R, Mpofu S, Rahman P, Tahir H, et al. Secukinumab improves active psoriatic arthritis symptoms and inhibits radiographic progression: primary results from the randomised, double-blind, phase III FUTURE 5 study. Annals of the Rheumatic Diseases. 2018 Jun; 77(6):890-897.
6. Deodhar A, Gottlieb AB, Boehncke WH, Dong B, Wang Y, Zhuang Y, et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis: a randomised, double-blind, placebo-controlled, phase 2 study. Lancet. 2018 06 02; 391(10136):2213-2224.
7. Mease P, Kellner H, Morita A, Kivitz A, Papp K, Aslanyan S. Efficacy and safety results from a phase 2 trial of risankizumab, a selective IL-23p19 inhibitor, in patients with active psoriatic arthritis. Arthritis rheumatol. 2017; 69(10).
8. Mease PJ, Gottlieb AB, van der Heijde D, FitzGerald O, Johnsen A, Nys M, et al. Efficacy and safety of abatacept, a T-cell modulator, in a randomised, double-blind, placebo-controlled, phase III study in psoriatic arthritis. Annals of the Rheumatic Diseases. 2017 Sep; 76(9):1550-1558.
9. Mease PJ, Gottlieb AB, Berman A, Drescher E, Xing J, Wong R, et al. The Efficacy and Safety of Clazakizumab, an Anti-Interleukin-6 Monoclonal Antibody, in a Phase IIb Study of Adults With Active Psoriatic Arthritis. Arthritis rheumatol. 2016 09; 68(9):2163-2173.
10. Mease PJ, Genovese MC, Weinblatt ME, Peloso PM, Chen K, Othman AA, et al. Phase II Study of ABT-122, a Tumor Necrosis Factor- and Interleukin-17A-Targeted Dual Variable Domain Immunoglobulin, in Patients With Psoriatic Arthritis With an Inadequate Response to Methotrexate. Arthritis rheumatol. 2018 Nov; 70(11):1778-1789.
11. Gladman D, Rigby W, Azevedo VF, Behrens F, Blanco R, Kaszuba A, et al. Tofacitinib for Psoriatic Arthritis in Patients with an Inadequate Response to TNF Inhibitors. New England Journal of Medicine. 2017 10 19; 377(16):1525-1536.
12. Mease P, Hall S, FitzGerald O, van der Heijde D, Merola JF, Avila-Zapata F, et al. Tofacitinib or Adalimumab versus Placebo for Psoriatic Arthritis. New England Journal of Medicine. 2017 10 19; 377(16):1537-1550.
13. Mease P, Coates LC, Helliwell PS, Stanislavchuk M, Rychlewska-Hanczewska A, Dudek A, et al. Efficacy and safety of filgotinib, a selective Janus kinase 1 inhibitor, in patients with active psoriatic arthritis (EQUATOR): results from a randomised, placebo-controlled, phase 2 trial. Lancet. 2018 12 01; 392(10162):2367-2377.

14. Vandendorpe AS, de Vlam K, Lories R. Evolution of psoriatic arthritis study patient population characteristics in the era of biological treatments. RMD Open. 2019; 5(1):e000779.
15. Ramiro S, Smolen JS, Landewe R, van der Heijde D, Dougados M, Emery P, et al. Pharmacological treatment of psoriatic arthritis: a systematic literature review for the 2015 update of the EULAR recommendations for the management of psoriatic arthritis. Annals of the Rheumatic Diseases. 2016 Mar; 75(3):490-498.
16. van der Heijde D, Aletaha D, Carmona L, Edwards CJ, Kvien TK, Kouloumas M, et al. 2014 Update of the EULAR standardised operating procedures for EULAR-endorsed recommendations. Ann Rheum Dis. 2015 Jan; 74(1):8-13.
17. Wells G. The Newcastle-Ottawa Scale (NOS) for assessing the quality of non randomised studies in meta-analyses. http://www ohri ca/programs/clinical_epidemiology/oxford asp. 2001.
18. Higgins JPT, Altman DG, Gøtzsche PC, Jüni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. 2011; 343:d5928.
19. Mease PJ, Gladman DD, Collier DH, Ritchlin CT, Helliwell PS, Liu L, et al. Etanercept and Methotrexate as Monotherapy or in Combination for Psoriatic Arthritis: Primary Results From a Randomized, Controlled Phase III Trial. Arthritis rheumatol. 2019 Jul; 71(7):1112-1124.
20. Kavanaugh A, Husni ME, Harrison DD, Kim L, Lo KH, Leu JH, et al. Safety and Efficacy of Intravenous Golimumab in Patients With Active Psoriatic Arthritis: Results Through Week Twenty-Four of the GO-VIBRANT Study. Arthritis rheumatol. 2017 11; 69(11):2151-2161.
21. Kristensen LE, Lie E, Jacobsson LT, Christensen R, Mease PJ, Bliddal H, et al. Effectiveness and Feasibility Associated with Switching to a Second or Third TNF Inhibitor in Patients with Psoriatic Arthritis: A Cohort Study from Southern Sweden. Journal of Rheumatology. 2016 Jan; 43(1):81-87.
22. Jorgensen KK, Olsen IC, Goll GL, Lorentzen M, Bolstad N, Haavardsholm EA, et al. Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial.[Erratum appears in Lancet. 2017 Jun 10;389(10086):2286; PMID: 28549661]. Lancet. 2017 06 10; 389(10086):2304-2316.
23. Kivitz AJ, Papp K, Devani A, Pinter A, Sinclair R, Ziv M, et al. Randomized, double-blind study comparing CHS-0214 with etanercept (ENBREL) in patients with psoriasis and psoriatic arthritis. Arthritis and rheumatology Conference: american college of rheumatology/association of rheumatology health professionals annual scientific meeting, ACR/ARHP 2016 United states Conference start: 20161111 Conference end: 20161116. 2016; 68:2142-2143.
24. Glintborg B, Sorensen IJ, Loft AG, Lindegaard H, Linauskas A, Hendricks O, et al. A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry. Annals of the Rheumatic Diseases. 2017 Aug; 76(8):1426-1431.
25. Van Der Heijde D, Okada M, Lee C, Shuler CL, Rathmann S, Lin CY, et al. Radiographic progression of structural joint damage in patients with active psoriatic arthritis treated with ixekizumab over 52 weeks. Annals of the rheumatic diseases Conference: annual european congress of rheumatology, EULAR 2017 Spain. 2017; 76(Supplement 2):144-145.
26. Coates LC, Kishimoto M, Gottlieb A, Shuler CL, Lin CY, Lee CH, et al. Ixekizumab efficacy and safety with and without concomitant conventional disease-modifying antirheumatic drugs (cDMARDs) in biologic DMARD (bDMARD)-naive patients with active psoriatic arthritis (PsA): results from SPIRIT-P1. RMD Open. 2017; 3(2):e000567.
27. Nash P, Behrens F, Orbai AM, Rathmann SS, Adams DH, Benichou O, et al. Ixekizumab is efficacious when used alone or when added to conventional synthetic disease-modifying antirheumatic drugs (cDMARDs) in patients with active psoriatic arthritis and previous inadequate response or intolerance to tumour necrosis factor inhibitors. RMD Open. 2018; 4(2):e000692.

28. Kavanaugh A, McInnes IB, Mease PJ, Hall S, Chinoy H, Kivitz AJ, et al. Efficacy of Subcutaneous Secukinumab in Patients with Active Psoriatic Arthritis Stratified by Prior Tumor Necrosis Factor Inhibitor Use: Results from the Randomized Placebo-controlled FUTURE 2 Study. Journal of Rheumatology. 2016 09; 43(9):1713-1717.
29. van der Heijde D, Landewe RB, Mease PJ, McInnes IB, Conaghan PG, Pricop L, et al. Brief Report: Secukinumab Provides Significant and Sustained Inhibition of Joint Structural Damage in a Phase III Study of Active Psoriatic Arthritis. Arthritis rheumatol. 2016 Aug; 68(8):1914-1921.
30. McInnes IB, Mease PJ, Ritchlin CT, Rahman P, Gottlieb AB, Kirkham B, et al. Secukinumab sustains improvement in signs and symptoms of psoriatic arthritis: 2 year results from the phase 3 FUTURE 2 study. Rheumatology. 2017 11 01; 56(11):1993-2003.
31. Mease PJ, Kellner H, Morita A, Kivitz AJ, Papp KA, Aslanyan S, et al. Efficacy and safety of risankizumab, a selective IL-23p19 inhibitor, in patients with active psoriatic arthritis over 24 weeks: results from a phase 2 trial. Annals of the rheumatic diseases Conference: annual european congress of rheumatology, EULAR 2018 Netherlands. 2018; 77(Supplement 2):200-201.
32. Araujo EG, Englbrecht M, Hoepken S, Finzel S, Kampylafka E, Kleyer A, et al. Effects of ustekinumab versus tumor necrosis factor inhibition on enthesitis: Results from the enthesial clearance in psoriatic arthritis (ECLIPSA) study. Seminars in Arthritis and Rheumatism. 2018.
33. Cutolo M, Myerson GE, Fleischmann RM, Liote F, Diaz-Gonzalez F, Van den Bosch F, et al. A Phase III, Randomized, Controlled Trial of Apremilast in Patients with Psoriatic Arthritis: Results of the PALACE 2 Trial. Journal of Rheumatology. 2016 09; 43(9):1724-1734.
34. Edwards CJ, Blanco FJ, Crowley J, Birbara CA, Jaworski J, Aelion J, et al. Apremilast, an oral phosphodiesterase 4 inhibitor, in patients with psoriatic arthritis and current skin involvement: a phase III, randomised, controlled trial (PALACE 3). Annals of the Rheumatic Diseases. 2016 Jun; 75(6):1065-1073.
35. Wells AF, Edwards CJ, Kivitz AJ, Bird P, Nguyen D, Paris M, et al. Apremilast monotherapy in DMARD-naive psoriatic arthritis patients: Results of the randomized, placebocontrolled PALACE 4 trial. Rheumatology (United Kingdom). 2018; 57(7):1253-1263.
36. Nash P, Ohson K, Walsh J, Delev N, Nguyen D, Teng L, et al. Early and sustained efficacy with apremilast monotherapy in biological-naive patients with psoriatic arthritis: a phase IIIB, randomised controlled trial (ACTIVE). Annals of the Rheumatic Diseases. 2018 May; 77(5):690-698.
37. Moverley A, Coates L, Marzo-Ortega H, Waxman R, Torgerson D, Cocks K, et al. A feasibility study for a randomised controlled trial of treatment withdrawal in psoriatic arthritis (REmoval of treatment for patients in REmission in psoriatic ArThritis (RETREAT (F)). Clinical Rheumatology. 2015 Aug; 34(8):1407-1412.
38. Araujo EG, Finzel S, Englbrecht M, Schreiber DA, Faustini F, Hueber A, et al. High incidence of disease recurrence after discontinuation of disease-modifying antirheumatic drug treatment in patients with psoriatic arthritis in remission. Annals of the Rheumatic Diseases. 2015 Apr; 74(4):655-660.
39. Haddad A, Li S, Thavaneswaran A, Cook RJ, Chandran V, Gladman DD. The Incidence and Predictors of Infection in Psoriasis and Psoriatic Arthritis: Results from Longitudinal Observational Cohorts. J Rheumatol. 2016 Feb; 43(2):362-366.
40. Zisman D, Bitterman H, Shalom G, Feldhamer I, Comanesther D, Batat E, et al. Psoriatic arthritis treatment and the risk of herpes zoster. Annals of the Rheumatic Diseases. 2016 Jan; 75(1):131-135.
41. Polachek A, Korobko U, Mader-Balakirski N, Arad U, Levartovsky D, Kaufman I, et al. Immunogenicity and safety of vaccination against seasonal 2012 influenza virus among patients with psoriatic arthritis and psoriasis. Clin Exp Rheumatol. 2015 Mar-Apr; 33(2):181-186.
42. Ogdie A, Yu Y, Haynes K, Love TJ, Maliha S, Jiang Y, et al. Risk of major cardiovascular events in patients with psoriatic arthritis, psoriasis and rheumatoid arthritis: a population-based cohort study. Annals of the Rheumatic Diseases. 2015 Feb; 74(2):326-332.

43. Eder L, Wu Y, Chandran V, Cook R, Gladman DD. Incidence and predictors for cardiovascular events in patients with psoriatic arthritis. Ann Rheum Dis. 2016 Sep; 75(9):1680-1686.
44. Li L, Hagberg KW, Peng M, Shah K, Paris M, Jick S. Rates of Cardiovascular Disease and Major Adverse Cardiovascular Events in Patients With Psoriatic Arthritis Compared to Patients Without Psoriatic Arthritis. J. 2015 Dec; 21(8):405-410.
45. Hellgren K, Dreyer L, Arkema EV, Glintborg B, Jacobsson LT, Kristensen LE, et al. Cancer risk in patients with spondyloarthritis treated with TNF inhibitors: a collaborative study from the ARTIS and DANBIO registers. Annals of the Rheumatic Diseases. 2017 Jan; 76(1):105-111.
46. Costa L, Caso F, Del Puente A, Di Minno MN, Peluso R, Scarpa R. Incidence of Malignancies in a Cohort of Psoriatic Arthritis Patients Taking Traditional Disease Modifying Antirheumatic Drug and Tumor Necrosis Factor Inhibitor Therapy: An Observational Study. Journal of Rheumatology. 2016 12; 43(12):2149-2154.
47. Dreyer L, Magyari M, Laursen B, Cordtz R, Sellebjerg F, Locht H. Risk of multiple sclerosis during tumour necrosis factor inhibitor treatment for arthritis: a population-based study from DANBIO and the Danish Multiple Sclerosis Registry. Annals of the Rheumatic Diseases. 2016 Apr; 75(4):785-786.
48. Choquette D, Faraawi R, Chow A, Rodrigues J, Bensen WJ, Nantel F. Incidence and Management of Infusion Reactions to Infliximab in a Prospective Real-world Community Registry. Journal of Rheumatology. 2015 Jul; 42(7):1105-1111.
49. Chandran V, Fleischmann R, Lespessailles E, Helliwell PS, Benichou O, Erickson J, et al. Efficacy and safety of ixekizumab in patients with active psoriatic arthritis: three year results from a phase 3 study (SPIRIT-P1). Annals of the rheumatic diseases Conference: annual european congress of rheumatology, EULAR 2018 Netherlands. 2018; 77(Supplement 2):385.
50. Orbai A-M, Gellett AM, Kerr L, Constantin A. Efficacy and Safety of Ixekizumab in Patients with Active Psoriatic Arthritis and Previous Inadequate Response to TNF Inhibitors: Two-Year Follow-up from a Phase 3 Study. Arthritis rheumatol; 2018: WILEY 111 RIVER ST, HOBOKEN 07030-5774, NJ USA; 2018.
51. Genovese MC, Mease PJ, Greenwald M, Ritchlin CT, Beaulieu A, Deodhar AA, et al. Two-year clinical response to brodalumab, an anti-interleukin-17 receptor antibody, in patients with psoriatic arthritis. Arthritis and rheumatology. 2015; 67(no pagination).
52. Kavanaugh A, Mease PJ, Gomez-Reino JJ, Adebajo AO, Wollenhaupt J, Gladman DD, et al. Longterm (52-week) results of a phase III randomized, controlled trial of apremilast in patients with psoriatic arthritis. Journal of Rheumatology. 2015 Mar; 42(3):479-488.
53. Kavanaugh A, Puig L, Gottlieb AB, Ritchlin C, Li S, Wang Y, et al. Maintenance of Clinical Efficacy and Radiographic Benefit Through Two Years of Ustekinumab Therapy in Patients With Active Psoriatic Arthritis: Results From a Randomized, Placebo-Controlled Phase III Trial. Arthritis Care Res (Hoboken). 2015 Dec; 67(12):1739-1749.
54. van der Heijde D, Deodhar A, FitzGerald O, Fleischmann R, Gladman D, Gottlieb AB, et al. 4-year results from the RAPID-PsA phase 3 randomised placebo-controlled trial of certolizumab pegol in psoriatic arthritis.[Erratum appears in RMD Open. 2018 Mar 26;4(1):; PMID: 29595841]. RMD Open. 2018; 4(1):e000582.
55. Burmester GR, FitzGerald O, Winthrop K, Azevedo VF, Rigby WFC, Kanik KS, et al. Integrated safety summaryof tofacitinib in psoriatic arthritis clinical studies. Journal of clinical rheumatology Conference: 20th pan-american league of associations of rheumatology congress, PANLAR 2018 Argentina. 2018; 24(3 Supplement 1):S8.
56. Safety Study Of Tofacitinib Versus Tumor Necrosis Factor (TNF) Inhibitor In Subjects With Rheumatoid Arthritis - Full Text View - ClinicalTrials.gov. [cited; Available from: https://clinicaltrials.gov/ct2/show/NCT02092467?term=NCT02092467&draw=2&rank=1
57. Increased risk of blood clots in lungs and death with higher dose of Xeljanz (tofacitinib) for rheumatoid arthritis | European Medicines Agency. [cited; 20/03/2019:[Available from:

https://www.ema.europa.eu/en/news/increased-risk-blood-clots-lungs-death-higher-dose-xeljanz-tofacitinib-rheumatoid-arthritis
58. Mease PJ, Chohan S, Fructuoso FJG, Chou RC, Nograles KE, Mendelsohn AM, et al. LB0002 RANDOMISED, DOUBLE-BLIND, PLACEBO-CONTROLLED, MULTIPLE-DOSE, PHASE 2B STUDY TO DEMONSTRATE THE SAFETY AND EFFICACY OF TILDRAKIZUMAB, A HIGH-AFFINITY ANTI-INTERLEUKIN-23P19 MONOCLONAL ANTIBODY, IN PATIENTS WITH ACTIVE PSORIATIC ARTHRITIS. BMJ Publishing Group Ltd 2019.
59. Ritchlin CT, Kavanaugh A, Merola JF, Schett G, Scher JU, Warren RB, et al. Bimekizumab in patients with active psoriatic arthritis: results from a 48-week, randomised, double-blind, placebo-controlled, dose-ranging phase 2b trial. Lancet. 2020 Feb 8; 395(10222):427-440.

Figure Legends

Figure 1: Flow chart for studies reporting efficacy and/or safety of disease modifying anti-rheumatic drugs in PsA, published 2015-2018.

Figure 2: Efficacy results of RCTs stratified by mode of action and disease domain. Data from previous SLRs is also accounted for in this figure. * different instruments used in studies; ACR: American College of Rheumatology Response; CD: cluster of differentiation; GKM: guselkumab; HAQ: Health Assessment Questionnaire Disability Index; IL: interleukin; JAK: Janus kinases; PDE-4: phosphodiesterase-4 inhibitor; PsA-mSvdHS: Psoriatic arthritis modified Sharp van der Heijde score; RKM: risankizumab; TNF: tumor necrosis factor alpha.

Table 1. Drugs investigated in PsA randomised controlled trials published 2015-2018.

Therapeutic compound	No. of articles/ abstracts	Drug target	Population
Biological DMARD			
Golimumab	1	**TNF**	csDMARD/NSAID-IR
Etanercept	1		MTX + DMARD naive
Adalimumab biosimilar (CT-P13)	1		csDMARD-IR
Etanercept biosimilar (CHS-0214)	1		csDMARD-IR
Ixekizumab	10	**IL-17A**	csDMARD-IR / TNFi-IR
Secukinumab	5		NSAID-IR / mixed csDMARD / TNFi-IR
ABT-122	1	**TNF/IL-17A**	csDMARD/TNFi-IR
Ustekinumab	1	**IL12/23**	Patients with active enthesitis
Risankizumab	1	**IL-23-19p**	NSAID/csDMARD/TNFi-IR
Guselkumab	1		csDMARD/TNFi-IR
Clazakizumab	1	**IL-6**	NSAID/csDMARD-IR
Abatacept	1	**CD80/86**	csDMARD/TNFi-IR
Targeted synthetic DMARD			
Apremilast	5	**PDE-4**	csDMARD-IR / TNFi-IR / csDMARD naive
Tofacitinib	2	**JAK 1/2/3**	csDMARD-IR / TNFi-IR
Filgotinib	1	**JAK 1**	csDMARD-IR

cs: conventional synthetic; DMARD: disease modifying anti-rheumatic drug; IL: interleukin; IR: insufficient responders; JAK: janus kinase; MTX: methotrexate; NSAID: non-steroidal anti-inflammatory drug; PDE: phosphodiesterase; TNF: tumor necrosis factor;

Table 2: Trials investigating non-TNF biological disease modifying drugs in PsA.

Study	Population	RoB	Treatment	n	Primary Endpoint	p	ACR20 (%)	ACR50 (%)	ACR70 (%)	ΔmTSS	ΔHAQ	Dactylitis resolution (%)	Enthesitis resolution (%)	PASI 75 (%)
IL-17A inhibitors														
Mease 2017b (SPIRIT-P1) [1]	csDMARD-IR	Low	Placebo ± csDMARD	106	ACR 20 (wk 24)	Ref.	30.2	15.1	5.7	0.49	-0.18	25	19.3	10.4
			IXE 80mg Q4W ± csDMARD	107		<0.001	57.9	40.2	23.4	0.17	-0.44	79.5	42.6	71.2
			IXE 80mg Q2W ± csDMARD	103		<0.001	62.1	46.6	34	0.08	-0.5	76.9	38.6	79.7
			ADA 40mg Q2W ± csDMARD	101		<0.001	57.4	38.6	25.7	0.1	-0.37	77.8	33.3	54.4
Nash 2017 (SPIRIT-P2) [2]	TNFi-IR	Low	Placebo ± csDMARD	118	ACR 20 (wk 24)	Ref.	19.5	5.1	0		-0.2			8.5
			IXE 80mg Q4W ± csDMARD	122		<0.001	53.3	35.2	22.1		-0.6			31.1
			IXE 80mg Q2W ± csDMARD	123		<0.001	48	33.3	12.2		-0.4			33.3
Nash 2018 (FUTURE-3) [3]	Mixed cs/bDMARD-IR	Low	Placebo ± MTX	137	ACR 20 (wk 24)	Ref.	16.1	8.8			-0.17	13.9	15.3	10.2
			SEC 300mg without LD ± MTX	139		<0.001	48.2	34.5			-0.38	47.8	39.8	46.8
			SEC 150mg without LD ± MTX	138		<0.001	42	18.8			-0.27	38.9	36.8	50
Kivitz 2018 (FUTURE-4) [4]	NSAID-IR	Abstract	Placebo ± MTX	114	ACR 20 (wk 16)	Ref.	18.4	6.1				8.1		8.1
			SEC 150mg with LD ± MTX	114		<0.001	41.2	22.8				2.5		52.7
			SEC 150mg without LD ± MTX	113		<0.001	39.8	16.8				17.2		50

Mease 2018c (FUTURE-5) [5]	Mixed	Low	Placebo ± MTX	332	ACR 20 (wk 16)	Ref.	27.4	8.1	4.2	0.5	-0.21	32.3	35.4	12.3
			SEC 300 mg with LD ± MTX	222		<0.001	62.6	39.6	20.3	0.08	-0.55	65.9	55.7	70
			SEC 150 mg with LD ± MTX	220		<0.001	55.5	35.9	18.2	0.17	-0.44	57.5	54.6	60
			SEC 150 mg without LD ± MTX	222		<0.001	59.5	32	14.9	-0.09	-0.45	56.3	41.9	58.1
IL-23p19 inhibitors														
Deodhar 2018 [6]	Mixed csDMARD/ TNFi-IR	Low	Placebo ± MTX	49	ACR 20 (wk 24)	Ref.	18	10	2		-0.06	17	29	13
			GKM 100 mg ± MTX	100		<0.001	58	34	14		-0.42	55	57	79
Mease ACR 2017 [7]	Mixed MTX/TNFi-IR	Abstract	Placebo ± MTX	42	ACR 20 (wk 16)	Ref.	35.7	11.9	0	0.6[a]	-0.09			9.5
			RKM 150 mg Q4W ± MTX	42		<0.05	57.1	23.8	14.3	-0.3[a]	-0.18			75.0
			RKM 150 mg wk 0, 4, 16 ± MTX	42		<0.01	61.9	23.8	7.1	0.2[a]	-0.16			70.0
			RKM 150 mg wk 0, 12 ± MTX	39		<0.05	59.0	38.5	25.6	-0.5[a]	-0.25			73.9
			RKM 75 mg wk 0 ± MTX	20		<0.05	65.0	25.0	15.0	-0.2[a]	-0.16			66.7
Other bDMARDs														
Mease 2016 [9]	NSAID/csDMARD-IR	Low	Placebo ± MTX	41	16	Ref.	29.3	7.3	0.1		-0.27			14.6
			CKM 25 mg ± MTX	41		0.101	46.3	29.3	28.6		-0.44			12.2
			CKM 100 mg ± MTX	42		0.039	52.4	35.7	24.9		-0.4			16.7
			CKM 200 mg ± MTX	41		0.178	39	17.1	16.5		-0.26			4.9
		Low	Placebo ± MTX	211		Ref.	22.3	19.2	10.3	0.3	-0.2	34	21.2	10.1

Mease 2017a (ASTRAEA) [8]	Mixed csDMARD/ TNFi-IR		ABA ± MTX	213	ACR 20 (wk 24)	<0.001	39.4	12.3	6.6	0.35	-0.33	44.3	32.9	16.4
Mease 2018a [10]	MTX-IR	Low	Placebo + MTX	24	ACR 20 (wk 12)	Ref.	25	12.5	4.2		-0.28			27
			ADA 40mg Q2W + MTX	72		NR	68.1	37.5	15.3		-0.58			57.6
			ABT-122 120mg Q2W	71		<0.001	64.8	36.6	22.5		-0.55			74.4
			ABT-122 240mg Q2W	73		<0.001	75.3	53.4	31.5		-0.56			77.6

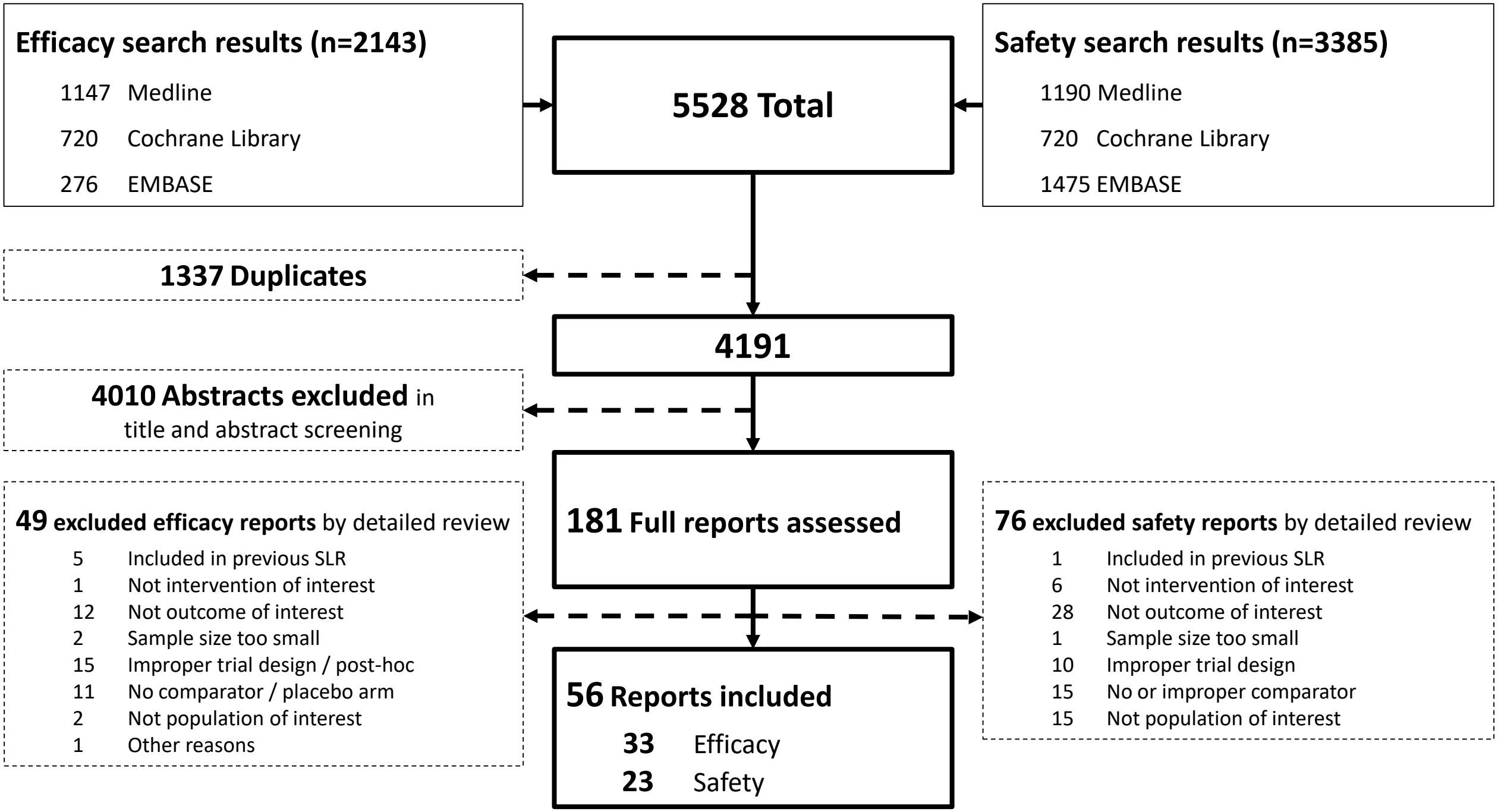
[a] week 24; [b] week 52; ACR: American College of Rheumatology; ABA: abatacept; ADA: adalimumab; bDMARD: biological disease modifying drug; CKM: clazakizumab; csDMARD: conventional synthetic disease modifying drug; GKM: guselkumab; HAQ-DI: Health Assessment Questionnaire Disability Index; IL: interleukin; IR: insufficient responders; IXE: ixekizumab; mTSS: PsA modified total Sharp score; NR: not reported; MTX: methotrexate; PASI: Psoriasis Area and Severity Index; QNW: every N weeks; Ref: reference arm; RKM: risankizumab; RoB: Risk of bias; SEC: secukinumab; TNF: Tumor necrosis factor; wk: week;

Table 3: Trials investigating targeted synthetic disease modifying anti-rheumatic drugs in PsA.

Study	Population	RoB	Treatment	n	Primary Endpoint	p	ACR 20 (%)	ACR50 (%)	ACR70 (%)	ΔmTSS	ΔHAQ-DI	Dactylitis resolution (%)	Enthesitis resolution (%)	PASI 75 (%)
Janus kinase inhibitors														
Mease 2018d (EQUATOR) [13]	csDMARD-IR	Low	Placebo ± csDMARD	66	ACR 20 (wk 16)	Ref.	33.3	15.2	6.1		-0.28			15
			FILGO 200mg OD ± csDMARD	65		<0.001	80	47.7	23.1		-0.57			45.2
Gladman 2017 (OPAL Beyond) [11]	TNFi-IR	Low	Placebo ± csDMARD	131	ACR 20 (wk 12) ΔHAQ (wk 12)	Ref.	24	15	10		-0.14	28.6	21.5	14
			TOFA 5mg BID ± csDMARD	131		<0.001 <0.001	50	30	17		-0.39	51.5	39.8	21
			TOFA 10mg BID ± csDMARD	132		<0.001 <0.001	47	28	14		-0.35	50.8	32.3	43
Mease 2017c (OPAL Broaden) [12]	csDMARD-IR	Low	Placebo ± csDMARD	105	ACR 20 (wk 12) ΔHAQ (wk 12)	Ref.	33	10	5	0.00 [b,c] / 0.09 [b,d]	-0.18	32.8	21.5	15
			TOFA 5mg BID ± csDMARD	107		<0.01 0.006	50	28	17	0.01[b]	-0.35	34.4	33.3	43
			TOFA 10mg BID ± csDMARD	104		<0.001 <0.001	61	40	14	-0.01[b]	-0.4	60	40.6	44
			ADA 40mg Q2W ± csDMARD	106		NR	52	33	19	-0.07[b]	-0.38	46.6	47.4	39
Phosphodiesterase-4 inhibitors														

Cutolo 2016 (PALACE-2) [33]	csDMARD / TNF-IR	Unclear	Placebo ± csDMARD	159	ACR 20 (wk 16)	Ref.	18.9	5	0.6		-0.07			2.7
			APR 20mg BID ± csDMARD	163		<0.001	37.4	14.7	3.7		-0.17			18.8
			APR 30mg BID ± csDMARD	162		0.006	32.1	10.5	1.2		-0.23			22.1
Edwards 2016 (PALACE-3) [34]	csDMARD / TNF-IR	Low	Placebo ± csDMARD	169	ACR 20 (wk 16)	Ref.	18.3	8.3	2.4		-0.07			8
			APR 20mg BID ± csDMARD	169		0.030	28.4	12.4	4.7		-0.13			20
			APR 30mg BID ± csDMARD	167		<0.001	40.7	15	3.6		-0.2			21
Wells 2018 (PALACE-4) [35]	csDMARD naïve	Unclear	Placebo	176	ACR 20 (wk 16)	Ref.	15.9	4.5	1.1		0.03	31.1	19.1	10.8
			APR 20mg BID	175		0.006	28	11.4	4		-0.17	40.4	21.4	17.3
			APR 30mg BID	176		0.001	30.7	11.4	4		-0.21	40.5	35.1	25.7
Nash 2018 (ACTIVE) [36]	bDMARD naïve	Unclear	Placebo	109	16	Ref.	20.2	4.6	0		-0.06		33.3	
			APR 30mg BID	110		0.004	38.2	18.2	6.4		-0.21		46.4	

[a] week 24; [b] week 52; [c] Placebo advancing to TOFA 5mg BID; [d] Placebo advancing to TOFA 10mg BID; ACR: American College of Rheumatology; ADA: adalimumab; APR: apremilast; bDMARD: biological disease modifying drug; BID: twice daily; csDMARD: conventional synthetic disease modifying drug; FILGO: filgotinib; HAQ-DI: Health Assessment Questionnaire Disability Index; IR: insufficient responders; mTSS: PsA modified total Sharp score; NR: not reported; PASI: Psoriasis Area and Severity Index; QNW: every N weeks; Ref: reference arm; RoB: Risk of bias; TNF: Tumor necrosis factor; wk: week; TOFA: tofacitinib;


Efficacy search results (n=2143)
1147 Medline
720 Cochrane Library
276 EMBASE
Safety search results (n=3385)
1190 Medline
720 Cochrane Library
1475 EMBASE
5528 Total
1337 Duplicates
4191
4010 Abstracts excluded in title and abstract screening
181 Full reports assessed
49 excluded efficacy reports by detailed review
5 Included in previous SLR
1 Not intervention of interest
12 Not outcome of interest
2 Sample size too small
15 Improper trial design / post-hoc
11 No comparator / placebo arm
2 Not population of interest
1 Other reasons
76 excluded safety reports by detailed review
1 Included in previous SLR
6 Not intervention of interest
28 Not outcome of interest
1 Sample size too small
10 Improper trial design
15 No or improper comparator
15 Not population of interest
56 Reports included
33 Efficacy
23 Safety

Target	Disease domain					
	Arthritis (ACR 70)	Physical function (HAQ)	Skin (PASI 75)	Enthesitis*	Dactylitis*	Radiographic damage (PsA-mSvdHS)
TNF [19, 20]						
IL-17A [25-30]						
TNF/IL17A [10]						
CD80/86 [8]						
IL-6 [9]						
IL-23-p19 [6, 7, 31]	GKM / RKM	GKM / RKM	GKM / RKM	GKM / RKM	GKM / RKM	
JAK [11-13]						
PDE-4 [33-36]						

	Statistically superior compared to placebo
	Statistically superior compared to placebo; pre-specified post-hoc analysis
	Not statistically different compared to placebo; numerically better results
	No difference compared to placebo
	Not evaluated / reported