Psoriatic arthritis

CLINICAL SCIENCE

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

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

Methods This is a 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 publications (efficacy: n=33; safety n=23) were analysed. The articles were on tumour necrosis factor (TNF) inhibitors (n=6; golimumab, etanercept and biosimilars), interleukin (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 (IL-12/23) with TNF inhibitor therapy in patients with entheseal disease. Three articles investigated DMARD tapering. Trials on targeted synthetic DMARDs investigated apremilast (phosphodiesterase-4 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 in PsA are available and have demonstrated efficacy against placebo. Efficacy varies across PsA manifestations. Safety must also be taken into account. This review informed the development of the European League Against Rheumatism (EULAR) 2019 updated PsA management recommendations.

Key messages

What is already known about this subject?
► The previous update of the European League Against Rheumatism (EULAR) recommendations on pharmacological management of psoriatic arthritis (PsA) was conducted in 2015.
► This systematic literature research was performed to inform the 2019 EULAR task force on the evidence that emerged on the efficacy and safety of pharmacological treatment of patients with PsA.

What does this study add?
► Biological disease-modifying antirheumatic drugs targeting interleukin (IL)-17A (secukinumab, ixekizumab), guselkumab (targeting the subunit p19 of IL-23) as well as Janus kinase inhibitors (JAKi) (tofacitinib, filgotinib) were effective in reducing signs and symptoms across all disease domains of patients with PsA.
► No new safety signals for tumour necrosis factor inhibitors and conventional synthetic disease-modifying antirheumatic drugs were identified, and no venous thromboembolic events or pulmonary embolisms were reported in the evaluated randomised controlled trials and their long-term extensions in JAKi-treated patients with PsA.

How might this impact on clinical practice or future developments?
► This systematic literature research provided the 2019 EULAR PsA management recommendations task force with evidence that emerged since 2015.

INTRODUCTION

Pharmacological treatment options for psoriatic arthritis (PsA) have significantly increased over the past years. Data from randomised controlled trials (RCTs) have provided evidence for efficacy of various novel agents, such as biological or targeted synthetic disease-modifying antirheumatic drugs (DMARDs). Among these are biological DMARDs (bDMARDs) targeting interleukin (IL)-17A (ixekizumab, secukinumab)8 9; the p19 subunit of IL-23 (guselkumab, risankizumab)9 10; the costimulation molecule CD80/86 (abatacept);11 the IL-6 cytokine (clazakizumab);12 and a bispecific antibody inhibiting tumour necrosis factor (TNF) and IL-17A...
Further, Janus kinase inhibitors (JAKi; including tofacitinib and filgotinib) have recently been assessed in PsA. Safety evaluation of pharmacological interventions in PsA has to be derived beyond the controlled period of RCTs and needs to account for long-term extension (LTE) phases of RCTs and patients included in observational clinical cohorts, registries and postmarketing monitoring; the 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.

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 SLR performed in 2015.

METHODS

The review protocol for this SLR was developed by the steering group in accordance with the EULAR standardised operating procedures for EULAR recommendations. The eligibility criteria for inclusion were defined, conforming to previous SLRs, as studies on adult patients (≥18 years) with PsA, classified according to the Classification Criteria for Psoriatic Arthritis (CASPAR) or Moll and Wright criteria. Population of interest was as follows: naive for conventional synthetic DMARDs (csDMARDs) or insufficient responders (IR) to non-steroidal anti-inflammatory drugs (NSAIDs) who reported, which was by the Psoriatic Arthritis Modified Sharp van der Heijde Score. For safety, RCTs and their LTE 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 (LF) in Embase, Medline and the Cochrane Library without language restriction. Based on the previous SLR, the search included all studies published between 1 January 2015 and 21 December 2018 (last date searched). For completeness, data of full articles published after the last date of the literature

Figure 1 Flow chart of studies reporting efficacy and/or safety of disease-modifying antirheumatic drugs in psoriatic arthritis, published in 2015–2018. SLR, systematic literature research.

Glucocorticoids or NSAIDs; and any combination of these treatments.

For efficacy evaluation, only randomised, controlled, double-blind trials (RCTs) were included. Phase II trials were included if no phase III 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 TNF inhibitor (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 task force 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 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; enthesis; skin disease (evaluated through the Psoriasis Area Severity Index (PASI) or psoriasis-affected body surface area); and physical function (Health Assessment Questionnaire Disability Index (HAQ-DI), Short-Form 36 Physical Component Score). Progression of structural damage was assessed as reported, which was by the Psoriatic Arthritis Modified Sharp van der Heijde Score.

For safety, RCTs and their LTE 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).

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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 online supplementary tables S1.1–S1.6. Title and abstract screening, as well as data extraction, was conducted by one researcher (AK). The results of the title and abstract screening process were discussed with several experienced authors (JS, LG, XB).

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 RoB. Cohort and case–control (ie, safety) studies were assessed using the Newcastle–Ottawa Score; RKM, risankizumab; TNF, tumour necrosis factor; PDE4, phosphodiesterase-4; PsA, psoriatic arthritis; TNF, tumour necrosis factor.

### RESULTS

Of 3528 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 flow chart 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 to have low RoB, while unclear RoB was most commonly due to insufficient reporting on random sequence generation. Open-label studies (n=3) and LTEs (n=13) included were considered to have high RoB. Detailed RoB results (efficacy: online supplementary table S2.2; safety: online supplementary table S4.2.3 and online supplementary table S4.2.4), baseline characteristics (efficacy: online supplementary tables S2.2- S2.5; safety: online supplementary table S4.2.4), and detailed results (online supplementary tables S1.1-S3.2) are presented in the online supplementary appendix.

### Efficacy of csDMARDs

No primary trial data were published from 2015 to 2018 on the efficacy of csDMARDs. Indirect evidence on the efficacy of methotrexate (MTX) was shown in the SEAM-PsA trial. While a placebo arm was absent, MTX monotherapy showed good efficacy regarding arthritis measures (50.7%, 30.6% and 13.8% for ACR20, ACR50 and ACR70 responses, respectively), as well as good skin responses (66.3% clear or almost clear skin) and improvement of physical function (–0.41 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 with 89.4% of patients not progressing in the Psoriatic Arthritis Modified Sharp van der Heijde Score. However, baseline radiographic damage was low in this population, possibly contributing to the low amount of radiographic progression across all treatment arms.19

### Efficacy of bDMARDs

#### TNF inhibitors

Two trials investigated the efficacy of TNF inhibition in csDMARD-naive (etanercept) and csDMARD-IR (golimumab).19 20

The SEAM-PsA study compared etanercept monotherapy or etanercept+MTX combination therapy with MTX monotherapy in csDMARD-naive patients. Etanercept monotherapy as well as combination therapy with MTX 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-DI did not differ between the etanercept group and the MTX group. Intravenous golimumab was superior compared with placebo (ACR20 at week 14: 75.1% vs 21.8%).19 Detailed results are shown in online supplementary 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

#### Targeted synthetic DMARDs

| Biological DMARDs | Articles/abstracts (n) | Drug target | Population |
|-------------------|-----------------------|-------------|------------|
| Golimumab         | 1                     | TNF csDMARD/NSAID-IR |          |
| Etanercept        | 1                     | MTX+csDMARD-naive |          |
| Adalimumab biosimilar (CT-P13) | 1     | csDMARD-IR |          |
| Etanercept biosimilar (CHS-0214) | 1     | csDMARD-IR |          |

| Secukinumab       | 5                     | IL-17A csDMARD-IR/TNF-IR/NSAID-IR/mixed csDMARD/TNF-IR |          |
| ABT-122           | 1                     | TNF/IL-17A csDMARD/TNF-IR |          |
| Ustekinumab       | 1                     | IL-12/23 Patients with active enthesis |          |
| Risankizumab      | 1                     | IL-23–19p NSAID/csDMARD/TNF-IR |          |
| Guselkumab        | 1                     | csDMARD csDMARD-IR |          |
| Clazakizumab      | 1                     | IL-6 NSAID/csDMARD-IR |          |
| Abatacept         | 1                     | CD80/86 csDMARD/TNF-IR |          |

| Targeted synthetic DMARDs | Articles/abstracts (n) | Drug target | Population |
|---------------------------|-----------------------|-------------|------------|
| Apremilast                | 5                     | PDE4 csDMARD-IR/TNF-IR/csDMARD-naive |          |
| Tofacitinib               | 2                     | JAK-1/2/3 csDMARD-IR |          |
| Filgotinib                | 1                     | JAK-1 csDMARD-IR |          |

| csDMARD, conventional synthetic disease-modifying antirheumatic drug; DMARD, disease-modifying antirheumatic drug; IL, interleukin; IR, insufficient responders; JAK, Janus kinase; MTX, methotrexate; NSAID, non-steroidal anti-inflammatory drug; PDE4, phosphodiesterase-4; PsA, psoriatic arthritis; TNF, tumour necrosis factor; TNF, tumour necrosis factor.

### Table 1

Drugs investigated in PsA randomised controlled trials published in 2015–2018

| Therapeutic compound | Articles/abstracts (n) | Drug target | Population |
|----------------------|-----------------------|-------------|------------|
| Biological DMARDs    |                       |             |            |
| Golimumab            | 1                     | TNF csDMARD/NSAID-IR |          |
| Etanercept           | 1                     | MTX+csDMARD-naive |          |
| Adalimumab biosimilar (CT-P13) | 1     | csDMARD-IR |          |
| Etanercept biosimilar (CHS-0214) | 1     | csDMARD-IR |          |
| Secukinumab          | 5                     | IL-17A csDMARD-IR/TNF-IR/NSAID-IR/mixed csDMARD/TNF-IR |          |
| ABT-122              | 1                     | TNF/IL-17A csDMARD/TNF-IR |          |
| Ustekinumab          | 1                     | IL-12/23 Patients with active enthesis |          |
| Risankizumab         | 1                     | IL-23–19p NSAID/csDMARD/TNF-IR |          |
| Guselkumab           | 1                     | csDMARD csDMARD-IR |          |
| Clazakizumab         | 1                     | IL-6 NSAID/csDMARD-IR |          |
| Abatacept            | 1                     | CD80/86 csDMARD/TNF-IR |          |
| Targeted synthetic DMARDs | 5                   | PDE4 csDMARD-IR/TNF-IR/csDMARD-naive |          |
| Apremilast           | 2                     | JAK-1/2/3 csDMARD-IR |          |
| Tofacitinib          | 1                     | JAK-1 csDMARD-IR |          |

| Biological DMARDs    | Articles/abstracts (n) | Drug target | Population |
|----------------------|-----------------------|-------------|------------|
| Golimumab            | 1                     | TNF csDMARD/NSAID-IR |          |
| Etanercept           | 1                     | MTX+csDMARD-naive |          |
| Adalimumab biosimilar (CT-P13) | 1     | csDMARD-IR |          |
| Etanercept biosimilar (CHS-0214) | 1     | csDMARD-IR |          |
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| Clazakizumab         | 1                     | IL-6 NSAID/csDMARD-IR |          |
| Abatacept            | 1                     | CD80/86 csDMARD/TNF-IR |          |
| Targeted synthetic DMARDs | 5                   | PDE4 csDMARD-IR/TNF-IR/csDMARD-naive |          |
| Apremilast           | 2                     | JAK-1/2/3 csDMARD-IR |          |
| Tofacitinib          | 1                     | JAK-1 csDMARD-IR |          |
Table 2  Trials investigating non-TNF biological disease-modifying antirheumatic drugs in PsA

| Study                  | Population | RoB   | Treatment                | n   | Primary endpoint | P value | ACr20 (%) | ACr50 (%) | ACr70 (%) | ΔmTss | ΔHAQ-DI | Dactylitis resolution (%) | Enthesitis resolution (%) | mSIS (%) |
|------------------------|------------|-------|--------------------------|-----|------------------|---------|-----------|-----------|-----------|-------|---------|----------------------------|--------------------------|----------|
| **IL-17A inhibitors**  |            |       |                          |     |                  |         |           |           |           |       |         |                            |                          |          |
| Mease et al (SPIRIT-P1) | csDMARD-IR | Low   | Placebo csDMARD          | 107 | ACr20 (week 24)  | >0.001  | 57.9      | 40.2      | 22.4      | 0.17  | −0.44  | 79.5                       | 42.6                     | 71.2     |
| Mease et al (SPIRIT-P1) | csDMARD-IR | Low   | Placebo csDMARD          | 107 | ACr20 (week 24)  | <0.001  | 62.1      | 46.6      | 34        | 0.08  | −0.5   | 76.9                       | 38.6                     | 79.7     |
| Nash et al (SPIRIT-P2)  | TNF-IR     | Low   | Placebo csDMARD          | 118 | ACr20 (week 24)  | Ref     | 19.5      | 5.1       | 0         | −0.2  | 8.5    |                            |                          |          |
| Nash et al (FUTURE-3)   | csDMARD/sTNF-IR | Low | Placebo sMTX           | 137 | ACr20 (week 24)  | >0.001  | 16.1      | 8.8       | 2.5       | 0.07  | −0.4   | 76.9                       | 38.6                     | 79.7     |
| Nash et al (FUTURE-4)   | NSAID-IR   | Abstract | Placebo sMTX        | 114 | ACr20 (week 16)  | Ref     | 18.4      | 6.1       |           |       | 8.1    |                            |                          |          |
| Mease et al (FUTURE-5)  | Low         |       | Placebo sMTX           | 132 | ACr20 (week 16)  | <0.001  | 27.4      | 8.1       | 4.2       | 0.5   | −0.21  | 32.3                       | 35.4                     | 12.3     |
| Mease et al (FUTURE-5)  | Low         |       | SEC 150 mg without LD+sMTX | 138 | ACr20 (week 16)  | <0.001  | 48.2      | 34.5      |           | 0.38  | −0.44  | 75.7                       | 54.6                     | 60       |
| Mease et al (FUTURE-5)  | Low         |       | SEC 150 mg without LD+sMTX | 138 | ACr20 (week 16)  | <0.001  | 42        | 18.8      |           | 0.27  | −0.45  | 56.3                       | 41.9                     | 58.1     |
| **IL-23p19 inhibitors** |            |       |                          |     |                  |         |           |           |           |       |         |                            |                          |          |
| Deodhar et al (SPIRIT-P1) | csDMARD/TNF-IR | Low | Placebo sMTX           | 42  | ACr20 (week 16)  | >0.001  | 25.7      | 19.8      | 11.9      | 0.6   | −0.28  | 67.9                       | 42.6                     | 67.9     |
| Mease et al (ACR)      | Mixed       |       | Placebo sMTX           | 42  | ACr20 (week 16)  | <0.001  | 57.1      | 23.8      | 14.3      | −0.3  | −0.18  | 75.0                       |                          |          |
| Mease et al (ASTRAEA)  | Mixed csDMARD/TNF-IR | Low | Placebo sMTX           | 41  | ACr20 (week 16)  | <0.001  | 59.5      | 32        | 14.9      | −0.09 | −0.45  | 56.3                       | 41.9                     | 58.1     |
| Other bDMARDs          |            |       |                          |     |                  |         |           |           |           |       |         |                            |                          |          |
| Mease et al (SPIRIT-P1) | NSAID/csDMARD-IR | Low | Placebo sMTX           | 41  | ACr20 (week 24)  | >0.001  | 29.3      | 7.3       | 0.1       | 0.27  | −0.04  | 14.6                       |                          |          |
| Mease et al (SPIRIT-P1) | csDMARD-IR | Low   | Placebo sMTX           | 41  | ACr20 (week 24)  | <0.017  | 46.3      | 29.3      | 28.6      | 0.44  | 12.2   |                            |                          |          |
| Mease et al (SPIRIT-P1) | csDMARD-IR | Low   | Placebo sMTX           | 41  | ACr20 (week 24)  | 0.039   | 52.4      | 35.7      | 24.9      | 0.4   | 16.7   |                            |                          |          |
| Mease et al (SPIRIT-P1) | csDMARD-IR | Low   | Placebo sMTX           | 41  | ACr20 (week 24)  | 0.178   | 39        | 17.1      | 16.5      | 0.26  | 4.9    |                            |                          |          |
| Mease et al (SPIRIT-P1) | csDMARD-IR | Low   | Placebo sMTX           | 211 | ACr20 (week 24)  | <0.001  | 39.4      | 12.3      | 6.6       | 0.35  | −0.33  | 44.3                       | 32.9                     | 16.4     |
| Mease et al (SPIRIT-P1) | csDMARD-IR | Low   | Placebo sMTX           | 213 | ACr20 (week 24)  | <0.001  | 39.4      | 12.3      | 6.6       | 0.35  | −0.33  | 44.3                       | 32.9                     | 16.4     |
| Mease et al (SPIRIT-P1) | csDMARD-IR | Low   | Placebo sMTX           | 24  | ACr20 (week 12)  | Ref     | 25        | 12.5      | 4.2       | 0.28  | 27     |                            |                          |          |
| Mease et al (SPIRIT-P1) | csDMARD-IR | Low   | Placebo sMTX           | 72  | ACr20 (week 12)  | NR      | 68.1      | 37.5      | 15.3      | 0.58  | 75.6   |                            |                          |          |
| Mease et al (SPIRIT-P1) | csDMARD-IR | Low   | Placebo sMTX           | 71  | ACr20 (week 12)  | <0.001  | 64.8      | 36.6      | 22.5      | 0.55  | 74.4   |                            |                          |          |
| Mease et al (SPIRIT-P1) | csDMARD-IR | Low   | Placebo sMTX           | 73  | ACr20 (week 12)  | <0.001  | 75.3      | 53.4      | 31.5      | 0.56  | 77.6   |                            |                          |          |

*Week 24.

ABA, abatacept; ACR, American College of Rheumatology; ADA, adalimumab; bDMARD, biological disease-modifying antirheumatic drug; CKM, certolizumab; csDMARD, conventional synthetic disease-modifying antirheumatic drug; GKM, guselkumab; HAQ-DI, Health Assessment Questionnaire Disability Index; IL, interleukin; IR, insufficient responders; IXE, ixekizumab; LD, loading dose; mTSS, PsA modified total Sharp score; MTX, methotrexate; NR, not reported; NSAID, non-steroidal anti-inflammatory drug; PASI, Psoriasis Area and Severity Index; PVA, psoriatic arthritis; Q4W, every 4 weeks; Q4W, every 2 weeks; Ref, reference arm; RKM, risankizumab; RoB, risk of bias; SEC, secukinumab; TNF, tumour necrosis factor; TNFi, TNF inhibitor.
Psoriatic arthritis
to a first TNFi. Patients achieved moderate efficacy results in their second, but only weak responses in their third TNFi course. The median drug survival was 64 months (second TNFi) and 14 months (third TNFi).

Biosimilar studies
Two non-inferiority studies demonstrated the bioequivalence of bio-originators and their respective biosimilars (infliximab (INF) vs CT-P13, low RoB; etanercept vs CHS-0214).

Registy data (high RoB) of non-medical switching between 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% to 88%; CT-P13: 86%, 95% CI 80% to 91%).

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

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 with placebo, with numerically similar ACR20, ACR50 and ACR70 rates as adalimumab (ADA) (included as reference arm; study not powered to show non-inferiority). Further, structural progression was significantly lower compared with placebo and similar to ADA (table 2); skin responses were also significantly better with IXE than placebo and appeared also better for IXE than ADA.

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 every 2 weeks (Q2W) and every 4 weeks (Q4W) at week 24 regarding signs and symptoms, physical disability, skin disease, and extra-articular manifestations (dactylitis, enthesitis) of PsA.

Secukinumab (FUTURE 1–5) continued to show efficacy in reducing signs and symptoms of arthritis as well as skin disease and extra-articular musculoskeletal manifestations (enthesitis, dactylitis) and inhibited radiographic progression when compared with placebo in NSAID-IR, csDMARD-IR and TNF-IR patients.

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 with placebo in reducing arthritis signs and symptoms, as well as enthesitis and dactylitis. 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 versus placebo in improving dactylitis, enthesitis or physical function.

Other bDMARDs
In an open-label RCT (high RoB) on patients with primary enthesal disease but unbalanced baseline characteristics, ustekinumab (UST) was reported to be superior to TNFi therapy in resolving enthesitis (Spondyloarthritis Research Consortium of Canada Enthesitis Index, 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 were observed between the groups.

A study on abatacept (anti-CD80/86) in patients with PsA with previous IR to csDMARDs or TNFIs showed significant but only modest efficacy compared with 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 with 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).

ABT-122 (a dual variable domain immunoglobulin directed against TNF and IL-17) was investigated in a 12-week phase II study in MTX-IR patients. ABT-122 was superior to placebo at both doses (120mg and 240mg), showing similar ACR20 responses compared with ADA (table 2); the 240mg dose showed significantly higher efficacy compared with placebo and ADA in ACR50 and ACR70 responses. PASI75 and PASI90 responses were similar to ADA and significantly higher in the ABT-122 group compared with placebo.

IL-6 inhibition through clazakizumab showed only modest efficacy compared with placebo, with no clear dose response and no difference in skin outcomes in a phase II trial.

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

Efficacy of tsDMARDs
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 ADA in OPAL Broader.

OPAL Beyond investigated tofacitinib in TNFi-IR patients and met its co-primary efficacy endpoints (ACR20 and HAQ-DI at week 12) for 5 mg and 10 mg two times per day, compared with placebo (p<0.001). Filgotinib, a selective JAK-1 inhibitor, also significantly reduced signs and symptoms of PsA compared with placebo in a phase II trial.

Evidence regarding the clinical efficacy of phosphodiesterase-4 (PDE4) inhibition using apremilast (APR) in csDMARD-IR patients was confirmed in two RCTs (one low RoB, one unclear RoB). Furthermore, APR was effective in reducing signs and symptoms of PsA in patients who were csDMARD-naive (PALACE-4, low RoB) or bDMARD-naive (ACTIVE), but the overall response rates were relatively low.

Detailed results are summarised in table 3 and online supplementary tables S3.1-S3.2.

Tapering/stopping treatment
A small pilot RCT (n=17, high RoB) on phased treatment tapering (of csDMARDs and bDMARDs) over a total time period of 4 months was performed in patients with stable MDA and on a stable treatment regimen for the past 6 months. While 5 of 11 patients in the withdrawal arm (45%) could be withdrawn from treatment without experiencing a flare (ie, losing MDA at follow-up), 6 patients experienced a flare (54.6%), 4 on bDMARD+MTX, 2 on MTX monotherapy) compared with none in the continuation (control) arm.

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). Of the patients, 76.9% experienced a flare after a mean of 74.5 (±51.7) days, with no difference between previous treatments or any other variable predictive of flare.
### Table 3: Trials investigating targeted synthetic disease-modifying antirheumatic drugs in PsA

| Study | Population | RoB | Treatment | n | Primary endpoint | P value | ACR20 (%) | ACR50 (%) | ACR70 (%) | ΔmTSS | ΔHAQ-DI | Dactylitis resolution (%) | Enthesitis resolution (%) | PASI75 (%) |
|-------|------------|-----|-----------|---|------------------|---------|------------|------------|------------|-------|----------|--------------------------|--------------------------|-----------|
| **Janus kinase inhibitors** | | | | | | | | | | | | | | | |
| Mease et al (EQUATOR) | csDMARD-IR | Low | Placebo±csDMARD/FILGO 200 mg OD±csDMARD | 66 | ACR20 (week 16) | Ref | 33 | 15.2 | 6.1 | −0.28 | 15 | | | 45.2 |
| | | | Tofacitinib 5 mg two times per day±csDMARD | 65 | <0.001 | 80 | 47.7 | 23.1 | | | 0.57 | | | | |
| Gladman et al (OPAL Beyond) | TNF-IR | Low | Placebo±csDMARD/Tofacitinib 10 mg two times per day±csDMARD | 131 | ACR20 (week 12) | Ref | 24 | 15 | 10 | −0.14 | 28.6 | 21.5 | 14 | |
| | | | | | | | | | | | <0.01 | 50 | 30 | 17 | | 21 |
| | | | | | | | | | | | <0.001 | 47 | 28 | 14 | | 43 |
| Mease et al (OPAL Broaden) | csDMARD-IR | Low | Placebo±csDMARD/Tofacitinib 10 mg two times per day±csDMARD | 105 | ACR20 (week 12) | Ref | 33 | 10 | 5 | 0.00*† | 0.09*‡ | −0.18 | 32.8 | 21.5 | 15 |
| | | | | | | | | | | | <0.01 | 50 | 28 | 17 | | 34.4 | 33.3 | 43 |
| | | | | | | | | | | | <0.001 | 61 | 40 | 14 | | 40 | 40.6 | 44 |
| Cutolo et al (PALACE-2) | csDMARD/TNF-IR | Unclear | Placebo±csDMARD/APREmilast 20 mg two times per day±csDMARD | 159 | ACR20 (week 16) | Ref | 18.9 | 5 | 0.6 | −0.07 | 2.7 |
| | | | | | | | | | | | <0.001 | 37.4 | 14.7 | 3.7 | | | 18.8 |
| | | | | | | | | | | | 0.006 | 32.1 | 10.5 | 1.2 | | | 22.1 |
| Edwards et al (PALACE-3) | csDMARD/TNF-IR | Low | Placebo±csDMARD/APREmilast 30 mg two times per day±csDMARD | 169 | ACR20 (week 16) | Ref | 18.3 | 8.3 | 2.4 | −0.07 | 8 |
| | | | | | | | | | | | 0.030 | 28.4 | 12.4 | 4.7 | | | 20 |
| | | | | | | | | | | | <0.001 | 40.7 | 15 | 3.6 | | | 21 |
| Wells et al (PALACE-4) | csDMARD-naive | Unclear | Placebo±csDMARD | 176 | ACR20 (week 16) | Ref | 15.9 | 4.5 | 1.1 | 0.03 | 31.1 | 19.1 | 10.8 |
| | | | | | | | | | | | 0.006 | 28 | 11.4 | 4 | | 40.4 | 21.4 | 17.3 |
| | | | | | | | | | | | 0.001 | 30.7 | 11.4 | 4 | | 40.5 | 35.1 | 25.7 |
| Nash et al (ACTIVE) | bDMARD-naive | Unclear | Placebo±csDMARD | 109 | ACR20 (week 16) | Ref | 20.2 | 4.6 | 0 | −0.06 | 33.3 |
| | | | | | | | | | | | 0.004 | 38.2 | 18.2 | 6.4 | | | 46.4 |

*Week 52.
†Placebo advancing to Tofacitinib 5 mg two times per day.
‡Placebo advancing to Tofacitinib 10 mg two times per day.
ACR, American College of Rheumatology; ADA, adalimumab; APR, apremilast; bDMARD, biological disease-modifying antirheumatic drug; csDMARD, conventional synthetic disease-modifying antirheumatic drug; FILGO, filgotinib; HAQ-DI, Health Assessment Questionnaire Disability Index; IR, insufficient responders; mTSS, PsA modified total Sharp score; NR, not reported; OD, once daily; PASI, Psoriasis Area and Severity Index; PsA, psoriatic arthritis; Q2W, every 2 weeks; Ref, reference arm; RoB, risk of bias; TNF, tumour necrosis factor; TNFi, TNF inhibitor; TOFA, tofacitinib.
**Safety**

CoHort and case–control studies

bDMARD therapy was associated with an increased risk of infection (OR 1.7 vs no bDMARD; 95% CI 1.33 to 2.18), while csDMARD therapy was not (OR vs no csDMARD 1.15; 95%CI 0.91 to 1.47). 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 to 1.13) and TNFi + csDMARD combination therapy (HR 2.37; 95%CI 1.32 to 4.22), but not with either csDMARD or TNFi monotherapy.

Influenza vaccination was safe and effective in inducing immune responses in patients with PsA receiving TNFi and/or csDMARD treatment.

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

No increased risk of cancer (risk ratio of TNFi-treated vs TNFi-naive: 0.9, 95% CI 0.7 to 1.1) was found in a study combining two large population-based registries from Sweden (ARTIS) and Denmark (DANBIO). 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 with csDMARD-treated patients after adjusting for conventional risk factors.

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

Adverse events of special interest of RCTs and LTEs

IXE showed increased rates of injection site reactions as compared with control arms (SPIRIT-P1: placebo 4.7% vs IXE Q4W 24.3% vs IXE Q2W 26.5% vs ADA 5.9%; SPIRIT-P2: PLC 4% vs IXE Q4W 11% vs IXE Q2W 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). During the placebo-controlled period, no incident case of inflammatory bowel disease (IBD) occurred. However, one event of IBD occurred after week 108 in SPIRIT-P2. In an LTE of a phase II study investigating brodalumab (IL-17 receptor inhibitor), 11 cases of oral candidiasis, 1 report of suicidal ideation and 1 case of neutropenia were observed.

No new safety signals were observed in studies investigating APR, with nausea and diarrhoea more commonly occurring in treatment groups as compared with placebo. In ACTIVE patients treated with APR experienced an adverse event of depression during the placebo-controlled period and another two during the extension APR-exposure period.

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

During the treatment period of guselkumab (IL-23-p19), most adverse events were mild and similar compared with placebo. One adjudicated major cardiovascular event (MACE) occurred in a patient receiving risankizumab (IL-23-p19), and two cases of depression, with none on placebo.

No new unexpected safety events were identified in LTEs of studies investigating UST and certolizumab-pegol.

JAK inhibition with tofacitinib showed higher rates of herpes zoster (incidence rate (IR): 2.05; 95%CI 1.17 to 3.33) and MACE were reported in three patients (IR 0.38; 95% CI 0.08 to 1.11). One case of herpes zoster and one MACE were observed in patients treated with filgotinib (vs none in the placebo group). While no venous thromboembolic events or pulmonary embolisms were observed in patients with PsA treated with tofacitinib or filgotinib, such events were seen in other indications when tofacitinib, baricitinib and upadacitinib were used, especially in an ongoing study on patients with RA 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.

**DISCUSSION**

To inform the task force conducting the 2019 update of the EULAR recommendations for pharmacological 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 time frame of this update, are currently under investigation.

The efficacy of TNF inhibition across various disease domains was confirmed, as well as the bioequivalence of biosimilars compared with their bio-originators. IL-17A inhibition was effective across all disease domains, while bispecific inhibition of TNF and IL-17A (ABT-122) showed numerically better results compared with ADA. Agents targeting the subunit p19 of IL-23 showed increased rates of herpes zoster found a significantly increased risk in patients treated with glucocorticoids (HR 1.17; 95% CI 0.91 to 1.47). A study investigating the risk of herpes zoster showed higher rates of herpes zoster as compared with placebo.

TNFi+csDMARD combination therapy (HR 2.37; 95% CI 1.32 to 4.22), but not with either csDMARD or TNFi monotherapy. 

No new unexpected safety events were identified in LTEs of studies investigating UST and certolizumab-pegol.

JAK inhibition with tofacitinib showed higher rates of herpes zoster (incidence rate (IR): 2.05; 95%CI 1.17 to 3.33) and MACE were reported in three patients (IR 0.38; 95% CI 0.08 to 1.11). One case of herpes zoster and one MACE were observed in patients treated with filgotinib (vs none in the placebo group). While no venous thromboembolic events or pulmonary embolisms were observed in patients with PsA treated with tofacitinib or filgotinib, such events were seen in other indications when tofacitinib, baricitinib and upadacitinib were used, especially in an ongoing study on patients with RA 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.
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 patients with PsA, but regulators issued warnings on the risk of venous thromboembolism (VTE) and pulmonary embolism 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, RoB analysis and data extraction were performed by one researcher only (AK); (2) due to the heterogeneity of the RCTs included, meta-analysis would not have led to representative results and 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; and (4) no trial has been published that investigated the efficacy of treatments on axial spondyloarthritis in patients with PsA and 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 pharmacological treatment in PsA.
Psoriatic arthritis

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