Revista Colombiana de
REUMATOLOGÍA
www.elsevier.es/rcreuma

Review article

Emerging treatment options for psoriatic arthritis

Ana Belén Azuaga, Julio Ramírez, Marta Bassas, Juan D. Cañete*

Rheumatology Department, Hospital Clinic Barcelona, Spain

ARTICLE INFO

Article history:
Received 10 June 2022
Accepted 7 February 2023

Keywords:
Psoriatic arthritis
Treatment
Biological therapy

ABSTRACT

Psoriatic arthritis (PsA) is a chronic, heterogeneous inflammatory disease that may cause joint destruction and functional disability. Treatment must be established early, using disease-modifying antirheumatic drugs to prevent structural damage and impaired function. The number of therapeutic options for PsA has increased over the last 20 years. However, there are still patients who do not achieve the therapeutic goals. For this reason, it is necessary to go further in the study of the pathogenesis of PsA to develop new treatment targets. New molecules are being introduced, mostly from psoriasis, such as IL23 and IL17 inhibitors, and from rheumatoid arthritis, such as new JAK inhibitors. The objective of this article was to review the ongoing and recently reported clinical trials of upcoming drugs for the treatment of PsA.

Novedades en el tratamiento de la artritis psoriásica

Palabras clave:
Artritis psoriásica
Tratamiento
Terapia biológica

RESUMEN

La artritis psoriásica es una enfermedad inflamatoria crónica de naturaleza heterogénea que puede llegar a producir destrucción articular y discapacidad funcional. Por esto, el tratamiento debe instaurarse de forma precoz, utilizando fármacos modificadores de la enfermedad como el metotrexato o las terapias biológicas. En la actualidad se dispone de varias dianas terapéuticas para el tratamiento de esta enfermedad. Sin embargo, aún hay pacientes que no alcanzan los objetivos terapéuticos. Durante los últimos años se han desarrollado nuevas moléculas para la artritis psoriásica que han tenido un desarrollo clínico previo en otras enfermedades inmunomediadas como la psoriasis o la artritis reumatoide. El objetivo de este artículo es revisar los ensayos clínicos en curso y publicados recientemente de nuevos fármacos para el tratamiento de la artritis psoriásica.

* *Corresponding author.*
E-mail address: julramga@gmail.com (J. Ramírez).

2444-4405 /

Introduction

Psoriatic arthritis (PsA) is a chronic immune-mediated disease with very heterogeneous manifestations. Clinical patterns at disease onset vary from dactylitis, enthesitis, and peripheral arthritis to spondylitis, along with skin manifestations such as psoriasis (PsO) plaques and nail lesions. The prevalence in developed countries is between 0.3 and 1%.[1] Up to 30% of patients with PsO may develop PsA, with a peak incidence at 10 years after the onset of PsO.[2] Delays in the diagnosis and initiation of treatment can lead to irreversible damage, functional disability, and impairment of the quality of life.[1,3]

The pathogenesis of PsA is complex and not entirely clear. Advances in the study of the physiopathology of PsA have revealed new and important inflammatory pathways involved in the development of psoriatic disease.[4] These new inflammatory axes, such as the Interleukin (IL) IL23/IL17 or JAK/STAT pathways have become potential targets for therapy. However, the different nature of the tissues affected and the different pathways that drive inflammation make therapeutic responses heterogeneous, constituting a challenge for clinicians. The objective of this paper was to provide an update on forthcoming therapeutic innovations in PsA.

New therapies for PsA

The most promising future drugs in PsA include 9 molecules: three IL23 inhibitors, two IL17 inhibitors and four JAK inhibitors. Fig. 1 shows an outline according to their mechanism of action.

IL 23 Inhibitors

Guselkumab

Guselkumab (GSK) is a monoclonal antibody that binds to the p19 subunit of IL23. The mechanism of action of GSK differs from that of ustekinumab, which inhibits IL23 by blocking the p40 subunit, shared by IL23 and IL12. Given that IL12 has been shown to have a protective role by limiting the recruitment of IL17-producing γδ-T cells, selective inhibition of IL23 through binding to the p19 subunit could offer a new mechanism to effectively treat the manifestations of PsA.[5] Phase 2 randomized controlled trials (RCT) have shown that GSK 100 mg at week 0, week 4, and then every 8 weeks is effective in the skin and joint domains and significantly improves the quality of life of PsA patients.[6] In addition, it showed a significant decrease in serum levels of IL17A and F, among other cytokines. Two phase 3 RCT in PsA have recently been reported. In the DISCOVER 1 trial, the objective was to evaluate the efficacy and safety of GSK in patients with PsA, including naïve to biological therapy and refractory patients (up to one-third were exposed to ≤2 TNFi). The primary endpoint was the ACR 20 response at week 24. A total of 382 patients with active PsA were included. Patients were randomized to three arms, two with GSK 100 mg at day 0, week 4, and then every 4 or every 8 weeks, and the third arm with placebo (PBO). Baseline characteristics were similar between groups, with a mean time of disease evolution of 6 years, a mean swollen joint count of 8–10, and a mean psoriatic body surface area (BSA) of 10 per cent. Sixty-five percent were taking concomitant treatment with csDMARDs, mainly MTX, and 31% had received at least one TNFi.

The ACR 20 response at week 24 was significantly higher in both GSK groups vs. PBO: 59% in the GSK group every 4 weeks achieved an ACR 20 response (delta vs. PBO of 37%, $p < 0.0001$) and 52% in the GSK group every 8 weeks (delta vs. PBO of 30%, $p < 0.0001$). The study was not designed to compare the efficacy of the two doses. A higher proportion of patients naïve to biological therapy achieved an ACR 20 response in comparison with those refractory or intolerant to TNFi (60% vs. 58% in patients treated with GSK every 4 weeks and 56% vs. 50% in patients treated with GSK every 8 weeks, respectively). Both doses of GSK significantly improved physical function at week 24. The cutaneous responses were high in patients treated with GSK every 8 weeks, with a PASI 90 and 100 response at week 24 of 50% and 26%, respectively. Regarding safety, at least 5% of patients in each group had infections (mainly upper respiratory tract) or an increase in transaminase serum levels. No patient treated with GSK had a severe infection. No differences were found in the rate of adverse events (AE) according to the previous use of TNFi.[7]

A second phase 3 RCT (DISCOVER 2) included 741 patients naïve to biological therapy. ACR 20, ACR 50, and ACR 70 responses in both groups of patients with GSK were significantly higher than PBO at week 24 (GSK 100 mg every 4 weeks: ACR 20 64%, ACR 50 33% and ACR 70 13%; GSK 100 mg every 8 weeks: ACR20 64%, ACR 50 31% and ACR 70 19%; PBO: ACR 20 33%, ACR 50 14% and ACR 70 4%, $p < 0.0001$). In contrast to the DISCOVER 1 study, radiographic progression was evaluated, and was significantly lower in the GSK group every 4 weeks (least squares mean 0.29 [95% CI −0.05 to 0.63] vs. 0.95 [0.61–1.29] PBO, p 0.011), with numerical differences in the GSK every 8 weeks compared with the PBO group, but without reaching significance (least squares mean 0.52 [0.18–0.86]; p 0.072). Changes in domains such as dactylitis and enthesitis were evaluated in conjunction with the patients included in DISCOVER 1, to increase the size of the sample. The resolution rate of dactylitis at week 24 was significantly higher in the GSK group every 4 weeks (64%, p 0.011) and GSK every 8 weeks (59%, p 0.03) than in PBO group (42%). Likewise, the resolution rate of enthesitis (Leeds Enthesitis Index) was significantly higher in both GSK groups vs. PBO (45% of patients treated with GSK every 4 weeks, 50% of those treated with GSK every 8 weeks and 29% of those treated with PBO; p 0.031). The rate of AE was 46% in the GSK group vs. 41% in the PBO group, with upper tract respiratory infections being the most frequent (5% with GSK every 4 weeks, 2% with GSK every 8 weeks, and 3% in the PBO group), followed by liver enzyme elevation (10% of patients with GSK every 4 weeks, 6% of those treated with GSK every 8 weeks and 4% in patients in the PBO arm).[8] In the 52-week extension study of DISCOVER 1, 90% of patients completed the follow-up. Seventy-three per cent achieved an ACR 20 response in the GSK group every 4 weeks and 60% in the GSK group every 8 weeks.[9]

The axial domain was not specifically evaluated in any of the DISCOVER trials. However, a post hoc analysis of both studies evaluated 312 patients who had axial involvement

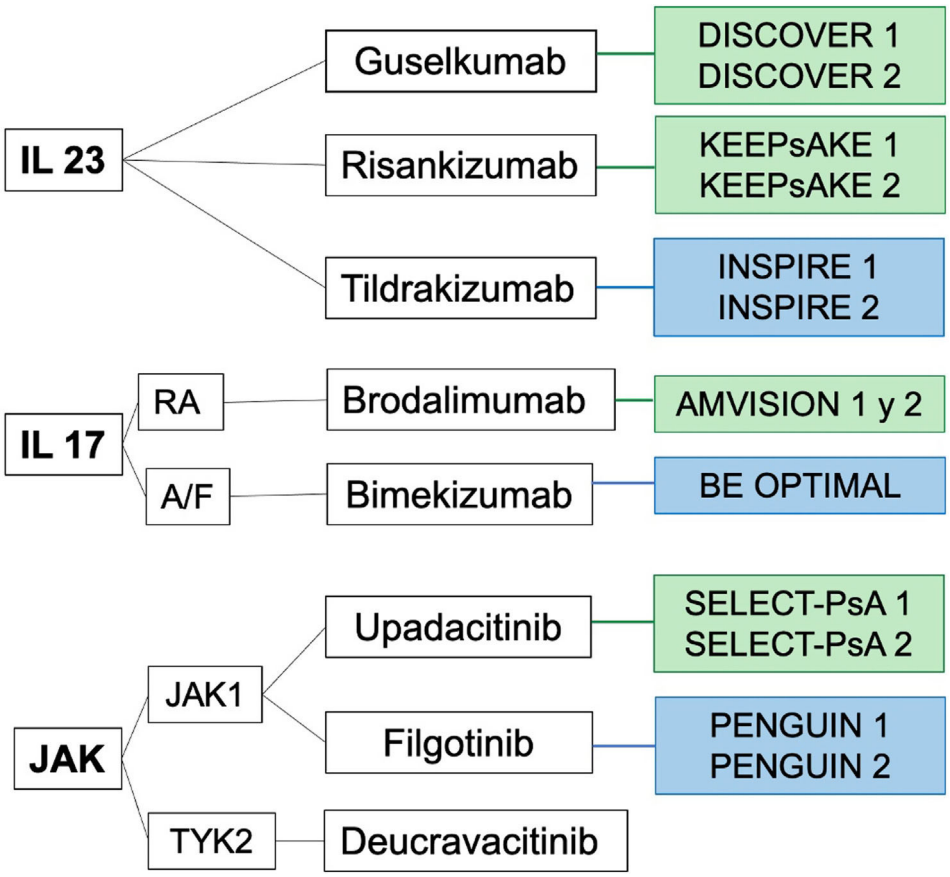

Fig. 1 – Phase 3 randomized controlled trials of new molecules for the treatment of PsA, in green those currently reported and in blue those under development.

according to physician criteria and had imaging tests showing sacroiliitis at baseline. Thirty percent of patients were HLB27 positive. Improvement in axial symptoms, measured by both the Bath Ankylosing Spondylitis Disease Activity Index (BASDAI) and Ankylosing Spondylitis Disease Activity Score-C Reactive Protein (ASDAS-CRP), was significantly higher in patients treated with GSK vs. PBO at week 24 (BASDAI least squares mean changes −2.7 [95% CI −3.2 to −2.2] vs. −1.3 [−1.8 to −0.9] in the PBO group, $p < 0.001$; ASDAS-CRP −1.4 [95% CI −1.7 to −1.2] in both groups of GSK and −0.7 [−0.9 to −0.5] in the PBO group, $p < 0.001$).[10]

IL 23 inhibition may be an alternative mechanism of action in patients not achieving a response to TNFi. The COSMOS study was a phase 3b RCT that evaluated the efficacy and safety of GSK (100 mg every 8 weeks) in patients who failed or were intolerant to ≤2 TNFi. A total of 285 patients were included in the study, of whom 88% completed the 44-week study. GSK was shown to be superior to PBO: 44.4% of patients in the GSK arm vs. 19.8% in the PBO group achieved an ACR 20 response at week 24 ($p < 0.001$). These changes were observed from week 4 (19% GSK arm vs. 4.2% PBO arm, $p < 0.001$). Secondary endpoints were significantly higher in patients on GSK vs. PBO (ACR 50: 19.6% in GSK group vs. 5.2% in PBO group, p 0.001; HAQ-DI score: −0.18 change in GSK vs. −0.01 in PBO arm, p 0.003 and PASI100: 30.8% in GSK group vs. 3.8% in PBO group, $p < 0.001$). The incidence of AEs leading to treatment discontinuation was 2.7/100 patient-year. Two patients treated with GSK had pneumonia and two had psychiatric symptoms that led to discontinuation of GSK. One patient had gastrointestinal symptoms without final confirmation of inflammatory bowel disease.[11]

Risankizumab

Risankizumab (RZK) is another IgG 1 monoclonal antibody that binds to the p19 subunit of IL23. The clinical development of RZK in PsA is a little behind that of GSK. The results of the KEEPsake 1 (patients naive to biological therapy)[12] and KEEPsake 2 (patients refractory or intolerant to TNFi) trials[13] have recently been reported.

In KEEPsake 1, 964 patients were enrolled and randomized to receive RZK (150 mg) or PBO. Most patients treated with RZK achieved an ACR 20 response at week 24 [57.3% compared with 33.5% with PBO (p 0.001).[14] Other outcomes were significantly higher in patients treated with RZK vs. PBO, such as the ACR 20 response at week 16 (56.3% vs. 33.4%, $p < 0.001$), PASI90 (52.3% vs. 9.9%, $p < 0.001$), nail improvement (modified Nail Psoriasis Severity Index [mNAPSI] −9.8 vs. −5.6, $p < 0.001$), among others. No significant differences were found between RZK and PBO in radiographic progression due to the low number of progressors. Regarding safety, one death was reported in the RZK group due to urosepsis, and one patient treated with RZK and 2 in the PBO group presented COVID19 infection. Similar results

were found in patients with an inadequate response to TNFi. The KEEPsake 2 study showed that 51.3% of patients treated with RZK achieved an ACR 20 response compared with 26.5% of those treated with PBO ($p < 0.001$) at week 24.[15] Secondary endpoints, including minimal disease activity (MDA), PASI, and ACR 20 at week 16, were significantly higher in patients treated with RZK vs. PBO.

The dactylitis and enthesitis outcome results s were pooled from the KEEPsake 1 and 2, with a greater proportion of patients achieving complete resolution of these domains in the RZK group vs. PBO (68.1% vs. 51.0% for dactylitis and 48.4 vs. 34.8% for enthesitis, $p < 0.001$).[14]

In the 2021 ACR meeting, the integrated data of efficacy and safety from the two phase 3 RCT were presented, showing a higher proportion of patients with RZK achieving an ACR 20 response at week 24 (55.5% vs. 31.3% of patients treated with PBO, p 0.001). These responses were maintained for other secondary objectives. The rate of adverse events was similar between both groups (45.5% of patients treated with RZK and 43.9% in the PBO group).[16]

Tildrakizumab

Tildrakizumab (TIL) is the third (in order of appearance) monoclonal antibody that binds to the p19 subunit of interleukin IL23. Currently, only the results of the phase 2 RCT have been reported, where the efficacy and safety of four treatment arms (200 mg every 4 weeks, 200 mg, 100 mg or 20 mg every 12 weeks) compared with PBO were measured. The primary endpoint was the ACR 20 response at week 24, reaching 71.4–79.5% in patients treated with different doses of TIL compared with 50.6% of patients in the PBO arm ($p = 0.05$). ACR 50/70 responses were better in patients treated with TIL 20m mg every 4 weeks and every 12 weeks. The responses were maintained after 52 weeks of follow-up.[17] Only one patient treated with TIL discontinued therapy due to an AE (hypertension in the 200 mg every 12 weeks arm). Most EA were mild and comparable between all the treatment arms.

Two-phase 3 RCT are currently ongoing, one in patients with previous exposure to TNFi (INSPIRE 1)[18] and another in patients naive to biological therapy (INSPIRE 2).[19]

IL-17 Inhibitors

Brodalumab

Brodalumab (BRO) is a fully human monoclonal antibody that binds with high affinity to the IL17 receptor subunit A (IL17RA), blocking the action of multiple cytokines of the IL17 family.[20]

In 2014, a phase 2 RCT was reported, showing the efficacy of two doses of BRO (140 and 180 mg every 2 weeks) vs. PBO.[21] The results of the two phase 3 RCT were reported in 2021. The AMVISION 1 and 2 trials were developed to evaluate the efficacy and safety of BRO in PsA. Patients with an inadequate response or intolerance to previous treatments, including biological therapy, were included. Patients were randomized to receive BRO 140 mg, 210 mg or PBO at weeks 0, 1, and then every 2 weeks until week 24. About 30% of patients had previously been exposed to biological therapy. After some events of suicidal ideation and behavior (SIB) were observed, patients with a history of SIB were excluded after a review of the protocol, which delayed the development of the trials and the publication of the results.

The primary endpoint of both studies was the ACR 20 response at week 16. Five hundred and seventy-eight patients were included in AMVISION 1 and 484 patients in AMVISION 2. At week 16, patients treated with BRO achieved a significantly higher ACR 20 response than those treated with PBO (45.8% in the BRO 140 mg arm and 47.9% in the BRO 210 mg arm vs. 20.9% in the PBO group ($p < 0.0001$). Overall, the responses in patients on BRO 210 mg were numerically higher than for BRO 140 mg, although comparison of the two doses was not one of the study objectives.

The pooled results of the two studies showed similar rates of AE among patients treated with BRO and PBO. Most AEs were mild or moderate. A patient with a history of SIB and depression in the BRO 140 mg arm in the AMVISION 2 study had suicidal ideation after the first dose of BRO. However, this event was not considered related to the drug, and withdrawal from the study was not necessary. The authors finally concluded that the safety data obtained were consistent with those from studies with other IL 17 inhibitors.[22] Currently, no attempts or completed suicides were reported in a two-year pharmacovigilance report from 2677 patients treated with BRO in the United States.[23]

Bimekizumab

Bimekizumab (BMK) is an IgG monoclonal antibody that binds to a peptide region shared by interleukins IL17A and IL17F. Currently, only the results of the phase 2 RCT have been reported. The BE ACTIVE trial evaluated the efficacy and safety of BMK in patients with PsA. The primary endpoint was the ACR 50 response at week 12. Patients were randomized to 5 arms: BMK 16 mg every 4 weeks, BMK 160 mg every 4 weeks, BMK 160 mg every 4 weeks with a loading dose of 320 mg, BMK 320 mg every 4 weeks or PBO. Patients in the BMK 16 mg arm or PBO were rerandomized at week 12 to receive BMK 160 mg or BMK 320 mg every 4 weeks. A total of 206 patients were included in the study. Twenty per cent of patients had previously received TNFi. Patients randomized to BMK 320 mg had more tender joints, higher pain scores, and a higher body mass index at inclusion. Patients in all BMK groups achieved a significantly higher ACR 50 response than PBO at week 12. The response was higher for patients with 160 mg doses who had received a previous loading dose (p 0.0004). At week 24, the proportion of patients in the BMK 320 mg arm who achieved an ACR 50 response was slightly lower than that of patients in the BMK160 mg arm (with or without loading dose). At week 48, the ACR 50 response rates were similar in all three groups. Differences in ACR 50 response rates between the BMK 160 mg group with loading dose and BMK 320 mg were found from week 4, even though the same dose of BMK had been received. Therefore, the authors considered that the discrepancy in the response at week 24 could be attributable to differences in baseline characteristics between groups. Forty-one per cent and 57% of patients reported AE in groups treated with BMK and PBO, respectively. Most AE were mild, with upper respiratory tract infections the most frequent. Fourteen cases (7%) of Candida infection were reported during the trial, with an adjusted incidence of 8.3 per 100 patients per year.[24]

At the EULAR 2020 conference, the results of the 2-year extension of the BE-ACTIVE trial were presented, showing more than 50% of patients maintaining the ACR 50 response, a BSA of 0%, and MDA status.[25] More recently, at the 2021 ACR meeting, the 3-year extension data from the BE ACTIVE study was presented, but only in the subgroup of patients naive to biological therapy. More than half of these patients achieved an ACR 50 response at weeks 48 and 152 (63.6% and 69.8% [cases observed], respectively).[26] A phase 3 RCT (BE OPTIMAL).[27] is currently ongoing, in which BMK and an active comparator (adalimumab [ADA]) are compared with PBO. The primary endpoint is the ACR 50 response at week 16. No results have been reported.

JAK inhibitors

Upadacitinib

Upadacitinib (UPA) is a Janus kinase (JAK) 1 membrane receptor inhibitor approved for patients with rheumatoid arthritis (RA).[28,29] Recently, the results of the two phase 3 RCT, SELECT-PsA 1 and 2, have been reported, with the objective of assessing the efficacy of UPA in PsA. SELECT-PsA 1 is a phase 3 RCT that compares the efficacy and safety of UPA with PBO and an active TNFi comparator (ADA). PsA patients with active disease (>3 swollen/tender joint count [TJC]) were included, excluding patients with previous use of biologics or JAK inhibitors. Patients were randomized to receive UPA 15 mg, UPA 30 mg once daily, ADA 40 mg every 2 weeks, or PBO. The primary endpoint was the ACR 20 response at week 12. Secondary endpoints included direct comparisons between UPA and ADA. A total of 1704 patients were included. The ACR 20 response with both UPA doses was significantly higher than PBO (70.6% of patients with UPA 15 mg, 78.5% of patients with UPA 30 mg, and 36.2% in the PBO arm, $p < 0.001$). UPA 15 mg was not inferior to ADA while UPA 30 mg showed superiority over ADA.

The incidence of AE at week 24 was numerically higher for patients treated with UPA 30 mg (72.3%) than for those treated with 15 mg (66.9%). The most common AE were upper respiratory tract infections. Herpes zoster infection was diagnosed in 4 patients on UPA 15 mg and 5 patients on UPA 30 mg. Only one case of pulmonary thromboembolism was reported, in a patient treated with 30 mg UPA. Two patients were diagnosed with deep vein thrombosis (DVT) in the ADA arm and one in the PBO group.[30]

The SELECT-PsA 2 trial evaluated the efficacy and safety of UPA in patients with PsA with previous failure or intolerance to ≥1 biological DMARD. A total of 642 patients were randomized to receive UPA 15 mg, 30 mg or PBO. The primary endpoint was the ACR 20 response at week 12, when there were significantly more patients who achieved an ACR 20 response in both UPA arms vs. PBO (UPA 15 mg 56.9%, UPA 30 mg 63.8%, and PBO 24.1% $p < 0.001$). Significant differences were observed between UPA and PBO from week 2 ($p < 0.001$). At week 12, patients on UPA 30 mg achieved a maximum response, while the ACR 20 response rate in patients on UPA 15 mg continued to increase until week 20. In week 24, a higher proportion of patients in both UPA arms achieved MDA vs. PBO (36% of patients with UPA 15 mg, 45.4% in UPA 30 mg vs. 12.3% of patients treated with PBO; p 0.001). At week 24, more AE were reported in patients who received UPA than in those who received PBO. The most frequent AE were nasopharyngeal and upper respiratory tract infections. The incidence of herpes zoster infection was higher in patients treated with UPA 30 mg (3.7%), although no case was considered serious. Only one episode of DVT was reported in the UPA 15 mg group.[31]

In addition, the 56-week extension of the SELECT-PsA 1 study has been recently reported: 1419 of the 1705 patients (83.2%) included in SELECT-PsA 1 completed the follow-up. At week 24, all patients initially in the PBO arm were rerandomized to receive UPA 15 or 30 mg. At week 56, ACR 20/50/70 response rates were higher for patients initially treated with any of the two doses of UPA compared with patients treated with ADA (UPA 15 mg: 74.4%; UPA 30 mg 74.7%; ADA 68.5%; PBO randomized to UPA 15 mg 73% and PBO randomized to UPA 30 mg 74.1%; p 0.046).[32]

Filgotinib

Filgotinib (FIL) is a selective JAK 1 inhibitor. In the EQUATOR study, a phase 2 RCT, 131 patients with active PsA, including patients with an inadequate response or intolerance to TNFi therapy, were randomized to two arms: FIL 200 mg once daily and PBO. The ACR 20 response at week 16 was achieved by 80% of patients treated with FIL and 33% of those treated with PBO (difference of 45% between both arms; $p < 0.0001$). The onset of action of FIL was rapid, with significant changes compared with PBO from the first week of treatment. AE were reported in 57% of patients treated with FIL and 59% of patients treated with PBO. Only one patient treated with FIL had a herpes zoster infection. No thromboembolic event was reported during the study.[33] The results of the 1-year extension of the EQUATOR study were presented at the EULAR 2020 conference, where patients initially treated with FIL maintained the clinical response after one year of treatment (ACR 50 64.8% and MDA 35.2%).[34]

There are currently two ongoing phase 3 RCTs with the objective of evaluating the efficacy and safety of FIL in patients without previous use of biological DMARDs (PENGUIN 1)[35] and patients with an inadequate response or intolerance to biological therapy (PENGUIN 2).[36]

Deucravacitinib

Deucravacitinib (DEU) is a selective allosteric (non-competitive) inhibitor of tyrosine kinase 2 (TYK2) inhibitor. The results of a phase 2 RCT with a one-year extension program were recently reported. The efficacy and safety of DEU were evaluated in 203 patients with active PsA, including patients with an inadequate response or intolerance to TNFi therapy. Patients were randomized to three arms: DEU 6 mg, DEU 12 mg daily or PBO. The primary endpoint was the ACR 20 response at week 16, which was significantly higher in patients treated with DEU 6 mg (52.9%; p 0.0134) and DEU 12 mg (62.7%; p 0.0004) vs. PBO (31.8%). No severe AE, herpes zoster infections, or thromboembolic events were reported.[37]

At the ACR 2021 meeting, a post hoc analysis from the phase 2 RCT of DEU was reported, evaluating the ACR 20 response at week 16 in patients with PsA with or without previous exposure to csDMARD treatment. All patients with DEU, regardless of being naïve to csDMARD, had similar clinical improvements.[38]

Currently, a phase 3 RCT is ongoing to assess the efficacy and safety of DEU in patients who have not previously received treatment with biological DMARDs as well as those who have previously received TNFi.[39]

Brepocitinib

Brepocitinib (BRE) is a dual tyrosine kinase 2 and JAK 1 inhibitor. It is currently being studied for oral and topical treatment in patients with moderate to severe PsO.[40] At the ACR convergence 2021 meeting, results from the phase 2b RCT in patients with active PsA were presented. Patients were randomized to receive once daily oral doses of BRE 10, 30, 60 mg, or PBO. Patients with previous use of DMARDs and those with prior use of one TNFi (up to one third) were included. A total of 218 patients were included, a significantly higher proportion of patients treated with BRE 30 mg (66.7%) and 60 mg (74.6%) achieved the primary endpoint vs. PBO (43.4%, $p < 0.05$) at week 16. Additionally, secondary endpoints such as ACR 50 (BRE 30 mg 48.3%, BRE 60 mg 44.1% vs. PBO 10.4%; $p < 0.05$) and ACR 70 (BRE 30 mg 26.7%, BRE 60 mg 23.7% vs. PBO 0.7%; $p < 0.05$) responses were also achieved. At week 16, dactylitis and enthesitis resolution (measured by Dactylitis Score Sheet [DSS] and Spondyloarthritis Research Consortium of Canada [SPARCC] enthesitis index, respectively) were observed in 78.6% and 56.8%, respectively, in the BRE 60 mg arm vs. PBO (DSS 32.5% and SPARCC 38.1%; $p < 0.059$). Skin endpoints were also analyzed, and the PASI 75 response was significantly higher for both doses of BRE vs. PBO (BRE 30 mg 59%, BRE 60 mg 69.2% vs. PBO 24.4%; $p < 0.05$). Patients treated with BRE had more AE (BRE 30 mg 55% and BRE 60 mg 66.7%) compared with PBO (47.8%). The AE rate leading to discontinuation at week 16 was 3.3% in patients treated with BRE 30 mg and 5% with BRE 60 mg. Herpes zoster and varicella infections were found in 1.7% of patients with BRE 30 mg. No thromboembolic events were reported.[41]

Discussion

The emergence of biological therapies at the beginning of the 21st century has changed the prognosis of patients with PsA. As the first family of biological therapy available, TNFi therapy has improved the quality of life and significantly reduced disability in patients with chronic arthritis. The success of TNFi therapy lies in the good balance between efficacy and safety, demonstrated in both the pivotal clinical trials and observational registers from clinical practice. Overall, after almost 20 years of biological therapies in PsA, the accumulated experience supports their efficacy and long-term safety. For these reasons, TNFi continue to be the first line of therapy after csDMARDs (usually methotrexate) in most international guidelines and recommendations.[42]

Despite the undeniable success of TNFi, there are still unmet needs in the treatment of PsA. Remission and/or low disease activity rates do not exceed 60%, and more than one-third of patients do not achieve the therapeutic objectives.[43] Moreover, a significant proportion of patients will need to change treatments in the medium term, either because of loss of efficacy or adverse events.[44] More than 50% of patients with PsA have comorbidities, which often influence treatment selection or precipitate therapy interruption.[45] Therefore, it is necessary to find new therapeutic options to cover these gaps and unmet needs.

In this context, thanks to the advances in our knowledge of the pathophysiology of psoriatic disease, new treatments have emerged during recent years, increasing the therapeutic options for PsA patients, such as an IL12/IL23 inhibitor (ustekinumab).[46,47] IL17 inhibitors (secukinumab[48,49] and ixekizumab,[50,51] a PDE4 inhibitor (apremilast)[52] and a JAK inhibitor (tofacitinib).[53,54] Currently, all are successfully used in PsA.

The objective of this review was to summarize current RCT of new drugs for PsA. All have been shown to be effective in most disease domains and have shown a good safety profile in the RCT and open-label extension studies. These new treatments can be divided into two groups. On the one hand, those whose clinical development in PsA has been preceded by vast clinical experience in PsO (mainly IL17 and IL23 inhibitors) and, on the other hand, those coming from the field of RA (mainly JAK inhibitors). Those who started their clinical development in PsA after the approval for PsO stand out due to a prominent cutaneous efficacy. Many of these drugs ran head-to-head trials in dermatology, demonstrating superiority to TNFi in patients with PsO.[55,56] These good cutaneous results are accompanied by good efficacy in the other domains in PsA trials. In addition, the safety profile was maintained, and high retention rates have been shown in RCT extension studies.

However, new data from clinical practice corroborating the good survival rates are still required. Experience of these molecules in PsO is a good source of data, mainly regarding safety, that could be potentially used in patients with PsA, as has been shown with other molecules such as ustekinumab and the PSOLAR registry, whose data has supported the use of this treatment in patients with PsA with complex safety profiles.[57]

From the current available data, treatments coming from PsO appear to have similar efficacy to TNFi in musculoskeletal domains such as synovitis or dactylitis, whereas their efficacy in the skin and nail domains is superior to TNFi.[55,56] A currently unsolved topic is whether the new therapeutic options such as IL23i and IL17i are superior to TNFi in enthesitis. A translational study showed that the profile of peripheral biomarkers in patients with PsA with predominant enthesitis was closer to PsO than PsA with exclusively articular involvement.[58] While C-reactive protein levels were only elevated in psoriatic synovitis, cutaneous biomarkers such as beta-defensins and lipocalin (cytokines related to the IL17 pathway), were elevated in both psoriatic enthesitis and PsO, but not in PsA patients with predominantly arthritic involvement. These data, together with the numerical superiority of secukinumab and ixekizumab over adalimumab in the resolution of the enthesitis in the head-to-head trials,[59,60] suggest that there might be a slight superiority of the new mechanisms of action in this domain. Therefore, it could be hypothesized that enthesitis is a domain halfway between skin and joint. It will be interesting to know if this data from direct comparisons between secukinumab, ixekizumab, and adalimumab is replicated in studies with the new molecules IL17i and IL 23i.

Moreover, the new JAK inhibitors, which have been preceded by a comprehensive clinical development in RA,[61–64] showed efficacy in joints but also in other more exclusive PsA domains such as enthesitis, dactylitis, and skin. While tofacitinib showed modest cutaneous efficacy,[54] UPA and FIL appeared to have similar efficacy as TNFi in the skin. Against the idea that JAK inhibitors work mainly in psoriatic synovitis but not in other domains, these molecules have been shown to be effective in all disease domains by RCT. Blocking many inflammatory pathways through JAK inhibition gives them great versatility, as it indicates their successful clinical development in other pathologies such as inflammatory bowel disease, atopic dermatitis, and ankylosing spondylitis.[65–68] For instance, studies of JAK inhibitors in ankylosing spondylitis showed promising efficacy data that could indirectly be useful for axial PsA, a currently controversial domain that does not respond equally to all mechanisms of action.[69] This possible efficacy in the axial domain, along with their oral administration, could be an advantage over other therapeutic options. However, the safety of JAK inhibitors is still controversial. Data from the recent ORAL surveillance showed that the use of tofacitinib in patients with RA aged > 50 years with cardiovascular risk factors was associated with a higher incidence of cardiovascular events, thrombotic events, infections, and malignancies compared with etanercept and adalimumab.[70] It is debatable whether these data can be extrapolated to JAK inhibitor molecules other than tofacitinib or other diseases such as PsA (with a different safety profile than RA). Currently, caution is necessary when issuing recommendations on the current or future use of these molecules. However, the greater selectivity of the new JAK inhibitors seems to imply fewer side effects. New studies in clinical practice will be necessary to place these molecules within the algorithm of PsA treatment.

Another important issue is the convenience of having several molecules inhibiting the same therapeutic target in clinical practice. It would be interesting to review the experience with TNFi, where having up to 5 molecules available has not caused an overlap and after long experience, they have been differentiated each other according to their clinical and pharmacokinetic properties. In the same way, loss of efficacy with a TNFi could be recovered by switching to another molecule blocking the same target. Similarly, a side effect would not necessarily have a cross-over effect on a second TNFi. Therefore, having several molecules inhibiting the same target could help us in some clinical situations.

The multiplicity of therapeutic targets will be a step forward in the treatment of PsA only if we make progress in the search for biomarkers of the therapeutic response. Although peripheral T-cell flow cytometry has been used in a simplistic study trying to approach to personalized medicine,[71] it will be the use of new "omic" techniques which will potentially lead to new biomarkers to guide the selection of the right treatment for the right patient. Meanwhile, the classic clinical approach will continue: identifying the dominant domain in patients with PsA, that is, the one that mainly undermines their quality of life, and use the molecule more effective in that domain, always in consensus with the patient and considering other factors such as associated comorbidities.

Conclusion

The treatment of patients with PsA continues to be a challenge in routine clinical practice, with a high rate of patients who do not achieve remission or low disease activity, patients with adverse events and loss of efficacy over time. Further steps forward will be needed in the field combining multiomics methodologies and artificial intelligence to identify tissue biomarkers of response to therapy as well as to develop new therapeutic target, with the final objective of achieving personalized medicine.

Funding

Authors do not have any acknowledgment or funding sources to declare to this manuscript.

Conflicts of interest

The authors declared the following potential conflicts of interest with respect to the research, authorship, and/or publication of this article: ABA has worked as a paid consultant or has been paid as a speaker for Novartis and Janssen. JR has received grants/research support, worked as a paid consultant or has been paid as a speaker for AbbVie, Amgen, Lilly, Janssen, MSD, Novartis, Pfizer and UCB. JDC has received fees for speaking and/or consulting from AbbVie, Celgene, Janssen, MSD/Shering Plough, Novartis, Pfizer and UCB.

Supplementary material

The Spanish translation of this article is available as supplementary material.

REFERENCES

1. Ritchlin CT, Colbert RA, Gladman DD. Psoriatic arthritis. N Engl J Med. 2017;376:957–70, http://dx.doi.org/10.1056/NEJMra1505557.
2. Alinaghi F, Calov M, Kristensen LE, Gladman DD, Coates LC, Jullien D, et al. Prevalence of psoriatic arthritis in patients with psoriasis: a systematic review and meta-analysis of observational and clinical studies. J Am Acad Dermatol. 2019;80:251–65, http://dx.doi.org/10.1016/j.jaad.2018.06.027, e19.
3. Siegel EL, Orbai AM, Ritchlin CT. Targeting extra-articular manifestations in PsA: a closer look at enthesitis and dactylitis. Curr Opin Rheumatol. 2015;27:111–7, http://dx.doi.org/10.1097/BOR.0000000000000155.
4. Veale DJ, Fearon U. The pathogenesis of psoriatic arthritis. Lancet. 2018;391:2273–84, http://dx.doi.org/10.1016/S0140-6736(18)30830-4.
5. Frieder J, Kivelevitch D, Haugh I, Watson I, Menter A. Anti-IL-23 and anti-IL-17 biologic agents for the treatment of immune-mediated inflammatory conditions. Clin Pharmacol Ther. 2018;103:88–101, http://dx.doi.org/10.1002/cpt.893.

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;391:2213–24, http://dx.doi.org/10.1016/S0140-6736(18)30952-8.
7. Deodhar A, Helliwell PS, Boehncke WH, Kollmeier AP, Hsia EC, Subramanian RA, et al. Guselkumab in patients with active psoriatic arthritis who were biologic-naive or had previously received TNFα inhibitor treatment (DISCOVER-1): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet. 2020;395:1115–25, http://dx.doi.org/10.1016/S0140-6736(20)30265-8.
8. Mease PJ, Rahman P, Gottlieb AB, Kollmeier AP, Hsia EC, Xu XL, et al. Guselkumab in biologic-naive patients with active psoriatic arthritis (DISCOVER-2): a double-blind, randomised, placebo-controlled phase 3 trial. Lancet. 2020;395:1126–36, http://dx.doi.org/10.1016/S0140-6736(20)30263-4.
9. Ritchlin CT, Helliwell PS, Boehncke WH, Soriano ER, Hsia EC, Kollmeier AP, et al. Guselkumab, an inhibitor of the IL-23p19 subunit, provides sustained improvement in signs and symptoms of active psoriatic arthritis: 1 year results of a phase III randomised study of patients who were biologic-naïve or TNFα inhibitor-experienced. RMD Open. 2021;7:e001457, http://dx.doi.org/10.1136/rmdopen-2020-001457.
10. Mease PJ, Helliwell PS, Gladman DD, Poddubnyy D, Baraliakos X, Chakravarty SD, et al. Efficacy of guselkumab on axial involvement in patients with active psoriatic arthritis and sacroiliitis: a post-hoc analysis of the phase 3 DISCOVER-1 and DISCOVER-2 studies. Lancet Rheumatol. 2021;3:e715–23, http://dx.doi.org/10.1016/S2665-9913(21)00105-3.
11. Coates LC, Gossec L, Theander E, Bergmans P, Neuhold M, Karyekar CS, et al. Efficacy and safety of guselkumab in patients with active psoriatic arthritis who are inadequate responders to tumour necrosis factor inhibitors: results through one year of a phase IIIb, randomised, controlled study (COSMOS). Ann Rheum Dis. 2022;81:359–69, http://dx.doi.org/10.1136/annrheumdis-2021-220991.
12. A study comparing risankizumab to placebo in participants with active psoriatic arthritis (PsA) who have a history of inadequate response to or intolerance to at least one disease modifying anti-rheumatic drug (DMARD) therapy (KEEPsAKE1). ClinicalTrials.gov. Identifier: NCT03675308, https://clinicaltrials.gov/ct2/show/NCT03675308.
13. A study comparing risankizumab to placebo in participants with active psoriatic arthritis including those who have a history of inadequate response or intolerance to biologic therapy(Ies) (KEEPsAKE2). ClinicalTrials.gov. Identifier: NCT03671148, https://clinicaltrials.gov/ct2/show/NCT03671148.
14. Kristensen LE, Keiserman M, Papp K, McCasland L, White D, Lu W, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 1 trial. Ann Rheum Dis. 2022;81:225–31, http://dx.doi.org/10.1136/annrheumdis-2021-221019.
15. Östör A, Van den Bosch F, Papp K, Asnal C, Blanco R, Aelion J, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week results from the randomised, double-blind, phase 3 KEEPsAKE 2 trial. Ann Rheum Dis. 2022;81:351–8, http://dx.doi.org/10.1136/annrheumdis-2021-221048.
16. Ostor A, Papp K, Moreno M, Spargo C, Barcomb L, Soliman A, et al. Efficacy and safety of risankizumab for active psoriatic arthritis: 24-week integrated results from 2 phase 3, randomized, double-blind clinical trials for CsDMARD-IR and Bio-IR patients [abstract]. Arthritis Rheumatol. 2021;73 Suppl. 10.
17. Mease PJ, Chohan S, Fructuoso FJG, Luggen ME, Rahman P, Raychaudhuri SP, et al. Efficacy and safety of tildrakizumab in patients with active psoriatic arthritis: results of a randomised, double-blind, placebo-controlled, multiple-dose, 52-week phase IIb study. Ann Rheum Dis. 2021;80:1147–57, http://dx.doi.org/10.1136/annrheumdis-2020-219014.
18. Efficacy and safety of tildrakizumab compared to placebo in subjects with active psoriatic arthritis I (INSPIRE 1). ClinicalTrials.gov. Identifier: NCT04314544, https://clinicaltrials.gov/ct2/show/NCT04314544.
19. Efficacy and safety of tildrakizumab compared to placebo in anti-tnf naïve subjects with active psoriatic arthritis II (INSPIRE 2). ClinicalTrials.gov. Identifier: NCT04314531, https://clinicaltrials.gov/ct2/show/NCT0431453.
20. Papp KA, Reid C, Foley P, Sinclair R, Salinger DH, Williams G, et al. Anti-IL-17 receptor antibody AMG 827 leads to rapid clinical response in subjects with moderate to severe psoriasis: results from a phase I, randomized, placebo-controlled trial. J Invest Dermatol. 2012;132:2466–9, http://dx.doi.org/10.1038/jid.2012.163.
21. Mease PJ, Genovese MC, Greenwald MW, Ritchlin CT, Beaulieu AD, Deodhar A, et al. Brodalumab, an anti-IL17RA monoclonal antibody, in psoriatic arthritis. N Engl J Med. 2014;370:2295–306, http://dx.doi.org/10.1056/NEJMoa1315231.
22. Mease PJ, Helliwell PS, Hjuler KF, Raymond K, McInnes I. Brodalumab in psoriatic arthritis: results from the randomised phase III AMVISION-1 and AMVISION-2 trials. Ann Rheum Dis. 2021;80:185–93, http://dx.doi.org/10.1136/annrheumdis-2019-216835.
23. Lebwohl M, Leonardi C, Wu J, Armstrong A, Rawnsley N, Merchant M, et al. Two-year US pharmacovigilance report on brodalumab. Dermatol Ther (Heidelb). 2021;11:173–80, http://dx.doi.org/10.1007/s13555-020-00472-x/.
24. 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;395:427–40, http://dx.doi.org/10.1016/S0140-6736(19)33161-7.
25. Mcinnes I, Merola JF, Mease PJ, Coates LC, Joshi P, Coarse J, et al. SAT0403 Efficacy and safety of 108 weeks' bimekizumab treatment in patients with psoriatic arthritis: interim results from a phase 2 open-label extension study. Ann Rheum Dis. 2020;79 Suppl. 1:1153–4, http://dx.doi.org/10.1136/annrheumdis-2020-eular.1850.
26. Mease P, Deodhar A, Merola J, McInnes I, Assudani D, Bajracharya R, et al. Bimekizumab in patients with psoriatic arthritis: 3-year results for overall and tumor necrosis factor inhibitor (TNFi)-naïve populations from a phase 2b open-label extension study [abstract]. Arthritis Rheumatol. 2021;73 Suppl. 9, https://acrabstracts.org/abstract/bimekizumab-in-patients-with-psoriatic-arthritis-3-year-results-for-overall-and-tumor-necrosis-factor-inhibitor-tnfi-naive-populations-from-a-phase-2b-open-label-extension-study/.
27. A study to test the efficacy and safety of bimekizumab in the treatment of subjects with active psoriatic arthritis (BE OPTIMAL). ClinicalTrials.gov. Identifier: NCT03895203, https://clinicaltrials.gov/ct2/show/NCT03895203.
28. Food and Drug Administration. FDA: RINVOQ (upadacitinib) Prescribing Information. https://www.fda.gov/drugs/new-drugs-fda-cders-new-molecular-entities-and-new-therapeutic-biological-products/novel-drug-approvals-2019 [accessed 7.11.21].
29. European Medicines Agency. EMA. RINVOQ (Upadacitinib) prescribing information. https://www.ema.europa.eu/en/medicines/human/EPAR/rinvoq [accessed 7.11.21].

30. McInnes IB, Anderson JK, Magrey M, Merola JF, Liu Y, Kishimoto M, et al. Trial of upadacitinib and adalimumab for psoriatic arthritis. N Engl J Med. 2021;384:1227–39, http://dx.doi.org/10.1056/NEJMoa2022516.
31. Mease PJ, Lertratanakul A, Anderson JK, Papp K, Van den Bosch F, Tsuji S, et al. Upadacitinib for psoriatic arthritis refractory to biologics: SELECT-PsA 2. Ann Rheum Dis. 2020;80:312–20, http://dx.doi.org/10.1136/annrheumdis-2020-218870.
32. McInnes IB, Kato K, Magrey M, Merola JF, Kishimoto M, Pacheco-Tena C, et al. Upadacitinib in patients with psoriatic arthritis and an inadequate response to non-biological therapy: 56-week data from the phase 3 SELECT-PsA 1 study. RMD Open. 2021;7:e001838, http://dx.doi.org/10.1136/rmdopen-2021-001838.
33. 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;392:2367–77, http://dx.doi.org/10.1016/S0140-6736(18)32483-8.
34. Gladman DD, Coates LC, Van den Bosch F, Helliwell, Tasset C, Meuleners L, et al. FRI0339 Long-term efficacy of the oral selective janus kinase 1 inhibitor filgotinib in psoriatic arthritis: week 52 response patterns in individual patients from an open-label extension (ole) study (EQUATOR2). Ann Rheum Dis. 2020;79:763.
35. Study to evaluate the efficacy and safety of filgotinib in participants with active psoriatic arthritis who are naive to biologic DMARD therapy (PENGUIN 1). ClinicalTrials.gov. Identifier: NCT04115748, https://clinicaltrials.gov/ct2/show/NCT04115748.
36. Study to evaluate the efficacy and safety of filgotinib in participants with active psoriatic arthritis who have an inadequate response or are intolerant to biologic DMARD therapy (PENGUIN 2). ClinicalTrials.gov. Identifier: NCT04115839, https://clinicaltrials.gov/ct2/show/NCT04115839.
37. Mease PJ, Deodhar AA, van der Heijde D, Behrens F, Kivitz AJ, Neal J, et al. Efficacy and safety of selective TYK2 inhibitor, deucravacitinib, in a phase II trial in psoriatic arthritis. Ann Rheum Dis. 2022;81:815–22, http://dx.doi.org/10.1136/annrheumdis-2021-221664.
38. Deodhar A, Nowak M, Ye J, Lehman T, Wei L, Banerjee S, et al. Deucravacitinib efficacy in psoriatic arthritis (PsA) by baseline DMARD use: exploratory analysis from a phase 2 study [abstract]. Arthritis Rheumatol. 2021;73 Suppl. 9, https://acrabstracts.org/abstract/deucravacitinib-efficacy-in-psoriatic-arthritis-psa-by-baseline-dmard-use-exploratory-analysis-from-a-phase-2-study/.
39. A study to determine the efficacy and safety of deucravacitinib compared with placebo in participants with active psoriatic arthritis (PsA) who are naïve to biologic disease modifying anti-rheumatic drugs or had previously received TNFα inhibitor treatment. ClinicalTrials.gov. Identifier: NCT04908189, https://clinicaltrials.gov/ct2/show/NCT04908189.
40. Papp K, Gordon K, Thaçi D, Morita A, Gooderham M, Foley P, et al. Phase 2 trial of selective tyrosine kinase 2 inhibition in psoriasis. N Engl J Med. 2018;379:1313–21, http://dx.doi.org/10.1056/NEJMoa1806382.
41. Mease P, Helliwell P, Silwinska-Stanczyk P, Miakisz M, Ostor A, Peeva E, et al. Efficacy and safety of brepocitinib (tyrosine kinase 2/janus kinase 1 inhibitor) for the treatment of active psoriatic arthritis: results from a phase 2b randomized controlled trial [abstract]. Arthritis Rheumatol. 2021;73 Suppl. 9, https://acrabstracts.org/abstract/efficacy-and-safety-of-brepocitinib-tyrosine-kinase-2-janus-kinase-1-inhibitor-for-the-treatment-of-active-psoriatic-arthritis-results-from-a-phase-2b-randomized-controlled-trial/.
42. Ogdie A, Coates LC, Gladman DD. Treatment guidelines in psoriatic arthritis. Rheumatology (Oxford). 2020;59 Suppl. 1:i37–46, http://dx.doi.org/10.1093/rheumatology/kez383.
43. Hagège B, Tan E, Gayraud M, Fautrel B, Gossec L, Mitrovic S. Remission and low disease activity in psoriatic arthritis publications: a systematic literature review with meta-analysis. Rheumatology (Oxford). 2020;59:1818–25, http://dx.doi.org/10.1093/rheumatology/keaa030.
44. Lindström U, Di Giuseppe D, Delcoigne B, Glintborg B, Möller B, Ciurea A, et al. Effectiveness and treatment retention of TNF inhibitors when used as monotherapy versus comedication with csDMARDs in 15 332 patients with psoriatic arthritis. Data from the EuroSpA collaboration. Ann Rheum Dis. 2021;80:1410–8, http://dx.doi.org/10.1136/annrheumdis-2021-220097.
45. Ramírez J, Azuaga-Piñango AB, Celis R, Cañete JD. Update on cardiovascular risk and obesity in psoriatic arthritis. Front Med (Lausanne). 2021;8:742713, http://dx.doi.org/10.3389/fmed.2021.742713.
46. McInnes IB, Kavanaugh A, Gottlieb AB, Puig L, Rahman P, Ritchlin C, et al. Efficacy and safety of ustekinumab in patients with active psoriatic arthritis: 1 year results of the phase 3, multicentre, double-blind, placebo-controlled PSUMMIT 1 trial. Lancet. 2013;382:780–9, http://dx.doi.org/10.1016/S0140-6736(13)60594-2.
47. Ritchlin C, Rahman P, Kavanaugh A, McInnes IB, Puig L, Li S, et al. Efficacy and safety of the anti-IL-12/23 p40 monoclonal antibody, ustekinumab, in patients with active psoriatic arthritis despite conventional non-biological and biological anti-tumour necrosis factor therapy: 6-month and 1-year results of the phase 3, multicentre, double-blind, placebo-controlled, randomised PSUMMIT 2 trial. Ann Rheum Dis. 2014;73:990–9, http://dx.doi.org/10.1136/annrheumdis-2013-204655.
48. McInnes IB, Sieper J, Braun J, Emery P, van der Heijde D, Isaacs JD, et al. Efficacy and safety of secukinumab, a fully human anti-interleukin-17A monoclonal antibody, in patients with moderate-to-severe psoriatic arthritis: a 24-week, randomised, double-blind, placebo-controlled, phase II proof-of-concept trial. Ann Rheum Dis. 2014;73:349–56, http://dx.doi.org/10.1136/annrheumdis-2012-202646.
49. McInnes IB, Mease PJ, Kirkham B, Kavanaugh A, Ritchlin CT, Rahman P, et al. Secukinumab, a human anti-interleukin-17A monoclonal antibody, in patients with psoriatic arthritis (FUTURE 2): a randomised, double-blind, placebo-controlled, phase 3 trial. Lancet. 2015;386:1137–46, http://dx.doi.org/10.1016/S0140-6736(15)61134-5.
50. 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. Ann Rheum Dis. 2017;76:79–87, http://dx.doi.org/10.1136/annrheumdis-2016-209709.
51. 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;389:2317–27, http://dx.doi.org/10.1016/S0140-6736(17)31429-0.
52. Schett G, Wollenhaupt J, Papp K, Joos R, Rodrigues JF, Vessey AR, et al. Oral apremilast in the treatment of active psoriatic arthritis: results of a multicenter, randomized, double-blind,

placebo-controlled study. Arthritis Rheum. 2012;64:3156–67, http://dx.doi.org/10.1002/art.34627.
53. Mease P, Hall S, FitzGerald O, van der Heijde D, Merola JF, Avila-Zapata F, et al. Tofacitinib or adalimumab vs. placebo for psoriatic arthritis. N Engl J Med. 2017;377:1537–50, http://dx.doi.org/10.1056/NEJMoa1615975.
54. 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. N Engl J Med. 2017;377:1525–36, http://dx.doi.org/10.1056/NEJMoa1615977.
55. Reich K, Armstrong AW, Foley P, Song M, Wasfi Y, Randazzo B, et al. Efficacy and safety of guselkumab, an anti-interleukin-23 monoclonal antibody, compared with adalimumab for the treatment of patients with moderate to severe psoriasis with randomized withdrawal and retreatment: results from the phase III, double-blind, placebo- and active comparator-controlled VOYAGE 2 trial. J Am Acad Dermatol. 2017;76:418–31, http://dx.doi.org/10.1016/j.jaad.2016.11.042.
56. Reich K, Gooderham M, Thaçi D, Crowley JJ, Ryan C, Krueger JG, et al. Risankizumab compared with adalimumab in patients with moderate-to-severe plaque psoriasis (IMMvent): a randomised, double-blind, active-comparator-controlled phase 3 trial. Lancet. 2019;394:576–86, http://dx.doi.org/10.1016/S0140-6736(19)30952-3.
57. Papp K, Gottlieb AB, Naldi L, Pariser D, Ho V, Goyal K, et al. Safety surveillance for ustekinumab and other psoriasis treatments from the psoriasis longitudinal assessment and registry (PSOLAR). J Drugs Dermatol. 2015;14:706–14.
58. Sokolova MV, Simon D, Nas K, Zaiss MM, Luo Y, Zhao Y, et al. A set of serum markers detecting systemic inflammation in psoriatic skin, entheseal, and joint disease in the absence of C-reactive protein and its link to clinical disease manifestations. Arthritis Res Ther. 2020;22, http://dx.doi.org/10.1186/s13075-020-2111-8.
59. McInnes IB, Behrens F, Mease PJ, Kavanaugh A, Ritchlin C, Nash P, et al. Secukinumab vs. adalimumab for treatment of active psoriatic arthritis (EXCEED): a double-blind, parallel-group, randomised, active-controlled, phase 3b trial. Lancet. 2020;395:1496–505, http://dx.doi.org/10.1016/S0140-6736(20)30564-X.
60. Smolen JS, Sebba A, Ruderman EM, Schulze-Koops H, Sapin C, Gellett AM, et al. Efficacy and safety of ixekizumab with or without methotrexate in biologic-naïve patients with psoriatic arthritis: 52-week results from SPIRIT-H2H study. Rheumatol Ther. 2020;7:1021–35, http://dx.doi.org/10.1007/s40744-020-00250-3.
61. Westhovens R, Taylor PC, Alten R, Pavlova D, Enríquez-Sosa F, Mazur M, et al. Filgotinib (GLPG0634/GS-6034), an oral JAK1 selective inhibitor, is effective in combination with methotrexate (MTX) in patients with active rheumatoid arthritis and insufficient response to MTX: results from a randomised, dose-finding study (DARWIN 1). Ann Rheum Dis. 2017;76:998–1008, http://dx.doi.org/10.1136/annrheumdis-2016-210104.
62. Kavanaugh A, Kremer J, Ponce L, Cseuz R, Reshetko OV, Stanislavchuk M, et al. Filgotinib (GLPG0634/GS-6034), an oral selective JAK1 inhibitor, is effective as monotherapy in patients with active rheumatoid arthritis: results from a randomised, dose-finding study (DARWIN 2). Ann Rheum Dis. 2017;76:1009–19, http://dx.doi.org/10.1136/annrheumdis-2016-210105.
63. Burmester GR, Kremer JM, Van den Bosch F, Kivitz A, Bessette L, Li Y, et al. Safety and efficacy of upadacitinib in patients with rheumatoid arthritis and inadequate response to conventional synthetic disease-modifying anti-rheumatic drugs (SELECT-NEXT): a randomised, double-blind, placebo-controlled phase 3 trial. Lancet. 2018;391:2503–12, http://dx.doi.org/10.1016/S0140-6736(18)31115-2.
64. Genovese MC, Fleischmann R, Combe B, Hall S, Rubbert-Roth A, Zhang Y, et al. Safety and efficacy of upadacitinib in patients with active rheumatoid arthritis refractory to biologic disease-modifying anti-rheumatic drugs (SELECT-BEYOND): a double-blind, randomised controlled phase 3 trial. Lancet. 2018;391:2513–24, http://dx.doi.org/10.1016/S0140-6736(18)31116-4.
65. Panés J, Sandborn WJ, Schreiber S, Sands BE, Vermeire S, D'Haens G, et al. Tofacitinib for induction and maintenance therapy of Crohn's disease: results of two phase IIb randomised placebo-controlled trials. Gut. 2017;66:1049–59, http://dx.doi.org/10.1136/gutjnl-2016-312735.
66. Sandborn WJ, Ghosh S, Panes J, Schreiber S, D'Haens G, Tanida S, et al. Efficacy of upadacitinib in a randomized trial of patients with active ulcerative colitis. Gastroenterology. 2020;158:2139–49, http://dx.doi.org/10.1053/j.gastro.2020.02.030, e14.
67. van der Heijde D, Song IH, Pangan AL, Deodhar A, van den Bosch F, Maksymowych WP, et al. Efficacy and safety of upadacitinib in patients with active ankylosing spondylitis (SELECT-AXIS 1): a multicentre, randomised, double-blind, placebo-controlled, phase 2/3 trial. Lancet. 2019;394:2108–17, http://dx.doi.org/10.1016/S0140-6736(19)32534-6.
68. Guttman-Yassky E, Thaçi D, Pangan AL, Hong HC, Papp KA, Reich K, et al. Upadacitinib in adults with moderate to severe atopic dermatitis: 16-week results from a randomized, placebo-controlled trial. J Allergy Clin Immunol. 2020;145:877–84, http://dx.doi.org/10.1016/j.jaci.2019.11.025.
69. Deodhar A, Gensler LS, Sieper J, Clark M, Calderon C, Wang Y, et al. Three multicenter, randomized, double-blind, placebo-controlled studies evaluating the efficacy and safety of ustekinumab in axial spondyloarthritis. Arthritis Rheumatol. 2019;71:258–70, http://dx.doi.org/10.1002/art.40728.
70. Ytterberg S, Bhatt D, Mikuls T, Koch G, Rivas J, Germino R, et al. Safety and efficacy of tofacitinib vs, TNF inhibitors in ra patients aged 50 years or older with one or more cardiovascular risks: results from a phase 3b/4 randomized safety trial [abstract]. Arthritis Rheumatol. 2021;73 Suppl. 10.
71. Miyagawa I, Nakayamada S, Nakano K, Kubo S, Iwata S, Miyazaki Y, et al. Precision medicine using different biological DMARDs based on characteristic phenotypes of peripheral T helper cells in psoriatic arthritis. Rheumatology (Oxford). 2019;58:336–44, http://dx.doi.org/10.1093/rheumatology/key069.