Advances in small molecule inhibitors for treatment of psoriasis

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To the Editor: Psoriasis is a chronic multisystemic inflammatory disease. Interleukin (IL)-23/T-helper (Th) 17 pathway, tumor necrosis factor-α, and many inflammatory cytokines are involved in the onset and development of psoriasis, and the discovery of biologic targets of relevant cytokines have modified the psoriasis treatment paradigm. Although biologics are effective in treating such diseases, the applications are still limited. Thus, small molecule inhibitors (SMIs) have gained considerable attention among researchers, owing to the simplified synthesis processes, low-cost production, and the possibility of oral or topical administration. This article summarizes SMIs in clinical development and those approved for the treatment of psoriasis.

Presently, both oral and topical phosphodiesterase 4 inhibitors (PDE4Is) are under development for the treatment of psoriasis. Apremilast is an orally administered PDE4I that was first approved by the United States Food and Drug Administration in 2014 for the treatment of adult patients with moderate-to-severe plaque psoriasis or active psoriatic arthritis (PsA). Hemay005 is a novel PDE4I with improved inhibition potency and fewer adverse events (AEs), which has been developed for the treatment of psoriasis and is currently being tested in a phase II clinical trial in China. Crisaborole is a topical PDE4I that is used to treat atopic dermatitis, and previous studies found that crisaborole is effective against mild-to-moderate psoriasis.[1] Additionally, crisaborole is currently in phase II trials for the treatment of psoriasis.

Previous phase IIb to IIIb studies[2,3] showed that 29% to 41% of patients who received apremilast 30 mg b.i.d (twice daily) achieved psoriasis area and severity index (PASI) 75 at week 16, and apremilast reduced pruritus and improved the quality of life. Furthermore, the LIBERATE trial[3] demonstrated that the efficiency of apremilast is similar to that of etanercept. In a French study that involved 14,147 patients with psoriasis, the usage of apremilast was compared with that of methotrexate, and it was revealed that the discontinuation rate at one year was 69% for apremilast and 58% for methotrexate.[4] Recently, the efficacy and tolerability of apremilast in pediatric patients with psoriasis was demonstrated in a phase II clinical trial.[5]

PALACE 1–3 trial was conducted to evaluate the efficacy of apremilast as a drug for PsA. The results showed that 67.2%, 44.4%, and 27.4% of patients who received apremilast achieved the following improvement scores, American college of rheumatology (ACR) 20, ACR 50, and ACR 70, respectively, for up to 5 years.[6] Regarding comorbidities of psoriasis, some case reports have revealed that apremilast improved serum lipid profile and glucose metabolism,[7,8] suggesting the potential of apremilast as a metabolic modulator. However, further studies are required to validate these results.

The most common AEs of apremilast were diarrhea, nausea, urinary tract infections, headache, and nasopharyngitis. Notably, 20.2% of patients experienced weight loss of >5% during long-term exposure to apremilast.

Janus kinase (JAK) inhibitors are small-molecule drugs that inhibit JAKs, and thereby hinder the function of the JAK-signal transducer and activator of transcription signaling pathway. JAK family includes JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK2). Various inflammatory cytokines bind to type I and II cytokine receptors, which leads to the activation of intracellular signaling mediated by JAKs, and this ultimately results in the activation of gene transcription. JAK inhibitors disrupt intracellular signaling initiated by cytokines, thereby reducing inflammation associated with psoriasis [Figure 1].

Tofacitinib (which targets JAK1, JAK2, and JAK3) is currently approved for the treatment of PsA, but not of psoriasis. A previous phase II–III study demonstrated superior efficacy of tofacitinib compared with that in

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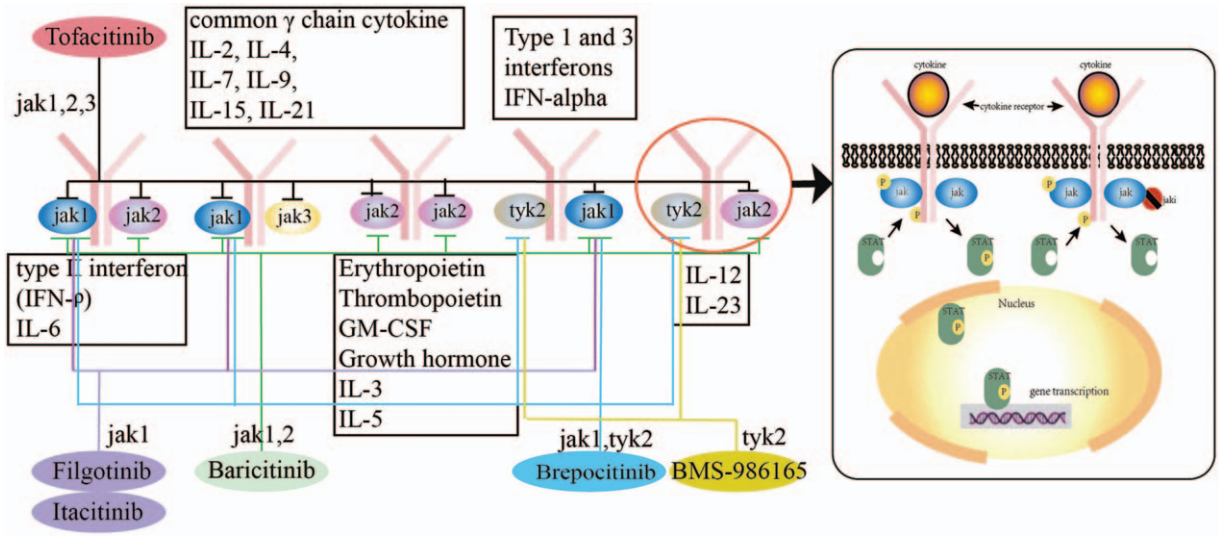

Figure 1: Selectivity of JAK inhibitors presented in this review (left). Cytokine receptor-associated JAK/STAT signaling pathway and the mechanism of action of JAK inhibitors (right). JAK: Janus kinase; STAT: Signal transducer and activator of transcription.

placebo, and this high efficacy was positively correlated with the drug dose. In OPT pivotal 1 and 2 studies, 59.2% and 59.6% of patients who received 10 mg tofacitinib, achieved PASI 75; in phase IIb study, 25.0%, 40.8%, and 66.7% of patients who received 2, 5, and 15 mg b.i.d., respectively, achieved PASI 75 at week 12.[9,10] Moreover, in Asia, the proportion of patients who achieved PASI 75 when administered tofacitinib 5 and 10 mg b.i.d. was 54.6% and 81.1%, respectively.[11] In addition, the proportion of pediatric patients receiving tofacitinib (5 mg b.i.d.) who achieved PASI 75 was 55.32% at week 12 and 70.21% at week 36.[12] However, the sample size was too small, and thus, the results need to be validated in larger multicenter trials.

High-dose tofacitinib was more effective than high-dose entanercept as PASI 75 was achieved in 58.8% of patients in the etanercept group, while the result was 39.5% and 63.6% in the 5 and 10 mg tofacitinib groups, respectively.[13] Unfortunately, the ointment formulation of tofacitinib was found to have no considerable effect at week 12 in comparison to that of the vehicle.[14]

Upper respiratory tract infections, nasopharyngitis, and headache were the most common AEs, and there was an increased risk of herpes zoster, serious infections, including tuberculosis, pneumonia, and influenza, as well as laboratory abnormalities in the tofacitinib treatment group. Thus, routine laboratory monitoring is necessary when tofacitinib is prescribed in clinical settings. Importantly, in the 10 mg b.i.d. group, pulmonary embolism and the subsequent death of a patient with rheumatoid arthritis was reported in February 2019. Consequently, tofacitinib has not received approval for the treatment of plaque psoriasis. However, tofacitinib (5 mg b.i.d.) can still be considered as a treatment option in patients with PsA and comorbid skin disease.

Baricitinib is an oral JAK1/JAK2 inhibitor that was approved for the treatment of RA, but not of psoriasis. However, a phase II study identified a definite curative effect of baricitinib on psoriasis. The PASI 75 response was 42.9% for 8 mg and 54.1% for 10 mg baricitinib, and 16.7% for placebo at week 12. Additionally, 81% of responders maintained their scores for 24 weeks.[15]

Filgotinib and itacitinib are both selective inhibitors of JAK1. Filgotinib is currently undergoing a phase III clinical trial in patients with PsA. It was demonstrated in a phase II study that the efficacy of 600 and 200 mg q.d. (once daily) itacitinib was significantly superior to that of placebo in achieving PASI 50 (81.8%, 66.7%, and 8.3%, respectively).[16] Nasopharyngitis, increased aspartate aminotransferase levels, headache, and hypertriglyceridemia are the commonly reported AEs. However, there has been no further investigation of itacitinib.

Peficitinib is a selective JAK3 inhibitor. A phase IIa randomized control trial showed that the proportion of patients achieving PASI 75 was 14.3% and 58.8% in the 25 and 100 mg b.i.d. peficitinib groups, respectively, and 3.4% in the placebo group.[17] No serious AEs were observed.

Brepocitinib, a potent TYK2/JAK1 inhibitor, is being evaluated for both oral and topical treatment. Brepocitinib was shown to modulate the central IL23/Th17 axis as early as week 2,[18] and a phase I study revealed that the mean percent change from baseline in PASI was 67.92% and 96.31% in the 30 and 100 mg q.d. groups, respectively, at week four. Brepocitinib usage was considered safe and well tolerated up to 200 mg q.d. in healthy subjects.[19] Upper respiratory tract infections and herpes zoster infection were reported to be the treatment-related AEs.

Because the earlier pan-JAK inhibitor is relatively nonspecific and has a high prevalence of AEs, selective TYK2 inhibitors have been developed. Two selective TYK2 inhibitors, namely PF-06826647 and BMS-986165, are under clinical trials for psoriasis.

BMS-986165 is a potent oral TYK2 inhibitor that binds to the pseudokinase domain of the enzyme and is functionally more selective than other TYK inhibitors. A phase II trial examined the effect of BMS-986165 3 mg q.o.d., 3 mg q.d., 3 mg b.i.d., 6 mg b.i.d., 12 mg q.d. or placebo and showed that a 75% or greater reduction in the PASI score was achieved in 9%, 39%, 69%, 67%, 75%, and 7% of the patients, respectively.[20] The BMS-986165 drug group had a higher lesion clearing rate in comparison with placebo.

Nasopharyngitis, headache, diarrhea, nausea, and upper respiratory tract infection are the most common AEs, and no significant laboratory abnormalities have been observed.[20]

In addition to the aforementioned types of SMIs, there are many other SMIs that are under clinical development, such as protein kinase C inhibitor, phosphoinositide 3-kinase δ inhibitor, retinoic acid receptor-related orphan nuclear receptor gamma t inhibitor, aryl hydrocarbon receptor modulating agents, and so on.

With the rapid development of drugs for the treatment of psoriasis, SMIs have the potential to mediate the functions between traditional oral systemic drugs and biologics for psoriasis treatment. However, further data are required to ascertain their role as effective, safe, and inexpensive alternatives to biologic treatments.

Conflicts of interest

None.

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