Emerging Oral Treatments for Psoriasis

Subjects: Dermatology
Contributor: Elena Carmona-Rocha, Lluís Rusiñol, Lluís Puig

Psoriasis is a chronic inflammatory disease with a worldwide prevalence of 1–3% that can be associated with psoriatic arthritis and other comorbidities and causes a significant burden and impairment of health-related quality of life. Psoriasis is an immune-mediated inflammatory disease (IMID) with a pathogenic admixture of autoinflammatory and autoimmune components and involvement of both innate and adaptive immune systems.

Keywords: psoriasis ; oral therapies ; topical therapies ; biologics

1. Jak Inhibitors

The Janus kinase/signal transducer and activator of transcription (Jak/STAT) pathways play an important role in diverse cellular processes [1]. They mediate the intracellular signaling of cytokines in both physiological and pathological conditions, notably IMIDs such as psoriasis [1][2].

Jaks are receptor-associated tyrosine kinases that act intracellularly as signal transducers. Four molecules compose the Jak family: Jak1, Jak2, Jak3, and Tyk2. When a circulating cytokine (e.g., IL-13) binds to its cell surface receptor, two Jak molecules (one from each receptor subunit) pair to form a dimer after a conformational change in the receptor. Jak dimers are composed of two different Jaks (heterodimers), except Jak2, which can also pair with itself (homodimer) [3][4]. Jak dimers phosphorylate the activated cytokine receptor, permitting the attachment, phosphorylation, and dimerization of STAT proteins. Seven distinct STAT proteins have been identified, namely STAT1, STAT2, STAT3, STAT4, STAT5a, STAT5b, and STAT6. Following dimerization, STATs move to the nucleus, where they act as transcription factors, inducing the expression of growth factor and proinflammatory cytokine genes [3][4].

Because of the significant involvement of the Jak/STAT pathway in the pathogenesis of IMIDs, numerous molecules with therapeutic potential have been developed; because of their small molecular size, they can be employed orally or topically [1].

One of the biggest concerns related to Jak inhibitors is their safety, related to their potential interference with the physiological roles of Jak/STAT pathways and the relative non-selectivity of orthosteric Jak inhibitors (blocking the kinase function of the JH1 catalytic domain). Most adverse events (AEs) observed in both clinical trials and real-world clinical settings correspond to mild and moderately severe infections involving the upper respiratory tract, urinary tract, and gastrointestinal system [1][2][5]. Some AEs of Jak inhibitors are considered class-related, mostly because of the rather limited selectivity of the first approved inhibitors of the Jak family. Jak1 inhibition may increase the serum levels of triglycerides, total cholesterol, low-density lipoprotein cholesterol, and high-density lipoprotein cholesterol. Jak2 mediates the action of growth factors involved in erythropoiesis, myelopoiesis, and platelet activation; hence, Jak2 inhibition can lead to anemia, neutropenia, thrombocytopenia, and thromboembolic events. The distribution of Jak3 is restricted to hematopoietic cells, and its function is exclusively linked with signal transduction of the common γc cytokine receptor subunit for interleukins that mediate the activation, function, and proliferation of lymphocytes. Lastly, Tyk2 inhibition interferes with signaling of type I and type III interferons, IL-6, IL-12, and IL-23, and thus can be associated with an increased risk of herpesvirus, staphylococcal, and mycobacterial infections.

Cytokine signaling involves the interaction of two receptor subunits and the formation of Jak dimers. The Jak2/Tyk2 dimer participates in signal transduction of IL-12 and IL-23; both are relevant in the pathogenesis of psoriasis, especially as regards the regulatory role of IL-23 on production of IL-17, the key effector cytokine in psoriasis [3][4][5]. Jak1/Tyk2 is involved in signal transduction of IFN-α and the IL-10 family, which are involved in the immunopathogenesis and epidermal proliferation of psoriasis. Selective targeting of Tyk2 may avoid production of Jak2-related—hematologic and thromboembolic—AEs [6][7].

1.1. Tofacitinib

Tofacitinib is an oral Jak1 and Jak3 inhibitor approved for the treatment of moderate-to-severe rheumatoid arthritis (2012), psoriatic arthritis (2017) at doses of 5 mg twice daily in adult patients, and ulcerative colitis at doses of 10 mg twice daily in adult patients by the Food and Drug Administration (FDA) of the United States (US) [8]. All these indications were also approved by the European Medicines Agency (EMA). Furthermore, the EMA also approved tofacitinib for the management of ankylosing spondylitis in adults and polyarticular juvenile idiopathic arthritis in children and adolescents aged 2 years

and older. The recommended dosages for both conditions involve an initial period of 10 mg twice daily for the initial eight weeks, followed by a maintenance dose of 5 mg twice daily [9].

Tofacitinib has been evaluated for the treatment of moderate to severe psoriasis in phase II and phase III clinical trials. Tofacitinib was compared with placebo in a phase IIb dose-ranging trial (NCT00678210) that included 197 participants who were randomly assigned to receive tofacitinib twice daily (*bis in die* [BID]) at doses of 2 mg, 5 mg, or 15 mg, or placebo [10]. The primary efficacy endpoint was 75% or more improvement in Psoriasis Area and Severity Index (PASI) with respect to baseline (PASI75 response) at 12 weeks. PASI75 response rates in patients treated with the different doses of tofacitinib (25%, 40.8%, and 66.7%, respectively) were significantly higher compared with placebo (2%). In addition, a PASI90 response was achieved by 22% of patients treated with any dose of tofacitinib [10].

Tofacitinib 5 mg and 10 mg BID were compared with subcutaneous etanercept 50 mg twice weekly and placebo in adult patients with plaque psoriasis and baseline PASI ≥ 12 in a randomized, placebo-controlled, non-inferiority phase III trial (NCT01241591) [11]. At week 12, PASI75 was achieved by 39.5%, 63.3%, 58.8%, and 5.6% of the tofacitinib 5 mg BID, tofacitinib 10 mg BID, etanercept 50 mg twice weekly, and placebo, respectively. Tofacitinib 5 mg BID was significantly inferior to etanercept ($p = 0.0009$). In addition, Physician Global Assessment (PGA) of psoriasis response was achieved by 47.1%, 68.2%, 66.3%, and 15%, respectively. Again, the tofacitinib 5 mg BID group showed significantly lower ($p < 0.0001$) results than etanercept; nevertheless, no differences were noted between tofacitinib 10 mg BID and etanercept. Regarding a significant improvement in the Dermatology Life Quality Index (DLQI), no differences were seen among tofacitinib (66.3% and 78.2%, respectively) and etanercept groups (74.7%). Similar rates of AEs were observed in both groups.

Two phase III clinical trials (OPT Pivotal 1 [901 patients] and OPT Pivotal 2 [960 patients]) [12][13] compared with facitinib 5 mg BID, tofacitinib 10 mg BID, and placebo. At 16 weeks, PASI 75 was achieved by 39.2%, 59.2%, and 9%, respectively, in OPT Pivotal 1. Similar results were observed in OPT Pivotal 2: 46%, 59.6%, and 11.4%, respectively. Tofacitinib 10 mg BID was more effective starting at week 16 and showed a higher PASI75 response rate between weeks 16 and 28, compared with tofacitinib 5 mg BID (68.8% vs. 55.6%, respectively). Among patients who achieved PASI75 at week 16, 74.1% of the 5 mg group and 79.4% of the 10 mg group maintained PASI75 at 52 weeks. Most patients maintained the response for 24 months [13]. At week 16, patients on both regimens showed improvement in ungual psoriasis, pruritus, and DLQI, which was sustained at week 52 [14][15]. Most AEs were of mild to moderate intensity, with nasopharyngitis being the most frequently reported. In the OPT Pivotal 1 trial, two patients receiving the 10 mg dose experienced severe infections (appendicitis, pneumonia, and pyelonephritis). Additionally, in OPT Pivotal 2, three patients treated with the 5 mg dose presented with severe infections (pneumonia, herpes zoster, and erysipelas). OPT1 revealed elevated cholesterol and creatine kinase levels in 2.5%, 2.5%, and 0.6% of the tofacitinib 5 mg BID, tofacitinib 10 mg BID, and placebo groups, respectively. OPT2 exhibited similar results: 5.2%, 5.2%, and 2%, respectively. Mild cytopenia, headache, upper respiratory tract infections, urinary tract infections, and diarrhea were the most prevalent side effects observed with tofacitinib at doses of 5 mg and 10 mg [12][13][14][15]. Furthermore, twelve patients across the tofacitinib groups developed reactivation of herpes zoster; analysis of the distribution by race and region of herpes zoster events observed was not reported.

No real-world studies of tofacitinib for the treatment of psoriasis have been conducted following its rejection by the FDA in October 2015 [16], and the application for EMA approval was dropped. The refusal was based on the stipulation that further studies assessing its long-term safety were deemed necessary.

1.2. Abrocitinib

Abrocitinib is an oral Jak1 inhibitor. Abrocitinib was approved in 2021 by the EMA and in 2022 by the FDA for the treatment of atopic dermatitis at the recommended initial dose of 200 mg/day in most patients [17]. The safety and tolerability of abrocitinib were demonstrated in a phase I trial (NCT01835197) [18]. Later, abrocitinib was evaluated in a phase II, placebo-controlled trial (NCT02201524), in which 59 patients with moderate to severe psoriasis were enrolled and randomly assigned to receive either placebo or abrocitinib at doses of 200 mg once a day (*quaque die* [QD]), 400 mg QD, or 200 mg BID [19]. At week 4, PASI75 response was achieved by 17%, 50%, and 60% of the patients treated with 200 mg QD, 400 mg QD, and 200 mg BID, respectively, and 17% of patients in the placebo arm. The predominant AEs reported included nausea, headache, neutropenia, and thrombocytopenia. Eight patients discontinued treatment due to AEs, the majority of which were due to cytopenia (one patient in the placebo group, one patient in the 200 mg QD groups, and six patients in the 200 mg BID group). Laboratory abnormalities, including low neutrophil, reticulocyte, and platelet counts, exhibited a higher frequency in the 200 mg BID group as opposed to the other groups. No serious infections or bleeding events related to neutropenia or thrombocytopenia, respectively, were reported. Abrocitinib has eventually been approved for the treatment of moderate to severe atopic dermatitis in adults who are candidates for systemic therapy, and there is no currently active clinical trial assessing the efficacy of abrocitinib as a therapeutic intervention for psoriasis.

1.3. Baricitinib

Baricitinib is an orally administered Jak1 and Jak2 inhibitor. Baricitinib was approved by the FDA and EMA for the treatment of rheumatoid arthritis and severe alopecia areata. Also, the EMA approved baricitinib for the treatment of atopic

dermatitis and active juvenile idiopathic arthritis in children aged 2 or older at a recommended dose of 4 mg/day in most patients [20][21].

The tolerability and safety of baricitinib were evaluated in two phase I clinical trials, in which no serious AEs were reported [22]. A phase IIb, randomized, double-blind, placebo-controlled, dose-ranging clinical trial (NCT01490632) evaluated the efficacy of baricitinib for the treatment of moderate to severe psoriasis [23]. A total of 271 patients were included. At 12 weeks, PASI75 response rates were 42.9% (8 mg QD) and 54.1% (10 mg QD), significantly higher than those of patients receiving placebo (16.1%). Infections, particularly nasopharyngitis, were the most commonly reported AEs [23]: nasopharyngitis was reported in 11.8%, 3.1%, 2.8%, 9.4%, and 8.7% of the treatment groups: placebo, baricitinib 2 mg, 4 mg, 8 mg, and 10 mg, respectively. Treatment-emergent AEs were similar in the placebo, 2 mg, and 4 mg dose groups (44.1%, 50.0%, and 47.2%, respectively), but were higher in the 8 mg and 10 mg dose groups (57.8% and 63.8%, respectively). There is currently no ongoing clinical trial evaluating baricitinib for the treatment of psoriasis.

1.4. Peficitinib

Peficitinib is an orally administered Jak inhibitor with moderate selectivity for Jak3 and Jak1 over Jak2 and Tyk2 [24]. A phase IIa (NCT01096862) randomized, placebo-controlled, double-blind trial evaluated the safety and efficacy of peficitinib in patients with moderate to severe psoriasis [25]. A total of 124 participants were enrolled and randomly allocated across five groups, with four receiving peficitinib 10 mg, 25 mg, 60 mg, and 100 mg BID, and one receiving 50 mg once daily (QD) as active treatment. Patients within each group were randomly allocated to peficitinib or placebo in a 3:1 ratio (namely, eighteen receiving peficitinib and six receiving placebo). After 6 weeks, all peficitinib groups exhibited a higher PASI reduction compared with placebo and a dose-dependent response, with the 100 mg BID group showing the greatest PASI reduction [25].

PASI75 response was achieved by 58.8% of individuals in the 100 mg BID group and 14.3% in the 25 mg BID group (representing the lowest response among the peficitinib groups); the response rates were in all cases significantly higher than those in the placebo group (3.4%). Peficitinib was well tolerated, with all AEs classified as mild or moderate. The most reported AEs included nasopharyngitis (10% in the placebo group and 18% in the 100 mg BID), diarrhea (7% in the placebo group and 6% in the 100 mg BID), acne (0% vs. 18%, respectively), back pain (0% vs. 12%, respectively), and contact dermatitis (7% vs. 0%, respectively) [25].

There is currently no ongoing clinical trial evaluating peficitinib as a treatment for psoriasis.

1.5. Solcitinib (GSK2586184)

Solcitinib is an orally administered Jak inhibitor with selectivity for Jak1 over Jak2 [26]. The efficacy and safety of solcitinib in patients with moderate to severe psoriasis were assessed in a phase IIa randomized placebo-controlled trial that enrolled a total of 68 participants (NCT01782664). Patients were randomly allocated to four cohorts, receiving either 100 mg, 200 mg, or 400 mg of solcitinib BID or a placebo. At week 12, PASI75 response was achieved by 0% of individuals in the placebo group, contrasting with 13%, 25%, and 57% of those in the 100 mg, 200 mg, and 400 mg solcitinib BID groups, respectively [26]. The incidence of AEs was similar among the treatment groups, with no discernible correlation between doses and the frequency of AEs. Headache, nasopharyngitis, nausea, diarrhea, fatigue, and upper abdominal pain were the most reported AEs [26].

There is currently no ongoing clinical trial evaluating solcitinib as a treatment for psoriasis.

1.6. Itacitinib Adipate

Itacitinib adipate is an orally administered Jak1 inhibitor. The efficacy and safety of itacitinib adipate in psoriasis were evaluated in a randomized, double-blind, placebo-controlled, phase II trial (NCT01634087) that included 50 patients [27]. PASI75 response was evaluated at 4 weeks, with a 0% response rate in the placebo group and 11.1%, 22.2%, and 27.7% in patients treated with Itacitinib adipate at doses of 100 mg QD, 200 mg QD, 200 mg BID, and 600 mg QD, respectively. However, only in the latter group was the difference significant compared with placebo. No relevant AEs were documented, the most frequent being nasopharyngitis (8.3% in placebo vs. 18.3% in itacitinib groups), elevated serum levels of aspartate aminotransferase (0 vs. 5.3%), headache (0 vs. 5.3%), and hypertriglyceridemia (0 vs. 5.3%). [27]. At present, there is no active clinical trial investigating the efficacy of itacitinib adipate as a therapeutic approach for psoriasis.

1.7. Brepocitinib

Brepocitinib (formerly PF-06700841) is an oral Tyk2 and Jak1 inhibitor that binds to the active sites of the Tyk2 catalytic domain [28]. A phase I trial confirmed the safety and tolerability of brepocitinib (NCT02310750) [29]. In a phase IIa trial (NCT02969018), 212 patients were enrolled and treated for four weeks with brepocitinib 30 mg QD, brepocitinib 60 mg QD, or placebo. Later, patients were randomly allocated and treated for 8 weeks with placebo, brepocitinib 10 mg QD, 30 mg QD, or 100 mg once weekly [30]. At 12 weeks, PASI75 was evaluated, which was achieved by: 60% of the 60 mg QD followed by 30 mg QD group, 24.1% of the 60 mg QD followed by 10 mg QD group, 57.7% of the 60 mg QD followed by

100 mg once weekly group, 24% of the 60 mg QD followed by placebo group, 86.2% of the 30 mg QD group, 24% of the 30 mg QD followed by 10 mg QD group, 36.7% of the 30 mg QD followed by 100 mg once weekly group, and 13% of the placebo group. Commonly reported AEs without differences among groups included nasopharyngitis, upper respiratory tract infection, and headache. Notably, there were no instances of herpes zoster infections reported, indicating a favorable tolerability profile for the treatment.

In June 2022, Pfizer granted Priovant global developmental rights for both oral and topical formulations, as well as commercial rights in the U.S. and Japan for brepocitinib [31]. The progression of oral brepocitinib has been halted for most of its potential applications, spanning psoriasis, psoriatic arthritis, vitiligo, ulcerative colitis, hidradenitis suppurativa, and Crohn's disease.

1.8. Ropsacitinib

Ropsacitinib (formerly PF-06826647) is an oral inhibitor of Tyk2 and Jak2 that binds to the active site in the catalytic domain (JH1) of each kinase, but with higher selectivity for Tyk2 [28]. The efficacy and safety of ropsacitinib in moderate to severe psoriasis were evaluated in two phase I trials (NCT02310750, NCT03210961) [32][33]. Subsequently, a randomized, double-blind, placebo-controlled phase IIb trial (NCT03895372) included 178 patients who were randomly allocated to receive placebo or ropsacitinib at doses of 50 mg, 100 mg, 200 mg, or 400 mg QD. [34]. The PASI75 response was assessed at week 16, with the 50 mg, 100 mg, 200 mg, and 400 mg QD cohorts achieving 18.2%, 9.5%, 46.7%, and 73.2%, respectively. Results from the 200 mg and 400 mg QD groups were significantly higher than those observed with placebo (14.3%). Nasopharyngitis (4.5% in the placebo group vs. 27.7% in the 400 mg QD group) and increased blood pressure were the most frequently reported AEs (4.35% in the placebo group vs. 11.63% in the 400 mg QD group). [34]. At present, there is no active clinical trial involving ropsacitinib, which has also been licensed by Pfizer to Priovant [31].

1.9. Deucravacitinib

Deucravacitinib is an oral allosteric Tyk2 inhibitor that binds to the pseudokinase or regulatory (JH2) domain, causing a conformational change that prevents the catalytic activity of the kinase (JH1) domain [35][36][37][38]. Consequently, deucravacitinib displays a great selectivity for Tyk2 over Jak1/3 (1000-fold) and Jak2 (2000-fold) [36][37].

Deucravacitinib was evaluated for the treatment of moderate to severe psoriasis in a randomized, placebo-controlled, phase IIa trial [39]. A total of 267 patients were included and randomly assigned to receive placebo or deucravacitinib with four dosing arms: 3 mg BID, 6 mg BID, and 12 mg QD. PASI75 response was evaluated at week 12 and achieved by 6.7% (placebo), 68.9% (3 mg BID), 66.7% (6 mg BID), and 75% (12 mg QD) of patients. The reported AEs were considered mild in all cases, and the most frequently reported were nasopharyngitis, headaches, diarrhea, nausea, and upper respiratory tract infections. No alterations in serum lipid levels or hematologic abnormalities were noted, as would correspond to the high selectivity of deucravacitinib for Tyk2 with negligible Jak1 or Jak2 interaction [39][40].

Two phase III trials compared deucravacitinib to placebo and apremilast for the treatment of moderate to severe psoriasis [41]. POETyk PSO-1 (NCT03624127) was a double-blind, 52-week trial with 666 patients who were randomly assigned in a 2:1:1 pattern to deucravacitinib 6 mg QD (n = 332), placebo (n = 166), or apremilast 30 mg BID (n = 168). At week 16, deucravacitinib showed significantly higher PASI75 response rates (58.4%) than placebo (12.7%) and apremilast (35.1%). Moreover, the efficacy of deucravacitinib improved beyond week 16 and was maintained through week 52 (68.3%). At week 24, PASI75 was achieved by 69.3% of the patients in the deucravacitinib group, compared with only 38.1% of the patients in the apremilast group. The most frequent AEs related to deucravacitinib were nasopharyngitis and upper respiratory tract infections. Similar rates were noted among the three groups: placebo, deucravacitinib, and apremilast: 4.2%, 6.3%, and 8.3%, respectively, for nasopharyngitis and 3.6%, 6.3%, and 1.8%, respectively, for upper respiratory tract infections. POETyk PSO-2 (NCT03611751) [42] was a 52-week trial that included 1020 participants randomized into three groups: deucravacitinib 6 mg QD (511), placebo (255), and apremilast 30 mg BID (254). Once more, deucravacitinib demonstrated superiority with a higher PASI75 response rate (53%) than placebo (9.4%) and apremilast (39.8%) at week 16. The efficacy persisted through week 52 with ongoing deucravacitinib administration. Nasopharyngitis was the most frequently reported adverse event, and no significant laboratory abnormalities were observed [42].

Armstrong et al. have recently published a systematic review and network meta-analysis in which deucravacitinib was indirectly compared with other systemic biologic and nonbiologic therapies [43]. Deucravacitinib PASI75 response at short-term (10–16 weeks) was 54.1% (46.5–61.6). These results were similar to the results observed with the first-generation of biologics: etanercept 39.7% (31.6–48.3) and infliximab 79.0% (74.0–83.5). At long-term follow-up (44–60 weeks), deucravacitinib PASI75 was 65.9% (58.0–73.4), also close to the PASI75 achieved by first-generation biologics adalimumab 62.8% (55.3–69.6) and ustekinumab 68.0% (64.6–71.5). Furthermore, a matching-adjusted indirect comparison (MAIC) of the long-term efficacy of deucravacitinib versus adalimumab for patients with moderate-to-severe plaque psoriasis was recently published [44]. This MAIC concluded that patients treated with deucravacitinib showed a higher long-term response rate at 2 years than with adalimumab. Adalimumab response rates declined by year two, whereas deucravacitinib response rates remained stable.

Several phase III and 4 trials are currently assessing the efficacy and safety of deucravacitinib in the treatment of moderate to severe psoriasis (NCT04036435), scalp psoriasis (NCT05478499), nail psoriasis (NCT05124080), and in pediatric patients with moderate to severe psoriasis (NCT04772079). Additionally, an upcoming phase IV observational post-marketing surveillance study will focus on AEs in patients with psoriasis in Japan (NCT05633264). Finally, a trial examining adherence in patients with psoriasis is expected to commence recruitment soon (NCT05570955).

Deucravacitinib 6 mg daily was approved by the FDA (2022) and EMA (2023) for the treatment of moderate to severe psoriasis [45][46][47]. In 2022, deucravacitinib was approved in Japan for the treatment of plaque psoriasis, generalized pustular psoriasis, and erythrodermic psoriasis.

1.10. BMS-986202

BMS-986202 is an oral Tyk2 inhibitor created by structural and molecular modifications applied to deucravacitinib [48] and shares its mechanism of action. Encouraging results have been observed in preclinical studies, but no clinical studies assessing its efficacy have been conducted yet [48]. A phase I trial testing its safety, tolerability, pharmacokinetics, and pharmacodynamics is already complete, but results have not been posted.

1.11. SAR-20347

SAR-20347 is an orally administered Tyk2 and Jak1 inhibitor that has been shown to be effective in attenuating pathologic alterations in the imiquimod murine model of psoriasis [49]. No trials testing its efficacy and safety have been performed yet.

1.12. Zasocitinib (TAK-279)

Zasocitinib (TAK-279) is an oral allosteric Tyk2 inhibitor developed by Nimbus Therapeutics (NDI-034858) and acquired by Takeda in 2022 [50]. A phase II, randomized, double-blind, placebo-controlled trial (NCT04999839) evaluated its efficacy, safety, and tolerability [51]. A total of 259 patients were enrolled and distributed among five groups: zasocitinib at doses of 2 mg, 5 mg, 15 mg, and 30 mg QD, and placebo. By week 12, PASI75 response rates for all zasocitinib groups (44%, 68%, and 67% for 5 mg, 15 mg, and 30 mg, respectively) were significantly higher compared with the placebo group (6%), except those of the 2 mg QD group [51].

Currently, two phase III trials that will evaluate zasocitinib efficacy, safety, and tolerability (NCT06088043 and NCT06108544) are still recruiting patients. NCT06108544 will compare zasocitinib to placebo and apremilast.

1.13. VTX958

VTX958 is an orally administered selective allosteric Tyk2 inhibitor developed by Ventyx Bioscience. Results of a randomized, multicenter, double-blind, placebo-controlled phase II trial in moderate to severe psoriasis (NCT05655299) with four oral doses (50 mg BID, 300 mg QD, 225 mg BID, and 300 mg BID) have been released. Even though PASI75 response rates with the two higher doses were significantly superior to placebo at week 16, the results have not met the sponsor’s expectations, and further development on psoriasis and psoriatic arthritis has been terminated [52].

2. Oral PDE4 Inhibitors

Apremilast was the first PDE4 inhibitor approved for the treatment of psoriasis in 2014 [53]. Roflumilast, another PDE4 inhibitor initially approved for chronic obstructive pulmonary disease with available generics, has also demonstrated its efficacy in the treatment of psoriasis in an investigator-initiated clinical trial [54], and new oral PDE4 inhibitors are being developed, such as orismilast [55], Hemay005 (mufemilast), and ME3183 [56].

Orismilast is a potent oral PDE4 inhibitor with enhanced selectivity for the PDE4B and PDE4D subtypes. A randomized, double-blind, placebo-controlled phase IIa trial involved 36 patients with moderate to severe psoriasis, randomly assigned to receive either placebo or orismilast 30 mg BID [55]. By week 16, 44.4% of patients receiving orismilast achieved PASI75, versus 5.6% in the placebo group. The predominant AE reported in the orismilast group included nausea and diarrhea [55]. Subsequently, a phase IIb randomized clinical trial enrolled 202 patients to assess the efficacy and safety of orismilast in individuals with moderate-to-severe plaque psoriasis (NCT05190419). Patients were randomly assigned to receive placebo or orismilast at doses of 20 mg, 30 mg, or 40 mg BID. The results of the trial have been published on the www.clinicaltrials.org (accessed on 31 January 2024) website, showing superiority of all doses vs. placebo regarding percent change from baseline in PASI score at week 16, but inconsistencies have been detected by the Food and Drug Administration quality control review.

Hemay005 (mufemilast) is an oral PDE4 inhibitor being developed for psoriasis treatment. A randomized, placebo-controlled phase II trial evaluated Hemay005’s safety and efficacy in patients with moderate to severe psoriasis (NCT04102241). A total of 216 patients were enrolled and divided into 4 groups: placebo and Hemay005 (15 mg, 30 mg, and 60 mg). However, results have not been posted yet. In addition, a randomized, multicenter, double-blind, placebo-controlled phase III trial will also evaluate its efficacy and safety in patients with moderate to severe psoriasis

(NCT04839328). This trial will divide patients into two groups: placebo and Hemay005 60 mg BID. Currently, the trial is still recruiting patients.

ME3183 is an oral PDE4 inhibitor under development for the treatment of psoriasis, atopic dermatitis, and other inflammatory diseases [56][57]. Two double-blind, placebo-controlled, single-ascending doses and multiple-ascending doses phase I studies (ME3183-1 and ME3183-2) evaluated its safety, tolerability, and pharmacokinetics. A total of 126 healthy patients were included. ME3183 demonstrated safety and tolerability up to a dosage of 25 mg (single dose) and up to 10 mg twice daily. Commonly reported treatment-emergent AE encompassed diarrhea and headache, aligning with established patterns associated with approved PDE4 inhibitors, thereby presenting no unprecedented safety considerations. A multicenter, randomized, double-blind, placebo-controlled, parallel group, phase IIa study, in which 136 patients were enrolled, evaluated ME3183 safety and efficacy (NCT05268016). Patients were divided into placebo and ME3183 (5 mg BID), 7.5 mg BID, 10 mg QD, and 15 mg QD [58]. PASI75 was evaluated after 16 weeks of treatment (primary endpoint). A significantly greater proportion of patients treated with ME3183 (5 mg BID, 7.5 mg BID, and 15 mg QD) achieved PASI75 compared with placebo (58.3%, 61.5%, and 52.0% vs. 14.8%, respectively). No differences were noted between ME3183 10 mg QD and placebo. Furthermore, a greater proportion of patients in the ME3183 groups versus placebo achieved PASI90 and PASI100. ME3183 was well tolerated, and the most frequent treatment-emergent AE reported were diarrhea, nausea, and headache.

2.1. Oral TNF Inhibitors

Since TNF participates in the pathogenesis of several IMIDs, research has focused on the development of oral agents inhibiting this key factor of the inflammatory pathways [59]. Small molecules that promote the stabilization of an asymmetrical configuration of the soluble TNF trimer may lead to attenuation of TNF signaling, consequently inhibiting TNF function [60][61].

Sanofi is currently working on SAR441566, an oral TNF inhibitor [62][63]. A randomized, double-blind, placebo-controlled phase I trial with 38 participants evaluated the efficacy and safety of SAR441566 in patients with moderate to severe psoriasis (NCT05453942). The trial is complete, but results have not been posted yet.

2.2. Oral IL-17 Inhibitors

Biologic drugs have made a huge impact in the management of psoriasis as well as in patients' quality of life. Therefore, research has focused on oral molecules directed at the same targets [64]. The intricate modulation of extensive protein-protein interactions through small molecules poses a complex challenge, but numerous research groups are dedicated to pursuing this objective [64][65].

At least three different molecules have been developed independently by Lilly, Leo Pharma, and DICE Therapeutics. In 2019, two phase I clinical trials with LY3509754 (Lilly) in psoriasis (NCT04152382, NCT04586920) were prematurely concluded due to safety issues associated with liver function [66]. The safety and tolerability of LEO 153339 (Leo Pharma) [64][65] were evaluated in a randomized, double-blind, phase I trial in which 108 participants with moderate to severe psoriasis were included (NCT04883333). The study was completed in July 2023, but results have not been posted yet.

The safety and pharmacokinetic properties of DC-806, an oral IL-17 inhibitor developed by DICE Therapeutics, were evaluated in a randomized, double-blind, placebo-controlled phase I trial in healthy volunteers [67]. The study encompassed three sequential parts: phase Ia involved a single ascending dose (n = 40), phase Ib comprised multiple ascending doses (n = 32), and phase Ic focused on proof-of-concept in psoriasis patients (n = 32). In the latter phase, patients were stratified into three groups: the high-dose group (comprising eight patients who received 800 mg BID), the low-dose group (comprising thirteen patients who received 200 mg BID), and the placebo group, which included eleven patients. PASI reduction at 4 weeks of treatment was significantly higher (p = 0.0008) in the high dose group (43.7%) compared with the placebo group (13.3%). Furthermore, both regimens of DC-806 showed a dose-dependent inhibition of IL-17 [67]. DICE Therapeutics is reportedly developing a fast follower of DC-806 and DC-853 with improved potency and metabolic stability, and Lilly has recently completed the acquisition of DICE Therapeutics with its DELSCAPE DNA-encoded library-based platform to discover small molecules targeting protein-protein interactions [68].

3. Oral IL-23 Inhibitors

Protagonist Therapeutics, in collaboration with Janssen Biotech, Inc., is developing JNJ-77242113, an oral IL-23 receptor antagonist peptide [69]. The results of an initial phase I trial (NCT05062200) were promising, and two phase II trials were started [70]. SUMMIT (NCT05357755) is a multicenter, randomized, double-blind, placebo-controlled phase IIa trial on 90 patients with moderate to severe psoriasis comparing a delayed-release tablet of JNJ-77242113 with placebo in adults with moderate-to-severe plaque psoriasis; its results have not been posted yet. FRONTIER 1 (NCT05223868), a multicenter, randomized, placebo-controlled, dose-ranging phase IIb trial that included 255 participants, evaluated the efficacy and safety of JNJ-77242113 in patients with moderate-to-severe plaque psoriasis. At week 16, PASI75 response rates (primary endpoint) were 37.2% at 25 mg QD, 51.2% at 25 mg BID, 58.1% at 50 mg QD, 65.1% at 100 mg QD, 78.6% at 100 mg BID, and placebo 9.3% (nominal $p \leq 0.002$ for all comparisons); the corresponding PASI90 response

rates were 25.6%, 26.8%, 51.2%, 46.5%, 59.5%, and 2.3%, respectively, and PASI100 response rates were 11.6%, 9.8%, 25.6%, 23.3%, 40.5%, and 0%, respectively [71]. No differences in AEs were noted among the placebo and the five treatment groups [70]. If confirmed in phase III trials, these levels of response would set a new standard of efficacy for oral treatments of moderate to severe psoriasis. Currently, two additional trials of JNJ-77242113 are in progress: a phase I trial involving a single dose to assess the pharmacokinetics, safety, and tolerability (NCT05703841), and FRONTIER 2 (NCT05364554), a phase II trial intended to evaluate the efficacy and safety of JNJ-77242113 at week 36 [70].

4. RORγT Inhibitors

The retinoic acid-related orphan receptors (ROR, including RORα, RORβ, and RORγ) function as transcription factors upon binding with their ligands [72][73]. The union of IL-23 to its receptor activates STAT3 and induces the expression of RORγT, an isoform of RORγ that promotes a Th17 response with transcription of IL-17A, IL-17F, IL-22, and IL-23R [74]. Inhibiting Th17 differentiation reverts this commitment and promotes the expansion of functional regulatory T cells that release anti-inflammatory cytokines, such as IL-10, thereby dampening the immune response [75]. Consequently, RORγ has been identified as a potential target for modulating the Th17 response.

Several RORγT inverse agonists have been tested on clinical trials for the treatment of moderate to severe psoriasis, with modest success to date: VTP-43742, JTE-451, AUR101, ABBV-157, IMU-935, BMS-986251, AZD0284, SAR441169, ABBV-553, and BI 730357 [72][76][77][78].

VTP-43742 was associated with a 30% reduction from baseline PASI after 4 weeks of treatment in a phase I clinical trial (NCT03724292), but the study had to be discontinued due to liver toxicity. The phase I/II studies evaluating ABBV-553 (NCT03145948), BMS-986251 (NCT03329885), and ABBV-157 (cedirogant) (NCT05044234) were also terminated due to undisclosed safety reasons, while phase I trials on AZD0284 (NCT03310320), SAR441169, and IMU-935 were terminated due to limited efficacy.

A randomized, placebo-controlled phase II trial evaluated JTE-451 (NCT03832738). A total of 152 patients were enrolled and divided into three groups (200 mg BID, 400 mg BID, or placebo). At 16 weeks, PASI75 (primary endpoint) was achieved by 11.8%, 22%, and 7.8%, respectively. No phase III trials have been started to date.

Regarding AUR101, two phase II trials (NCT04207801 and NCT04855721) were performed. NCT04207801 was a double-blind, placebo-controlled, randomized, multicentric phase II trial involving 90 participants who were allocated to three treatment arms: 400 mg BID, 800 mg BID, or placebo. By week 12, the PASI75 response was attained by 60%, 63.3%, and 26.7% of individuals in the respective treatment groups. INDUS-3 (NCT04855721) was a randomized, double-blind, placebo-controlled, phase IIb clinical trial that evaluated three doses of AUR101 (200 mg BID, 400 mg QD, and 400 mg BID) with disappointing results; only the 400 mg BID group was superior to placebo regarding the primary endpoint (PASI75), and further development of AUR101 by Aurigene Oncology was halted [79].

Two phase II trials investigating BI 730357 in psoriasis (NCT03635099 and NCT03835481) have been completed. NCT03635099 was a randomized, double-blind, placebo-controlled phase II trial that assessed the safety, tolerability, and efficacy of BI 730357 in individuals with moderate to severe psoriasis [80]. A total of 274 participants were enrolled and distributed across eight treatment arms, considering the fasting status upon administration: placebo (fasted), 25 mg (fasted), 50 mg (fasted), 100 mg (fasted), 200 mg (fasted), placebo (fed), 400 mg (fed), and 200 mg BID (fed). At week 12, the PASI75 response was achieved by 0%, 5%, 7.7%, 10.3%, 30%, 0%, 25.6%, and 23.8% of patients in the respective groups. An upper respiratory tract infection was reported in 21 patients [80]. NCT03835481 was a long-term extension trial in patients with moderate to severe psoriasis that had completed the preceding trial (NCT03635099); it enrolled 165 patients, some of whom were up-dosed. The primary outcome was treatment-induced emergent AEs, which were reported in 60.9% of the patients in the higher dose regimen (400 mg), with a 37.5% PASI75 response rate. The study was terminated due to the sponsor's decision, and no further trials have been conducted to date.

Other molecules under development, like VTP-45489, have not yet been evaluated in clinical trials.

5. Sphingosine-1-Phosphate Receptor 1 Antagonist

Sphingosine-1-phosphate (S1P) is a bioactive lipid that binds five G-protein-coupled receptors and governs essential cellular functions, including proliferation, survival, migration, and adhesion [81][82]. The $S1P_1$ receptor ($S1P_1R$) is notably expressed in the skin, lymphoid tissue, and cardiovascular system [83][84]. Ponesimod, an oral, selective modulator of $S1P_1R$, has demonstrated efficacy in diminishing the populations of circulating T and B cells, particularly CD4+ cells, in healthy human subjects [85][86] and has been tested in two phase II trials (NCT01208090 and NCT00852670) for treatment of moderate to severe psoriasis. NCT01208090 was a randomized, multicenter, double-blind, placebo-controlled phase II trial with 326 patients who were allocated to three treatment groups: 20 mg QD, 40 mg BID, or placebo. PASI75 at 16 weeks of treatment (primary endpoint) was achieved by 46%, 48.1%, and 13.4% of the patients in each group, respectively ($p < 0.0001$ versus placebo for both active treatment arms) [87]. Subsequently, patients were re-randomized during the maintenance period to receive: 20 mg, 40 mg, or placebo. By the 28th week of the follow-up period, 71.4% of patients maintaining the 20 mg dosage and 77.4% of those continuing with 40 mg achieved a PASI75 response.

Conversely, individuals re-randomized to the placebo from the 20 mg and 40 mg groups exhibited a swift decline in effectiveness, with PASI75 attainment recorded at 42.2% and 40.4% for patients initially treated with ponesimod 20 mg and 40 mg, respectively. Dyspnea, liver enzyme abnormalities, and dizziness were the most frequently reported AEs [87]. Results from NCT00852670 have not been published yet. Currently, there is no ongoing clinical trial for ponesimod.

6. A3 Adenosine Receptor Agonist

A3 adenosine receptor (A3AR) is a Gi protein-coupled receptor that can be found on the cell surface and is overexpressed in inflammatory skin conditions as well as in peripheral blood mononuclear cells [88].

Piclidenoson (formerly named CF101) is an orally administered, water-insoluble agonist of the A3 adenosine receptor (A3AR) [88][89]. Upon activation of the A3AR, there is a downregulation of the NF-κB signaling pathway, resulting in a decrease in the expression of inflammatory cytokines such as TNF, IL-12, IL-17, and IL-23. Consequently, piclidenoson induces an anti-inflammatory effect and inhibits keratinocyte proliferation [73][90]. In fact, activation of A3AR is the predominant mechanism of action of methotrexate in IMIDs [91]. Piclidenoson has already been evaluated in phase II and phase III trials with satisfactory results [92].

Firstly, in a multicentric, double-blinded, placebo-controlled phase II trial (NCT00428974), 75 patients with moderate to severe psoriasis were included. Patients were randomized to receive a placebo or piclidenoson 1, 2, or 4 mg BID. At 12 weeks of treatment, the 2 mg BID group showed a statistically significant reduction in PASI score from baseline compared with the placebo. PASI50 was achieved by 35.3% of the patients treated with the 2 mg BID regimen. The 1 mg dose exhibited no therapeutic effect, and the 4 mg group exhibited less improvement compared with the 2 mg group.

Subsequently, a randomized, double-blind, placebo-controlled, phase II/III study (NCT01265667) was carried out [92]. Patients were randomly allocated to parallel dosing groups receiving CF101 2 mg or corresponding placebo tablets BID. Despite not achieving the primary study endpoint (statistically significant improvement in PASI75 response rate compared with placebo at week 12), subsequent data analysis uncovered statistically significant cumulative and linear improvement from weeks 16 to 32. By week 32, 33%, 25%, and 11% of patients treated with CF101 2 mg BID achieved PASI75, PASI90, and PASI100 responses, respectively. During the follow-up period, the treatment was also well-tolerated. In addition, an indirect comparison was conducted between the data from the piclidenoson phase II/III trial and the data from the apremilast phase III trials [92]. The efficacy of apremilast plateaued at week 16, with 30% of patients attaining PASI75 response, while piclidenoson presented a response rate of 35.3% in terms of PASI75 at week 32, showing no visible plateau.

Recently, results from COMFORT (NCT03168256), a multicenter, randomized, phase III placebo- and active (apremilast)-controlled trial, have been published. A total of 529 patients were included and randomized into four treatment groups: placebo, CF101 2 mg BID, CF101 3 mg BID, and apremilast 30 mg BID. PASI75 was evaluated at week 16, and results are posted on the www.clinicaltrials.org (accessed on 31 January 2024) website. However, inconsistencies have been detected by the Food and Drug Administration quality control review.

7. Heat Shock Protein 90

Heat shock protein 90 (HSP90), one of the most ubiquitous chaperone proteins, participates in folding, stabilizing, and activating substrate proteins, such as transcriptional factors and intracellular signaling molecules that mediate inflammation [73]. Increased expression of Heat Shock Proteins (HSP) across distinct layers of the skin is believed to play a role in the pathogenesis of psoriasis; interestingly, the number of psoriasis flares over the course of one year appears to correlate with an increase in HSP90 expression [93][94].

RGRN-305 (CUDC-305) is a HSP90 inhibitor with promising results in a xenograft mouse model of psoriasis [95]. In vitro studies demonstrated a reduction in the expression of genes coding for inflammatory cytokines such as TNF or IL-23 [96]. In an open-label, single-arm, dose-selection, single-center proof-of-concept phase Ib trial (NCT03675542), 11 patients with psoriasis were treated with RGRN-305 250 mg or 500 mg QD [97]. After 12 weeks of treatment, six out of eleven patients showed ≥50% improvement (range 71–94%) with respect to baseline PASI, without a clear dose effect. Although four of the seven patients treated with the 500 mg dose developed an exanthematous reaction, no serious AEs were reported. Furthermore, a skin transcriptome analysis disclosed a prompt and maintained decrease of relevant inflammatory transcripts induced by TNF and IL-17, such as IL36G and CXCL8.

Inhibition of HSP90, even as a topical treatment option, could emerge as an innovative therapeutic strategy, applicable not only to psoriasis but also to various other immune-mediated skin disorders [98].

8. ROCK-2 Inhibitor

The Rho-associated protein kinases (ROCK) 1 and 2 are the downstream mediators of Rho proteins, which conform to a GTP-binding protein family [99]. These kinases play a pivotal role in various cellular processes, encompassing cell

migration, adhesion, proliferation, and apoptosis [99]. The anti-inflammatory effect of ROCK2 inhibitors is mediated by a downregulation of the T cell response [9].

Belumosudil (KD025, Rezurock®) is a ROCK inhibitor formulated by Kadmon Pharmaceuticals [100]. It became the first selective ROCK-2 inhibitor with a 100-fold specificity for ROCK-2 over ROCK-1. In addition, compared with dual ROCK inhibitors, belumosudil possesses an improved safety profile [99]. KD025 has been tested in multiple phase I trials with healthy volunteers, with good tolerance and no serious AEs, including cardiovascular side effects [101][102]. Subsequently, belumosudil has been tested in multiple phase II clinical trials for the treatment of chronic graft-versus-host disease, idiopathic pulmonary fibrosis, systemic sclerosis, and psoriasis (NCT02317627). The latter was an open-label, phase II trial in which 38 patients were included and randomized into three groups: 200 mg belumosudil BID, 400 mg belumosudil QD, and 400 mg belumosudil BID. After 12 weeks of treatment, a PASI50 response was achieved by 71%, 42%, and 29% of patients in each treatment arm, respectively, suggesting a higher benefit with the lower dosage strategy. However, the PASI75 response was achieved only by 14.2%, 16.7%, and 14.2% of patients, respectively. These results are apparently inferior to those that can be achieved with methotrexate, apremilast, or Jak inhibitors. Diarrhea was the most frequently reported adverse event. Two additional phase II double-blind, placebo-controlled studies have recently been conducted (NCT02852967, NCT02106195). NCT02852967 included 110 patients, which were randomized to receive placebo, belumosudil 200 mg QD, 200 mg BID, 400 mg QD, or 600 mg/day. PASI75 response was evaluated after 16 weeks of treatment (primary endpoint) and was achieved by 55.6%, 60.9%, 68.2%, 81.0%, and 61.5% of patients in the respective treatment arms. Despite the numerically high response rate in the 400 mg QD group (PASI75 81.0%), no significant superiority to placebo could be demonstrated. Apart from occasional serious AEs such as natural death (n = 1), pneumonia (n = 1), hypercholesterolemia (n = 1), thalamic infarction (n = 1), and chronic obstructive pulmonary disease (n = 1), the treatment was well tolerated, and the most frequently reported AEs were headache, nausea, increased serum levels of liver enzymes, and upper respiratory tract infections. NCT02106195 included eight patients and was intended to determine the safety and tolerability of belumosudil. Two patients had to discontinue the treatment due to AEs.

References

1. Garcia-Melendo, C.; Cubiró, X.; Puig, L. Janus Kinase Inhibitors in Dermatology: Part 1—General Considerations and Applications in Vitiligo and Alopecia Areata. Actas Dermo-Sifiliográficas (Engl. Ed.) 2021, 112, 503–515.
2. Nogueira, M.; Puig, L.; Torres, T. JAK Inhibitors for Treatment of Psoriasis: Focus on Selective TYK2 Inhibitors. Drugs 2020, 80, 341–352.
3. Villarino, A.V.; Kanno, Y.; Ferdinand, J.R.; O'Shea, J.J. Mechanisms of Jak/STAT Signaling in Immunity and Disease. J. Immunol. 2015, 194, 21–27.
4. O'Shea, J.J.; Schwartz, D.M.; Villarino, A.V.; Gadina, M.; McInnes, I.B.; Laurence, A. The JAK-STAT pathway: Impact on human disease and therapeutic intervention. Annu. Rev. Med. 2015, 66, 311–328.
5. Kreins, A.Y.; Ciancanelli, M.J.; Okada, S.; Kong, X.F.; Ramírez-Alejo, N.; Kilic, S.S.; El Baghdadi, J.; Nonoyama, S.; Mahdaviani, S.A.; Ailal, F.; et al. Human TYK2 deficiency: Mycobacterial and viral infections without hyper-IgE syndrome. J. Exp. Med. 2015, 212, 1641–1662.
6. Ghoreschi, K.; Augustin, M.; Baraliakos, X.; Krönke, G.; Schneider, M.; Schreiber, S.; Schulze-Koops, H.; Zeißig, S.; Thaçi, D. TYK2 inhibition and its potential in the treatment of chronic inflammatory immune diseases. JDDG J. Ger. Soc. Dermatol. 2021, 19, 1409–1420.
7. Shawky, A.M.; Almalki, F.A.; Abdalla, A.N.; Abdelazeem, A.H.; Gouda, A.M. A Comprehensive Overview of Globally Approved JAK Inhibitors. Pharmaceutics 2022, 14, 1001.
8. Tian, F.; Chen, Z.; Xu, T. Efficacy and safety of tofacitinib for the treatment of chronic plaque psoriasis: A systematic review and meta-analysis. J. Int. Med. Res. 2019, 47, 2342–2350.
9. Marushchak, O.; Yakubov, R.; Yakubov, R.; Goldenberg, G. Review on Novel Oral Therapies for Psoriasis. J. Clin. Aesthet. Dermatol. 2021, 14, 55–63.
10. Papp, K.A.; Menter, A.; Strober, B.; Langley, R.G.; Buonanno, M.; Wolk, R.; Gupta, P.; Krishnaswami, S.; Tan, H.; Harness, J.A. Efficacy and safety of tofacitinib, an oral Janus kinase inhibitor, in the treatment of psoriasis: A Phase 2b randomized placebo-controlled dose-ranging study. Br. J. Dermatol. 2012, 167, 668–677.
11. Bachelez, H.; Van De Kerkhof, P.C.M.; Strohal, R.; Kubanov, A.; Valenzuela, F.; Lee, J.H.; Yakusevich, V.; Chimenti, S.; Papacharalambous, J.; Proulx, J.; et al. Tofacitinib versus etanercept or placebo in moderate to severe chronic plaque psoriasis: A phase 3 randomised non-inferiority trial. Lancet 2015, 386, 552–561.
12. Papp, K.A.; Menter, M.A.; Abe, M.; Elewski, B.; Feldman, S.R.; Gottlieb, A.B.; Langley, R.; Luger, T.; Thaci, D.; Buonanno, M.; et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: Results from two randomized, placebo-controlled, phase III trials. Br. J. Dermatol. 2015, 173, 949–961.
13. Papp, K.A.; Krueger, J.G.; Feldman, S.R.; Langley, R.G.; Thaci, D.; Torii, H.; Tyring, S.; Wolk, R.; Gardner, A.; Mebus, C.; et al. Tofacitinib, an oral Janus kinase inhibitor, for the treatment of chronic plaque psoriasis: Long-term efficacy and safety results from 2 randomized phase-III studies and 1 open-label long-term extension study. J. Am. Acad. Dermatol. 2016, 74, 841–850.

14. Merola, J.F.; Elewski, B.; Tatulych, S.; Lan, S.; Tallman, A.; Kaur, M. Efficacy of tofacitinib for the treatment of nail psoriasis: Two 52-week, randomized, controlled phase 3 studies in patients with moderate to severe plaque psoriasis. J. Am. Acad. Dermatol. 2017, 77, 79–87.e1.
15. Feldman, S.R.; Thaçi, D.; Gooderham, M.; Augustin, M.; de la Cruz, C.; Mallbris, L.; Buonanno, M.; Tatulych, S.; Kaur, M.; Lan, S.; et al. Tofacitinib improves pruritus and health-related quality of life up to 52 weeks: Results from 2 randomized phase III trials in patients with moderate to severe plaque psoriasis. J. Am. Acad. Dermatol. 2016, 75, 1162–1170.e3.
16. Reuters Staff. FDA Declines to Expand Approval of Pfizer Arthritis Drug. 14 October 2015. Available online: https://www.reuters.com/article/pfizer-psoriasis-fda-idUSL1N12E2OW20151014 (accessed on 24 May 2023).
17. Pfizer. U.S. FDA Approves Pfizer's CIBINQO® (Abrocitinib) for Adults with Moderate to Severe Atopic Dermatitis. 2022. Available online: https://www.pfizer.com/news/press-release/press-release-detail/us-fda-approves-pfizers-cibinqor-abrocitinib-adults (accessed on 31 January 2024).
18. Peeva, E.; Hodge, M.R.; Kieras, E.; Vazquez, M.L.; Goteti, K.; Tarabar, S.G.; Alvey, C.W.; Banfield, C. Evaluation of a Janus kinase 1 inhibitor, PF-04965842, in healthy subjects: A phase 1, randomized, placebo-controlled, dose-escalation study. Br. J. Clin. Pharmacol. 2018, 84, 1776–1788.
19. Schmieder, G.J.; Draelos, Z.D.; Pariser, D.M.; Banfield, C.; Cox, L.; Hodge, M.; Kieras, E.; Parsons-Rich, D.; Menon, S.; Salganik, M.; et al. Efficacy and safety of the Janus kinase 1 inhibitor PF-04965842 in patients with moderate to severe psoriasis: Phase II, randomized, double-blind, placebo-controlled study. Br. J. Dermatol. 2018, 179, 54–62.
20. Olumiant—European Medicines Agency. 2023. Available online: https://www.ema.europa.eu/en/medicines/human/EPAR/olumiant (accessed on 31 January 2024).
21. FDA Approves OLUMIANT® (Baricitinib) 2-mg Tablets for the Treatment of Adults with Moderately-to-Severely Active Rheumatoid Arthritis. 2018. Available online: https://investor.lilly.com/news-releases/news-release-details/fda-approves-olumiantr-baricitinib-2-mg-tablets-treatment-adults (accessed on 24 May 2023).
22. Shi, J.G.; Chen, X.; Lee, F.; Emm, T.; Scherle, P.A.; Lo, Y.; Punwani, N.; Williams, W.V.; Yeleswaram, S. The pharmacokinetics, pharmacodynamics, and safety of baricitinib, an oral JAK 1/2 inhibitor, in healthy volunteers. J. Clin. Pharmacol. 2014, 54, 1354–1361.
23. Papp, K.A.; Menter, M.A.; Raman, M.; Disch, D.; Schlichting, D.E.; Gaich, C.; Macias, W.; Zhang, X.; Janes, J.M. A randomized phase 2b trial of baricitinib, an oral Janus kinase (JAK) 1/JAK2 inhibitor, in patients with moderate to severe psoriasis. Br. J. Dermatol. 2016, 174, 1266–1276.
24. Ito, M.; Yamazaki, S.; Yamagami, K.; Kuno, M.; Morita, Y.; Okuma, K.; Nakamura, K.; Chida, N.; Inami, M.; Inoue, T.; et al. A novel JAK inhibitor, peficitinib, demonstrates potent efficacy in a rat adjuvant-induced arthritis model. J. Pharmacol. Sci. 2017, 133, 25–33.
25. Papp, K.; Pariser, D.; Catlin, M.; Wierz, G.; Ball, G.; Akinlade, B.; Zeiher, B.; Krueger, J.G. A phase 2a randomized, double-blind, placebo-controlled, sequential dose-escalation study to evaluate the efficacy and safety of ASP015K, a novel Janus kinase inhibitor, in patients with moderate to severe psoriasis. Br. J. Dermatol. 2015, 173, 767–776.
26. Ludbrook, V.J.; Hicks, K.J.; Hanrott, K.E.; Patel, J.S.; Binks, M.H.; Wyres, M.R.; Watson, J.; Wilson, P.; Simeoni, M.; Schifano, L.A.; et al. Investigation of selective JAK1 inhibitor GSK2586184 for the treatment of psoriasis in a randomized placebo-controlled phase IIa study. Br. J. Dermatol. 2016, 174, 985–995.
27. Bissonnette, R.; Luchi, M.; Fidelus-Gort, R.; Jackson, S.; Zhang, H.; Flores, R.; Newton, R.; Scherle, P.; Yeleswaram, S.; Chen, X.; et al. A randomized, double-blind, placebo-controlled, dose-escalation study of the safety and efficacy of INCB039110, an oral janus kinase 1 inhibitor, in patients with stable, chronic plaque psoriasis. J. Dermatol. Treat. 2016, 27, 332–338.
28. Krueger, J.G.; McInnes, I.B.; Blauvelt, A. Tyrosine kinase 2 and Janus kinase–signal transducer and activator of transcription signaling and inhibition in plaque psoriasis. J. Am. Acad. Dermatol. 2022, 86, 148–157.
29. Banfield, C.; Scaramozza, M.; Zhang, W.; Kieras, E.; Page, K.M.; Fensome, A.; Vincent, M.; Dowty, M.E.; Goteti, K.; Winkle, P.J.; et al. The Safety, Tolerability, Pharmacokinetics, and Pharmacodynamics of a TYK2/JAK1 Inhibitor (PF-06700841) in Healthy Subjects and Patients With Plaque Psoriasis. J. Clin. Pharmacol. 2018, 58, 434–447.
30. Forman, S.B.; Pariser, D.M.; Poulin, Y.; Vincent, M.S.; Gilbert, S.A.; Kieras, E.M.; Qiu, R.; Yu, D.; Papacharalambous, J.; Tehlirian, C.; et al. TYK2/JAK1 Inhibitor PF-06700841 in Patients with Plaque Psoriasis: Phase IIa, Randomized, Double-Blind, Placebo-Controlled Trial. J. Investig. Dermatol. 2020, 140, 2359–2370.e5.
31. Nick Paul Taylor. Pfizer Sells Midphase Inflammatory Drugs to Mystery Startup, Exiting Race against Bristol Myers. BIOTECH. 2021. Available online: https://www.fiercebiotech.com/biotech/pfizer-sells-midphase-inflammatory-drugs-to-mystery-startup-exiting-race-against-bristol#:~:text=Biotech-,Pfizer%20sells%20midphase%20inflammatory%20drugs%20to%20mystery,exiting%20race%20against%20Bristol (accessed on 24 May 2023).
32. Tehlirian, C.; Peeva, E.; Kieras, E.; Scaramozza, M.; Roberts, E.S.; Singh, R.S.P.; Pradhan, V.; Banerjee, A.; Garcet, S.; Xi, L.; et al. Safety, tolerability, efficacy, pharmacokinetics, and pharmacodynamics of the oral TYK2 inhibitor PF-06826647 in participants with plaque psoriasis: A phase 1, randomised, double-blind, placebo-controlled, parallel-group study. Lancet Rheumatol. 2020, 3, e204–e213.

33. Singh, R.S.P.; Pradhan, V.; Roberts, E.S.; Scaramozza, M.; Kieras, E.; Gale, J.D.; Peeva, E.; Vincent, M.S.; Banerjee, A.; Fensome, A.; et al. Safety and Pharmacokinetics of the Oral TYK2 Inhibitor PF-06826647: A Phase I, Randomized, Double-Blind, Placebo-Controlled, Dose-Escalation Study. Clin. Transl. Sci. 2021, 14, 671–682.

34. Tehlirian, C.; Singh, R.S.P.; Pradhan, V.; Roberts, E.S.; Tarabar, S.; Peeva, E.; Vincent, M.S.; Gale, J.D. Oral tyrosine kinase 2 inhibitor PF-06826647 demonstrates efficacy and an acceptable safety profile in participants with moderate to severe plaque psoriasis in a phase 2b, randomized, double-blind, placebo-controlled study. J. Am. Acad. Dermatol. 2022, 87, 333–342.

35. Chimalakonda, A.; Burke, J.; Cheng, L.; Catlett, I.; Tagen, M.; Zhao, Q.; Patel, A.; Shen, J.; Girgis, I.G.; Banerjee, S.; et al. Selectivity Profile of the Tyrosine Kinase 2 Inhibitor Deucravacitinib Compared with Janus Kinase 1/2/3 Inhibitors. Dermatol. Ther. 2021, 11, 1763–1776.

36. Burke, J.R.; Cheng, L.; Gillooly, K.M.; Strnad, J.; Zupa-Fernandez, A.; Catlett, I.M.; Zhang, Y.; Heimrich, E.M.; McIntyre, K.W.; Cunningham, M.D.; et al. Autoimmune pathways in mice and humans are blocked by pharmacological stabilization of the TYK2 pseudokinase domain. Sci. Transl. Med. 2019, 11, 1736.

37. Wrobleski, S.T.; Moslin, R.; Lin, S.; Zhang, Y.; Spergel, S.; Kempson, J.; Tokarski, J.S.; Strnad, J.; Zupa-Fernandez, A.; Cheng, L.; et al. Highly Selective Inhibition of Tyrosine Kinase 2 (TYK2) for the Treatment of Autoimmune Diseases: Discovery of the Allosteric Inhibitor BMS-986165. J. Med. Chem. 2019, 62, 8973–8995.

38. Moslin, R.; Zhang, Y.; Wrobleski, S.T.; Lin, S.; Mertzman, M.; Spergel, S.; Tokarski, J.S.; Strnad, J.; Gillooly, K.; McIntyre, K.W.; et al. Identification of N-Methyl Nicotinamide and N-Methyl Pyridazine-3-Carboxamide Pseudokinase Domain Ligands as Highly Selective Allosteric Inhibitors of Tyrosine Kinase 2 (TYK2). J. Med. Chem. 2019, 62, 8953–8972.

39. Papp, K.; Gordon, K.; Thaçi, D.; Morita, A.; Gooderham, M.; Foley, P.; Girgis, I.G.; Kundu, S.; Banerjee, S. Phase 2 Trial of Selective Tyrosine Kinase 2 Inhibition in Psoriasis. N. Engl. J. Med. 2018, 379, 1313–1321.

40. Gordon, K.; Papp, K.; Gooderham, M.; Morita, A.; Foley, P.; Thaçi, D.; Kundu, S.; Kisa, R.; Wei, L.; Banergee, S. BMS-986165, an Oral, Selective Tyrosine Kinase 2 (TYK2) Inhibitor: Evaluation of Changes in Laboratory Parameters in Response to Treatment in a Phase 2 Trial in Psoriasis Patients. SKIN J. Cutan. Med. 2020, 4, s28.

41. Armstrong, A.W.; Gooderham, M.; Warren, R.B.; Papp, K.A.; Strober, B.; Thaçi, D.; Morita, A.; Szepietowski, J.C.; Imafuku, S.; Colston, E.; et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: Efficacy and safety results from the 52-week, randomized, double-blinded, placebo-controlled phase 3 POETYK PSO-1 trial. J. Am. Acad. Dermatol. 2023, 88, 29–39.

42. Strober, B.; Thaçi, D.; Sofen, H.; Kircik, L.; Gordon, K.B.; Foley, P.; Rich, P.; Paul, C.; Bagel, J.; Colston, E.; et al. Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: Efficacy and safety results from the 52-week, randomized, double-blinded, phase 3 Program fOr Evaluation of TYK2 inhibitor psoriasis second trial. J. Am. Acad. Dermatol. 2023, 88, 40–51.

43. Armstrong, A.W.; Warren, R.B.; Zhong, Y.; Zhuo, J.; Cichewicz, A.; Kadambi, A.; Junqueira, D.; Westley, T.; Kisa, R.; Daamen, C.; et al. Short-, Mid-, and Long-Term Efficacy of Deucravacitinib Versus Biologics and Nonbiologics for Plaque Psoriasis: A Network Meta-Analysis. Dermatol. Ther. 2023, 13, 2839–2857.

44. Armstrong, A.W.; Park, S.H.; Patel, V.; Hogan, M.; Wang, W.-J.; Davidson, D.; Chirikov, V. Matching-Adjusted Indirect Comparison of the Long-Term Efficacy of Deucravacitinib Versus Adalimumab for Moderate to Severe Plaque Psoriasis. Dermatol. Ther. 2023, 13, 2589–2603.

45. Hoy, S.M. Deucravacitinib: First Approval. Drugs 2022, 82, 1671–1679.

46. Sotyktu; Deucravacitinib. European Medicines Agency Approval. EMA. 2023. Available online: www.ema.europa.eu/en/documents/smop-initial/chmp-summary-positive-opinion-sotyktu_en.pdf (accessed on 7 May 2023).

47. Bristol Myers Squibb Receives European Commission Approval of Sotyktu (Deucravacitinib), a Once-Daily Oral Treatment for Adults with Moderate to Severe Plaque Psoriasis. Bristol Myers Squibb. 2023. Available online: https://news.bms.com/news/details/2023/Bristol-Myers-Squibb-Receives-European-Commission-Approval-of-Sotyktu-deucravacitinib-a-Once-Daily-Oral-Treatment-for-Adults-With-Moderate-to-Severe-Plaque-Psoriasis/default.aspx (accessed on 7 May 2023).

48. Liu, C.; Lin, J.; Langevine, C.; Smith, D.; Li, J.; Tokarski, J.S.; Khan, J.; Ruzanov, M.; Strnad, J.; Zupa-Fernandez, A.; et al. Discovery of BMS-986202: A Clinical Tyk2 Inhibitor that Binds to Tyk2 JH2. J. Med. Chem. 2021, 64, 677–694.

49. Works, M.G.; Yin, F.; Yin, C.C.; Yiu, Y.; Shew, K.; Tran, T.-T.; Dunlap, N.; Lam, J.; Mitchell, T.; Reader, J.; et al. Inhibition of TYK2 and JAK1 Ameliorates Imiquimod-Induced Psoriasis-like Dermatitis by Inhibiting IL-22 and the IL-23/IL-17 Axis. J. Immunol. 2014, 193, 3278–3287.

50. Takeda. Takeda to Acquire Late-Stage, Potential Best-in-Class, Oral Allosteric TYK2 Inhibitor NDI-034858 from Nimbus Therapeutics. Takeda. 2022. Available online: https://www.takeda.com/newsroom/newsreleases/2022/takeda-to-acquire-late-stage-potential-best-in-class-oral-allosteric-tyk2-inhibitor--ndi-034858-from-nimbus-therapeutics/ (accessed on 5 June 2023).

51. Takeda. Takeda Announces Positive Results in Phase 2b Study of Investigational TAK-279, an Oral, Once-Daily TYK2 Inhibitor, in People with Moderate to Severe Plaque Psoriasis. Takeda. 2023. Available online:

https://www.takeda.com/newsroom/newsreleases/2023/takeda-announces-positive-results-in-phase-2b-study-of-investigational-tak-279/ (accessed on 5 June 2023).

52. Patti Bank. Ventyx Biosciences Announces Results from the Phase 2 Trial of VTX958 in Patients with Moderate to Severe Plaque Psoriasis and Provides Corporate Update; Ventyx Biosciences: Encinitas, CA, USA, 2023.
53. Fala, L. Otezla (Apremilast), an Oral PDE-4 Inhibitor, Receives FDA Approval for the Treatment of Patients with Active Psoriatic Arthritis and Plaque Psoriasis. Am. Health Drug Benefits 2015, 8, 105–110. Available online: http://www.ncbi.nlm.nih.gov/pubmed/26629274 (accessed on 31 January 2024).
54. Gyldenløve, M.; Meteran, H.; Zachariae, C.; Egeberg, A. Long-term clearance of severe plaque psoriasis with oral roflumilast. J. Eur. Acad. Dermatol. Venereol. 2023, 37, e429–e430.
55. Warren, R.B.; Strober, B.; Silverberg, J.I.; Guttman, E.; Andres, P.; Felding, J.; Tutkunkardas, D.; Kjøller, K.; Sommer, M.O.A.; French, L.E. Oral orismilast: Efficacy and safety in moderate-to-severe psoriasis and development of modified release tablets. J. Eur. Acad. Dermatol. Venereol. 2023, 37, 711–720.
56. Kubota-Ishida, N.; Kaji, C.; Matsumoto, S.; Wakabayashi, T.; Matsuhira, T.; Okura, I.; Cho, N.; Isshiki, S.; Kumura, K.; Tabata, Y. ME3183, a novel phosphodiesterase-4 inhibitor, exhibits potent anti-inflammatory effects and is well tolerated in a non-clinical study. Eur. J. Pharmacol. 2024, 962, 176202.
57. Kato, S.; Cho, N.; Koresawa, T.; Otake, K.; Kano, A. Safety, Tolerability, and Pharmacokinetics of a Novel Oral Phosphodiesterase 4 Inhibitor, ME3183: First-in-Human Phase 1 Study. Clin. Pharmacol. Drug Dev. 2023.
58. Miyazawa, Y. Meiji Seika Pharma Presents Positive Findings from Phase II Study of ME3183, Novel Highly-Potent Selective PDE4 Inhibitor, in Patients with Plaque Psoriasis at EADV Congress 2023; Meiji Seika Pharma Co., Ltd.: Tokyo, Japan, 2023.
59. Dömling, A.; Li, X. TNF-α: The shape of small molecules to come? Drug Discov. Today 2022, 27, 3–7.
60. McMillan, D.; Martinez-Fleites, C.; Porter, J.; Fox, D.; Davis, R.; Mori, P.; Ceska, T.; Carrington, B.; Lawson, A.; Bourne, T.; et al. Structural insights into the disruption of TNF-TNFR1 signalling by small molecules stabilising a distorted TNF. Nat. Commun. 2021, 12, 582.
61. O'Connell, J.; Porter, J.; Kroeplien, B.; Norman, T.; Rapecki, S.; Davis, R.; McMillan, D.; Arakaki, T.; Burgin, A.; Fox Iii, D.; et al. Small molecules that inhibit TNF signalling by stabilising an asymmetric form of the trimer. Nat. Commun. 2019, 10, 5795.
62. Vugler, A.; O'Connell, J.; Nguyen, M.A.; Weitz, D.; Leeuw, T.; Hickford, E.; Verbitsky, A.; Ying, X.; Rehberg, M.; Carrington, B.; et al. An orally available small molecule that targets soluble TNF to deliver anti-TNF biologic-like efficacy in rheumatoid arthritis. Front. Pharmacol. 2022, 13, 1037983.
63. Pharmaceutical Technology. SAR-441566 by Sanofi for Psoriasis: Likelihood of Approval; Pharmaceutical Technology: Iselin, NJ, USA, 2023.
64. Andrews, M.D.; Dack, K.N.; De Groot, M.J.; Lambert, M.; Sennbro, C.J.; Larsen, M.; Stahlhut, M. Discovery of an Oral, Rule of 5 Compliant, Interleukin 17A Protein-Protein Interaction Modulator for the Potential Treatment of Psoriasis and Other Inflammatory Diseases. J. Med. Chem. 2022, 65, 8828–8842.
65. Goedken, E.R.; Argiriadi, M.A.; Dietrich, J.D.; Petros, A.M.; Krishnan, N.; Panchal, S.C.; Qiu, W.; Wu, H.; Zhu, H.; Adams, A.M.; et al. Identification and structure-based drug design of cell-active inhibitors of interleukin 17A at a novel C-terminal site. Sci. Rep. 2022, 12, 14561.
66. Armstrong, M.; Elmhirst, E. Lilly's Oral Interleukin Exit Hints at a Dicey Future. Evaluate Vantage. 2022. Available online: https://www.evaluate.com/vantage/articles/news/corporate-strategy/lillys-oral-interleukin-exit-hints-dicey-future (accessed on 8 May 2023).
67. Budwick, D. DICE Therapeutics Announces Positive Topline Data from Phase 1 Clinical Trial of Lead Oral IL-17 Antagonist, DC-806, for Psoriasis. 2022. Available online: https://www.globenewswire.com/news-release/2022/10/11/2531642/0/en/DICE-Therapeutics-Announces-Positive-Topline-Data-from-Phase-1-Clinical-Trial-of-Lead-Oral-IL-17-Antagonist-DC-806-for-Psoriasis.html (accessed on 31 January 2024).
68. Jordan Bishop. Lilly Completes Acquisition of DICE Therapeutics. Lilly Investors. 2023. Available online: https://investor.lilly.com/news-releases/news-release-details/lilly-completes-acquisition-dice-therapeutics (accessed on 5 January 2024).
69. Protagonist Therapeutics. Protagonist Reports Positive Results from Phase 1 and Pre-Clinical Studies of Oral Interleukin-23 Receptor Antagonist JNJ-2113. Protagonist Therapeutics, Inc. 2023. Available online: https://www.prnewswire.com/news-releases/protagonist-reports-positive-results-from-phase-1-and-pre-clinical-studies-of-oral-interleukin-23-receptor-antagonist-jnj-2113-301823039.html (accessed on 24 May 2023).
70. Bader, K. New Positive Results of Oral IL-23 Receptor Antagonist for Psoriasis. Dermatology Times. 2023. Available online: https://www.dermatologytimes.com/view/new-positive-results-of-oral-il-23-receptor-antagonist-for-psoriasis (accessed on 24 May 2023).
71. Kimmel, B. Janssen Announces Positive Topline Results for JNJ-2113—A Novel, First and Only Oral IL-23 Receptor Antagonist Peptide in Development for Moderate to Severe Plaque Psoriasis; Johnson & Johnson: Hoboken, NJ, USA, 2023.

72. Jetten, A.M. Retinoid-related orphan receptors (RORs): Critical roles in development, immunity, circadian rhythm, and cellular metabolism. Nucl. Recept. Signal. 2009, 7, e003.

73. Ben Abdallah, H.; Johansen, C.; Iversen, L. Key Signaling Pathways in Psoriasis: Recent Insights from Antipsoriatic Therapeutics. Psoriasis Targets Ther. 2021, 11, 83–97.

74. Tang, L.; Yang, X.; Liang, Y.; Xie, H.; Dai, Z.; Zheng, G. Transcription Factor Retinoid-Related Orphan Receptor γt: A Promising Target for the Treatment of Psoriasis. Front. Immunol. 2018, 9, 1210.

75. Lee, G.R. The Balance of Th17 versus Treg Cells in Autoimmunity. Int. J. Mol. Sci. 2018, 19, 730.

76. Gege, C. RORγt inhibitors as potential back-ups for the phase II candidate VTP-43742 from Vitae Pharmaceuticals: Patent evaluation of WO2016061160 and US20160122345. Expert Opin. Ther. Pat. 2017, 27, 1–8.

77. Pandya, V.B.; Kumar, S.; Sachchidanand, S.; Sharma, R.; Desai, R.C. Combating Autoimmune Diseases with Retinoic Acid Receptor-Related Orphan Receptor-γ (RORγ or RORc) Inhibitors: Hits and Misses. J. Med. Chem. 2018, 61, 10976–10995.

78. Capone, A.; Volpe, E. Transcriptional Regulators of T Helper 17 Cell Differentiation in Health and Autoimmune Diseases. Front. Immunol. 2020, 11, 348.

79. The Pharma Letter. Aurigene's AUR101 Disappoints in Phase IIb Study in Moderate to Severe Psoriasis. Thepharmaletter. 2022. Available online: https://www.thepharmaletter.com/article/aurigene-s-aur101-disappoints-in-phase-ii-study-in-moderate to severe-psoriasis (accessed on 24 May 2023).

80. Ooi, Q.X.; Kristoffersson, A.; Korell, J.; Flack, M.; L Plan, E.; Weber, B. Bounded integer model-based analysis of psoriasis area and severity index in patients with moderate to severe plaque psoriasis receiving BI 730357. CPT Pharmacomet. Syst. Pharmacol. 2023, 12, 758–769.

81. Blankenbach, K.V.; Schwalm, S.; Pfeilschifter, J.; Meyer Zu Heringdorf, D. Sphingosine-1-Phosphate Receptor-2 Antagonists: Therapeutic Potential and Potential Risks. Front. Pharmacol. 2016, 7, 167.

82. Obinata, H.; Hla, T. Sphingosine 1-phosphate and inflammation. Int. Immunol. 2019, 31, 617–625.

83. Herzinger, T.; Kleuser, B.; Schäfer-Korting, M.; Korting, H.C. Sphingosine-1-phosphate signaling and the skin. Am. J. Clin. Dermatol. 2007, 8, 329–336.

84. Schaper, K.; Kietzmann, M.; Bäumer, W. Sphingosine-1-phosphate differently regulates the cytokine production of IL-12, IL-23 and IL-27 in activated murine bone marrow derived dendritic cells. Mol. Immunol. 2014, 59, 10–18.

85. Yiu, Z.Z.N.; Warren, R.B. Novel Oral Therapies for Psoriasis and Psoriatic Arthritis. Am. J. Clin. Dermatol. 2016, 17, 191–200.

86. D'Ambrosio, D.; Steinmann, J.; Brossard, P.; Dingemanse, J. Differential effects of ponesimod, a selective S1P1 receptor modulator, on blood-circulating human T cell subpopulations. Immunopharmacol. Immunotoxicol. 2015, 37, 103–109.

87. Vaclavkova, A.; Chimenti, S.; Arenberger, P.; Holló, P.; Sator, P.G.; Burcklen, M.; Stefani, M.; D'Ambrosio, D. Oral ponesimod in patients with chronic plaque psoriasis: A randomised, double-blind, placebo-controlled phase 2 trial. Lancet 2014, 384, 2036–2045.

88. Bellinato, F.; Gisondi, P.; Girolomoni, G. Latest advances for the treatment of chronic plaque psoriasis with biologics and oral small molecules. Biol. Targets Ther. 2021, 15, 247–253.

89. Fishman, P. Drugs Targeting the A3 Adenosine Receptor: Human Clinical Study Data. Molecules 2022, 27, 3680.

90. Cohen, S.; Barer, F.; Itzhak, I.; Silverman, M.H.; Fishman, P. Inhibition of IL-17 and IL-23 in Human Keratinocytes by the A3 Adenosine Receptor Agonist Piclidenoson. J. Immunol. Res. 2018, 2018, 2310970.

91. Cutolo, M.; Sulli, A.; Pizzorni, C.; Seriolo, B.; Straub, R.H. Anti-inflammatory mechanisms of methotrexate in rheumatoid arthritis. Ann. Rheum. Dis. 2001, 60, 729–735.

92. David, M.; Gospodinov, D.K.; Gheorghe, N.; Mateev, G.S.; Rusinova, M.V.; Hristakieva, E.; Solovastru, L.G.; Patel, R.V.; Giurcaneanu, C.; Hitova, M.C.; et al. Treatment of Plaque-Type Psoriasis With Oral CF101: Data from a Phase II/III Multicenter, Randomized, Controlled Trial. J. Drugs Dermatol. 2016, 15, 931–938.

93. Damasiewicz-Bodzek, A.; Szumska, M.; Tyrpień-Golder, K. Antibodies to Heat Shock Proteins 90α and 90β in Psoriasis. Arch. Immunol. Ther. Exp. 2020, 68, 9.

94. Czajkowski, R.; Kaszewski, S.; Tadrowski, T.; Grzanka, D.; Ziandarska, J.; Drewa, G.; Marek-Józefowicz, L. Does HSP90 play an important role in psoriasis? Postepy Dermatol. Alergol. 2021, 38, 319–326.

95. Stenderup, K.; Rosada, C.; Gavillet, B.; Vuagniaux, G.; Dam, T.N. Debio 0932, a new oral Hsp90 inhibitor, alleviates psoriasis in a xenograft transplantation model. Acta Derm. Venereol. 2014, 94, 672–676.

96. Hansen, R.S.; Thuesen, K.K.H.; Bregnhøj, A.; Moldovan, L.I.; Kristensen, L.S.; Grek, C.L.; Ghatnekar, G.S.; Iversen, L.; Johansen, C. The HSP90 inhibitor RGRN-305 exhibits strong immunomodulatory effects in human keratinocytes. Exp. Dermatol. 2021, 30, 773–781.

97. Bregnhøj, A.; Thuesen, K.K.H.; Emmanuel, T.; Litman, T.; Grek, C.L.; Ghatnekar, G.S.; Johansen, C.; Iversen, L. HSP90 inhibitor RGRN-305 for oral treatment of plaque-type psoriasis: Efficacy, safety and biomarker results in an open-label proof-of-concept study. Br. J. Dermatol. 2022, 186, 861–874.

98. Ben Abdallah, H.; Seeler, S.; Bregnhøj, A.; Ghatnekar, G.; Kristensen, L.S.; Iversen, L.; Johansen, C. Heat shock protein 90 inhibitor RGRN-305 potently attenuates skin inflammation. Front. Immunol. 2023, 14, 1128897.
99. Yoon, J.-H.; Nguyen, T.-T.-L.; Duong, V.-A.; Chun, K.-H.; Maeng, H.-J. Determination of KD025 (SLx-2119), a Selective ROCK2 Inhibitor, in Rat Plasma by High-Performance Liquid Chromatography-Tandem Mass Spectrometry and its Pharmacokinetic Application. Molecules 2020, 25, 1369.
100. Blair, H.A. Belumosudil: First Approval. Drugs 2021, 81, 1677–1682.
101. Hyun Lee, J.; Zheng, Y.; Bornstadt, D.; Wei, Y.; Balcioglu, A.; Daneshmand, A.; Yalcin, N.; Yu, E.; Herisson, F.; Atalay, Y.B.; et al. Selective ROCK 2 inhibition in focal cerebral ischemia. Ann. Clin. Transl. Neurol. 2014, 1, 2–14.
102. Zanin-Zhorov, A.; Weiss, J.M.; Nyuydzefe, M.S.; Chen, W.; Scher, J.U.; Mo, R.; Depoil, D.; Rao, N.; Liu, B.; Wei, J.; et al. Selective oral ROCK2 inhibitor down-regulates IL-21 and IL-17 secretion in human T cells via STAT3-dependent mechanism. Proc. Natl. Acad. Sci. USA 2014, 111, 16814–16819.