Taylor & Francis
Taylor & Francis Group

Expert Opinion on Investigational Drugs

ISSN: (Print) (Online) Journal homepage: https://www.tandfonline.com/loi/ieid20

Psoriasis: talking points from recent clinical trials

Andrea Chiricozzi, Francesco Bellinato, Paolo Romita & Paolo Gisondi

To cite this article: Andrea Chiricozzi, Francesco Bellinato, Paolo Romita & Paolo Gisondi (2022) Psoriasis: talking points from recent clinical trials, Expert Opinion on Investigational Drugs, 31:12, 1265-1267, DOI: 10.1080/13543784.2022.2160314

To link to this article: https://doi.org/10.1080/13543784.2022.2160314

EXPERT OPINION ON INVESTIGATIONAL DRUGS
2022, VOL. 31, NO. 12, 1265–1267
https://doi.org/10.1080/13543784.2022.2160314

Taylor & Francis
Taylor & Francis Group

EDITORIAL

Psoriasis: talking points from recent clinical trials

Andrea Chiricozzi [a,b], Francesco Bellinato [c], Paolo Romita[d] and Paolo Gisondi [c]

[a]UOC di Dermatologia, Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario A. Gemelli - IRCCS, Rome, Italy; [b]Dermatologia, Dipartimento di Medicina e Chirurgia Traslazionale, Università Cattolica del Sacro Cuore, Rome, Italy; [c]Department of Medicine, Section of Dermatology and Venereology, University of Verona, Verona, Italy; [d]Department of Biomedical Science and Human Oncology, Section of Dermatology, University of Bari, Bari, Italy

ARTICLE HISTORY Received 30 September 2022; Accepted 14 December 2022

1. Introduction

Psoriasis is a chronic inflammatory skin disease that includes a wide spectrum of clinical variants. The most common form of psoriasis is chronic plaque psoriasis, which manifests as well-demarked, erythematous, and scaly plaques. The pathogenic mechanisms underlying either plaque or pustular psoriasis overlap because of the central role of the interleukin-(IL-)23/IL-17A axis in both conditions, though pustular psoriasis is characterized by a more prominent contribution of the innate immune compartment involving the IL-1 cytokine family [1]. Besides the development of antibodies targeting either soluble pathogenic cytokines or their receptor, the inhibition of the intracellular signaling induced by multiple cytokines and chemokines has been proposed as an alternative therapeutic strategy. Nowadays, the therapeutic paradigm for plaque psoriasis includes topical, phototherapy, conventional systemic treatments, different classes of biological agents, and small molecules. Contrary to plaque psoriasis, only one biologic agent has received approval for the treatment of pustular psoriasis. The pipeline of plaque psoriasis consists of topical and systemic agents that showed promising results in phase II trials, as well as for pustular psoriasis, with one additional IL-36 receptor antagonist under investigation. This editorial aimed to collect and discuss clinical outcomes deriving from the most advanced trials testing promising agents, either topical or systemic. A narrative review for selected agents with a robust clinical trial program was performed.

2. Drugs in development for plaque psoriasis

2.1. Systemic agents: deucravacitinib

Deucravacitinib is an oral, small molecule that selectively inhibits TYK2 through the binding of TYK2 regulatory pseudokinase (JH2) domain. TYK2 is a Janus Kinase (JAK) mediating signals the downstream signaling of pathogenic cytokines such as IL-12, IL-23, and type I interferon. Not interfering with the activity of the conserved active domain, deucravacitinib is highly selective for TYK2, conversely to other JAK inhibitors that own variable affinity for different JAKs. A randomized, double-blind, placebo-controlled, dose-ranging phase II trial investigated efficacy and safety of deucravacitinib at different doses, in 267 patients through 12 weeks of therapy [2]. A significantly higher percentage of patients treated with 3-mg daily or higher doses of deucravacitinib achieved at least 75% improvement of the baseline PASI Psoriasis Area Severity Index score (PASI 75) response, compared to placebo [2]. Notwithstanding the higher percentage of deucravacitinib-treated patients reporting adverse events compared to placebo, safety profile did not reveal any warning signal. Nasopharyngitis, headache, and diarrhea were the most common adverse events, whereas no cases of herpes zoster infection, opportunistic infections, or cardiovascular events were reported [2]. Acne was reported only in the highest deucravacitinib dose arm [2]. Because greater therapeutic response rates (meant as PASI reductions and improvements in Dermatology Life Quality Index [DLQI]) were detected in patients treated with at least 6-mg deucravacitinib daily, the dose of 6 mg daily was selected for being tested in phase III trials, that have been designed to compare deucravacitinib with placebo and apremilast [3,4]. They described the superior efficacy of deucravacitinib associated with a lower percentage (2.4%) of patients discontinuing treatment because of the occurrence of adverse events compared to placebo (3.8%) or apremilast (5.2%), through week 16 [3,4].

2.2. Topical agents: Tapinarof

Tapinarof (3,5-dihydroxy-4-isopropylstilbene, DMVT-505 also known as WBI-1001 and GSK2894512) is a small molecule identified as an anti-inflammatory metabolite of *Photorhabdus luminescens*. It was investigated in a phase IIb trial involving 61 patients as a 1% concentration cream. At week 12, the affected Body Surface Area (BSA) decreased by almost 80% from baseline [5]. In a subsequent phase IIb trial, tapinarof was tested at different doses, ranging from 0.5% to 1%, once and twice daily. The primary endpoint was the Physician Global Assessment (PGA) score of 0 or 1 and a 2-grade or greater improvement after 12 weeks of therapy. The proportion of patients achieving the primary endpoint was significantly higher in all tapinarof

CONTACT Andrea Chiricozzi chiricozziandrea@gmail.com UOC di Dermatologia, Dipartimento di Scienze Mediche e Chirurgiche, Fondazione Policlinico Universitario A. Gemelli - IRCCS, Largo Agostino Gemelli 8, 00168, Rome, Italy

Supplemental data for this article can be accessed online at https://doi.org/10.1080/13543784.2022.2160314

groups compared to vehicles, with highest response rate (65%) observed in patients treated with tapinarof 1% twice daily [6]. Phase II trials revealed an acceptable safety profile characterized by folliculitis and contact dermatitis as the most common adverse events. Treatment-emergent adverse events led to permanent discontinuation in 10% of the patients. Albeit the superior efficacy of tapinarof vs. vehicle was confirmed in two identical phase 3 randomized trials (PSOARING 1 and PSOARING2), response rates resulted lower compared to phase II outcomes [7].

2.3. Topical agents: Roflumilast

Phosphodiesterase-4 (PDE-4) is an enzyme that mediates inflammatory responses and plays a role in psoriasis pathogenesis. A topical PDE-4 inhibitor, 0.3% roflumilast cream, has been recently approved by the U.S. Food and Drug Administration (FDA) for the treatment of plaque psoriasis, including intertriginous areas, in patients with 12 years of age or older [8]. Efficacy and safety of roflumilast was investigated in a randomized, double-blind, vehicle-controlled phase IIb trial including 331 patients affected by plaque psoriasis [9]. Subjects were randomized 1:1:1 to roflumilast 0.3% cream, roflumilast 0.15% cream or vehicle cream once daily for 12 weeks. At week 6, 28% of the patients treated with roflumilast 0.3% cream and 23% of those treated with roflumilast 0.15% cream reached a 0–1 IGA score (vehicle: 8%). At the same timepoint, the mean change of PASI score from baseline was −50.0% and −49.0% in the 0.3% and 0.15% roflumilast group, respectively. A subset of 47 patients affected by inverse psoriasis were separately evaluated obtaining an IGA score of 0 or 1 in 73% of the patients after 6 weeks of 0.3%-roflumilast therapy [9].

Preliminary data deriving from two phase III randomized vehicle-controlled studies (DERMIS-1 and DERMIS-2) confirmed roflumilast efficacy in a larger population consisting of more than 800 psoriasis patients [10].

3. Drugs in development for pustular psoriasis

3.1. Systemic agents: spesolimab and imsidolimab

Spesolimab and imsidolimab are two IL-36 receptor antagonists which completed early phases of clinical development program with promising outcomes in terms of efficacy and safety, achieving a fast control of generalized pustular psoriasis (GPP) flares. A 12-week, placebo-controlled, phase II study evaluated efficacy, safety and tolerability of a single intravenous dose of spesolimab (EffisayilTM 1) in GPP patients (n = 53) presenting with an acute flare of moderate-to-severe intensity (GPPGA score 3–4) [11]. At the end of Week 1, the percentage of patients with a pustulation subscore of 0 (no visible pustules) was significantly greater in the spesolimab group than in the placebo group (54% vs 6%, respectively; $p < 0.001$) [11]. Regarding safety, 42 of the 51 (82%) patients who received spesolimab reported an adverse effect at week 12, and 6 (12%) of them were considered serious, with one report of drug-induced liver injury. Moreover, a higher proportion of patients treated with spesolimab had infections and systemic drug reactions (eosinophilia, pyrexia, arthritis) compared to placebo [11]. A 5-year open-label extension trial (EffisayilTM ON) (Anonymized) is ongoing to evaluate spesolimab long-term safety. Another phase II study is being conducted to evaluate the efficacy and safety of spesolimab (EffisayilTM2) at different doses versus placebo in preventing GPP flares (Anonymized). Promising efficacy data related to the use of imsidolimab in GPP patients derived from the GALLOP (phase II) trial [12], while a phase III, international, multicenter, randomized, double-blind, placebo-controlled trial called Gemini-1 (ANB019-301) has been planned [13].

4. Expert opinion box

The long-term management of moderate-to-severe plaque psoriasis is centered on biologic agents, especially, on IL-17 and IL-23 antagonists, that demonstrated great efficacy in obtaining a complete or almost complete clearance of skin lesions. Nevertheless, a satisfactory control of the disease is not achieved in all patients, with primary or secondary lack of efficacy that is still observed. Thus, a place in the therapeutic algorithm for novel effective and safe therapies can be foreseen. Notwithstanding the large therapeutic armamentarium that is currently available for the treatment of plaque psoriasis, the available topical agents as well as targeted oral therapies are limited. In this scenario, the development of topical (tapinarof and reflumilast) and oral (deucravacitinib) therapies is highly promising. Of interest, the advantageous long-lasting effect that is observed after withdrawing tapinarof treatment, could potentially lessen the issue related to patient adherence to topical treatments. Indeed, an extension study, PSOARING3, assessing tapinarof response after treatment withdrawal in patients who achieved a PGA score of 0, showed a successful reintroduction of tapinarof in case of PGA ≥2 until PGA score of 0 was re-obtained. The re-treatment with tapinarof re-obtained a complete clearance in 40.9% of the patients, after a mean time-to-relapse of 130 days [4]. In addition, tapinarof has also demonstrated great efficacy in atopic dermatitis trials, suggesting that its use might have dual validity in controlling both AD and psoriasis when concomitantly occur [14,15].

For moderate-to-severe plaque psoriasis, an additional and valid option would be represented by deucravacitinib that showed superior efficacy compared with apremilast and a more favorable safety profile compared with other JAK inhibitors, because of its mode-of-action that reduces off-target effects (herpes zoster reactivation, opportunistic infections, thromboembolic events, dyslipidemia, JAK2-dependent hematopoietic function). Contrary to plaque psoriasis, only one biologic agent (spesolimab) has been approved for the treatment of GPP so far. Because the management of pustular psoriasis often results unsatisfactory with the available treatment options, a therapeutic need is still not fulfilled. The evaluation of efficacy and safety of any therapeutic investigated for GPP might result challenging in a clinical trial setting in particular for patient recruitment, mostly due to the rarity of the condition. Notably, the occurrence of GPP could have been further reduced through the last two decades because of the continuous, long-term use of biologic treatments for plaque psoriasis that has likely prevented the onset of GPP after withdrawal from systemic steroids or cyclosporine in

patients with plaque psoriasis. However, the future of GPP treatment is encouraging and offers the potential of better patient care improving quality of life for patients affected by this severe and potentially life-threatening disease.

Funding

This paper was not funded.

Declaration of interest

A. Chiricozzi served as advisory board member and consultant and has received fees and speaker's honoraria or has participated in clinical trials for AbbVie, Almirall, Leo Pharma, Lilly, Janssen, Novartis, Sanofi Genzyme, Pfizer, and Incyte. Paolo Gisondi has received honoraria for acting as a consultant and/or as a speaker from AbbVie, Almirall, Amgen, Bristol-Myers Squibb, Celgene, Eli Lilly, Janssen, Leo Pharma, MSD, Novartis, Pfizer, Sandoz, Sanofi, and UCB. The authors have no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.

Reviewer disclosures

A reviewer on this manuscript has disclosed that they have received research, speaking and/or consulting support from Eli Lilly and Company, GlaxoSmithKline/Stiefel, AbbVie, Janssen, Alovtech, vTv Therapeutics, Bristol-Myers Squibb, Samsung, Pfizer, Boehringer Ingelheim, Amgen, Dermavant, Arcutis, Novartis, Novan, UCB, Helsinn, Sun Pharma, Almirall, Galderma, Leo Pharma, Mylan, Celgene, Ortho Dermatology, Menlo, Merck & Co, Qurient, Forte, Arena, Biocon, Accordant, Argenx, Sanofi, Regeneron, the National Biological Corporation, Caremark, Teladoc, Eurofins, Informa, UpToDate and the National Psoriasis Foundation. They are also founders and part owners of Causa Research and hold stock in Sensal Health. Peer reviewers on this manuscript have no other relevant financial relationships or otherwise to disclose.

ORCID

Andrea Chiricozzi http://orcid.org/0000-0002-6739-0387
Francesco Bellinato http://orcid.org/0000-0002-6163-6921
Paolo Gisondi http://orcid.org/0000-0002-1777-9001

References

Papers of special note have been highlighted as: • of interest. •• of considerable interest

1. Genovese G, Moltrasio C, Cassano N, et al. Pustular psoriasis: from pathophysiology to treatment. Biomedicines. 2021;9(12):1746.
2. Papp K, Gordon K, Thaçi D, et al. Phase 2 trial of selective tyrosine kinase 2 inhibition in psoriasis. N Engl J Med. 2018;379(14):1313–1321.
3. Armstrong A, Gooderham M, Warren RB, et al.POS1042 - Efficacy and safety of Deucravacitinib, an oral, selective tyrosine kinase 2 (TYK2) inhibitor, compared with placebo and apremilast in moderate to severe plaque psoriasis: results from the phase 3 POETYK PSO-1 STUDY. Ann Rheum Dis. 2021;80(Suppl 1):795–796.

• **Head-to-head trial comparing deucravacitinib vs. placebo and vs. apremilast.**

4. Warren R, Armstrong A, Gooderham M, et al. Abstract N° 2857 - deucravacitinib, an oral, selective tyrosine kinase 2 inhibitor, in moderate to severe plaque psoriasis: 52-week efficacy results from the phase 3 POETYK PSO-1 and POETYK PSO-2 Trials. EADV 30th Congr. 2021 [cited 2022 Sep 12]. Available from: https://s3.eu-central-1.amazonaws.com/cst.eadv/eadv2021/abstracts/26128.html.pdf
5. Bissonnette R, Poulin Y, Zhou Y, et al., Efficacy and safety of topical WBI-1001 in patients with mild to severe atopic dermatitis: results from a 12-week, multicentre, randomized, placebo-controlled double-blind trial. Br J Dermatol. 2012;166(4):853–860.

• **Clinical outcomes showing superiority of deucravacitinib vs. placebo and vs. apremilast.**

6. Robbins K, Bissonnette R, Maeda-Chubachi T, et al. Phase 2, randomized dose-finding study of tapinarof (GSK2894512 cream) for the treatment of plaque psoriasis. J Am Acad Dermatol. 2019;80(3):714–721.
7. Lebwohl MG, Stein Gold L, Strober B, et al. Phase 3 trials of tapinarof cream for plaque psoriasis. N Engl J Med. 2021;385(24):2219–2229.
8. McCulloch T. FDA approves arcutis' zoryve (roflumilast) cream 0.3% for the treatment of plaque psoriasis in individuals age 12 and older. Arcutis Biotherapeutics. Published July 29, 2022. cited 2022 Aug 22. Available from: https://www.arcutis.com/fda-approves-arcutis-zoryve-roflumilast-cream-0-3-for-the-treatment-of-plaque-psoriasis-in-individuals-age-12-and-older/
9. Lebwohl MG, Papp KA, Stein Gold L, et al. Trial of roflumilast cream for chronic plaque psoriasis. N Engl J Med. 2020;383(3):229–239.
10. Lebwohl M, Kircik LH, Moore A, et al. Once-daily roflumilast cream 0.3%, a potent phosphodiesterase-4 inhibitor, provided safe and effective treatment of psoriasis in the DERMIS-1 and DERMIS-2 phase 3 trials [abstract 2063]. EADV 30th Congress; 2021. *Effects of roflumilast in phase III trials for the treatment of psoriasis
11. Bachelez H, Choon SE, Marrakchi S, et al., Trial of spesolimab for generalized pustular psoriasis. N Engl J Med. 2021;385(26):2431–2440.

•• **Evidence on beneficial effects deriving from IL-36 pathway inhibition with spesolimab in pustular psoriasis in a relatively large patient cohort.**

12. GlobeNewswire. AnaptysBio presents updated data from imsidolimab phase 2 GALLOP trial in generalized pustular psoriasis 2021 [cited 2022 Sep 12]. Available from: https://www.globenewswire.com/news-release/2021/10/02/2307446/0/en/AnaptysBioPresents-Updated-Data-From-Imsidolimab-Phase-2-GALLOPTrial-in-Generalized-Pustular-Psoriasis.html
13. Gudjonsson JE, Randazzo B, Zhou J, et al. Imsidolimab in the treatment of adult subjects with generalized pustular psoriasis: design of a pivotal phase 3 clinical trial and a long-term extension study. Presented at: the 2022 American Academy of Dermatology Annual Meeting, Boston. 2022 [cited 2022 Mar 25–29]. Abstract/Poster 34617
14. Barry K, Zancanaro P, Casseres R, et al. Concomitant atopic dermatitis and psoriasis - a retrospective review. J Dermatolog Treat. 2021;32(7):716–720.
15. Caldarola G, Pirro F, Di Stefani A, et al. Clinical and histopathological characterization of eczematous eruptions occurring in course of anti IL-17 treatment: a case series and review of the literature. Expert Opin Biol Ther. 2020;20(6):665–672.