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REVIEW ARTICLE

A Systematic Review on Psoriasis and Its Treatment

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ABSTRACT
Psoriasis is a chronic, systemic immune-mediated condition marked by the formation of red, thickened, scaly, itchy, and frequently painful skin lesions. While biologic therapies for psoriasis have demonstrated both effectiveness and safety in clinical studies, they are often expensive, can provoke immune responses, and necessitate intravenous or subcutaneous administration. In contrast, oral treatments, particularly those involving small molecules and microbiome-based therapies, may offer greater convenience and cost efficiency. This manuscript examines oral treatment options for psoriasis, identified through a review of Clinica lTrials.gov. Among the small molecules currently in development are inhibitors of tumor necrosis factor, IL-23, IL-17, and phosphodiesterase-4. Additionally, early-phase studies have shown promise for oral microbial therapies. To enhance understanding of these novel oral treatments in clinical practice, further real-world data and comparative trials are essential. The objective of this review article is to clarify the efficacy and safety profiles of various systemic therapies to optimize treatment outcomes for patients suffering from moderate-to-severe psoriasis.
Keywords: Psoriasis, imide derivatives, synthesis, molecular docking, biological activity, TNF-α, IL-17, anti-inflammatory, antiproliferative

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INTRODUCTION

Psoriasis is a painful, disfiguring, debilitating, chronic, noncommunicable disorder that has no cure and significantly lowers the quality of life (QoL) of those who have it. While it can occur at any age, those between the ages of 50 and 69 experience it most often. There are severe cases of psoriasis all across the world; prevalence rates range from 0.09% to 11.4%, according to reports. Worldwide, psoriasis is prevalent. It affects people of various ages, genders, and ethnic backgrounds everywhere. The variation of psoriasis prevalence across different countries is 0.09% to 11.4%. In most developed countries, the prevalence ranges from 1.5 to 5%. There is also evidence that the prevalence of psoriasis is on the rise. Many studies have shown that psoriasis may have a significant influence on QoL even when it affects a relatively small body surface area (BSA)[1]. The disease affects 2–3% of the world's population and is associated with several comorbidities including cardiovascular disease, inflammatory bowel disease, and psoriatic arthritis [2-4]. Treatment requires an individualized approach, as mild cases are often managed with topical therapies, while moderate-to-severe disease (>5–10% body surface area) may require the addition of systemic therapies [5,6].

Pathophysiology

Although there is no clear immunogen associated with psoriasis, the disease's basic pathophysiology is thought to be excessive activation of certain adaptive immune system components [7]. More precisely, a variety of cell types, including T, dendritic, and keratinocyte cells, are responsible for the chronic inflammation that results from their cytokine production [8–12]. Psoriasis can also occur as a result of genetic mutations and heredity, environmental factors, infections, stress, and skin lesions [13,14].

Epidemiology

Psoriasis is a severe public health concern that affects at least 125 million individuals globally. Psoriasis is equally common in men and women [15], although it varies greatly between geographical areas, with

rates as low as 0.5% in Asia and as high as 8% in some parts of Europe [15–17]. A little over 3.2% of adults and 0.13% of children in the US have psoriasis [18–20]. Psoriasis can start at any age, however it usually manifests itself between the ages of 15 and 30 [21]. The age at which psoriasis first appears can be influenced by both genetic and environmental variables. For example, early onset of psoriasis is strongly correlated with the human leukocyte antigen (HLA)-C*06 allele [22]. Besides, patient ethnicity, UV exposure, and the climate they live in are also considered to influence the prevalence of psoriasis, and recent studies have found a weak association between latitude and psoriasis prevalence [23].

Clinical diagnosis

Based on its clinical signs, which include silver-white scales that easily peel off the skin and vivid pink or red lesions with well-defined edges, psoriasis is a common skin disease that most dermatologists can detect with ease. When the scales are scraped off of the damp skin, little bleeding spots will show up on the pink, sensitive, and moist flesh beneath the scales. A clinical examination of the skin and nails, which includes an evaluation of the location and morphology of psoriatic lesions, and an inquiry into any family history of psoriasis would typically be the main emphasis of the diagnosis process. Sometimes, when psoriasis patients have atypical clinical presentations, dermatologists may also use skin biopsies or scrapes and blood analysis to eliminate otherdiseases and to verify the diagnosis. In addition, the Psoriasis Area and Severity Index (PASI) score is widely used to evaluate the severity of lesions in patients with psoriasis [24], and lattice system physician's global assessment (LSPGA) or psoriasis global assessment (PGA) have been used in routine clinical practice [25].

Approach for the treatment of psoriasis

Recent studies have focused on small compounds, which have a molecular weight of less than one kilodaltons and can penetrate cell membranes to obstruct intracellular signaling pathways [26, 27]. These medicines can be applied topically or orally, which improves patient convenience and quality of life. They are also less expensive to produce than biologics [26, 27]. Although studies on oral microbials are still in their early stages, they are being conducted [28]. Apremilast, an inhibitor of phosphodiesterase-4 (PDE4), and deucravacitinib, a tyrosine kinase 2 (TYK2) inhibitor that was just licensed, are two of the available small molecule treatments for psoriasis [29, 30]. Despite being widely used in clinical practice, apremilast is linked to gastrointestinal side effects and low efficacy [31, 32]. Clinical trials have shown that deucravacitinib is more efficacious than apremilast, however, real-world data are lacking, and it remains unclear how this agent will perform against existing biologics [33,34]. New oral therapies are needed for the treatment of psoriasis. TNF-α inhibitors, interleukin-17 (IL-17) inhibitors, IL-12/IL-23 inhibitors, and PDE4 inhibitors have emerged as a promising candidate in clinical treatment.

Phosphodiesterase-4 Inhibitors

The primary phosphodiesterase that is expressed by keratinocytes and immune cells is PDE4 [35]. By hydrolyzing 30–50-cyclic adenosine monophosphate (cAMP), a significant second messenger molecule, to adenosine monophosphate (AMP), it mediates inflammatory reactions [36–38]. Therapeutically, PDE4 enzyme inhibitors are advantageous because they increase intracellular cAMP levels and stimulate mechanisms that promote an anti-inflammatory response by preventing the synthesis of proinflammatory cytokines and promoting the generation of anti-inflammatory mediators [36–38].

In the skin, PDE4 is primarily expressed in keratinocytes, neutrophils, Langerhans cells, and T cells, which contribute to the psoriatic plaque formation[39]. Owing to broad anti-inflammatory activities, PDE4 inhibitors have been investigated and applied for the treatment of various skin disorders or rheumatic diseases, such as psoriasis, psoriatic arthritis (PsA), and AD. Psoriasis is a chronic skin inflammatory disorder, which has an estimated global prevalence of 1–3% [40].

Apremilast is an oral PDE4 inhibitor that inhibits inflammatory responses. It has been tested against various cells and has shown significant effects on psoriasis and arthritis in preclinical models. It also reduces arthritis severity in mice. Apremilast has a wide therapeutic index in ferret lung neutrophilia. It was approved for treatment in 2014 for adults with active PsA and moderate-to-severe plaque psoriasis. However, its exposure is reduced when coadministered with CYP450 inducers, potentially affecting its therapeutic efficacy[41].

Orismilast, an oral PDE4 inhibitor, has shown potential in treating psoriasis, atopic dermatitis, and hidradenitis suppurativa. A phase IIb, randomized, dose-finding study found that orismilast was 2-5 times more potent than apremilast in inhibiting the PDE4 subtype, specifically the PDE4B and PDE4D splice variants linked to inflammation. The study found significant improvements in PASI 75 and 90 responses across all treatment groups. However, tolerability may be a limiting factor to treatment, especially at higher doses. Further phase III studies are needed to better understand the long-term efficacy, safety, and tolerability of orismilast.[42]

ME3183 is a selective PDE4 inhibitor developed by Meiji Seika Pharma. It is 5- to 40-fold more potent than apremilast in inhibiting inflammatory cytokine production. A phase II, double-blind, placebo-controlled trial showed that ME3183 significantly reduced PASI scores in participants treated once or twice daily. It was well-tolerated with common adverse events like diarrhea, headaches, and nausea[43-44]. Mufemilast, a potent PDE4 inhibitor, is being investigated in phase III for psoriasis patients. The primary endpoint is achieving a PASI 75 response at 16 weeks. Results from previous studies are not yet published[45].

Interleukin-17 (IL-17) inhibitors

The primary effector cytokine in psoriasis is IL-17 [46]. It is generated by Th17 cells, and once created, it acts on keratinocytes to encourage their growth and the release of chemokines, cytokines, and antimicrobial peptides that aid in the development of psoriasis plaques [47–49]. The six subunits that make up the IL-17 family's structure are IL-17A–IL-17F. Particularly connected to psoriasis signaling are IL-17A and IL-17F, which together form the IL-17A/F heterodimer and two homodimers [47–49]. Therapeutic use of antibodies that block these subunits has been effective, and research is currently being done on oral formulations.

The small molecule inhibitor DC-806 (Eli Lilly and Company, Indianapolis, IN, USA) inhibits the IL-17A subunit [50]. Forty subjects in a phase I proof-of-concept research (unlisted) reported a substantially higher mean PASI score reduction after four weeks after receiving DC-806 800 mg twice daily as opposed to those who got a placebo (probability = 0.0008, exploratory p = 43.7% vs. 13.3%) [50]. Therapeutic efficacy from low-dose DC-806 (175 mg twice daily) was not observed. There was no dose-dependent trend and the adverse effects ranged in severity from mild to moderate. Headaches, stomach discomfort, and COVID-19 infection were common side effects. There were no reports of discontinuations because of adverse events or clinically meaningful adjustments to test abnormalities [50].DC-806 is currently being investigated in a phase IIb dose-ranging trial (NCT05896527),with the PASI 75 response at 12 weeks defined as its primary endpoint.

Among the IL-17 inhibitors in the early stages of development are DC-853 (Eli Lilly and Company), a fast follower of DC-806, and LEO 153339 (LEO Pharma, Ballerup, Denmark), which was recently studied in a phase I single ascending dose (SAD) and multiple ascending dose (MAD) trial in healthy subjects (NCT04883333). DC-853 provides better metabolic stability and has a stronger affinity for the IL-17A cytokine, according to Lilly [51]. Nevertheless, there are no published preclinical or clinical trial data on these medications.

IL-12/IL-23 inhibitors

One important regulator of the Th17 pathway is IL-23 [52]. Produced by macrophages and myeloid dendritic cells, it induces naïve T helper cells to differentiate into Th17 lymphocytes and encourages these cells to release pro-inflammatory cytokines such TNF, IL-12, IL-23, and IL-17 [53-55]. Agents that block this pathway typically target either the p19 or p40 subunits of the cytokine and must be administered intravenously or subcutaneously [55]. A comparable method of action is also being studied for oral small compounds.

JNJ-2113 is an orally available peptide that binds to the IL-23 receptor, blocking downstream cytokine signaling. It has shown efficacy in reducing skin thickness and cytokine production in psoriasis-like mouse models. A phase IIb clinical trial showed significant improvements in PASI 75 response and PASI 90 and 100 responses. JNJ-2113 is currently being investigated in two phase III studies for psoriasis, with a 36-week extension study pending results[56, 57].

Tumor Necrosis Factor Inhibitors

A pleiotropic cytokine, TNF has a role in the development of a number of inflammatory and autoimmune disorders [58, 59]. There are two physiologically active forms of it: soluble protein (sTNF) and membrane-bound form (mTNF); the latter is generated when TNF converting enzyme cleaves the former through proteolytic cleavage [60]. When in their trimeric state, both mTNF and sTNF are active and send signals through TNFR1 and TNFR2, two cognate receptors [61-63]. The majority of TNF's biological effects are attributed to TNFR1, which is widely expressed. It does this by triggering the pathways of nuclear factor kappa B (NF-B) and mitogen-activated protein kinase (MAPK) and encouraging a proinflammatory response [63, 64]. The activation of TNFR2, which is limited to immune cells, endothelial cells, and glia and only reacts to mTNF, enhances cell proliferation, survival, andand lineage stability [65, 66]. Psoriasis patients overexpress TNF, causing inflammation through lymphocyte recruitment, adhesion molecules, and keratinocyte differentiation. Current biologic agents inhibit both mTNFand sTNF, making them important therapies for the disease. Oral small molecules with similar mechanisms are under investigation[67-70]. Sanofi's SAR441566 is a small molecule inhibitor of the TNF cytokine, which is used in early phase development for psoriasis. In a phase I, double-blind, placebo-

controlled, randomized trial, 58% of participants in the treatment group achieved a one-point reduction in the Investigator Global Assessment score at 4 weeks compared to placebo. Mean changes in Target Lesion Severity and Psoriasis Area and Severity Index scores also favored the treatment group. The drug was well-tolerated and is currently being investigated in a phase II trial for psoriasis[71, 72].

CONCLUSION

Psoriasis therapy should be cost-effective, easy to use, efficacious, and safe with minimal adverse events. Biologic agents have seen the greatest advancement in psoriasis treatment, with several new agents approved. Oral therapies, despite being more cost-effective and popular, have been slower to follow suit. Current oral agents with well-validated mechanisms of action are under development for psoriasis. JNJ-2113, targeting the IL-23 receptor, is in phase III trials. Orismilast, a selective PDE4 inhibitor, reduced disease severity in phase II trials, but larger trials are needed to determine safety and tolerability. New oral therapies for psoriasis require long-term trials and comparative studies with existing agents to understand their role in the current treatment algorithm. Agent-specific characteristics, including tolerability and dosing regimen, are crucial, especially for medications requiring twice-daily dosing schedules. Studies investigating oral therapies in patients with psoriasis comorbidities will also inform optimal patient selection.

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REFERENCES

1. WHO Global Report on Psoriasis. (Retrieved on- 07/10/2022)
2. Papp, K.A.; Gniadecki, R.; Beecker, J.; Dutz, J.; Gooderham, M.J.; Hong, C.H.; Kirchhof, M.G.; Lynde, C.W.; Maari, C.; Poulin, Y.;et al. (2021). Psoriasis prevalence and severity by expert elicitation. Dermatol. Ther. 11, 1053–1064.
3. 4. Damiani, G.; Bragazzi, N.L.; Aksut, C.K.; Wu, D.; Alicandro, G.; McGonagle, D.; Guo, C.; Dellavalle, R.; Grada, A.; Wong, P.; et al. (2021). The global, regional, and national burden of psoriasis: Results and insights from the global burden of disease 2019 study. Front.Med. 8, 743180.
4. 5. Takeshita, J.; Grewal, S.; Langan, S.M.; Mehta, N.N.; Ogdie, A.; Van Voorhees, A.S.; Gelfand, J.M. (2017). Psoriasis and comorbid diseases: Epidemiology. J. Am. Acad. Dermatol. 76, 377–390.
5. Elmets, C.A.; Leonardi, C.L.; Davis, D.M.R.; Gelfand, J.M.; Lichten, J.; Mehta, N.N.; Armstrong, A.W.; Connor, C.; Cordoro, K.M.; Elewski, B.E.; et al. (2019). Joint AAD-NPF guidelines of care for the management and treatment of psoriasis with awareness and attention to comorbidities. J. Am. Acad. Dermatol. 80, 1073–1113.
6. Armstrong, A.W.; Gordon, K.B.; Menter, M.A.;Wu, J.J. (2018). The evolving landscape for psoriasis treatment. Semin. Cutan. Med. Surg. 37, S39–S43.
7. Nestle FO, Kaplan DH, Barker J. Mechanisms of disease: psoriasis. N Engl J Med 2009; 361: 496-509.
8. Bos JD, Rie MAD, Teunissen MBM, Piskin G. (2005). Psoriasis: dysregulation of innate immunity. Br J Dermatol ; 152:1098-107.
9. Deguchi M, Aiba S, Ohtani H, et al. (2002). Comparison of the distribution and numbers of antigen-presenting cells among T-lymphocyte-mediated dermatoses: CD1a+, factor XIIIa+, and CD68+ cells in eczematous dermatitis, psoriasis, lichen planus and graft-versus-host disease. Arch Dermatol Res ; 294: 297-302.
10. Nickoloff BJ. (1991). The cytokine network in psoriasis. Arch Dermatol ; 127: 871-84.
11. Trefzer U, Hofmann M, Sterry W, Asadullah K. (2003). Cytokine and anticytokine therapy in dermatology. Exp OpinBiol Ther ; 3: 733-43.
12. Griffiths CE, Barker JN. (2007). Pathogenesis and clinical features of psoriasis. Lancet; 370: 263-71.
13. Gordon-Elliott JS, Muskin PR. (2013). Managing the patient with psychiatric issues in dermatologic practice. ClinDermatol ; 31: 3-10.
14. De AzevedoFraga NA, De Oliveira MDFP, Ivonise F, et al. (2012). Psoriasis and uveitis: a literature review. An BrasilDermatol ; 87: 877-83.
15. Parisi R, Symmons DPM, Griffiths CEM, Ashcroft DM. (2013). Identification and Management of Psoriasis and Associated ComorbidiTy (IMPACT) project team. Global epidemiology of psoriasis: a systematic review of incidence and prevalence. J Investig Dermatol ; 133: 377-85.
16. World Health Organization. Global Report on Psoriasis: World Health Organization (https://apps.who.int/iris/handle/10665/204417).
17. Tsai TF, Wang TS, Hung ST, et al. (2011). Epidemiology and comorbidities of psoriasis patients in a national database in Taiwan. J DermatolSci ; 63: 40-6.
18. Michalek IM, Loring B, John SM. (2017). A systematic review of worldwide epidemiology of psoriasis. J EurAcad Dermatol Venereol ; 31: 205-12.
19. Rachakonda TD, Schupp CW, Armstrong AW. (2014). Psoriasis prevalence among adults in the United States. J Am Acad Dermatol ; 70: 512-6.

20. Paller AS, Singh R, Cloutier M, et al. (2018). Prevalence of psoriasis in children and adolescents in the United States: a claimsbased analysis. J Drugs Dermatol ; 17: 187-94. 22.
21. Gudjonsson JE, Elder JT. (2007). Psoriasis: epidemiology. ClinDermatol ; 25: 535-46. 23.
22. Nair RP, Stuart PE, Nistor I, et al. (2006). Sequence and haplotype analysis supports HLA-C as the psoriasis susceptibility 1 gene. Am J Human Genet ; 78: 827-51.
23. Jacobson CC, Kumar S, Kimball AB. (2011). Latitude and psoriasis prevalence. Dermatology ; 65: 870-3.
24. Schmitt J, Wozel G. (2005). The psoriasis area and severity index is the adequate criterion to defifi ne severity in chronic plaque-type psoriasis. Dermatology ; 210: 194-9.
25. Langley RG, Ellis CN. (2004). Evaluating psoriasis with psoriasis area and severity index, psoriasis global assessment, and lattice system physician's global assessment. J Am AcadDermatol ; 51: 563-9.
26. Chen,W.-J.; Peng, C.; Lu, J.-J.; Ding, Y.-F.; Li, X.-Z. (2021). Advances in small molecule inhibitors for the treatment of psoriasis. Chin. Med.J. 134, 1364–1366.
27. Torres, T.; Filipe, P. (2015). Small molecules in the treatment of psoriasis. Drug Dev. Res. 76, 215–227.
28. Mahmud, M.R.; Akter, S.; Tamanna, S.K.; Mazumder, L.; Esti, I.Z.; Banerjee, S.; Akter, S.; Hasan, M.R.; Acharjee, M.; Hossain, M.S.; et al. (2022). Impact of gut microbiome on skin health: Gut-skin axis observed through the lenses of therapeutics and skin diseases. Gut Microbes. 14, 2096995.
29. Carrascosa, J.-M.; Del-Alcazar, E. (2020). Apremilast for psoriasis treatment. G. Ital. Dermatol. Venereol. 155, 421–433.
30. Estevinho, T.; Lé, A.M.; Torres, T. Deucravacitinib in the treatment of psoriasis. J. (2023). Dermatolog. Treat. 34, 2154122.
31. Papp, K.; Reich, K.; Leonardi, C.L.; Kircik, L.; Chimenti, S.; Langley, R.G.B.; Hu, C.; Stevens, R.M.; Day, R.M.; Gordon, K.B. (2015). Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, in patients with moderate to severe plaque psoriasis: Results of a phase III, randomized controlled trial (efficacy and safety trial evaluating the effects of apremilast in psoriasis [ESTEEM] 1). J. Am. Acad. Dermatol. 73, 37–49.
32. Ighani, A.; Georgakopoulos, J.R.; Shear, N.H.; Walsh, S.; Yeung, J. (2018). Short-term reasons for withdrawal and adverse events associated with apremilast therapy for psoriasis in real-world practice compared with in clinical trials: A multicenter retrospective study. J. Am. Acad. Dermatol. 78, 801–803.
33. Armstrong, A.W.; Gooderham, M.;Warren, R.B.; Papp, K.A.; Strober, B.; Thaçi, D.; Morita, A.; Szepietowski, J.C.; Imafuku, S.;Colston, E. (2023). Deucravacitinib versus placebo and apremilast in moderate to severe plaque psoriasis: Efficacy and safety results from a 52-week, randomized, double-blinded, placebo-controlled phase 3 POETYK PSO-1 trial. J. Am. Acad. Dermatol, 88, 29–39.
34. Armstrong, A.W.; Warren, R.B.; Zhong, Y.; Zhuo, J.; Cichewicz, A.; Kadambi, A.; Junqueira, D.; Westley, T.; Kisa, R.; Daamen, C. (2023) Short-, mid-, and long-term efficacy of deucravacitinib versus biologics and nonbiologics for plaque psoriasis: A network meta-analysis. Dermatol. Ther. 13, 2839–2857.
35. Li, H.; Zuo, J.; Tang, W. (2018). Phosphodiesterase-4 inhibitors for the treatment of inflammatory diseases. Front. Pharmacol. 9, 1048.
36. Blauvelt, A.; Langley, R.G.; Gordon, K.B.; Silverberg, J.I.; Eyerich, K.; Sommer, M.O.A.; Felding, J.; Warren, R.B. (2023). Next generationPDE4 inhibitors that selectively target PDE4B/D subtypes: A narrative review. Dermatol. Ther. 13, 3031–3042.
37. Milakovic, M.; Gooderham, M.J. (2021). Phosphodiesterase-4 inhibition in psoriasis. Psoriasis 11, 21–29.
38. Wittmann, M.; Helliwell, P.S. (2013). Phosphodiesterase 4 inhibition in the treatment of psoriasis, psoriatic arthritis and other chronic inflammatory diseases. Dermatol. Ther. 3, 1–15.
39. Chiricozzi, A., Caposiena, D., Garofalo, V., Cannizzaro, M. V., Chimenti, S., and Saraceno, R. (2016). A new therapeutic for the treatment of moderate-to severe plaque psoriasis: apremilast. Expert Rev. Clin. Immunol. 12, 237–249. doi: 10.1586/1744666X.2016.1134319
40. Gisondi, P., and Girolomoni, G. (2016). Apremilast in the therapy of moderate-to-severe chronic plaque psoriasis. *Drug Des. Devel. Ther.* 10:1763–1770. doi: 10.2147/DDDT.S108115
41. Li, H.; Zuo, J.; Tang, W. (2018). Phosphodiesterase-4 Inhibitors for the Treatment of Inflammatory Diseases. Frontiers in Pharmacology 9. https://doi.org/10.3389/fphar.2018.01048.
42. (1)Drakos, A.; Torres, T. (2024). Vender, R. Emerging Oral Therapies for the Treatment of Psoriasis: A Review of Pipeline Agents. Pharmaceutics 16 (1), 111–111. https://doi.org/10.3390/pharmaceutics16010111.
43. Kaji, C.; Suzuki, K.; Kano, A. (2022). Inhibitory effects of ME3183, a novel phosphodiesterase-4 inhibitor, on stimulants-induced production of proinflammatory cytokines and chemokines in whole blood cell cultures of patients with plaque psoriasis. J. Am.Acad. Dermatol. 87, AB72.
44. Meiji Seika Pharma Co., Ltd. (2023) 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.
45. Liu, X.; Chen, R.; Zeng, G.; Gao, Y.; Liu, X.; Zhang, D.; Hu, P.; Wang, H.; Jiang, J. (2018). Determination of a PDE4 inhibitor Hemay005 inhuman plasma and urine by UPLC-MS/MS and its application to a PK study. Bioanalysis 10, 863–875.
46. Brembilla, N.C.; Boehncke, W.-H. (2023). Revisiting the interleukin 17 family of cytokines in psoriasis: Pathogenesis and potential targets for innovative therapies. Front. Immunol. 14, 1186455.
47. McGeachy, M.J.; Cua, D.J.; Gaffen, S.L. (2019). The IL-17 family of cytokines in health and disease. Immunity 50, 892–906.

48. Ghoreschi, K.; Balato, A.; Enerbäck, C.; Sabat, R. (2021). Therapeutics targeting the IL-23 and IL-17 pathway in psoriasis. Lancet 397,754–766.
49. Soderstrom, C.; Berstein, G.; Zhang, W.; Valdez, H.; Fitz, L.; Kuhn, M.; Fraser, S. (2017) Ultra-sensitive measurement of IL-17A andIL-17F in psoriasis patient serum and skin. AAPS J. 19, 1218–1222.
50. Warren, R.B. (2023). DC-806, an oral IL-17A inhibitor: Proof-of-concept in adults with mild to moderate psoriasis. In Proceedings of theAAD Annual Meeting, New Orleans, LA, USA, 17–21 March 2023.
51. DICE Therapeutics. Unlocking the Potential of Oral Medicines. Available online: https://www.dicetherapeutics.com/pipeline.
52. Hawkes, J.E.; Yan, B.Y.; Chan, T.C.; Krueger, J.G. (2018). Discovery of the IL-23/IL-17 signaling pathway and the treatment of psoriasis. J.Immunol. 201, 1605–1613.
53. Singh, R.; Koppu, S.; Perche, P.O.; Feldman, S.R. (2021). The cytokine mediated molecular pathophysiology of psoriasis and its clinicalimplications. Int. J. Mol. Sci. 22, 12793.
54. Chan, T.C.; Hawkes, J.E.; Krueger, J.G. (2018). Interleukin 23 in the skin: Role in psoriasis pathogenesis and selective interleukin 23blockade as treatment. Ther. Adv. Chronic Dis. 9, 111–119.
55. Yang, K.; Oak, A.S.W.; Elewski, B.E. (2021). Use of IL-23 inhibitors for the treatment of plaque psoriasis and psoriatic arthritis: A comprehensive review. Am. J. Clin. Dermatol. 22, 173–192.
56. Fourie, A.; Cheng, X.; Chang, L.; Greving, C.; Patrick, A.; Knight, B.; Patch, R.; Bhandari, A.; Liu, D.; Huie, K. (2023) First-in-classoral peptide systemically targeting the IL-23 pathway. In Proceedings of the ISID Meeting, Tokyo, Japan.
57. Johnson & Johnson. Janssen Announces Positive Topline Results for JNJ-2113—A Novel, (2023). First and Only Oral IL-23 Receptor Antagonist Peptide in Development for Moderate-to-Severe Plaque Psoriasis.
58. Jang, D.-I.; Lee, A.-H.; Shin, H.-Y.; Song, H.-R.; Park, J.-H.; Kang, T.-B.; Lee, S.-R.; Yang, S.-H. (2021). The role of tumor necrosis factoralpha (TNF-a) in autoimmune disease and current TNF-a inhibitors in therapeutics. Int. J. Mol. Sci. 22, 2719.
59. Brenner, D.; Blaser, H.; Mak, T.W. (2015). Regulation of tumour necrosis factor signaling: Live or let die. Nat. Rev. Immunol. 15, 362–374.
60. 24. Black, R.A.; Rauch, C.T.; Kozlosky, C.J.; Peschon, J.J.; Slack, J.L.;Wolfson, M.F.; Castner, B.J.; Stocking, K.L.; Reddy, P.; Srinivasan, S. (1997). A metalloproteinase disintegrin that releases tumour-necrosis factor-alpha from cells. Nature 385, 729–733.
61. Vanamee, É.S.; Faustman, D.L. (2018). Structural principles of tumor necrosis factor superfamily signaling. Sci. Signal. 11, eaao4910.
62. Gough, P.; Myles, I.A. (2020). Tumor necrosis factor receptors: Pleiotropic signaling complexes and their differential effects. Front.Immunol. 11, 585880.
63. Chédotal, H.; Narayanan, D.; Povlsen, K.; Gotfredsen, C.H.; Brambilla, R.; Gajhede, M.; Bach, A.; Clausen, M.H. (2023). Small-molecule modulators of tumor necrosis factor signaling. Drug Discov. Today 28, 103575.
64. Zhang, N.;Wang, Z.; Zhao, Y. (2020). Selective inhibition of tumor necrosis factor receptor-1 (TNFR1) for the treatment of autoimmune diseases. Cytokine Growth Factor Rev. 55, 80–85.
65. Medler, J.; Wajant, H. (2019). Tumor necrosis factor receptor -2 (TNFR2): An overview of an emerging drug target. Expert Opin. Ther.Targets 23, 295–307.
66. Faustman, D.; Davis, M. (2010). TNF receptor 2 pathway: Drug target for autoimmune diseases. Nat. Rev. Drug Discov. 9, 482–493.
67. Ovcina-Kurtovic, N.; Kasumagic-Halilovic, E. (2022). Serum levels of tumor necrosis factor—alpha in patients with psoriasis. Mater.Sociomed. 34, 40–43.
68. Yost, J.; Gudjonsson, J.E. (2009). The role of TNF inhibitors in psoriasis therapy: New implications for associated comorbidities. F1000Med. Rep. 1, 30.
69. Campanati, A.; Paolinelli, M.; Diotallevi, F.; Martina, E.; Molinelli, E.; Offidani, A. (2019). Pharmacodynamics of TNF-a inhibitors for the treatment of psoriasis. Expert. Opin. Drug Metab. Toxicol. 15, 913–925.
70. Chima, M.; Lebwohl, M. (2018). TNF inhibitors for psoriasis. Semin. Cutan. Med. Surg. 2018, 37, 134–142.
71. Vugler, A.; O'Connell, J.; Nguyen, M.A.;Weitz, D.; Leeuw, T.; Hickford, E.; Verbitsky, A.; Ying, X.; Rehberg, M.; Carrington, B. (2022). An orally available small molecule that targets soluble TNF to deliver anti-TNF biologic-like efficacy in rheumatoid arthritis. Front. Pharmacol. 13, 1037983.
72. Fishbein, A.; Nguyen, M.A.; Chow, O.; Matos, T.; Dreis, C.; Hong, Z.; Poirel, M.; Gassenhuber, J.; Dufault, M.; Frank-Dietrich, W. (2023). The potential of an oral TNFinhibitor with TNFR1 specificity: Results of a phase 1b proof-of-mechanism trial in psoriasis. Arthritis Rheumatol. 75 (Suppl. 9).890