

The efficacy of apremilast in pemphigus: a systematic review of case reports

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Abstract

Pemphigus is a severe autoimmune blistering disorder that significantly affects patients' quality of life. While corticosteroids and immunosuppressive agents are commonly used, they have substantial side effects, highlighting the need for safer alternatives. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, has shown efficacy in treating other autoimmune diseases and may offer promise for pemphigus. This systematic review evaluated the clinical outcomes, safety, and potential role of apremilast in the treatment of pemphigus by synthesizing available case reports

and series. A literature search was conducted across multiple databases (PubMed, EMBASE, Cochrane, Web of Science, ScienceDirect, and Google Scholar) for case reports and series involving apremilast in pemphigus. Inclusion criteria were a confirmed pemphigus diagnosis and apremilast treatment. Five studies (four case reports and one case series) involving 7 patients were included. Apremilast led to significant clinical improvement in 4 patients, with reductions in disease activity, lesion severity, and symptom scores (Pemphigus Disease Area Index [PDAI], Autoimmune Bullous Skin Disorder Intensity Score [ABSIS], Visual Analog Scale [VAS], and Numerical Rating Score [NRS]). Increases in regulatory T cells and decreases in anti-desmoglein antibodies were observed. No serious adverse events were reported, although one study noted treatment failure, possibly due to short follow-up or concurrent infections. Apremilast appears to be a promising treatment for therapy-resistant or corticosteroid-intolerant pemphigus patients. Although the evidence is limited, it supports apremilast's efficacy and favorable safety profile. Further research with larger sample sizes and randomized controlled trials is necessary to confirm these findings.

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Introduction

Pemphigus is a severe, chronic autoimmune blistering disorder that significantly impacts patients' quality of life.^{1,2} Characterized by painful blisters and erosions on the skin and mucous membranes, it results from autoantibodies against desmogleins, critical for cell-cell adhesion in the epidermis.² The disease includes four main clinical types: pemphigus vulgaris (PV), pemphigus foliaceus (PF), paraneoplastic pemphigus, and IgA pemphigus (IGAP).³ Both PV and PF can cause substantial morbidity, with PV being more severe, often involving both skin and mucous membranes.^{4,5} Pemphigus has high mortality, primarily due to complications like infections, comorbidities, or treatment side effects, highlighting the need for effective treatments to reduce mortality and improve quality of life.^{6,7}

Managing pemphigus remains challenging due to the severe side effects of conventional therapies.⁸ The primary treatment for moderate-to-severe cases includes high-dose corticosteroids, often combined with immunosuppressives like azathioprine, mycophenolate mofetil, and rituximab.⁹ While these treatments control disease activity, they are linked to significant adverse effects, such as osteoporosis, hyperglycemia, and increased infection risk.¹⁰ Some patients poorly tolerate these agents, and certain individuals are contraindicated due to comorbidities.¹¹ Rituximab has become an important therapy for those resistant to other treatments, but it carries risks like infusion reactions and infection.^{12,13}

Given these limitations, there is a need for alternative treat-

ments, especially for therapy-resistant patients or those with contraindications to standard therapies. Apremilast, an oral phosphodiesterase 4 (PDE4) inhibitor, modulates inflammatory pathways and has shown efficacy in diseases like psoriasis and psoriatic arthritis.¹⁴ Its potential for pemphigus treatment has been explored in case reports.^{11,14-18} Apremilast is promising due to its relatively favorable safety profile, with fewer concerns about infections and systemic side effects compared to traditional therapies.¹⁹ However, evidence on its efficacy and safety in pemphigus is limited, mainly from case reports rather than large-scale randomized controlled trials (RCTs).^{11,15-18} To date, no RCTs have been conducted on apremilast for pemphigus. A comparison of apremilast and rituximab in pemphigus management was mentioned in Table 1.^{13,20-22} This systematic review aims to synthesize available case reports on apremilast in pemphigus treatment, evaluating clinical outcomes, safety, and its potential as an alternative or adjunctive therapy. Given the lack of RCTs and the need for safer treatments, this review will provide valuable insights into apremilast's role in pemphigus management and highlight the need for further research to confirm its place in treatment.

Materials and Methods

This systematic review was conducted following PRISMA (Preferred Reporting Items for Systematic Reviews and Meta-Analyses) guidelines.²³

Search strategy

A literature search was performed on September 2024 using multiple databases (PubMed, EMBASE, Cochrane, Web of Science, ScienceDirect, and Google Scholar) with key words such as “apremilast”, “phosphodiesterase 4 inhibitor”, “PDE-4 inhibitor”, “small-molecule” AND “pemphigus”, “blistering disorders”, “auto-immune bullous disease”, AND “regulatory T cells”, “T follicular regulatory (Tfr) cell”.

Inclusion and exclusion criteria

We included case reports or case series examining patients

diagnosed with pemphigus confirmed by clinical, histopathological, and immunofluorescence criteria who received apremilast. Studies involving animals or *in vitro* studies were excluded.

Screening and data extraction

After the literature search, the web application Rayyan was used to screen the titles and abstracts of the retrieved articles.²⁴ Two independent review authors screened the studies, resolving discrepancies through discussion or involving a third reviewer. Relevant studies were reviewed at the full-text stage, and reasons for excluding studies were documented (Figure 1). Data extraction was performed independently by two authors, with disagreements resolved through discussion or a third reviewer. Extracted data included study design, patient demographics (age, gender, comorbidities, disease severity), treatment details (previous treatments, dosage, frequency, follow-up), and reported outcomes, such as adverse effects, clinical responses evaluated by the Pemphigus Disease Area Index (PDAI), Numerical Rating Scale (NRS), Visual Analog Scale (VAS) or Autoimmune Bullous Skin Disorder Intensity Score (ABSIS), anti-desmoglein levels, corticosteroid tapering, and flow cytometry analysis of T cells. A summary table was created to compile this information (*Supplementary Table 1*).

The risk of bias and methodological quality were assessed using the tool proposed by Murad *et al.*²⁵

Results

The initial search retrieved 269 records after duplicates were removed. Five studies were eligible for full-text screening, all of which met the inclusion criteria (Figure 1).

Study characteristics

A total of five studies were included: four case reports and one case series, comprising 7 patients. Studies were published between 2020 and 2024 and were all written in English (*Supplementary Table 1*).^{11,15-18} The four case reports included female patients,^{11,15,17,18} while the case series included 2 female and 1 male participant.¹⁶ The studies were conducted in China,^{11,16,17} France,¹⁸ and Germany.¹⁵ Due to their design, the studies were

Table 1. Comparison of apremilast and rituximab in pemphigus management.

Feature	Apremilast	Rituximab
Mechanism of action	PDE4 inhibitor; modulates inflammatory pathways	Anti-CD20 monoclonal antibody; depletes B cells
Indication	Psoriasis, psoriatic arthritis, adults with oral ulcers associated with Behcet's disease, investigational for pemphigus	FDA-approved for moderate-to-severe pemphigus vulgaris Used also for treating NHL, CLL, autoimmune and inflammatory diseases, pediatric hematologic malignancies
Efficacy	Limited case reports, data; inconsistent findings, but most studies showed the efficacy of apremilast in alleviating the symptoms of pemphigus and some patients saw significant clinical improvement	High efficacy with long-term remission in pemphigus
Onset of action	Variable (weeks to months)	Typically within 4-12 weeks
Adverse events	No serious or unexpected adverse events	Infusion reactions, increased infection risk, prolonged B-cell depletion, reactivation of latent infections
Use in steroid-sparing	Potential steroid-sparing effect observed in case reports	Proven steroid-sparing therapy
Contraindications	Severe infections, active tuberculosis	Severe infections, hepatitis B history, immunocompromised patients, pregnancy
Cost	Moderate	High
Administration	Oral	Intravenous infusion

PDE4, phosphodiesterase-4; FDA, Food and Drug Administration; NHL, non-Hodgkin's lymphoma; CLL, chronic lymphocytic leukemia.

classified with low evidence levels: case reports as level V and case series as level IV.²⁶ All studies presented methodological issues.²⁵ Four case reports had a high risk of bias due to selective patient inclusion.^{11,15,17,18} One study by Zhang *et al.* (2024a) did not properly ascertain outcomes, lacking standardized treatment response evaluation methods and having a short follow-up period.¹⁶ Low bias was observed in other methodological areas, as detailed in Table 2.

Efficacy outcomes

All studies assessed the efficacy of apremilast for alleviating pemphigus symptoms using measures like PDAI, ABSIS, NRS, and VAS (*Supplementary Table 2*). Significant clinical improvement occurred in four of the seven cases (57%). Zhang *et al.* (2024b) reported a mild PF case that improved and stabilized after one month of apremilast (60 mg), without the need for corticosteroids or other immunosuppressives. No relapse occurred during the nine-month follow-up.¹¹ In Zhou *et al.*, a patient with moderate-to-severe refractory IGAP showed complete resolution of eruptions and pruritus after 12 weeks of apremilast (60 mg), with no recurrence during a six-month follow-up.¹⁷ Meier *et al.* documented a severe refractory PV case where apremilast (60 mg) improved the ABSIS score from 38 to 0, and allowed prednisone tapering from 20 mg to 5 mg without symptom worsening.¹⁵ Delvaux *et al.* showed that apremilast (60 mg) reduced pain and lesions in a PV patient with severe mucosal involvement, with relapse after discontinuation and improvement upon reintroduction.¹⁸ Zhang *et al.* (2024a) reported no response to apremilast (60 mg) in 3 patients with moderate-to-severe PV or PF and comorbid infections (sepsis, cellulitis, syphilis), who failed to improve after two months of treatment.¹⁶

Three studies analyzed anti-Dsg1 and anti-Dsg3 antibodies and T cell subsets (*Supplementary Table 2*). In Zhang *et al.* (2024b), anti-Dsg1 antibodies decreased from 28.18 to 1.48 kU/L after three months of apremilast treatment, with an increase in Treg and iTreg cells.¹¹ Meier *et al.* reported a decrease in anti-Dsg1 antibodies from 200 to 139 kU/L and anti-Dsg3 antibodies from 117 to 8 U/mL, along with increased Treg and Tfr cells.¹⁵ Delvaux *et al.* showed a reduction in anti-Dsg3 antibodies from 129 to 14 U/mL.¹⁸

Zhang *et al.* (2024a), Zhang *et al.* (2024b), and Zhou *et al.* reported no adverse events associated with apremilast.^{11,16,17} Delvaux *et al.* and Meier *et al.* did not specify whether adverse events occurred.^{15,18}

Discussion

This systematic review assessed the clinical outcomes, safety, and potential role of apremilast in treating pemphigus, synthesizing findings from four case reports and one case series.^{11,15-18} The results suggest that apremilast shows promise as an alternative or adjunctive treatment, particularly for therapy-resistant patients or those with contraindications to standard immunosuppressives. While the evidence is limited, notable improvements in clinical symptoms and biomarkers were observed in several cases, with a relatively favorable safety profile.

The studies in this review showed varying degrees of efficacy with apremilast treatment. Four of seven patients experienced significant improvement, including reductions in lesion severity, pain, pruritus, and better scores on the PDAI, ABSIS, NRS and VAS.^{11,15,17,18} These results align with apremilast's known mechanism as a PDE4 inhibitor that modulates inflammatory pathways, benefiting other autoimmune conditions like psoriasis and psoriatic arthritis.^{27,28} For example, in a mild PF case with contraindication to corticosteroids or immunosuppressive agents due to diabetes and atrophic gastritis, apremilast led to complete resolution without other medications.¹¹ Similarly, a severe refractory PV patient saw substantial improvement in disease activity and corticosteroid dosage with no symptom worsening.¹⁵ These outcomes suggest apremilast may be a valuable option, especially when traditional therapies are ineffective or poorly tolerated.

Apremilast also showed promising results in patients with other forms of pemphigus, such as recalcitrant IGAP. One study reported a patient with moderate-to-severe IGAP who achieved complete resolution of eruptions and pruritus after 12 weeks of apremilast treatment, with no relapse during a six-month follow-up.¹⁷ Unlike other bullous dermatoses, IGAP often does not respond well to systemic corticosteroids alone, despite being the primary treatment, making apremilast a potentially valuable option for more refractory cases.^{29,30} However, as Zhou *et al.* noted, further research is needed to understand apremilast's mechanism in IGAP and evaluate its potential as a standard treatment for this pemphigus subtype.¹⁷

Some studies combined apremilast with other therapies, such as steroids and rituximab, complicating the interpretation of its sole efficacy.^{15,16,18} For instance, in one study, apremilast was used in combination with prednisone and mycophenolate mofetil. This likely contributed to the observed clinical improvements, even though the patient had previously been unresponsive to rituximab combined with the same drugs. The systemic steroid dose was

Table 2. Methodological quality assessment of the included studies.

Quality assessment questions	Zhang <i>et al.</i> , China (2024a) ¹¹	Zhou <i>et al.</i> , China (2023) ¹⁷	Meier <i>et al.</i> , Germany (2020) ¹⁵ ,	Delvaux <i>et al.</i> , France (2024) ¹⁸	Zhang <i>et al.</i> , China (2024b) ¹⁶
Does the patient(s) represent(s) the whole experience of the center?	No	No	No	No	Yes
Was the exposure adequately ascertained?	Yes	Yes	Yes	Yes	Yes
Was the outcome adequately ascertained?	Yes	Yes	Yes	Yes	No
Were other alternative causes that may explain the observation ruled out?	Yes	Yes	Yes	Yes	Yes
Was there a challenge/rechallenge phenomenon?	N/A	N/A	N/A	N/A	N/A
Was there a dose-response effect?	N/A	N/A	N/A	N/A	N/A
Was follow-up long enough for outcomes to occur?	Yes	Yes	Yes	Yes	No
Is the case(s) described with sufficient details to allow other investigators to replicate the research or to allow practitioners to make inferences related to their own practice?	Yes	Yes	Yes	Yes	No

successfully reduced to 5 mg, despite previous unsuccessful attempts to lower it below 20-30 mg using other treatments.¹⁵ Another study showed significant improvement in PV with apremilast alone, followed by complete remission two months after switching to rituximab and prednisone.¹⁸ The rapid relapse after discontinuation and subsequent improvement upon reintroduction support apremilast's efficacy.¹⁸ The potential of apremilast as an add-on therapy warrants further study, as it may provide a safe and effective adjunct to traditional treatments, as seen in various dermatological diseases such as psoriasis.^{31,32}

In addition to clinical outcomes, this review examined changes in biomarker levels and immune cell subsets. Three studies found that apremilast treatment was associated with a decrease in anti-Dsg1 and Dsg3 antibodies, key markers of pemphigus activity.^{11,15,18,32} Furthermore, an increase in Tregs and iTregs was observed, suggesting that apremilast may help restore immune tolerance.^{11,15} By inhibiting PDE4, apremilast promotes cyclic adenosine monophosphate (cAMP) accumulation and protein kinase A (PKA) activation, leading to decreased expression of pro-inflammatory mediators like interleukin (IL)-17 and interferon (IFN)- γ , and an increase in Tregs and regulatory IL-10-producing B cells.^{33,34} Meier *et al.* showed consistent increases in Treg and Tfh cells, with decreased autoantibody levels, suggesting that the expansion of Treg/Tfh cells may inhibit T follicular helper (Tfh) and B cell activity, thereby reducing the autoimmune response in pemphigus.¹⁵ These findings are notable, as Treg expansion is linked to the suppression of autoimmune responses in other diseases, supporting the idea that apremilast may exert its therapeutic effects through immune modulation.^{33,35}

While most cases showed apremilast efficacy, not all patients responded.^{11,15-18} One study found that 3 patients with moderate-to-severe PV or PF did not improve after two months of treatment.¹⁶ The authors suggested a slower regulatory effect and short follow-up as potential causes for the lack of efficacy.¹⁶ These patients also had infections like sepsis, cellulitis, and syphilis, which may have contributed to treatment failure and highlight the need to consider comorbidities, especially infections, when prescribing apremilast.¹⁶ Although not contraindicated for psoriasis, apremilast may need caution in immunocompromised or infected patients.^{16,36} Two other studies supported apremilast's efficacy despite comorbidities like diabetes, hypertension, and dyslipidemia.^{11,18} In psoriasis, apremilast has shown better efficacy in diabetic patients compared to non-diabetic patients and improved biomarkers linked to cardiometabolic disease.^{37,38}

Apremilast's innovative mechanism of action, which does not induce immunosuppression like steroids or rituximab, makes it an attractive option in terms of safety.³⁹⁻⁴¹ Furthermore, its good tolerance and lack of severe side effects observed in most cases make it an appealing choice in the management of pemphigus.^{11,16,17} As such, apremilast could be considered a valuable alternative to steroids, either as a monotherapy or in combination with other agents like rituximab, particularly in cases of steroid resistance or intolerance. Importantly, a pooled analysis of 15 RCTs in other dermatologic diseases showed that the most common side effects associated with apremilast were mild gastrointestinal events that usually resolved within 30 days, while the incidence of serious adverse events was similar to that of placebo despite long-term exposure.¹⁹

However, there are significant limitations to consider. The small sample size, varying disease severity, and lack of uniform treatment protocols across the studies limit the possibility of drawing definitive conclusions.⁴² The inherent bias of case series and case reports, along with issues like inadequate outcome measurement and insufficient follow-up, also affect the reliability of the

findings.^{16,43} Additionally, although some studies showed encouraging results, the lack of response in others suggests that apremilast's effectiveness may vary across patient populations.^{11,15-18} Further research, including well-designed RCTs with larger sample sizes, is needed to confirm these findings and provide more robust evidence on apremilast's role in pemphigus management.⁴⁴ Future studies should also assess the long-term safety and efficacy of apremilast, including its potential to reduce relapse rates and minimize reliance on long-term corticosteroids and other immunosuppressive therapies.

Conclusions

In conclusion, apremilast holds promise as an efficacious and safe treatment option for pemphigus, particularly in patients with therapy-resistant or corticosteroid-intolerant forms of the disease. The current evidence is limited and requires further validation through larger studies.

References

- Schmitt T, Waschke J. Autoantibody-Specific Signalling in Pemphigus. *Front Med* 2021;8.
- Polat AK, Mülayim MK, Gür TF, et al. Evaluation of the Quality of Life and the Demographic and Clinical Characteristics of Patients With Pemphigus With Oral Mucosal Involvement: A Multicenter Observational Study. *Dermatol Pract Concept* 2024;14:e2024099.
- Costan VV, Popa C, Hâncu MF, et al. Comprehensive review on the pathophysiology, clinical variants and management of pemphigus (Review). *Exp Ther Med* 2021;22:1-13.
- Miyachi H, Konishi T, Hashimoto Y, et al. Clinical course and outcomes of pemphigus vulgaris and foliaceus: A retrospective study using a nationwide database in Japan. *J Dermatol* 2023;50:212-21.
- Brodzsky V, Tamási B, Hajdu K, et al. Disease burden of patients with pemphigus from a societal perspective. *Expert Rev Pharmacoecon Outcomes Res* 2021;21:77-86.
- Kridin K, Schmidt E. Epidemiology of Pemphigus. *JID Innov* 2021;1:100004.
- Hasanaj A, Zaki F, Harman KE, et al. Cause-specific mortality in people with bullous pemphigoid and pemphigus vulgaris: a systematic review and meta-analysis. *Br J Dermatol* 2022;186:359-61.
- Kridin K, Mruwat N, Ludwig RJ. Association of Rituximab With Risk of Long-term Cardiovascular and Metabolic Outcomes in Patients With Pemphigus. *JAMA Dermatol* 2023;159:56-61.
- Zhao W, Wang J, Zhu H, Pan M. Comparison of Guidelines for Management of Pemphigus: a Review of Systemic Corticosteroids, Rituximab, and Other Immunosuppressive Therapies. *Clin Rev Allergy Immunol* 2021;61:351-62.
- Sparling K, Butler DC. Oral Corticosteroids for Skin Disease in the Older Population: Minimizing Potential Adverse Effects. *Drugs Aging* 2024;41:795-808.
- Zhang Q, Yu L, Wan L, et al. Case report: Managing pemphigus foliaceus using apremilast without systemic glucocorticosteroids or immunosuppressive agents. *Front Immunol* 2024;15:1408116.
- Dadkhahfar S. Chapter 15 - Adverse events following rituximab therapy in pemphigus patients. In: Cho WCS, editor.

- Resistance to Anti-Cd20 Antibodies and Approaches for their Reversal. Academic Press 2024;2:335-45.
13. Lee MS, Yeh YC, Tu YK, Chan TC. Network meta-analysis–based comparison of first-line steroid-sparing adjuvants in the treatment of pemphigus vulgaris and pemphigus foliaceus. *J Am Acad Dermatol* 2021;85:176-86.
 14. Sigmund AM, Winkler M, Engelmayr S, et al. Apremilast prevents blistering in human epidermis and stabilizes keratinocyte adhesion in pemphigus. *Nat Commun* 2023;14:116.
 15. Meier K, Holstein J, Solimani F, et al. Case Report: Apremilast for Therapy-Resistant Pemphigus Vulgaris. *Front Immunol* 2020;11:588315.
 16. Zhang Q, Yu L, Wan L, et al. Ineffectiveness of apremilast in moderate-to-severe pemphigus: A case series of three patients. *Australas J Dermatol* 2024;65:e121-2.
 17. Zhou Y, Xiao Y, Wang Y, Li W. Refractory atypical IgA pemphigus successfully treated with apremilast. *J Dermatol* 2024;51:e86-7.
 18. Delvaux C, Bohelay G, Sitbon IY, et al. Activity of apremilast in a patient with severe pemphigus vulgaris: case report. *Front Immunol* 2024;15:1404185.
 19. Mease PJ, Hatemi G, Paris M, et al. Apremilast Long-Term Safety Up to 5 Years from 15 Pooled Randomized, Placebo-Controlled Studies of Psoriasis, Psoriatic Arthritis, and Behçet's Syndrome. *Am J Clin Dermatol* 2023;24:809-20.
 20. Joly P, Maho-Vaillant M, Prost-Squarcioni C, et al. First-line rituximab combined with short-term prednisone versus prednisone alone for the treatment of pemphigus (Ritux 3): a prospective, multicentre, parallel-group, open-label randomised trial. *Lancet* 2017;389:2031-40.
 21. DrugBank. DB05676: Uses, interactions, mechanism of action [Internet]. DrugBank Online; [cited 2025 Apr 3]. Available from: <https://go.drugbank.com/drugs/DB05676>
 22. DrugBank. Rituximab: Uses, interactions, mechanism of action [Internet]. DrugBank Online; [cited 2025 Apr 3]. Available from: <https://go.drugbank.com/drugs/DB00073>
 23. Liberati A, Altman DG, Tetzlaff J, et al. The PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate health care interventions: explanation and elaboration. *J Clin Epidemiol* 2009;62:e1-34.
 24. Ouzzani M, Hammady H, Fedorowicz Z, Elmagarmid A. Rayyan—a web and mobile app for systematic reviews. *Syst Rev* 2016;5:210.
 25. Murad MH, Sultan S, Haffar S, Bazerbachi F. Methodological quality and synthesis of case series and case reports. *BMJ Evid Based Med* 2018;23:60-3.
 26. Burns PB, Rohrich RJ, Chung KC. The levels of evidence and their role in evidence-based medicine. *Plast Reconstr Surg* 2011;128:305-10.
 27. Liu Y, Li Y, Du H. Efficacy of apremilast for psoriasis: a meta-analysis of randomized controlled studies. *Postepy Dermatol Alergol* 2023;40:165-70.
 28. Alharthy RF, Alharthy JM, Bawazir RO, et al. The Efficacy and Safety of Apremilast in the Management of Psoriatic Arthritis: A Systematic Review and Meta-Analysis. *Cureus* 16:e55773.
 29. Kridin K, Patel PM, Jones VA, et al. IgA pemphigus: A systematic review. *J Am Acad Dermatol* 2020;82:1386-92.
 30. Cho YT, Fu KT, Chen KL, et al. Clinical, Histopathologic, and Immunohistochemical Features of Patients with IgG/IgA Pemphigus. *Biomedicines* 2022;10:1197.
 31. Gyldenløve M, Alinaghi F, Zachariae C, et al. Combination Therapy with Apremilast and Biologics for Psoriasis: A Systematic Review. *Am J Clin Dermatol* 2022;23:605-13.
 32. Hassanandani T, Panda M, Jena AK, Raj C. Methotrexate monotherapy versus methotrexate and apremilast combination therapy in the treatment of palmoplantar psoriasis: A prospective, randomised, assessor-blinded, comparative study. *Indian J Dermatol Venereol Leprol* 2023;89:213-20.
 33. Uchida H, Kamata M, Shimizu T, et al. Apremilast downregulates interleukin-17 production and induces splenic regulatory B cells and regulatory T cells in imiquimod-induced psoriasisiform dermatitis. *J Dermatol Sci* 2021;104:55-62.
 34. Medvedeva IV, Stokes ME, Eisinger D, et al. Large-scale Analyses of Disease Biomarkers and Apremilast Pharmacodynamic Effects. *Sci Rep* 2020;10:605.
 35. Chen Y, Li Z, Li H, et al. Apremilast Regulates the Tef/Treg Balance to Ameliorate Uveitis via PI3K/AKT/FoxO1 Signaling Pathway. *Front Immunol* 2020;11:581673.
 36. Megna M, Lauletta G, Tommasino N, et al. Management of Psoriasis Patients with Serious Infectious Diseases. *Adv Ther* 2024;41:2099-111.
 37. Mazzilli S, Lanna C, Chiaramonte C, et al. Real-life experience of apremilast in psoriasis and arthritis psoriatic patients: Preliminary results on metabolic biomarkers. *J Dermatol* 2020;47:578-82.
 38. Gelfand JM, Shin DB, Armstrong AW, et al. Association of Apremilast With Vascular Inflammation and Cardiometabolic Function in Patients With Psoriasis: The VIP-A Phase 4, Open-label, Nonrandomized Clinical Trial. *JAMA Dermatol* 2022;158:1394-403.
 39. Nassim D, Alajmi A, Jfri A, Pehr K. Apremilast in dermatology: A review of literature. *Dermatol Ther* 2020;33:e14261.
 40. Varley CD, Winthrop KL. Long-Term Safety of Rituximab (Risks of Viral and Opportunistic Infections). *Curr Rheumatol Rep* 2021;23:74.
 41. Meneghini M, Bestard O, Grinyo JM. Immunosuppressive drugs modes of action. *Best Pract Res Clin Gastroenterol* 2021;54-55:101757.
 42. Dehkordi AH, Mazaheri E, Ibrahim HA, et al. How to Write a Systematic Review: A Narrative Review. *Int J Prev Med* 2021;12:27.
 43. Roukis TS. Case reports/series & bias considerations. *Foot Ankle Surg Tech Rep Cases* [Internet] 2021[cited 2024 Nov 29];1. Available from: [https://www.fastracjournal.org/article/S2667-3967\(21\)00057-4/fulltext](https://www.fastracjournal.org/article/S2667-3967(21)00057-4/fulltext)
 44. Zabor EC, Kaizer AM, Hobbs BP. Randomized Controlled Trials. *Chest* 2020;158:S79-87.

Online Supplementary Material:

Supplementary Table 1. Baseline characteristics of the included cases.

Supplementary Table 2. Treatment characteristics and outcomes in the included studies.