Apremilast Coadministered with Secukinumab for Safe and Effective Control of Psoriasis with Resultant Reduction of Maintenance Dose of the Biologic

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Abstract
Psoriasis is a chronic immune-mediated inflammatory condition, affecting 2–3% of the population. In recent years, advent of biologics, including secukinumab, have been a major advancement in the management of difficult-to-treat plaque psoriasis. However, high cost of biologics is often a deterrent, especially for Indian socioeconomic condition. Apremilast is an oral phosphodiesterase 4 inhibitor that is safe for use along with many other systemic therapies of psoriasis, including biologics. We report two cases of psoriasis on secukinumab therapy for long duration with good response to therapy. Later, addition of apremilast, allowed halving the dose of secukinumab with maintenance of improvement.

Key Words: Apremilast, psoriasis, secukinumab

Introduction
Psoriasis is a chronic immune-mediated inflammatory condition, affecting 2–3% of the population. In recent years, advent of biologics, including secukinumab, has been a major advancement in the management of difficult-to-treat moderate-to-severe plaque psoriasis. However, high cost of biologics is often a deterrent, especially for Indian socioeconomic condition, for using them in long-term maintenance. Apremilast is an oral phosphodiesterase 4 (PDE4) inhibitor that is safe to use along with many other systemic therapies of psoriasis, including biologics like TNF-α inhibitors and ustekinumab.\(^1\) However, its safety and efficacy when coadministered with IL17 inhibitors, like secukinumab, is largely unknown.

Here, we report two patients with history of plaque-type psoriasis recalcitrant to topical, oral, and systemic medications who attained and maintained near-complete remission after therapy with a combination of secukinumab and apremilast.

Case History
Case 1
A 23-year-old man with 3 years history of plaque-type psoriasis presented to clinic after failing several therapies, including topical therapy (Class I topical steroids included), methotrexate, and cyclosporine. At the time of presentation, the patient was on secukinumab (300 mg every 4 weeks) therapy for 6 months. At the time of initiation of secukinumab therapy, his PASI was 38, which was reduced to 5 at 7\(^{th}\) month. But the patient noted steady recurrence of disease during the seventh month of secukinumab therapy. Physical examination revealed scattered psoriatic plaques on the patient’s chest, abdomen, back, and all four extremities [Figure 1]. Apremilast (uptitrated to 30 mg twice per day) was added to his secukinumab therapy (at the standard therapeutic dose). One month later, secukinumab dose was reduced to 150 mg every 4 weeks...
and apremilast continued at standard therapeutic dose. Four months since the combined use of apremilast and secukinumab therapy, the patient had noted significant improvement and was almost clear of psoriasis. PASI also reduced to 1.2 at 5th month after starting apremilast with continuation of secukinumab at reduced dosage. The patient did not report any side effect like, nausea, diarrhea, headache, or infection. Laboratory workup was also within normal limits.

**Case 2**

We report another patient, a 32-year-old male with 6 years history of severe plaque psoriasis who achieved near-complete clinical clearance on a combination of apremilast and secukinumab. The patient did not improved significantly to topicals, PUVA, and systemic treatment including methotrexate, cyclosporine and etanercept. Although disease improvement was achieved on cyclosporine initially with 3.5 mg/kg/day dose, response was lost after some time and even PASI increased to 42 from 28. At this point, treatment with secukinumab 300 mg every month was initiated and the patient responded well to secukinumab therapy in 5 months. Marked improvement was noted in terms of PASI (from 42 to 7). But the patient was not willing to continue secukinumab due to the cost factor. Hence, dose of secukinumab was halved and apremilast was added and uptitrated to 30 mg twice daily. After 4 months of combination therapy, patient had few scattered erythematous scaly plaques on his legs and trunk [Figure 2]. Patient reported mild diarrhea, which subsided on its own. Laboratory workup was within normal limits.

**Discussion**

Although multiple, highly efficacious treatments are available for moderate-to-severe psoriasis, patients with refractory disease or contraindications to different treatment modalities present therapeutic challenges without a consensus algorithm to guide drug selections. Apremilast is an oral PDE4 inhibitor that offers a favorable tolerability profile, ease of administration, and is economically feasible as compared to biologic agents. Efficacy of apremilast for plaque psoriasis is well demonstrated in two, 16-week, phase III ESTEEM studies; patients who had no prior oral or biologic agents showed significantly better response rates. Apremilast appears to have lower efficacy than some biologic agents, which achieve a PASI-75 in approximately 70% of patients after 12–16 weeks of therapy. However, its ease of administration as an oral agent coupled with safety profile makes it an attractive option for psoriasis management.

Combination therapy of TNF blockers and methotrexate can provide greater disease control compared to biologic monotherapy alone and is a treatment strategy currently implemented in up to 30% of patients on TNF-α inhibitors. Combination therapy with apremilast has been reported in case reports with adalimumab and secukinumab. Additionally, its combination is also well documented with other antipsoriatic agents like methotrexate, acitretin, cyclosporine, phototherapy, and other biologic therapy in a retrospective analysis of 81 patients. Even recently published guideline recommends combined use of apremilast with biological agents and conventional therapies like methotrexate, cyclosporine, etc.
We hereby report two cases of apremilast with secukinumab as combination therapy for the management of plaque psoriasis, which led to significant disease improvement without any adverse effect.

In both the cases, patients achieved improvement with secukinumab, but on addition of apremilast, not only the dose of secukinumab but entire cost of therapy was also reduced. However, it warrants further investigation to determine the safety of using these agents together.

Declaration of patient consent
The authors certify that they have obtained all appropriate patient consent forms. In the form the patient(s) has/have given his/her/their consent for his/her/their images and other clinical information to be reported in the journal. The patients understand that their names and initials will not be published and due efforts will be made to conceal their identity, but anonymity cannot be guaranteed.

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Conflicts of interest
There are no conflicts of interest.

References
1. Nast A, Spuls PI, van der Kraaij G, Gisondi P, Paul C, Ormerod AD, et al. European S3-Guideline on the systemic treatment of psoriasis vulgaris - Update Apremilast and Secukinumab-EDF in cooperation with EADV and IPC. J Eur Acad Dermatol Venereol 2017;31:1951-63.
2. Paul C, Cather J, Gooderham M, Poulin Y, Mrowietz U, Ferrandiz C, et al. Efficacy and safety of apremilast, an oral phosphodiesterase 4 inhibitor, in patients with moderate to severe plaque psoriasis over 52 weeks: A phase III, randomized, controlled trial (ESTEEM 2). Br J Dermatol 2015;173:1387-99.
3. Papp K, Reich K, Leonardi CL, Kircik L, Chimienti S, Langley RG, et al. 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 2015;73:37-49.
4. Kim IH, West CE, Kwatra SG, Feldman SR, O'Neill JL. Comparative efficacy of biologics in psoriasis: A review. Am J Clin Dermatol 2012;13:365-74.
5. Gottlieb AB, Matheson RT, Lowe N, Krueger GG, Kang S, Goffe BS, et al. A randomized trial of etanercept as monotherapy for psoriasis. Arch Dermatol 2003;139:1627-32.
6. Menter A, Tyring SK, Gordon K, Kimball AB, Leonardi CL, Langley RG, et al. Adalimumab therapy for moderate to severe psoriasis: A randomized, controlled phase III trial. J Am Acad Dermatol 2008;58:106-15.
7. Leonardi CL, Kimball AB, Papp KA, Yeilding N, Guzzo C, Wang Y, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 76-week results from a randomized, double blind, placebo-controlled trial (PHOENIX 1). Lancet 2008;371:1665-74.
8. Papp KA, Langley RG, Lebwohl M, Krueger GG, Szapary P, Yeilding N, et al. Efficacy and safety of ustekinumab, a human interleukin-12/23 monoclonal antibody, in patients with psoriasis: 52-week results from a randomized, double blind, placebo-controlled trial (PHOENIX 2). Lancet 2008;371:1675-84.
9. Zachariae C, Mork NJ, Reunala T, Lorentzen H, Falk E, Karvonen SL, et al. The combination of etanercept and methotrexate increases the effectiveness of treatment in active psoriasis despite inadequate effect of methotrexate therapy. Acta Derm Venereol 2008;88:495-501.
10. Gottlieb AB, Langley RG, Strober BE, Papp KA, Klekotka P, Creamer K, et al. A randomized, double-blind, placebo-controlled study to evaluate the addition of methotrexate to etanercept in patients with moderate to severe plaque psoriasis. Br J Dermatol 2012;167:649-57.
11. Warren RB, Brown BC, Carmichael AJ, Griffiths CE. Long-term control of recalcitrant psoriasis with combination infliximab and methotrexate. Clin Exp Dermatol 2009;34:415-6.
12. Driessen RJ, Boezeman JB, van de Kerkhof PC, de Jong EM. Three-year registry data on biological treatment for psoriasis: The influence of patient characteristics on treatment outcome. Br J Dermatol 2009;160:670-5.
13. Danesh MJ, Beroukhim K, Nguyen C, Levin E, Koo J. Apremilast and adalimumab: A novel combination therapy for recalcitrant psoriasis. Dermatol Online J 2015;21.
14. Rothstein BE, McQuade B, Greb JE, Goldminz AM, Gottlieb AB. Apremilast and secukinumab combined therapy in a patient with recalcitrant plaque psoriasis. J Drugs Dermatol 2016;15:648-9.
15. Abu Hilal M, Walsh S, Shear N. Use of apremilast in combination with other therapies for treatment of chronic plaque psoriasis: A retrospective study. J Cutan Med Surg 2016;20:313-6.