Review of apremilast combination therapies in the treatment of moderate-to-severe psoriasis

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Background

- Psoriasis is a chronic inflammatory skin disease. Moderate-to-severe psoriasis with ineffective results from monotherapy with topicals, oral agents, phototherapy, and biologics is generally followed by combination therapy.
- There are various combination therapies but combination therapy with apremilast has been less extensively studied.
- Apremilast is an FDA-approved oral phosphodiesterase-4 inhibitor for the treatment of moderate-to-severe plaque psoriasis in patients who are eligible for phototherapy or systemic therapy. Recommended dosage is up-titration to 30 mg twice daily.

Objective

- Identify and classify scientific literature reporting on apremilast in combination with any topical, oral agent, biologic, and/or phototherapy in treating moderate-to-severe psoriasis including psoriasis refractory to biologic monotherapy and traditional therapy (e.g., phototherapy and topicals).
- Critically evaluate and analyze clinical outcome data from included articles regarding treatment with apremilast combination therapy for moderate-to-severe psoriasis.

Methods

- An electronic literature search was performed by one reviewer using the PubMed database on April 7, 2020 with the following search terms (apremilast AND psoriasis) AND (topical OR oral agents OR biologics OR combined therapy OR combination therapy) during the years 2015 - 2019.
- Articles were excluded if pathology did not include psoriasis, treatment did not include concurrent combination therapy with apremilast, information on combination therapy agents was unavailable, or were review papers.

Results

- The literature search yielded 262 original articles and after removal of irrelevant articles a total of 17 articles were included: 1 randomized controlled trial, 2 nonrandomized interventional studies, 5 retrospective chart reviews, and 9 case reports.
- Included articles evaluated one or more therapies combined with apremilast namely biologic(n=11), topical(n=7), other oral agent(n=6), and phototherapy(n=5).
- Significance was found in 3 studies ($P < 0.05$) providing strong evidence that apremilast offers benefit when added to existing therapy (i.e., DMARDs and oral corticosteroids, topical steroids, and biologics over a treatment period of 16, 16, and 24 weeks respectively).

Results continued

TABLE 1.

Studies (n= 8)					
Study	**Study Design**	**Treatment (# of patients)**	**Time for Therapeutic Response**	**Results**	**Safety**
AbuHilal et al.	Retrospective Chart Review	Biologic + apremilast, Oral agent + apremilast, Phototherapy + apremilast (n= 67)	12 weeks	81% achieved PASI-75, largest difference in PASI-75 was between NB-UVB/apremilast (89%) and acitretin/apremilast (60%)	Diarrhea (25%), nausea (24%), weight loss (15%), headache, rash, URI (3% each) Discontinuation due to GI AE (n=9)
Aljaser et al.	Nonrandomized Interventional Study	Topical + apremilast (n=20)	16 weeks	40% achieved PASI-50 and 30% achieved PASI-75. Mean BSAxPGA was reduced at week 16 (P=0.006)*. Reduced pruritus* and improved DLQI*	Heartburn, diarrhea, nausea, abdominal pain, stomach cramps Discontinuation (n=1)
Bagel et al.	Nonrandomized Interventional Study	Phototherapy + apremilast (n=29)	12 weeks	73% achieved PASI-75 and 45% achieved PASI-90. Improved DLQI, VAS, and PGA from baseline	First-degree burn (38%), second-degree burn (n=1), fever, headache, itching (10.3% each) Discontinuation due to AEs (n=3) Lost to follow up (n=4)
Edwards et al.	Randomized Controlled Trial	Oral agent + apremilast +/- topicals (n=336)	52 weeks	41% achieved PASI-50 at week 16 (P=0.0098)*. There was sustained clinical improvement through week 52.	Diarrhea, nausea, headache, URI, nasopharyngitis, vomiting (≥5% each), worsening of psoriatic arthritis, weight loss, Discontinuation due to GI AE (<2%) Lost to follow up, withdrawal, noncompliance, and other (n= 12)
Ighani et al.	Retrospective Chart Review	Biologic + apremilast, Oral agent + apremilast, or Phototherapy + apremilast +/- topicals (n=89)	16 weeks	37.1% achieved PASI-75 or PGA 0/1	Headache, diarrhea, nausea, weight loss
Ighani et al.	Retrospective Chart Review	Biologic + apremilast, Oral agent + apremilast, or Phototherapy + apremilast +/- topicals (n=27)	52 weeks	Apremilast CT and monotherapy similarly maintained therapeutic response through week 52	Headache (n=2), diarrhea, increased bowel movements, papules on nose (n=1 each), concurrent chest pain/palpitations/ dyspnea/feeling unbalanced (n=1)
Metyas et al.	Retrospective Chart Review	Biologic + apremilast (n=22)	4-52 weeks	Patients reported 50% improvement of rash and pain compared to biologics alone	Nausea, diarrhea, stomachache, weight loss Discontinuation (n=1)
Takamura et al.	Retrospective Chart Review	Biologic + apremilast (n=14)	24 weeks	50% achieved PASI-50 and 29% achieved PASI-75. Mean PASI was reduced at 24 weeks (P<0.05)*	Diarrhea (n=5), weight loss (n=2), nausea (n=1)

Abbreviations: CT: combination therapy, BSA: Body Surface Area, PASI: Psoriasis Area Severity Index score, DLQI: Dermatology Life Quality Index, VAS: Visual Analog Scale for pain and itch, PGA: Physician Global Assessment, AE: adverse event, GI: gastrointestinal *indicates that significance was found

Conclusion

- A larger number of studies (n=15) found apremilast combination therapy to have better skin clearance capability versus existing monotherapy compared to studies that did not (n=2).

Discussion

- Apremilast/biologic combination therapy can provide improved skin clearance in patients with biologic fatigue.

Discussion continued

- A study limitation is majority of results were case reports which lack statistical power for making broad conclusions about treatment outcomes.

Disclosure

Dr. Wu is or has been an investigator, consultant, or speaker for AbbVie, Almirall, Amgen, Arcutis, Boehringer Ingelheim, Bristol-Myers Squibb, Celgene, Dermavant, Dermira, Dr. Reddy's Laboratories, Eli Lilly, Janssen, LEO Pharma, Novartis, Regeneron, Sanofi Genzyme, Sun Pharmaceutical, UCB, Valeant Pharmaceuticals North America LLC. Dr. Liao has been funded in part by grants from the National Institutes of Health (U01AI119125) and has served as a research investigator for Abbvie, Amgen, Janssen, Novartis, Pfizer, Regeneron, Sanofi, and TRex Bio.