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Apremilast in the Treatment of Psoriasis and Psoriatic Arthritis

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ABSTRACT

Phosphodiesterase 4 (PDE4) is a key enzyme in the regulation of immune responses of inflammatory diseases through degradation of the second messenger, cyclic adenosine 3',5'-monophosphate (cAMP). Apremilast, a selective PDE4 inhibitor, has been shown to reduce the production of pro-inflammatory cytokines by increasing intracellular levels of cAMP and promoting the production of anti-inflammatory cytokines. The efficacy and safety of apremilast in the treatment of psoriasis and psoriatic arthritis has been demonstrated in phase 2 and 3 studies and will be reviewed here. Across all studies, treatment was generally well-tolerated with some mild gastrointestinal complaints that occurred early and resolved over time, resulting in few drop-outs. Meaningful changes in dactylitis and enthesitis were also observed. Routine monitoring is not required given the absence of drug associated physiologic, biochemical, and haematological changes. Apremilast proves to be a new promising systemic therapy for treating psoriatic disease.

Key words: psoriasis, chronic plaque psoriasis, apremilast, PDE4 inhibitors, psoriatic arthritis, immunology, inflammation

Introduction

Psoriasis is a disease complex involving skin, joints, and possibly the bowel.[1] Each manifestation of the psoriasis disease complex is expressed through an inflammatory, immune-mediated process. This has been described in the skin,[2] joints[3] and bowel[4]. Therefore, interference in the immunological pathways common to psoriasis and psoriatic arthritis (PsA) could demonstrate clinical improvement of both. Recent clinical studies have shown precise blockade of phosphodiesterase 4 (PDE4) to be effective in the treatment of psoriasis[5] and PsA[6,7].

PDE4 belongs to the phosphodiesterase family of enzymes involved in the breakdown of cyclic adenosine 3',5'-monophosphate (cAMP).[8,9] cAMP is a secondary messenger central for immune response regulation, and the inhibition of its breakdown leads to a cascade of cellular events resulting in a reduction of inflammatory mediators such as tumor necrosis factor (TNF)-alpha and interleukin (IL)-23, as well as production of anti-inflammatory cytokines such as IL-10.[8,9]

PDE4, found in cells of the immune system and keratinocytes, is the key enzyme responsible for cAMP breakdown. Through their cAMP-blocking actions, PDE4 inhibitors can prolong or enhance the effects of cAMP resulting in the reduction of both T-helper 1 (Th1) and Th2 immune responses.[10] PDE4 is expressed selectively in immune cells and plays a central role in the activation of these cells, which are upregulated in chronic plaque psoriasis and other inflammatory conditions such as PsA.[9] Inhibition of PDE4 leads to an increase in the intracellular cAMP concentration, thereby reducing the production of inflammatory mediators and increasing anti-inflammatory mediators.[8,11] PDE4 inhibitors and their immune-modulating effects are currently under investigation in a variety of inflammatory conditions such as asthma, chronic obstructive pulmonary disease (COPD), atopic dermatitis, psoriasis and PsA.[8-10]

PDE4 Inhibitor in the Treatment of Psoriasis

The PDE4 inhibitor, apremilast (CC-10004, Otezla™), has been shown to block the production of interferon (IFN)-gamma, TNF-alpha, IL-12 and IL-23 – the pro-inflammatory cytokines that play a major role in the pathogenesis of psoriasis. Apremilast, through its action to increase intracellular cAMP concentration, demonstrated a range of anti-inflammatory effects on a variety of cell lines *in vitro*,[12] reduction in the psoriasiform response in a preclinical model of psoriasis *in vivo*, as well as biologic activity in a pilot study in humans[13].

To date, apremilast has been evaluated in a number of phase 2[14-16] and phase 3 clinical trials (Efficacy and Safety Trial Evaluating the Effects of Apremilast in Psoriasis [ESTEEM] 1 and 2), demonstrating efficacy in psoriasis[17,18] and PsA[6,7,19-21]. Another phase 3b study evaluating the efficacy and safety of apremilast, compared with etanercept and placebo in patients with moderate

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to severe plaque psoriasis, is ongoing (ClinicalTrials.gov Identifier: NCT01690299).

Apremilast Use in Psoriasis

Results from Phase 2 Studies in Plaque Psoriasis

Apremilast demonstrated efficacy in phase 2 clinical trials.[14-16] In a 12-week, phase 2, randomized, placebo-controlled trial in 259 patients, apremilast 20 mg twice daily (BID) achieved a Psoriasis Area and Severity Index (PASI)-75 in 24.4% of patients vs. 10.3% in the placebo group. A dose-response was observed with a mean percent reduction in PASI from baseline of 17.4%, 30.3% and 52.1% for placebo, apremilast 20 mg once daily (OD) and apremilast 20 mg BID, respectively.[14]

Efficacy of apremilast was also shown in the phase 2b double-blind, randomized, placebo-controlled crossover trial in 352 patients, which compared apremilast 10 mg, 20 mg, 30 mg or placebo BID for 16 weeks, at which point patients receiving placebo were then randomized to 20 mg or 30 mg BID up to 24 weeks. Primary endpoint of PASI-75 at 16 weeks was 11% for 10 mg, 29% for 20 mg, and 41% for 30 mg BID vs. 6% of patients on placebo.[15]

Treatment with apremilast also resulted in significant improvement on patient-reported quality of life outcomes, with particular benefit noted at the 30 mg BID dose.[16] Adverse effects were mild to moderate, and included headache, nausea, urinary tract infection (UTI) and diarrhea. No significant changes in laboratory values were observed in any of the trials.

Results from Phase 3 Studies in Plaque Psoriasis

The efficacy and safety of apremilast 30 mg BID was evaluated in two phase 3 randomized, placebo-controlled studies ESTEEM 1[17] and ESTEEM 2[18]. The efficacy and safety of apremilast compared with etanercept and placebo in patients with moderate to severe plaque psoriasis is being evaluated in a phase 3b study (NCT01690299).

In ESTEEM1, 844 patients with moderate to severe plaque psoriasis (PASI ≥12, Body Surface Area [BSA] ≥10%, static Physician's Global Assessment [sPGA] ≥3) were randomized 2:1 to apremilast 30 mg BID (n=562) or placebo (n=282). At Week 16, all patients in the placebo group were switched to apremilast 30 mg BID through Week 32. At Week 32, all patients in the apremilast 30 mg BID group who achieved PASI-75 were randomized (1:1, blinded) to continue apremilast 30 mg BID or receive placebo. Upon loss of PASI-75, patients who were re-randomized to placebo resumed apremilast 30 mg BID.[17]

In ESTEEM 2, 413 patients with moderate to severe psoriasis (PASI ≥12, BSA ≥10%, and sPGA ≥3) were randomized to placebo (n=138) or apremilast 30 mg BID (n=275) through Week 16. As in ESTEEM 1, at Week 16, all patients receiving placebo were switched to apremilast 30 mg BID through Week 32, followed by a randomized withdrawal phase through Week 52. At Week 32, all patients in the apremilast 30 mg BID group who achieved PASI-50 were randomized (1:1, blinded) to continue apremilast 30 mg BID or receive placebo. Upon loss of PASI-50, patients who were re-randomized to placebo resumed apremilast 30 mg BID.[18]

Patients re-started apremilast at the time of loss of effect, defined as time of loss of 75% (ESTEEM 1) and 50% (ESTEEM 2) of the PASI improvement obtained at Week 32 compared with baseline, but no later than Week 52. Patients initially on placebo or randomized to apremilast 30 mg BID who did not attain a PASI-75 or PASI-50, in ESTEEM 1 and ESTEEM 2, respectively, were able to add topicals and/or ultraviolet B (UVB) phototherapy at Week 32 at the discretion of the investigator.[17,18] Study design of ESTEEM clinical trial program is shown in Figure 1.

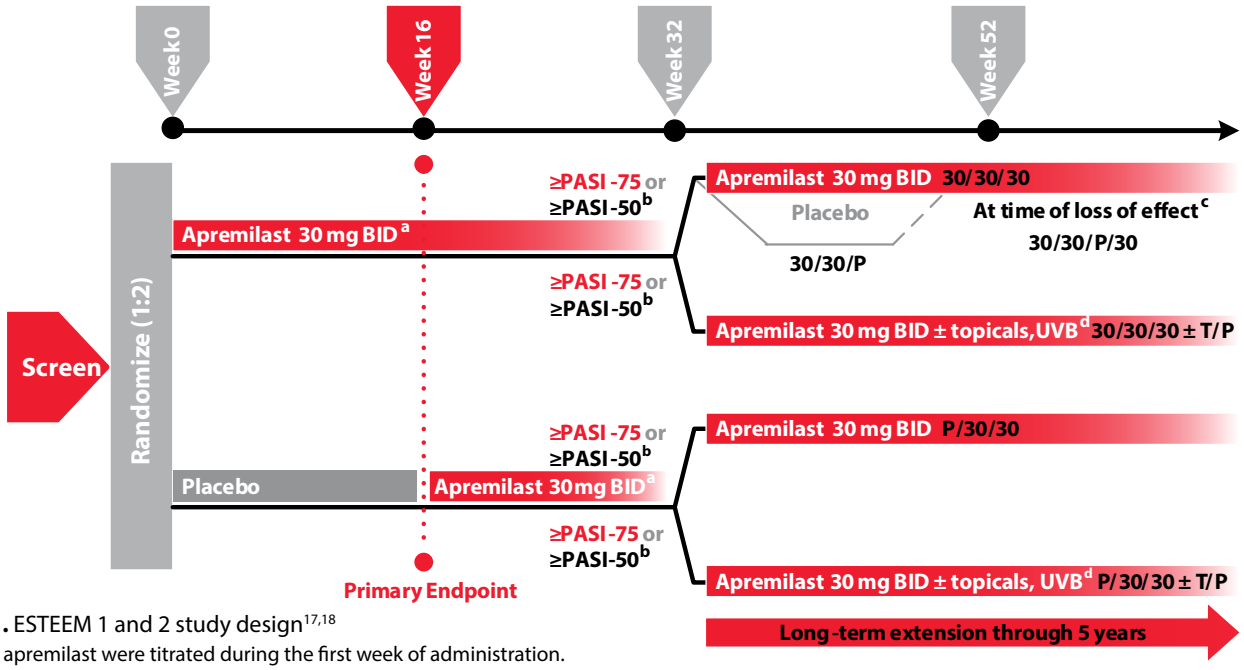


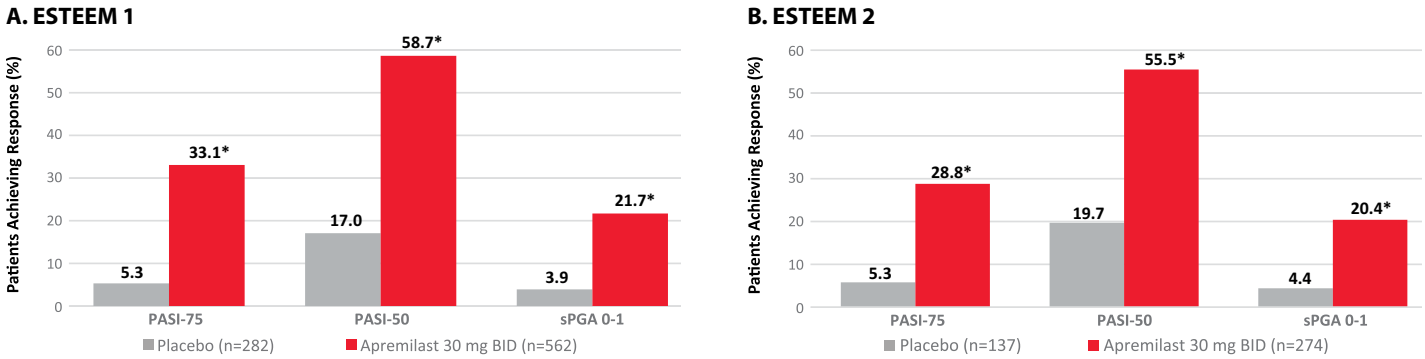
Figure 1. ESTEEM 1 and 2 study design[17,18]

[a]Doses of apremilast were titrated during the first week of administration.

[b]A responder was defined as a patient achieving ≥PASI-75 (ESTEEM 1) or ≥PASI-50 (ESTEEM 2) at Week 32.

[c]In ESTEEM 1, patients were switched to apremilast at the time of loss of PASI-75, but no later than Week 52. In ESTEEM 2, patients were switched to apremilast at time of loss of effect, defined as time of loss of 50% of the PASI improvement obtained at Week 32 compared with baseline, but no later than Week 52.

[d]At Week 32, patients will have the option of adding topical and/or UVB therapy. The decision may be made at Week 32 only, but does not need to be initiated at this visit. T = topicals; P = UVB phototherapy.



Figures 2A and 2B. PASI-75 (primary endpoint), PASI-50, and sPGA response at Week 16[17,18]

Patients achieving PASI-75, PASI-50, and sPGA response with apremilast 30 mg BID vs. placebo. A. Response at Week 16 in ESTEEM 1. B. Response at Week 16 in ESTEEM 2. sPGA score of clear (0) or almost clear (1) with at least a 2-point reduction from baseline. *P<0.0001 vs. placebo.

Significant improvements with apremilast 30 mg BID were observed at Week 16 for PASI-75 (a reduction of ≥75% in PASI scores) and sPGA scores. In ESTEEM 1, significantly more patients in the apremilast group achieved PASI-75 (33.1%), PASI-50 (58.7%) and sPGA 0-1 (21.7%) vs. placebo (*P<0.0001, all),[17] and in ESTEEM 2, patients treated with apremilast achieved PASI-75 (28.8%), PASI-50 (55.5%) and sPGA 0-1 (20.4%) vs. placebo (*P<0.0001, all)[18]. (Figure 2)

Improvements with apremilast 30 mg BID were also seen in the Nail Psoriasis Severity Index (NAPSI-50), scalp PGA (ScPGA 0-1), Palmoplantar Psoriasis Physician's Global Assessment (PPPGA), Dermatology Life Quality Index (DLQI), and pruritus scores on the Visual Analogue Scale (VAS).[17,18]

More patients treated with apremilast 30 mg BID achieved NAPSI-50 response at Week 16 vs. placebo. In ESTEEM 1, 33.3% of patients in the apremilast group achieved NAPSI-50 response vs. 14.9% with placebo (P<0.0001),[17] and in ESTEEM 2, 44.6% of patients in the apremilast 30 mg BID group achieved NAPSI-50 vs. 18.7% with placebo (P<0.0001)[18].

As well, a higher proportion of patients in the apremilast 30 mg BID group achieved ScPGA 0-1 (Clear-Minimal) at Week 16 vs. those in the placebo group. In ESTEEM 1, 46.5% in the apremilast group vs. 17.5% with placebo (P<0.0001),[17] and in ESTEEM 2, 40.9% of patients in the apremilast group achieved ScPGA 0-1 vs. 17.2% with placebo (P<0.0001)[18]. In ESTEEM 2, 65.4% of patients treated with apremilast 30 mg BID achieved PPPGA 0-1 (Clear-Minimal) vs. 31.3% of patients treated with placebo.[18] PPPGA 0-1 was not reported in ESTEEM 1.[17]

Apremilast 30 mg BID was associated with a significantly higher proportion of patients who achieved minimum clinically important difference (MCID) in DLQI and pruritus VAS from baseline at Week 16. Over 90% of patients receiving apremilast 30 mg BID, who were PASI-75 responders at Week 16, achieved MCID in DLQI and pruritus VAS. In ESTEEM 1, 70.2% of patients in the apremilast group achieved a MCID DLQI response vs. 33.5% with placebo (P<0.0001),[17,22] and in ESTEEM 2, 70.8% of patients treated with apremilast achieved a MCID DLQI response vs. 42.9% with placebo (P<0.0001)[23]. For pruritus VAS, 70.6% of patients in ESTEEM 1 treated with apremilast achieved MCID vs. 33.7% with placebo (P<0.0001) in ESTEEM 1.[22]

Time to loss of PASI improvement and PASI-75 response were also evaluated at 52 weeks in ESTEEM 1. Of the patients re-randomized to placebo, 70.3% regained PASI-75 response after re-initiation of treatment with apremilast 30 mg BID. The duration of re-treatment ranged from 3.4-22.1 weeks.[17] The median time to loss of PASI-75 response was 5.2 and 15.7 weeks for patients re-randomized to placebo and apremilast 30 mg BID, respectively. For the subgroup of patients who received apremilast 30 mg BID from Day 0 and continued on therapy, with PASI-75 responders at Week 32, there was a mean percent change from baseline in PASI score of -80% at Week 52.[17]

Safety and Tolerability Profile

Apremilast demonstrated an acceptable safety profile and was generally well-tolerated for up to 52 weeks in the treatment of plaque psoriasis. Most adverse events (AEs) were mild or moderate in severity. Discontinuation rates for diarrhea and nausea were each <2% in the apremilast 30 mg BID group through Week 52. The most frequently reported AEs during the placebo-controlled period and apremilast-exposure period were diarrhea, upper respiratory tract infection (URTI), nausea, nasopharyngitis, tension headache, and headache.[24]

In ESTEEM 1, apremilast 30 mg BID was generally well-tolerated for up to 52 weeks with no increase in the incidence of AEs over time. Serious AEs – including serious infections, malignancies, and cardiovascular events – and laboratory value changes were not significantly affected, which is consistent with prior apremilast trials. AEs in ≥5% reported during Weeks 0-16 and over the entire apremilast-exposure period (Weeks 0-52) of either placebo or apremilast 30 mg BID group are shown in Table 1.[17]

In ESTEEM 2, the majority of AEs were mild or moderate in severity and discontinuation rates due to AEs during Weeks 0-16 were low (placebo: 5.1%; apremilast: 5.5%). In patients receiving apremilast, diarrhea and nausea were mostly mild in severity, with the highest incidence during the first week of dosing, generally resolving within 1 month, with few patients reporting use of concomitant medications. Serious AEs – including serious infections, malignancies, and cardiovascular events – and laboratory value changes again were consistent with prior apremilast studies; laboratory values were not significantly changed and serious AEs were low across treatment groups. AEs reported during Weeks 0-16 in ≥5% are presented in Table 2.[18]

Patients (%)	Placebo-Controlled Period Weeks 0-16		Apremilast-Exposure Period Weeks 0-52
	Placebo n=282	Apremilast 30 mg BID n=560	Apremilast 30 mg BID n=804
Diarrhea	7.1	18.8	18.7
Upper respiratory tract infection	7.4	10.2	17.8
Nausea	6.7	15.7	15.3
Nasopharyngitis	8.2	7.3	13.4
Tension headache	4.3	7.3	9.6
Headache	4.6	5.5	6.5

Table 1. Adverse events ≥5% any treatment group in ESTEEM 1[17]

The apremilast-exposure period (Weeks 0-52) included all patients who received apremilast 30 mg BID, regardless of when treatment was initiated. Exposure-adjusted incidence rate (EAIR) per 100 patient-years is defined as 100 times the number (n) of patients reporting the event divided by patient-years within the phase (up to the first event start date for patients reporting the event).[17]

Patients (%)	Placebo-Controlled Period Weeks 0-16	
	Placebo n=136	Apremilast 30 mg BID n=272
Nausea	6.6	18.4
Diarrhea	5.9	15.8
Vomiting	3.7	5.1
Nasopharyngitis	4.4	7.4
Tension headache	1.5	7.4
Headache	0.7	6.3
Psoriasis	5.1	1.5

Table 2. Adverse events ≥5% any treatment group in ESTEEM 2[18]

Apremilast Use in Psoriatic Arthritis

Results from Phase 3 Studies in Psoriatic Arthritis

The efficacy and safety of apremilast were evaluated in the phase 3 Psoriatic Arthritis Long-term Assessment of Clinical Efficacy (PALACE) clinical trial program studies in patients with PsA.[6,7,9,19-21]

The key inclusion criteria in PALACE 1 and 2 were adults with a documented diagnosis of PsA at baseline (duration ≥6 months; met the Classification Criteria for Psoriatic Arthritis [CASPAR] criteria), ≥3 swollen and ≥3 tender joints despite past or current disease-modifying antirheumatic drugs (DMARDs) and/or biologics.[6,7,9,19] In PALACE 3, in addition to the above inclusion criteria for PALACE 1 and 2, patients also had to have at least one psoriatic lesion ≥2 cm, and PALACE 4 was in DMARD and/or biologics naïve patients.[20,21] Study design for the PALACE clinical trial program is shown in Figure 3.[20]

The results of a 24-week placebo-controlled phase of PALACE 1 have been published, as well as the 52-week period results, and will be presented here.[6,7] Patients with active PsA (n=504) were randomized (1:1:1) to placebo, apremilast 20 mg BID or apremilast 30 mg BID. At Week 16, patients without ≥20% reduction in swollen and tender joint counts were required to be re-randomized equally to either apremilast dose if initially randomized to placebo or remained on their initial apremilast dose. Patients on background concurrent DMARDs continued stable doses. Primary outcome was the proportion of patients achieving 20% improvement in modified American College of Rheumatology 20% improvement criteria (ACR20) at Week 16.[6,7]

At Week 16, significantly more patients receiving apremilast 20 mg BID (30.4%; P=0.0166) and 30 mg BID (38.1%; P=0.0001) achieved an ACR20 response vs. placebo (19.0%).[7] At Week 24, a significantly greater proportion of patients receiving apremilast 20 mg BID and 30 mg BID achieved ACR20, ACR50 and ACR70 vs. placebo, and these response rates were maintained in the active treatment groups (P≤0.0001 vs. placebo, all). An ACR20 response of 45.3% was observed at Week 24 in patients treated with apremilast 30 mg BID independent of their response at Week 16.[7] At Week 52, ACR20 response was observed among patients receiving apremilast continuously for 52 weeks (n=254) in 63.0% (20 mg BID) and 54.6% (30 mg BID) of patients.[7]

Patients who continued receiving apremilast through Week 52 demonstrated sustained rates of ACR20 response over 52 weeks. At Week 52, 63.0% of patients who received apremilast 20 mg BID from baseline and 54.6% who received 30 mg BID achieved an ACR20. ACR50 and ACR70 responses were observed in 24.8% and 15.4% of patients receiving apremilast 20 mg BID and 24.6% and 13.8% of patients receiving apremilast 30 mg BID, respectively.[7]

Patients treated with apremilast had a statistically significant improvement in physical function, as measured by changes from baseline in Health Assessment Questionnaire–Disability Index (HAQ-DI) score (P=0.0004 vs. placebo) and the 36-Item Short-Form Health Survey v2 Physical Functioning domain score (P=0.0001 vs. placebo). Significant improvements were also seen in most ACR component scores, particularly swollen and tender joint counts and patient assessment of pain (P<0.0001 vs. placebo).[6]

Significant improvements in key secondary measures (physical function, psoriasis) were evident with both apremilast doses compared to placebo (P<0.0001 vs. placebo) at Week 24.[6] Among patients receiving apremilast continuously for 52 weeks, response was also maintained across secondary outcomes, including measures of PsA signs and symptoms, skin psoriasis severity, and physical function.[6]

In patients with baseline enthesitis, the mean change from baseline in the Maastricht Ankylosing Spondylitis Enthesitis Score (MASES) was significantly higher for apremilast 30 mg BID vs. placebo (P=0.0334), and significantly greater proportions of patients receiving apremilast 20 mg BID (32.0%; P=0.0037) and 30 mg BID (33.6%; P=0.0013) achieved a MASES score of 0 at Week 24 vs. placebo (14.4%). In patients with baseline dactylitis, mean change from baseline in dactylitis severity score was higher with apremilast vs. placebo. Greater proportions of patients with dactylitis achieved scores of 0 at Week 24 with apremilast

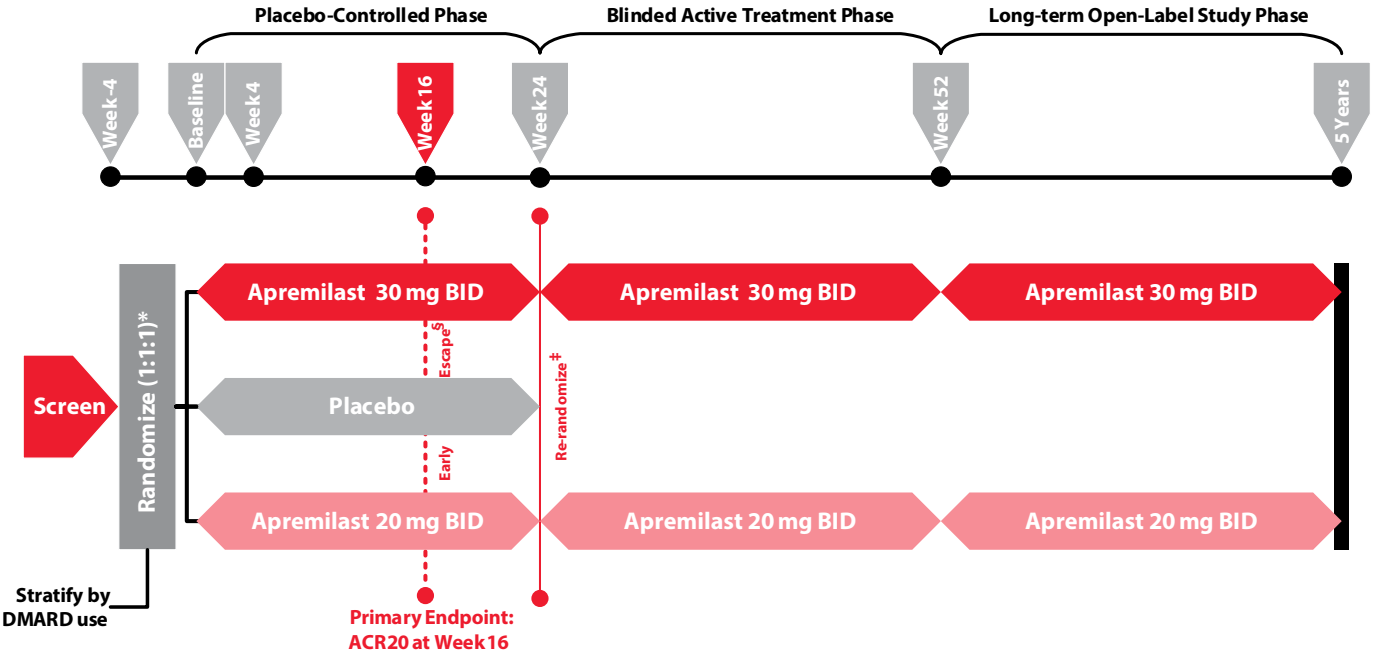


Figure 3. PALACE Study Design[6,7,19-21]

Note: Plasma samples for the biomarker assay were obtained at baseline and Weeks 4, 16, 24, and 40.

*All doses were titrated over the first week of treatment.

§Patients whose swollen and tender joint counts had not improved by ≥20% at Week 16 were considered non-responders and were required to be re-randomized (1:1) to apremilast 20 mg BID or 30 mg BID if they were initially randomized to placebo. Apremilast-treated patients continued on their initial apremilast dose.

‡At Week 24, all remaining placebo patients were re-randomized to apremilast 20 mg BID or 30 mg BID.

20 mg BID (50.9%), apremilast 30 mg BID (47.7%) vs. placebo (40.9%); these differences did not reach statistical significance at Week 24.[6] At Week 52, in patients with enthesitis and dactylitis at baseline who received apremilast continuously through Week 52, the median change from baseline in MASES at Week 52 was 100% with apremilast 20 mg BID and 66.7% with apremilast 30 mg BID, and a MASES score of 0 was observed in 50.7% (35/69) of patients receiving apremilast 20 mg BID and 38.2% (34/89) receiving apremilast 30 mg BID.[7]

At Week 16, treatment with apremilast was associated with significantly greater reductions (improvements) in HAQ-DI vs. placebo (key secondary endpoint, SE). The mean SE changes from baseline were -0.09 (0.04) (placebo), -0.20 (0.04) (apremilast 20 mg BID; P=0.0252 vs. placebo), and -0.25 (0.04) (apremilast 30 mg BID; P=0.0015 vs. placebo).[6]

As well, HAQ-DI scores were maintained in both apremilast groups over 52 weeks with continued treatment. At Week 52, mean reductions in HAQ-DI score were −0.37 (0.48) with apremilast 20 mg BID and −0.32 (0.55) with apremilast 30 mg BID, with improvements of ≥0.13 observed in 60.0% and 59.8%, respectively, and improvements of ≥0.30 observed in 45.8% and 44.7%, respectively.[7]

The most common AEs in the PALACE 1 trial were gastrointestinal (GI), mild or moderate in severity, occurred early, self-limited, did not recur, and infrequently led to discontinuation (<2.5%) in the apremilast 20 mg BID and 30 mg BID groups through Week 24. No imbalance in major adverse cardiac events, serious or opportunistic infections, malignancies or laboratory abnormalities was observed. For an overview of AEs occurring in ≥5% in any treatment group during the placebo-controlled phase (Weeks 0-24) and apremilast exposure period (Weeks 0-52) of PALACE 1 see Table 3. There were no new emergent AEs over the 52-week period.[7]

Patients (%)	Placebo-Controlled Period Weeks 0-24			Apremilast-Exposure Period Weeks 0-52	
	Placebo	Apremilast		Apremilast	
	n=168	20 mg BID n=168	30 mg BID n=168	20 mg BID n=245	30 mg BID n=245
Diarrhea	2.4	11.3	19.0	11.0	19.0
Nausea	6.5	9.5	18.5	9.8	14.3
Headache	4.8	10.1	10.7	9.0	9.8
Upper respiratory tract infection	3.6	6.0	4.2	7.8	5.7
Nasopharyngitis	3.0	3.6	4.8	6.9	6.5

Table 3. Adverse events ≥5% any treatment group in PALACE 1[7]

Warnings and Precautions: Data from Studies in Psoriasis and PsA

Weight Decrease

Psoriasis: During the controlled period of the trials, weight decrease between 5%-10% of body weight was reported in 12% of psoriasis patients treated with apremilast 30 mg BID vs. 5% treated with placebo. Weight decrease of ≥10% of body weight occurred in 2% of patients treated with apremilast 30 mg BID vs. 1% in the placebo group. It is recommended that patients treated with apremilast should have their weight monitored.

PsA: During the controlled period of the trials, weight decrease between 5%-10% of body weight was reported in 10% of patients with PsA treated with apremilast 30 mg BID vs. 3.3% of placebo. It is recommended that patients treated with apremilast should have their weight monitored regularly.[25]

Depression

Psoriasis and PsA: While treatment with apremilast was associated with a risk of depression, data from the clinical trials do not suggest an increase in depression nor suicidal ideation in subjects treated with apremilast vs. placebo.[25]

Drug Interactions

Psoriasis and PsA: The use of cytochrome P450 enzyme inducers (e.g., rifampin, phenobarbital, carbamazepine, phenytoin) with apremilast is not recommended. It has been shown that the co-administration of strong cytochrome P450 enzyme inducer, rifampin, resulted in a reduction of systemic exposure of apremilast, which may result in a loss of its efficacy.[25]

Conclusion

Treatment with apremilast demonstrated efficacy in reducing the severity of moderate to severe plaque psoriasis[17,18] and improving signs, symptoms and physical function in PsA.[6,7,19-21] Apremilast demonstrated an acceptable safety profile and was well-tolerated with generally mild GI complaints occurring early in the course of the treatment and resolving with time, and there was no requirement for laboratory monitoring.[6,7,19-21,24] Based on these results, apremilast should be considered as a therapeutic option in the treatment of plaque psoriasis and PsA.

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New Antibiotics in the Management of Acute Bacterial Skin and Skin Structure Infections

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ABSTRACT

Acute bacterial skin and skin-structure infections (ABSSSIs), often caused by aerobic gram-positive cocci, are most often mild-to-moderate infections that can easily be treated in an outpatient setting. With the rates of these infections substantially increasing in the past decade, owing in part to the emergence of community acquired methicillin-resistant Staphylococcus aureus *(CA-MRSA), alternative options for the treatment of ABSSSIs are necessary. This editorial reviews the mechanism of action, efficacy, bacterial coverage, and potential side effect profiles for dalbavancin and oritavancin, both semisynthetic lipoglycopeptide antibiotics, and tedizolid, an oxazolidinone. Dalbavancin, oritavancin, and tedizolid have been extremely valuable additions to treatment options for ABSSSIs due to the convenient dosing regimen and the fact that there are fewer resistant organisms to these therapies at this time.*

Key words: acute bacterial skin and skin-structure infections, antibiotics, glycopeptide, dalbavancin, oritavancin, tedizolid

Introduction

Acute bacterial skin and skin-structure infections (ABSSSIs), often caused by aerobic gram-positive cocci, are estimated to cause more than 15 million infections and 870,000 hospital admissions annually in the United States.[1] SSSIs are most often mild-to-moderate infections that can easily be treated in an outpatient setting. Rates of these infections have substantially increased in the past decade, owing in part to the emergence of community acquired methicillin-resistant *Staphylococcus aureus* (CA-MRSA).[2] The economic burden of SSSIs remains substantial and is driven by the high costs of hospitalization, which is often required for severe SSSIs since the agents used to treat these infections require daily intravenous (IV) administration for multiple days.[3] Early clinical detection of severe or necrotizing SSSIs is difficult because the disease is often indistinguishable from its milder counterparts early in the disease course. Signs of a severe infection include pain disproportionate to the clinical findings, violaceous bullae, cutaneous hemorrhage, skin sloughing, skin anesthesia, rapid progression, and gas in the tissue.[4] Additionally, it is recommended that patients with SSSIs accompanied by signs and symptoms of systemic toxicity, such as hypotension, fever, hypothermia, tachycardia, increased creatinine level, decreased serum bicarbonate, increased creatinine phosphokinase, marked left shift, or C-reactive protein >13 mg/L, be considered for hospitalization.[4]

Glycopeptide antibiotics, such as vancomycin, have been used in treatment of SSSIs for over half a century and are still used extensively today; however, reduced vancomycin susceptibility in CA-MRSA strains as well as difficulty in therapeutic drug monitoring compromise the clinical efficacy of vancomycin.[2,5] Second generation semisynthetic lipoglycopeptide derivatives such as dalbavancin and oritavancin, which possess a broader spectrum of activity and improved pharmacokinetic properties, will be discussed in this article. The new glycopeptide antibiotics provide efficacious alternatives for the treatment of complicated ABSSSIs.[1] A major benefit is management in an outpatient setting, which could significantly decrease or omit the costs and risks of hospitalization, as well as eliminating the need for laboratory monitoring.[1]

Oxazolidinones are another important class of antibiotics used in the treatment of ABSSSIs, particularly vancomycin resistant *Enterococcus* (VRE) infections. Historically, linezolid has been the antibiotic of choice; however, tedizolid is a novel oxazolidinone that offers enhanced antimicrobial potency, low rates of bacterial resistance, and potential safety advantages. Additionally, the recommended dosing of once per day may be more convenient and is associated with higher compliance than twice per day dosing for linezolid.[6]

To maintain effectiveness of new antibiotics, their use should be limited to ABSSSIs where the bacteria are susceptible to the new medication and are resistant to other more cost effective options. Although tedizolid, dalbavancin, and oritavancin have been approved for SSSIs caused by MRSA, they probably should not be used as a first-line treatment when there are less expensive and more easily accessible antibiotics, such as trimethoprim-sulfamethoxazole or doxycycline, that are very effective for MRSA infections.[7]

Glycopeptide Therapeutics - Dalbavancin and Oritavancin

Dalbavancin is a long-acting IV semisynthetic lipoglycopeptide antibiotic with bactericidal activity against gram-positive cocci, including MRSA.[6-10] It is the first US FDA approved drug for adults with ABSSSIs that requires only 2 IV doses administered 1 week apart: the first dose is 1000 mg IV infused over 30 minutes, followed 1 week later by the second dose of 500 mg IV.[6-10]

Dalbavancin is effective for treatment of adult patients with ABSSSI caused by susceptible isolates of gram-positive organisms. Susceptible gram-positive organisms include *Staphylococcus aureus* (*S. aureus*), including MRSA and MSSA, and *Streptococcus* groups (*S. pyogenes*, *S. agalactiae*, and *S. anginosus*).[6-11] *In vitro* studies suggest it may also be effective against vancomycin-susceptible *Enterococcus faecium* and *Enterococcus faecalis* (*E. faecalis*), as well as vancomycin-intermediate *S. aureus*; however, clinical importance has not been established.[6,11] The safety and efficacy in pediatric patients 18 years of age and younger has not been demonstrated.[8,11] However, vancomycin has been successfully used in treating these bacterial infections in the pediatric patient population.[11] Dalbavancin is pregnancy category C meaning there has been some fetal toxicity in animals, but no adequate human studies.[6,8,11]

The adverse effects most commonly experienced include nausea, diarrhea, and headaches, reported in 5% or less of patients.[6-8,10,11] Infrequent serious hypersensitivity reactions, including anaphylaxis, have been reported and caution should be exercised with patients who have a known allergy to other glycopeptides.[8,10] Additionally, rapid IV infusion could cause infusion-related reactions (pruritus, urticaria, and flushing).[6-8,10] Slowing or interrupting the infusion may be helpful if this occurs.[7]

Oritavancin is a long-acting IV semisynthetic lipoglycopeptide antibiotic with potent activity against gram-positive pathogens, including MRSA.[3] Oritavancin is bactericidal and has an extended plasma half-life.[3,11,12] It is the first single-dose antibacterial drug approved by the US FDA for treatment of adult patients with ABSSIs.[12] The recommended single dose is 1200 mg IV infused over 3 hours.[7,11] Dose adjustment for advanced age, decreased renal function, or moderate hepatic impairment is not required.[3,7]

Oritavancin is approved for use in adults with ABSSSIs caused by susceptible gram-positive microorganisms. Susceptible gram-positive microorganisms include *S. aureus* (including MRSA and MSSA), various *Streptococcus* groups (*S. pyogenes*, *S. agalactiae*, *S. dysgalactiae*, and *S. anginosus*), and *E. faecalis* (vancomycin-susceptible isolates only).[11] The safety and efficacy have not been established in patients 18 years of age and younger.[11] Oritavancin is pregnancy category C.[11]

The adverse effects most often reported include nausea, headache, vomiting and diarrhea, all occurring in less than 10% of patients.[3,7,11,12] Osteomyelitis is a rare adverse event occurring in 0.3% of patients.[11,12] If osteomyelitis is suspected an antibacterial agent other than oritavancin should be used.[11,12] Infrequent reports of serious hypersensitivity reactions have occurred.[3,11] It is important to be aware of patients who have a history of allergies to other glycopeptides, including vancomycin.[11] Additionally, infusion-related reactions (pruritus, urticaria, flushing) have been experienced, as with other glycopeptides.[3,11,12] If this occurs, slowing or interrupting the infusion should be considered.[11]

The current therapeutic options for the treatment of ABSSSIs require multidose and multiday regimens, with some patients requiring dosage adjustments for renal insufficiency or monitoring of plasma drug concentration.[3] Multiday regimens may require patients to be hospitalized over their course of treatment, which increases the risk of nosocomial complications.[3] Additionally, oral antibiotic regimens have an increased rate of noncompliance, which increases the potential for pathogen resistance. Oritavancin achieves a sustained clinical response with a single dose and does not require dosage adjustments for renal insufficiency. Oritavancin and dalbavancin could potentially reduce or eliminate hospital stays, improve treatment compliance, reduce utilization of health care resources, and add flexibility to the treatment of these serious infections. Despite the advantages, other more cost effective antibiotics with a history of effective use in treatment of ABSSSIs should be considered before deciding to treat with dalbavancin or oritavancin.

Oxazolidinone Therapeutic - Tedizolid Phosphate

The oxazolidinones are a synthetic class of agents now commonly relied on for the treatment of ABSSSIs, including more serious infections like MRSA and VRE.[13] With increasing utilization of linezolid, resistant pathogens have begun to emerge.[13] Tedizolid phosphate is a second-generation oxazolidinone antibiotic that offers enhanced antimicrobial potency and low rates of bacterial resistance.[13-15] Available in both IV and oral forms, tedizolid exhibits bacteriostatic activity by binding the 50S subunit of the bacterial ribosome, resulting in inhibition of bacterial protein synthesis.[11,13-15] The recommended dosage is 200 mg once daily for 6 days,[6,7,14,16] which may offer increased convenience and compliance when compared to twice daily linezolid.

Clinical studies have proven tedizolid phosphate to be effective against susceptible isolates of gram-positive organisms including *S. aureus* (including MRSA and MSSA), various *Streptococcus* groups (*S. pyogenes*, *S. agalactiae*, and *S. anginosus*), and *E. faecalis* (including VRE).[6,7,11,13-16] *In vitro* studies have suggested it may also exhibit activity against some strains of *Staphylococci* and *Enterococci* that are not susceptible to vancomycin or linezolid; however, the clinical importance of this data has not been established.[6,11,13,14,16] The safety and effectiveness in pediatric patients 18 years of age or younger has not been demonstrated; whereas, linezolid is indicated for use in pediatric patients.[11,16] Tedizolid phosphate is pregnancy category C.[6,11,16]

Structural differences between tedizolid and linezolid are thought to contribute to tedizolid's decreased rates of resistance and enhanced potency.[13,14] Bacteria confer resistance to linezolid by acquiring the chloramphenicol-florfenicol resistance gene, which can be horizontally transferred.[13,15] However, because of structural distinctions, tedizolid has decreased vulnerability to this resistance mechanism.[13,15] Interactions with the ribosomal subunit are thought to contribute to the increased potency of tedizolid.[13,15]

Another potential advantage of tedizolid compared to linezolid is an improved safety profile.[14,15] The most common adverse effects are similar to those seen with linezolid and include nausea, headache, diarrhea, vomiting, and dizziness, each occurring in less than 8% of patients.[6,7,14-16] Toxicity linked to duration of treatment with linezolid includes peripheral and optic neuropathy as well as hematologic toxicity and thrombocytopenia.[13,16] Tedizolid has not had reports of peripheral and optic neuropathy.[13,16] Although tedizolid exposure has been limited to 21 days or less in patients, a rat study using tedizolid doses up to 10-fold greater than human doses did not induce a neuropathy.[13] This data indicates a possible safety advantage of tedizolid. Additionally, at recommended doses, tedizolid has not been associated with hematologic

toxicity or thrombocytopenia[13]; however, higher doses or longer treatment durations might increase the risk. Linezolid has been associated with the occurrence of myelosuppression, especially in patients who have underlying hematologic abnormalities or renal insufficiency, which requires complete blood counts to be monitored weekly.[13] An additional concern exists for the oxazolidinone class, which has been shown to act as weak, reversible monoamine oxidase (MAO) inhibitors in some *in vitro* studies.[6,13] However, based on two randomized, double-blind, placebo-controlled crossover studies, as well as another study including both humans and animals, tedizolid failed to interact with serotonergic drugs, adrenergic agents, or result in MAO inhibitor activity.[6,13,16] Data from post marketing experience will be beneficial to confirm the encouraging results that are currently available.

Conclusion

Dalbavancin, oritavancin, and tedizolid have been extremely valuable additions to treatment options for ABSSSIs due to the convenient dosing regimen and the fact that there are fewer resistant organisms to therapy at this time. In practice, other antibiotics with a history of effective use for ABSSSIs, which also cost less, should be considered first in order to prevent bacterial resistance.

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Update on Drugs

Name/Company	Approval Dates/Comments
Nivolumab IV infusion *Opdivo®* Bristol-Myers Squibb	The European Commission (EC) approved this human programmed death receptor-1 (PD-1) blocking monoclonal antibody in June 2015 for the treatment of advanced (unresectable or metastatic) melanoma in adults, regardless of BRAF status.
Pembrolizumab IV infusion *Keytruda®* Merck & Co.	The EC approved this anti-PD-1 therapy in July 2015 for the treatment of advanced (unresectable or metastatic) melanoma in adults. Pembrolizumab received EC regulatory approval based on phase 3 data that showed it is the first and only anti-PD-1 therapy to provide a statistically superior survival benefit as a monotherapy vs. ipilimumab, the current standard of care for advanced melanoma.
Sonidegib phosphate capsules *Odomzo®* Novartis Pharmaceuticals	The US FDA approved sonidegib in July 2015 to treat patients with locally advanced basal cell carcinoma that has recurred following surgery or radiation therapy, or who are not candidates for surgery or radiation therapy. This once-daily oral treatment works by inhibiting a molecular pathway, called the Hedgehog pathway, which is active in basal cell cancers. By suppressing this pathway, sonidegib may inhibit the growth of cancerous lesions.
Azelaic acid 15% foam *Finacea® Foam* Bayer HealthCare	The FDA approved azelaic acid 15% foam in July 2015 for the topical treatment of the inflammatory papules and pustules of mild to moderate rosacea.
Adapalene 0.3% + benzoyl peroxide 2.5% gel *Epiduo® Forte* Galderma Laboratories	The FDA approved this new formulation of adapalene 0.3% and benzoyl peroxide (BP) 2.5% gel in July 2015 for the once-daily, topical treatment of acne vulgaris. Epiduo® Forte Gel is the first combination of these strengths of the retinoid, adapalene, and BP, developed to treat moderate to severe acne.
Deoxycholic acid injection *Belkyra™* Kythera Biopharmaceuticals	Health Canada approved this first-in-class adipolytic agent in July 2015 for improvement in the appearance of moderate to severe convexity or fullness associated with submental fat (SMF) in adults. Treatment of fat outside of the submental area is not approved and is not recommended. Deoxycholic acid (ATX-101) is an injectable treatment for the reduction of SMF, which commonly presents as a double chin. The drug destroys fat cells when properly injected into SMF.
Erratum: Due to an editing error, the incorrect US FDA approval date of April 2014 for deoxycholic acid injection (Kybella™, Kythera Biopharmaceuticals) was inadvertently published in *Skin Therapy Letter* 2015 Jul-Aug;20(4):12. The correct approval date is April 2015. The publisher apologizes for any inconvenience.	
Hyaluronic acid gel injectable dermal filler *Restylane® Lyft with Lidocaine* Galderma	The FDA granted approval in July 2015 to market this injectable gel to increase volume and smooth wrinkles in the face of patients aged >21 years. Restylane® Lyft was formerly marketed as Perlane-L®. Restylane® Lyft with Lidocaine is indicated for implantation into the deep dermis to superficial subcutis for the correction of moderate to severe facial folds and wrinkles, such as nasolabial folds, and for subcutaneous to supraperiosteal implantation for cheek augmentation and correction of age-related midface contour deficiencies.
Dermal filler with calcium hydroxylapatite (CaHA) + integral 0.3% lidocaine *Radiesse® (+)* Merz Pharma Canada	In July 2015, Health Canada approved Radiesse® (+) injectable implant dermal filler that contains a small quantity of local anesthetic (lidocaine). Radiesse® (+) is indicated for subdermal implantation for the correction of moderate to severe facial wrinkles and folds, such as nasolabial folds, and for rejuvenation of the hands.