Apremilast Was Associated With an Acceptable Safety Profile in ESTEEM Trials

Written by Toni Rizzo

Two phase 3 randomized controlled trials were performed to evaluate the safety and efficacy of oral apremilast (CC-10004) in patients with moderate to severe plaque psoriasis. Kristian Reich, MD, Dermatologikum Hamburg and SCIderm Research Institute, Hamburg, Germany, presented the safety analysis from the pooled data of the ESTEEM 1 [NCT01194219] and ESTEEM 2 trials [NCT01232283].

Patients (n = 1255) with moderate to severe plaque psoriasis were randomized 2:1 to treatment with the selective phosphodiesterase 4 inhibitor apremilast (30 mg, BID; n = 836) or placebo (n = 419) for 16 weeks. At week 16, patients treated with placebo were switched to apremilast, and all patients received apremilast through week 32. At week 32, patients entered a randomized treatment withdrawal phase through week 52. Thus, a total of 1184 patients had received apremilast at 1 year. Adverse events (AEs) were assessed for weeks 0 to 16 (the placebo-controlled period) and weeks 0 to 52 (the apremilast exposure period). Baseline characteristics were similar between the placebo and apremilast groups.

Most AEs were mild to moderate in severity for all treatment durations. Long-term data did not indicate an increase in AEs, based on exposure-adjusted incidence rates (EAIRs) per 100 patient-years. The incidence of serious AEs was similar between the apremilast (2.0%) and placebo (2.6%) groups (Table 1).

The most frequently reported AEs in all treatment periods were diarrhea, nausea, upper respiratory tract infection, nasopharyngitis, tension headache, and headache (Table 2).

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Table 1. Overview of Adverse Events

	Placebo Controlled (wk 0 to 16)				Apremilast Exposure (wk 0 to ≥52)	
	Placebo[a]		Apremilast[b]		Apremilast[c]	
Adverse Events	No. (%)	EAIR/100	No. (%)	EAIR/100	No. (%)	EAIR/100
≥1	239 (57.2)	350.3	573 (68.9)	536.4	953 (80.5)	287.4
≥1 serious	11 (2.6)	9.5	17 (2.0)	7.2	68 (5.7)	6.2
≥1 severe	15 (3.6)	13.0	32 (3.8)	13.7	97 (8.2)	8.9
Leading to discontinuation	16 (3.8)	13.8	45 (5.4)	19.2	99 (8.4)	8.8
Leading to death	1 (0.2)[d]	0.9	1 (0.1)[e]	0.4	2 (0.2)[e,f]	0.2

EAIR/100, exposure-adjusted incidence rate per 100 patient-years, defined as 100 times the number of patients reporting the event, divided by patient-years (up to the first event start date for patients reporting the event).

[a]Patients, n = 418; patient-years, 116.5.

[b]Patients, n = 832; patient-years, 236.8.

[c]Patients, n = 1184; patient-years, 1127.9.

[d]Completed suicide.

[e]The final autopsy report revealed diffuse lung congestion and bilateral edema, consistent with acute cardiac failure in association with likely sleep apnea and morbid obesity.

[f]Cerebrovascular accident (patient had a history of diabetes mellitus, hypertension, and hyperlipidemia).

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Table 2. Adverse Events ≥5% in Any Treatment Group

	Placebo Controlled (wk 0 to 16)				Apremilast Exposure (wk 0 to ≥52)	
	Placebo[a]		Apremilast[b]		Apremilast[c]	
Adverse Events	No. (%)	EAIR/100	No. (%)	EAIR/100	No. (%)	EAIR/100
Diarrhea	28 (6.7)	25.5	148 (17.8)	74.2	208 (17.6)	22.1
Nausea	28 (6.7)	25.3	138 (16.6)	68.2	188 (15.9)	19.6
Upper respiratory tract infection	27 (6.5)	23.9	70 (8.4)	30.9	200 (16.9)	20.7
Nasopharyngitis	29 (6.9)	25.9	61 (7.3)	26.8	178 (15.0)	17.8
Tension headache	14 (3.3)	12.4	61 (7.3)	27.5	109 (9.2)	10.7
Headache	14 (3.3)	12.4	48 (5.8)	21.2	76 (6.4)	7.1

EAIR/100, exposure-adjusted incidence rate per 100 patient-years, defined as 100 times the number of patients reporting the event, divided by patient-years (up to the first event start date for patients reporting the event).

[a]Patients, n = 418; patient-years, 116.5.

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Discontinuations due to AEs were low for weeks 0 to 16 and did not increase with longer apremilast exposure, based on EAIRs per 100 patient-years.

No serious diarrhea or nausea AEs were reported in any treatment group for any treatment period. During the apremilast exposure period, discontinuation rates due to diarrhea or nausea were 0.9% and 1.4%, respectively. Diarrhea and nausea were mostly mild, with the highest incidence during the first 2 weeks of treatment. Rates of major and potential major adverse cardiac events, malignancies, and serious infections were similar between the groups.

At week 16, the mean change in weight from baseline was –1.51 kg with apremilast and +0.01 kg with placebo. At week 52, the mean change in weight from baseline was –1.99 kg with apremilast. Weight loss associated with apremilast did not lead to overt medical complications. There was no association between weight loss and diarrhea or nausea.

Based on EAIRs per 100 patient-years, there was no evidence of an increased incidence of depression or suicidality with longer apremilast treatment. At week 16, depression had occurred in 1.2% of patients treated with apremilast and 0.5% of patients treated with placebo; suicide was attempted by 1 patient (0.1%) treated with apremilast and was completed by 1 patient (0.2%) treated with placebo. No clinically relevant effects of apremilast on laboratory measurements were observed.

The investigators concluded that apremilast (30 mg, BID) demonstrated an acceptable safety profile and was generally well tolerated for > 52 weeks.

Selective Photothermolysis of Sebaceous Follicles With Gold Particles Rapidly Reduces Acne Lesions

Written by Toni Rizzo

Acne occurs with large overactive sebaceous glands as a result of excessive sebum production, abnormal desquamation of follicular epithelium, and proliferation of *Propionibacterium acnes*, which may block the gland opening and cause inflammation. Photothermolysis of the sebaceous gland targets these contributors of acne. High absorption and contrast are needed to achieve effective sebaceous gland photothermolysis; however, there is no wavelength that selectively targets the sebaceous follicle. Katarzyna Podolec, MD, Jagiellonian University Medical College, Krakow, Poland, presented the results of 2 studies evaluating a novel approach to the photothermolysis of acne lesions via the delivery of gold microparticles into the sebaceous follicle.

Submicron-sized particles (0.150-µm diameter) consisting of inert gold surrounding a silica core were developed for strong plasmon absorption at 800 nm and were suspended in a topical formulation. When massaged into the skin, the particle suspension is selectively delivered into the sebaceous follicle without epidermal, dermal, or systemic exposure. The excess suspension is wiped from the skin, and the follicle is irradiated with a laser. The particles convert the laser light into heat, which deactivates