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.

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

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

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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

the sebaceous gland via classical photothermolysis. The gold particles limit heat delivery to the follicle.

In study 1, 48 patients were randomized to 1 of 2 arms: immediate treatment or delayed crossover (control). Patients in the former were treated with the particle suspension and 800-nm laser applied 3 times, at 2-week intervals. Patients in the control arm were treated with a salicylic acid wash for 12 weeks, after which they received only the particle-laser treatment.

The particle-laser treatment was associated with a mean pain level of 4 (scale, 0 to 10) and mild erythema that resolved within 30 minutes. At 12 weeks, there was a significant difference in the mean percentage change in inflammatory lesions from baseline in the treated arm (–34%) vs the control arm (–16%). The rapid decrease of inflammatory lesions in the treated arm continued, with a –61% change at 28 weeks.

After crossing over to treatment, patients in the control arm had a rapid decrease in inflammatory lesions that lasted for 6 months.

In study 2, 49 patients were randomized to 3 particle-laser treatments 1 week apart or 3 sham vehicle–laser treatments 1 week apart. At 16 weeks, the treatment arm had a –38% change in inflammatory lesions, compared with a –16% change in the control arm, at which point the placebo arm follow-up ended. The rapid decrease continued in the treatment arm to –61% at 28 weeks. The Investigator's Global Assessment score (percentage with change > –2%) was 32% in the treatment arm vs 0% in the control arm.

These studies demonstrated the effectiveness of acne treatment with selective photothermolysis of sebaceous follicles via gold particles as compared with controls. The particle-treated patients experienced a mean 61% reduction of inflammatory lesions at 6 months from baseline. The particle-laser treatment was well tolerated with minimal side effects. This new acne treatment is a promising addition to the armamentarium available to physicians.

Vismodegib Improved DOR in mBCC and laBCC

Written by Toni Rizzo

Vismodegib is the first oral hedgehog pathway inhibitor approved by the European Medicines Agency for the treatment of adults with symptomatic metastatic basal cell carcinoma (mBCC) or locally advanced basal cell carcinoma (laBCC), both of which are not suitable for treatment with surgery or radiotherapy. The pivotal Erivance BCC trial [NCT00833417] was an international 2-cohort nonrandomized study of oral vismodegib (150 mg daily) in patients with laBCC or mBCC. The primary analysis (November 26, 2010, data cutoff) found an objective response rate of 30.3% in patients with mBCC (n = 33) and 42.9% in patients with laBCC (n = 63) according to independent review [Sekulic A et al. *N Engl J Med*. 2012]. The median duration of response (DOR) according to independent review was 7.6 months for both groups.

Aleksander Sekulic, MD, Mayo Clinic, Scottsdale, Arizona, USA, presented the safety and investigator-assessed efficacy results of the analysis, performed 30 months after the primary analysis (May 30, 2013, data cutoff). Ninety-six patients with radiographically measurable laBCC (n = 63) or mBCC (n = 33) were treated with vismodegib until disease progression or intolerable toxicity occurred. The secondary end points included investigator-assessed objective response rate, progression-free survival, DOR, overall survival, and safety.

At the 30-month analysis, the objective response rates were 48.5% in the mBCC group and 60.3% in the laBCC group, which were comparable to the primary analysis results. The median DOR was 14.8 months in the mBCC group and 26.2 months in the laBCC group. The median progression-free survival at the 30-month analysis was 9.3 months in the mBCC group and 12.9 months in the laBCC group. The median overall survival at the 30-month analysis was 33.4 months in the mBCC group but not evaluable in the laBCC group.

The adverse event (AE) profile of vismodegib was consistent with that previously reported. At the 30-month analysis, 58 patients (55.8%) reported grade 3 to 5 AEs. The most common of these were weight loss, muscle spasms, and fatigue. Two of 6 women of childbearing potential (33%) in the laBCC cohort reported amenorrhea. Serious AEs were reported in 36 patients (34.6%), including pneumonia, syncope, hip fracture, heart failure, cellulitis, gastrointestinal hemorrhage, squamous cell carcinoma, pulmonary embolism, deep vein thrombosis, and death.

At the 30-month analysis, 33 all-cause deaths (31.7%) had been reported, compared with 16 (15.4%) at the primary analysis. The most common causes of death were progressive disease (n = 17; 16.3%) and AEs (n = 8; 7.7%). The AEs resulting in death included unknown (n = 3), hypovolemic shock (n = 1), myocardial infarction (n = 1), meningeal disease (n = 1), ischemic stroke (n = 1), and general physical health deterioration (n = 1). None of the deaths were considered by the investigators to be related to vismodegib treatment.

The estimated median DOR substantially improved with vismodegib treatment. The median DOR approximately tripled in the laBCC cohort as compared with the primary analysis result. The safety profile of vismodegib was consistent with that reported in the primary analysis.