Acne is a chronic inflammatory disease of the pilosebaceous unit driven by four main pathogenic factors: sebum production, overgrowth of *C. acnes* bacteria, follicular hyperkeratinization, and inflammation. We now know that inflammation is the driving factor in acne and precedes development of the microcomedone. Pro-inflammatory cytokines and blood cells are present around the pilosebaceous unit even in clinically normal appearing skin in acne-prone patients. Treatment guidelines recommend topical retinoids as a foundational treatment for most acne. They offer comedolytic benefits, reduce follicular hyperkeratinization, and provide direct anti-inflammatory effects.

Retinoids for acne have been studied since the 1920s. In 1925, it was discovered that vitamin A deficiency in rats led to abnormal keratinization. High-dose oral vitamin A therapy was first considered for acne in the 1940s. Tretinoin was synthesized in 1946 and publicly released in 1971, and isotretinoin, initially made in the lab in 1955, became available in 1982. Adapalene came to market in 1995, followed by tazarotene in 1997. It has been more than 20 years since a new topical retinoid has been developed with the recent release of topical trifarotene.

**PRE-CLINICAL DATA**

Retinoids exert their effects through nuclear retinoid receptors. There are two main families (RARs and RXRs), and each receptor is a heterodimer of three subtypes: alpha, beta, and gamma. These receptors stimulate transcription of target genes involved in normalization of cell proliferation and inflammation. RARg is the predominant retinoid receptor subtype in the skin. Trifarotene has a 20 times greater selectivity for RARg over RARa and RARB, whereas tretinoin and adapalene have less specificity.

In experimental models, trifarotene activates gene expression of retinoid-modulated pathways. Studies have been performed on trifarotene using ex vivo cultured human skin, fuzzy rat in vivo, and non-inflammatory skin in acne patients. It has been shown to induce expression of genes responsible for activities including epidermal differentiation, cell proliferation, response to stress, proteolysis, proliferation, and cellular adhesion.

Preclinical studies have evaluated the interactions of trifarotene with the skin. Through mass spectrometry, trifarotene was shown to penetrate the pilosebaceous unit in facial skin. Using the rhino mouse model, the comedolytic properties of trifarotene were demonstrated, with reductions in comedones compared with non-treated skin. Finally, trifarotene was stable in human keratinocytes for more than 24 hours.

**CLINICAL DATA**

The Phase 3 clinical trials PErFeCt 1 and PErFeCt 2 were conducted in the US, Canada, Europe, and Russia from 2015 to 2017. In the multi-center, double-blind, randomized, vehicle-controlled trials, trifarotene was compared to vehicle over 12 weeks. The studies enrolled 1,208 and 1,212 patients, respectively, and randomized 1:1 to receive active drug or vehicle. The drug met its primary endpoints in both studies.

At week 12, treatment success (clear or almost clear with a two-grade improvement in global assessment score) was achieved by trifarotene versus vehicle, 29.7 percent and 42.8 percent vs 20 percent and 25.8 percent, respectively.

Evaluation of truncal acne was a secondary endpoint in the study, and there was statistical superiority in treatment success at week 12 in the trifarotene arm versus the vehicle, 35.8 percent and 43.1 percent vs 25.7 percent and 30.1 percent. Moreover, trifarotene offered a rapid onset of effect, with significant reductions in both inflammatory and comedonal lesion counts as early as one week on face and two weeks on trunk.

Trifarotene was safe and well tolerated. Most treatment-related emergent adverse events were cutaneous application site reactions including erythema, scaling, dryness, and stinging/burning. Severe cutaneous reactions including skin irritation, sunburn, dermatitis allergic, application site pain, erosion, and irritation occurred in the trifarotene arm. Roughly 350 patients completed a 52-week safety study, which showed...
that trifarotene was well tolerated on the face and trunk. Skin irritation peaked at week one on the face and between weeks two and four on the trunk before subsiding. Notably, only four patients (0.9 percent) discontinued due to lack of efficacy, and 16 (3.5 percent) discontinued because of an adverse event.

Efficacy was also captured in the 52-week study with treatment success on the face seen in 65.1 percent of patients and on the trunk in 66.9 percent of patients.

CONCLUSION

Trifarotene is the first new topical retinoid to come to the market in 20 years. It is a first-in-class RARg-selective retinoid. It has been shown in vitro and in animal models to activate expression of retinoid-modulated genes, effectively penetrate the follicle, normalize cell turnover, and reduce inflammation.

In its pivotal Phase 3 trials, trifarotene demonstrated rapid improvement after one week on the face and two weeks on the trunk. Clinical improvement continued over 52 weeks, with treatment success achieved in more than 65 percent of patients on the face and the trunk.

Trifarotene is a promising new therapeutic option to treat acne patients with lesions on the face and the trunk.

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Disclosures: Dr. Zeichner is a consultant for Almirall, Burt’s Bees, Dermavant, Derrnira, Galderma, Johnson and Johnson, L’Oreal, LEO Pharma, Menlo Therapeutics, Ortho Dermatologics, Pfizer, Sanofi/Regeneron, Sun Pharma, and Unilever.

DID YOU KNOW?

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