Clinical Pharmacokinetics and Drug Metabolism of Tazarotene
A Novel Topical Treatment for Acne and Psoriasis

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Abstract

Tazarotene (AGN 190168) is a new acetylenic retinoid which is effective for the topical treatment of patients with stable plaque psoriasis and mild to moderate acne vulgaris. Topical gel application provides direct delivery of tazarotene into the skin. At 10 hours after a topical application of 0.1% tazarotene gel to the skin of healthy individuals and patients with psoriasis, approximately 4 to 6% of the dose resided in the stratum corneum and 2% of the dose distributed to the viable epidermis and dermis.

Tazarotene is rapidly hydrolysed by esterases to its active metabolite, tazarotenic acid. Tazarotenic acid does not accumulate in adipose tissue, but undergoes further metabolism to its sulfoxide and to other polar metabolites and is rapidly eliminated via both urinary and faecal pathways with a terminal half-life of about 18 hours.

Percutaneous absorption is similar between healthy individuals and patients with facial acne, leading to plasma concentrations below 1 μg/L. The systemic bioavailability of tazarotene (measured as tazarotenic acid) is low, approximately 1% after single and multiple topical applications to healthy skin. In patients with psoriasis under typical conditions of use, systemic bioavailability increased during the initial 2 weeks of treatment from 1% (single dose) to 5% or less (steady state).
state). The increased bioavailability is probably related to decreases in plaque elevation and scaling due to successful treatment, resulting in a less effective skin penetration barrier to tazarotene.

Steady-state concentrations of tazarotenic acid are achieved within 2 weeks of topical treatment in both healthy and psoriatic skin types. The large variability in plasma concentrations observed in patients with psoriasis is probably because of the large differences in lesional skin condition, the amount of drug applied and the surface area of application. There was no significant drug accumulation in the body with long term treatment of patients with psoriasis.

Topical administration of tazarotene requires dosages much smaller than those usually required for oral retinoids, such as isotretinoin, acitretin and etretinate, and it delivers the drug directly into the target skin tissues. The low systemic absorption and rapid systemic elimination of tazarotene and tazarotenic acid results in limited systemic exposure. Thus, topical tazarotene has a low potential for systemic adverse effects and is effective in the treatment of patients with acne and psoriasis.

Tazarotene (AGN 190168) is a novel synthetic acetylenic retinoid in a topical gel formulation which provides direct drug delivery to the skin and limited systemic exposure. Being a prodrug itself, tazarotene was designed to undergo rapid and complete metabolism to its active metabolite tazarotenic acid. Tazarotenic acid has a short systemic residence time and limited tissue distribution in animals.[1-3]

First and second generation retinoids contain several alternating single and double bonds which confer great conformational flexibility, allowing the molecules to adopt a variety of shapes and creating the potential to interact with multiple receptors. Tazarotenic acid is a conformationally-locked retinoid designed to interact selectively with receptors, thereby enhancing its therapeutic index. It has selective affinity for the retinoic acid receptor (RAR) family of retinoid receptors, particularly RARβ and RARγ.[4] It is highly active in cell culture and in vivo assays related to epidermal proliferation and differentiation. Tazarotene as a prodrug does not bind to the nuclear retinoic acid receptors.

The exact mechanism of action for tazarotenic acid in patients with psoriasis and acne is unknown. When topically applied, tazarotene blocks the induction of ornithine decarboxylase (ODC) activity by the tumour promoter 12-O-tetradecanoylphorbol 13-acetate (TPA) in the epidermis of the hairless mouse. ODC catalyses the first step in polyamine synthesis and is associated with cell proliferation and hyperplasia. Both ODC activity and hyperplasia are elevated in the psoriatic plaque.

In human epidermal cell cultures, tazarotene suppresses the gene expression of 2 marker proteins, MRP-8 (calgranulin A) and SKALP (skin derived anti-leukoproteinase), highly elevated in psoriatic epidermis.[5] In clinical pharmacology studies, a 2-week treatment of psoriatic skin with tazarotene decreases expression of inflammatory markers in both the epidermis and dermis. The effects of tazarotene in psoriasis may, therefore, include direct suppression of inflammation as well as inhibition of proliferation and normalisation of differentiation in the epidermal layer.[6]

In clinical trials in patients with plaque psoriasis, tazarotene 0.05% and 0.1% gels have demonstrated superior efficacy over vehicle gel as measured by significant decreases in plaque elevation, scaling, erythema and significantly greater treatment response rates.[7,8] Tazarotene has a rapid onset of action which is evident as early as the first week of treatment and a sustained therapeutic effect which lasts up to 12 weeks after the discontinuation of treatment.[8] Compared with twice daily fluocinonide cream, once daily tazarotene was generally as effective but demonstrated better maintenance of therapeutic effect than fluocinonide cream for 12 weeks after the discontinuation of treatment.[9]