Tapinarof: A Novel Topical Agent For Psoriasis

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Introduction

Psoriasis is a chronic, relapsing, inflammatory skin condition accounting for 2.3% of dermatology outpatients in India.[1] The treatment of psoriasis depends on several factors, such as extent of involvement, comorbid conditions, and cost of treatment. In mild disease, topical treatment as monotherapy is effective. In moderate-to-severe disease, topical agents are used concurrently with either ultraviolet light or systemic medications. Although the treatment of psoriasis has significantly advanced after the introduction of biologics targeting specific immune pathways, the availability of newer topical agents with novel mechanisms is limited. Topical agents include coal tar, anthralin, corticosteroids, vitamin D derivatives, and vitamin A derivatives.[2]

Despite the availability of numerous topical treatments for psoriasis, there is a demand for alternatives that provide greater effectiveness and satisfactory safety levels.[2] Coal tar is a conventional topical agent in psoriasis, which targets aryl hydrocarbon receptor (AhR) in a nonspecific mode, but its unpleasant odor and property to stain tissue limits its use. Tapinarof is a novel, nonsteroidal, topical therapeutic AhR-modulating agent (TAMA) approved by the United States Food and Drug Administration (US FDA) on May 23, 2022, in adults with plaque psoriasis.[3]

AhR signaling and psoriasis

AhR is a ligand-dependent transcription factor expressed widely in keratinocytes, T cells, antigen-presenting cells, mast cells, fibroblasts, and macrophages. On binding to the ligand, the cytoplasmic receptor translocates into the nucleus followed by dimerization with the AhR nuclear translocator (ARNT), leading to the activation of various genes. AhR signaling regulates the differentiation of T-helper (Th) 17 and Th22 cells and the expression of interleukin (IL)-17 and IL-22 cytokines. AhR signaling also has a role in maintaining skin barrier integrity.[4-6] In skin biopsy specimens of psoriatic patients, increased AhR expression was noted.[7]

Structure

The molecular formula of tapinarof is C17H18O2. Tapinarof is chemically 5-[(E)-2-phenylethenyl]-2-[propan-2-yl] benzene-1,3-diol), a synthetic stilbene molecule with a hydroxyl group [Figure 1].[4]

Mechanism of action

Tapinarof acts as an AhR modulator. This results in the following effects:

1. **Role of tapinarof in AhR signaling in immunomodulation-**
   Tapinarof by binding to AhR downregulates the expression of IL-17 and IL-22.[5]
2. **Role of tapinarof in AhR-mediated regulation of keratinocyte function-**
   Tapinarof induces the expression of skin barrier genes that are downregulated in psoriasis, which include filaggrin and loricrin. It helps in the normalization of skin barrier.[4,5]
3. **Role of tapinarof in AhR-mediated reduction of oxidative stress**
   Tapinarof has an intrinsic antioxidant activity due to the direct scavenging of reactive oxygen species (ROS).[8] It activates the AhR–nuclear factor erythroid 2-related factor 2 (AhR-Nrf2) transcription factor pathway, which causes the expression of antioxidant enzyme genes reducing ROS.[4,8] This dual mechanism of tapinarof reduces epidermal oxidative stress, which is significant in the pathogenesis of psoriasis.

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Source of tapinarof

Tapinarof is a secondary metabolite of the gram-negative bacteria *Photorhabdus luminescens*, which lives in the gut of nematodes of the genus *Heterorhabditis*. It was found that insects infected with these nematodes did not decay after death, and it was proven to be due to the presence of the metabolites produced by *Photorhabdus luminescens*.[2]

Pharmacokinetics

In vitro studies have shown that 99% is plasma protein bound. No significant systemic absorption was demonstrated. It was found to have a lower than quantifiable limit of plasma concentration. Metabolism occurs in the liver, through oxidation, sulfation, and glucuronide conjugation reactions.[4]

Indications

Tapinarof is indicated and FDA approved for use in adults in the treatment of plaque psoriasis.[9] Its use in atopic dermatitis is under phase 3 trial.

Composition and storage

Tapinarof is commercially available as 1% cream (10 mg/gm). It should be stored at 20–25 degrees Celsius.

Method of application

Patients should be advised to apply the cream once daily over the skin lesions.[9]

Efficacy

In a phase 2 trial of tapinarof, 60% of patients with psoriasis showed more than 75% improvement in the Psoriasis Area Severity Index (PASI) with once-daily treatment.[10] In two phase 3 multicenter randomized double-blind vehicle-controlled trials Phase 3 Trials of Tapinarof Cream for Plaque Psoriasis (PSOARING 1 and PSOARING 2), tapinarof was found to be more effective than vehicle control in patients with psoriasis affecting 3% to 20% of the body surface area when treated for 12 weeks.[11] The PSOARING 3 trial, which was an open-labeled follow-up study of 40-week duration of patients who had completed the 12-week PSOARING 1 or 2 trial, showed consistent results in safety and efficacy. This study also demonstrated a remission period of 4 months of treatment on follow-up.[12] There are no studies available on its efficacy in extensive psoriasis involving >20% of the body surface area. Hence, the maximum amount of drug that can be safely applied per day has to be assessed by further studies involving extensive psoriasis.

Adverse effects and safety profile

The adverse effects are mild and infrequent. The adverse effects documented include folliculitis, contact dermatitis, pruritus, and headache.[12] Available data are insufficient for its safety in pregnancy and lactation. Safety and outcome have not been established at ages less than 18 years. No additional risk has been reported for the elderly.[4,9] No evidence of mutagenicity and carcinogenicity were found in animal studies.[9]

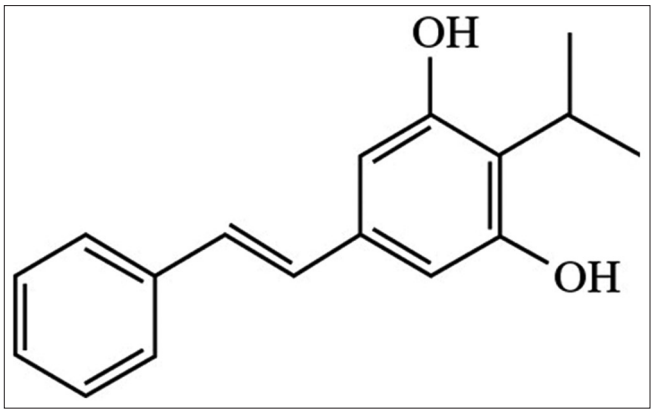

Figure 1: Chemical structure of tapinarof

Contraindications

Based on existing studies, there are no known contraindications. Based on the lack of safety data, it is better to avoid it during pregnancy, lactation, and at ages less than 18 years.[9]

Conclusion

Tapinarof is a novel TAMA approved for the treatment of plaque psoriasis in adults. It seems to be a promising topical agent in the management of psoriasis with a novel mechanism of action. Further studies are required to compare the safety and effectiveness with existing topical agents. Further studies are also needed to prove whether it can be combined with other existing topical agents and phototherapy. Trials are in progress for its use in atopic dermatitis and in the pediatric population.

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Nil.

Conflicts of interest

There are no conflicts of interest.

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