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Tazarotene and Psoriasis: Biologic Underpinnings That Impact Disease Control

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Oldie But Goodie

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Research over the past several years has elucidated the pathophysiology of psoriasis, yielding both new treatment options and enhanced knowledge of the mechanisms of action of existing treatments. As we have developed a fuller picture of this common inflammatory disease, we have uncovered new insights into the benefits of one of the most forgotten and undervalued topical psoriasis treatment—TAZAROTENE. Accumulated evidence shows that this drug, now used for more than two decades mostly for acne vulgaris, is a multifunctional treatment that targets numerous drivers of psoriatic skin disease.

As a topical retinoid, tazarotene works to normalize keratinocyte hyperproliferation—which accounts for initial interest in the drug as a potential psoriasis treatment. Its effects on keratinocytes are numerous and even include changes in gene expression.[1] In fact, the reversal of gene expression associated with tazarotene treatment is similar to the effects conferred by systemic biologic treatments.[2] It is now thought that effects on gene expression contribute to the hypothetical "remittive effect" of tazarotene in psoriasis; patients continue to maintain therapeutic benefit for several weeks after treatment is withdrawn,[3] which I call the "durability effect" rather than "remittive effect" in a chronic disease setting.

Of note, tazarotene has been shown to have immunologic impact that directly reduces the inflammatory drivers of psoriasis. Tazarotene has numerous effects on the pro-inflammatory state of epidermal keratinocytes, including the suppression of numerous IL-1 family cytokines induced by TNF-alpha or IL-17.[1] Other immunologic effects include regulation of dendritic cells, macrophages, and neutrophils.[4] Additionally, tazarotene has been shown to have direct anti-angiogenic effects. It appears to inhibit platelet aggregation and reduce the migration and adhesion of monocytes and lymphocytes.[5] Ironically, tazarotene has given its name to three genes; TIG-1, TIG-2, and TIG-3 (tazarotene induced genes 1,2,3) which may mediate an antiproliferative effect.[6]

The growth of systemic and biologic therapies has provided new treatment options for patients with moderate to severe psoriasis, and much attention is focused on these newer treatments. However, the majority of patients with psoriasis are still candidates for topical treatments. What's more, patients using biologic and systemic treatments may additionally require a topical treatment to address areas of recalcitrant disease or flare ups.

Topical treatment has been and will always be the mainstay treatment in dermatology. Dermatology providers must therefore be prepared to make topical treatment recommendations most likely to provide the best outcomes for each patient. In summary, tazarotene shows remarkable efficacy on its own by downregulating the markers of keratinocyte differentiation, keratinocyte proliferation, and inflammation.[6] It can also be used in combination with other topical treatments, such as topical corticosteroids to overcome possible irritation with retinoid use.

Unique among topical therapies in its ability to confer a durable effect on psoriasis, topical tazarotene is an "OLDIE BUT GOODIE" over 20 years of its clinical use.

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ORIGINAL ARTICLE

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A Reappraisal of Fixed-Combination Halobetasol Propionate and Tazarotene for the Treatment of Psoriasis: Biological Underpinnings, Therapeutic Mechanisms, and Economic Considerations

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ABSTRACT

Psoriasis is a complex inflammatory disease, which can be triggered by the interplay among keratinocytes, various immune cells, and even dermal vascular endothelial cells. Understanding of the key players and cytokine/chemokine messengers involved in the initiation and maintenance of psoriasis has significantly evolved and led to numerous systemic biologic therapies targeting those specific components. These therapies, despite their successes, do not ubiquitously affect all pathogenic cellular pathways. They also carry their risks and may be contraindicated in certain patient populations. Therefore, other therapeutics are still necessary. Tazarotene, a decades-old topical retinoid, has been successfully used for treating cutaneous psoriasis. Its retinoid effect via binding to retinoic acid receptors (RAR)/retinoic X receptors (RXR) alters cellular gene expression of numerous pathogenic cells and leads to a long-standing maintenance effect despite discontinuation — a phenomenon known as remittance. Concurrent use of tazarotene with topical corticosteroids results in reduced incidence of treatment-related adverse events. A fixed-combination lotion containing halobetasol propionate (HP) and tazarotene (HP 0.01%/TAZ 0.045%, Duobrii, Ortho Dermatologics) was developed implementing polymeric emulsion technology that demonstrates efficacy in psoriasis while mitigating adverse events associated with each component alone as monotherapy. In this paper, we review the pathogenesis of psoriasis and illuminate the effect of tazarotene and HP on key cellular pathways. In addition, we review the clinical efficacy of fixed-combination HP 0.01%/TAZ 0.045% lotion in psoriasis as well as its long-term treatment maintenance, applicability in skin of color, and beneficial economic impact for patients and healthcare stakeholders. As HP 0.01%/TAZ 0.045% lotion is safe and exhibits excellent efficacy, it should be within the therapeutic toolbox for every psoriasis patient.

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INTRODUCTION

Psoriasis is a chronic inflammatory autoimmune condition that affects the skin and leads to a significantly reduced quality of life. Approximately 125 million people globally are estimated to be affected.[1] Its pathogenesis is multifactorial, resulting from alterations in multiple skin cells including keratinocytes, immune cells, and dermal vascular endothelial cells. These alterations lead to the release of pro-inflammatory mediators inducing the recruitment of a diverse array of immune cells, increased vascularization, and, ultimately, hyperproliferation of keratinocytes in the epidermis, which result in raised, scaly plaques with a compromised epidermal barrier.[2]The inflammatory milieu causes a cycle of cellular damage and further cytokine/chemokine release, thus maintaining a disease state that is difficult to break.[3] Furthermore, patients with greater body surface area involvement are at increased risk of cardiovascular co-morbidities.[4] While systemic therapies such as biologics have resulted in incredible therapeutic outcomes, especially in those with severe disease, topical therapy remains critical as patients may not necessarily be candidates for systemic therapies or there may be residual cutaneous psoriatic plaques despite systemic therapy that could be cleared with additional topicals.[5] These therapies target a particular cytokine/chemokine "hub" such as tumor necrosis factor (TNF)-α, interleukin-17 (IL-17), or interleukin-23 (IL-23). Although these molecules are among the most important mediators of psoriasis, therapies that target them do not necessarily exert direct effects on all key cellular pathways. Thus, there remains a need for comprehensive therapeutics that can simultaneously target all pathogenic cells, thus optimizing efficacy and reducing the likelihood of disease relapse.

Retinoids have long been used in many skin diseases as both topical and systemic therapeutics. As they have been in existence for decades, their effects have been well-studied in numerous cells. They are particularly interesting as they cause various changes in gene expression, which lead to long-standing effects even after their removal. This is clinically beneficial as retinoids may help achieve and maintain an effective therapeutic outcome despite discontinuation, thereby reducing adverse effects and increasing patient compliance.

Tazarotene is a retinoid that was approved for the topical treatment of psoriasis over 20 years ago.[6] Tazarotene has also been shown to have a desirable remittent effect for several weeks after discontinuation, likely due to its effect on gene expression and reversing the psoriatic transcriptome back toward a normal skin baseline.[7,8] This review serves to highlight the cellular mechanisms underpinning the success of tazarotene in psoriasis and to provide a rationale for its use in almost all patients due to its broad effects on almost every cell type implicated in the pathogenesis of psoriasis. Furthermore, this review will discuss the clinical data and implications of the FDA-approved fixed-combination lotion

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containing the potent-to-superpotent corticosteroid halobetasol propionate (HP) and tazarotene (HP 0.01%/TAZ 0.045%, Duobrii, Ortho Dermatologics) for the treatment of psoriasis.

Overview of Psoriasis Pathophysiology

The pathophysiologic mechanisms of psoriasis have become significantly better understood over the past few decades. As psoriasis is a multifaceted condition with numerous cellular players, it is helpful to compartmentalize these players to better illustrate key areas for therapeutic intervention. This compartmentalization is organized into 3 major components: (1) epidermal/keratinocyte component, (2) immunological/immune cell component, and (3) vascular/endothelial cell component (Figure 1). There is interplay among all compartments, and therapies that can address the greatest number of components simultaneously are likely to be most efficacious.

Epidermal/Keratinocyte Component: Epidermal keratinocytes are undoubtedly one of the key players in the pathogenesis of psoriasis. They are involved in the initiation of disease as well as its maintenance via amplification of psoriatic inflammation.[9] In normal homeostatic conditions, keratinocytes are terminally differentiated. In psoriatic disease, they exhibit abnormal differentiation and excessive proliferation. These changes are governed by numerous cellular processes (Figure 1). Increased expression of keratin (K) 6, K16, and K17 are found in hyperproliferative psoriatic keratinocytes but not in normal epidermis.[10,11] Keratinocyte transglutaminase (TGase-K), a protein found in the stratum corneum and critical for the formation of the cornified envelope, and the differentiation marker involucrin are also upregulated in psoriatic epidermis.[12,13] Other hyperproliferative markers induced in psoriatic lesions include migration inhibitory factor-related protein (MRP-8), skin-derived antileukoproteinase (SKALP), and ornithine decarboxylase.[14] Tumor suppressors tazarotene-induced gene (TIG)-2 and TIG-3, which regulate keratinocyte proliferation and survival, are expressed at lower levels in psoriatic skin compared to non-lesional psoriatic or normal skin.[7,15,16] Downregulation of TIG-3 also leads to inflammatory angiogenesis via upregulation of placental growth factor expression.[17]

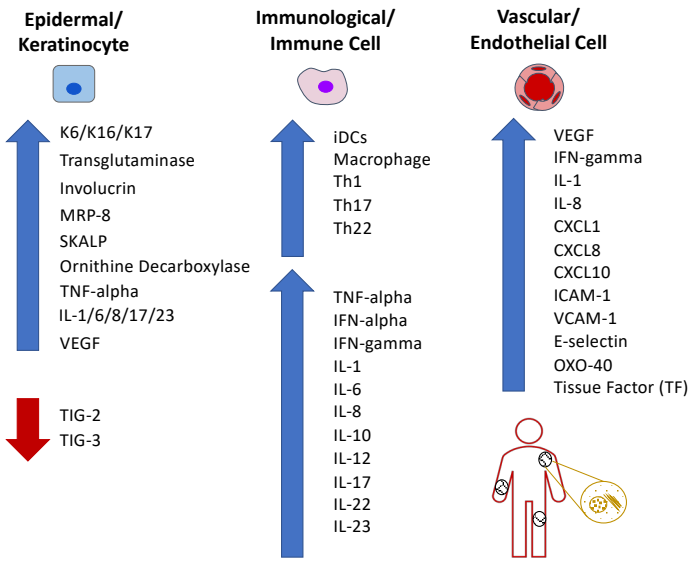
In addition to altering epidermal structure, psoriatic keratinocytes also play a role in inflammation. Stressed keratinocytes release numerous pro-inflammatory and pro-angiogenic cytokines, chemokines, and factors that activate immune and endothelial cells as well as neighboring keratinocytes via paracrine signaling to further promote keratinocyte stress/activation and continue the pro-inflammatory cycle.[18] Critical pro-inflammatory cytokines produced by keratinocytes implicated as major drivers of psoriasis include TNF-α, IL-1α, IL-1β, IL-6, IL-8, IL-17C, IL-17E, and IL-23(p19).[19-22] Vascular endothelial growth factor (VEGF), a pro-angiogenic molecule that causes increased vascular permeability and production of endothelial cell cytokines, is also upregulated in psoriatic keratinocytes.[23]

Immune Cell Component: It is thought that a trigger (ie, cutaneous injury, infection, drug) initially causes keratinocyte dysfunction, which then drives the development and progression of psoriasis via activation of both the innate and adaptive immune systems[24] (Figure 1). In the initiation phase, damaged keratinocytes activate innate cells via release of TNF-α, IL-8, VEGF, self-nucleotides, and other factors. These molecules induce plasmacytoid dendritic cells (DCs) and macrophages to produce interferon (IFN)-α and TNF-α, which lead to the maturation of resident dermal myeloid DCs (CD1c+ DCs) and monocyte differentiation into CD11c+, CD1c-, and CD141- inflammatory DCs (iDC). These pro-inflammatory DCs, in turn, secrete IL-12, IL-23, and TNF-α that lead to the differentiation of naïve T cells into T-cell subsets Th1, Th17, and Th22 lymphocytes that further secrete IFN- γ, IL-17, and IL22.[25] Macrophages are also increased in psoriatic immune infiltrates and produce pro-inflammatory cytokines such as IL-1α, IL-6, IL-23, and TNF-α.[26] Thus, they have an established role in the development and maintenance of psoriatic lesions.[27] Cytokines produced by DCs and macrophages ultimately act on epidermal keratinocytes leading to abnormal differentiation, hyperproliferation, and the release of more immunological mediators, thus perpetuating the pro-inflammatory cycle. The cutaneous vasculature is also affected by immune cell-released cytokines resulting in angiogenesis and endothelial cell changes that enhance immune cell recruitment, trafficking, and infiltration into local tissue.

Neutrophils are additional innate immune cells found in psoriatic lesions.[26,28] Neutrophils are recruited via IL-17C and CXCL8 produced by keratinocytes.[29] They help sustain psoriatic adaptive inflammation via release of neutrophil elastase, which contributes to Th17 cell development by cleavage of CXCL8 released by DCs into the active short form.[30]

In addition to an increase in number and function of pro-inflammatory innate and adaptive immune cells, psoriatic lesions have impaired regulator T cell (Treg) function. Tregs function to suppress the immune response by releasing inhibitory cytokines (ie, transforming growth factor (TGF)- β, IL-10) and directly

FIGURE 1. Cellular processes altered by psoriasis.



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interacting with inflammatory effector immune cells (ie, Th17). They are characterized by the expression of the transcription factor forkhead box protein 3 (FoxP3).[31] In psoriasis, IL-23 causes transdifferentiation of Tregs into pro-inflammatory Th17 cells while IL-17A reduces the expression of FoxP3. The combination of IL-17A and IL-23, therefore, suppress Treg activity both intrinsically and through depletion, respectively.[32-34] Therapies aimed at restoring Treg function and frequency may be impactful on psoriasis pathogenesis.[35]

Vascular/Endothelial Cell Components: The cutaneous vasculature also plays an active part in psoriatic inflammation along with keratinocytes and immune cells. VEGF secreted by keratinocytes results in angiogenesis and vascular dilation with increased fenestration causing vessels to be "leaky" and allowing for increased leukocyte trafficking.[36] Formation of new blood vessels is also necessary for the sustained survival of immune cells as endothelial cells are active inflammatory mediators. Endothelial cells stimulated by TNF-α increased expression and secretion of numerous pro-inflammatory factors including GM-CSF, CXCL10, CCL2, VCAM-1, E-selectin, matrix metalloproteinases, and IFN-γ leading to Th1 response.[36-40] Direct gene expression profiling of psoriatic endothelial cells versus controls also revealed up-regulation of IL-1b, IL-8, CXCL1, CXCL10, ICAM-1, and VCAM-1, among other inflammatory genes.[41] Immunohistochemistry has also confirmed the increased expression of adhesion molecules (ICAM-1, VCAM-1, E-selectin) in psoriatic endothelial cells, which are critical for immune cell adhesion and trafficking during inflammation.[42] CXCL8 secretion by endothelial cells is also another chemokine that attracts neutrophils and leads to their diapedesis across blood vessels into tissue.[43] Endothelial cells also participate in the adaptive immune response through expression of MHC molecules and co-stimulators such as CD2, ICOS, and OX-40.[44] Inflammatory psoriatic vessels are also in a hypercoagulable state, which leads to increased cardiovascular morbidity. The inflammatory milieu induces expression of tissue factor (TF) in endothelial cells and augments platelet activity.[45] As vascular inflammation is a substantial contributor to psoriasis, a therapeutic strategy would be to reverse endothelial cell angiogenesis and pro-inflammatory phenotype.

Role of Retinoic Acid Receptor Signaling in Psoriasis and Effect of Tazarotene

Tazarotene Mechanism of Action: Retinoic acids (RAs) have been well-studied for their effect on numerous cell types over the last few decades and have been employed for numerous cutaneous inflammatory and neoplastic disorders. The effects elicited by RAs are due to their effect on cellular gene expression changes via binding to retinoic acid receptors (RAR) or retinoic X receptors (RXR). RAR and RXR are nuclear receptor families that heterodimerize with each other (eg, RAR/RXR) upon RA binding and interact with portions of DNA containing retinoic acid response elements (RAREs) that regulate the transcriptional expression of different genes.[46] In humans, there are 3 isotypes of RAR (RARα, RARβ, RARγ) and 3 isotypes of RXR nuclear receptors (RXRα, RXRβ, RXRγ). Any of the RAR isotypes can heterodimerize with any of the RXR isotypes, leading to numerous permutations with various transcriptional outcomes.[47] Furthermore, different RAs have different nuclear receptor affinities, thus leading to unique gene expression changes and various clinical effects.[48] Notably, RARγ is the most frequently found RAR (>90% of all RARs) and is primarily found in the skin.[7]

In addition to direct effect on gene expression via the binding of RAR/RXR dimers to RAREs, another major effect of RA signaling is repression of the transcription factor AP-1.[49] AP-1 is a heterodimer of Fos and Jun proteins or Jun homodimers. There are numerous Fos and Jun isotypes that can also mix and match, leading to various transcriptional changes. AP-1 is expressed in skin and implicated in cutaneous homeostasis and pathogenic states.[50] In psoriasis, lesional skin exhibits enriched genes that contain AP-1 binding sites.[51] Antagonism of AP-1 is therefore a therapeutic approach to reverse this psoriatic gene signature. RAs binding to RARs has been shown to inhibit AP-1 and are thought to be effective in psoriasis, partially due to this mechanism.[49,52]

Tazarotene is a retinoid pro-drug that is metabolized into the tazaratonic acid, which is the bioactive form that selectively binds to RARβ and RARγ nuclear receptors.[7] It is the first topical retinoid used for the treatment of psoriasis and garnered approval over 20 years ago.[6] Its selectivity for RARγ may account for its efficacy in psoriasis given the ubiquity of RARγ in the skin. Notably, clinical improvement or remission of cutaneous psoriasis has been noted for extended periods of time despite discontinuation of tazarotene monotherapy — a phenomenon that is not found with topical corticosteroids or vitamin D monotherapy.[8] It is believed that such remittive effect is due to tazaraotene's ability to alter pathogenic cell gene expression at the transcriptomic level and return them toward normal healthy baseline.[7] The effects of tazarotene on the numerous cellular players in psoriasis, which contribute to its overall excellent and remittive efficacy, are reviewed next (Figure 2).

Role in Keratinocyte Differentiation, Proliferation, and Inflammation

RAR signaling regulates the expression of numerous genes involved in keratinocyte differentiation and proliferation. Hyperproliferative K6 and K16 as well as TGase-K are under such regulation.[53,54] Application of tazarotenic acid to psoriatic lesions results in the downregulation of K6, K16, and TGase-K. Tazarotene also downregulates numerous other over-expression differentiation and proliferation markers including involucrin, MRP-8, and SKALP.[7] On the other hand, the downregulation of TIG-1, TIG-2, and TIG-3 in psoriatic lesions is also reversed by tazarotene.[7,55] This reversal of epidermal keratinocyte gene expression changes from the psoriatic disease state to near normal non-disease state by tazarotene is therapeutic and similar to other efficacious systemic therapeutics such as ustekinumab.[19]

Tazarotene also has numerous effects on the pro-inflammatory state of epidermal keratinocytes. Numerous IL-1 family cytokines induced by TNF-α or IL-17 in cultured normal human keratinocytes were suppressed by retinoic acid.[56] Lesional psoriatic skin treated with retinoic acid also resulted in reduction of IL-1β.[57] VEGF

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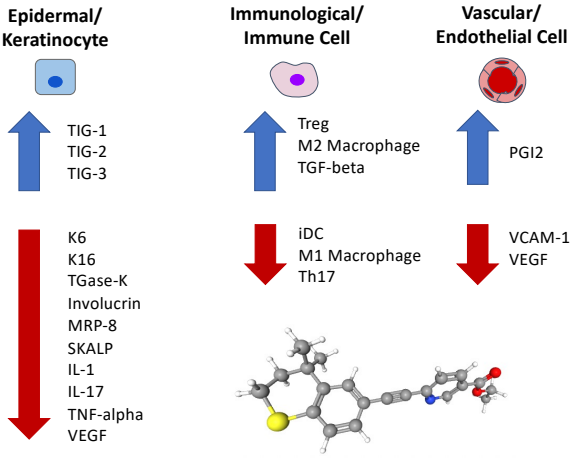
FIGURE 2. Cellular processes altered by tazarotene.



expression in normal human keratinocytes as well as psoriatic epidermal keratinocytes was also attenuated by all-trans-retinoic acid.[58]

Role as an Immunomodulator: The immune landscape in psoriasis is evidently complex with significant interconnectivity. While therapeutics aimed at targeting critical mediators (ie, biologics inhibiting TNF-α, IL-17, IL-23) have had great efficacy, patients often rebound.[59] Aside from the potential of neutralizing antibodies, this may be due to these treatments incompletely addressing the entire immune cell milieu. Thus, treatments aimed at blocking pro-inflammatory mediators, reducing the number and function of inflammatory effector immune cells as well as inducing tolerance (ie, increasing Treg development and function) are ideal. RA is an ideal therapy as it has been shown to affect numerous immune cell players via direct cellular effects.

With regard to innate inflammation, RA alters DCs, macrophages, and neutrophils. DCs treated with RA developed a tolerogenic phenotype with increased ÇD141 and GARP expression, which are essential for inducing Tregs.[60] Pro-inflammatory M1 macrophages can be converted to anti-inflammatory M2 macrophages by RA.[61] RA also reduces the production of neutrophil elastase produced by neutrophils, thus blunting the expansion of Th17 effector cells.[30]

RA additionally affects cellular players of adaptive inflammation. It potentiates the differentiation of naïve T cells into Tregs along with TGF-β produced by tolerogenic DCs.[62] It also upregulates FoxP3 expression in the presence of IL-6, which causes defective T-reg function.[63,64] Furthermore, RA inhibits Th17 cell differentiation and therefore suppresses the pathogenic pro-inflammatory Th17 effector response.[65]

Effects of RA on the Vascular Component of Psoriasis: RA has direct effects on blood vessel endothelial cell function that further promote disease resolution. An in vitro study showed an anti-angiogenic inhibitory effect on endothelial cell proliferation, migration, and tube formation.[66] Pre-treatment of human dermal microvascular endothelial cells (HDMECs) with all-trans-retinoic acid prior to treatment with TNF-α blunted the stimulatory effect of TNF-α on VCAM-1.[67] VCAM-1 is a critical adhesion protein found on blood vessel endothelial cells that promotes the adhesion of immune cells and guides their migration to sites of inflammation. Thus, downregulation or inhibition of VCAM-1 is an anti-inflammatory strategy. The vasculo-centric anti-inflammatory effect of RA is also mediated by its induction of prostaglandin I2 (PGI2) in endothelial cells, which inhibits platelet aggregation as well as monocyte and lymphocyte adhesion and migration.[68] Moreover, RA reduces the expression of the procoagulant protein TF in endothelial cells activated by TNF-α.[69]

Combination Tazarotene and Topical Corticosteroids

Topical tazarotene, while having numerous therapeutic mechanisms for psoriasis, may cause adverse effects for patients that limit its use. These commonly include application site pain, dermatitis, pruritus, and erythema.[70] To mitigate these adverse effects, concurrent use of topical corticosteroids (TCS) with tazarotene has been assessed.[71] In addition, corticosteroids have additional biological effects that are complementary to tazarotene.

Corticosteroids, such as HP, activate the glucocorticoid receptor to exert both genomic and non-genomic actions like activated RARs.[70] These actions regulate the transcription of genes involved in immune cell function and inflammation (eg, IL-6, TNF-α, NF-κB), endothelial cell function (eg, vasoconstriction, nitric oxide production), as well as keratinocyte cell hyperproliferation (eg, lipocortin). Psoriasis therapies employing combination tazarotene with TCS demonstrated greater efficacy over monotherapy with either treatment given the aforementioned mechanisms,[72,73]

In addition, combination therapy with tazarotene and TCS mitigates the safety and tolerability concerns associated with each alone as monotherapy.[71] TCS reduces retinoid-induced irritation, erythema, itching, and pain. The addition of a retinoid to TCS therapy protects against TCS-induced epidermal atrophy[74] by increasing epidermal thickness.[75] Pigmentary changes due to TCS as well as skin inflammation are also improved with retinoid therapy.[76]

HP 0.01%/TAZ 0.045% Lotion Formulation and Safety

Given the benefits of concurrent use of TCS and TAZ, a fixed-combination HP 0.01%/TAZ 0.045% lotion was developed in a single formulation. A novel 3-dimensional polymeric emulsion-based vehicle technology was implemented to allow active ingredients and moisturizing excipients to be encapsulated together within the same oil droplets and to be evenly distributed throughout a mesh matrix that breaks apart upon contact with the skin.[77] This innovative vehicle technology allows for rapid and efficient delivery of moisturizing and active ingredients in a uniformly spreadable formulation[78] thereby maximizing therapeutic benefit as well as patient tolerability and adherence to treatment.[79] Acceptability of the vehicle lotion was very high with nearly 100% of patients responding favorably to questions regarding its hydrating properties, feel, and application.[77]

Combination HP 0.01%/TAZ 0.045% lotion is associated with low incidence of adverse events in psoriasis patients including

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contact dermatitis and application site pruritus and pain. Rates of application site adverse events are lower relative to TAZ monotherapy due to the anti-inflammatory actions of HP. A phase 2 study comparing HP 0.01%/TAZ 0.045% lotion and TAZ monotherapy applied daily over 8 weeks revealed treatment-related adverse events to be 33.9% and 46.6%, respectively.[80] Pooled phase 3 studies also demonstrated significant reductions in the severity of itching, dryness, and burning/stinging skin symptoms with HP 0.01%/TAZ 0.045% lotion compared to vehicle after 8 weeks.[81] Furthermore, incidences of skin atrophy were rare in phase 2 and phase 3 clinical trials with daily application over 8 weeks and tend to resolve by the study's end.[80] Long-term daily application over 24 weeks in an open-label study revealed only 0.7% of patients exhibited skin atrophy.[82]

HP 0.01%/TAZ 0.045% Lotion Efficacy in the Treatment of Psoriasis

Topical therapy is mainstay in the treatment of psoriasis irrespective of severity. The ideal topical therapy is one requiring the least frequency of application with the greatest efficacy, safety, and patient tolerability. Furthermore, this treatment should aim to affect numerous components of the disease process while also reducing the economic burden of disease and obtaining treatment. HP 0.01%/TAZ 0.045% lotion is the optimal treatment in this regard for patients with psoriasis. The clinical efficacy of HP/TAZ lotion in moderate-to-severe and mild psoriasis as well as skin of color is discussed next. The long-term benefits of HP/TAZ lotion after treatment discontinuation as well as economic implications are also discussed.

Moderate-to-Severe Psoriasis: Once daily application of fixed-combination HP 0.01%/TAZ 0.045% lotion has demonstrated efficacy in phase 2 and phase 3 trials. Two phase 3 randomized, double-blinded trials assessed the rate of treatment success (defined as at least ≥2-grade reduction in IGA score and a score of 0/1 (clear/almost clear) of HP/TAZ lotion over 8 weeks of treatment vs vehicle in patients with moderate-to-severe psoriasis.[81] Pooled data from those trials revealed that at week 12 (4 weeks post-treatment), 40.6% of participants using HP/TAZ lotion (n=276) achieved treatment success compared to 9.9% using vehicle (n=142).[83] Post-hoc analysis showed consistent effects across both male and female participants.[84] A long-term open-label study in 555 adult participants with daily application of HP/TAZ lotion also demonstrated treatment success in 54.4% at week 8.[82]

Mild Psoriasis: Topical therapy in mild psoriasis is mainstay. While fixed-combination HP 0.01%/TAZ 0.045% lotion has been extensively investigated in moderate-to-severe plaque psoriasis, data on its use in mild psoriasis is limited. Recent studies show that HP/TAZ lotion applied daily is also of benefit in patients with psoriasis with lower levels of BSA involvement. A post hoc analysis by Tanghetti et al assessed the efficacy of once daily HP/TAZ lotion compared to vehicle in 232 patients with baseline psoriasis BSA involvement of 3% to 5%.[85] Primary efficacy was the proportion of patients achieving ≥2-grade improvement from baseline in IGA score and a score of 0 (clear) or 1 (almost clear) at week 8. They found a statistically significantly greater response in the HP/TAZ group compared to vehicle with treatment success rates of 42.7% and 11.4%, respectively. A real-world Canadian multicenter retrospective chart review assessed the use of HP/TAZ lotion in 109 patients with mild-to-moderate plaque psoriasis (≤7% BSA) as monotherapy, adjunct to a stable dose of systemic therapy, or in combination with other topical medications.[86] At week 8, 45.3% achieved treatment success (as defined immediately above) with 66.0% IGA 0/1 without ≥2-grade improvement and 40.0% achieving Psoriasis Area and Severity Index (PASI) 75.

HP 0.01%/TAZ 0.045% Lotion in Skin of Color: Psoriasis in patients with skin of color provides an additional challenge due to greater severity and distribution of disease as well as dyspigmentation with resolution of the psoriasis.[87] Pigmentary changes can have significant psychosocial impact as well.[88] Studies assessing therapeutic outcomes specifically in this patient population are severely lacking. However, recent retrospective analyses point toward treatment efficacy and remittance of HP 0.01%/TAZ 0.045% lotion. Desai et al report on a case of a Black male patient who was enrolled in a randomized, vehicle-controlled study assessing HP/TAZ lotion for moderate-to-severe psoriasis (NCT02462070).[89] After 8 weeks of once-daily treatment, he achieved treatment success with an improvement to "almost clear" (IGA score of 1) at week 4 and was maintained for 4 weeks post-treatment (week 12). His quality of life significantly improved with a decrease from 9 ("moderate effect" on life) at baseline to 1 ("no effect" on life) from week 4 onwards. Furthermore, hypopigmentation, which was greatest at week 4, had returned to normal by week 12. Alexis et al later performed a similar post hoc subgroup analysis but pooled across 2 phase 3 vehicle-controlled trials investigating HP 0.01%/TAZ 0.045% lotion (NCT02462070 and NCT02462122).[90] They assessed efficacy across non-mutually exclusive subgroups of self-identified non-White or White and Hispanic/Latino participants. Treatment successes (IGA 2-grade improvement from baseline) at week 4 were significantly greater than vehicle in each subgroup and maintained 4 weeks post-treatment (week 12). While the sample size is low, these findings highlight a preliminary positive effect of HP/TAZ lotion across different racial/ethnic groups. Future studies are necessary to assess patients with skin of color and outcome measures more relevant to them (eg, pigmentary changes).

Adjunctive TAZ in Psoriasis Patients with Inadequate Response to Biologics: Adjunctive use of tazarotene is also critical in patients with moderate-to-severe psoriasis who undergo monotherapy with systemic biologic agents but do not achieve a satisfactory response. While switching biologics may be of benefit in some cases, additional costs and safety issues are incurred.[91] Thus, combination therapy with biologics and another modality (eg, topical therapy) is more effective than biologics alone.

Bagel et al performed the first open-label trial evaluating adjunctive therapy with HP 0.01%/TAZ 0.045% lotion in 25 patients with moderate-to-severe plaque psoriasis (BSA of 2% to 10%) with mean duration of 18.9 years, treated with biologics.[5] Patients who enrolled had been treated with biologics for at least 24 weeks at baseline and were not concomitantly using oral systemic

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medications for psoriasis or psoralen plus UVA phototherapy for ≤ 4 weeks, other topical antipsoriatic therapies for ≤ 2 weeks or UVB phototherapy for ≤2 weeks prior to study initiation. Patients applied HP/TAZ lotion once daily for 8 weeks then once every other day for an additional 4 weeks while maintaining their biologic therapy. Biologic monotherapy was maintained for an additional 4 weeks posttreatment. Treatment success was defined by the National Psoriasis Foundation recommendation of "treat-to-target" with achievement of BSA of 0% to 1%. The proportion of patients achieving treatment success was 20.0%, 64.7%, and 50.0% at weeks 8, 12, and 16, respectively. In addition, mean DLQI score decreased from 4.00 at baseline to 2.45, 2.18, and 2.33 at weeks 8, 12, and 16, respectively. Taken together, adjunctive use of HP/TAZ lotion in combination with biologics for psoriasis treatment is effective and improves quality of life.

Economic Considerations of Fixed-Combination HP 0.01%/TAZ 0.045% Lotion in Psoriasis Treatment: Psoriasis presents a significant socioeconomic burden on patients with access to affordable treatment remaining a barrier to care.[92] With numerous topical and systemic therapies available, physicians are tasked with choosing the most effective intervention at the lowest cost to the patient. As previously noted, many patients with moderate-to-severe psoriasis on biologics do not achieve a satisfactory response.[5] Bagel et al found almost 90% of these patients were likely to switch biologics due to unacceptable response. Addition of adjunct HP 0.01%/TAZ 0.045% lotion reduced the proportion of biologic non-responders and the proportion of participants rated as likely to switch biologics. Estimated total costs of 16-week maintenance dosing of biologics plus adjunct HP/TAZ lotion ranged from $14,675 to $54,025, with the majority costing less than $30,000; whereas switching biologics for 16 weeks is estimated to cost $33,340 to $106,400 given treatment induction and subsequent maintenance phases. Thus, potential cost savings range from $4,816 to $91,725 with the addition of adjunct HP/TAZ lotion.

HP/TAZ lotion monotherapy may also be more cost effective than other topical monotherapies for psoriasis. An incremental cost-per-responder analysis was performed comparing calcipotriene 0.005%/betamethasone dipropionate 0.064% (Cal/BD) foam to HP/TAZ lotion.[93] Revised calculation of this analysis by Glick et al found cost savings for HP/TAZ lotion daily application over 8 weeks vs Cal/BD foam daily application over 4 weeks.[94] They estimated that the incremental cost per Physician Global Assessment (PGA) 0/1 responder was $3,560 and $3,988 for HP/TAZ lotion and Cal/BD foam, respectively. HP/TAZ lotion, therefore, had a lower cost with a difference of $428 to reach treatment success. This difference in relative cost, along with therapeutic effectiveness, favorably positions HP/TAZ lotion for healthcare stakeholders and patients.

Long-term Maintenance of Effect with HP 0.01%/TAZ 0.045% Lotion: Combination treatments where tazarotene is added to a TCS are particularly effective given the dual mechanism of action of the retinoid effect with the steroid effect while also promoting long-term remittance.[95] The maintenance effect after drug cessation is likely due to transcriptional effects of tazarotene on lesional skin and returning the psoriatic gene signature back to a "pre-lesional" or normal skin phenotype. In addition, long-term benefit is likely due to the ability of tazarotene to simultaneously affect the numerous cellular players implicated in the pathogenesis of psoriasis (Figures 1 and 2).

In one clinical trial, tazarotene monotherapy was applied once daily for 12 weeks and then discontinued with follow-up for another 12 weeks. When compared to vehicle control, tazarotene was able to elicit a significant therapeutic effect that was maintained throughout the 12-week follow-up period.[8] This effect was observed in another similar clinical trial comparing combination tazarotene/mometasone furoate TCS to TCS alone where sustained therapeutic effect was found to be significantly greater in the tazarotene group.[73]

Fixed-combination HP 0.01%/TAZ 0.045% lotion also exhibits a durable remittive effect. From the pooled phase 3 clinical trials, Stein Gold et al showed that 63% of participants achieving treatment success with HP/TAZ daily application at week 8 remained treatment successes 4 weeks after discontinuation of treatment.[84] Of those participants, 75% further maintained or improved their reductions in affected BSA. In the 1-year open-label trial with once daily application of HP/TAZ lotion for 8 weeks followed by intermittent treatment in 4-week cycles as needed (based on achievement of treatment success) over 52 weeks, retreatment was not required for >4 weeks in 55.3% with 6.6% not requiring any retreatment.[82] At 52 weeks, 77.5% of participants maintained BSA ≥5%.

CONCLUSION

Tazarotene, a selective RARβ and RARγ retinoid, has a long-standing history in successfully treating cutaneous psoriasis. It is effective as monotherapy and in combination therapies such as those with topical corticosteroids. Furthermore, due to its retinoid effect on altering gene expression and interacting therapeutically with many of the cellular pathogenic players (ie, keratinocytes, immune cells, vascular endothelial cells), tazarotene demonstrates a remittive maintenance effect that lasts long after its discontinuation. This outcome allows clinicians to rethink the use of tazarotene in the treatment of psoriasis among a therapeutic armamentarium now dominated by systemic biologics that target only certain components of pathogenesis (ie, TNF-α, IL17, IL-23). Despite the success of biologics, there remain many patients who do not achieve control of their disease and would benefit from adjunctive tazarotene topical therapy. In addition, tazarotene will be of utmost importance in patients who are not candidates for biologics or systemic immunosuppressive therapies such as active cancer patients or those with an active hepatitis infection. Fixed-combination HP 0.01%/TAZ 0.045% lotion is a single treatment that packs a "one-two punch" in terms of clinical efficacy and economic benefit. Given the excellent safety profile, limited contraindications, superb efficacy, and long-term maintenance of effect, HP 0.01%/TAZ 0.045% lotion can fit into the therapeutic toolkit for any patient afflicted with psoriasis.

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DISCLOSURES

Dr. Kircik has served either as an investigator, consultant, or a speaker to Abbvie, Allergan, Almirall, Amgen, Arcutis, BMS,BI, Cellceutix, Cipher, Dermavant, Dr Reddys, Eli Lilly, J&J, Leo, Maruho, Merck, Novartis, Ortho Dermatologics, Pfizer, Sun Pharma,Taro, UCB. Dr. Issa has no conflicts of interest to declare.

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