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TREATMENT CONSIDERATIONS IN THE SHORT- AND LONG-TERM MANAGEMENT OF PLAQUE PSORIASIS: IS THERE A ROLE FOR TAZAROTENE?

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Treatment Considerations in the Short- and Long-Term Management of Plaque Psoriasis: Is There A Role for Tazarotene?

Tazarotene is almost a forgotten entity in management of psoriasis, despite quality data showing it can be both tolerable and effective—when used appropriately.

Although itching is often cited as among the most irritating symptoms associated with plaque psoriasis, the mere presence of the hallmark scales on the skin may be enough to impact quality of life, especially because it often affects visible skin areas. Involvement of certain skin zones, such as the scalp or intertriginous areas, is known to cause discomfort that leads many patients to alter daily life activities. In addition, presence of certain disease features, like psoriatic nail disease, which is estimated to occur in between 10% and 55% of cases, may lead to physical abnormalities, including unsightly nail bed separation, and negatively impact patients' social, mental, and physical well-being.[1]

Fundamentally, as demonstrated by a number of surveys and studies, psoriasis can have psychological consequences. For example, patients' experience with psoriasis has been reported to lead to alteration of daily activities, suicidal ideation, and work and school absenteeism.[2-5]

What these data suggest is that psoriasis—of any severity from mild to severe—remains a significant clinical problem. For the approximately 80% of patients with mild to moderate psoriasis, topical therapy is often a mainstay of therapy, with several factors impacting the choice of agent.[6] Typically, topical corticosteroids, because they imbue anti-inflammatory, antiproliferative, immunosuppressive, and vasoconstrictive effects, as well as regulate gene transcription for proinflammatory cytokines, are a popular starting point for topical psoriasis therapy.[6] Due to the availability of topical corticosteroid agents in varying degrees of potency and formulated in a variety of different vehicles, they are viewed by patients and physicians as a versatile option, especially for individuals with limited body surface area involvement.

An extensive review of the safety and efficacy of the various corticosteroid options for short- and long-term management of psoriasis, and their potential role in maintenance therapy and/or adjuvant therapy, is beyond the scope of this article. Suffice it to say, a plethora of studies in the literature supports the important role of topical corticosteroids in the management of psoriasis, despite well-known concerns for local side effects (ie, epidermal atrophy) and potential to exacerbate preexisting dermatoses, such as rosacea, perioral dermatitis, acne, and purpura.

In addition, as most clinical trials to date have evaluated short duration of corticosteroid therapy for treatment of psoriasis, long-term safety and efficacy are uncertain.[6]

Yet, while the breadth of currently available treatment options for psoriasis facilitates treatment of patients at all stages of the disease, it also appears evident that some options are underutilized, which may be contributing to some perceived unmet need in management. Specifically, the retinoid tazarotene is unfortunately plagued by some early bad experiences with the agent that may be contributing to undue confusion and misunderstanding about its utility. For example, use of tazarotene has been associated with skin irritation in lesional and perilesional skin,[6] which may lead some prescribers to reject the agent and cause some patients to stop therapy.[7]

In particular, despite strong evidence to support the use of topical tazarotene for psoriasis, local irritation (especially with the gel formulation) has limited its wider adoption. Even in that gel formulation, however, tazarotene, when used appropriately, is a highly effective agent for both short-term therapy and long-term maintenance in the treatment of psoriasis.[6]

TAZAROTENE: MECHANISM, SAFETY, AND EFFICACY

Topical tazarotene has been available for clinical use since 1997.[6] It has a mechanism of action that is complementary to other frequently used topicals in the treatment of psoriasis. When it binds to nuclear retinoic acid recep-

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tors, tazarotene induces normalization of keratinocyte differentiation and diminishes hyperproliferation of abnormal skin cells. It also reduces the formation of pro-inflammatory cytokines and interleukins.

It is plausible that normalization of keratinocyte differentiation may induce long-term benefit, even after cessation of therapy, thereby lowering the risk for recurrence.[9]

In clinical studies, topical tazarotene monotherapy has demonstrated superior efficacy compared with vehicle.[7,8] At the conclusion of two vehicle-controlled, 12-week clinical trials that enrolled 1,303 patients, 40% of subjects who used tazarotene 0.1% cream and 51% of patients who used tazarotene cream 0.05% once daily had no, minimal, or mild psoriasis, compared with 25% of subjects who used vehicle alone.[8] In one study, tazarotene was found to be as efficacious as fluocinonide 0.05% cream after 12 weeks of treatment, although tazarotene demonstrated superior maintenance of effect after cessation of therapy.[9]

However, tazarotene provides its greatest benefit when it is used in combination with topical corticosteroids, because of the complementary mechanisms of action. In one of the early studies to establish the merits of this combination regimen, Guenther and colleagues showed that tazarotene 0.1% gel plus the corticosteroid mometasone furoate 0.1% used once daily yielded significantly greater reductions in body surface area involvement compared with calcipotriene 0.005% ointment twice daily.[10]

Relative to other retinoids, tazarotene is highly specific with a low systemic absorption, potentially yielding fewer side effects compared to in-class comparators.

In addition, concurrent use of corticosteroids serves to reduce the potential for dermal irritation with tazarotene. Potential for irritation can also be ameliorated by use of the cream formulation, combination with moisturizers, application on alternate days, and through use of short-contact treatments.[11] Tazarotene should also not be used on the groin area where it may lead to irritation.

Steroid Phobia In Focus

Although steroid phobia is clearly not new, attention to the issue has been increasing. Much research on the phenomenon has come from investigations of children with atopic dermatitis (AD) and their parents. One analysis of the literature found that there was significant variation in how phobia was defined.

When studies compared nonadherence with corticosteroid therapy for AD between a phobia group and a nonphobia group, patients in the phobia groups were found to have a significantly higher rate of nonadherence. Features of corticosteroid phobia are commonly reported by patients across cultures.

— JAMA Dermatol. 153(10):1036-1042

CLINICAL IMPRESSIONS: CONSIDERATIONS FOR TAZAROTENE USE

Corticosteroids for treatment of psoriasis are a blessing and a curse. They have a rapid onset of action, which helps patients achieve rapid relief of symptoms that might be negatively impacting quality of life. In the short-term, topical corticosteroids are associated with a favorable side effect profile (with the caveat that potency, formulation, site of administration, coexisting conditions, and a variety of other factors might elevate risk for developing any known adverse effects).[10]

Although less commonly seen, systemic side effects may occur with use of topical corticosteroids, especially higher potency agents used over a large surface area and/or under occlusion. The potential to induce rare but serious systemic

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complications is likely a significant factor in so-called steroid phobia—among both patients and providers. As for the former, most patients are looking for fast relief of symptoms; any reticence in using topical steroids, in our experience, is easily overcome with proper education about how to appropriately use these agents, particularly with respect to the amount of medication/size of the dose administered to affected skin areas.

The suggestion for proper usage of corticosteroids includes the treating physician, as side effects may be ameliorated by concurrent use with tazarotene or a vitamin D-based formulation (ie, calcipotriol or calcipotriene). Combination calcipotriene/betamethasone dipropionate formulations are highly effective, yielding greater therapeutic effect than either agent as monotherapy in short-term studies.[12] Achieving rapid control with combination agents may reduce the need for topical corticosteroid use over time, thereby mitigating the risk of steroid-induced epidermal atrophy if longer-term maintenance is achieved with a second topical.

While less convenient for patients than currently available products, the concurrent use of tazarotene and corticosteroid topicals appears to yield greater benefit in reducing complications of steroid use than what is achieved with combination calcipotriene/betamethasone dipropionate. As noted earlier, concurrent corticosteroid use improves the side effect profile and therapeutic benefit of tazarotene. Emerging data suggest that concurrent use of tazarotene also reduces the risk of steroid-induced epidermal atrophy.[13] This synergistic effect has not been seen with concurrent use of topical corticosteroids and vitamin D. In addition to the suggested mechanistic benefit of using tazarotene in combination with corticosteroids, their concurrent use also facilitates the ability to reduce the usage requirement with the topical corticosteroid, thereby yielding additional reduction in complication risk.

Using separate topicals in combination requires adequate patient education. Although tazarotene is intended for use in small amounts (eg, a pea-sized application), patients are often under the mistaken impression that using tazarotene liberally will yield faster or more profound relief, whereas this practice only serves to increase irritation and potential for adverse outcomes.

Compounded formulations are a consideration, although availability, insurance coverage, and/or local legal restrictions in one's practice locale might obviate this option.

Symptoms most frequently reported in psoriasis

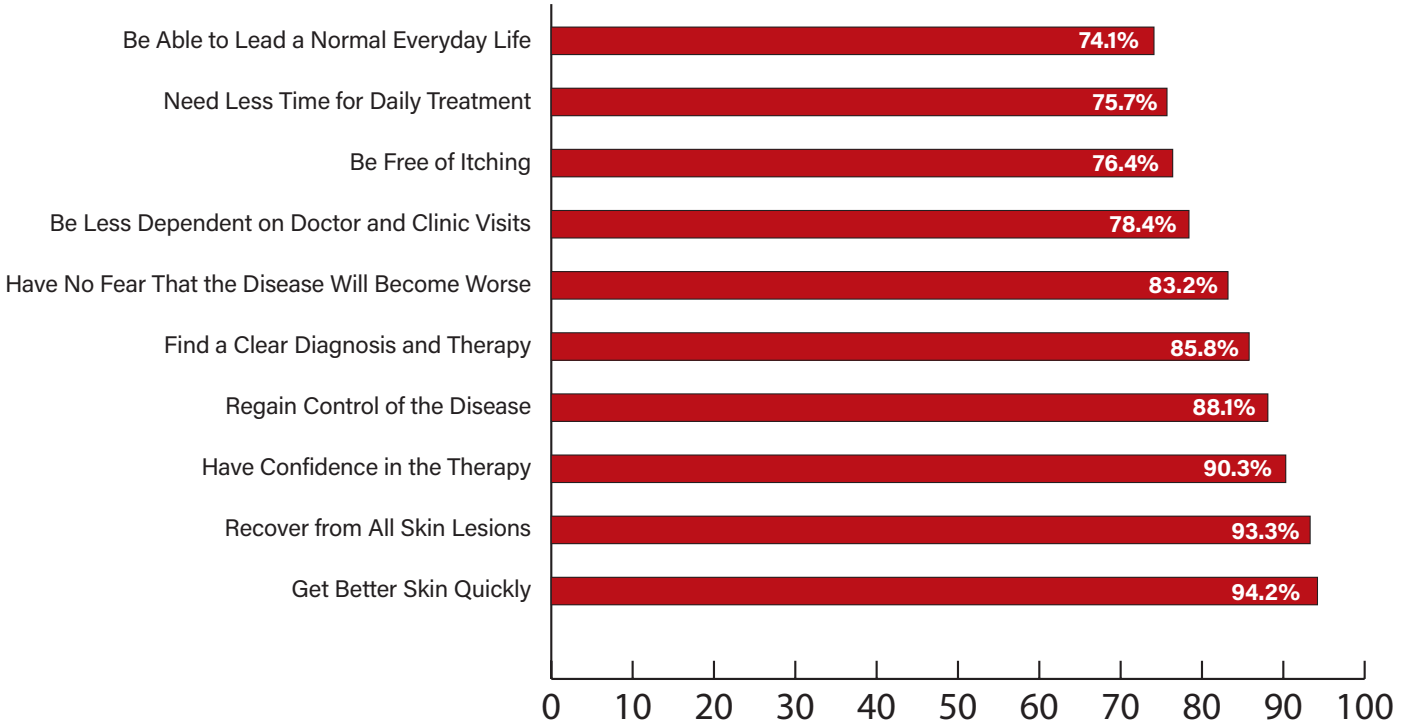
Scaling of the skin	92%
Itching	72%
Erythema	69%
Fatigue	27%
Swelling	23%
Burning	20%
Bleeding	20%

—Br J Dermatol. 155(4):729–36

UNMET NEED IN PSORIASIS TREATMENT

While there are legitimate treatment gaps in treatment of psoriasis, some of the perceptions about unmet need may be due to misconceptions about currently available options. For instance, there has been suggestion that long-term use of tazarotene for treatment of psoriasis may expose patients to undue risk and/or continual irritation of the skin. However, longer-term tazarotene regimens are routinely used in treatment of acne without issue. There may also be a role for tazarotene in conjunction with

Patients' Therapeutic Goals



— Global Report on Psoriasis 2016. WHO, ISBN 978 92 4 156518 9

phototherapy, including enhancing the efficacy of phototherapy and reducing the dose of ultraviolet light required to achieve a clinical response.[14]

The potential role of tazarotene as an adjuvant to phototherapy is one suggestion for how the agent may be used in longer-term maintenance. Because of its complementary mechanism of action, tazarotene is a reasonable option to add to steroid or calcipotriene monotherapy regimens, or steroid/calcipotriene combination regimens. The point mentioned earlier about the combined use of tazarotene and corticosteroids as initial therapy should be reiterated in this context: use of this combination may make it less likely a patient will require use of a high-potency steroid in the initial phase of therapy, and, therefore, when patients are transitioned to the maintenance phase, corticosteroids remain an option.

Long-term use of highly potent corticosteroids increases the risks for more serious side effects, such as Cushing syndrome, osteonecrosis of the femoral head, cataracts, glaucoma, and symptomatic hypothalamic-pituitary-adrenal (HPA) axis suppression; if their use can be modulated in the early phase of treatment, longer-term risks become less of a concern.

It should be noted that tazarotene can also be used adjunctively in patients using biologic agents for more severe skin manifestations. The discretionary use of biologic agents has proven to be a boon for the treatment of certain psoriasis patients, but adjunctive therapy becomes useful in two scenarios:

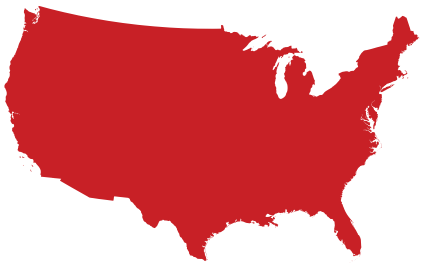
1) although systemic therapy is effective, some skin areas may require additional treatment, and

2) topical therapy in addition to systemic approaches may cover a patient while the systemic takes time to be effective or by itself engender a faster response to treatment.

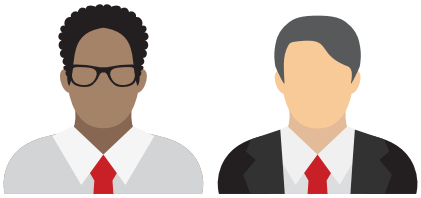
CONCLUSION

Tazarotene has been somewhat delegated to a secondary consideration in psoriasis management, in large part because it was introduced as monotherapy; as monotherapy, the agent can be irritating, and thus, negatively impact adherence. However, existing data point to a definite role for this drug in the initial treatment phase of psoriasis, in

PSORIASIS PSTATS



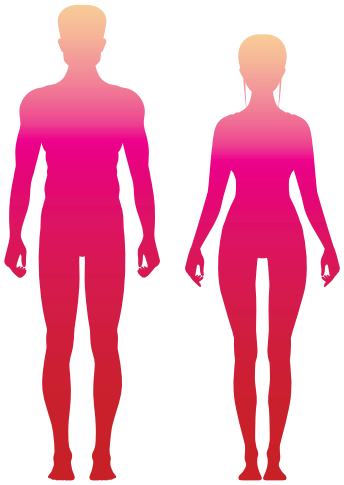
Approx. **7.5 million** Americans have psoriasis. That's about **2.2%** of the population.



Psoriasis prevalence in African Americans is **1.3%** compared to **2.5%** of Caucasians.

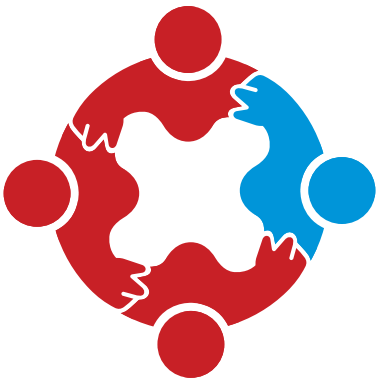
(J Am Acad Dermatol. 2005 Jan;52(1):23-6)

Psoriasis often appears between the ages of **15 and 25**, but can develop at any age.



The National Psoriasis Foundation defines mild psoriasis as affecting **less than 3%** of the body.

Moderate disease affects **3-10%**; more than **10%** is considered severe.



About **three-quarters of people** with psoriasis have cases that are considered mild or mild-to-moderate.

In the US, the prevalence of psoriasis is

3.6% Male

3.1% Female

Adherence is **lowest** with topical drugs, partly due to insufficient communication regarding instructions on how to use the drug, misperception of possible adverse events, and mistaken expectations about the speed and degree of improvement.

(J Dermatolog Treat. 2017 Nov;28(7):613-622)

Nearly **2/3** of topical prescriptions do not include required information to help patients manage their topical treatment in psoriasis correctly.

(Br J Dermatol. 2011 Dec;165(6):1332-6.)

$1,101,600 Total annual loss to managed care organization associated with PA requirements for new topical psoriasis drugs. Total annual costs were **$28,573,600** when PA was required and **$27,472,000** when PA was not required.

(J Dermatolog Treat. 2010 May;21(3):178-84)

Tazarotene and Topical Corticosteroids

Tazarotene

- Normalizes keratinocyte differentiation
- Antiproliferative
- Reduces pro-inflammatory cytokines and interleukins.
- Reduces risk of steroid-induced epidermal atrophy

Corticosteroids

- Vasoconstrictive
- Antiproliferative
- Anti-inflammatory
- Immunosuppressive

the longer-term maintenance phase, and adjunctively to other treatment approaches, such as phototherapy and systemic biologics.

Tazarotene is best used in combination with topical corticosteroids, which extends the safety and efficacy of each agent. A reassessment of tazarotene, especially with respect to combined use, might address some of the real and perceived unmet need in the treatment of patients with psoriasis.

New tazarotene agents, including combination compounds, that demonstrate benefits for treating psoriasis in rigorous clinical trials are being welcomed by prescribers.

On a practical level, giving patients the option to use a single agent portends greater adherence. As well, in our experience, patients tend to gravitate toward using the less irritating application if there is any skin discomfort. If separate agents are used concurrently, patients may opt to choose the one that is more comfortable, irrespective of efficacy.

There is definitely room for formulations with vehicles that are more skin friendly. With the current armamentarium, it is not uncommon to provide patients different options for the face, groin, scalp, and the rest of the body. Having agents that can be used on multiple skin zones would certainly be more patient friendly. In the meantime, it might behoove the dermatology community to re-evaluate the existing data regarding tazarotene and its role in short- and long-term management of psoriasis.

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