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PSORIASIS (J WU, SECTION EDITOR)

Halobetasol Propionate and Tazarotene Combination Lotion 0.01%/0.045% for Psoriasis

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Abstract

Purpose of Review This article reviews in detail the merits and unique nature of this combination lotion and also discusses a new type of strategy for treating psoriasis topically.

Recent Findings The combination lotion proved much more efficacious than the vehicle. Moreover, when the combination lotion was compared head-to-head with each of the components alone (halobetasol, tazarotene) and vehicle lotion, the combination was clearly more efficacious after 8 weeks. In terms of safety, the combination lotion was well tolerated by the patients. The combination lotion is also unique in that it is the only superpotent topical steroid with long-term safety data of 1 year.

Summary Now that the FDA has approved a superpotent topical steroid containing a topical agent for unlimited "intermittent" use, compliance and treatment efficacy can be greatly improved. Due to this, the combination lotion can greatly enhance topical therapy for psoriasis and make maintenance therapy practical.

Keywords Psoriasis · Topical therapy · Combination lotion · Halobetasol · Tazarotene

Purpose of Review

While there has been remarkable progress regarding biologic agents and JAK inhibitor medications in recent years for the systemic treatment of psoriasis, the fact remains that the majority of patients with psoriasis have localized involvement where topical therapy is the mainstay of the treatment plan. Over the past few decades, there has been many attempts at improving the efficacy and safety of topical agents starting with the advent of superpotent topical steroids. However, despite this endeavor, clobetasol and halobetasol remain the most efficacious topical steroids available and it appears difficult to create a new topical steroid compound with more efficacy than either of these two medications.

Therefore, one logical attempt to provide better efficacy with topical agents is to develop a combination topical agent where a superpotent topical steroid is combined with a non-steroidal medication which works by a completely different mechanism of action in the treatment of psoriasis. Halobetasol propionate and tazarotene combination lotion 0.01%/0.045% (Duobrii®) is the first-ever combination topical agent for psoriasis involving a class I superpotent topical steroid. The efficacy of this lotion is better than either halobetasol propionate alone or tazarotene alone, because both agents are fully active in this combination [1•]. This article reviews in detail the merits and unique nature of this combination lotion and also discusses a new type of strategy for treating psoriasis. This new strategy is made possible with the development of an agent like this one, which has efficacy beyond just a solitary superpotent topical steroid.

This article is part of the Topical Collection on *Psoriasis*

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Recent Findings

In two separate studies (as required by the US Food and Drug Administration), the combination lotion proved much more efficacious than the vehicle. This study consisted of two multicenter, randomized double-blind, vehicle-controlled phase III studies where 418 subjects were randomized (2:1) to halobetasol propionate and tazarotene combination lotion 0.01%/0.045% or vehicle once daily for 8 weeks with a 4-week follow-up. The treatment success, for the purpose of this

required FDA pivotal study, was defined as at least a 2-grade Investigator Global Assessment (IGA) improvement from baseline and "clear" or "almost clear" (score of 0 or 1). As seen in Fig. 1, after 8 weeks, the rate of treatment success for the combination agent ranged between 35.8 and 45.3% compared to the success rate for the vehicle which ranged from 7 to 12.5% [2•]. This difference was statistically significant.

Moreover, when the combination lotion was compared head-to-head with each of the components alone (halobetasol, tazarotene) and vehicle lotion, the combination was clearly more efficacious after 8 weeks (Fig. 2) [1•]. More specifically, the combination lotion achieved treatment success in 52.5% of patients, halobetasol alone achieved treatment success in 33.3% of patients, tazarotene alone achieved treatment success in 18.6% of patients, and the vehicle alone achieved treatment success in 9.7% of patients.

In terms of safety, the combination lotion was well tolerated by the patients. However, due to the fact that tazarotene (a topical retinoid) is part of the combination and is known to be more irritating than the topical steroid or vehicle lotion, it is not surprising that the application site pain was reported by a higher percentage of patients using the combination lotion (2.6%) as compared to vehicle lotion (0.7%). Also, irritant contact dermatitis was reported by 6.3% of patients who used the combination lotion as compared to 0% of patients who used the vehicle lotion. It is important to remember that these irritation rates of patients using the combination lotion are likely to be much lower than the original studies involving tazarotene cream. In those studies, the most frequent adverse reactions with tazarotene 0.05% and 0.1% cream included, in descending order, pruritus, erythema, and burning, which occurred in 10 to 23% of patients. Reactions occurring in greater than 1 to less than 10% of subjects, in descending order, included irritation, desquamation, stinging, and contact dermatitis (tazarotene cream [package insert] Irvine, CA; Allergan; 2013). This is in line with the fact that tazarotene is frequently much less irritating when combined with a strong topical steroid.

Halobetasol propionate and tazarotene combination lotion 0.01%/0.045% is also unique in that it is the only superpotent topical steroid with long-term safety data of 1 year (Fig. 3). Most superpotent topical steroids or other topical steroid preparations for psoriasis were only studied for 2–4 weeks. Combination calcipotriene ointment with betamethasone dipropionate ointment is a rare exception because this combination does have 1-year safety data [3]. The combination calcipotriene and betamethasone dipropionate ointment did prove to be well tolerated and safe for prolonged use after 1 year. However, betamethasone dipropionate in this combination was only high strength, not superpotent, and therefore, the current data for halobetasol propionate and tazarotene combination lotion 0.01%/0.045% is the first-ever 1-year safety data involving a combination superpotent topical steroid agent in dermatology.

It should be noted that in this 1-year study, the patients had to use the medication intermittently after 8 weeks into the study so they were not allowed to use the combination lotion daily for the entire year. In this study, participants were treated with the combination lotion once daily for 8 weeks and intermittently as needed in 4-week intervals if they demonstrated improvement (treated with halobetasol propionate and tazarotene combination lotion 0.01%/0.045% lotion once daily if they had not achieved treatment success or are receiving no treatment until the next evaluation if they had achieved treatment success). The result of this first-ever 1-year study with a superpotent topical steroid was that approximately 90% of the patients had no side effects [4•]. Even though hypothalamic–pituitary–adrenal (HPA) axis suppression was not actively checked (no blood work or official tests were conducted), not a single patient in this 1-year study was found to have symptoms of HPA axis suppression based on clinician monitoring of signs and symptoms. The result of this strong safety

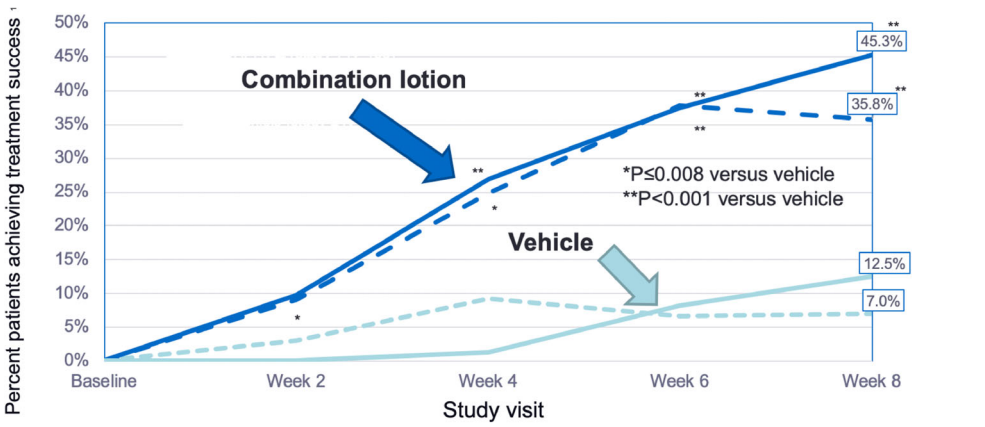

Fig. 1 Duplicate data demonstrating that the efficacy of combination lotion is greater than the vehicle

[1]defined as at least a 2-grade improvement from Baseline in the IGA score and a score of Clear or Almost Clear

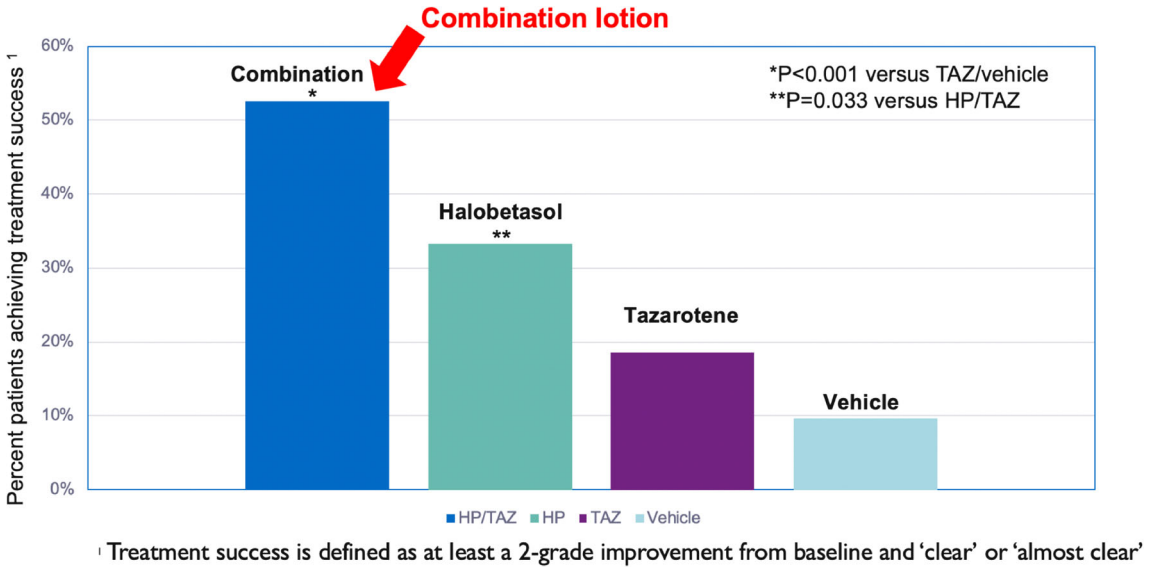

Fig. 2 Combination lotion is more efficacious than halobetasol lotion (8 weeks)

profile from this 1-year study was that FDA did not put any time limit regarding the use of halobetasol propionate and tazarotene combination lotion 0.01%/0.045%, unlike the other superpotent topical steroids that usually have 2–4-week time limit for use, as detailed in their respective package inserts.

Also, in clinical trials, when the patients completely discontinued halobetasol propionate and tazarotene combination lotion 0.01%/0.045%, 55% of the patients were still clear or almost clear (PGA 0 or 1) after 1 month of no treatment, attesting to the fact that intermittent treatment involving a "therapeutic holiday" of 1-month duration appeared to be feasible (data on file, Ortho Dermatologics). A majority of the patients are unlikely to flare during a break of 1 month. This suggests that the use of this agent intermittently, such as 1 month on and 1 month off, is practical.

Given that this medication contains a retinoid, use in pregnancy is contraindicated and the medication should be discontinued as soon as pregnancy is recognized. The possibility that a female of reproductive potential is pregnant at the time of institution of therapy should be considered. A negative result for pregnancy should be obtained within 2 weeks prior starting therapy. Furthermore, this medication should be initiated during menstruation.

Summary

In the section above, the data regarding the efficacy and safety of halobetasol and tazarotene combination lotion 0.01%/0.045% was reviewed. It is well known that psoriasis is a chronic disorder that requires both a clearance and a maintenance therapy. The fact that there now exists a combination agent containing a superpotent topical steroid that has been shown to be more efficacious than a solitary superpotent

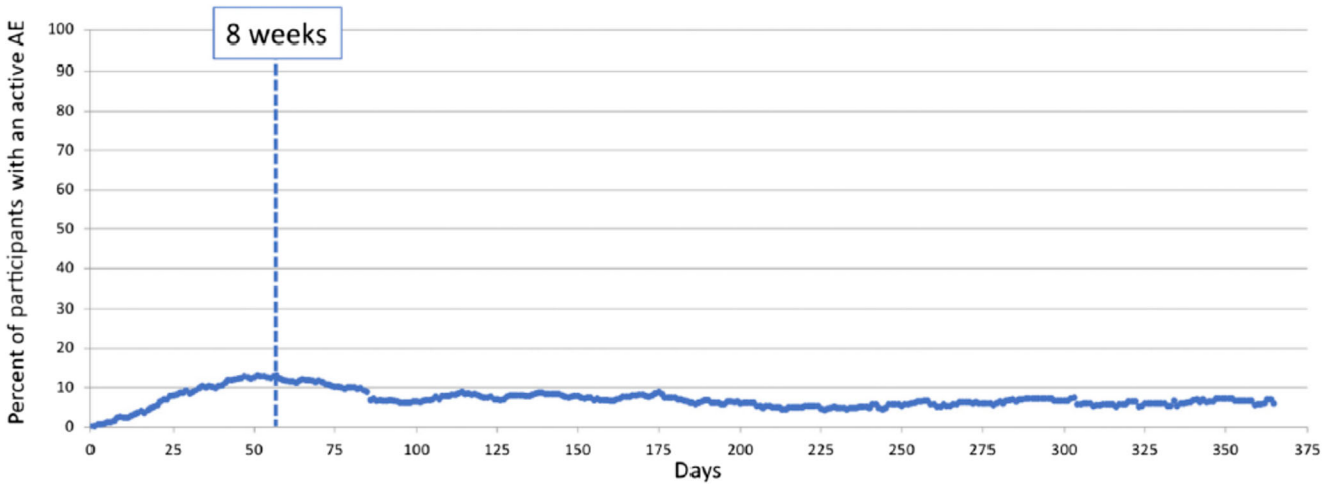

Fig. 3 One-year safety data on halobetasol propionate and tazarotene lotion 0.01%/0.045%. Approximately 90% of patients had no local side effects

topical steroid (halobetasol) can change the way that psoriasis is treated topically. In terms of this combination agent achieving a better efficacy than a superpotent topical steroid, it is important to note that this is first time that such data was obtained in the history of dermatology.

The fact that superpotent topical steroids when combined with a non-steroid can achieve better efficacy was initially shown by Lebwohl et al. when halobetasol ointment was combined with calcipotriene ointment [5]. This combination was shown to be more efficacious in a head-to-head comparison than the use of halobetasol or calcipotriene ointment alone. Koo et al. demonstrated a similar principle that a superpotent topical steroid in combination with a non-steroid can be more efficacious than a solitary superpotent topical steroid with the use of a combination of clobetasol foam (Olux®) and calcipotriene ointment. [6] However, both of these scenarios involved two separate agents manually used together by either one in the morning and one at night, as the former scenario, or one on top of the other which was the latter scenario. The novel lotion discussed here is the first time a single preparation allowed the combination of superpotent topical steroid with a non-steroid and demonstrated significant superior efficacy against the use of a solitary superpotent topical steroid (halobetasol). As shown in Fig. 4, the traditional strategy for treating psoriasis topically has been to improve the severe flares of disease as quickly as possible using strongest topical steroid applied daily (often twice a day), and then, once psoriasis significantly improves, "rank down" the topical steroid to one that is weaker but safer (such as triamcinolone) and instruct the patient to apply it every day.

This usual strategy is generally effective with patients in clearing disease but compliance for the maintenance phase of therapy is highly questionable since the motivation for continuing any type of treatment for maintenance goes down once the patient is out of an acute disease flare. Steve Feldman and his colleagues have demonstrated how difficult compliance is with any type of topical agent in dermatology [7]. Now that we have a combination agent halobetasol propionate and tazarotene combination lotion 0.01%/0.045% that is significantly more efficacious than a superpotent topical steroid, there is a possibility that we can solve this compliance problem during the maintenance phase by simply using the same efficacious agent with a superpotent topical steroid but simply cut back the frequency of application. An example of this would be to use the medication on the weekend only, every other month, possibly even indefinitely. Since the FDA did not put a time limit on this combination lotion, the intermittent use regimen for maintenance following daily use for clearance is an option provided that the patient is properly supervised by a dermatologist.

Fig. 4 New agents allow new treatment strategies

Obviously, this combination lotion should never be used in sensitive areas such as the face, axilla, or groin because it contains a superpotent topical steroid. However, in terms of the risk of skin atrophy, this side effect should be detected promptly with proper periodic supervision if it happens. There is even data attesting to the fact that tazarotene discourages the skin atrophy effect of the long-term use of topical steroids [8–10]. However, there is a legitimate concern regarding HPA axis suppression when a superpotent topical steroid is used long term. The available data suggests that HPA axis suppression is much less of a clinical concern when the agent is used intermittently such as every other month. Even as far back as 1991, Katz et al. demonstrated that intermittent use of superpotent topical steroid augmented betamethasone dipropionate ointment (Diprolene®) appeared quite safe [11]. The intermittent use maintained psoriasis much better than the use of vehicle alone even though augmented betamethasone was only used on weekends. In 90 patients studied, not a single patient exhibited signs of cutaneous atrophy using a superpotent topical steroid (augmented betamethasone dipropionate) on weekends only. Furthermore, only 4% of patients showed subnormal morning cortisol levels but no clinical sign or symptom of adrenal suppression.

Even though the ultimate choice of what agent is used for what type of psoriatic lesion is up to the individual providers, the authors can make some general recommendations given that there are a few other topical combination agents available for psoriasis today. Halobetasol propionate and tazarotene combination lotion 0.01%/0.045% may be especially advantageous for patients who have a particularly hard time using topical medications consistently for a chronic disease. This is because halobetasol propionate and tazarotene combination lotion 0.01%/0.045% can be trusted to work well even when it is used intermittently over time for maintenance, as already discussed. Also, if a psoriasis patient has unusually thick scaling, retinoids are known to be particularity effective for decreasing the thickness of the dead skin layer regardless of underlying pathology. On the other hand, other topical combination agents may be more appropriate to use for reproductive woman and also for the small proportion of patients who are particularly sensitive to the skin irritation effect of topical retinoids.

Conclusion

Now that the FDA has approved a superpotent topical steroid containing a topical agent for unlimited "intermittent" use, compliance and treatment efficacy can be greatly improved. Due to this, halobetasol propionate and tazarotene combination lotion 0.01%/0.045% can greatly enhance topical therapy for psoriasis by not only providing quick relief but also finally making maintenance therapy practical and efficacious for patients.

Compliance with Ethical Standards

Conflict of Interest The authors declare that they have no conflict of interest.

Human and Animal Rights and Informed Consent This article does not contain any studies with human or animal subjects performed by any of the authors.

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• Of importance

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