Topical Steroid Withdrawal in Atopic Dermatitis


Exploring the important role and proper use of topical corticosteroids in the management of eczema.

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>> Topical Corticosteroids (TCS) are currently first-line treatment for many acute and chronic inflammatory skin disorders, including atopic dermatitis (AD), due to their powerful anti-inflammatory and anti-pruritic properties. These agents have numerous well-documented benefits that result in a positive impact on patient quality of life, and have been shown to be a safe treatment option in both short-term daily use and long-term intermittent application.[1] Topical Steroid Withdrawal (TSW), also known as Red Skin Syndrome, has been a hot topic in social media in recent years, but there are numerous outstanding questions including the prevalence of TSW, consensus diagnostic criteria, and risk factors for developing the disease. The concern for TSW and the increasing reports addressing side effects of chronic TCS use are potentially contributing to reduced adherence and therapeutic failure among patients, making this an important topic for discussion whether or not one accepts TSW as an actual nosological entity.[1]

This review serves to initiate a conversation regarding TSW and the use of TCS to treat AD. We seek to define a functional and practical approach to using TCS as part of the treatment regimen of AD and to raise awareness of the delicate balance that exists between safe, effective treatment and avoidance of side effects, specifically withdrawal. Additionally, we discuss the use of steroid-alternatives or complementary therapies to both reduce the need for escalation of TCS and reduce the risk of TSW.

UNDERSTANDING TOPICAL STEROID WITHDRAWAL

TSW is a poorly understood clinical adverse effect of inappropriate, prolonged, or frequent use of TCS, generally those of mid- to high-potency. The mechanism behind this phenomenon remains unclear, but one hypothesis is that it is due to a rebound effect caused by the sudden absence of TCS, leading to increased nitric oxide (NO) levels and exaggerated vasodilation of cutaneous blood vessels.[2] TSW is associated with increased duration of treatment due to factors such as overprescribing of TCS or lax monitoring of refills. At-risk populations include adult women applying these agents to the face or genital area.[1-3]

Two distinct subtypes of TSW have been identified. The erythematoedematous type develops more frequently in patients with underlying chronic eczematous conditions (such as AD) and is classically associated with the aforementioned signs of burning, erythema, and edema; the papulopustular type, on the other hand, is more rosacea-like and is characterized by papules, pustules, and nodules, and less frequently swelling and stinging.[1,3] This type seems to develop more frequently in patients using TCS for pigmentary conditions, acneiform disorders, or cosmetic reasons. Both subtypes can be difficult to distinguish from other clinical entities, such as allergic contact dermatitis

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and even a flareup of an underlying inflammatory skin condition such as AD. Misdiagnosis often leads to mistreatment, in which a withdrawal episode is confused for a flare of the underlying disease and thus may continue to be treated inappropriately, often with escalation of steroid therapy. Alternatively, a flare of underlying AD can be confused for TSW and therefore may not be properly treated. In both situations, the condition worsens and the patient is subjected to unnecessary morbidity.

Signs and symptoms of TSW occur days to weeks following discontinuation of TCS, with erythema being the most common sign, and burning and stinging being the most frequently reported symptoms.[1,3] Other distinctive features include skin exfoliation, edema—especially of the eyelids and ankles—and skin sensitivity.[4,5] Frequently described features include the descriptive but not agreed upon "elephant wrinkles" (thickened skin with reduced skin elasticity), reported in up to 56 percent of adult patients, and "red sleeve" (rebound eruption on the upper or lower limb, with sparing of the palms and soles), reported in up to 40 perent of adult patients.[4,5] Notably, adults and children often exhibit the same features of TSW, suggesting that any diagnostic criteria established for adults may also be applicable for younger patients.[5] In a clinical report following 10 children who developed features of TSW following discontinuation of TCS, all 10 children developed erythema, manifesting as diffusely red skin, with 80 percent of the children developing either "elephant wrinkles" or "red sleeve."[4,5] Less common supporting features for TSW include sleep and mood disturbances, papules or pustules, and the headlight sign, defined as erythema of the full face, with sparing of the nasal and perioral regions.

As no gold standard diagnostic approach exists, and even the terminology is not adequately defined, most cases of TSW are self-diagnosed rather than identified by a physician. In differentiating between an AD flare and a TSW episode, clinicians should specifically look for the following features favoring TSW:

1. the predominant symptom is burning,
2. confluent erythema occurs days to weeks following discontinuation of TCS, and

TABLE 1: KEY FEATURES TO DIAGNOSIS TSW[1]

Burning	The most frequently reported symptom of TSW, seen in 65% of patients[4]
Confluent Erythema	Severe and widespread erythema, beginning in areas of disease involvement and spreading to areas of skin where TCS have not been applied; the most common sign reported in TSW, leading to the name "red skin syndrome", seen in 92% of patients[4]
History of frequent and prolonged TCS use, especially on the face	Up to 97% of cases involve the face, 98.6% of cases involve mid- or high-potency TCS, and 85.2% of cases involve application >12 months[1,4]

TABLE 2: TREATMENT OF TSW AND ADVERSE EFFECTS OF TCS

Author	Year	Study Type	Withdrawal Phenomenon	Treatment	Duration of Treatment	Effectiveness
Pabby A, An KP, Laws RA	2003	Case Report	Steroid-induced peri-ocular rosacea	Tacrolimus .1% ointment + oral tetracycline	3 weeks	Marked improvement with no following reoccurrences
Chu C-Y	2007	Open Label Pilot Study	Steroid induced rosacea	Pimecrolimus cream	6 weeks	Clearance in 48.6% of patients
Goldman D	2001	Case Series	Steroid induced rosacea	Tacrolimus ointment	7-10 days	Pruritus, tenderness, and erythema were resolved in all 3 patients after 7 to 10 days
Abbas O, Kibbi AG, Chedraoui A, Ghosn S	2008	Retrospective Chart Review	Steroid-induced Red Scrotum Syndrome	Oral Doxycycline	2-3 months	All patients reported significant improvement of erythema and complete resolution of additional symptoms
Dhossche J, Simpson E, Hajar T	2017	Case Report	TSW in AD	Oral Doxycycline	1 month	Complete clearance of pustular dermatosis rash of face
Brodell R	2015	Case Study	Steroid-induced acne	Oral erythromycin, Topical Clindamycin	6 weeks	Complete clearance of steroid-induced acne
Arnold K, Treister A, Lio P	2018	Case Series	TSW in AD	Dupilumab	8-32 weeks	45% mean decrease from baseline in Body Surface Area (BSA)

3. a history of frequent and prolonged TCS use on the face and genital area (Table 1).[1,2,4]

This is in contrast to AD, in which the presence of eczema, pruritus, and a relapsing and remitting course are characteristic features.[6]

Once TSW has been identified, the first step is discontinuation of all steroids (topical, inhaled, and systemic) if not already done so, and provided that they can be stopped safely. After that, definitive guidelines do not exist, but numerous therapeutic approaches have been reported to treat withdrawal episodes (Table 2), including tetracycline antibiotics, antihistamines, calcineurin inhibitors (topical tacrolimus and pimecrolimus, and oral cyclosporine), and dupilumab.[1,2,7] Because flares of the pre-existing underlying disease may also occur with discontinuation of TCS, and because it is often difficult to distinguish from TSW, it has been suggested that oral corticosteroids or a TCS taper be started.[2]

MANAGEMENT OF ATOPIC DERMATITIS

AD, a highly prevalent and complex, chronic inflammatory skin condition, is thought to be due to immune dysregulation, skin barrier dysfunction, and dysbiosis.[8] Interestingly, the increasing understanding of psoriasis as a systemic disease has shed light on the management of AD.

Psoriasis has been the model for targeted inflammatory disease modulators, driving early, aggressive treatment of this condition. This aggressive approach is propelled in part by the relatively low toxicity of biologic agents, which lowers the threshold for treatment in the management of psoriasis. In the past, indications for systemic agents for psoriasis included a minimum of 10 percent body surface area (BSA) involvement or more limited disease with debilitating symptoms.[9] Currently, however, patients with moderate psoriasis, defined by as little as five percent body surface area (BSA) affected, are considered eligible for starting systemic treatment, and the American Academy of Dermatology (AAD) guidelines for the management of psoriasis recommend transitioning to systemic agents for limited disease not responsive to topical treatment or phototherapy.[10]

The threshold for systemic therapy is much higher for AD, with the only indications for use of systemic therapy being: 1.) disease refractory to topical treatment or phototherapy, or 2.) disease with significant negative physical, social, or emotional effect. Additionally, assessment of disease in meeting these standards remains somewhat ambiguous.[10]

Ultimately, the advances in understanding and man-

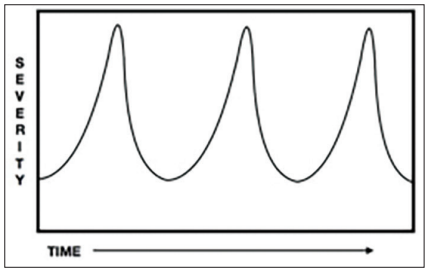

Figure 1: Untreated or undertreated pattern with recurrent disease flares of similar severity.

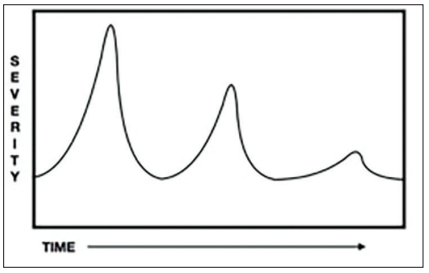

Figure 2: Damping pattern that suggests improved control and decreased TCS use.

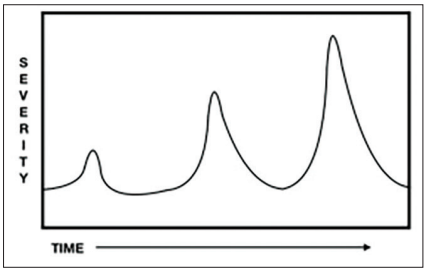

Figure 3: Escalating pattern that suggests worsening control and may herald TSW.

agement of psoriasis and its application towards AD are raising the bar for the standard of care expected for these patients. An argument is now being made for use of a similar aggressive approach in the management of AD, given the numerous similarities between AD and psoriasis in terms of comorbidities. Once thought of as "just a rash," AD is now known to be a multifactorial and heterogeneous systemic disease that greatly impacts quality of life (QoL) through detrimental effects on sleep, school, work, and overall well-being, making adequate treatment of AD an important priority for both clinicians and patients alike.[11] In adopting a more aggressive approach, the first goal for AD patients should remain prevention, and the second goal should be to get patients clear—and have them stay that way without placing them at risk for adverse effects. The addition of systemic therapy will not only continue to provide effective treatment once the limits of TCS have been reached, but will also prevent overuse and prolonged use of TCS, and in turn may reduce risk of TSW.

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BALANCING TREATMENT WITH SIDE EFFECTS

A fine balance exists between using TCS effectively and avoiding adverse side effects of these agents, including topical steroid addiction (TSA) and TSW. Because TSA tends to precede withdrawal, prevention through proper treatment of AD is key.

One can think about AD as ocurring in three different stages, with the most severe stage being unstable or poorly controlled AD. In this form, there may be frequent flares (Fig. 1) or perhaps just sustained severity with minimal fluctuations. From here, the goal is progression downwards to increasingly intermittent flares and ultimately no or minimal AD along with good control.[7] In mild AD where disease is fairly stable and generally well-controlled, one should be able to control symptoms with TCS in just a few days, with the patient requiring less steroid over time and remaining clear for days or weeks off of medications.

In more moderate or severe AD, one should attempt to dampen the disease before it escalates, with the hope that each subsequent flare will require less TCS exposure than the prior flare, resulting in an overall disease pattern resembling that of a sinusoidal wave that dampens over time (Figure 2). One such approach may include initial use of rescue therapy in the form of short-term systemic corticosteroids followed by transition to site-specific use of TCS as soon as is appropriate, and ultimately tapering off steroids. The inappropriate prolonged use of TCS, at least in some individuals it seems, may result in a "driving" or "amplifying" pattern that is the exact opposite of treatment goals (Figure 3). In such a scenario, the removal or reduction of strength of TCS would cause disease to progress upward in stage, as the body has essentially become dependent on TCS. This results in episodes of AD reoccurring soon after discontinuation, demonstrating the

process of TSA, where skin develops more severe or diverse skin manifestations following withdrawal from TCS than at preapplication.[12] We hypothesize that the detection of TSA (and thus the potential to prevent TSW) may be possible by observing these patterns.

In using TCS, choice of potency, frequency, and duration ought to be an individualized decision for each patient based on the severity, location, and chronicity of AD.[7] The patient should be given clear instructions on the quantity of TCS to use with each application and attempts should be made to control acute flares within seven to 14 days. Additionally, discontinuing TCS or decreasing potency of agents once active lesions have diminished may reduce associated skin atrophy. TCS may also be used for maintenance as intermittent hot-spot therapy, where agents are applied to areas known to relapse commonly. Multiple studies support that these types of intermittent regimens do not result in reduced efficacy and have found no reports of skin thinning or atrophy with this so-called proactive approach, though it may be prudent to use TCIs or other non-steroidal agents, such as crisaborole, in this role to minimize overall steroid exposure.[7,13]

It is clear that the use of TCS is our best bet for gaining control of the disease. However, adjunctive treatments should be employed before increasing potency or duration of the steroid whenever possible. It is important to note that interprofessional gaps may exist between dermatologists and pharmacists or other physicians regarding TCS use, duration, and counseling of adverse effects, with pharmacists suggesting patients discontinue TCS after only two weeks, a strategy that is uncommon among dermatologists.[14] Improved collaboration and communication between health care providers may improve adherence and proper use of TCS in our patients.

THERAPEUTIC ALTERNATIVES TO TOPICAL CORTICOSTEROIDS

There are many tools in the toolbox for managing AD. When TSW is suspected, rather than continuing to escalate treatment with steroids, one may consider the use of other therapeutic options. Topical calcineurin inhibitors (TCI), such as tacrolimus, are topical immunomodulators that are recommended by NICE guidelines as a treatment option for moderate to severe AD.[7] A meta-analysis of more than 4,000 patients found tacrolimus 0.1% to be as effective as potent TCS use after three weeks of treatment, which suggests that this is an important option in long-term treatment of patients with resistant AD in whom chronic TCS use may lead to development of adverse effects.[15] For patients with persistent and refractory AD, systemic agents, such as cyclosporine, methotrexate, and azathioprine, may be considered, albeit cautiously due to their potential for end-organ toxicity and immunosuppression.[10,16] Antimicrobial therapy is another potential option, as infection with *Staphylococcus aureus* is the most common complication the AD population faces. In fact, it has been estimated that AD patients carry Staph in approximately 90 percent of clinically affected areas and 75 percent of uninvolved areas.[7] Long-term, low-dose antibiotics, such as tetracyclines and erythromycin, have been shown to decrease staphylococcal skin colonization. While chronic use of systemic antibiotics is often discouraged, there are many innovations with topical antibacterials and microbiome therapies that may be considered, some still in early phases of development.[1,17-20]

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With all the medical therapeutic options available, non-pharmacologic treatments are often overlooked. The use of emollients to increase the moisture content of skin is a mainstay in the management of AD. These agents should be applied as frequently as two to three times daily both during active flares and as maintenance therapy. When used as an adjunct to TCS, they have been found to significantly reduce high-potency TCS consumption and risk of relapse.[7]

Wet-wrap therapy is yet another attempt at improving the epidermal barrier and increasing water content of the skin. In this approach, topical medication or moisturizers are applied to the skin, followed by a damp layer and a second, dry layer of gauze or clothing, and then left in place for several hours. A 2006 literature review concluded that

wet-wrap therapy is an effective short-term treatment for severe or refractory AD that can help reduce the frequency and quantity of TCS.[21]

Dilute beach baths, used independently or prior to wet-wrap therapy, also have good evidence to be reasonably effective in patients with frequent infections and a tendency towards open, oozing wounds, though more recent evidence suggests that they may be more anti-inflammatory rather than anti-bacterial in this context.[7,16,17,22]

Phototherapy, or the use of ultraviolet light, is arguably one of the most effective treatment modalities in AD, with reports of clinical improvement evident in four to six weeks and maximum clinical response occurring in just two weeks.[23] Different light types exist and have different therapeutic uses, with ultraviolent A1 appearing to be most effective for acute flares and narrowband ultraviolet B best for managing chronic AD and as maintenance therapy.[16,23] Treatment consists of two to three sessions per week and is optimal for refractory cases or when TCS addiction is thought to be developing. Increasing use of this powerful and relatively safe modality can decrease TCS use and potentially avoid the need for systemic medication.

More recently, discussion has started regarding the use of cannabinoids in AD. These agents demonstrate notable anti-inflammatory and anti-pruritic properties, resulting in their exploration for dermatologic conditions such as acne, melasma, psoriasis, and AD. Effectiveness of topical cannabinoids can range from alleviation of symptoms of itch and pain to clinical resolution and prevention of relapse. In one clinical trial, 20 percent of subjects using palmitoylethanolamide (PEA)-containing creams discontinued their topical immunomodulators, 38 percent discontinued their oral antihistamines, and 33.6 percent discontinued their topical steroid regimen.[24] Due to hurdles in researching applications of cannabinoids and stigma surrounding the intoxicating effects of THC, these agents are only available in certain states and as prescription medications from physicians with a special license.[25] However, they represent a potentially promising and exciting addition to our toolbox against AD and TSW.

CONCLUSION

Much remains to be uncovered about TSW, but with the growing prevalence of social media, more cases are being brought to light. As clinicians seek to find better regimens for management of AD, TCS should remain at the forefront of management. When used appropriately, these agents are an effective and well-established treatment. However, misuse of these agents can lead to serious side effects, including withdrawal. Thus, physicians ought to be better equipped to diagnose TSW early on. Caution should be exercised in patients using high-potency TCS, with close follow-up and frequent reassessment of the need for these agents, as well as the potency and frequency of application. Additional proactive measures may include the use of alternative and adjunctive agents. Through this regimen, the clinician is able to use his/her most powerful tool against AD, and the patient is given the best chance at control of the disease with the least risk of adverse effects. ■

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