What's New in the Medicine Cabinet?

A Panoramic Review of Clinically Relevant Information for the Busy Dermatologist

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ABSTRACT

This article is the first in a periodic series of therapeutic topics with short reviews gleaned from major dermatology meetings, especially Scientific Poster Sessions, and is designed to provide information that may assist the readers in adapting information from the literature to their clinical practice. The topics covered in this issue are discussions of the clinical relevance of newer information about acne pathophysiology, acne in adult women, and topical corticosteroid spray formulations for chronic plaque psoriasis. (*J Clin Aesthet Dermatol.* 2014;7(1):26–30.)

With the advent of so many changes related to technology, clinicians are bombarded with a never-ending plethora of information about treatment approaches, study results, new devices, cautions and warnings with various therapies, and several other topics of interest in dermatology. Unfortunately, it is not humanly possible to keep up with all of the new information. More importantly, one may catch a few pieces of information; however, because of time limitations, and sometimes difficulties with access, the interested clinician is not able to capture salient details that differentiate specific study designs and outcomes or correlations that may be clinically relevant. The following is the first in a periodic series of therapeutic topics with short reviews gleaned from the 2013 Fall and Winter Clinical Dermatology Meetings and Scientific Poster Sessions and the 2013 Alabama Dermatology Society meetings. "What's New in the Medicine Cabinet?" is designed to provide information that may assist the reader in adapting information from the literature to their clinical practice. The topics covered in this issue are the clinical relevance of acne pathophysiology, acne in adult women, and topical corticosteroid spray formulations for chronic plaque psoriasis.

ACNE VULGARIS

Correlations of pathophysiology, biomarkers, and topical therapy. Several technological advances have allowed researches to determine the presence and quantification of specific cell types, various chemical messengers, and gene expressions in acne and other skin disorders.[1–3] More recent information has demonstrated that a relative sequence of inflammatory processes occurs from the start of development of an acne lesion along with follicular hyperkeratinization, which has long been recognized as the microcomedone. Inflammation is also persistent after individual acne lesions flatten as they progress toward resolution. Current data suggest that a combination therapy approach utilizing benzoyl peroxide (with or without a topical antibiotic) and a topical retinoid from the outset of treating acne is advantageous as the speed and magnitude of acne lesion reduction is augmented, especially as acne severity increases.[4–7] This observation,

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which is supported by multiple clinical studies, is consistent with a synergistic effect demonstrated by preliminary *in vitro* research evaluating specific biomarkers that reflect pathophysiological factors believed to be operative in acne.[2,4–12]

Take Home Message—The question then is not whether to start first with a topical retinoid or a benzoyl peroxide-containing formulation, but rather to incorporate both in combination early in the course of acne management whenever possible. The pre-emptive incorporation of proper skin care from the outset of acne treatment and the availability of vehicle formulations that enhance tolerability allow for this approach in many patients, although some may require staggered introduction of individual topical therapies.[13,14]

Topical therapy in adult women with acne. The subject of adult women with acne has become increasingly popular in the literature as the number of such patients showing up for care at dermatology offices has increased. Most of the educational and publication emphasis on management of adult women with acne has focused on the use of oral contraceptives and oral spironolactone, with a conspicuous absence of information on topical therapy in this subset of acne patients.[13,15,16] There are also common clinical assumptions that acne in adult women is predominantly inflammatory; presents with a "U-shaped pattern" that affects the lower cheeks, jawline, and lateral neck; and occurs mostly in women who had little-to-no acne as teenagers. Recent data collections have shown that approximately three-fourths of affected adult females also had acne during their teenage years, and often with the same pattern of mixed inflammatory and comedonal lesions.[15,17] Subset analyses of three topical therapies used to treat acne show that post-teenage female subjects included in their pivotal studies had a minimum of 20 facial comedones and 17 to 20 inflammatory lesions based on protocol-mandated entry criteria, with such studies limiting inclusion to only facial acne above the jawline.[17,18]

Take Home Message—Many of the women we see in clinical practice that are no longer teenagers warrant incorporation of a topical therapy approach that correlates with their present clinical presentation and with the specific needs of their skin type, color, and other secondary cutaneous changes.

A review by the author of available data in adult females with currently available topical therapies, either in the literature or through communication with manufacturers, uncovered clinical study data on three topical therapies—dapsone 5% gel twice daily, adapalene 0.3% gel once daily, and clindamycin phosphate 1.2%/benzoyl peroxide 2.5% gel once daily.[17–19]

Dapsone 5% gel. Subset analysis of data from two Phase 3 pivotal trials of patients with facial acne treated with dapsone 5% gel twice daily shows efficacy in both male and female patients, with a greater magnitude of efficacy in the latter group demonstrated, especially by global assessment.[20] A further subset analysis demonstrated a similar observation in post-adolescent women (≥18 years of age) as compared to adolescent girls (<18 years of age).[17] Reduction in facial oiliness was also noted across both groups, which likely represents favorable characteristics of the dapsone gel vehicle.[17] In addition, both the favorable tolerability of dapsone 5% gel and the lack of bleaching effects when in contact with colored fabric allow for convenient use on the neck and/or trunk region, both of which are sometimes involved in adult women with acne.[15–17] The submandibular and lateral neck are frequently affected along with the face in adult women who present with the U-shaped acne pattern.[15,16] As long-term data with dapsone 5% gel predominantly shows a reduction of inflammatory lesions, combination use with a topical retinoid appears to be an effective approach based on studies in combination with either adapalene or tazarotene.[21–23]

Adapalene 0.3% gel. A subset analysis of pivotal trial data on adapalene 0.3% gel for facial acne evaluated outcomes in post-adolescent women (>18 years of age) as compared to adolescent girls (<18 years of age).[18] The analysis showed comparable results in both groups with effective reduction of both inflammatory and comedonal lesions demonstrated along with favorable tolerability. The use of a topical retinoid offers additional benefits afforded by the modes of action of retinoid therapy, such as normalization of epidermal differentiation, improvement of dyschromia (such as postinflammatory hyperpigmentation), and reduction in dermal matrix degradation, all of which are clinically relevant in adult women with acne.[24,25] An obvious concern is whether or not most patients would be able to tolerate application of a topical retinoid on the neck region when this area is affected. It is likely the clinician would need to start with a cautious approach using a very thin layer on just a few nights of the week then building up as tolerated. Treating the neck region with a moisturizer at bedtime for 3 to 5 days before starting retinoid application ("priming the skin") and continuing its use along with the retinoid, may reduce the potential for skin irritation.[26] The favorable tolerability profile, long-term data demonstrating continued efficacy, and the multiple therapeutic benefits provided by topical retinoid use support adapalene 0.3% gel as a viable choice in adult women with acne.[18,27] To add, it may be used in combination with dapsone 5% gel or other therapies (benzoyl peroxide-containing formulations, oral spironolactone, oral contraceptives, etc.) in this patient subset.

Clindamycin phosphate 1.2%/benzoyl peroxide 2.5% gel. A subset analysis of pivotal trials of clindamycin phosphate 1.2%/benzoyl peroxide 2.5% gel once daily for facial acne demonstrated effective and comparable reduction in both inflammatory and comedonal lesions in two groups of female patients divided by age. The two groups were women >25 years of age and those <25 years of age.[19] If selected, the clinician is reminded that use of benzoyl peroxide (especially "leave on" formulations) for acne off of the face can bleach fabric if there is contact with

colored clothing and there is a greater likelihood for irritant dermatitis when used on neck skin.[23,24] Clindamycin phosphate 1.2%/benzoyl peroxide 2.5% gel can be used in combination with other therapies (i.e., topical retinoid, oral contraceptives, oral spironolactone, oral antibiotics, etc.) in this patient subset.

Take Home Message—Acne in adult women warrants selection of a topical regimen that addresses the clinical pattern of acne that is present, has data supporting its use in this subset, and addresses other secondary skin features that are often present in the post-teen female population.

CHRONIC PLAQUE PSORIASIS

Update on corticosteroid spray formulations. *Clobetasol propionate 0.05% spray—speed of onset appears to predict later therapeutic outcome.* Data from two Phase 3 pivotal trials of clobetasol propionate (CP) 0.05% spray (n=120) versus vehicle (n=120) used twice daily in adult patients with moderate-to-severe chronic plaque psoriasis affecting >2% body surface area evaluated if early response at Week 1 would be predictive of the response at Week 4 (active study endpoint).[28] Most subjects on CP spray who had an overall disease severity (ODS) score at Week 1 of almost clear (100%, n=9), mild (86%, n=61), moderate (67%, n=24), or severe/very severe (50%, n=2) achieved treatment success (clear or almost clear) at Week 4, which was markedly superior to the vehicle group. The results of this *post hoc* analysis demonstrated that results achieved with CP 0.05% spray at one week were reasonably predictive of successful outcomes after four weeks of use. This analysis also showed the same prediction results with assessment of pruritus scores at Week 1 and Week 4 from both study groups.[28]

Take Home Message—Clobetasol propionate 0.05% spray twice daily has been shown to induce a rapid onset of clinical efficacy, which is reflective of a favorable therapeutic outcome for chronic plaque psoriasis after one month of therapy. The quick onset of visible improvement may encourage consistent patient adherence.

Add-on therapy in patients on biologic agents. A large community-based trial (N=1421) was previously completed evaluating the use of clobetasol propionate (CP) 0.05% spray used twice daily for up to four weeks as either monotherapy or add-on therapy in adult patients with moderate-to-severe chronic plaque psoriasis.[29,30] A subset analysis evaluated the use of CP 0.05% spray twice daily as add-on therapy in patients already on a stable dosage of a biologic agent used for treatment of psoriasis for at least three months (83% TNF-blockers [78% etanercept]).[30] The effectiveness evaluable population in this subset analysis included all patients in this biologic-treated subgroup for whom baseline and Week 4 data was available (n=159). With regard to global assessment of improvement, 68.7 percent of patients already on their stable biologic regimen were clear/almost clear after the addition of CP 0.05% spray used twice daily over a duration of four weeks, with 89 percent demonstrating greater than 75 percent improvement.[30] Other reported outcomes that were shown to be favorable overall in this subset were clearance or marked improvements in target plaques, high levels of patient satisfaction, and positive improvements in quality-of-life indices.

Take Home Message—It is not uncommon for patients treated with biologic agents for psoriasis to exhibit scattered "breakthrough" plaques on treatment, especially on the legs, although other sites may be involved. Clobetasol propionate 0.05% spray has been shown to be an effective add-on therapy in such cases, administered twice daily for up to four weeks in a community-based trial. Once adequate clearance is observed, the clinician may adjust to a lesser frequency of application with topical corticosteroid therapy and can also institute therapy with a topical vitamin D analogue.

Desoximetasone 0.25% spray. Two Phase 3, double-blind, randomized, vehicle-controlled parallel studies evaluated the efficacy and safety of desoximetasone (desox) 0.25% spray (n=120) administered twice daily versus vehicle spray (n=120) twice daily for 28 days in adult patients with moderate-to-severe plaque psoriasis.[31,32] This 0.25% spray is the first topical formulation of desox to be ranked above high potency based on vasoconstrictor assay data submitted to the United States Food and Drug Administration (FDA) and has been marketed in the United States since its FDA-approval in May 2013 as a Class 1 topical corticosteroid (TCS).[33,34] The other available formulations of desox are ranked in TCS potency as follows: the 0.05% ointment and cream are ranked as mid-potency, the 0.05% gel is ranked as high potency, and the 0.25% ointment and cream are ranked as high potency.[35] These differentiations emphasize the important effects that both vehicle formulation and concentration can have on TCS potency rankings with a given corticosteroid compound.

An important distinction in the Phase 3 pivotal trials with desox 0.25% spray is that study entry required greater than 10-percent body surface area (BSA) with chronic plaque psoriasis, which is substantially greater than the BSA requirement typically used to assess Class 1 TCS agents.[31,32] In the active treatment group, the mean percent BSA affected by psoriasis that was used to determine the percent of patients achieving clinical success (clear or almost clear) in these trials ranged from 13 to 17 percent at baseline, and the average target lesion size used to rate treatment success (clear or almost clear) measured 45.93 cm^2. The pooled data from the two Phase 3 pivotal trials showed that 42 percent of subjects treated with desox 0.25% spray were clear or almost clear based on physician (investigator) global assessment of their fully involved BSA at Week 4 compared to 12 percent with vehicle, and 46 percent of target plaques were clear or almost clear in the actively treated group after four weeks as compared to 12 percent in the vehicle

group.[31,32] With regard to speed of onset of desox 0.25% spray, 61 percent of target lesions improved in severity score by greater than 50 percent within one week. Tolerability and safety were favorable with no subjects reporting stinging or burning after spray application in the Phase 3 pivotal trials.[31–33] Suppression of the hypothalamic-pituitary-adrenal (HPA) axis was noted in three subjects who underwent cosyntropin stimulation testing at end of study; 2 of these 3 patients were available for retesting at 28 days post therapy, and in both cases HPA axis suppression was reversible.[33,34]

Take Home Message—It is important to take into account baseline severity including BSA when evaluating therapeutic response based on data reported in clinical trials. In addition, it is not valid to compare results between clinical trials or package inserts that utilize different topical corticosteroid products as study protocol criteria, actual disease severity range of the study populations, and/or methods of analysis are often very different. Desoximetasone 0.25% spray twice daily proved to be highly effective in patients with chronic plaque psoriasis presenting with a mean BSA range of 17 percent over one month of therapy with favorable safety and tolerability and absence of stinging and burning. A rapid onset of effect was observed in many subjects based on target plaque evaluation, which reflects efficacy against individual plaque lesions that were moderate or greater in thickness in these pivotal trials. The vast majority of subjects did not experience HPA axis suppression and in two who did, no adverse sequelae occurred and both cases reversed on subsequent testing.

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