What's New in Acne Treatment in Canada?

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Introduction

Acne vulgaris is the most common skin disorder affecting children and young adults in North America. Patients with acne often experience significant psychological morbidity due to decreased self-esteem, including concomitant depression and anxiety. As a result, there persists an unmet demand for new and more effective acne treatments.[1] In Canada, recently introduced and horizon therapies for acne include dapsone gel, clindamycin phosphate + tretinoin gel, adapalene + benzoyl peroxide gel, and doxycycline capsules.

Pathogenic Factors

- The pathogenesis of acne involves four main abnormalities of the pilosebaceous unit:
  1. Follicular hyperkeratinization
  2. Increased sebum production
  3. Proliferation of the *Propionibacterium acnes* (*P. acnes*) bacteria
  4. Inflammation
- Current anti-acne therapies that target these abnormalities include benzoyl peroxide, antibiotics, retinoids, and hormonal agents.
- Combination therapy is often used to achieve optimal results, since most anti-acne medications do not target all four of the aforementioned pathogenic features of acne.[1]

Dapsone 5% Gel (Aczone®)

- Dapsone 5% gel is a new, recently available, twice-a-day application, topical treatment for acne vulgaris. It represents the first new anti-acne medication to gain North American regulatory approval in the past decade.
- Oral dapsone, typically used in the treatment of *Mycobacterium leprae* (leprosy) infections, as well as prophylaxis against pneumocystis pneumonia in HIV patients, has both anti-inflammatory and antimicrobial properties. In dermatology, it is used in autoimmune blistering diseases of the skin, such as dermatitis herpetiformis.[2]
- The mechanism by which topical dapsone gel improves acne has not yet been confirmed, but it is effective against both inflammatory and non-inflammatory acne, with more prominent improvement occurring in inflammatory lesions.[1]
- Dapsone 5% gel applied twice-daily has been shown to decrease both inflammatory and non-inflammatory acne lesions. In two identical 12-week, double-blind, randomized, parallel group, phase III studies, 3010 patients aged ≥12 years used either dapsone 5% gel or vehicle on affected facial areas.[3]
  - Dapone-treated patients experienced significantly greater reductions from baseline to 12 weeks in inflammatory, non-inflammatory, and total lesion counts compared with controls. After 12 weeks, the mean reduction in inflammatory lesion count was 48%, and 41% of treated patients achieved a Global Acne Assessment Score of "none" or "minimal."
  - Most common reported side-effects included oiliness, erythema, dryness, and peeling; there were no significant differences in the adverse event rates between dapsone-treated and vehicle control groups.
- Long-term safety was demonstrated in a 1-year open-label trial of twice-daily topical dapsone involving 506 patients ≥12 years of age.[2]
  - Following topical treatment with dapsone gel, total systemic exposure to dapsone was about 100-fold less when compared with the recommended dose of oral dapsone. Therefore, dapsone gel is associated with minimal systemic absorption even with prolonged therapy.
  - Patients with glucose-6-phosphate dehydrogenase (G6PD) deficiency are at an increased risk of hemolytic anemia while taking oral dapsone. However, this association has not been found in G6PD enzyme deficient patients using topical dapsone.[2,4]
- It is worth noting that dapsone is a sulfone, not a sulfonamide. The two compounds differ in their chemical structures and activities - sulfonamides are antimicrobial agents, whereas sulfones have both anti-inflammatory and anti-bacterial properties. Because sulfa allergies are caused by sulfonamides, dapsone gel can be used in patients with a sensitivity to sulfa drugs.[2,4]

Dosing Considerations

- Available preparations include a 60 g laminate tube and 3 g physician sample.
- Treatment is applied twice-daily, using a pea-size amount to cover the acne-affected area.
- The most common adverse reactions include oiliness, peeling, dryness, and erythema at the application site.
- Trimethoprim-sulfamethoxazole (TMP-SMX) increases the level of dapsone and its metabolites.

- Patients should be warned that the concomitant use of dapsone gel with benzoyl peroxide can lead to temporary yellow to orange discoloration of the skin and hair. If both drugs are prescribed for combination treatment of acne, patients should be instructed to administer at separate times of the day and wash the skin between applications.[5]

Clindamycin Phosphate 1.2% + Tretinoin 0.025% Gel (Biacna™)

- This new once-a-day, fixed-dose gel formulation contains solubilized clindamycin phosphate 1.2% and tretinoin 0.025% (CT gel).
- The anti-inflammatory and antibacterial properties of clindamycin are combined with the comedolytic and anticomedogenic actions of tretinoin to target several mechanisms in acne pathogenesis.[6]
  - Clindamycin is a lincosamide antibiotic that reversibly binds to the 50S ribosomal subunit, thereby inhibiting bacterial protein synthesis. Its role in the treatment of acne is attributed to its activity against *P. acnes* proliferation and subsequent suppression of inflammatory lesion formation.
  - Topical tretinoin promotes follicular keratinocyte desquamation, which facilitates expulsion of current lesions and inhibits formation of new microcomedones.[1]
- The efficacy of CT gel versus monotherapy with either agent (clindamycin 1% hydrogel or tretinoin 0.025% hydrogel) or vehicle (hydrogel) was examined in two 12-week randomized, double-blind, controlled trials in 2219 subjects.[7] The combination CT gel:
  - was superior to monotherapy and vehicle in the reduction of inflammatory, non-inflammatory, and total lesions.
  - showed a 48.7% reduction in total lesion count at the end of 12 weeks, compared to 38.3%, 40.3%, and 23.2% for clindamycin hydrogel, tretinoin gel, or vehicle, respectively.[7]
- The CT gel has also been shown to have a favourable side-effect profile. A study examining tolerability of CT gel versus monotherapy in 4550 participants found that:
  - the overall discontinuation rate due to adverse effects was less than 1% for the CT gel.
  - 91%, 92%, and 94% of participants reported no burning, no pruritus, or no stinging, respectively.[8]
- A 4-week randomized study of mild to moderate acne investigated the safety and tolerability of combination CT gel with morning use of a BP wash, widening the number of pathologic factors targeted and suppressing the potential emergence of clindamycin-induced *P. acnes*-resistant bacterial strains.[9]
  - Side-effects were mild and included transient dryness, scaling, erythema, burning, stinging, and itching during the first week of treatment, then improved within 1-2 weeks.
  - CT gel + BP wash limited the potential for bacterial resistance and was found to be a well-tolerated, safe and efficacious regimen in treating acne.

Dosing Considerations

- CT gel is available in 2 g samples and 60 g tubes.
- Treatment is indicated for patients ≥12 years of age and is applied topically to affected areas once-daily at bedtime.
- Common side-effects include skin irritation (dryness, peeling, burning, or pruritus), which usually decrease after 2 weeks.
- Contraindications include Crohn's disease, ulcerative colitis, or colitis with previous antibiotic use.
- Patients should be made aware of enhanced photosensitivity and potential interaction with general anesthetics; safety in pregnant women has not been established.[10]

Adapalene 0.1% + Benzoyl Peroxide 2.5% Gel (Tactuo™)

- This new once-a-day adapalene-benzoyl peroxide combination gel treats mild to moderate acne.
- The two active agents have complementary modes of action.
  - Adapalene is a topical, retinoid-like compound that has been shown to be a potent modulator of cellular differentiation, keratinization and inflammation, thereby decreasing microcomedone formation.
  - Benzoyl peroxide (BP) is a bactericidal oxidizing agent (not a true antibiotic) with activity against *P. acnes*. It has exfoliative and keratolytic properties and decreases the development of antibiotic resistance when used in combination with topical or oral antibiotics.
- Adapalene + BP target three factors known to contribute to the pathogenesis of acne: formation of microcomadones via altered follicular growth and differentiation, colonization of the pilosebaceous unit with *P. acnes*, and inflammation.[11]
- Clinical trials have demonstrated favourable results with adapalene-BP gel compared to adapalene gel or BP gel monotherapies, as well as control gel vehicle.[12,13] At the end of 12 weeks, the combination gel reduced the median number of total acne lesions by over 50%, which was significantly better than monotherapy with adapalene (35.4%) or benzoyl peroxide (35.6%) alone.[12]
  - Safety and tolerability profile of the fixed-dose agent were comparable with adapalene monotherapy.
  - The majority of adverse effects occurred early in the study and resolved without residual effects. Dry skin was the most frequent side-effect, reported by 9.4% of individuals in the combination treatment group, 10.1% for adapalene, 2% for BP, and 1.4% for placebo.[12]

Dosing Considerations

- It is available in 5 g physician samples and 60 g tubes.
- In patients ≥12 years of age, treatment should be used once-daily at bedtime.
- Common side-effects include skin dryness, skin irritation, burning sensation, and redness. Patients should be advised to stop using the medication if skin becomes very dry, itchy, red, swollen, blistered, or sunburned.
- Avoid use in pregnant women and patients with eczema, very irritated skin, or allergies to any of the ingredients in the gel.
- Female patients of childbearing years should receive contraceptive counseling before prescribing.[11]

Oral Doxycycline

- Doxycycline 40 mg is a subantimicrobial low-dose medication in the oral tetracycline family and is currently under Health Canada review for treating inflammatory lesions (papules and pustules) of rosacea.
- In acne, the low-dose regimen exploits the anti-inflammatory effects of doxycycline without altering the antimicrobial susceptibility of the skin flora, thereby preventing *P. acnes* resistance.
- Tetracyclines have been used in treating bacterial infections for over 50 years, but the non-antibiotic therapeutic properties of tetracyclines are a more recent discovery.[14]
- Tetracyclines have been shown to possess significant anti-inflammatory properties via matrix metalloproteinase inhibition and reduce several pro-inflammatory mediators, such as prostaglandins, nitric oxide and cytokines, among other mechanisms.[15]
- These therapeutic effects were examined in a randomized control trial by Skidmore et al. comparing doxycycline 40 mg with placebo for moderate acne.[16]
  - At 6 months, the active treatment group showed significant differences in mean percent decrease in both inflammatory and non-inflammatory lesions, comedonal lesions, and total inflammatory lesions.
  - These non-antimicrobial, anti-inflammatory effects are evident at lower drug concentrations than those needed for antibiotic activity. Thus, unlike the traditional doses of doxycycline used for bacterial infections, treatment administered at lower, sub-antimicrobial doses, typically given as 40 mg once-daily, exploits its anti-inflammatory effects on acne without increasing antibiotic resistance.
- A randomized control trial by Farshchian et al. in 2008 demonstrated that doxycycline at sub-antimicrobial (40 mg) and antimicrobial (100 mg) doses have similar efficacy with regard to decrease in mean inflammatory lesion count. However, the higher antimicrobial doses were associated with increased rates of adverse events and the emergence of resistant bacteria.[17]

Dosing Considerations

- It will be available in 40 mg capsules and should be taken once-daily on an empty stomach 1 hour before or 2 hours after meals.
- Patients should be advised about possible side-effects including photosensitivity, gastrointestinal upset, and sinusitis.
- As with other tetracyclines, treatment is contraindicated in children and pregnant women due to interference with tooth and skeletal development.[18]

Combination Therapy Improves Adherence

- Until recently, the topical treatment of acne using an antibiotic and retinoid involved the combination of two separate products.
- Studies have shown that the inconvenience of using multiple therapies in the treatment of acne reduces adherence, and ultimately, decreases efficacy.[19,20]
  - A study comparing once-a-day combination clindamycin + tretinoin gel with the separate use of clindamycin and tretinoin revealed 67% adherence in the combination therapy group versus only 8% in patients using clindamycin and tretinoin separately.[19]
- A simplified dosing regimen, such as combination therapy using topical clindamycin + tretinoin, retinoid + BP, or antibiotic + BP compared with single-agent treatment can, therefore, be more clinically effective and convenient.

Conclusion

Acne is a multifactorial skin disorder, typically requiring combination therapy that targets as many pathogenic factors as possible. The availability of topical dual-agent fixed dose therapies, such as antibiotic/BP and newer pairings including clindamycin/tretinoin and adapalene/BP achieves this goal, as well as simplifies the dosing regimen. In conjunction with the introduction of topical dapsone, these compounds further widen the therapeutic arsenal, enabling clinicians to tailor treatment according to patient preference, tolerability, and lifestyle considerations, with the anticipation of enhancing adherence and optimizing outcomes.

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