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Clinical Evidence. Practical Advice

Editor-in-Chief: Dr. Stuart Maddin

Dr. Stuart Maddin, MD, FRCPC
EDITOR-IN-CHIEF

Dr. Stuart Maddin is the Chairman of SkinCareGuide. He is one of North America's leading dermatologists and the author of numerous dermatologic journal articles, monographs and textbooks. In addition to providing consultative input to a number of pharmaceutical and biotech companies, he is the director of the Clinical Trials Unit at the Department of Dermatology and Skin Science, University of British Columbia. Dr. Maddin has also acted in an advisory capacity to a number of drug regulatory agencies, such as the Health Protection Branch (Ottawa), the AAD-FDA Liaison Committee, and World Health Organization (Geneva). He is the founder of the Dermatology Update symposia, now in its 27th year. As well, he is Past President of the Canadian Dermatology Association and served as Secretary-General of the International Committee of Dermatology – International League of Dermatological Societies.

Karen Yan, RPh, BScPharm
PHARMACIST ADVISOR

Karen is a registered pharmacist working in Vancouver, BC. She is a graduate from the Faculty of Pharmaceutical Sciences at the University of British Columbia. Karen has a keen interest in continuing pharmacy professional development. In addition, during her senior year of undergraduate studies, she participated in research and development in pharmaceutics. Presently, Karen works as a community pharmacist at Laurel Prescriptions, a pharmacy that specializes in parenteral and topical compounding.

Therapeutic Update on External Genital Warts

Marni C. Wiseman, MD, FRCPC

Section of Dermatology, University of Manitoba, Faculty of Medicine, Winnipeg, MB

CancerCare Manitoba, Winnipeg, MB

Introduction

External genital warts (EGW) are a common infection caused primarily by human papillomavirus (HPV) types 6 and 11. EGW negatively impacts upon patient psychosocial function and is a co-factor for infection with other sexually transmitted infections (STI), by allowing an easier portal of entry into the skin. Both patient and provider-applied therapies can be utilized in tandem to effectively treat EGW. More recently, prophylactic strategies using vaccines have been instituted to prevent HPV acquisition and resultant disease. As well, the recent introduction of a new formulation topical immunomodulator has further widened the spectrum of available therapies.

Pathogenesis

- EGW is caused by human papillomavirus (HPV)
- An HPV viron is small and non-enveloped; its protein coat (capsid) is composed of two structural proteins
- The viral genome consists of single, supercoiled double-stranded circular DNA of approximately 8000 base pairs in size[1]
- >200 types of HPV have been identified, approximately 40 infect the anogenital tract[2]
- HPV infections are categorized as low risk or high risk based upon oncogenic potential[3,4]
- High risk-types include HPV 16, 18
  - Responsible for 100% cases of cervical cancer and 80% cases of anogenital cancers
- Low risk types include HPV 6, 11[4]
  - Responsible for 95% EGW cases
  - HPV 6: 74.4%
  - HPV 11: 14.2 %
  - HPV 6 and 11: 3.7%
- Low risk HPV types are also responsible for 10% of cervical intraepithelial neoplasia grade 1, 42% of related low-grade vulvar intraepithelial neoplasia, and 100% of recurrent respiratory papillomatosis

Disease Overview

Epidemiology

- The World Health Organization estimated 300 million cases worldwide of HPV infection without any detectable abnormality; 30 million cases worldwide of active EGW
- Approximately 1 million new cases annually of EGW in the US[5]
- Prevalence in Manitoba (2004): 165.2 per 100,000 for men; 128.4 per 100,000 for women[6]
- Incidence in British Columbia (2004): 1.54 per 1000 males; 1.23 per 1000 females[7]
- In Canada, the incidence of genital warts was estimated to be 107 per 100,000 person-years in 1999, increasing to 126 per 100,000 person-years in 2006.[7]
- Incidence highest in women between the ages of 20-24 years (3.38 per 1000 women)
- Incidence highest in men aged 25-29 years (3.03 per 1000 men)

ALSO IN THIS ISSUE: **Topical Vitamin D Analogues in Psoriasis Treatment** *(page 5) and* **Optimizing Topical Acne Therapy** *(page 9)*

Burden of Disease

- Psychosocial impact[8]
  - Feelings of anger, disgust, embarrassment
  - Fear of cervical cancer
  - Concern over recurrence, transmission, and treatment efficacy
  - Change in lifestyle
- Socioeconomic burden
  - 60% increase in office visits (US) in last decade[9]
  - $220 million in health care costs (US 2004, private insurance)[10]
  - A population-based study of EGW treatment in British Columbia confirmed its significant burden on the health care system:[7]
    - Between 1998 to 2006, 39,493 patients were diagnosed with EGW, with 43,586 episodes
    - Overall incidence was 1.26 per 1000 population, at an average cost of $190 per episode for treatment, which translates into about $1 million annually in direct medical costs.
    - The incidence and prevalence of EGW are comparable across Canada.

Natural History

- EGW noted by patient in 65% of cases (52% females; 79% males)[8]
- EGW noted at physician visit in 16% of cases (30% females; 1% males)[8]
- Transmitted most commonly through sexual contact (i.e., genital-genital, oral-genital, genital-anal)
- Infection may also rarely occur due to perinatal transmission (laryngeal papillomatosis) or fomites[11]
- HPV gains access to basal epithelium via abrasions or microabrasions
- Incubation (1-8 months)
- Individual patient immune response results in active growth or host containment (6-9 months)
- Clinical course of EGW include remission or persistent infection with recurrences
- 30% spontaneously resolve within 4 months, 50% at 6 months[12]

Treatment Options (Table 1)

- Patients may prefer self-applied therapies for initial treatment
- Combination therapy may be more effective than monotherapy
- Inadequate responders may improve with transition to or addition of other therapies or modification of the existing approach
- According to Canadian STI Guidelines[13] therapies are broadly grouped as patient-applied or office-based treatments:
  - Office-based treatments
    - Podophyllin resin (when no other treatment is available)
    - Surgical excision
    - Cryotherapy
    - Bichloracetic acid or trichloroacetic acid
  - Patient-applied treatments
    - Podophyllotoxin
    - Imiquimod
- Cytodestructive therapies involve the physical removal or chemical destruction of EGW:
  - Cryotherapy (liquid nitrogen)
  - Surgical/ablative techniques (surgical excision, carbon dioxide laser, electocautery)
  - Trichloroacetic or bichloroacetic acid
  - Podophyllin resin
  - Podophyllotoxin (0.5%) - standardized concentration of purified podophyllin
- Immunomodulatory therapy with topical imiquimod
  - Immune response modifier
  - Antiviral and antitumor effects
  - TLR-7 agonist
  - Induces Th1-type immune response and the generation of cytokines such as IFN-alpha
  - Pregnancy Category C
  - Due to its favourable efficacy, safety, and tolerability profiles, as well as lowest recurrence rate, Canadian Consensus Guidelines on HPV[14] recommends the use of imiquimod prior to initiating more invasive strategies, such as destructive/excision or laser therapies.
  - Imiquimod 5% cream (Aldara™)
    - Approved by Health Canada in 1999
    - Officially indicated for the treatment of external genital and perianal warts in immunocompetent adults
    - Applied 3 times weekly for up to 16 weeks to a specific treatment area
    - In a Phase 3 clinical trial, 72% of women and 33% of men had complete clearance of baseline target warts (analyses did not include non-target or new warts)[15]
    - Side-effects include erythema (67%), erosion (32%), excoriation/flaking (25%), edema (16%)[15]
  - Imiquimod 3.75% cream (Vyloma™)
    - Approved by Health Canada in March 2011 for the topical treatment of external genital warts and perianal warts (whether present at the start of therapy or emerging during therapy) in immunocompetent adults.
    - Developed with the goal to shorten treatment duration, simplify dosing regimen, and improve tolerability, thereby encouraging adherence.
    - Two recent identical, gender stratified, randomized, placebo-controlled clinical studies involving 981 patients >12 years of age with 2-30 lesions in the inguinal area, perineal region, perianal area, penile shaft/glans/foreskin, scrotum, or vulva demonstrated imiquimod 3.75% applied once-daily for up to 8 weeks was well tolerated and efficacious in the treatment of EGW (Table 2 and Figure 1).[16,17]
    - Efficacy was measured in terms of number of EGW (baseline and new).
    - In patients achieving complete clearance, almost 70% maintained clearance at 12 weeks post-treatment.[17]
    - Common side-effects included pain, irritation, and pruritus at the treatment site.

Method	Treatment	Comments
Antiproliferative Therapies	Podophyllum resin 10%-25%	• Physician-administered • Removal of warts by destruction of infected tissue • Potential for systemic toxicity, especially if applied to large areas or in patients with renal insufficiency • Teratogenic (fetal death reported) • Antimitotic (causing tissue necrosis) • Local side-effects include erythema, edema, pain, burning, itching, severe necrosis, and scarring • Modest efficacy and potency; shelf-life unpredictable
	Podophyllotoxin 0.5% solution or gel	• Can be applied by the patient (twice-daily for 3 days, then off for 4 days; may repeat treatment cycle for up to 4 weeks); skin protectant, e.g., petroleum jelly, should be used on normal adjacent skin • Low cost, low toxicity • It does not contain any mutagenic substances, unlike those found in podophyllum resin • Potential systemic toxicity if applied to large area, limit use on EGW 3 times weekly for up to 4 consecutive weeks
Immunomodulatory Therapies	Imiquimod cream	• Self-administration may improve patient adherence • Enhances the cytotoxic immune reaction, usually seen as an inflammatory response • Low rate of recurrence due to reduction of the viral load and/or induction of HPV-specific cellular immune memory • Side-effects are mild to moderate and include local erythema and erosion at the site of application
	Imiquimod 5%	• For 5% imiquimod apply directly to the affected skin 3 times/week for up to 16 weeks; use on alternating days - leave on affected skin for 6-8 hours before washing off with soap and water • Reduce frequency of application or temporarily interrupt therapy if there is concern over the degree of inflammation
	Imiquimod 3.75%	• For 3.75% imiquimod apply daily at bedtime for up to 8 weeks • Reduces treatment duration; simplified once-daily dosing improves tolerability
Destruction/Excision Therapies • For more extensive disease • May require local or general anesthesia • Scaring and pigmentary changes common	Topical trichloroacetic acid 85% (TCA) or bichloroacetic acid	• Causes cellular destruction by chemical cautery • Most effective when treating small, moist lesions • Damage to surrounding tissue can be minimized by protection with petroleum jelly • If TCA is applied to nonaffected tissue, instruct patients to wash the area with liquid soap or baking soda • Can cause pain and ulceration • Inexpensive; safe in pregnancy
	Local cryotherapy	• Most common destructive mode; inexpensive • Involves freezing with liquid nitrogen • Offers ease of use with no systemic effects • Can cause pain, ulceration, and pigmentary changes • Safe for use during pregnancy
	Electrodesiccation	• Warts are burned off with a low-voltage electrical current
	Excision by scissors, curette, or scalpel	• Provides definitive clearance of abnormal tissue • Particularly suitable for larger exophytic warts • Local anesthesia is required
	Ablative laser	• CO2 laser therapy is usually reserved for extensive and/or treatment-resistant warts • May require a long time for recovery and is expensive
Combination Therapy • Can provide a better result over monotherapy	Excision/destruction + imiquimod	• Cryotherapy combined with imiquimod appears to be very commonly used • Initial therapy with imiquimod may reduce wart size and improve surgical outcomes • Initial treatment with imiquimod followed by excision of residual lesions may provide long-term clearance of EGWs, especially if prior monotherapy was insufficient
	Excision/destruction + cidofovir	• Due to cidofovir's broad antiviral activity, it has been used successfully as a topical gel for refractory patients

Table 1: Overview of therapeutic options for external genital warts[14-20]

Location	Complete Clearance (Per-protocol)	Complete Clearance (ITT)	Partial (≥75%) Clearance (Per-protocol)
Overall	33.8	28.3	45.9
Women overall	43.1	36.6	56.2
Vulva	51.0		
Perineum	64.9		
Perianal	78.5		
Inguinal	45.0		
Men overall*	22.7	18.6	33.6

Table 2: Overall and anatomic site-specific clearance rates, by gender, following treatment with imiquimod 3.75% cream[16,17]
* Anatomic site-specific clearance rates in men have not yet been published.
ITT = intent-to-treat; primary analysis includes all randomized subjects
Per-protocol = only data from adherent subjects are analyzed

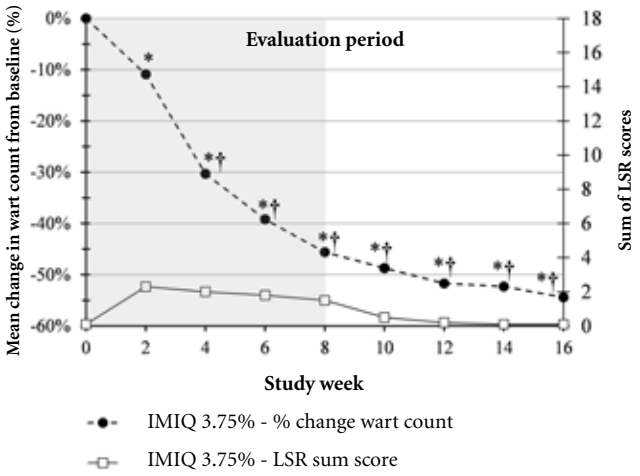

Figure 1: Change in wart count compared with baseline (left axis, circle) compared with local skin reaction (LSR) sum score (right axis, square) for imiquimod 3.75% in women. Modified from Baker et al.[16]

Prevention

Two vaccines available for the prevention of HPV acquisition:

- Quadrivalent (HPV types 6, 11, 16, 18) vaccine (Gardasil®)[21]
  - Prevention of EGW caused by HPV 6, 11 and cervical cancer and other cancers caused by HPV 16, 18 including vulva and vaginal cancers, cervical intraepithelial neoplasia, vulvar intraepithelial neoplasia, and vaginal intraepithelial neoplasia
  - Indicated in females aged 9-45 years
  - Indicated in males aged 9-26 years
- Bivalent (HPV types 16, 18) vaccine (Cervarix®)[22,23]
  - Adjuvant results in very high serum antibody levels against HPV, excellent subtype cross-protection
  - Excellent for prevention of cervical cancer and other cancers caused by HPV 16, 18
  - Does not protect against EGW acquisition
  - Indicated in females aged 10-25 years

Conclusion

EGW is a worldwide problem. The scope of diseases, both oncogenic and nononcogenic, caused by HPV is broad. EGW is a manifestation of nononcogenic HPV subtypes 6 and 11. Therapeutic strategies to eradicate EGW have been developed and preventative vaccines are now widely available. Hopefully, the development of novel therapeutic molecules targeting EGW will supplement current tools in the treatment armamentarium against HPV and facilitate the eradication of this prevalent disease.

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Topical Vitamin D Analogues in Psoriasis Treatment

Adam Natsheh, BScPharm, MD, FRCPC (Dermatology)[1,2,3]
Cindy Truong Natsheh, BScPhm, ACPR, PharmD[4,5]
[1] Division of Dermatology, University of Toronto, Toronto, ON
[2] Womens College Hospital, Toronto, ON
[3] The Dermatology Group, North York, ON
[4] Department of Pharmacy,University Health Network, Toronto, ON
[5] Leslie Dan Faculty of Pharmacy, University of Toronto, Toronto, ON

Introduction

Psoriasis is a common, chronic, recurrent, and inflammatory skin disease that can be associated with significant psychosocial impact. While at present there is no known cure, there are many good treatment options to control psoriasis. This article will outline the role of a newer class of topical medications known as vitamin D analogues in the management of psoriasis.

What is Psoriasis?

- Psoriasis affects approximately 2% of the North American population.[1]
- The exact cause is not known, but is multifactorial in origin- with a combination of genetic and environmental factors (e.g., streptococcal infections, stress, or medications).
  - Medications that can exacerbate psoriasis include gold salts, beta blockers, interferon, antimalarials (e.g., hydroxychloroquine), lithium, and oral steroids.
  - There is a positive family history in approximately one-third of individuals.[2]
- Anxiety, smoking, and skin trauma may exacerbate psoriasis.
- It can occur at any age, but there is a bimodal peak distribution for age of onset - in the 20s and 60s.
- Psoriasis is characterized by a chronic course consisting of recurrent flares and periods of remission.
- Typical lesions appear as itchy pink plaques with silvery/shiny scales that can be quite thick, and are most commonly seen on:
  - extensor surfaces of limbs (e.g., knees, elbows, buttocks)
  - hands and feet (usually palms and soles); patients complain of very dry skin with cracking and sometimes pain
  - nails (yellowing), pitting (indents), onycholysis (lifting of nail plate from nail bed)
  - scalp and ears (posterior and sides of scalp most common)
- It is somewhat itchy, but usually less so than atopic and other types of dermatitis (eczema)
- Being chronic, its impact on physical and mental function has been demonstrated to be similar to that of cancer, arthritis, hypertension, heart disease, diabetes, and depression.[3]
- There is a growing body of evidence suggesting that severe psoriasis may be an independent risk factor for cardiovascular disease.[4-6]

Treatment Rationale

- Psoriasis is dominated by four skin abnormalities: redness or erythema, inflammation, hyperproliferation of the keratinocytic layer, and altered epidermal differentiation.[7]
- Treatment of psoriasis is often multimodal, using a combination of non-drug and pharmacological modalities.
- Like other chronic diseases (e.g., hypertension, diabetes, asthma) treatment requires long-term patient adherence, making choice of therapy that is acceptable to the patient even more important. Clinicians should not only choose therapies that work, but those that the patient will work with.[8]
- Topical treatments vary depending on body location, characteristics of the psoriasis being treated, including lesion thickness, degree of redness, and amount of scaling, as well as patient preference.
- The goal of therapy is to gain rapid control of flares, induce and prolong remission, and maintain normal skin, while preventing long-term complications from therapy.

Treatment Options

Topical Corticosteroids

- High-potency corticosteroids play a central role in the topical treatment of psoriasis. Their multiple mechanisms of action include anti-inflammatory, immunosuppressive, and antiproliferative effects.[1]
- Corticosteroids are the most widely used agents for the topical treatment of psoriasis and have been the mainstay of therapy. They are well tolerated and come in a variety of vehicles, including ointments, creams, gels, foams, lotions, sprays, and solutions.
- Different potencies of corticosteroid treatment are available (Table 1), ranging from Class 1 (highest potency) to Class 7 (lowest potency).
- Typically, higher potency topical steroids are commonly prescribed for rapid clearing in acute flares. Following initial control of psoriasis, it is recommended that a gradual reduction in dosing be instituted.
- Very potent steroids (Class 1 or 2) are suitable for pulse therapy, chronic recalcitrant plaques, control of flares, or thickened lesions (i.e., palms and soles). They should not be used on thinner skin, such as the face, neck, or intertriginous areas (axillae or groin).

- The risk of adverse effects (e.g., atrophy or striae) increases if they are used continuously for longer periods of time.

- Fear of side-effects is a key reason patients use steroids less often than prescribed, leading to treatment failure. Similar to oral antibiotics, topical steroids should be used as directed.
- A more detailed discussion on topical steroids in psoriasis may be found at: http://www.skintherapyletter.ca/fp/2010/6.3/1.html

Vitamin D Analogues (Table 2)

- Vitamin D analogues induce differentiation and suppress proliferation of keratinocytes, thus reversing the abnormal keratinocyte changes in psoriasis.[9]
- Unlike their oral counterpart, topical vitamin D analogues have minimal effects on systemic calcium metabolism. However, serum calcium levels should be monitored if risk factors for hypercalcemia are present, such as renal disease or impaired calcium metabolism.
- There are two available vitamin D analogues available in Canada - calcitriol and calcipotriol. Combination products with betamethasone dipropionate are also available.
- Calcitriol and calcipotriol were found to be comparably effective in one study with 250 subjects treated twice-daily with mild to moderate psoriasis over a 12 week period.[10]
- In addition to topical corticosteroids, the Canadian Psoriasis Consensus Guidelines recommends vitamin D analogues, i.e., either calcipotriol or combination calcipotriol/betamethasone diproprionate, as first-line options for mild psoriasis.[8]
- Vitamin D compounds can induce a steroid-sparing effect, resulting in reduced adverse reactions such as skin atrophy, tachyphylaxis, and other side-effects associated with corticosteroid use.

Calcitriol (Silkis™)

- It is the naturally occurring and biologically active metabolite of vitamin D3 [1 alpha-25-dihydroxyvitamin D3, abbreviated as 1,25 (OH)2 D3], which is primarily produced in the skin by exposure to ultraviolet light.
- It is indicated to treat mild to moderate plaque-type psoriasis in adults ≥18 years of age with up to 35% body surface area (BSA) involvement and is suitable for long-term therapy.[9]
- Calcitriol has been found to be very well tolerated in intertriginous areas with minimal irritation on application.[7] It is not suitable for use on the face.
- In a 52-week uncontrolled, open label study of 324 patients, efficacy did not appear to diminish over time.[11]
- It is available as an ointment and recommended dosing is twice-daily. The maximum weekly dose should not exceed 200 g.
- Calcitriol ointment produces little systemic absorption of calcitriol and does not result in systemic hypercalcemia even when applied to approximately one-third of BSA.[11]

Relative Potency Class	Corticosteroid	%	Preparation
1	Betamethasone dipropionate glycol	0.05	Cream, ointment, lotion
	Clobetasol propionate	0.05	Cream, ointment, lotion, spray, shampoo
	Halobetasol propionate	0.05	Cream, ointment
2	Amcinonide	0.1	Cream, ointment, lotion
	Betamethasone dipropionate	0.05	Ointment
	Desoximetasone	0.05	Gel
	Desoximetasone	0.25	Cream, ointment
	Diflucortolone valerate	0.1	Cream, oily cream, ointment
	Fluocinonide	0.05	Cream, ointment, gel
	Halocinonide	0.1	Cream, ointment, lotion
3	Betamethasone dipropionate	0.05	Cream
	Betamethasone valerate	0.1	Ointment
	Mometasone furoate	0.1	Ointment
	Triamcinolone acetonide	0.5	Cream
4	Desoximetasone	0.05	Cream
	Fluocinolone acetonide	0.025	Ointment
	Hydrocortisone valerate	0.2	Ointment
	Mometasone furoate	0.1	Cream, lotion
	Triamcinolone acetonide	0.1	Ointment
5	Betamethasone valerate	0.1	Cream, lotion
	Fluticasone propionate	0.05	Cream
	Fluocinolone acetonide	0.025	Cream
	Hydrocortisone valerate	0.2	Cream
	Triamcinolone acetonide	0.1	Cream, lotion
6	Desonide	0.05	Cream, ointment, lotion
	Fluocinolone acetonide	0.01	Cream, lotion, oil
7	Hydrocortisone acetate	0.5-2.5	Cream, ointment, lotion

Table 1: Potency rankings of common topical corticosteroids in Canada

Calcipotriol (Dovonex®)

- It is a derivative of the naturally occurring vitamin D3 and is as potent as 1,25 (OH)2 D3 in regulating cell proliferation and cell differentiation.
- Calcipotriol has been compared with Class 2 (potent) corticosteroid ointments and found to be comparable or slightly more effective than these agents.[12]
- In comparison with other topical therapies, vitamin D3 analogues were associated with a relatively low rate of adverse events. The most common adverse effect associated with calcipotriol is a mild irritant contact dermatitis.[13] Avoid application on the face.
- Hypercalcemia has also been reported, but is rare with the doses used in clinical settings, which should be limited to 100 g of calcipotriol cream or ointment per week.[14]
- It is available as a cream, ointment, and scalp solution.
- Calcipotriol is clinically effective in children with very little risk of local or systemic side-effects.[8]

Combination Treatment

Calcipotriol and Betamethasone Dipropionate (Dovobet®, Xamiol®)

- In general, combination therapy is more efficacious and can result in reduced incidence of adverse effects when compared with monotherapy, as more than one pathogenic factor is targeted.
- Studies have shown that the two agents in combination have a more rapid onset of action and greater efficacy than monotherapy with either agent.[15-17]
- As a fixed combination, the different modes of action of the two molecules become synergistic, resulting in enhanced efficacy and reduced side-effects.[17]
- In a 52-week study comparing once-daily use of (a) combination product, (b) combination alternating with calcipotriol, and (c) calcipotriol alone, the combination product was consistently more effective than the other treatment groups. Furthermore, patients treated throughout with combination product had the fewest side-effects.[18]
- In the same study above, the combination product was also found to be safe and well tolerated by patients, whether used on its own or alternating with calcipotriol.[19]
- Betamethasone dipropionate is a Class 2 corticosteroid, and therefore, to minimize local cutaneous side-effects, the combination product should not be used on the face and intertriginous sites.
- It is available as an ointment or scalp gel. The scalp gel is alcohol free, which makes it less irritating for patients.
- A study investigating the combination scalp gel formulation showed that 92% of patients achieved marked improvement to clearance of their scalp psoriasis following once-daily use for up to 8 weeks with very few side-effects.[20]
- It is an appropriate first-line therapy that is effective and well tolerated across all grades of psoriasis severity.[8]
- Although treatment is indicated for once-daily application for 4 weeks, long-term studies of both the ointment[19] and scalp gel[13] formulations have demonstrated good tolerability and safety with as-needed use over 52 weeks.

Tips for the Pharmacist

Counsel Patients on How Much to Apply

- A "Finger Tip Unit" is the amount of cream applied from end of finger to first knuckle (about 500 mg of cream) and should be enough to cover one of the patient's "hand-sized" amount of skin, or approximately 1% BSA.
- Apply a sufficient amount of medication on plaques in a circular motion until the medication is distributed evenly (i.e., a visible thin film covering the psoriatic lesion).
- Counselling patients on proper usage (e.g., sufficient dosage, application, and duration) and therapeutic objectives can optimize adherence and outcomes.
- Avoid using the term "apply sparingly", particularly in association with topicals, which may convey to patients the prescribed medication is harmful, inadvertently contributing to poor treatment follow-through.

Trade Name	Composition	Availability	Indicated Dosage
Dovonex®	• Calcipotriol 50 mcg per g/mL	• Ointment: 60 g • Cream: 120 g • Scalp solution: 60 g and 120 cc	• Twice-daily • Once-daily for maintenance • Maximum weekly dose: 100 g
Dovobet®	• Calcipotriol 50 mcg/g • Betamethasone dipropionate 0.5 mg/g	• Ointment: 60 g and 120 g	• Once-daily for up to 4 weeks continuous • Maximum weekly dose: 100 g
Xamiol®	• Calcipotriol 50 mcg/g • Betamethasone dipropionate 0.5 mg/g	• Scalp gel: 60 g	• Once-daily to affected areas of scalp • 4 weeks continuous duration • Maximum dose 15 g per application • Up to 30% BSA • 100 g per week
Silkis™	• Calcitriol 3 mcg/g	• Ointment: 60 g	• Twice-daily • For mild to moderate psoriasis with up to 35% BSA involvement • Maximum daily dose: 30 g • Maximum weekly dose: 200 g

Table 2: Available vitamin D analogs in Canada[9]

Avoid Triggers

- Encourage patients to quit smoking, if possible, and review cardiac risk factors.
- Avoid known triggers or medications that may exacerbate psoriasis.

Compounding

- Calcipotriol can be unstable under certain circumstances, particularly when compounded with a more acidic product (e.g., salicylic acid).[21] Therefore, other products should be applied at another time, e.g., Dovobet® ointment applied at bedtime and a salicylic acid-containing product applied in the morning.
- Calcipotriol should not be repackaged in a smaller plastic container (e.g., 30 g) because the product loses stability. Dovobet® should be dispensed in its original container and once opened it is stable for 1 year.[22]
- The individual components should not be mixed together (i.e., calcipotriol compounded with betamethasone dipropionate or another high potency corticosteroid), as the resultant preparation is unstable and not equivalent to the combination product due to the degradation of calcipotriol.
- Similarly, there have not been any studies showing the efficacy of calcipotriol used at the same time with another high potency steroid cream, and therefore should not be applied directly at the same time.

Conclusion

Vitamin D analogues are a newer class of topical medications that have been shown to be safe and effective in the treatment for psoriasis. Single product, fixed-dose, once-daily topical combination therapy is a significant advance in treating psoriasis. The synergistic effects from dual agent therapies, such as calcipotriol/betamethasone diproprionate, able to target multiple pathogenic factors (e.g., erythema, inflammation, hyperproliferation, and epidermal differentiation) provide simplified dosing and enhanced efficacy and safety, which can lead to improved patient adherence and treatment outcomes.

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Optimizing Topical Acne Therapy

Maha Dutil, MD, MEd, FRCPC
Division of Dermatology, University of Toronto, Toronto, ON, Canada
Women's College Hospital, Toronto, ON, Canada

Introduction

Acne vulgaris is a disease of the pilosebaceous follicle characterized by non-inflammatory (open and closed comedones) and inflammatory lesions (papules, pustules, and nodules). Its pathogenesis is multifactorial - the interplay of hormonal, bacterial, and immunological (inflammatory) factors results in the formation of acne lesions. Although acne is not a life-threatening condition, it can have detrimental effects on the quality of life of affected individuals. Fortunately, acne is readily responsive to the wide-range of available medications, with the goals of therapy being to clear the lesions, prevent scarring, and limit any treatment-related side-effects and psychosocial sequelae. Newer fixed-dose combination products target multiple acne pathogenic factors and offer simplified dosing regimens, which may potentially enhance both efficacy and patient adherence when compared with single agent therapy.

Acne Overview

Pathogenesis

- All forms of acne involve one or more of these pathophysiologic factors:
  - hyperkeratinization of the follicular epithelium with comedo formation
  - increased sebum production
  - bacterial proliferation of *Propionibacterium acnes* (*P. acnes*)
  - local immune activity causing inflammation
- Hormones are known to affect sebum production, but may also play a role in follicular hyperkeratinization independent of the effect on the sebaceous gland. During adrenarche, an increase in adrenal androgens leads to:
  - enlargement of sebaceous glands that results in increased sebum production.
  - abnormal desquamation and greater adhesion of the exfoliated keratinocytes in the sebaceous follicle, leading to obstruction in the follicle, and resulting in production of the microcomedo (a plug of keratin and sebum - the precursor of all acne lesions).
- Colonization of the pilosebaceous apparatus by *P. acnes* occurs in this anaerobic environment where sebum provides the nutrition for its survival. This gram-positive bacterium contributes to the inflammation by:
  - releasing enzymes
  - inducing cytokine release from other cells
  - triggering an immune response (e.g., antibody production)

Prevalence and Disease Features

- Acne affects about 85% of individuals between the ages of 12-24 years.[1] Persistent acne (beyond the teenage years) and adult-onset are increasingly common.[2]
- Grading to determine acne severity is inherently subjective, as the process is largely based on clinical observation. Many grading systems have been developed that take into account lesion type and extent of involvement for measuring severity. Depending on the chosen technique, the measurement spectrum can range from Grades 1 to 4 all the way up to Grades 1 to 12. Acne may be classified according to predominance of specific skin lesions and the number of each lesion determines classification from mild to severe:
  - Comedonal (non-inflammatory) - mild, moderate, or severe
  - Papular (inflammatory) - mild, moderate, or severe
  - Pustular (inflammatory) - mild, moderate, or severe
  - Nodular - mild, moderate, or severe
- Acne can be physically and emotionally scarring, causing significant psychosocial morbidity and reduced self-esteem independent of acne severity.

Treatment Overview

- The majority of patients present with mild-to-moderate comedonal or papulopustular acne that can be treated with topical agents (Table 1).
- Severe cases with nodules, cysts, or scarring will require the addition of systemic therapy.
- Available topical anti-acne compounds have a direct or indirect influence on the above mentioned pathogenetic factors.
- Treatment selection is guided by the predominant acne lesion type.

- Because most anti-acne agents prevent the formation of microcomedoes (the precursors to acne lesions), patients should be instructed to apply medications to all skin areas where acne can develop and not limit use on visible lesions only. Therefore, improvement may not be noticeable for several weeks, as the treatment acts to inhibit the formation of microcomedoes, thereby preventing their progression into acne lesions.

Drug Type	Topical Acne Agents	Comments
Antimicrobials	• Benzoyl peroxide (BP) • Clindamycin • Erythromycin • Sodium sulfacetamide	• Directed against *P. acnes* • Formulated as creams, ointments, lotions, gels, and foams • May induce irritation and dryness • BP has mild comedolytic activity • BP can bleach coloured fabrics

Combination products	• Topical antibiotic + BP
	  • erythromycin + BP
	  • clindamycin +BP
	• Topical retinoid + antibiotic
	  • tretinoin + erythromycin
	  • tretinoin + clindamycin
	• Topical retinoid + BP
	  • adapalene + BP
		• Facilitate treatment of multiple pathogenic factors
		• Combined efficacy is greater than either agent alone
		• Gel formulations
		• BP + antibiotic can inhibit bacterial resistance
		• Simplifies treatment regimen and reduces dosing frequency (i.e., once-daily application) and drug exposure time
		• Retinoid + antibiotic may increase tolerability
		• Potentially more cost effective

Retinoids	• Adapalene • Tazarotene • Tretinoin	• May be used for all grades of acne and for maintenance therapy • Non-inflammatory (comedonal) acne is best treated with a topical retinoid; noticeable improvement may take several months • Common side-effects include irritation (e.g., stinging or burning sensation), redness or inflammation, scaling or dryness and photosensitivity • Formulated as gels, creams, and solutions • Advancements in vehicle delivery reduce irritation and enhance efficacy (e.g., emollient cream and microsponge gel)

Table 1: The spectrum of approved topical acne medications[2-4]

Rationale for BP/Antibiotic Combination

Effective treatment considers all pathogenic factors and single-agent therapy does not address all four major pathophysiologic features of acne.

- Topical antibiotics have been used to treat acne for more than 40 years and are still widely used. The efficacy of antibiotics is attributable to their inhibitory effects on both the proliferation of *P. acnes* and inflammatory mediators.
- The emergence of resistant strains has, in some cases, been associated with a failure to respond to antibiotic therapy, which was first reported with the topical antibiotics clindamycin and erythromycin.[3]

Combination Treatment	Study Design/Results
5% BP/3% erythromycin (BP/E) gel vs. erythromycin alone applied for 6 weeks	• Double-blind study of patients with mild-to-moderate acne[5] • The number of erythromycin-resistant strains of *P. acnes* was significantly reduced in the BP/E group compared with the group that received erythromycin alone.
5% BP/3% erythromycin gel vs. erythromycin alone applied for 6 weeks	• Open study of patients with erythromycin-resistant strains of *P. acnes*[5] • Highly significant reductions were also seen in acne grade and lesion counts with the BP/E combination.
BP/clindamycin (BP/C) combination, BP, clindamycin, or vehicle gels applied once nightly for 11 weeks	• Two double-blind, randomized, parallel, vehicle-controlled trials of acne patients[6] • The combination gel was significantly superior to the two individual agents in global improvement and reduction of inflammatory lesions.
5% BP/1% clindamycin, 5% BP/3% erythromycin, or 5% BP applied twice daily for 10 weeks	• Randomized, multicenter, single-blind trial of moderate-to-severe acne patients[7] • Both BP/C and BP/E were comparable and demonstrated significantly greater reductions in inflammatory lesions over BP alone.

Table 2: Clinical trials demonstrating efficacy for combination treatments with BP and erythromycin or clindamycin

- The use of BP reduces the occurrence of resistance and can be effective in the treatment of both nonresistant and resistant *P. acnes* strains.[4]
- BP does not promote antimicrobial resistance and has been shown to prevent such resistance when used concomitantly with topical erythromycin or topical clindamycin.
- A number of clinical studies have demonstrated improved efficacy and safety of combinational BP/antibiotic approach to acne management (Table 2).

Combination Treatment Considerations

- Mild-to-moderate inflammatory acne can usually be managed with two topical drugs. Typically one is applied in the morning and the other at bedtime.
- A retinoid is used to deal with the precursor of all acne lesions (i.e., the microcomedo) and an antibacterial agent for its effects on *P. acnes*. Topical antibacterial options include BP or a BP/antibiotic combination.
- BP is extremely effective against *P. acnes*, but can be irritating. The irritation can be minimized by using the lowest concentration of BP in a water-based vehicle that does not reduce its efficacy. Another way to reduce the irritation induced by BP is to combine it with an antibiotic.
- BP/antibiotic combinations also reduce the irritation that can be induced by a topical retinoid. Only if a patient is allergic to BP (estimates range from 1%-2% of the population[8]) should a topical retinoid be used with a topical antibiotic alone. The topical antibiotic should be discontinued as soon as possible and the retinoid can be used for maintenance alone.

Prescribing Recommendations to Minimize Bacterial Resistance

- Antibiotics should not be used as monotherapy, nor should they be used to treat mild acne.
- Avoid topical antibiotics if non-antibiotic topical preparations will suffice.
- Use alternatives to antibiotics for maintenance.
- Stop antibiotic treatment when the skin clears or if no further improvement is noted.
- If there is a failure to respond to oral antibiotics or a rapid relapse after discontinuation, consider other therapy (e.g., systemic retinoid, anti-androgens in women).
- If the antibiotic is needed again, use the same antibiotic.
- Use full doses of antibiotics and do not taper.
- Avoid concomitant topical and systemic use of different antibiotics to reduce the risk of developing resistance to both agents.
- Do not switch or rotate antibiotics in non-responding patients.
- Use BP during antibiotic therapy.

Other Prescribing Tips

- BP bleaches clothing and hair, and thus, patients should be warned when prescribed.
- Limit the use of BP on the chest and back to night-time due to its bleaching effect on clothing or recommend that patients wear a white T-shirt under clothing for daytime application.

Non-Adherence

- Patient non-adherence to treatment can influence outcomes, which is of particular concern with topical medications (e.g., proper application and accurate dosing).
- Some clinical strategies to promote treatment adherence include:
  - advocating patient involvement in therapeutic decision-making
  - devoting time to patient education on acne and the selected treatments, instructions for use, potential side-effects, and expected rate of improvement
  - selecting treatments that facilitate ease of use (i.e., once-daily dosing)
  - modifying current treatment if patient dissatisfaction is encountered

Conclusion

Since multiple factors are involved in acne pathogenesis, treatment that targets the majority of these elements can be expected to achieve optimal results. When considering the options for reducing the *P. acnes* population, it is best to choose therapeutic agents that do not encourage resistance patterns. Evidence for improved efficacy, safety, and onset of action, as well as longer remission, has been noted with combination therapies. Advances in dual agent fixed-dose compounds offer simpler dosing regimes that can promote patient adherence. Furthermore, the cumulative benefits of these advances may lead to improved therapeutic outcomes and overall improvements in quality of life for acne patients.

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