Advances in Topical Acne Therapy: New Molecules, Vehicles and Delivery Mechanisms

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Introduction

Acne vulgaris is a multifactorial disease characterized by different types of lesions at various stages of development. The most frequently used therapeutic agents for acne are topical. While first generation topicals are primarily composed of single agent preparations, the increased knowledge of acne pathogenesis and the numerous steps involved in comedone formation have led to increasing development and clinical use of combination products (Table 1). Numerous studies have shown that combination therapy is more efficacious and better tolerated compared to monotherapy. Consequently, current consensus guidelines recommend the use of combination treatment as first-line therapy for most patients with acne. Nevertheless, several obstacles encountered in the treatment of acne, including irritation resulting from topical medications and the emergence of bacterial resistance to both topical and oral antibiotics, remain significant barriers to patient adherence to therapy. It is estimated that 30-40% of patients using topical formulations do not comply with their prescribed regimen. However, recent advances in vehicle technology have improved efficacy, local tolerance and adherence. Additionally, delivery mechanisms, such as pumps are convenient and preferred by patients, and may improve adherence.

Combination Therapy

Because the typical clinical presentation of acne vulgaris exhibits lesions at different stages, employing combination therapy that utilizes multiple agents to produce additive or synergistic benefits is logical.

- Studies have shown that the topical combination of retinoids and antimicrobial agents expedites a clinical response. This may be due to enhanced penetration of agents by the retinoids.
- Retinoids may be prescribed as initial therapy. If inflammatory lesions are present, the addition of a BPO alone, or in combination with a topical or oral antibiotic, should be the next step.
- Data show that the combined use of a clindamycin 1%/BPO 5% formulation with a 0.04% tretinoin microsphere gel can result in good resolution of post-inflammatory hyperpigmentation in ethnic skin, i.e., individuals of colour.
- A once-daily, fixed-dose gel formulation containing solubilized and crystalline clindamycin phosphate 1.2% and tretinoin 0.025% (CT gel) was recently introduced in Canada.
- Clindamycin has anti-inflammatory and antibacterial properties and tretinoin exerts comedolytic and anticomedogenic activities to target several mechanisms in acne pathogenesis.
Retinoids  • Adapalene  
• Tretinoin  
• Tazarotene

Antimicrobials  • Benzoyl peroxide (BPO)  
• Clindamycin  
• Erythromycin  
• Dapsone  
• Sodium sulfacetamide

Combination products  • Topical antibiotic + BPO  
• Clindamycin + BPO  
• Erythromycin + BPO  
• Topical retinoid + antibiotic  
• Tretinoin + clindamycin  
• Tretinoin + erythromycin  
• Topical retinoid + BPO  
• Adapalene + BPO

Table 1: Topical acne medications

• A 4-week randomized study investigated the safety and tolerability of combination CT gel with morning use of a BPO wash for mild to moderate acne. This regimen widens the number of targeted pathogenic factors and suppresses the emergence of clindamycin-induced Propionibacterium acnes (P. acnes) resistant bacterial strains.

• Combination products offer much higher levels of patient compliance with 67% adherence observed in the combination therapy group versus 8% in patients using both agents separately.

Topical Dapsone for Inflammatory Lesions

• Dapsone 5% gel is a new, twice daily topical treatment that is effective against both inflammatory and non-inflammatory acne, however greater improvement occurs with inflammatory lesions.

• In two identically designed 12-week, phase 3, double-blind, randomized, vehicle-controlled trials in acne (total N=3010), significant reduction in non-inflammatory, inflammatory, and total lesion counts were noted with dapsone gel versus vehicle groups (32% versus 24%, 39% versus 32%, 48% versus 42%, all P<0.001, respectively).

• An investigator-blinded, randomized, split-face study assessed female subjects aged 18-40 years, with Fitzpatrick skin types I, II, or III. The results suggest that dapsone applied prior to tretinoin 0.1% may mitigate the irritation potential of tretinoin.

Retinoids for Initial/Maintenance Therapy

Retinoids are pivotal for treatment in the early stages of acne as well as for maintenance therapy, and have both anti-comedonal and anti-inflammatory activities.

• Topical retinoids can be used for all types and grades of acne, either initially or early in the therapy.

• Topical retinoids are effective as monotherapy in pure comedonal acne.

• Topical retinoids down-regulate TLR2 and CD14 messenger RNA, which, in turn, reduces their cell surface expression, resulting in anti-inflammatory activity.

• Evidence shows that retinoids can enhance the effects of topical antibiotic-BPO combination creams. In addition to their synergistic effect, this may be because retinoids can improve the penetration of other topical agents.

• Maintenance therapy or long-term use of retinoids may help to prevent the re-emergence of micro-comedones.

• The tretinoin gel microsphere (TGM) 0.04% pump formulation protects tretinoin from degradation by BPO and from photoinactivation in daylight: this enables its use in the morning, and with a BPO wash, without diminishing efficacy.

• A phase 4 study showed that TGM resulted in a 95% compliance rate.

• Maintenance therapy with retinoids may diminish the need for chronic antibiotic use, especially oral antibiotics. This may lead to decreased bacterial resistance associated with long-term oral and topical antibiotic use.

• Due to a complex pathogenesis, maintenance therapy may need to be continued for months to years after resolution.

• Therapy with topical antibiotics but without BPO should be avoided so as to prevent development of resistance to P. acnes.

• Adapalene is photostable and may be applied immediately before or after a BPO containing product.

Tretinoin Microsphere Technology and Pump Delivery Systems

Tretinoin has been formulated with a patented microsphere delivery system and a novel metered pump bottle design, which, according to the manufacturer, allows for proper dosage and clean dispensing of the active agent. Clinical trials have shown:

• Lower levels of irritation due to the slow release of tretinoin from the microspheres into the epidermis.

• Reduced irritation may increase tolerability and patient adherence.

• This is a less irritating water-based gel formulation that contains no alcohol and may be applied to the face immediately after washing with no waiting period.

• TGM delivery entraps the active ingredient, releasing it in a time-controlled manner, reducing irritation.

• The controlled dispensing with this delivery system can mitigate the overuse of tretinoin, thus reducing irritation and increasing treatment adherence.

• A multicenter trial of 544 acne patients who were dissatisfied with their current treatment used TGM for 12 weeks. Most patients (82.3%) rated the pump as an excellent or very good method of dispensing acne medication. The tretinoin pump system significantly increased adherence, quality of life, and treatment satisfaction for study patients.

• The dual chambered pump dispenser releases the correct pea-sized amount for full face application and may help to maintain the optimal dosing level.

• Microsphere technology allows for 3-fold greater deposition of tretinoin in the deep dermis and the pilosebaceous unit and may account for its stability.

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Vehicle Technology Advancements

Patient preferences go beyond side-effects and studies have shown that several variables decrease adherence including vehicle composition, difficulty of use, lack of early improvement, messiness, odours, and staining.22

• In a Patient Preferences in Acne: A Point-of-Care Educational Initiative, a survey of 1709 patients across Canada found that pump delivery systems are the preferred format (42% of patients).3
• Many new topical acne formulations have aqueous-based gel vehicle delivery systems that do not contain alcohol and are suitable for use in all skin types.
• It is known that topical acne agents cause cutaneous irritation related in part to impaired epidermal barrier function.23
• The use of gentle cleansers and moisturizers has been shown to reduce this cutaneous irritation.24
• Moisturizers containing ceramides can be considered to improve skin barrier function in acne.
• Dimethicone’s occlusive properties result in less greasiness for enhanced cosmetic acceptability.
• Vehicle advances, such as microsphere technology and solubilized crystalline formulations reduce the potential of irritation from tretinoin.
• Microsphere tretinoin and adapalene do not increase photosensitivity, allowing for morning application.
• Clindamycin/BPO formulations with humectants and emollients may reduce the dry skin associated with BPO use.
• Clindamycin/BPO formulations without preservatives may reduce the irritation associated with these agents.25
• The risk of bacterial resistance is decreased by the addition of BPO to topical antibiotic agents, and the use of BPO with long-term oral antibiotics.

Conclusion

The multifactorial nature of acne vulgaris often requires a combination of topical and/or oral agents for successful management. Common challenges of this multipronged approach include the potential development of skin irritation, which results in nonadherence, as well as concern over bacterial resistance. Recent advances in topical acne agents offer simpler dosing regimes that can promote patient adherence. Furthermore, the cumulative benefits of these advances may lead to improved therapeutic outcomes and overall increase in quality of life.

References

Rosacea: Update on Management and Emerging Therapies

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Introduction

Rosacea is a common chronic skin disorder that has significant impact on the self-esteem and quality of life of affected individuals. It is currently understood as an inflammatory condition that occurs in the context of an altered innate immune response, hence, the available topical and systemic therapies function as immunomodulators to restore cutaneous homeostasis. The goals of therapy include reduction of papules, pustules, erythema and physical discomfort with improved quality of life. Standard topical treatments include azelaic acid and metronidazole, although many other agents and regimens have been presented. Subantimicrobial low-dose oral doxycycline is a recently approved therapeutic option for the management of rosacea. Additionally, several emerging therapies are on the horizon.

Overview of Rosacea

- Rosacea is a chronic skin disorder characterized by facial erythema, telangiectasia, inflammatory papules and pustules with intermittent episodes of exacerbation and remission.
- There are four generally accepted clinical subtypes which have been described by the National Rosacea Society: erythematotelangiectatic, papulopustular, phymatous, and ocular.1
  - Two variants, granulomatous and neurogenic, have also been presented.1,2
- Affecting approximately 10% of the general population, rosacea is more prevalent in women, although impacted men often have more disfiguring skin changes.3
- Patients often present between 30 and 50 years of age but manifestations can occur throughout the life course.4
- Up to one-third of patients have a family history of rosacea.
  - There is an increased prevalence among individuals of Northern European descent, supporting an underlying genetic predisposition.3
- While the etiology of rosacea remains unclear and despite clinical heterogeneity, basic science has developed a possible unified understanding of rosacea as an inflammatory disorder in the context of an altered innate immune response.5
- It is proposed that environmental changes, which may include UV light exposure, hormone balances and microbe challenges (by pathogens such as Demodex folliculorum), are sensed by pattern recognition receptors of the immune system. Subsequent signaling induced effector molecules such as reactive oxygen species, cytokines, cathelicidin and chemokines may then modify dermal structure through vascular changes, collagen degeneration, lymphohistiocytic infiltration and neutrophil recruitment, which may perpetuate this response.6,7
- Given this model, it is clear why most current therapies attempt to modulate various points of this inflammatory cascade.

Psychosocial Impact

- Although the relationship between psychological factors and rosacea remains to be determined, 75% of affected patients report low self-esteem with a significant odds ratio of 4.81 for diagnosed depressive disorder in this population compared to the general population.8
- The use of validated assessment tools has demonstrated the impact of rosacea on quality of life and the improvement that can occur with treatment.9

Patient Education

- Once rosacea is diagnosed patients should be reassured of the benign but chronic nature of the condition.
- Counselling should be directed toward the identification and avoidance of triggers, diligent photoprotection, concealing cosmetics, and proper skin care.3
- It is also prudent to review medications to identify, and discontinue if possible, those that may exacerbate flushing, such as beta blockers.3
Treatment Overview

- Topical pharmacotherapeutic options include azelaic acid, erythromycin, metronidazole or sodium sulfacetamide 10% + sulfur 5%.10
- As in the management of other dermatological conditions, the choice of vehicle for topical rosacea preparations is also an important consideration.
- The choice of lotion, cream, gel or foam can influence efficacy, compliance, and tolerability, which is especially relevant for patients who often have heightened skin sensitivity.11
- In patients with moderate to severe papulopustular subtype or ocular involvement, systemic therapy is often required and includes doxycycline, erythromycin, metronidazole, minocycline, tetracycline or, in select severe cases, low dose isotretinoin.10
- Laser, light-based therapies and surgical interventions may also be warranted in select patient populations.12
- Recent research has added low-dose doxycycline to the therapeutic armamentarium and two additional treatments, ivermectin and alpha-adrenergic receptor antagonists, hold promise for the future.
- This article focuses on approved therapies for the management of the cutaneous manifestations of rosacea.

Topical Metronidazole

- Topical metronidazole has demonstrated greater efficacy compared with placebo in multiple trials, with both statistically significant and clinically important results.13
- There is no statistically significant difference between the two concentrations of topical metronidazole (0.75% or 1%). It has also been shown to be effective in maintaining remission.15
- Topical metronidazole is available in a 0.75% gel, lotion, and cream format for twice daily use and a 1% cream and gel for once daily use.
- Once daily dosing of 1% metronidazole cream appears to be as effective as twice daily dosing.14
- A recent systematic review of nine trials demonstrated the efficacy of topical metronidazole versus placebo.15,16
- A reduction in inflammatory lesions and erythema scores was observed, including improvement in physician’s global evaluation and patient-assessed measures.
- No benefits were noted for telangiectasia in these studies, however, a study by Tan et al, showed improvement in telangiectasias scores as well as erythema and inflammatory lesion counts using a 1% metronidazole cream with a sun protection factor of 15.17
- Given its favourable efficacy and tolerability profile, topical metronidazole will continue to play an important role in the management of rosacea.
- Metronidazole has also been proposed as the most cost-effective topical regimen, which may be an important consideration for some patients.18

Topical Azelaic Acid

- Azelaic acid (AzA) is a naturally occurring saturated dicarboxylic acid approved for the treatment of mild to moderate rosacea.
- It can be found in dietary sources (e.g., whole grains), lacks toxicity, is non-teratogenic and non-mutagenic.19
- It has multiple biologic activities including anti-inflammatory, anti-keratinizing and anti-bacterial effects. In rosacea, its therapeutic properties are derived via inhibition of reactive oxygen species produced by neutrophils.20
- A 15% gel formulation is available for the treatment of rosacea. A 20% cream formulation is approved in the US for acne vulgaris.
- The 15% gel, although formulated to a lower concentration than the cream, is significantly more bioavailable than the cream because of an optimized aqueous gel vehicle.
- Patients using AzA had an improvement of 70-80% in their rosacea compared with 50-55% in the placebo group.13
- AzA 15% gel administered once daily has demonstrated equivalent efficacy to twice daily application, although recommended dosing is twice daily.21
- Two pivotal phase 3 trials have shown that AzA 15% gel applied twice daily for 12 weeks was superior when compared with the vehicle in the treatment of papulopustular rosacea.22
- In these studies, a mean reduction in inflammatory lesion counts and improvements in erythema scores were observed in AzA-treated group vs. placebo.
- There was no improvement in telangiectasia severity in any study of AzA for rosacea.
- Studies have shown that AzA is a safe and effective treatment for papulopustular rosacea and has a favourable tolerability profile.

Topical Metronidazole versus Azelaic Acid

- Two studies comparing topical metronidazole and AzA found no statistically significant difference between the treatment groups with respect to patient-assessed outcomes.23,24
- However, in the split-face comparison clinical trial by Maddin patients favoured the outcome of AzA.25
- In both the Maddin and Elewski et al trials, the investigators were of the opinion that treatment with AzA was more effective than metronidazole.23,25

Subantimicrobial Low-dose Oral Doxycycline

- Tetracyclines (pregnancy category D) have numerous anti-inflammatory properties thought to be responsible for their efficacy in the management of rosacea.26,27 However, a clear bacterial pathogen has not been implicated in rosacea pathophysiology.28
- Standard antimicrobial dosing may affect endogenous flora and risks the development of antibiotic resistant strains.
- Subantimicrobial, low-dose doxycycline 40 mg capsules, formulated as 30 mg immediate-release and 10 mg delayed-release beads and dosed once daily, provide a subantimicrobial dose that reduces the inflammatory response without producing drug concentrations required to treat bacterial diseases, thus avoiding concerns regarding selective pressures generating microbial resistance.29
- The efficacy of oral doxycycline 40 mg capsules once daily in the treatment of adults with rosacea was demonstrated in two large, randomized, double-blind, placebo-controlled, multicenter trials.30
- Assessed after 16 weeks of therapy, doxycycline 40 mg provided a significantly greater reduction in the total inflammatory lesion count than placebo.
The treatment was generally well-tolerated by patients; adverse events (approximately 4% of patients) were of mild to moderate intensity, with headache, nasopharyngitis and gastrointestinal side effects reported most frequently.

No photosensitivity was observed, although tetracyclines as a class of medications have been associated with this effect.

Combination therapy with doxycycline 40 mg plus either AzA gel 15% or metronidazole gel 1% were also safe, efficacious and well-tolerated.31,32

Emerging Therapies

Ivermectin Cream

Ivermectin cream is a new 1% cream formulation of the acaricidal compound, ivermectin, and is currently under investigation.33

One hypothesis for the etiology of rosacea is the presence of Demodex mites in the pilosebaceous unit of affected individuals and although the association is well known, the pathophysiology is yet to be elucidated. Reports have been published on cutaneous demodicidosis responding to oral ivermectin and topical permethrin but data are lacking on the topical application of ivermectin alone.34

Adrenergic Receptor Antagonists: Brimonidine and Oxymetazoline

The adrenergic receptor antagonists brimonidine tartrate and oxymetazoline, which have potent vasoconstrictive activity and anti-redness capabilities, are currently found in eye drops for glaucoma and a nasal decongestant spray, respectively.

Brimonidine tartrate, an alpha-2 agonist, has been shown in case reports to be an effective agent for reducing facial erythema. It has been formulated into a cream and is currently in clinical development for the treatment of erythematotelangiectatic rosacea.35

Other Treatments with Limitations in the Evidence

Topical sodium sulphacetamide 10% + sulphur 5%
Systemic isotretinoin
Topical antibiotic + tretinoin
Topical benzoyl peroxide 5% + clindamycin 1% gel
Pulsed dye laser or intense pulsed light
Pimecrolimus 1% cream
Oral zinc sulfate

Due to the chronic nature of the condition, patients frustrated with medical therapy may turn to marketed botanicals and herbal remedies in hopes of improved control. Although there is a paucity of data surrounding the effects of these cosmeceuticals, the prudent clinician should be aware of additional products that may be used by patients such as niacinamide, feverfew, turmeric, colloidal oatmeal and quassia extract.37

Conclusion

The chronic course of rosacea requires early intervention and continuous management to treat visible symptoms, control disease progression, and mitigate psychosocial impact. Disease subtype and patient-specific characteristics (including preferences) will guide therapeutic decisions, which may involve a combination of therapies. Generally, topical therapy is first-line, but in moderate to severe cases, or those with ocular involvement, systemic therapy may be necessary. Patient education regarding the triggers of rosacea, proper skin care, photoprotection, and camouflaging cosmetics are also useful nonpharmacologic strategies.

References

The Health Controversies of Parabens

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Introduction
Parabens are preservatives used in a wide range of cosmetic, pharmaceutical and food products. Parabens are esters of para-hydroxybenzoic acid and commonly include methylparaben, ethylparaben, propylparaben and butylparaben.1 The recent health concerns regarding parabens stem from a study published in 2004 that detected parabens in breast tissue from patients with breast cancer.2 Public pressure has persuaded several governments to introduce regulations on the use of parabens in consumer products. In this review, we examine the data regarding the health effects of parabens to provide a better understanding of this issue.

Consumer Products and Parabens
Parabens have been used in food, cosmetic and pharmaceutical products since the 1930s.
- Their use is most prevalent in cosmetic products.
- Common consumer paraben-containing products include hand soap, facial cleansers, shampoo, conditioners, hair spray/mousse/gel, face lotion, body lotion, foundation, lipstick, mascara, toothpaste, and sunscreen.1,3,4
- One study identified parabens in 44% of cosmetics tested.3 In personal care products tested in the US, concentrations of up to 1.0% methylparaben were found, with lipstick having the highest concentration.1
- The other parabens are used at concentrations lower than methylparaben in personal care products.
- Methyl and propylparaben are the most commonly used parabens in pharmaceutical products.1
- Methyl and propylparaben are also used in food products such as jams, jellies, fillings and toppings.1,5

Parabens in the Human Body
- Parabens can enter the human body through the skin, parenterally and intravenously.
- The average daily total personal paraben exposure is estimated to be 76 mg, with cosmetics and personal care products accounting for 50 mg, pharmaceuticals for 25 mg, and food for 1 mg.6,7,8
- Parabens applied to the skin are metabolized by keratinocyte carboxylesterases and the conjugated metabolites are excreted in urine and bile.9,10
- Oral or intravenous parabens are metabolized by esterases within the intestine and liver.1
- Parabens have been detected in urine, serum, breast milk and seminal fluid: most worrisome has been the detection in breast tissue from patients with breast cancer.7,11-15
- Some have hypothesized that the higher concentration in the upper lateral breast near the axilla correlates with exposure from underarm deodorant and an increased incidence of breast cancer development in the area.16,17 Still, absolute concentrations indicate that levels of parabens within human fluids and tissue are low [average urine concentrations in the US range from 0.5 to 680 ng/mL and breast tissue concentrations range from 0 to 5100 ng/g of breast tissue (the median being 85.5 ng/g)].14,15
- These low concentrations should be interpreted in the context of known estrogenic effects of parabens.

Toxicity and Adverse Effects of Parabens
- Human and animal studies have failed to show that parabens have any acute toxicity by various routes of administration.
- Many studies examining paraben toxicity have focused on the long-term effects of chronic exposure.
- The estrogenic activity of parabens was first identified in 1998 and subsequently validated in vitro and in vivo.1,18,19
- Parabens bind human estrogen receptors, although with affinities 10,000 to 1,000,000 times less than estradiol.18,20 Butyl and propylparaben have higher estrogenic activity than methyl or ethylparaben but are detected at concentrations 10 to 1000 times less than methylparaben in humans.21
- The estrogenic effects in vivo have been demonstrated by uterine growth assays in mice and rats.1,22 However, this effect did not prevent implantation of a fertilized egg, which is considered the most sensitive measure of estrogen toxicity.22,23
- It has been hypothesized that the estrogenic activity of parabens may promote breast cancer development.
- The concentration of estradiol in normal human breast tissue is 55.3 pg/g, suggesting there is a safety margin of 10 to 1000 times for parabens to approximate normal estradiol activity.1,14,21
- Paraben breast cancer data show no or low parabens in a subset of patients and there are no comparisons with normal controls.2-14
- With no established correlation, it is difficult to put forth a causal relationship between parabens and breast cancer development.
- Another major area of study has been the effect of parabens on the male reproductive system but results are conflicting.24
Men with fertility problems including low sperm count and decreased motility were assayed for paraben exposure by measuring urine paraben levels. No correlation between sperm count or motility and parabens levels was found.

Parabens, as is the case for many preservatives, can be allergenic in a small subset of the population, and commonly manifests as an eczematous rash.

The rates of reported sensitization to parabens range from 0.5% to 3.5% and are among the lowest of all preservatives. Additionally, there are reports of immediate IgE-mediated allergic reactions to parabens resulting in urticaria and, in one case, bronchospasm. However, these immediate allergic reactions are extremely rare.

Paraben Alternatives

Numerous preservatives could be used in place of parabens. Various other compounds have also been reviewed by the European Scientific Committee on Consumer Products (SCCP).

In 2006, the SCCP concluded that parabens can be safely used in cosmetic products at concentrations of 0.4% for any individual paraben and 0.8% for total paraben concentrations. These limits echo the legislative limits put in place by the EU.

In 2011, the Danish government banned the use of parabens in personal care products intended for children younger than 3 years of age.

In the US, the Cosmetic Ingredient Review (CIR) has recommended the same maximum paraben concentrations as suggested by the SCCP and as legislated by the EU. However, the CIR recommendations are only guidelines which manufacturers are not required to follow.

In Canada, there are no laws regulating paraben concentrations but Health Canada agrees with the US FDA and the CIR regarding the safety of parabens and the adoption of maximum concentration guidelines.

Paraben Alternatives

Numerous preservatives could be used in place of parabens. Some other commonly used preservatives include:

- formaldehyde, quaternium-15, imidazolidinyl urea, diazolidinyl urea, and dimethyloldimethyl hydantoin.
- These preservatives more commonly cause allergic reactions and some have more serious health implications such as formaldehyde and its causal link with cancer.

Some have advocated for the use of "natural" preservatives such as grapefruit seed extract (GSE).

- GSE can interact with medications due to its ability to inhibit CYP3A4, a key enzyme involved in drug metabolism.

- Other "natural" preservatives include thymol, cinnamaldehyde, allyl isothiocyanate, citric acid, ascorbic acid, and rosemary extract.

- These "natural" preservatives inhibit microbial growth in vitro but the few studies testing antimicrobial activity in food products have provided equivocal results, and therefore require further study.

Conclusions

We have come to expect long shelf-lives and micro-organism free consumer products. This mandates the use of preservatives. Ideally, preservatives should be active against a wide variety of microorganisms, at low concentrations, without interfering with other ingredients in the product, while being nontoxic to humans and low cost to manufacturers. Parabens have been used for over 80 years and despite reports of adverse reactions, they have proven to be amongst the safest and most well tolerated preservatives. While the possible role of parabens in decreased sperm quality and breast cancer does warrant continued examination, the current data does not support drastic regulations or personal restrictions to exposure. Other recently regulated chemicals, such as phalates and bisphenol-A, may serve as archetypes for continued vigilance and investigation.

References

Therapeutic Options for Vitiligo

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Introduction

Vitiligo affects approximately 1% of the population and is characterized by well-demarcated, depigmented macules and patches that occur after destruction of melanocytes. It is an acquired disorder of unknown etiology. Vitiligo can appear at any time of life but is most common around the age of 20. It can be psychologically devastating, especially in patients with darker skin types. There is no cure but with appropriate management many patients can reduce its progression, achieve repigmentation, and attain cosmetically acceptable results. Recent guidelines have helped inform physicians in their approach to this disease.

Epidemiology

- The prevalence of vitiligo is approximately 1% but can vary regionally. For example, Gujarat state in western India has the highest prevalence in the world at 8.8%.1
- Men and women are equally affected.
- Average age of onset is 20 years.
- Women are more likely to seek treatment with vitiligo presenting earlier in the first decade of life versus the fifth decade of life for men.
- It is more frequently diagnosed in the spring and summer.
- There is a familial tendency in approximately 18% of cases.4

Etiology

- The cause of vitiligo remains unknown.
- Several different pathophysiological mechanisms are likely involved.
- The autoimmune hypothesis is most favoured due to an association with other autoimmune diseases (e.g., thyroid disease, alopecia areata, diabetes mellitus, pernicious anemia, rheumatoid arthritis, and psoriasis). There are numerous genetic associations and linkage studies.5
- The neurohumoral hypothesis is also supported by the development of segmental vitiligo along the distribution of nerves.
- Cytotoxic and oxidative stress hypotheses also have moderate support.

Quality of Life (QoL)

- Vitiligo can be psychologically devastating and comparable in impact to severe psoriasis.
- QoL assessments should be considered during the first clinic visit.
- Psychosocial impacts to patients can include feelings of embarrassment, depression and shame; negative emotional sequelae can result in sexual difficulties, sleep disturbance and anxiety.6
- Psychotherapy can be offered to select patients.

Diagnosis

- Classic presentation consists of depigmented macules and patches with convex borders surrounded by normal skin.
- Common sites affected include face, hands, nipples, axillae, umbilicus, inguinal and anogenital regions.
- Slow progression can occur.
- Koebnerization is a common finding and this refers to the development of new lesions in areas affected by trauma.5
- Two general categories include segmental and non-segmental vitiligo:
  - Segmental vitiligo is unilateral, begins in childhood, usually involves one dermatome and tends to be stable.
  - Non-segmental vitiligo is more common, appears later in life, is symmetrical and can be progressive.
- There are several other uncommon variants (trichrome, quadrichrome, blue, punctue and inflammatory vitiligo).
- Differential diagnosis:
  - Three of the most common mimickers include tinea versicolour, piebaldism, and idiopathic guttate hypomelanosis but many others can be considered.

Work-up

- Initial steps include a thorough clinical history and physical examination.
- Through emission of ultraviolet A light (365 nm), the Wood’s lamp can identify areas of depigmentation not readily visible to the naked eye, especially in lighter skin types.
If diagnosis is still uncertain, lesional and normal skin should be biopsied for direct comparison with special staining to identify melanocytes.

Bloodwork includes thyroid-stimulating hormone (TSH) and antinuclear antibody (ANA) as a minimum, with consideration for other autoimmune disease screening.

Consider eye and ear exams as there is an association with hearing loss and ocular abnormalities.

If part of a greater syndrome, referral to a geneticist should be considered.

QoL assessment and referral for counselling has been shown to benefit patients.

Prognostic Features

- Certain features point to a poorer prognosis and should be identified early (e.g., mucosal involvement, family history of vitiligo, non-segmental disease, positive Koebner phenomenon).
- Certain features point to a more favourable response to treatment (e.g., younger patients, darker skin types, recent onset, lesions on the head, neck and trunk).

Treatment

Vitiligo can be a lifelong disease and choosing the appropriate treatment can be difficult given the variety of options available. There are numerous medical, surgical, and light-based treatments for repigmentation. Options for depigmentation also exist. First-line treatments should be safe, effective, minimally invasive, and cost efficient. Advanced treatments are reserved for recalcitrant disease. Most treatments take time before an effect is evident, so patience on the part of the physician and patient is essential.

Topical Treatments

- **Topical corticosteroids (TCS)**
  - This is the usual first-line treatment
  - Optimal dosing parameters remain to be determined
  - High potency topical steroids (clobetasol, fluticasone) used for a two-month period appear to be safe
  - Side effects include atrophy, telangiectasia, striae, folliculitis, and hypertrichosis
- **Topical calcineurin inhibitors (tacrolimus or pimecrolimus)**
  - Provide almost equal results to topical steroids
  - Safe for short-term and intermittent long-term use.
  - The most common side effect is a transient burning sensation upon application
  - To date, there is no evidence to suggest an increased risk of lymphoma in adults or children using these products, refer to Canadian Dermatology Association position statement. Available at: [http://www.dermatology.ca/wp-content/uploads/2012/01/TopicalCalcineurinInhibitorsEN.pdf](http://www.dermatology.ca/wp-content/uploads/2012/01/TopicalCalcineurinInhibitorsEN.pdf)
- **Vitamin D3 analogues (calcipotriol/calcipotriene)**
  - Monotherapy is inferior to TCS and not recommended
  - When combined with TCS, efficacy increases and the fixed-dose combination of calcipotriol 0.005% and betamethasone dipropionate 0.05% once daily is a simple option
  - Vitamin D3 analogues are not recommended in combination with light therapy

Systemic Medications

- **Systemic corticosteroids**
  - These can be effective in halting disease progression and inducing repigmentation but are not recommended due to an unacceptable risk of side effects
- **Antioxidants**
  - Theoretically, they may play a role in protecting melanocytes from reactive oxygen species
  - Gingko biloba, vitamin E, vitamin C and other antioxidants cannot be recommended as additional research is needed
  - **Tumor necrosis factor (TNF)-alpha inhibitors**
    - Theoretically, they may play a role as TNF-alpha is a pro-inflammatory cytokine that can induce melanocyte death and inhibit melanocyte stem cell differentiation
    - Further research is necessary before recommendations can be made
  - **Other immunosuppressive agents**
    - No recommendation can be made regarding azathioprine, cyclophosphamide or cyclosporine due to a lack of evidence

Phototherapy

- **Phototherapy** should be reserved for patients who fail topical treatment.
- Treatment requires a commitment from the patient as dosing varies from 2 to 3 times per week for several months.
- Phototherapy does not alter the natural history of vitiligo.
- The exact mechanism of action is unknown but believed to have immunosuppressive and melanocyte stimulating effects.
- Narrow band ultraviolet-B (nb-UVB) is superior and easier to administer than psoralen + UVA therapy (PUVA).
- Treatment limits are necessary to prevent the possibility of skin malignancies: an arbitrary limit of 200 treatments for nb-UVB and 150 treatments for PUVA has been suggested.
- Combination therapy with topical treatments can enhance results:
  - **Topical corticosteroids are recommended**
  - **Topical calcineurin inhibitors are recommended**
  - **Topical vitamin D analogues are NOT recommended**

Laser Therapy

- Lasers provide targeted treatment to lesions and emit less overall radiation, thereby reducing adverse impacts on healthy skin.
- 308 nm monochromatic excimer laser is well studied and superior to conventional light therapy.
- This therapeutic modality for vitiligo is not readily available in Canada at this point in time.
- Combination therapy with topical treatments can enhance results:
  - **Topical corticosteroids are recommended**
  - **Topical calcineurin inhibitors are recommended**
  - **Topical vitamin D analogues are NOT recommended**

Surgical Treatments

- **Surgical techniques** are among the most effective treatment options but are not yet available in Canada.
- The concept is to transplant functioning melanocytes to the depigmented areas.
• Treatment is reserved for recalcitrant, segmental vitiligo in cosmetically sensitive areas that have been stable for at least one year without evidence of Koebner phenomenon:
  • Requires a donor site that may be subject to scarring and Koebnerization
  • Requires a recipient site that may be subject to scarring, graft failure, pigment mismatch, cobblestone appearance, infection, and Koebnerization
• Documented techniques include:
  • Punch graft
  • Suction blister graft
  • Split thickness skin graft
  • Autologous melanocyte transfer
    • Graft tissue is harvested and after exposure to enzymes, individual melanocytes are released into a suspension that is transplanted onto a de-epithelialized recipient site
    • The advantage is that a smaller graft site can result in a suspension that can cover much larger areas

Depigmentation Therapy
• Select patients may benefit from depigmentation therapy, including those who have >50% body surface area involvement, experienced failure with repigmentation therapy, and accept the permanence of this technique.
• Treatment can take many months before the effect is visible; however, the improvement may not be permanent.
• Side effects with topical agents are common and include irritation, contact dermatitis, and ocular changes.
• Topical agents include:
  • Monobenzyl ether of hydroquinone
  • 4-methoxyphenol
  • The Q-switched ruby laser is also effective and has a more rapid onset of action; it can be used in combination with topical products.

No Treatment and Non-pharmacologic Adjuncts
• No treatment is viable in patients with skin types I and II.
• All patients should be offered sunscreen to protect the depigmented skin and reduce contrast with surrounding tanned skin.

Camouflage
• All patients should be made aware of camouflage cosmetics as a noninvasive strategy to diminish the appearance of visible patches. Temporary options include makeup and self-tanning agents containing dihydroxyacetone.
• Permanent options include tattooing but Koebnerization, colour mismatch, and scarring must be considered.

Psychotherapy
• Emotional and psychological effects from vitiligo can be severe.
• Cognitive behavioural therapy has been shown to improve QoL, self esteem, and perceived body image, but further work is needed to clearly define its role.7

Conclusion
Vitiligo is a disease that presents with depigmented skin and is associated with significant psychosocial effects. Disease progression can occur and is unpredictable. Management is challenging and many options are available. Topical treatments are considered first-line and more advanced therapies are often necessary with recalcitrant disease. Further research is needed to define the exact cause and to investigate potential therapies. Recent guidelines are useful in assisting physicians to optimize their treatment approach.

References