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CANADIAN DERMATOLOGY TODAY

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Advances in vitiligo: pathophysiology, psychosocial impact and emerging therapy

Introduction

Vitiligo is a chronic autoimmune skin disorder that affects approximately 0.5–2% of the world's population.¹ It is characterized by the loss of pigment-producing melanocytes, resulting in depigmented patches on the skin. Vitiligo occurs equally in all genders and across the skin colour spectrum. Although vitiligo can start at any age, 50% of affected individuals experience the onset of the condition before the age of 20.² Recent developments in vitiligo research have advanced the understanding of its pathophysiology, epidemiology, and psychosocial impact on patients. While traditional treatment options have been of limited benefit, several emerging therapies are in development and may soon be available to Canadian patients with vitiligo.

Vitiligo is primarily classified into two morphologic types, which are non-segmental vitiligo and segmental vitiligo. Non-segmental vitiligo is the most common presentation. Segmental vitiligo presents with depigmented patches occurring in a Blaschkovian distribution pattern. These depigmented patches may be single or multiple. Segmental vitiligo is seen in only 5% of adults with vitiligo, however, up to 20% of children are affected. Segmental vitiligo is not

associated with thyroid disease or other autoimmune comorbidities.¹

Vitiligo pathophysiology

Recent advances in the understanding of vitiligo's pathophysiology have highlighted its autoimmune nature, which involves complex interactions between genetic, environmental, and immunological factors.

Immunological dysregulation:³

One of the central pillars of vitiligo pathophysiology is the immune system's role in melanocyte destruction. Changes in both innate and adaptive immunity play a role in the pathophysiology of vitiligo.

Innate immunity:

- The innate immune system appears to be the bridge between oxidative stress **Figure 1** and adaptive immunity in vitiligo.
- Activated CD56+ / granzyme B+ natural killer (NK) cells and interferon (IFN)- γ -producing cells have

been identified in the blood and non-lesional skin of patients with vitiligo.

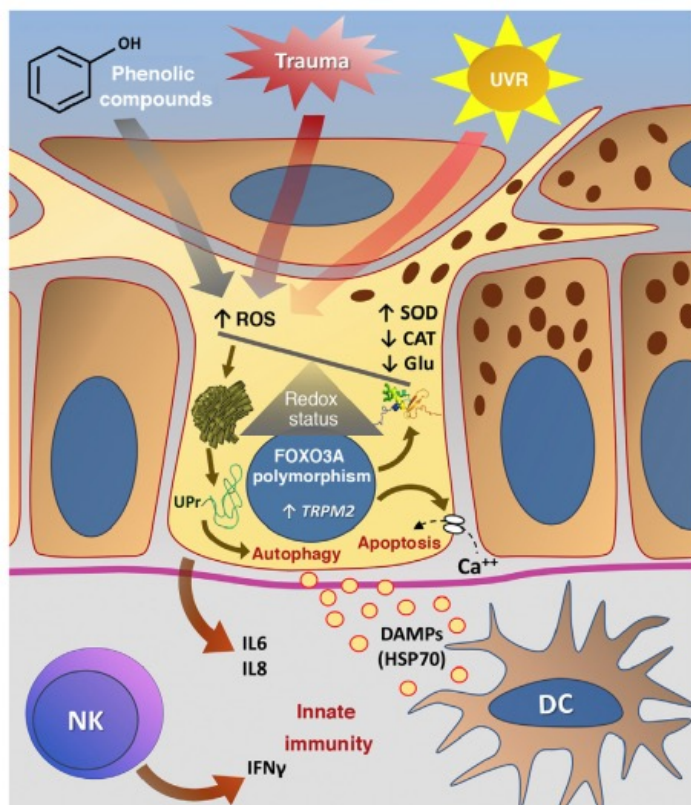


Figure 1: Representation of oxidative stress and activation of innate immunity in vitiligo. CAT, catalase; DAMPs, (damage-associated molecular patterns); DC, dendritic cells; FOXO3A, forkhead transcription factor 3A; Glu, glutathione; IL, interleukin; NK, natural killer cells; ROS, reactive oxygen species; SOD, superoxide dismutase enzyme; TRPM2, transient receptor potential cation channel subfamily M member 2; UPr, unfolded proteins; UVR, ultraviolet radiation.³

Adaptive Immunity:

- There is an increase in proinflammatory cytokines in both the serum and skin of patients with vitiligo, including interleukin (IL)-1 α , IL-1 β , IL-6, IL-8, IL-12, IL-15, and tumour necrosis factor (TNF)- α .
- Activated NK-cell driven expression of IFN- γ is a central event in a host of adaptive immune system responses in vitiligo.
- CD8⁺ cytotoxic T lymphocytes (CTLs) are major players in melanocyte destruction in vitiligo. These CTLs recognize melanocyte antigens and induce apoptosis, leading to the loss of melanocytes.
- The role of anti-melanocyte antibodies is still being elucidated. These antibodies do occur, but their titers do not correlate with disease activity.
- Elevated levels of IFN- γ have been observed in vitiligo lesions, contributing to melanocyte damage. IFN- γ promotes the expression of major histocompatibility complex class I molecules on melanocytes, making them more susceptible to CTL-mediated cytotoxicity.

- Dysregulation of regulatory T cells (T_{regs}) has been implicated in vitiligo pathogenesis. Reduced T_{reg} function allows for uncontrolled activation of autoreactive T cells against melanocytes.

Genetic factors:

Genetic susceptibility plays a crucial role in the development of vitiligo. Recent advances in genomics have identified several susceptibility genes associated with the disease.

- Human leukocyte antigen (HLA) genes: Variants in HLA genes have been strongly linked to vitiligo susceptibility. Specific HLA alleles, such as *HLA-A02* and *HLA-DRB107* (among several others), are associated with an increased risk of developing vitiligo.
- Non-HLA genes: Genome-wide association studies have identified non-HLA genes, including *NACHT leucine-rich-repeat protein 1 (NLRP1)*, *Lymphoid protein tyrosine phosphatase non-receptor type 22 (PTPN22)*, and *Tyrosinase (TYR)*, as potential genetic risk factors for vitiligo. These genes are involved in immune regulation and melanocyte function.

Oxidative stress and melanocyte damage:^{3,5}

Oxidative stress-induced damage to melanocytes is a critical pathophysiological mechanism in vitiligo. It may well contribute to many of the pathophysiologic mechanisms implicated in vitiligo. Ultraviolet light, exposure to phenolic compounds, or mechanical trauma may increase production of reactive oxygen species (ROS) within melanocytes, causing oxidative stress, which can trigger apoptosis and melanocyte destruction.

- ROS: Recent studies have elucidated the role of ROS and its impact on melanocyte destruction as a trigger for aberrant mitochondrial function, and as a trigger for a host of innate immune system responses.
- Antioxidant deficiency: Vitiligo-affected skin also has reduced levels of antioxidants, such as catalase and superoxide dismutase.
- Antioxidant supplementation: (eg, superoxide dismutase and polypodium leucotomos) may have a protective role against melanocyte damage.

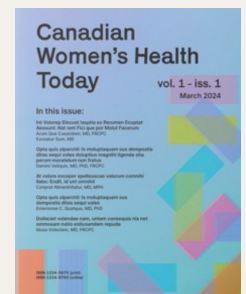
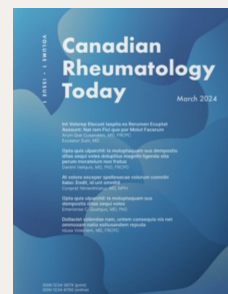
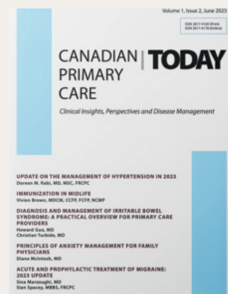
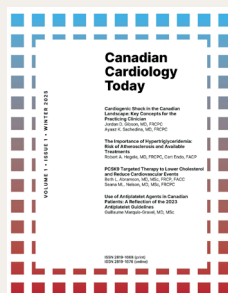
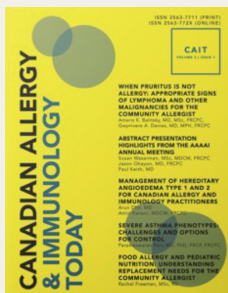
Mitochondria and melanocyte interactions:⁴

- As noted above, oxidative stress can impact both mitochondrial function and mitochondria-associated gene expression.
- Disruption of mitophagy, a biochemical process that protects cells by removing damaged mitochondria, has been implicated as one pathogenetic factor in vitiligo.



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- Mitochondrial-melanosome crosstalk might be perturbed by the alteration of several key genes in vitiligo.

Neuroimmunology:⁴

Emerging evidence suggests a link between the nervous system and vitiligo pathophysiology.

- Neurotransmitters and neuropeptides: The presence of neurotransmitters and neuropeptides, such as substance P and calcitonin gene-related peptide, in vitiligo-affected skin has been demonstrated. These neurochemicals modulate immune responses and melanocyte function.
- Neural-melanocyte interactions: Neural-melanocyte interactions, including the release of neurotransmitters by nerve endings near melanocytes, play a role in melanocyte dysfunction and autoimmune responses.

Psychosocial impact of vitiligo

Vitiligo's visible nature can have a profound psychosocial impact on affected individuals, leading to diminished quality of life, depression, anxiety, and social isolation. These patients experience a high level of stress and psychiatric disorders in addition to physical involvement. Depression, anxiety, suicidal ideation and behaviour, embarrassment, social isolation, discomfort, cognitive impairment, and physical limitation were reported in vitiligo patients.⁶

While vitiligo can occur across the skin colour spectrum, it disproportionately affects people with more richly pigmented skin. This is partly owing to depigmentation being more strikingly visible in patients with constitutively more melanized skin. However, societal biases and limited understanding of the nature of vitiligo unfortunately still play a role. Patients with vitiligo who identify as female tend to experience more of a significant impact on psychosocial functioning than those who identify as men. These effects are magnified based on the extent of disease as well as by the involvement of more visible areas (ie, facial and hand involvement).⁷

Patients with vitiligo are hospitalized for mental health concerns at a higher rate than patients without vitiligo, and their hospitalizations last longer and cost more.⁸

Approximately 17% of patients begin antidepressants or anxiolytics in the year following a vitiligo diagnosis due to self-injurious behaviour as a result of their diagnosis. Rates of anxiety and depression may be as high as 60%, and suicidal ideation may occur in up to 25% of patients.⁹

Intriguingly, there is some evidence of a bidirectional relationship between vitiligo and mental health diagnoses, specifically major depression.¹⁰

Vitiligo therapy

Traditional therapeutic approaches:

There is widespread support for a shared decision-making model in vitiligo to determine desired versus expected outcomes.¹¹ Stabilization of disease, repigmentation or, less frequently, depigmentation therapy may all be appropriate therapeutic targets. Further, the therapeutic target may evolve through the course of the disease and after considering the patient's response to treatment. In addition, therapeutic outcome targets will also evolve as new therapeutic options emerge.

Steroid oral minipulse therapy (OMP):^{12,13} For active and progressive vitiligo, OMP steroid therapy is considered the standard of care. The suggested dosing is betamethasone (5 mg), dexamethasone (2.5–5 mg) or prednisone (15–30 mg, depending on body weight) twice weekly, on 2 consecutive days per week, for up to 3 months.⁹

Methotrexate (MTX): MTX is a treatment alternative for disease stabilization, but its efficacy is less clear.

Topical corticosteroids and calcineurin inhibitors: Topical corticosteroids and calcineurin inhibitors continue to be standard treatments for localized vitiligo. These agents are often used as adjunctive therapies with systemic agents or phototherapy.

Narrowband ultraviolet B (UVB) phototherapy: Stabilizing disease (for example, treatment with OMP steroids) is often not enough to induce repigmentation. Combination (or sequential) narrowband UVB phototherapy effectively promotes repigmentation in vitiligo lesions. While narrowband UVB phototherapy is considered the first-line standard of care for repigmentation in some published guidelines,¹⁴ access and convenience may limit its utility to some extent.

Excimer laser: Excimer laser therapy is a treatment option that delivers targeted UVB light to depigmented areas, offering improved results for segmental vitiligo.

Polypodium leucotomos and SOD: Polypodium leucotomos, an orally administered photoprotective antioxidant, has been used as adjuvant therapy for vitiligo patients also being treated with phototherapy. Repigmentation rates are higher with combination therapy that includes polypodium leucotomos and psoralen and UVA (PUVA) or narrow band UVB (NB-UVB) compared with either photochemotherapy or NB-UVB phototherapy alone.¹⁵

Emerging vitiligo therapies:

As the understanding of the pathogenesis of vitiligo continues to be elucidated, more directed therapies are being developed. For example, Janus kinase (JAK) inhibitors may represent a potential breakthrough in vitiligo treatment, with recent clinical trials demonstrating their effectiveness in repigmentation.

Topical ruxolitinib: Approved for the treatment of vitiligo in the EU and in the US, topical ruxolitinib cream offers excellent repigmentation rates. However, patient and physician expectations need to be aligned, since achieving meaningful repigmentation may take as long as 24 months. In a recent poster presentation, patients who showed no significant repigmentation at 24 weeks who had continued therapy with ruxolitinib, achieved high repigmentation rates by weeks 52 and 104.¹⁶

Povorcitinib: Povorcitinib is a selective oral JAK1 inhibitor. The results of a phase 2b, placebo-controlled dose-ranging study that included 171 patients showed significant rates of repigmentation (measured as Total Vitiligo Area Scoring Index and Facial Vitiligo Area Scoring Index) at week 24, and continued to improve up to week 52. Significantly, this response was maintained at a high rate during a 24-week withdrawal period. Safety assessments were consistent with the selective JAK inhibitor class of medications.¹⁷

Upadacitinib: Upadacitinib is an oral selective anti-JAK1 inhibitor (already approved in Canada for atopic dermatitis, inflammatory bowel disease, and inflammatory arthritides), shows promise for vitiligo in its Phase 2 trials.¹⁸

Ritlecitinib: Ritlecitinib is a selective oral JAK3/TEC inhibitor that is expected to receive approval for alopecia areata in Canada and is also being assessed for vitiligo. Ritlecitinib also showed statistically significant and clinically meaningful repigmentation versus placebo at week 24, and “accelerated improvement was observed after week 28 during the extension period.”¹⁹

Baricitinib: Baricitinib, in combination with NB-UVB, has also shown benefit in a recent double-blinded phase 2 proof of concept trial.²⁰

Other agents in development: As our understanding of the immunologic basis of vitiligo improves, many more agents are likely to be assessed for their potential to control vitiligo outcomes. Along with JAK inhibitors, on the horizon are many other novel therapeutic options in development, including Wnt-signalling agonists, cytokine targeting agents, Treg inducers, and anti-IL-15 agents, among others.²¹

Surgical options for vitiligo, such as punch grafting, can be of benefit. In addition, more recent developments in autologous melanocyte transplantation

techniques, such as non-cultured epidermal suspension and follicular unit extraction, may be procedural alternatives in the future.

Conclusion

Recent advancements in vitiligo research have expanded our understanding of the disease's pathophysiology, epidemiology, and psychosocial impact. These insights have paved the way for innovative therapeutic approaches that offer new, more targeted approaches to management of vitiligo. While new treatment options will reduce vitiligo's overall impact, efforts to reduce stigma and improve the psychosocial well-being of affected individuals remain crucial aspects of comprehensive vitiligo management, particularly among Black, Indigenous, Hispanic, and Asian patients in addition to other patients of colour.

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Simple superficial chemical peels to complement a medical dermatology practice

Introduction

In an era of exciting new drug therapies and cutting-edge laser devices, it is easy to forget about simpler, “low-tech” treatments that have stood the test of time but are not being championed by industry. One such example is a superficial chemical peel, which produces a controlled injury that is limited to the epidermis. This is a simple and inexpensive procedure that can complement the treatments provided by dermatologists for acne, melasma or postinflammatory hyperpigmentation.

This article will address two simple superficial peels that can be quickly implemented in a busy medical dermatology practice, which are the salicylic acid peel and the Jessner's peel.¹ Peels that require neutralization (glycolic peels and pyruvic acid peels), medium depth peels (usually requiring pretreatment with either Jessner's solution or CO₂ followed by trichloroacetic acid 35%) or deep peels (phenol-croton oil peel) are beyond the scope of this article.²

Salicylic acid peel

Salicylic acid is a lipid-soluble beta-hydroxy acid. It is a well-known active ingredient in the treatment of acne, psoriasis, seborrheic dermatitis, warts, and

many other conditions. Over-the-counter cleansers and leave-on products for acne often contain 2–3% salicylic acid, while prescription topicals and custom compounds contain much higher concentrations. Salicylic acid is thought to be anti-inflammatory, antimicrobial, sebolytic and to inhibit tyrosinase. Because of its lipophilic and comedolytic effects, it is particularly well suited to treating comedonal acne.

Salicylic acid 30% is available in a hydroalcoholic solution or in polyethylene glycol (PEG). The 20–30% salicylic acid hydroalcoholic solution crystallizes on the skin when the ethanol component evaporates, leaving a “pseudofrost” that can be wiped from the face if desired. This peel is self-limiting—the crystals cannot penetrate the dermis. Minimal stinging can occasionally be felt during application, and 1–3 days of desquamation can follow. Rarely, focal “hot spots” of overpenetration can lead to postinflammatory hyperpigmentation. The PEG vehicle enhances follicular penetration while resulting in slower penetration and a more even distribution. It leaves a shiny appearance on the skin and can be slightly occlusive, and some practitioners recommend wiping it off with water after >5 minutes of contact. This peel results in either no or minimal desquamation, making recovery from the procedure easier on patients. A split-face study comparing 30% salicylic acid in PEG versus 30%

salicylic acid in a hydroalcoholic solution to treat acne favored the solution in PEG.³ However, this treatment should be avoided during pregnancy, breastfeeding and in patients with Aspirin (acetylsalicylic acid) allergy.

In the author's practice, salicylic acid 30% in PEG peels are primarily used in combination with a prescription topical treatment (**Figure 1**). The peeling agent is poured over a 4×4 gauze, and the gauze is used to apply three coats to the full face. No more than 5 mL of peel solution is required for a treatment. The skin is gently wiped with a dry gauze to minimize shine approximately 5 minutes after the application of the peel. These peels can be performed weekly, however, in practice patients return for treatments every 2–4 weeks, which also allows for their topical treatment to take effect (**Figure 1**). Because of the simplicity of the peel process and the absence of specialized equipment required to perform the procedure, a salicylic acid peel can be a quick “add-on” treatment during an appointment without affecting clinic workflow.



Figure 1: Patient treated with a dapsone 5% gel twice a day and four peels with salicylic acid 30% in polyethylene glycol over a two-month period; courtesy of Vincent Richer, MD, FRCPC

Jessner's peel

Jessner's solution consists of 14% resorcinol, 14% salicylic acid, and 14% lactic acid in a 95% ethanol base. It can be used as an adjunctive treatment for acne, and for pigmentary disorders such as melasma and postinflammatory hyperpigmentation. Since this peel also contains salicylic acid, a pseudofrost can develop over the skin during treatment. The resorcinol component can also leave very light, reticulate frosting.

There is a greater immediate discomfort (stinging) with the application of Jessner's solution compared to a salicylic acid peel. Forced cool air or a handheld fan can be helpful for symptom control. Of note, the resorcinol molecule is chemically similar to hydroquinone, and contact hypersensitivity is possible with repeat exposure. In the event that a patient is sensitized to

resorcinol, a modified Jessner's solution is available that increases the concentrations of salicylic acid and lactic acid to 17% and replaces resorcinol with 8% citric acid.

In the author's practice, Jessner's solution is not used as a stand-alone treatment for hyperpigmentation, but rather as a complement to topical brightening agents, laser devices or oral tranexamic acid. It is delivered in a similar fashion to the salicylic acid peel described above.

Other superficial peels

Other superficial peels include tretinoin peels (containing 5–10% tretinoin). These are usually applied to the full face and left on for 6 hours. After the specified time, they are rinsed off at home. These peels require in-office reconstitution using crystals that leave a bright yellow residue on the patient's skin.

Trichloroacetic acid is also considered a superficial peel at concentrations ranging from 10–30%. Trichloroacetic acid in concentrations higher than 35% is recommended for focal treatment of individual lesions, and not for field treatment. In the author's practice, 70–90% trichloroacetic acid is one of the treatment options for the management of xanthelasma.



Figure 2: An example of chemical peeling agents and a skin prepping agent; courtesy of Vincent Richer, MD, FRCPC

Practical takeaways

- Prepping/degreasing the skin is an important consideration prior to administering a peel. This process allows for an even distribution and absorption of the peel. A solution of equal parts alcohol/acetone ("Peel Prep") can serve this purpose effectively.
- Peels can be obtained from your local compounding pharmacy or ordered from a company that specializes in peels. The author's personal choice is to order from an established company to minimize variation in vehicle composition (**Figure 2**).
- If you work with extenders (nurse practitioners or physician assistants) that you closely supervise and train, superficial peels can be effectively delegated.

Conclusion

Salicylic acid and Jessner's solution are superficial chemical peels that can complement the treatments a dermatologist provides for acne and melasma. Choosing salicylic acid in a PEG solution rather than in a hydroalcoholic solution appears to maximize outcomes and minimize recovery/risks for patients when treating acne. Proactively managing the stinging sensation that may occur during a Jessner's peel, using tools such as handheld fans, is key to successful implementation of this procedure.

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Clinical manifestations and treatment of ocular rosacea

Introduction

Rosacea is a common chronic inflammatory skin condition primarily affecting the central face, including the cheeks, nose, chin, forehead, and eyes.¹ The prevalence of rosacea is higher in middle-aged individuals and those with light skin phototypes (Fitzpatrick skin types I-II).² Ocular symptoms occur in up to 58% to 72% of those with rosacea.^{1,3} Clinical manifestations of ocular rosacea include chronic blepharitis; conjunctivitis; meibomian gland dysfunction (MGD); corneal vascularization; infiltration; and scarring.⁴ Patients may report symptoms of ocular dryness, burning and stinging, sensitivity to light, blurred vision, and foreign body sensation.¹ Clinical signs include telangiectasias of the lid margin, conjunctival telangiectasias, MGD, and chalazia.¹

Delay to diagnosis

Unfortunately, the diagnosis of ocular rosacea is often delayed leading to a delay in treatment.⁵ Diagnosis is challenging as the symptoms of ocular rosacea are not specific to the disorder alone, and other ophthalmic disorders may present with similar findings.⁶ The Global Rosacea Consensus Panel highlights that even with minimal skin involvement, ocular rosacea can be identified by specific features like lid margin abnormalities, corneal issues, or scleral inflammation (**Table 1**).⁴

For effective diagnosis of ocular rosacea in patients presenting with ocular symptoms with or without cutaneous features, a systematic approach is recommended. The assessment includes history taking, physical examination, and asking about the patient's subjective experience through questionnaires like Ocular Surface Disease Index (OSDI). Assessment tools such as the OSDI help in establishing a diagnosis,

Ocular rosacea features	Description
Lid margin telangiectasias	Visible blood vessels on the eyelid margin.
Blepharitis	Erythema and inflammation of the eyelid margin, most commonly arising from meibomian gland dysfunction.
Keratitis	Inflammation of the cornea that can lead to defects and in severe cases loss of visual acuity.
Conjunctivitis	Inflammation of the mucosa lining the inner surface of the eyelids and bulbar conjunctiva. Typically associated with conjunctival injection or vascular congestion.
Anterior uveitis	Inflammation of the iris and/or ciliary body.

Table 1. Features of ocular rosacea.⁴

grading of symptoms and evaluating the subjective effectiveness of treatments.^{1,4,7}

Notably, the severity of ocular symptoms is often not related to the severity of the cutaneous findings in patients with rosacea.^{6,8} In 20% of patients with rosacea, ocular findings may precede cutaneous involvement, and in up to 90% of cases of ocular rosacea, skin findings may be subtle, posing a further challenge to accurate diagnosis.⁹

A recent systematic review of ocular rosacea in children showed that over half (55%) of patients presented with ocular signs and symptoms prior to cutaneous manifestations.⁵ Unfortunately, ocular rosacea in children is often misdiagnosed as a viral or bacterial infection and patients may go undiagnosed for years until cutaneous features of rosacea arise. Consequently, the majority of children with ocular rosacea (83%) experienced a delay in diagnosis,

with a mean of approximately two years, with some experiencing a delay of up to 10 years.⁵

Ocular rosacea also presents a diagnostic challenge given its non-specific manifestations. Longstanding ocular rosacea left untreated may lead to corneal inflammation, scarring and possibly even corneal perforation with loss of visual acuity.¹ Therefore, diagnosis in the early stages of the disease is crucial to prevent complications.

Treatments

Given the multifactorial nature of ocular rosacea, a variety of treatment modalities have been utilized to target the etiologic factors associated with this condition. Contributing factors to ocular rosacea include staphylococcal infection; innate immune response; meibomian gland inflammation; *Demodex folliculorum*; vascular dysfunction; and environmental triggers such as sunlight. Commonly employed treatment options for ocular symptoms in rosacea include lid hygiene; topical and oral antibiotics; cyclosporine ophthalmic emulsion; ivermectin; isotretinoin; and intense pulsed light (IPL).

Lid hygiene

Lid hygiene is safe and often recommended as a first-line therapy for ocular rosacea and dry eye disease. Lid hygiene involves the use of warm compresses and artificial tears as a treatment for ocular rosacea. A recent systematic review concluded that 64% of patients treated with lid hygiene routines alone showed a positive treatment response, with 34% of patients showing a complete response (**Figure 1**). It is likely that for patients with mild symptoms, lid hygiene is sufficient to provide relief – however, for those with moderate or severe symptoms, lid hygiene alone may not be adequate and should be used in combination with other treatments.¹⁰

Compliance with lid hygiene can also pose a challenge. A survey study of lid hygiene and subjective patient response of dry eye symptoms showed that of 188 patients surveyed, only 55% reported compliance.¹¹ However, of those who adhered to treatment, 92% (n=96/104) described an improvement in dry eye symptoms. Furthermore, a Cochrane systematic review of treatments for chronic blepharitis concluded that lid hygiene routines may provide symptomatic relief.¹²

Various approaches to lid hygiene have been described, and generally involve the use of warm compresses alone or in combination with gentle shampoo lid scrubs using a cotton pad, cotton tip applicator or washcloth. Convenient over-the-counter lid scrubs, including OcuSoft (Rosenberg, Texas),

Eye Scrub® (Novartis, Switzerland) and LidHygenix (Advanced Eye Care Products, Inc. Atlanta, GA), among others, may be used in place of gentle shampoos for eyelid cleansing.¹¹ Lid hygiene may improve dry eye symptoms via removal of inflammatory debris from the eyelid margin and through an improvement of tear film stability.¹³

Topical antimicrobials

The use of topical antimicrobials on the eyelids and/or ocular surface has been reported for metronidazole, azithromycin and povidone iodine. A recent systematic review showed that overall, topical antimicrobials achieved a partial response in 39% of treated patients and a complete response in a further 52% (**Figure 1**).¹⁰ Topical antimicrobials may provide benefits via a decrease of eyelid flora, anti-inflammatory properties, or by helping to soften collarettes on the eyelid margin.⁶

Cyclosporine ophthalmic emulsion

The use of cyclosporine ophthalmic emulsion is commonplace in optometry and ophthalmology, and has been reported previously for patients with ocular rosacea.¹⁴ A recent systematic review with a pooled analysis of 46 patients showed that overall, cyclosporine ophthalmic emulsion achieved a complete response in 30% of treated patients, and a partial response in a further 57% (**Figure 1**).¹⁰

There are likely two mechanisms by which cyclosporine exerts a beneficial effect in ocular rosacea and MGD in general. First, cyclosporine inhibits trafficking of T-lymphocytes and thereby decreases inflammation of the meibomian glands.¹⁵ Second, cyclosporine modulates immune cell populations in the conjunctiva and lacrimal gland, thereby ameliorating dry eye symptoms.¹⁶ Importantly, in contrast to corticosteroids, cyclosporine ophthalmic emulsion is safe with no significant adverse effects, no risk of microbial overgrowth, and no increased risk of ocular infection reported.¹⁶

Oral antimicrobials

The use of a variety of oral antimicrobial agents has been reported for the treatment of ocular rosacea, including tetracyclines, nitroimidazoles, macrolides, and lincosamides. A recent systematic review found that oral antimicrobials as a class lead to a complete response in 20% of treated individuals and partial response in 70% (**Figure 1**).¹⁰

Overall, doxycycline was the most commonly reported oral antimicrobial agent used in ocular

rosacea dosed at 50 mg daily to 100 mg twice daily for treatment courses ranging from 1 to 3 months.^{14,17-19} A commonly used treatment regimen involves doxycycline 100 mg twice daily for the first month and once daily for the following two months.^{14,18} A recent pooled analysis of 206 patients showed that doxycycline led to a complete response in 23% of treated patients with a partial response in 64% (**Figure 1**).¹⁰ Doxycycline may be effective in treating ocular rosacea by decreasing the growth of ocular microflora and inhibiting enzymes such as metalloproteinases, collagenases and bacterial lipases.⁶ The most common adverse event reported with doxycycline is gastrointestinal upset, occurring in up to 52% of treated individuals.²⁰ Successful use of a 3-month course of oral metronidazole at a dose between 20 and 30 mg/kg per day has been reported as an alternative to oral doxycycline in children with ocular rosacea.²¹

Although the effectiveness and safety of doxycycline 40 mg (30 mg immediate release and 10 mg delayed release) once daily for the treatment of papulopustular rosacea has been demonstrated, its efficacy in ocular rosacea has not yet been established.²² A randomized, single-blind, noninferiority trial demonstrated that minocycline 100 mg is noninferior to doxycycline 40 mg in efficacy over a 16-week treatment period in rosacea patients.²³ However, the effects on ocular rosacea specifically have not been investigated.

Ivermectin

Ivermectin is an anti-parasitic drug that is proposed to manage ocular rosacea by targeting *Demodex folliculorum* mites and through its anti-inflammatory properties. The use of oral ivermectin in the treatment of ocular *Demodex folliculorum* has been demonstrated.²⁴ In addition, a single dose of oral ivermectin led to complete resolution in a 12-year-old girl with severe ocular and cutaneous rosacea unresponsive to oral doxycycline.²⁵

Topical ivermectin 1% cream once weekly in combination with eyelid hygiene significantly improved ocular symptoms, redness, swelling, and telangiectasia compared to eyelid hygiene alone.²⁶ A recent randomized trial compared ivermectin 1% cream and doxycycline 40 mg modified release capsules vs ivermectin 1% cream and placebo in patients with severe rosacea and with >40% having ocular symptoms. Both treatments reduced the proportion of participants with ocular signs and symptoms from baseline to week 12: -60.0% with combination therapy and 60.7% with monotherapy.²⁷ Thus, topical ivermectin 1% cream is safe, well tolerated, and may be effective

in patients with ocular rosacea by decreasing *Demodex folliculorum* mites at the eyelid margin.²⁸

Isotretinoin

The use of isotretinoin for ocular rosacea is reported in several clinical studies in the literature. Despite the beneficial role of low-dose isotretinoin in select rosacea patients, a pooled analysis of isotretinoin in ocular rosacea showed that the majority of patients had no response (60%) with only 40% achieving a partial response (**Figure 1**).¹⁰ Thus, isotretinoin has limited benefit and may even aggravate ocular rosacea by exacerbation of dry eye symptoms and MGD.

Intense pulsed light

The use of IPL for dry eye and ocular symptoms has garnered increased attention in recent years. Treatment protocols generally involve a total of four treatment sessions 2-3 weeks apart using a double-pass protocol developed by Toyos and colleagues.²⁹ The treatment areas include the malar region (from tragus to tragus, including the nose) and the periocular area up to the eye protection positioned along the lower eyelid margin.²⁹ A recent systematic review

and meta-analysis showed that IPL treatment led to an improvement in OSDI scores post-treatment.³⁰ Adjunctive treatments, such as meibomian gland expression; sodium hyaluronate eye drops; heated eye mask; warm compress; lid hygiene; antibiotic drops; cyclosporine drops; omega-3 supplements; and warm compresses, were shown to increase IPL effectiveness.³⁰

Another systematic review showed that patients with ocular rosacea treated with IPL had a >90% rate of treatment response (**Figure 1**).¹⁰ While the treatment protocol varies across published studies, overall, IPL therapy has been shown to be safe and may have a positive impact on the signs and symptoms of ocular rosacea and MGD-related dry eye disease.³⁰ It is likely that patients in the early stages of disease can benefit more from IPL therapy.

Although the mechanism of action of IPL in ocular rosacea remains to be elucidated, one proposed mechanism involves the warming effect produced by IPL on increasing the outflow of viscous meibum.³¹ The increased outflow of meibum may reduce the bacterial proliferation typically seen in meibum stasis, therefore decreasing ocular inflammation and irritation.³¹

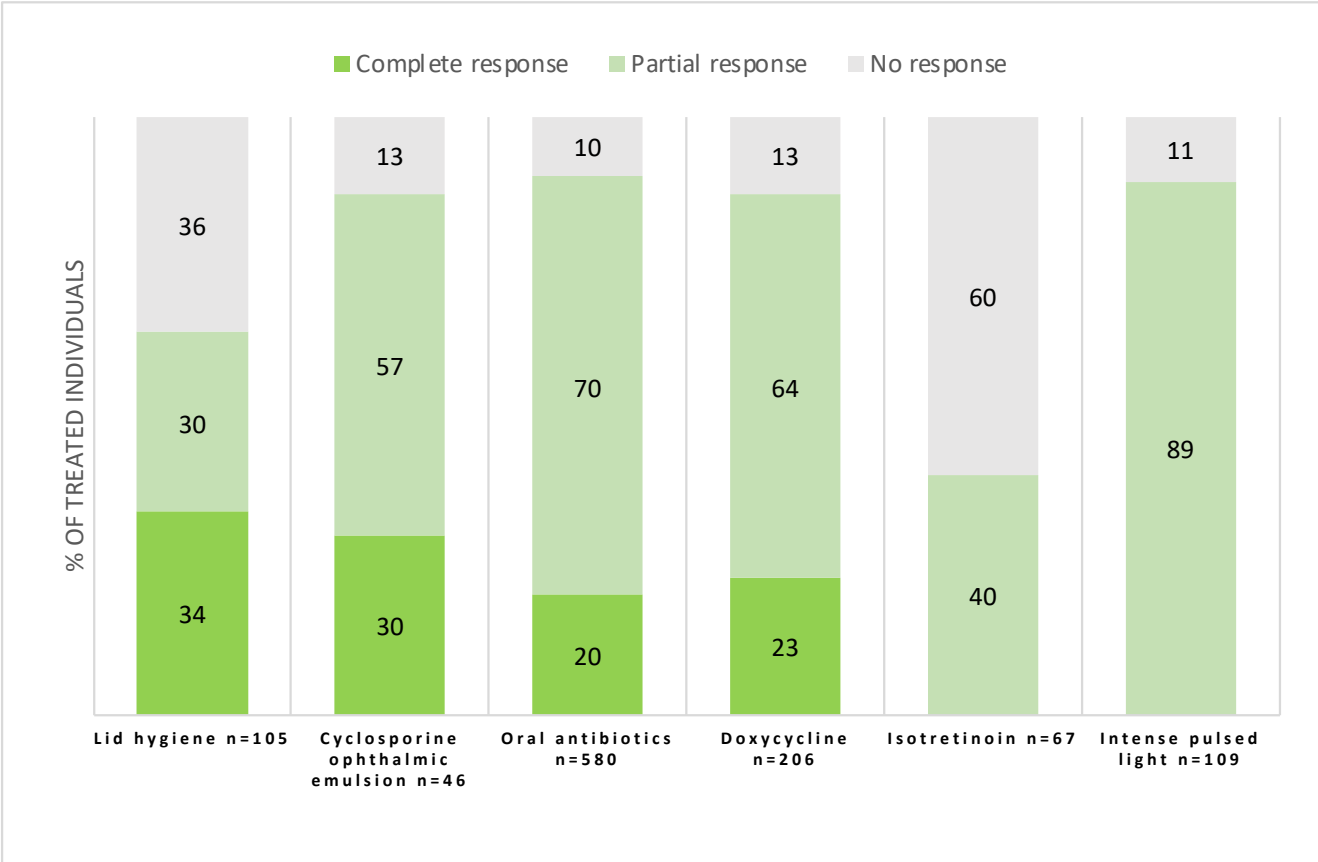


Figure 1. Treatment responses in ocular rosacea by treatment modality.¹⁰

Conclusion

Ocular rosacea presents a significant diagnostic challenge due to its varied clinical manifestations and the absence of specific diagnostic tests. Despite its potential to lead to serious complications, diagnosis and treatment of ocular rosacea are often delayed.⁵

A systematic and stepwise approach to diagnosis, including a thorough history, questionnaire assessments like the OSDI, and careful clinical examination, is crucial for early identification of ocular rosacea. Importantly, ocular symptoms may precede cutaneous manifestations, further complicating diagnosis.

Various treatment modalities have been employed to manage ocular rosacea, ranging from lid hygiene and topical antimicrobials to oral medications like doxycycline and isotretinoin, and therapies such as cyclosporine ophthalmic emulsion and IPL therapy. Lid hygiene and topical antimicrobials have shown promising results, particularly in mild cases, while more severe cases may require oral medications. Topical ivermectin 1% cream and IPL have demonstrated efficacy in many patients with ocular rosacea as both adjunctive and standalone treatments.^{10,27,31}

Overall, early diagnosis and management are essential to prevent complications and improve outcomes in patients with ocular rosacea. As rosacea is a clinical diagnosis, the entire clinical picture must be taken into consideration including family history, dermatologic changes and ocular findings. Further research into diagnostic techniques and treatment modalities is warranted to better understand and address this challenging condition.

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Cutaneous manifestations of IBD: Potential role of vedolizumab

Introduction

Knowledge of the pathophysiology of immune-mediated diseases continues to advance. In the past decade there has been a rapid evolution of immune-targeted therapies that have grown in precision. Overlapping immune abnormalities results in overlapping diseases, co-morbidities, and treatments. Dermatologists, gastroenterologists, rheumatologists, respirologists, allergists, and oncologists now share and co-manage more patients who often have more complex issues. Understanding how our therapies impact these immunologically related and often comorbid conditions is necessary to provide comprehensive care. Frequently, the dermatologist makes therapeutic decisions that have a positive impact on numerous comorbidities without exacerbating other conditions. This is especially prevalent in some parts of the country that have long wait times to receive care and a dearth of specialists. Of interest is the idea that as our therapies become even more precise and disease specific, they may no longer have an overlapping therapeutic effect on common comorbidities. For instance, the evolving landscape of inflammatory bowel disease (IBD) treatments, and the increased use and development of gut-specific therapies introduces the question of whether these treatments will have any impact on the incidence and management of extraintestinal

manifestations (EIMs) of IBD. The intent of this article is to review the more common and important EIMs of IBD and to explore the available evidence on the impact of vedolizumab, which is a gut-specific medication, on these EIMs.

Extra-intestinal Manifestations (EIMs)

IBD, Crohn's Disease (CD), and ulcerative colitis (UC) can have a broad range of associated EIMs which affect various body systems. Most commonly affected are the joints, skin, and eyes. At least 10% of patients with IBD have mucocutaneous EIMs, which are more common in CD where they have been reported in up to 44% of patients.^{1,2} In fact, mucocutaneous manifestations can sometimes be the presenting feature of IBD.³ Risk factors for mucocutaneous manifestations in CD and UC include female gender, younger age at diagnosis, and eye or joint involvement. Additional risks in CD include a family history of IBD and disease that requires immunomodulatory therapy.⁴

The possible mucocutaneous EIMs of IBD are numerous and it is therefore not feasible to discuss every condition in this review; only the more common and significant mucocutaneous EIMs will be addressed. They are best approached by classification according to pathophysiologic origin, including those that are IBD specific, reactive conditions, associated conditions, nutritional deficiencies, and treatment-related

conditions (**Table 1**). I aim to highlight those EIMs that mirror gut disease activity and have the potential to be inadvertently treated with gut-specific molecules used to treat the underlying IBD. In addition, EIMs with activity that has a reduced potential to be managed with more precise gut-specific molecules will be highlighted. Considering that nutritional deficiencies are not directly impacted by these immune therapies, they will not be reviewed in any detail.

lacking, and the condition is most likely underdiagnosed due to its varied morphology.² MCD typically occurs in well-established GI disease. Skin disease that precedes GI disease is seen more commonly in children and manifests with skin and genital lesions. There does not appear to be an association between MCD activity and GI activity. MCD can have numerous morphologies, including erythematous plaques, nodules, and linear ulcerations occurring more often than pustules,

IBD specific lesions	Reactive conditions	Associated conditions	Nutritional deficiencies	Therapy related lesions
Fissures & fistulas (perianal and peri-stomal)	Apthous Ulcers	Finger Clubbing	Acrodermatitis Enteropathica	Alopecia
Metastatic Crohns Disease	Epidermolysis Bullosa Aquisita	Hidradenitis Suppurativa	Glossitis	Drug rash/Drug Hypersensitivity Syndrome
Oral Crohns Disease	Erythema Nodosum	Lichen Planus	Pellagra	Neutrophilic Dermatoses
	Sweet Syndrome	Linear IgA Dermatitis	Phrynoderma	TNF-alpha induced skin changes
	Polyarteritis Nodosa	Palmar Erythema	Scurvy	Toxic Epidermal Necrolysis/Steven's Johnson Syndrome
	Pyoderma Gangrenosum	Psoriasis		
		Vitiligo		

Table 1. Common and important mucocutaneous extraintestinal manifestations ; courtesy of Jennifer Lipson, MD
Abbreviations: IBD, irritable bowel disease; IgA, immunoglobulin A; TNF-alpha, tumour necrosis factor-alpha

IBD-specific mucocutaneous conditions

IBD-specific mucocutaneous conditions affect the skin by the same mechanisms as in the gastrointestinal (GI) tract and share the same pathology, non-caseating granulomas. This category includes metastatic CD, oral CD, and contiguous lesions (perianal ulcers, fissures/ fistulas).²

Metastatic Crohn’s disease (MCD) is an extremely rare entity. Accurate prevalence and incidence data are

papules, or abscess-like lesions. The most commonly affected site is the genitals; this occurs in two-thirds of children and half of adults with MCD. Consequently, MCD is typically classified as genital and non-genital MCD.² Genital MCD may present with genital edema, knife-like fissures, condyloma-like papules, and skin tags which show granulomas on pathology.² Vulvar CD occurs as four primary presentations: ulceration,

vulvar swelling, hypertrophic lesions, and chronic suppuration.⁵ Non-genital MCD most commonly affects the legs, abdomen, trunk, and intertriginous sites, and rarely occurs on the face. Because MCD is a rare manifestation of CD, treatment reflects anecdotal evidence from case reports and case series, and none of the available treatments are reliably efficacious.² Treatments with reported efficacy include intralesional and systemic glucocorticosteroids, oral metronidazole, tumour necrosis factor α (TNF α) inhibitors, azathioprine, methotrexate, cyclosporine, thalidomide, and surgical excision.² A recent case report has shown vedolizumab improved a single patient with MCD.⁶

The granulomatous process of CD extends to the oral cavity (known as oral CD) in 8%–9% of patients. This can present as a cobblestone appearance of the mucosa, deep linear ulcers, indurated mucosal skin tags, gingivitis, or swelling of the face, tongue, or lips. The lips are the most common site of swelling and may develop painful vertical fissures. This disease entity is referred to as granulomatous cheilitis (**Figure 1**).⁷ Oral lesions typically respond to treatment of the underlying disease; however, local treatment with topical or intralesional steroids, topical calcineurin inhibitors, topical anesthetic, acetylsalicylic acid, mouth rinses, topical non-steroidal anti-inflammatory paste, and antiseptic washes to prevent infection can also be used. Other treatments used include hydroxychloroquine, colchicine, dapsone, thalidomide, clofazimine, TNF α alpha inhibitors, ustekinumab, infliximab, and surgery.^{8,9} A case report of a patient with CD and granulomatous cheilitis refractory to three biologics has shown the condition had resolved with vedolizumab administered concurrently with doxycycline and triamcinolone.⁸



Figure 1. Typical granulomatous cheilitis with lip swelling and fissuring

Photo courtesy of DermNetNZ.org

Controversy exists regarding whether perianal fissures and fistulas should be considered to be EIMs. The European Crohn's and Colitis Organization (ECCO) 2016

guidelines do not consider perianal fissures and fistulas to be EIMs when they occur within the GI tract.^{3,10}

Reactive conditions

Reactive conditions are felt to be due to cross antigenicity between skin and the intestinal mucosa and have different pathology from the underlying IBD. The most common mucocutaneous EIMs in the reactive category are erythema nodosum (EN) affecting approximately 7.4% of patients, pyoderma gangrenosum (PG) affecting approximately 2.3% of patients, and aphthous stomatitis.¹⁰

EN is an acute inflammatory process of the subcutaneous fat, also known as panniculitis. It presents with a rapid onset of tender, deep, non-ulcerating red to purple-brown bruise-like nodules that are 1 cm–5 cm in size (**Figure 2**). The most characteristic location of these nodules is the shins,



Figure 2: Red-brown indurated plaques on the lower extremity typical of erythema nodosum

Photo courtesy of ©Massimo Defilippo (Symptomeundbehandlung.com)

however the nodules can occur anywhere on the body. Patients may have associated fever, malaise and arthralgias. EN is the most common cutaneous condition affecting patients with IBD, although it is certainly not exclusive to IBD. EN occurs in up to 10% of patients with UC and in up to 15% of patients with CD.¹ It is typically present in the setting of established IBD; however, it precedes IBD in 15% of patients.¹¹ EN is more common in female patients, patients with arthritis, and in patients positive for human leukocyte

antigen B27 (HLA-B27). In patients with CD, EN is often associated with colonic involvement.¹ EN activity tends to parallel IBD disease activity, often occurring during IBD flares; however, the severity of skin flares does not necessarily mirror IBD flare severity.^{1,3,10} Typically, EN is a self-limiting process or resolves with treatment of the underlying condition. Supportive measures such as leg elevation, non-steroidal anti-inflammatory drugs for pain control, and compression are helpful. Some patients may require systemic corticosteroids, steroid sparing anti-inflammatories such as colchicine, dapsone and potassium iodide, and occasionally immunomodulators such as methotrexate, azathioprine, or TNF α inhibitors. Interestingly, infliximab can treat and on occasion trigger EN, in particular in patients with ankylosing spondylitis.¹¹ EN has been reported to respond to vedolizumab in some reports and not respond in others.¹²

Pyoderma gangrenosum (PG) is a neutrophilic dermatosis that can occur both idiopathically and concomitant with a variety of systemic diseases. IBD is the most commonly associated systemic disease, with a reported incidence of up to 3%.³ PG has greater prevalence in patients with UC, a family history of UC, women, colonic involvement, permanent stoma, ocular involvement, and EN.³ Patients with IBD and PG are more likely to have arthritis and uveitis.¹⁰ PG has variable presentations with five recognized subtypes. The most common subtypes of PG associated with IBD are ulcerative and pustular, followed by peristomal, bullous and vegetative.¹ PG presents as a papule, pustule or nodule which rapidly ulcerates, becoming a severely tender ulcer with a classic inflammatory gunmetal grey border, ragged undermined edges, epithelial stranding, and a purulent covering (**Figure 3**).¹ Owing to its appearance and the intense pain it causes, PG is frequently misdiagnosed and treated as an infection. Diagnostic considerations for PG include pathergy (occurring in an area of trauma) and often initiates as a pustule, which occurs in 30% of patients, although this often remains unnoticed before the pustule ulcerates. PG occurs most commonly on the extensor lower extremities and peristomal, though it can occur anywhere on the body.¹ PG classically heals with “cribriform scarring” which has a honeycomb-like appearance.

Similar to EN, patients with PG may have associated fever, malaise, and arthralgias. Unlike EN, which typically occurs in the setting of well-established IBD, PG can precede, coincide with, or occur following the onset of IBD.³ It does not typically parallel underlying IBD disease activity, with the exception of the pustular variant.

An erosive pustular eruption of the lips and oral mucosa, termed pyostomatitis vegetans, is considered

by many as a mucosal variant of pustular PG. This is thought to be more common in men aged 20–59 years, and typically occurs in the course of well-established IBD.³

PG treatment initially involves the use of anti-inflammatories and/or immunomodulators to treat the inflammation, followed by treatment of the ulcer with appropriate wound care. Initial treatment may include intralesional and potent topical steroids and/or calcineurin inhibitors if the condition is in the early or mild stages. For more severe disease, prednisone and/or cyclosporine, mycophenolate mofetil, or a TNF α inhibitor are frequently used. To date there are more published reports of patients developing PG while on vedolizumab than there are of PG responding to vedolizumab.^{12,13,14} Debridement should not be performed owing to the risk of pathergy. Unfortunately, PG has a recurrence rate of up to 25%.³

Sweet syndrome, otherwise known as acute febrile neutrophilic dermatosis, is a rare neutrophilic



Figure 3. Pyoderma gangrenosum with classic ragged, gunmetal Grey border and epithelial stranding between ulcerations. Photo credit courtesy of: Healthmd.net

dermatosis seen in a variety of inflammatory, drug-induced, or malignant settings. It can occur in the context of IBD, both during an IBD flare and in quiescent disease.¹⁵ It is more common in CD, women in the third to fifth decade of life, and CD with colonic involvement.¹ Sweet syndrome presents with tender edematous purple-red papules, plaques, pustules, and sometimes bullae or “pseudobullae,” with a predilection for the head and hands. Patients often have systemic symptoms including fever, malaise, and arthralgia and,

less commonly, can have inner organ involvement. This is often a self-limiting disorder. Treatment is very similar to that of EN and PG, specifically, topical and systemic anti-inflammatories; this disease is highly responsive to systemic steroid treatment.¹⁵ There are reports of Sweet syndrome occurring in a patient with vedolizumab-treated CD,¹⁶ and improvement in a patient with oral corticosteroid UC treatment with the addition of vedolizumab.¹⁷

Bowel-associated dermatosis-arthritis syndrome (BADAS) is an extremely rare neutrophilic dermatosis which has been reported in patients with IBD or post-gastric bypass surgery. It manifests with fever, arthralgias, myalgias, abdominal pain, and polymorphous skin lesions mimicking PG, EN or hidradenitis suppurativa (HS). It is thought to be secondary to immune complexes which develop due to overgrowth of bacteria in the gut.¹ Treatment includes surgery, antibiotics, and systemic steroids. There are no reports regarding the role of vedolizumab with this condition.

Aphthous ulcers affect approximately 20% of the general population and up to 33% of patients with CD and UC.³ Aphthous stomatitis manifests with recurring, painful, round, and oval ulcers with an erythematous border and cream-colour base. The presence of aphthous stomatitis should trigger suspicion about IBD, especially in children with IBD because it occurs more frequently in this cohort and may precede the diagnosis of IBD.⁷ The oral aphthae correlate with active GI disease and HLA-B27 positivity.¹ A systematic review and meta-analysis identified a trend for lower prevalence of aphthous ulcers in patients treated with infliximab compared to vedolizumab.¹⁸

Cutaneous polyarteritis nodosa (cPAN) is an uncommon, recurring vasculitis of the small and medium vessels of the skin. Approximately 10% of all cPAN cases are associated with IBD and it can precede the diagnosis of IBD. cPAN presents with erythematous nodules, most commonly on the lower extremities. Clinically, it can mimic EN, PG, or metastatic CD. Biopsy is required for diagnosis. Disease activity does not parallel activity of the underlying IBD.³ Interestingly, there have been reports of cutaneous vasculitis occurring in patients with both UC and CD on vedolizumab treatment.^{19,20}

Epidermolysis bullosa acquisita (EBA) is an extremely rare autoimmune bullous disorder caused by autoantibodies against collagen VII. It presents with non-inflammatory bullae in areas of trauma, most commonly the hands and feet. The bullae heal with scarring and milia formation. Thirty percent of patients with EBA have IBD and CD, more often than UC, and the majority of patients having a long-standing history of IBD. The co-occurrence of EBA and IBD is thought

to be due to the phenomenon of epitope spreading.¹ Treatment of the underlying IBD typically results in improvement of the associated skin lesions.¹ There are currently no reports of the effect of vedolizumab on EBA.

Associated conditions

Numerous inflammatory skin conditions are associated with IBD. A recent clinical study demonstrated that rosacea, psoriasis, and atopic dermatitis have a strong association with IBD, while vitiligo and alopecia areata had a lesser or non-existent association.³

Psoriasis

The association between psoriasis and IBD is complex. There is a higher incidence of psoriasis, in particular plaque psoriasis, in 11.2% of patients with CD and 5.7% of patients with UC.¹ In addition, patients with psoriasis are predisposed to IBD. The severity of the psoriasis does not correlate with IBD activity. Additionally, certain therapies used to treat IBD can trigger drug-induced psoriasis. The co-occurrence of these inflammatory conditions and their therapeutic overlap suggest shared genetics and inflammatory pathways. In fact, it has been established that these conditions share genetic characteristics.

Psoriasis can be triggered or exacerbated by a variety of medications, including TNF α inhibitors. Drug-induced psoriasis occurs in 2% of patients treated with TNF α inhibitors and appears to occur most commonly in patients with underlying CD and receiving treatment with infliximab.^{1,21} Considerations for TNF α -induced psoriasis include a greater proportion of patients with palmoplantar pustular involvement, generalized pustular involvement, severe post-auricular involvement, severe scalp disease resulting in alopecia, and more than one morphology (rather than typical plaque psoriasis).²¹ Fortunately, most patients have been reported to resolve (47%) or improve (46%) following cessation of the TNF α inhibitor. However, nearly 50% of patients did not improve after transitioning to a different TNF α inhibitor.²¹ Preliminary reports suggest that the phenomenon can occur with other biologics as well, such as ustekinumab.²² There are also cases of psoriasis induced by vedolizumab.^{23,24}

Oral lichen planus can be associated with IBD. It presents with reticulated, white plaques in the mouth (buccal mucosa, tongue, gingiva) which can ulcerate. In addition, oral lichenoid eruptions have been reported with the TNF α inhibitors sulfasalazine and mesalazine.

Cutaneous lichen planus, which presents with itchy, violaceous flat-topped papules and plaques, has

also been reported secondary to TNFα inhibitors.^{7,25,26} There are no published reports of vedolizumab induced lichen planus to date.

Hidradenitis suppurativa (HS) is a chronic, inflammatory disease manifesting with open comedones, cysts, nodules, scarring, and fistulous tracts. It occurs predominantly in skin folds. This disease is seen with a 9-fold greater prevalence in patients with IBD, particularly CD. In patients with HS, the CD is often localized to the large bowel. It precedes the HS, which is often located in the perineal or perianal sites.²⁷ HS activity does not typically mirror luminal activity. Vedolizumab-induced HS has been reported.²⁸

Interestingly, the rare syndromes **SAPHO** (synovitis, acne, pustulosis, hyperostosis, osteitis) and **PAPA** (pyogenic arthritis, PG, acne) can be associated

with IBD. SAPHO most commonly affects young patients with UC.¹

Linear IgA bullous dermatosis (LABD) is a rare blistering condition of the skin and mucous membranes which occurs in both children and adults. It is characterized by severe pruritus, with the tense vesicles and bullae appearing in an annular “crown of jewels” arrangement. It has been reported with both CD and UC. In a clinical study, linear IgA in association with UC was reported to remit with colectomy.²⁹ This disease typically responds well to systemic steroids and the sulfone dapsone. There are no published reports of vedolizumab induced LABD to date.

Additional associated conditions such as vitiligo, finger clubbing, and palmar erythema occur to a lesser degree and have less impact on patients’ overall health.

	More common in CD vs. UC	More common in female(F) vs. male(M)	Typically parallels course IBD	Associations	Typically responds to treatment of underlying disease
Erythema	CD > UC	F > M	Yes	Arthritis and uveitis	Yes
Pyoderma Gangrenosum	UC > CD (similar)	M > F	Not necessarily	Increased risk uveitis and arthritis	No
Sweets Syndrome	CD > UC	F > M	Not necessarily	Fever, arthralgias, Other EIMs	Yes
Aphthous stomatitis	CD > UC	M > F Children>adult	Yes	HLA B27+	Sometimes
EBA	CD > UC		-		Yes
PAN	CD > UC		No		No
PsO	CD > UC		No		No

Table 3. Characteristics of common, major reactive and associated mucocutaneous extraintestinal manifestations of inflammatory bowel disease; courtesy of Jennifer Lipson, MD
Abbreviations: CD, Crohn’s disease; EIMs, extraintestinal manifestations; HLA B27, human leukocyte antigen B27; IBD, inflammatory bowel disease; UC, ulcerative colitis

The characteristics of various reactive and associated EIMs of IBD are described in (Table 3).

Treatments and treatment-related conditions

Fortunately, treatments for IBD, immune-mediated associated diseases, and dermatologic EIMs frequently overlap, allowing for these diseases to be treated with the same medication. For example, medications include systemic immunosuppressants (prednisone, methotrexate, cyclosporine, azathioprine, sulfasalazine) and immunomodulators (TNF α inhibitors, interleukin 12/23 [IL12/23] inhibitor, IL23 inhibitors, Janus kinase inhibitors). Further research is needed to establish whether the early introduction of advanced therapies, such as biologics and small molecules, to patients with IBD may prevent EIMs, and which treatments are optimal for co-managing IBD and EIMs.

Many of these therapies also have many possible cutaneous side effects. TNF α inhibitors are commonly used to treat IBD and many of the associated immune conditions (psoriasis, psoriatic arthritis, spondyloarthropathies, HS). They have also been reported to cause a variety of skin eruptions including, but not limited to, drug-induced lupus, sarcoidosis, eczema, alopecia areata, pityriasis lichenoides et varioliformis acuta (PLEVA), and vasculitis.²⁶ Sulfasalazine and azathioprine have both been reported to cause morbilliform eruptions and Sweet syndrome, as well as potentially fatal drug hypersensitivity syndrome,³⁰ Stevens-Johnson syndrome, and toxic epidermal necrolysis.³¹⁻³³ Azathioprine has also been reported to cause azathioprine hypersensitivity syndrome, alopecia, Kaposi sarcoma, and non-melanoma skin cancer. Mesalamine is reported to cause photosensitivity in rare cases, alopecia, and pruritus.³⁴

Vedolizumab, a gut-specific monoclonal antibody that targets $\alpha 4\beta 7$ -integrin, was approved by Health Canada in 2016 for the treatment of CD and UC. The mechanism of action is through selective inhibition of leukocyte $\alpha 4\beta 7$ -integrin binding to its main ligand, mucosal addressin adhesion molecule-1, an adhesion molecule specifically expressed on blood vessels of the GI tract and is upregulated in inflamed venules.¹⁸ This interaction inhibits leukocyte adhesion and migration into the gut, counteracting the lymphocyte trafficking seen in IBD.³⁵ Vedolizumab has proven efficacy in CD and UC, as well as having a favourable side effect profile. This is currently the only IBD therapy that selectively targets the digestive tract, though more therapeutics are in development. Studying the possibility of gut-specific vedolizumab resulting in an increase in EIMs is challenging. For instance, it is confounded by a significant number of patients transitioning from TNF α inhibitors—which are known

to treat numerous EIMS—in order to initiate the gut-specific agent.³⁶ The effectiveness of vedolizumab in treating the EIMS of IBD is slowly emerging; however, the clinical data have shown inconsistent results. In 2018, a retrospective comparison study reported a lower incidence of EIMs, including EN and aphthous stomatitis, in patients treated with TNF α inhibitors versus vedolizumab.³⁷ A systemic review that looked at the effect of vedolizumab treatment on EIMs concluded that there is no strong evidence that vedolizumab effectively treats the cutaneous EIMs of IBD, although it may decrease the occurrence of new EIMs.³⁸ A small prospective study demonstrated the successful resolution of EN and arthritis EIMs in patients with IBD.¹² The efficacy of vedolizumab on EIMs may be due to its enhanced control of gut disease considering that the activity of certain EIMs (including arthritis and EN) parallels gut activity.¹¹ In a published case report of vedolizumab-induced psoriasis, the condition was shown to resolve with the cessation of the drug.²³ The expectation is that future clinical studies and real world evidence will better clarify the relationship between gut-targeted IBD treatment such as vedolizumab and EIMs.

Conclusion

Mucocutaneous EIMs are common and are important to recognize because they not only cause

Key clinical pearls

Mucocutaneous EIMs are common

Mucocutaneous EIMs may precede the diagnosis of GI disease

Not all EIMs parallel underlying GI disease activity

A growing number of therapies are available which treat IBD and numerous mucocutaneous EIMs

Currently, the impact of vedolizumab on mucocutaneous EIMs is unclear

significant patient morbidity, but may also be the first presentation of IBD, or may indicate ongoing disease activity in the absence of symptoms. With published reports of both improvement and induction of mucocutaneous EIMs with vedolizumab therapy, the final verdict is yet to be delivered regarding the impact of this gut-targeted therapy on these EIMs. With more gut-targeted therapies in development, a deeper understanding of the relationship between this class of drugs and EIMs will be crucial. Moreover, publishing and

presenting cases on vedolizumab therapy and EIMs will help bring clarity to this issue. A key take away is that a collaborative relationship between dermatologists and gastroenterologists remains vital in providing comprehensive care to patients with IBD.

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A literature review of COVID 19 vaccination and Lichen Planus Pigmentosus: is there a correlation?

Introduction:

The global response to the COVID-19 pandemic involved rapidly developing and distributing various vaccines to curb the spread of the SARS-CoV-2 virus. While these vaccines are effective in preventing severe illness and hospitalization due to COVID-19, they have also prompted rigorous monitoring for potential side effects and adverse events. Among the vast array of reported post-vaccination side effects, the emergence or worsening of dermatological conditions has attracted significant attention from both clinicians and researchers.

One dermatological condition linked to COVID-19 vaccinations is lichen planus pigmentosus (LPP).¹ LPP is a rare dermatosis characterized by the development of hyperpigmented macules or patches on the skin.² The exact etiology of LPP remains uncertain; however, one theory is that LPP is an autoimmune disease in which CD4+ and CD8+ lymphocytes are activated to attack the basal keratinocytes.³ Many factors could trigger lymphocytes. These factors include, but are not limited to, infection and/or vaccines.³ A potential association between COVID-19 vaccinations and LPP has recently

emerged as a subject of clinical interest and scientific inquiry.

This review aims to provide an overview of current knowledge regarding the possible relationship between COVID-19 vaccinations and LPP by delving into available data from the literature, in the form of existing case reports, clinical observations, and scientific hypotheses.

Search strategy:

Keywords for literature review: The following terms were used for the search: "Covid-19," "SARS-CoV-2," "Lichen Planus Pigmentosus," "Dermatological Manifestations," "Viral Infections," "Lichen Planus Pigmentosus Etiology"

Relevant databases: Publications were searched for relevant papers employing PubMed, Google Scholar, and Web of Science databases.

Inclusion and exclusion criteria: The beginning of the time period searched was the COVID-19 outbreak date of November 17, 2019. The end point was February 2023.

Findings:

According to our search criteria, there have been 43 reports of lichen planus following various COVID-19 vaccinations; of these, only four of the reported cases were of COVID-19 vaccine-associated LPP.^{1,3-5}

The first case involved a 64-year-old female with a case of LPP-inversus, who reported symptoms of LPP after receiving her first dose of the Oxford-AstraZeneca COVID-19 vaccine. She reported worsening symptoms after the second dose of the same vaccine. The patient had no prior medical history that would explain the onset of LPP. After diagnosis, the patient received

treatment with topical betamethasone 0.05% ointment. After two months of treatment, a slight improvement in her symptoms was observed, which was a reduction in pigmentation.⁴

The second case of LPP involved a 43-year-old male with multiple lesions on his face. A punch biopsy of his chin lesions showed that he had developed LPP after his second dose of the Oxford-AstraZeneca COVID-19 vaccine. The patient had no prior medical history that would explain the onset of LPP. The patient was treated with topical corticosteroid mometasone cream and a slight improvement in his symptoms was observed.⁵

Medication	Description
Prednisone	An oral corticosteroid prescribed to decrease inflammation by suppressing polymorphonuclear neutrophils. ⁶
Topical Betamethasone	A topical corticosteroid prescribed to decrease inflammation by suppressing polymorphonuclear leukocytes. ⁶
Topical Triamcinolone	A corticosteroid taken topically, orally, or intramuscularly. Local injections at lesion sites have been effective. ⁶
Topical Halobetasol	A topical corticosteroid used to decrease inflammation and improve hyperpigmentation. ⁶
Topical Clobetasol Propionate	A similar topical corticosteroid used to decrease inflammation and improve hyperpigmentation. ⁶
Topical Mometasone	A similar topical corticosteroid used to decrease inflammation and improve hyperpigmentation. ⁶
Topical Tacrolimus	A calcineurin inhibitor that works to inhibit the calcium-dependent reactions involved in the T-cell immune response to reduce LPP symptoms. ⁷
Topical Pimecrolimus	A similar calcineurin inhibitor that works to inhibit the calcium-dependent reactions involved in the T-cell immune response to reduce LPP symptoms. ⁷
Topical Cyclosporine	A topical immunosuppressant that can be effective at reducing genital LPP lesions and improving hypertrophic lesions. ⁸
Isotretinoin	An oral retinoid-like agent that can work to stop sebaceous gland differentiation and abnormal keratinization to help treat LPP. ⁹
Oral JAK Inhibitors	Off-label indication, small molecule inhibitor that inhibits the JAK-STAT pathway.

Table 1. Medications used to treat lichen planus pigmentosus ; courtesy of Marisa Ponzo, MD
Abbreviations LPP, lichen planus pigmentosus; JAK, Janus kinase; JAK-STAT, Janus kinase-signal transducer and activator of transcription

The third case involved a 52-year-old male with LPP-inversus with nail involvement (an uncommon subtype of LPP) after receiving a third dose of the Oxford-AstraZeneca COVID-19 vaccine. The patient presented with skin lesions on the axilla, right antecubital fossa, left popliteal fossa, right inguinal region, and on various fingernails. The patient had no prior medical history that would explain the onset of LPP. The recommended treatment for this patient was topical clobetasol propionate 0.05% ointment paired with injections of triamcinolone acetonide into the matrix of the nail.³

The final case involved a 50-year-old male patient diagnosed with LPP after a second dose of the Oxford-AstraZeneca COVID-19 vaccine. The patient had no prior medical history that would explain the onset of LPP. The patient received treatment with topical betamethasone 0.05% ointment, which resulted in a slight improvement that was noted at a 2-month check-in appointment.¹

Management of LPP:

Treatment for LPP is challenging and it is important to point out that no single treatment has been proven effective. However, various medications can manage the complications of LPP. For example, LPP often occurs in sun-exposed areas; thus, it is essential to use sun protection in conjunction with other treatments. Listed below in **Table 1** presents a few medications used to treat LPP. Post-inflammatory hyperpigmentation, especially in those with richly pigmented skin, can be particularly distressing to the patient as it presents its own unique treatment challenges, which are further reviewed elsewhere.

Analysis and conclusion:

The pathogenesis of lichen planus and thus LPP is thought to involve upregulation of the T helper 1 pathway. As such, cytokines including interleukin-2 (IL-2), tumour necrosis factor- α (TNF- α), and interferon- γ (IFN- γ) are involved in the development and progression of lichen planus.³ Furthermore, reports suggest that the COVID-19 vaccine increases the levels of cytokines such as IL-2, TNF- α , and IFN- γ in humans.³ Given the currently proposed pathogenesis including the fact that LPP is mediated by CD4+ and CD8+ lymphocytes, and their significant role in cytokine production, it is plausible to consider that LPP could result from a COVID-19 vaccination.⁴ However, it is important to be mindful that these are novel studies of the development of LPP following COVID-19 vaccination. Thus, more robust research is needed to identify a correlation between LPP and COVID-19 vaccination. The expert opinion among dermatologists in Canada is that there is an increased

prevalence of LPP following the pandemic. However, concrete data to support this expert opinion are lacking. Moreover, while LPP is a rare condition, it has been reported to occur more commonly in individuals with richly pigmented skin, particularly those of Skin Type III and higher.² Post-inflammatory hyperpigmentation can be quite distressing to these patients; therefore, early recognition of the disease and treatment to prevent this complication is of paramount importance. In sharp contrast to its prevalence within the person of colour population, there has been a notable scarcity of research on this condition in these individuals. We must intensify our research efforts on this disease.

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