

ISSN 2563-7681

**VOL 3
ISSUE 1
2022**

CANADIAN DERMATOLOGY TODAY

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EDITORS WELCOME

Dear Canadian Dermatology Community,

Welcome to our first issue of *Canadian Dermatology Today* in 2022! It is hard to believe how quickly the third year of this journal has arrived at our doorstep! We are tremendously proud of the content and incredibly grateful to all the authors who have contributed to this journal. Of course, we also want to thank all the advertising partners for their continued support as well.

As the journal continues to grow (now with close to 700 regular readers), we always welcome new ideas, new topics and new submissions which can be sent directly to info@catalytichealth.com. Our aim remains the same: to provide practical and pragmatic real-world content that helps to inform disease management for Canadian clinicians.

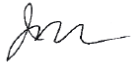
In this issue we discuss bullous pemphigoid, IL-17 inhibitors and their risk of malignancy, an overview of JAK inhibitors and the pathogenesis, diagnosis and treatment of post-inflammatory hyperpigmentation. We also provide an overview of rosacea and discuss the role of diluted and hyperdiluted calcium hydroxyapatite for skin tightening.

We hope you enjoy these articles and topics. Please encourage your peers to register at canadiandermatologytoday.com so that they can receive future issues!

Best wishes,



Kim Papp, MD



Jensen Yeung, MD



Melinda Gooderham, MD



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BULLOUS PEMPHIGOID: CURRENT AND EMERGING THERAPIES

Bullous pemphigoid (BP) is the most common autoimmune blistering condition. It preferentially affects the elderly population between the ages of 60 to 80. Younger populations can be afflicted such as in cases involving drug-induced bullous pemphigoid and, rarely, in childhood bullous pemphigoid. The incidence of BP has been rising recently, partly due to increased overall life expectancy.

The pathophysiology of BP involves IgG circulating autoantibodies targeting components of the hemidesmosomes at the basement membrane zone involving BP230 (BPAG1) and BP180 (BPAG2, type XVII collagen). Clinically, BP is characterized by generalized pruritus followed by tense vesiculobullae that commonly present on erythematous or urticarial base (**Figure 1**). The non-bullous phase of BP presents as eczematous patches and urticarial wheals. Vesicles and bullae may appear hemorrhagic or serous. Oral mucosal involvement is seen in 10-30% of patients.



Figure 1: Patient with bullous pemphigoid with tense bullae on an urticarial base and serous and hemorrhagic crusting; photos courtesy of Bahar Bahrani, MD

The objective of treatment in BP is to halt disease development, heal existing blisters and to reduce pruritus. Rapid and effective treatment is critical in cases of widespread disease involvement. Management of BP should be personalized for each patient depending on the severity of the disease as well as the patient's age, comorbidities and preferences. Elderly patients are more likely to have multiple co-existing medical conditions where polypharmacy may be a concern. Careful consideration should be given to drug interactions and medication side effects when treating this population to avoid unnecessary harm.

The management of BP is usually classified into mild/localized and severe/extensive disease based on development of new blisters per day but can also be based on body surface area involvement. Disease severity can be further classified based on the subjective Bullous Pemphigoid Disease Area Index (BPDAI) and objective Bullous Pemphigoid Disease Area Index.¹ A ladder approach to treatment depending on severity is recommended (**Figure 2**), however treatment recommendations vary widely amongst various consensus guidelines (**Table 1**). Despite various therapeutic options available for the treatment of BP, there is a lack of large randomized clinical trials to support strong evidence of these treatments (**Figure 3**). This is likely due to the low prevalence of the disease and underpowered studies. Outlined below are the current and emerging therapeutic options for BP as well the level of evidence to support their use in BP.

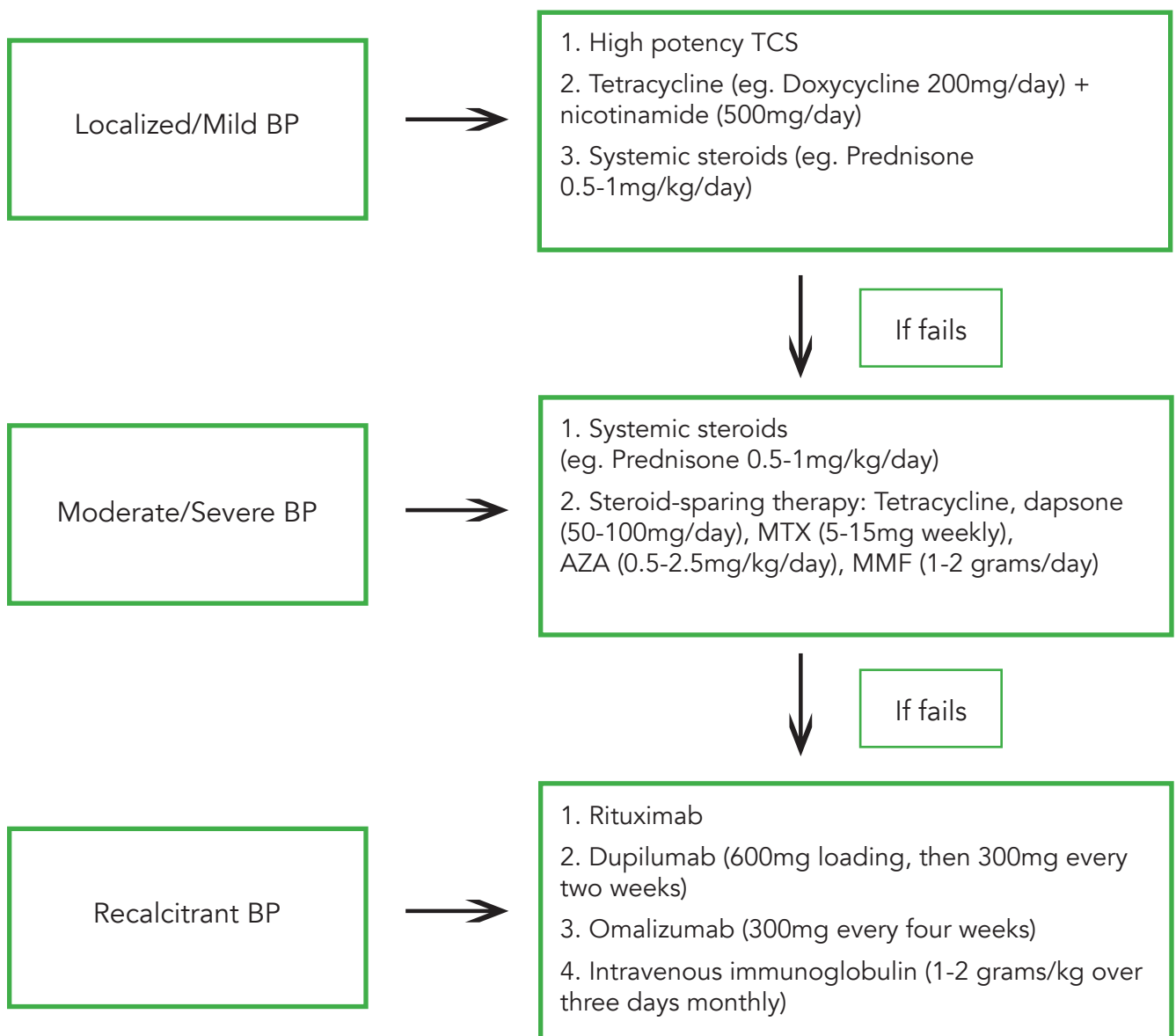


Figure 2. Algorithm for treatment of bullous pemphigoid; adapted from Pratasava et al.²

	First Line	Second Line	Adjuvants	Refractory
Association of the Scientific Medical Societies in Germany	Mild: TCS Moderate: TCS + Systemic steroids Severe: TCS + systemic steroids +/- listed adjuvants; monotherapy with doxycycline +/- nicotinamide, dapsone, MTX	Same agents listed in adjuvants and refractory	AZA, dapsone, MMF, MTX, doxycycline +/- nicotinamide	IVIG, immunoadsorption, plasma exchange, rituximab, cyclophosphamide, anti-IgE monoclonal antibody
Brazilian Society of Dermatology	Localized: TCS Extensive: Systemic steroids + TCS	Extensive: Same agents listed in adjuvants Mucosal: Dapsone	Oxytetracycline, doxycycline +/- nicotinamide, AZA, MMF, MTX, dapsone, chlorambucil	Rituximab, anti-IgE monoclonal antibody, IVIG, plasma exchange, cyclophosphamide
British Association of Dermatologists	Mild: TCS, systemic steroids +/- TCS, anti-inflammatory antibiotics +/- nicotinamide Moderate-Severe: Systemic steroids + TCS, TCS, anti-inflammatory antibiotics +/- nicotinamide	Switch or addition of adjuvants	Systemic steroids +/- TCS, anti-inflammatory antibiotics +/- nicotinamide, AZA, MTX, dapsone, chlorambucil, MMF	IVIG, cyclophosphamide, plasma exchange
Cutaneous Immunology Group of the Italian Society of Medical Dermatology	Mild: TCS Generalized: Systemic steroids +/- TCS	Mild: Systemic steroids +/- tetracycline + nicotinamide, dapsone Generalized: Combine or introduce adjuvants	AZA, MMF, tetracycline + nicotinamide, MTX, chlorambucil	IVIG, immunoadsorption, rituximab, anti-IgE monoclonal antibody, cyclophosphamide, plasma exchange
European Dermatology Forum & European Academy of Dermatology and Venereology	Mild: TCS Generalized: Systemic steroids +/- TCS	Mild: Systemic steroids, but can consider tetracycline + nicotinamide Generalized: Combine or introduce adjuvants	AZA, MMF, tetracycline + nicotinamide, MTX, chlorambucil	Rituximab, anti-IgE monoclonal antibody, IVIG, immunoadsorption, cyclophosphamide, plasma exchange
French Society of Dermatology	Any severity: TCS	Localized: MTX Mild: MTX +/- tetracycline Extensive: Systemic steroids +/- AZA, or MMF, MTX	AZA, MMF, MTX, tetracycline	Same as adjuvants
Japanese Dermatological Association	Mild: TCS + adjuvants Moderate/severe: Systemic steroids + TCS +/- tetracycline/ minocycline + nicotinamide, dapsone	Mild: Manage as severe Moderate/severe: Combine with adjuvants	Mild: TCS/ minocycline + nicotinamide, systemic steroids Moderate/severe: AZA, CsA, mizoribine, cyclophosphamide, dapsone, MMF, MTX, pulse IV steroids, IVIG	Cyclophosphamide IV pulse, plasma exchange, rituximab

Table 1: Guideline treatment recommendations for bullous pemphigoid; adapted from Patel et al. ²

AZA azathioprine, CsA cyclosporine, IVIG intravenous immunoglobulin, MMF mycophenolate mofetil, MTX methotrexate, TCS topical corticosteroid

Topical Steroids

In mild disease, first-line treatment is clobetasol propionate ointment or cream.⁵ A landmark French study compared the use of topical steroids (clobetasol propionate 40 g/day) versus oral prednisone (0.5 mg per kilogram of body weight per day for those with moderate disease and 1 mg per kilogram per day for those with extensive disease).⁶ Researchers found that topical steroids were associated with improved overall survival at 1 year (76% vs 58%, respectively), and had fewer severe complications (29% vs. 54%, respectively) in patients with extensive disease. In the cohort of patients with moderate bullous pemphigoid, there were no significant differences between the topical-corticosteroid group and the oral-prednisone group in terms of overall survival, the rate of control at three weeks, or the incidence of severe complications. Another study compared clobetasol propionate cream 20g b.i.d. (standard regimen) to 10-30 g/day (mild regimen) depending on severity.⁷ The mean cumulative dose of steroid cream was 70% less in the mild regimen group, while the time to regression as well as relapse rate in both groups were the same. The standard regimen group had higher numbers of reported side effects of diabetes, cardiovascular disorders, severe infections, cutaneous atrophy, striae and purpura. There are some practical limitations to the use of topical steroids, as elderly patients likely require assistance to apply topicals on large body surface areas.

Topical Tacrolimus

Topical immunomodulators have been reported to be effective in localized and mild generalized BP; however data is limited to case reports. Three to five grams of tacrolimus 0.1% daily can help in reduction of oral steroids and improvement in disease as early

as 2 weeks.⁸ Side effects include burning and local irritation and cost may also limit the use of this topical agent. Nonetheless, it can be used as an alternative in localized disease with the advantage of not causing steroid atrophy.

Systemic Steroids

Systemic steroids are considered the mainstay treatment for severe generalized disease. Prednisone at a dose of 0.5-1 mg/kg/day should be initiated for severe systemic disease, with a dose of 0.5 mg/kg usually sufficient for mild disease.³ Greater than 1mg/kg/day of systemic steroids is rarely required. A randomized multicentre study compared prednisone dosed at 0.75 mg/kg/day versus 1.25 mg/kg/day and found that the outcomes in these groups were not statistically significant.⁹ Intravenous systemic steroids do not confer any benefit over oral systemic steroids.¹⁰

Tetracycline and Nicotinamide

The mechanism by which tetracycline works in bullous pemphigoid is via the inhibition of chemotaxis of neutrophils and eosinophils. Nicotinamide decreases the inflammatory pathway by inhibiting phosphodiesterase, inhibition of histamine release and inhibition of chemotaxis. A randomized prospective study evaluating the efficacy of doxycycline vs prednisolone as initial therapy showed that doxycycline was non-inferior to prednisolone in disease control.¹² Patients who received doxycycline also had fewer severe adverse events. These results may suggest that tetracycline is more appropriate in patients with comorbidities and in those who have contraindications to systemic steroids. A retrospective study compared tetracycline and nicotinamide combined with clobetasol cream vs prednisone 0.5 mg/kg, with the former

Mild and/or localized disease
Super potent topical corticosteroids
Oral corticosteroids
Minocycline, doxycycline or tetracycline +/- nicotinamide
Topical immunomodulators
Dapsone and sulfonamides
Erythromycin
Penicillin
Extensive/persistent disease
Super potent topical corticosteroids
Oral corticosteroids
Azathioprine
Mycophenolate mofetil
Methotrexate
Intravenous immunoglobulin
Rituximab
Omalizumab
Dupilumab
Plasma exchange
Immunoadsorption
Cyclophosphamide
Chlorambucil
Legend
Prospective Controlled Trial
Retrospective study or large case series
Small case series/individual case reports

Figure 3. Therapies for mild and extensive bullous pemphigoid with corresponding levels of evidence⁴

having higher efficacy and better survival rates.¹³ A meta-analysis showed that tetracycline plus nicotinamide had better outcomes than either tetracycline alone or systemic steroids.¹⁴ It is important to note that doxycycline is renally cleared and that in patients with renal impairment, minocycline should be used as an alternative.

Azathioprine

Azathioprine is a commonly-used steroid-sparing agent in BP, and is administered as an adjuvant treatment in doses up to 2.5 mg/kg/day. Despite this, the evidence to support the use of azathioprine is limited and conflicting. One small RCT showed that the use of azathioprine resulted in a 45% reduction in cumulative prednisolone dose over a 3-year period, and supported its use in the management of BP.¹⁵ Another study revealed that prednisolone compared with prednisolone plus azathioprine was not associated with a difference in remission rates.¹⁶ In this same study there was also an increased number of adverse events in the azathioprine group, which may have been the result of no azathioprine dose adjustments based on thiopurine methyl transferase (TPMT) levels. It is also important to note that a normal TPMT does not exclude the possibility of myelotoxicity, and regular monitoring of blood counts is critical.

Methotrexate

There are no controlled trials studying the use of methotrexate in BP. Several case series have revealed that low-dose methotrexate either alone or in combination with topical or systemic steroids may work in controlling BP.¹⁷⁻²⁰ Doses of methotrexate ranging from 5-15 mg/wk have been reported to be effective.¹¹ Methotrexate is excreted renally, which should be taken into consideration especially in elderly patients in whom renal impairment or dysfunction is a concern. This may explain why low doses of methotrexate are often

sufficient in BP patients. Folic acid at a dose of 5 mg on non-methotrexate treatment days is recommended to reduce adverse effects, however this has not been adequately studied.

Mycophenolate mofetil

Mycophenolate mofetil is a prodrug of mycophenolic acid and is an inhibitor of the purine synthesis pathway in T and B cells. Several studies have shown that mycophenolate mofetil is effective, either alone or in combination with steroids, for the treatment of BP.²¹⁻²³ A study comparing mycophenolate mofetil dosed at 1g b.i.d. and azathioprine dosed at 2 mg/kg daily showed that both drugs had 100% remission when combined with systemic steroids.²⁴ A similar number of relapses and adverse events were seen amongst both groups, however, the average time to complete remission was shorter in the azathioprine group.

Dapsone

Dapsone is an antimicrobial belonging to the sulfonamide class of antibiotics with anti-inflammatory properties. Doses of 50-200 mg daily are commonly administered in BP. The time to response in patients receiving dapsone is slower compared to patients taking steroids. Three retrospective case series involving the use of dapsone demonstrated that the response rate was around 45%.²⁵⁻²⁷ There is no strong correlation between the density of neutrophilic infiltration on pathology and response to dapsone.²⁵ Dapsone must be used with caution in elderly patients and should be utilized if other treatments are contraindicated or ineffective in this population. Dapsone should be started at 50 mg daily and be increased by 50 mg every 2 weeks to a maximum of 150-200 mg daily. Frequent blood work monitoring is required in the first few months of treatment.

Rituximab

Rituximab is a monoclonal antibody targeting CD20+ mature B cells, which causes B-cell depletion and

a reduction in antibody production. Recently, rituximab has been used for the treatment of refractory BP. The dose of rituximab for BP has not been established, however most clinical diseases use the non-Hodgkin lymphoma or rheumatoid arthritis dosing, which is an intravenous infusion of 375 mg/m²/week for four weeks or 1000 mg/week for two consecutive weeks, respectively. Rituximab may achieve only temporary remission of BP, and as such a maintenance treatment may be required. Improvement of BP is usually seen after 4 weeks of treatment with rituximab and complete remission of BP has been estimated at 65-70% in recent studies.²⁸

Dupilumab

Dupilumab is a fully human monoclonal antibody that inhibits IL-4 α subunit that is shared by IL-4 and IL-13 receptors. The pathogenesis of BP involves circulating IgG autoantibodies to BP180 and BP230, but IgE autoantibodies have also been identified which contribute to the Th2 regulation. Th2 cells that produce IL-4 and IL-13 are increased in BP patients. Given this mechanism, dupilumab has been considered as a possible treatment in BP.²⁹ A small case series reviewed the use of dupilumab in 13 elderly patients with BP recalcitrant to traditional immunosuppressants. Results demonstrated that 12/13 (92%) had disease clearance or a satisfactory response, 7/13 (54%) obtained clearance defined as no bullae or pruritus, and 5/13 (38%) obtained clearance with the addition of an immunosuppressive.³⁰ A large portion of the patients that developed clearance received dupilumab more often than every two weeks.

Omalizumab

Omalizumab is a humanized monoclonal antibody that binds free serum immunoglobulin E (IgE) and prevents it from binding to the receptor on mast cells and basophils. It works in BP by

preventing the interaction of IgE with FcεRI receptors on mast cells and other effector cells to reduce the release of inflammatory mediators. Omalizumab has been used in refractory cases of BP. The dose of omalizumab is based on its use in chronic urticaria and asthma, and most patients benefit from subcutaneous injection of 300 mg every 4 weeks. The use of omalizumab in BP, has led to a reduction in itching, blister formation and eosinophil levels as early as a few weeks within initiation of treatment. Peripheral eosinophil levels have been linked to a positive response with omalizumab.³¹

IVIG

Clinical response to the use of IVIG in BP is often rapid but short-lasting, thus requiring repeat infusions or the addition of an adjunctive therapy. The treatment regimen for BP is typically 2 g/kg administered in equally-divided doses over 3 days. Treatment is repeated every 4 weeks until remission is achieved, after which interval cycles are increased gradually. In a small retrospective study involving 15 patients, IVIG was administered to patients with steroid-dependence and treatment-related side effects.³² The use of IVIG allowed for the tapering of prednisone in all patients within 1-5 months, and remission was maintained for 17-27 months thereafter. The mean number of cycles of IVIG used in this retrospective study was fifteen. IVIG can be effective for the treatment of BP, however due to cost barriers it should be reserved for refractory patients, cases requiring rapid control, and when contraindications to other treatments are present.

Other

Other treatment options for BP include cyclophosphamide, chlorambucil, plasma exchange and apheresis. Due to their severe toxic side effect profiles, cyclophosphamide and chlorambucil should only be used in extremely recalcitrant cases which are refractory to conventional immunosuppressants. The role of plasma exchange in the management of BP is not known, as results have been mixed with one randomized controlled trial (RCT) documenting a steroid-sparing effect whereas another RCT not showing a benefit.^{33, 16} Cyclosporine has no good evidence supporting its use in BP and is not recommended as routine treatment.¹⁰

Emerging Treatment Options

The current mainstay treatment for BP includes the use of steroids and traditional immunosuppressive therapies. To date there have been no approved biologics for BP, however increased understanding of the pathophysiology of the disease gives rise to various biomarker targets for potential treatment. There are several emerging therapies that are currently undergoing clinical trials (**Table 2**).

Biologic	Target	Mechanism	Clinical Trial Studies In progress
Omalizumab	Antibodies	Humanized monoclonal antibody that targets free IgE preventing binding on mast cells and basophils	Phase 3
Dupilumab	Th2 Axis	Monoclonal antibody that inhibits IL-4α subunit that is shared by IL-4 and IL-13 receptors	Phase 3
Sutimlimab	Complements	Humanized IgG ₄ monoclonal antibody inhibits the C1s complements in the classical complement pathway	Phase 1
Avdoralimab	Complements	Antibody against C5aR1, which inhibits BP180 IgG-induced pathogenicity	Phase 2
Bertilimumab	Eosinophils	Human monoclonal antibody targeting eotaxin-1 (CCL-11) which is involved in the recruitment of eosinophils from peripheral circulation to skin	Phase 2
Benralizumab	Eosinophils	Humanized IgG1 κ monoclonal antibody against IL-5Rα subunit which blocks downstream of IL-5 leading to decrease eosinophils and basophils	Phase 3
Ustekinumab	Th17 Axis	Humanized monoclonal antibody targeting p40 shared subunit of IL-12 and IL-23	Phase 2
Tildrakizumab	Th17 Axis	Humanized monoclonal antibody targeting p19 subunit of IL-23	Phase 1

Table 2: New emerging biologic therapies undergoing clinical trials for the treatment of BP³⁴

Practical Management

In mild BP disease, first line therapy should remain potent topical steroids. In severe or generalized cases, systemic steroids with the addition of an adjuvant therapy should be considered. Choice of adjuvant therapy should be based on the severity of the disease, underlying medical comorbidities and patient preference. In severe cases, adjuvant therapy should be started with or shortly after systemic steroids to allow for the slow onset of action of this therapy, followed by the gradual tapering of steroids once clinical response has been maintained. First line adjuvant therapy can be initiated with anti-inflammatory antibiotics from the tetracycline family with or without niacinamide. In patients who fail this regimen, low dose methotrexate can be used. Subsequent therapeutic regimens may include the use of mycophenolate mofetil or azathioprine. Careful consideration should be made with respect to methotrexate and doxycycline in renally impaired patients. It should be noted that mycophenolate mofetil causes increased infections, whereas azathioprine is more likely to cause hepatotoxicity. Treatments for refractory cases may include rituximab and IVIG, although cost may be a barrier to access.

Conclusion

Potent topical steroids should be the mainstay of treatment in localized disease, and oral steroids must be used cautiously in elderly patients with BP. Adjuvant therapies can reduce the cumulative steroid dose required to keep the disease quiescent. However, steroid-sparing immunosuppressants may also lead to increased morbidity and mortality due to their unfavourable side effects. Larger randomized clinical trials are necessary to study the efficacy of the treatment agents in BP.

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DILUTED AND HYPERDILUTED CALCIUM HYDROXYAPATITE FOR SKIN TIGHTENING

Introduction

Biostimulatory fillers, such as calcium hydroxylapatite (CaHA), have been used for more than a decade for facial volumization and HIV-induced lipoatrophy.¹ Over the last few years, CaHA has also been increasingly utilized to tighten skin and improve skin quality.¹ CaHA is a biodegradable and resorbable filler composed of microspheres suspended in an aqueous carboxymethyl cellulose gel carrier.² The biostimulatory nature of CaHA distinguishes it from other fillers: while the carrier provides initial volume replacement, the particles induce a delayed fibroblast and histiocyte response leading to increased collagen and elastin formation, and ultimately dermal remodelling.²

CaHA reconstitutions can be categorized based on ratios: none/undiluted, dilute (1:1), and hyperdiluted ($\geq 1:2$) (**Table 1**). In hyperdiluted forms, CaHA causes biostimulation without volumization. Overall, this leads to skin tightening and improvement of various skin parameters, such as elasticity, firmness, superficial wrinkles, and overall appearance.¹ The use of diluted and hyperdiluted CaHA for skin tightening is a relatively new technique growing in popularity. It can be used in various areas of the body such as the upper arms, abdomen, and thighs. Hyperdiluted CaHA has also been used to treat cellulite and striae.^{1,4}

This article reviews considerations for diluted and hyperdiluted CaHA and some target areas, including the face, neck and décolletage, and buttocks.

Patient Selection & Education

Appropriate patient selection for hyperdiluted CaHA therapy is the first step in attaining an aesthetically desirable and safe outcome. A proper diagnosis will guide therapy: practitioners must be able to distinguish between volume loss and skin laxity, as only the latter will improve with hyperdiluted CaHA. For the face, diluted CaHA will not improve ptosis due to midface fat pad descent. For treatment of the abdomen or

thighs, hyperdiluted CaHA cannot be used if the apparent laxity is to due excess subcutaneous tissue.⁶

Patient expectations must be evaluated. Patients should be aware that hyperdiluted CaHA for skin tightening is an off-label use. In addition, patients must understand that dermal remodelling is a delayed and long-term process, taking 4 to 6 weeks to appreciate initial effects.⁶ Patients should also be informed that CaHA is radiopaque. It is clearly visible on computerized tomography (CT) scan and may appear on plain x-ray films.

CaHA is contraindicated in patients with known hypersensitivity to CaHA or any of its components.

Reconstitution

Undiluted CaHA is a highly viscous product with immediate volumizing and delayed biostimulatory effects. Dilution of CaHA with saline and/or lidocaine disperses the carboxymethyl cellulose, rendering it less viscous.³ Dilution ratios of 1:1 provide both volumizing and remodelling effects. In contrast, hyperdiluted ratios of $\geq 1:2$ provide biostimulatory effects without

voluminization. For smooth product placement, dilutions can be adjusted based on the skin thickness and degree of laxity. More dilute reconstitutions should be used for thinner skin to reduce the risk of product visibility and palpability.⁴

There are a few considerations for the reconstitution process (**Box 1**). A female transfer adaptor can connect the original CaHA syringe to a LuerLock syringe with the diluent. A minimum of 20 passes between the two syringes should be completed to ensure equal product dispersion. Once homogeneity is achieved, the mixture should be placed into the original syringe for injection. Given that the diluted version tends to separate, the reconstitution process should be completed immediately prior to the treatment.

Anesthesia

Pain management during aesthetic procedures is an important consideration. A reconstitution protocol approved by the U.S. Food and Drug Administration suggests mixing CaHA with lidocaine to a concentration of 0.3%.⁵ Reconstituted mixtures

should not exceed maximum lidocaine doses (3 mg/kg without epinephrine and 7 mg/kg with epinephrine).⁶ Topical anesthesia or injections of local anesthetic at the canula entry point can also be utilized.

Technique Considerations

There are various technique considerations involved with the use of CaHA (**Box 2**). Needles or cannulas can be used to inject CaHA. Researchers have compared precision differences between the two injection modalities in a cadaver study and found that the cannula technique resulted in product placement and confinement to the deep anatomic layers, while needle usage led to product placement in multiple layers. As use of needles can result in superficial placement of CaHA, great caution must be exercised with this approach.³

The plane of injection is critical to treatment success and varies with reconstitutions ratios (**Table 1**). Due to its non-viscous nature, hyperdiluted CaHA can be distributed across a larger surface area and relatively more superficial levels. The aim is to distribute a thin and even layer at

Dilution	Properties: Viscosity and Elasticity	Ideal Plane for Injection	Voluminization Effect	Biostimulation Effect	Overall treatment effect
None	High	Deep-dermal, subdermal, or suprapariosteal	++	+	Voluminization and secondary skin quality improvement
Diluted 1:1 (1.5 mL CaHA + 1.5 mL diluent)	Intermediate	Subdermal	+	+	Volume restoration with easy and even product distribution
Hyperdiluted $\geq 1:2$ (e.g. 1:2 dilution is 1.5 mL CaHA + 3.0 mL diluent)	Low	Dermal-subcutaneous junction	-	+	Skin tightening for large surface areas

Table 1. CaHA Reconstitutions and Properties (Adapted from Lorenzc et al.⁶)

1. Dilution to be performed immediately before injection.
2. Use syringes large enough to hold the desired volume.
3. Use a female adapter to connect the original CaHA syringe and the additional LuerLock syringe.
4. A minimum of 20 passes should be completed to ensure product homogeneity. Considerable force will be required to move the product between the syringes; however, caution must be taken to avoid forcibly pushing the plunger out of the barrel.
5. Transfer the reconstituted mixture into the original syringe for injection.

Box 1. Hyperdiluted CaHA Reconstitution Considerations (Adapted from Goldie et al').

1. Treatment aim: distribute a thin and even layer throughout the entire treatment zone, at the dermal-subcutaneous junction.
2. Use 22-25 gauge for canula or 27-30 gauge for needle.
3. For facial treatments, the entry point should be perpendicular to the direction of major arteries.
4. Massage vigorously after treatment.

Box 2. Injection Technique Considerations (Adapted from Goldie et al').

the dermal-subcutaneous junction of the entire treatment area. In contrast, undiluted CaHA is viscous and thus must be placed at the deep-dermal, subdermal, or suprapariosteal levels.

For hyperdiluted CaHA injected with a canula, fanning or parallel serial retrograde linear threading injection techniques are recommended.¹ To ensure uniform product distribution, the treatment area should then be vigorously massaged.

Treatment Intervals

CaHA initiates dermal neocollagenesis in which type III is gradually replaced with type I collagen. This process may occur as early as 4 weeks.⁵ Deposition of collagen and elastin starts at 4 months and is completed around 9 months.¹ Various follow-up cycles have been suggested with some indicating 1 follow-up session within 12 months.³ Other protocols recommend follow-up in 3-4 months after the initial treatment, for a total of one to 3 treatments in the first year, followed by annual maintenance sessions.¹

Face

Soft tissue fillers remain a mainstay of facial augmentation and contouring. Diluted and hyperdiluted CaHA provide global treatment as opposed to localized volumization. In these forms, CaHA can be distributed evenly in the immediate subdermal plane to provide general skin tightening.² Hyperdiluted CaHA is not used in the forehead and temples as these areas require volume and contour treatments, or the lips and nasolabial folds due to increased risk of nodule formation.¹ Diluted CaHA with a 1:1 ratio is recommended initially. Hyperdilutions may be utilized for thin skin or areas of greater laxity.¹ Cannulas can be used for even product distribution. Entry points should be perpendicular to the direction of major arteries to reduce the risk of vessel puncture.¹

Neck & Decolletage

Neck restoration procedures are on the rise. Hyperdiluted CaHA is a safe and non-invasive modality for tightening the skin in the neck and decolletage.^{4,8} For this area, patients with mild laxity or

crepey skin will benefit the most from treatment. Patients must understand that excess skin will not disappear; rather, dermal remodelling will make it appear tighter and thus less visible.

The skin in the neck is very thin, increasing the risk of too-superficial product placement and possible subsequent nodule formation. As such, the use of cannulas and hyperdiluted ratios are recommended, as follows: 1:2 to 1:3 for mild skin laxity and/or photoaging, and 1:4 or greater for those with increased photo-induced atrophy.¹ Product can be injected in retrograde fashion with 3-5 entry sites.³ Approximately 0.5-1 syringe is required per session. While results may be visible after one treatment, full rejuvenation may require more sessions, especially if higher dilutions are used.

Buttocks

Patients present with various complaints of the buttocks, such as gluteal sagging or cellulite-associated textural irregularities. Increasing skin tightness and dermal elasticity can address these

patient concerns. Approximately one syringe is required per side.¹ For skin laxity, the dilution ranges from 1:1 to 1:4. Lower ranges of 1:1 or 1:2 can be used for cellulite dimples. CaHA should be injected with a canula in the subdermal layer. A fanning or vertical line technique can be used for contouring the upper and lateral regions, whereas a horizontal cross-hatching technique can be used for the lower region.^{1,2} Three treatment sessions every 4 months are recommended for desired outcomes.¹ Patients with a higher body mass index may not have improvement from CaHA injections alone.⁹

Adverse Effects

In general, CaHA in all its forms is safe. In long-term studies on undiluted CaHA, adverse effects were minor and were mainly injection-related, such as erythema, ecchymosis, and edema.^{10, 11, 12} The development of noninflammatory nodules due to product accumulation has been associated with CaHA injected in the lips, or with superficial placement of product in the nasolabial fold.^{12, 13} In recent studies on diluted or hyperdiluted CaHA, all adverse effects were injection-related and included ecchymoses, swelling, induration and mild pain.^{4, 14, 15}

The most severe complication of soft tissue injectable treatments is vascular compromise in which product is injected into a blood vessel, leading to occlusion and necrosis. To date, no cases of vascular compromise with hyperdiluted CaHA have been reported.¹

Summary

The use of diluted and hyperdiluted CaHA for skin tightening and improvement of skin quality is on the rise. When injected in the subdermal plane in reconstituted forms, CaHA stimulates the production of collagen and elastin, thereby promoting dermal remodelling. Although off-label, it is an efficacious and safe technique used widely.

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IL-17 INHIBITORS AND THE RISK OF MALIGNANCY

Introduction

The modern era of psoriasis treatment has provided dermatologists with an array of systemic medications to address this serious inflammatory skin disease. In most patients, psoriasis requires chronic treatment and management and, thus, long-term data on medication safety is of utmost importance. The risk of malignancy is a primary concern for both the prescribing dermatologist and the psoriatic patient.

Studies on commonly used systemic agents to treat psoriasis associated with malignancy have been previously reviewed.¹ For example, there have been several reports on Epstein-Barr virus-associated lymphomas in psoriasis patients treated with methotrexate. The use of cyclosporine has been associated with a 2-fold increased risk of overall malignancy, and upward of 6-fold increased risk for squamous cell carcinoma (SCC), specifically. Psoralen combined with ultraviolet A phototherapy (PUVA) has been associated with an increased risk of non-melanoma skin cancers. Tumor necrosis factor alpha (TNF α) inhibitors have also been associated with an increased risk of both SCC and lymphoma. Given their relatively recent introduction, newer biologic agents, such as IL-17 inhibitors, have had limited data regarding malignancy risk.

IL-17 inhibitors

The IL-17 family of cytokines includes IL-17A to IL-17F and is implicated in numerous aspects of immune defense and regulatory function.² Increased levels of IL-17 contribute to the development of psoriasis, by inducing the production of antimicrobial peptides and mediating the formation of proliferative and proinflammatory cytokines that affect keratinocyte turnover.² IL-17 inhibition through targeted monoclonal antibodies is an efficacious treatment approach for psoriasis, psoriatic arthritis and ankylosing spondylitis. The anti-IL-17 agents currently approved are the anti-IL-17A monoclonal antibodies secukinumab and ixekizumab, as well as the anti-IL-17 receptor monoclonal antibody, brodalumab. This article will provide a focused overview of recently published analyses on the risk of malignancy in patients with psoriasis, psoriatic arthritis (PsA) and ankylosing spondylitis (AS) treated with IL-17 inhibitors. The reader may appreciate that indirect treatment comparisons regarding the risk of malignancy between secukinumab, ixekizumab and brodalumab are challenging given the inherent differences in study design for these agents.

19 Risk of malignancy in patients treated with IL-17 inhibitors:

Secukinumab

The risk of malignancy in patients with psoriasis, PsA and AS treated with secukinumab from pooled data of 49 clinical trials, as well as post-marketing safety surveillance, has been recently reported.³ This pooled analysis of 14,519 patients (10,685 psoriasis, 2,523 PsA and 1,311 AS) which represented ~24,000 patient-treated years includes patients followed up to a maximum of five years, with the mean follow up time for patients on secukinumab being 1.54 years for psoriasis, 1.96 years for PsA, and 2.03 years for AS.

The authors evaluated safety using exposure adjusted incidence rates (EAIR; number of cases of malignancy per total exposure time) to report their findings. The EAIR of malignancy was 0.85 per 100 patient treated years [95% confidence interval (CI) 0.74–0.98] in secukinumab-treated patients, corresponding to 204 patients per 23,908 patient treated years, with the most common malignancies being basal cell carcinoma (BCC) (58 cases / 23,988 patient treated years equating to an EAIR of 0.24 per 100 patient treated years), breast cancer, prostate cancer, SCC and thyroid cancer. When compared to an external reference population (United States general population), the authors found that the observed vs. expected number of malignancies from the secukinumab clinical trial data were comparable, as indicated by an SIR of 0.99 (95% CI 0.82–1.19) across indications.

A total of 242 (1.7%) clinical trial patients had a remote history of malignancy greater than 5 years prior (patients with a confirmed malignancy within the previous 5 years prior to screening were excluded, with few exceptions). From the pooled clinical trial data, 25 patients reported a recurrence

Category	Combined ixekizumab (N = 5898)	IR ^a
Non-melanoma skin cancer, n (%)	51 (0.9)	0.3
Basal cell carcinoma, n (%)	42 (0.7)	0.2
Squamous cell carcinoma, n (%)	12 (0.2)	0.1
Malignancies excluding NMSC, n (%)	86 (1.5)	0.5
Prostate cancer ^b , n (%)	12 (0.3)	0.1
Squamous cell carcinoma, n (%)	6 (0.1)	<0.05
Invasive ductal breast carcinoma, n (%)	5 (0.1)	<0.05
Colon cancer, n (%)	4 (0.1)	<0.05
Lung cancer metastatic, n (%)	3 (0.1)	<0.05

Table 1. Malignancies in ixekizumab pooled analysis; Armstrong et al, 2020
IR incidence rate, N total number of patients, n number of patients in category, NMSC non-melanoma skin cancer

^a Incidence rates are per 100 patient-years
^b Calculated in men only; N = 4000 men with 11,714.2 patient-years of exposure

of malignancy with 18 of the 25 recurrences being non-melanoma skin cancer and 3 out of 25 recurrences being melanoma. The authors also reported post-marketing surveillance data for secukinumab-treated patients (cumulative between 2014-2018). In the post-marketing surveillance analysis, they estimated a malignancy reporting rate of 0.27 per 100 patient treated years with cumulative secukinumab exposure of 285,811 patient treated years.

Ixekizumab

Safety data for ixekizumab from 13 pooled clinical trials has been recently reported, with ~17,000 patient years of ixekizumab exposure for 5,898 patients receiving at least one dose of ixekizumab for the treatment of moderate-to-severe psoriasis.⁴ Of note, 2,749 patients had ≥4 years of ixekizumab exposure.

A total of 51 of 5,898 (0.9%) patients developed non-melanoma skin cancer of which 42 (0.7%) were BCC and 12 (0.2%) were SCC, resulting in an incidence rate of 0.3 for non-melanoma skin cancers (Table 1). The authors highlight that the incidence rate of non-melanoma skin cancers for patients treated with ixekizumab was slightly lower than the rates associated with TNFα inhibitors such as etanercept and adalimumab, as well as the IL-12/23 inhibitor, ustekinumab. Malignancies, excluding non-melanoma skin cancers, occurred in 86 of 5,898 patients (1.5%) and represented an incidence rate of 0.5. From this analysis, prostate cancer was the most reported (n=12) with an incidence rate of 0.1 per 100 patient years in male patients. The results of this pooled analysis of malignancies, other than non-melanoma skin cancers, in patients treated with ixekizumab point to similar malignancy rates

seen in other long-term studies with etanercept, adalimumab and ustekinumab.

A subsequent study by Genovese et al.⁵ expanded the original pooled analysis to include ixekizumab clinical trials with data on PsA (4 clinical trials) and axial spondyloarthritis (4 clinical trials), representing a total of 8,228 patients with 20,896 cumulative patient years of ixekizumab exposure. In these analyzed clinical trial populations, the incidence rates of malignancy in ixekizumab-treated patients with arthritis were comparable to those with psoriasis only (IR $\leq$ 0.8).

Brodalumab

Analyses of pooled data from four clinical trials reported malignancy rates in brodalumab-treated patients with moderate-to-severe psoriasis.⁶ Within this analysis, a group of 4,464 patients with a mean duration of 23.3 months of exposure and a total of 9,174 patient years of follow up was studied. The reported time-adjusted event rate for non-melanoma skin cancer was 0.6 per 100 patient years. For malignancies excluding non-melanoma skin cancer, the follow up time-adjusted event rate was 0.4 per 100 patient years, with prostate cancer being the most common. These event rates are in line with malignancy rates seen in psoriasis patients on other IL-17 inhibitor treatments.

A real-world summary based on pharmacovigilance data reported by US patients and healthcare providers from August 15, 2017, through August 14, 2019 of 2,677 brodalumab patients with a cumulative treatment exposure of 1,656 patient years during a two-year analysis was conducted in the United States.⁷ The analysis of this pharmacovigilance data revealed a malignancy rate of 0.9 events per 100 patient years, of which none were deemed to be related to brodalumab.

Discussion

The lack of head-to-head randomized controlled trials comparing different IL-17 inhibitors in terms of malignancy rates is a key consideration in the interpretation of this pooled analysis data. Additionally, the mean duration of follow up in these reported analyses ranges from 1.9 years to 3.2 years. Therefore, the potential for increased rates of malignancy beyond these timepoints cannot be determined which highlights the need for patient registries and ongoing pharmacovigilance studies in real-world populations to better follow the patients outside of a clinical trial setting. Furthermore, the baseline demographics of the study populations included in these analyses do not allow us to easily translate learnings to clinical practice. For example, patients in these pooled analyses were, on average, relatively young (mean age of pooled data from trials of secukinumab: 57.8 years, ixekizumab: 45.8 years and brodalumab: 44.8 years) which may further confound malignancy risk in a population in whom de novo malignancy rates would not be expected to be high to begin with. Finally, the data from these analyses are predominantly from a Caucasian population (percentage from pooled data from trials of secukinumab: 94%, ixekizumab: 88% and brodalumab: 90%), which does not fully account for the potential risk of malignancy of IL-17 inhibitor treatment in patients of varying skin tones.

This article provided a general overview of published analyses on the risk of malignancy in IL-17 inhibitors. Psoriasis itself confers a slight increase in the development of non-melanoma skin cancers and lymphomas⁸ and ongoing research continues to demonstrate an increased risk of other malignancies.

Although excluded from clinical trials, the reality of dermatology practice today is that clinicians will inevitably encounter patients with malignancies that may be recently diagnosed, remitting or relapsing. Although there have been case reports and case series on the use of IL-17 inhibitors in patients with malignancy⁹, there are no large-scale studies demonstrating the use of biologics in treating psoriasis patients with active malignancies. Ultimately, the risk-benefit considerations are centered on the patient, with the need to balance the risk of progression and recurrence of malignancy with the need to treat severe and debilitating psoriasis in the hopes of improving the patient's quality of life.

The continued study of the long-term malignancy risk of IL-17 inhibitors, and other biologic molecules, will better assist clinicians in treating patients with psoriasis, PsA, AS and possibly other inflammatory conditions.

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POST-INFLAMMATORY HYPERPIGMENTATION: PATHOGENESIS, DIAGNOSIS, AND TREATMENT

Post-inflammatory hyperpigmentation (PIH) is a common, acquired pigmentary condition. Although it can occur in all skin phototypes, it more commonly affects individuals with darker skin phenotypes. PIH can result from endogenous inflammation such as acne vulgaris or exogenous injury or trauma to the skin, such as that associated with an energy-based procedure. PIH does not affect the patient symptomatically; however the appearance and prolonged duration can be a source of distress. This holds true especially in patients with darker skin tones as PIH is most noticeable in skin types 3 to 6. It is not a surprise therefore that PIH is one of the most common reasons for patients with darker skin tones to seek treatment from a dermatologist.

With respect to pathogenesis, PIH is caused by either endogenous or exogenous inflammation.¹ There are two mechanisms by which inflammation can cause PIH. First, inflammatory cytokines can stimulate melanocyte activity, hyperplasia, and hypertrophy.² Second, inflammation in the dermoepidermal junction (DEJ) can cause melanin to dropout from the epidermis into the dermis (melanin incontinence), which is then phagocytized by macrophages (melanophages).³ The location of the melanophages determines the type of PIH; if the melanophages are more predominant in the epidermis, the resulting colour of the PIH will be tan-to-brown. In contrast, melanophages located in the deeper dermis layer will produce a blue-grey colour.⁴ This colour difference is attributed to the Tyndall effect.⁵ Other relevant factors that play a role in the clinical presentation of PIH would include: the patient's inherent pre-existing skin tone, the degree and depth of inflammation, and the degree of injury to the DEJ where melanocytes and pigmented keratinocytes are located.⁶ The clinical presentation and understanding of the pathogenesis of PIH can be helpful in predicting the potential duration of disease and setting realistic clinical expectations for the patient.

The differential diagnosis of PIH involves the evaluation of other hyperpigmentation disorders such as melasma, hyperpigmented mycosis fungoides (rare variant most commonly affecting skin of colour), and drug-induced hyperpigmentation.⁶ Drug-induced hyperpigmentation may be caused by antibiotics (minocycline), anti-neoplastic agents, antimalarials, amiodarone, and metals. There are also hyperpigmentation disorders that result in PIH and for which the differential diagnoses would include lichen planus pigmentosus (uncommon variant of lichen planus), ashy dermatosis (otherwise known as erythema dyschromicum perstans), and Riehl melanosis. The distinguishing features of these diseases include the fact that lichen planus pigmentosus presents on the sun-exposed areas such as the face, neck, and upper extremities and ashy

dermatosis typically presents on the trunk, proximal extremities and neck. Riehl melanosis, otherwise known as pigmented contact dermatitis, is classically described and commonly manifests in young middle-aged women on the forehead, temporal, and zygoma areas of the face. Other differential diagnoses of hyperpigmentation conditions which can result in PIH include phytophotodermatitis, frictional melanosis, and periorbital hyperpigmentation.⁷

The diagnosis of PIH begins with a thorough physical examination. As part of the examination, it may be beneficial for the clinician to make a visual comparison of the affected area against the patient's baseline normal skin colour either from inspecting the unaffected skin or a photograph. A useful and simple addition to the physical examination would be a Woods lamp.⁸ Enhancement of the pigment would indicate epidermal PIH whereas no enhancement would indicate dermal PIH. Finally, a skin biopsy is considered helpful in delineating the diagnosis and, at the very least, useful in excluding certain differentials such as hyperpigmented mycosis fungoides.⁹ Ideally, two biopsies should be done for the pathologist to compare specimens from normal and hyperpigmented skin. Histopathologic features of PIH include an increased number of superficial dermal melanophages as well as increased epidermal melanin.

There are multiple therapeutic agents available for the treatment of PIH. Prior to initiating pharmacological intervention, it is important to set realistic expectations and take sufficient time to counsel patients that PIH can be very difficult to treat, especially if predominantly dermal in nature. If the patient is unbothered by their PIH, non-active intervention and monitoring may be a very reasonable management approach. However, since this is rare and many patients

seek treatment for their PIH, this paper will focus on the topical agents that most dermatologists typically prescribe to treat PIH.

One of the most common treatment options for PIH is hydroquinone 2-4 % (HQ). The mechanism of action involves the inhibition of the enzyme tyrosinase, the result of which blocks conversion of DOPA to melanin. HQ also works by degrading melanosomes and melanocytes.¹⁰ A popular combination treatment is Kligman's formula, which is the triple combination of HQ, retinoids, and corticosteroids.¹¹ This treatment regimen has the most evidence and is widely considered an effective treatment for PIH. Kligman's formula is generally well-tolerated and can be used safely in all skin phototypes. The potential side effects of prolonged use may include irritation, contact dermatitis, ochronosis, and theoretical risk of carcinogenicity (demonstrated only in animal studies).⁶

The mechanism of action of retinoids is three-fold; it increases turnover of keratinocytes, inhibits tyrosinase transcription which reduces production of melanin, and reduces the transfer of melanosomes from melanocytes to keratinocytes.¹² Researchers have demonstrated that tretinoin 0.1% applied nightly yielded over 20% and just shy of 50% reductions in epidermal and dermal melanin levels respectively, compared to 3% and 7% respectively in the placebo-vehicle group¹³. In a double-blinded, placebo-vehicle-controlled study of 74 patients from darker racial ethnic groups who had acne, results showed that tazarotene 0.1% applied once-daily resulted in a 500% greater improvement in overall PIH severity and a 120% greater reduction in pigment level within 18 weeks¹⁴. Another randomized, investigator-blinded study in patients with moderate-to-severe acne compared tazarotene 0.1%

cream to adapalene 0.3% gel and found that tazarotene was significantly more effective at treating PIH, (25% achieving resolution in the tazarotene group versus 12% in the adapalene group).¹⁵

Another class of medications which are commonly used to treat PIH are hydroxy acids. These agents remove the superficial layers of the skin by increasing cellular turnover of keratinocytes and decreasing melanin content within the epidermis. A randomized, evaluator-blinded, split-face study of ten subjects with Fitzpatrick skin phototypes IV to VI evaluated 20-30% salicylic acid to one-half of the face and no treatment to the contralateral half. Statistical analysis of evaluators' rating of the photographs did not yield a significant difference between the treated and untreated side, but patients reported a 40% improvement on the treated side compared to 8% on the untreated side ($p=0.004$).¹⁶ Two randomized studies compared the use of 20% salicylic-10% mandelic acid peel to 35% glycolic acid peels for PIH following acne and found significant improvements of 66-72% and 43-47% respectively compared to baseline.^{17,18} A randomized, double-blinded, split-faced study involving 36 subjects compared 30% salicylic acid peel to Jessner's solution (14g resorcinol, 14g salicylic acid, 14g lactic acid in 100mL ethanol) for the treatment of PIH following acne and found that both treatments were equally effective after 8 weeks.¹⁹

Corticosteroids may also be used for PIH as they have anti-inflammatory properties and work by reducing mononuclear and phagocytic cells, as well as by decreasing epidermal melanin levels by interfering with melanin synthesis in melanocytes.²⁰ A randomized, double-blinded, placebo-controlled study evaluated desonide, a low potency corticosteroid, for

axillary PIH and showed a 30% improvement in PIH, compared to a 6% improvement in the placebo group. However, another randomized, double-blinded study evaluated betamethasone valerate 0.12% foam for PIH in stasis dermatitis and found that although there was no overall difference between the foam and vehicle-treated leg at days 14 and 28, the steroid-treated leg, but not the vehicle-treated leg, showed statistical improvement over baseline.²¹ PIH which results from stasis dermatitis is likely primarily due to hemosiderin and hemosiderophages within the dermis, which would account for the lack of efficacy²².

Niacinamide reduces melanosome transfer from melanocytes to keratinocytes.²³ A randomized, double-blinded, placebo-controlled study evaluated 4% niacinamide for axillary PIH in a small cohort of women aged 19-27 years, and showed a 24% improvement compared to 6% improvement in the placebo group.²⁰

Thiamidol, a derivative of resorcinol and an ultrapotent inhibitor of tyrosinase, was evaluated in a randomized, double-blinded, split-face study for PIH. A statistically significant improvement from baseline was found when it was applied twice daily and 4 times daily for 12 weeks.²⁴ Unlike hydroquinone derivatives, thiamidol is not a substrate of tyrosinase and will not be converted to a toxic quinone that can potentially induce leukoderma²⁵. More studies on this promising agent are needed.

Alpha-bisabolol, a monocyclic sesquiterpene alcohol, inhibits α -melanocyte-stimulating hormone-induced melanogenesis through suppression of tyrosinase production.²⁶ A randomized, double-blinded, vehicle-controlled trial involving 28 females evaluated once daily application of 0.5% alpha-bisabolol and found a 73% greater improvement in

UV-induced PIH after 8 weeks compared to vehicle for the majority of the subjects who tested the alpha-bisabolol-containing cream.²⁷

Glehoma hederacea, a plant commonly used in oriental medicine with anti-inflammatory effects via the inhibition of nitric oxide synthase and TNF- α , has been used to treat UV-induced PIH. A randomized, double-blinded, placebo-controlled study involving 23 female subjects found that Glehoma hederacea resulted in faster and more significant improvement in UV-induced PIH compared to placebo-treated and untreated areas.²⁸

The approach to the treatment of PIH should always consider individual patient characteristics such as their skin phenotype, and, additionally, the etiology of PIH. The author recommends a step-wise approach beginning with therapeutic agents that are safe, effective, and well-tolerated to ensure adherence. Beyond behavioural modifications such as strict photoprotection and the setting of realistic expectations, clinicians may consider a trial of hydroquinone or combination, topical retinoids, and hydroxy acids before pursuing additional or alternative options.

PIH is a common skin condition that predominantly affects individuals with skin of darker phenotypes. Its pathogenesis involves either endogenous or exogenous inflammation and the diagnosis of PIH requires clinicians to be aware of other hyperpigmentation disorders that may present as PIH. Common treatments for PIH include HQ, retinoids, hydroxy acids and corticosteroids. As always, the choice of treatment should consider the patient's age, underlying comorbidities and quality of life goals while balancing appropriate risks and benefits for the optimal management of PIH.

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AN OVERVIEW OF ROSACEA

Rosacea is a well-described chronic cutaneous syndrome with a constellation of different clinical signs and symptoms, with key components including persistent facial erythema and inflammatory papules and pustules primarily affecting the central face, and often with repeated remissions and exacerbations.¹ Characteristic additional features are facial telangiectasias, frequent facial flushing, facial erythema and edema that is non-pitting and ocular and phymatous changes (**Figure 1**).

Epidemiology

Rosacea is commonly diagnosed in Caucasian females, being less common in men, with a typical age of onset after age 30, but can occur at any age.^{2,3} In women it occurs at a younger age and in children, rosacea-like conditions such as periorificial dermatitis and steroid-induced rosacea are quite common. Surveys on the racial/ethnic distribution of rosacea range from approximately 2 to 4% in patients of black, Asian, Latino or Hispanic descent. However, the disease is underrecognized as epidemiologic reports often point to rosacea as a disease of fair-skinned people with Fitzpatrick skin phototypes I and II, leading to the erroneous perception that rosacea does not occur in people with skin of color.⁴ Recent studies have found that adults greater than 60 years of age and with rosacea, may be at increased risk for Alzheimer's disease.⁵

Pathogenesis

Key factors in the pathogenesis of rosacea include neurovascular dysregulation, an abnormal innate as well as adaptive immune response and mast cells, which can lead to abnormal inflammation of the skin.⁶ *Demodex* mites, both *demodex folliculorum* and *demodex brevis*, are present on the face normally as commensal microbes; however, in rosacea, a significantly greater number of these mites are detected.^{7,8} The mites are associated with a bacterium (*Bacillus oleronius*) and colonize pilosebaceous follicles, stimulating inflammation. They are often seen as a dense perifollicular infiltrate on histopathology, and upregulate local proteases and cause dysregulation of the innate immune response in the skin.^{9,10}

27 **Current Classification System**

In 2017, the global ROSacea COnsensus (ROSCO) panel recommended transitioning to a phenotype-based approach to rosacea diagnosis and classification. The output of the panel's recommendations included establishing two features as independent diagnostic markers for rosacea: (i) persistent, centrofacial erythema associated with periodic intensification; and (ii) phymatous changes. The ROSCO panel concluded that flushing, telangiectasia, inflammatory lesions and ocular manifestations were not considered to be individually diagnostic and reached agreement

on dimensions for phenotype severity measures and established the importance of assessing the patient burden of rosacea. This current classification system bases rosacea on phenotype-observable characteristics that can result from genetic and/or environmental influences, in order to provide a means of assessing and treating rosacea (**Table 1**).¹³

Previous Classification System

The diagnosis of rosacea is based on clinical observation and patient history, which is essential as features may often not be visually present at the time of presentation.¹¹ Rosacea was previously categorized into four

subtypes: erythematotelangiectatic rosacea (subtype 1; ETTR), which consists of flushing, persistent facial erythema and telangiectasias; papulopustular rosacea (subtype 2; PPR), characterized by an eruption consisting of papules and pustules in varying stages of evolution; phymatous rosacea (subtype 3), which manifests through sebaceous gland hypertrophy and fibrosis, occurring commonly in men, and ocular rosacea (subtype 4), which commonly presents as a spectrum of disease with nonspecific symptoms of dryness, crusting, styes and pruritus, and signs of concretions and scaling of the eyelids and blepharitis, eyelid swelling and conjunctival

Diagnostic Features (≥ 75% consensus)	Major Features (≥ 50% agreement)	Minor Features (≥ 75% consensus)
Persistent centrofacial erythema associated with periodic intensification by potential trigger factors Phymatous changes	Flushing/transient centrofacial erythema Inflammatory papules and pustules Telangiectasia Ocular manifestations • Lid margin telangiectasia • Blepharitis • Keratitis/conjunctivitis/sclerokeratitis	Burning sensation of the skin Stinging sensation of the skin Oedema Dry sensation of the skin

Table 1. Diagnostic, major and minor features of rosacea; adapted from Tan et al, 2017

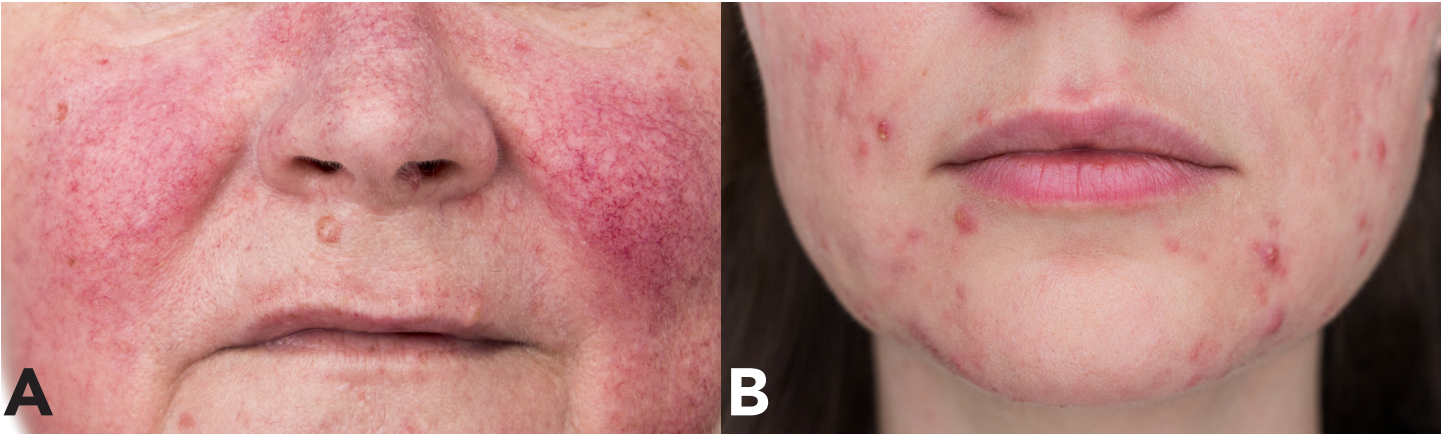


Fig 1. A, Erythema of rosacea on white skin. B, Papules and pustules of rosacea on white skin.

injection.¹ Approximately 20% of patients with rosacea have ocular findings before evidence of skin involvement.¹² In addition to the above subtypes, in granulomatous rosacea, there are small (1 to 3 mm) monomorphous and persistent skin papules colored reddish-brown involving the central face, occurring in both adults and children and often with spontaneous resolution after a few years.

Pathology
Histologic changes in rosacea vary with subtypes, such as subtle vascular ectasia and mid edema seen with ETTR and prominent perivascular and perifollicular lymphohistiocytic infiltrate present in PPR.¹ In phymatous rosacea, sebaceous hyperplasia is prominent with dermal fibrosis. In all forms of rosacea, comedone formation is not identified. In granulomatous rosacea, non-caseating epithelioid

granulomas are identified within the perifollicular inflammation. Lupus miliaris disseminatus faciei is thought to be a severe form of granulomatous rosacea showing central caseation necrosis in granulomas¹⁴, which commonly affects the periocular region and lesser central face and can subsequently involve facial scarring.

Treament options	Persistent erythema	Phymas	
		Active (inflamed)	Fixed (not inflamed)
Topical therapies			
Brimonidine	●●		
Oxymetazoline	●●		
Retinoids		○/●	
Devices and surgical interventions			
Intense pulsed light	○○		
Pulsed dye laser	○○		
Potassium titanyl phosphate	○○		
Carbon dioxide		●	○○○○
Erbium†		●	○○○○
Cold steel†		●	○○○○
Electrosurgery†		●	○○○○
Radiofrequency†		●	○○○○
Oral therapies			
Carvedilol	○		
Doxycycline (subantimicrobial)	○	○/●	
Doxycycline	○	○/●	
Minocycline	○	○/●	
Tetracycline	○	○/●	
Izotretinoin		○○/●	
Azithromycin		○/●	
Trimethoprim/sulfamethoxazole		○/●	

C Used in combination therapy only
* The number of circles indicates the committee’s expert opinion on relative efficacy up to 4, with 4 indicating the most effective. Filled vs open circles indicate strength of trial evidence, with solid circles as strong as open circles are weak.
† Skill dependent; postinflammatory hyperpigmentation risk.

Table 2. Treatment options for diagnostic features; adapted from Thiboutot et al, 2020

Management

Rosacea can be managed through a combination of appropriate skin care, lifestyle management changes, a range of topical and oral therapies and light devices¹¹, and effective therapies that are used to target specific features of each patient (e.g. erythema).

Skin care and lifestyle management

Gentle skin care is important as rosacea patients have sensitive skin that is easily irritated. Patients need to use cleansers and moisturizers that are non-occlusive and that do not irritate the skin. A gentle cleansing regimen using a non-irritating cleanser, or a synthetic detergent is recommended. In addition, washing the face gently and waiting for the face to dry completely before applying topical therapies is advised, as stinging tends to occur when the skin is wet.¹¹ The appearance of redness may be reduced with cosmetics containing a tint of green or yellow. Education on the importance of sun avoidance and regular sunscreen use is advised to prevent further progression and improve flushing and erythema. Mineral inorganic products containing zinc oxide or titanium dioxide are recommended, as they primarily (physically) reflect light and do not produce heat as a by-product. Cosmetics with protective silicones may help as well. Moisturizers containing humectants such as glycerin and occlusives such as petrolatum can help to repair the epidermal barrier. There are many over-the-counter topical skin care products containing forms of sulfur and botanical ingredients that may potentially provide a degree of anti-inflammatory effect; however, published clinical studies of their effectiveness is lacking.¹¹ Avoidance of astringents, toners and abrasive exfoliators and

cosmetics that contain alcohol, menthols, camphor, fragrance, peppermint and eucalyptus oil is recommended.^{1,15,16,17}

Patient education is critical in the management of rosacea and directing patients to easily accessible information on websites such as the National Rosacea Society (www.rosacea.org) may be beneficial in augmenting adherence and compliance with therapy and making lifestyle changes.¹ Rosacea patients need reassurance about the benign nature of the condition and a constant reminder that it is a chronic disease requiring ongoing vigilance in order to optimize outcomes. It is important for patients with rosacea to identify and avoid personal triggers, as these may provoke a worsening of the condition and become a source of stress which can further trigger exacerbations.^{18,19} The use of a daily diary of lifestyle and environmental factors that patients notice affects their rosacea may be an important tool in identifying triggers. Common factors that are typically identified include: sun exposure, emotional stress, hot and cold weather, humidity, wind, heavy exercise, consumption of alcohol, hot baths, spicy foods, certain fruits and vegetables, dairy products, marinated meats, specific medications and underlying medical conditions.²⁰

Topical and oral therapies

Patient education on the importance of compliance with topical and oral regimens is of paramount importance, as clinical response to therapy will take time. A combination of topical and oral therapies are often initially prescribed, followed by long-term use of a single therapy alone to maintain remission (Tables 2, 3).¹¹ For persistent erythema (a diagnostic feature of the current classification system),

topical agents brimonidine tartrate (0.33% gel) or topical oxymetazoline HCL (1% cream), both selective alpha adrenergic agonists, can improve erythema.¹ For inflammatory papules and pustules (a major feature of the current classification system), metronidazole (0.75% gel or cream or 1% cream), ivermectin 1% cream, azelaic acid (15% gel), or sodium sulfacetamide (10%) and sulphur (5%) in a cream or lotion (often with 10% urea) can be used. Topical erythromycin (2% solution), clindamycin (1% lotion) or benzoyl peroxide 5% plus clindamycin 1% can also help clear inflammatory lesions. In addition, tretinoin (0.025% cream, 0.05% cream or 0.01% gel) and pimecrolimus (1% cream) or tacrolimus (0.03% or 0.1% ointment), have been shown to improve inflammation and also erythema, but both may be poorly tolerated by patients (irritation, exacerbations).¹

Modified-release doxycycline capsules (40 mg) are approved by Health Canada for the treatment of papules and pustules and have been shown to have fewer side effects than higher doses and have not demonstrated an association with bacterial resistance.²¹ Many systemic therapies, can be used off-label such as oral antibiotics like tetracycline, doxycycline, minocycline, azithromycin, and erythromycin, often for a 4- to 8-week course, and oral retinoids isotretinoin (0.3 mg/kg/day). Off-label systemic medications used for severe flushing and erythema include beta blockers such as carvedilol or propranolol, antihistamines and nonsteroidal anti-inflammatory drugs.²²

Ocular rosacea therapy

The treatment of ocular rosacea is based on eyelash hygiene and oral omega 3 supplementation, with topical azithromycin or calcineurin inhibitors.¹¹ Eyelash hygiene

Treatment options	Papules/pustules	Telangiectasia	Flushing
Topical therapies			
Ivermectin	●●●		○
Azelaic acid	●●		
Metronidazole	●●		
Clyndamycin	○		
Retinoids	○	○	
Sulfacetamide sodium/sulfa	○		
Brimonidine	c		○
Oxymetazoline			○
Oral therapies			
Doxycycline (subantimicrobial)	●●●		
Azithromycin	○○○		
Doxycycline	○○○		
Minocycline	○○○		
Izotretinoin	○○○		
Trimethoprim/sulfamethoxazole	○○○		
Tetracycline	○○		
Clyndamycin	○		
Carvedilol			○
Clonidine			○
Propranolol			○
Light devices			
Intense pulsed light		○○○○	○○
Pulsed dye laser		○○○○	
Potassium titanyl phosphate		○○○○	○

c Used in combination therapy only

* The number of circles indicates the committee's expert opinion on relative efficacy up to 4, with 4 indicating the most effective. Filled vs open circles indicate strength of trial evidence, with solid circles as strong as open circles are weak.

Table 3. Treatment options for major features; adapted from Thiboutot et al, 2020

with the regular application of warm compresses with baby shampoo on a wet washcloth rubbed onto the eyelashes of closed eyes, to cleanse the eyelashes twice a day is recommended.²³ Antibiotic ointments or topical cyclosporine drops may be beneficial in decreasing the bacterial burden and decreasing inflammation, respectively, in these patients. An oral tetracycline such as doxycycline may be used, but recent studies have shown that topical azithromycin is equally effective as oral doxycycline, with fewer side effects.^{24,25} For severe ocular rosacea, or if there is the presence of corneal ulceration, inflammation or red eye, immediate referral to an ophthalmologist is recommended, in order to prevent reduced visual acuity.¹¹

Light treatments

Two types of lasers, pulsed dye and potassium titanyl phosphate, have both been shown to be highly effective in treating telangiectasias and reducing erythema.^{26,27} To reduce flushing, intense pulsed light has been found to be effective.^{28,29} Intense pulsed light for cutaneous types of rosacea has been found to also improve ocular rosacea (likely a field effect).^{30,31} Ablative lasers using carbon dioxide and erbium, and radiofrequency can remove tissue from and resculpt nose rhinophyma. In patients with darker skin, all laser therapies should be used with caution.¹¹

Summary

Rosacea is a chronic and relapsing cutaneous disorder with numerous triggers and varying presentations which often overlap and evolve. Patient education is of paramount importance in both understanding the disorder, preventing exacerbations and progression and in treatment compliance. The mainstay of therapies include a combination of topical and oral therapies, often with adjunctive laser treatments.

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JAK-STAT PATHWAY INHIBITORS: A NEW JACKPOT FOR DERMATOLOGY

Introduction

Dermatology is experiencing an explosion of new therapies targeting the Janus kinase (JAK)-signal transducer and activator of transcription (STAT) pathway. This pathway plays a critical role in regulating immune cells, especially the polarization of T helper cells via cytokine receptors.¹ Already, a number of dermatologic therapies target the extracellular environment, decreasing the levels of free inflammatory cytokines such as interleukin (IL)-17, IL-23, and tumour necrosis factor alpha (TNF α), or inhibiting cytokine receptors such as IL-17 receptors or IL-4 receptors. Such therapies are usually delivered as large antibody-like molecules called biologics and need to be given by injection. The new therapies, in the form of small molecules that inhibit intracellular kinases, can be given orally or topically. They are called JAK inhibitors (JAKi). For several years, they have found use in rheumatology (tofacitinib), hematologic oncology (ruxolitinib), veterinary medicine (oclacitinib) and basic science research. They are gaining increasing traction in dermatology.

Basic Science

The JAK-STAT pathway is found in many immune cells and it amplifies the signal from cytokine receptors at the surface of the cell to induce the transcription of messenger RNA in the nucleus.² The key protein-encoding genes in this pathway

were identified using primers to amplify, from the DNA of lymphoid tissue, a conserved kinase domain that phosphorylates tyrosine residues on substrate proteins.^{3,4} This conserved domain led to the discovery of 4 related protein tyrosine kinases (PTKs): JAK1, JAK2, JAK3 and tyrosine kinase 2 (TYK2). Members of this family, in fact, contain two kinase domains located near their C-terminal. The kinase domain closest to the C-terminal has kinase activity and phosphorylates the tyrosine residue on target proteins while the second kinase-like domain has a molecular regulation function.⁵ This characteristic feature of two kinases next to each other explains why three of the proteins in the family were ultimately named after Janus, a figure in Roman mythology with two faces. The domain that involves catalytic activity is targeted by competitive JAKi, while the domain that involves molecular regulation is targeted by non-competitive or allosteric JAKi.

Further research has demonstrated that the JAK family kinases associate with the cell membrane.⁶ JAK family proteins form heterodimers with other JAK family proteins, with the exception of JAK2 which can form homodimers and heterodimers.⁷

Each dimerized complex transduces signals from a unique group of receptors (**Table 1**). Ultimately, they use their kinase domain to phosphorylate and activate one of the members of the STAT family.⁸ There are seven STAT proteins. Each STAT has a

JAK protein	Dimers	Cytokine	Outcome
JAK1	JAK1:JAK2	IFN- γ	Inflammation
		IL-6, IL-11, IL-13, OSM, LIF	- T cell proliferation and survival - Wound healing
	JAK1:JAK3	IL-2, IL-4, IL-7, IL-9, IL-15, IL-21	- T cell proliferation and survival - T cell memory - B cell function
		IL-10, IL-19, IL-20, IL-22, IL-26	Anti-inflammatory
	JAK1:TYK2	IFN- α , IFN- β	Antiviral
JAK2	JAK2:JAK1	IFN- γ	Inflammation
		IL-6, IL-11, IL-13, OSM, LIF	- T cell proliferation and survival - Wound healing
	JAK2:JAK2	EPO, TPO, G-CSF, GM-CSF, GH, leptin, prolactin, IL-3, IL-5	- Hematopoiesis - Growth - Anabolic metabolism
	JAK2:TYK2	IL-12, IL-23	Psoriasis
JAK3	JAK3:JAK1	IL-2, IL-4, IL-7, IL-9, IL-15, IL-21	- T cell proliferation and survival - T cell memory - B cell function
		IL-10, IL-19, IL-20, IL-22, IL-26	Anti-inflammatory
TYK2	TYK2:JAK1	IFN- α , IFN- β	Antiviral
	TYK2:JAK2	IL-12, IL-23	Psoriasis

Table 1: The four different JAK proteins, their dimers, the cytokines that signal through these dimers and their biologic outcomes. Adapted from Salas, A et al, 2020.

different function, but all are transcription factors that enter the nucleus and activate transcription after they are phosphorylated. A critical component of skin immunology, T helper cells proliferate and are polarized to a specific set of functions based on the proteins they transcribe after STAT protein activation.

In addition to dictating immune cell activation, the JAK-STAT pathway is important for receptors that bind other ligands such as prolactin, growth hormone, erythropoietin, and colony-stimulating factors. These receptors generally rely on JAK2.⁷ Given the importance of JAK2 for hematopoiesis, JAKi that are non-specific or target multiple JAK proteins are finding more use in dermatologic conditions as topical formulations. Thus, JAKi can be divided into different classes that preferentially inhibit a single kinase and those that target multiple kinases (**Table 2**). This article focuses mainly on JAKi that have a dermatologic application, however there are many JAKi used in research for numerous other disease states that are beyond the scope of this review (**Table 3**).

Black box warning

Although some JAKi are still undergoing regulatory approval, all of them will likely carry a class-wide black box warning in Canada about the potential risk of serious infections, malignancies, major adverse cardiovascular events, and thrombotic events like deep vein thrombosis and pulmonary embolism.⁹ This black box warning may change as more data are collected about the topical formulations, the oral selective JAK1 and TYK2 inhibitors and the impact of patient age, especially during post marketing surveillance.

Upadacitinib

Upadacitinib (Rinvoq, Abbvie Inc.) was recently approved in Canada for patients ≥ 12 years, weighing more than 40 kg,

with moderate-to-severe atopic dermatitis. This agent is already approved in Canada for people ≥ 18 years of age with rheumatoid arthritis or psoriatic arthritis. In vitro, upadacitinib has selectivity for JAK1 over the other 3 JAK proteins: JAK2 (42-fold), JAK3 (133-fold) and TYK2 (194-fold).¹⁰ It is given orally once-a-day and formulated as an extended-release tablet that contains either 15 mg or 30 mg of upadacitinib. The 15 mg dose is more widely recommended while the 30 mg dose should only be used in patients 18-64 years of age with a high atopic dermatitis burden or inadequate response to the 15 mg dose.¹¹

The most common adverse reactions with upadacitinib were upper respiratory tract infections and acne.^{12,13} It is also associated with shingles, cytopenia, elevated lipids, nausea and malignancy. Although not seen in the trials for atopic dermatitis, it has been associated with gastro-intestinal perforation in people taking it for rheumatoid arthritis. It is contraindicated in pregnancy, breastfeeding, hypersensitivity to upadacitinib, severe cytopenias, Child-Pugh C hepatic impairment or active infection, including local and chronic infections.

Abrocitinib

Abrocitinib (Pfizer Inc) has completed phase 3 trials in patients ≥ 12 years of age with moderate-to-severe atopic dermatitis.^{14,15} It has gained approval in the United States, United Kingdom and Japan, but it is still under review by Canadian drug regulatory bodies. In vitro, it has selectivity for JAK1 over the other 3 JAK proteins: JAK2 (28-fold), JAK3 (> 340 -fold) and TYK2 (43-fold).¹⁶ It is given orally once-a-day and formulated as a film-coated tablet that contains either 50 mg, 100 mg, or 200 mg of abrocitinib. The key registration studies have examined the 100 mg and 200 mg formulations

while the 50 mg formulation may be an option for patients with severe renal impairment (eGFR < 30 mL/min) or those taking strong inhibitors of CYP 2C¹⁹.

Abrocitinib has reported similar adverse reactions as other oral JAKi with nausea, shingles, headache, dizziness, and acne being most common. Cytopenias, hyperlipidemia and pneumonia were rare. Venous thrombotic events, including pulmonary embolisms, occurred in the 200 mg group at a rate of 0.23 per 100 patient years but was even more rare in the 100 mg group. It is contraindicated in people with a hypersensitivity to abrocitinib, an active serious systemic infection such as tuberculosis, a severe hepatic disease or in people who are pregnant or breast-feeding.

Deucravacitinib

Deucravacitinib (Bristol-Myers Squibb Inc) has completed phase 3 trials in patients ≥ 18 years of age with moderate-to-severe plaque psoriasis.¹⁷ In vitro, it has selectivity for TYK2 over the other 3 JAK proteins: JAK1 (> 100 -fold), JAK2 (> 2000 -fold), and JAK3 (> 100 -fold).¹⁸ This high degree of selectivity relates to its unique method of inhibition. It binds the regulatory domain of TYK2 and inhibits the kinase domain allosterically.¹⁹ It is given orally once-a-day and formulated as a tablet that contains 6 mg of deucravacitinib.

The most common adverse reactions reported with deucravacitinib include nasopharyngitis, upper respiratory tract infection, headache, diarrhea, and nausea.²⁰ Rates of malignancy, thrombotic events and serious infections were not elevated with deucravacitinib. Contraindications have not been fully identified but they will likely include hypersensitivity to deucravacitinib, pregnancy, breast-feeding and active infection.

Ritlecitinib

Ritlecitinib (Pfizer Inc.) is a covalent kinase inhibitor that inhibits JAK3, and the tyrosine kinase expressed in hepatocellular carcinoma (TEC) kinase family. It has no activity against JAK1, JAK2 and TYK2. It has completed phase 2 trials for moderate-to-severe alopecia areata.²¹

Tofacitinib

Tofacitinib (Xeljanz, Pfizer Inc) is a JAK1 and JAK3 inhibitor that also has inhibitory activity against JAK2 (30-fold) and TYK2 (10-fold).²² Its oral formulation is approved in Canada for rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis. It has been used off-label as a treatment for recalcitrant alopecia areata²³ and case reports suggest it is effective for vitiligo when combined with phototherapy²⁴. The oral formulation is associated with infections, malignancies, and thrombosis, which limit its wide-spread use.

As a 2% ointment, it has been studied as a treatment for chronic plaque psoriasis²⁵, mild-to-moderate atopic dermatitis²⁶, vitiligo (in combination with phototherapy) and alopecia areata²⁷. Adverse reactions have been reported to be similar to vehicle alone, although acne and folliculitis occur more commonly.

Ruxolitinib

Ruxolitinib (Jakavi, Novartis Inc.) is a JAK1 and JAK2 inhibitor that has weaker activity against JAK3 (100-fold) and TYK2 (>10-fold) as compared to other JAKi mentioned in this review.²⁸ Its oral formulation is approved in Canada for the treatment of recalcitrant polycythemia vera and splenomegaly with myelofibrosis. It has been used off-label as a treatment for extensive alopecia areata²⁹ and it carries a black box warning about serious infections. Case reports suggest that it can cause Kaposi sarcoma.^{30,31} As a 1.5% or 0.75% cream applied twice-a-day, it has been used for atopic dermatitis in people who are ≥ 12 years of age (TRuE-AD).³² It has also been studied for vitiligo (TRuE-V), although these results are not yet published (NCT04057573). Local adverse reactions have been reported to be less common than with vehicle cream.

	Kinase Inhibitor	Selectivity	Formulation relevant to dermatology	Uses in dermatology	Pivotal trials	Efficacy	Adverse effects
Single JAK family kinase specificity	Upadacitinib	JAK1	15 mg or 30 mg (extended release tablet) once daily	Health Canada approved: atopic dermatitis ≥ 12 years of age	MEASURE UP 1, MEASURE UP 2, AD UP and Heads Up	EASI-75 at week 16: 30mg (76%) 15mg (65%) Placebo (15%)	Upper respiratory infections, acne, herpes simplex/zoster, cytopenia, elevated lipids, nausea
	Abrocitinib	JAK1	50 mg, 100 mg or 200 mg (film-coated tablet) once daily	Not approved by Health Canada: Atopic dermatitis ≥ 12 years of age	JADE MONO-1, JADE MONO-2, JADE COMPARE and JADE REGIMEN	EASI-75 at week 12: 200mg (62%) 100mg (42%) placebo (11%)	Upper respiratory infections, acne, herpes simplex/zoster, cytopenia, elevated lipids, nausea
	Deucravacitinib	TYK2	6 mg tablet once daily	Not approved by Health Canada: plaque psoriasis ≥ 18 years of age, PsA	POETIK PSO-1 and POETIK PSO-2	PASI-75 at week 16: 6mg (56%) 30mg apremilast (38%) Placebo (11%)	Nasopharyngitis, upper respiratory tract infection, headache, diarrhea, and nausea
	Ritlecitinib	JAK3 and TEC kinase	30 mg, 50 mg or 200 mg once daily	Not approved by Health Canada: Alopecia areata	No phase 3 trials	No phase 3 trials	Headache, acne, folliculitis, dermatitis, diarrhea

	Kinase Inhibitor	Selectivity	Formulation relevant to dermatology	Uses in dermatology	Pivotal trials	Efficacy	Adverse effects
Multiple JAK family kinase targets	Tofacitinib	JAK1 and JAK3 > TYK2 > JAK2	5 mg b.i.d. up to 25 mg per day	Off-label: Alopecia areata	No phase 3 trials	No phase 3 trials	Transaminitis, elevated liver enzymes
			2% ointment or cream	Not approved by Health Canada: Psoriasis, atopic dermatitis, vitiligo, alopecia areata	No phase 3 trials	No phase 3 trials	Acne, folliculitis
	Ruxolitinib	JAK1 and JAK2 > TYK2 > JAK3	20 mg b.i.d. or 25 mg/m ² BSA/day	Off-label: Alopecia areata	No phase 3 trials	No phase 3 trials	Upper respiratory infections, acne, herpes simplex/zoster, cytopenia, elevated lipids, nausea
			0.75% or 1.5% cream b.i.d.	Not approved by Health Canada: Atopic dermatitis, vitiligo aged ≥12	TRuE AD1 TRuE AD2 TRuE V1 TRuE V2	EASI-75 at week 8: 0.75% cream (54%) 1.5% cream (62%) Vehicle (20%)	Nasopharyngitis, Upper respiratory tract infection
	Baricitinib	JAK1 and JAK2 > TYK2 > JAK3	2 mg, 4 mg	Off-label: Atopic dermatitis aged ≥18, alopecia areata	BREEZE-AD5 for atopic dermatitis, only phase 2 for alopecia areata	EASI-75 at week 16: 2mg (30%) Placebo (8%) SALT-20 at week 36: 2mg (33%) 4mg (52%) Placebo (4%)	Upper respiratory infections, acne, herpes simplex/zoster, cytopenia, elevated lipids, nausea
	Delgocitinib	pan-JAK	0.25% or 0.5% ointment b.i.d.	Not approved by Health Canada: Atopic dermatitis aged ≥2	Phase 3 studies completed	mEASI-75 at week 4: 0.5% ointment (26%) vehicle (6%)	Nasopharyngitis, eczema herpeticum, folliculitis, acne, skin papilloma
	Brepocitinib	JAK1 and TYK2	30 mg or 60 mg once daily	Not approved by Health Canada: Alopecia areata	No phase 3 trials	No phase 3 trials	Rhabdomyolysis, upper respiratory tract infection, acne, abdominal pain, oropharyngeal pain

*Efficacy averaged from monotherapy trials of a single agent if more than one trial exists. Note that efficacy cannot be compared across different agents given differences in trial design and study populations.

Table 2: Different JAK family kinase inhibitors, their selectivity, formulations, uses and pivotal trials.

Kinase Inhibitor	Target	Notes
Filgotinib	JAK1	Approved for RA in EU and Japan but stopped clinical trials due to concerns of testicular cancer raised by the FDA
Itacitinib	JAK1	Under investigation for graft-versus-host disease; phase II for psoriasis and rheumatoid arthritis
Oclacitinib	JAK1	Used in veterinary medicine to treat pruritus in dogs
Solcitinib	JAK1	Discontinued development due to interaction with statins
Momelotinib	JAK1, JAK2, ACVR1	Under investigation for myelofibrosis
Fedratinib	JAK2	Approved by Health Canada for myelofibrosis
Gandotinib	JAK2, STAT3	Under investigation for myeloproliferative neoplasms due to JAK2 V617F mutation
Pacritinib	JAK2, FLT3, IRAK1, and CFS1R	Under investigation for myelofibrosis
Decernotinib	JAK3	Investigated for rheumatoid arthritis and graft-versus-host disease but development was terminated
Peficitinib	Pan-JAK	Approved in Japan as an oral treatment for rheumatoid arthritis

Table 3: Other JAK inhibitor medications that are currently used for non-dermatologic conditions or basic science.

Baricitinib

Baricitinib (Olmiant, Eli Lilly and Company) is a JAK1 and JAK2 inhibitor that has weaker activity against JAK3 (70-fold) and TYK2 (10-fold) as compared to other JAKi mentioned in this review.³³ Its oral formulation

(2 mg tablet) is approved in Canada as a treatment for rheumatoid arthritis when combined with methotrexate. It has been studied in adults with moderate-to-severe atopic dermatitis (BREEZE-AD5 and AD7)³⁴ and adults with severe alopecia areata³⁵.

Adverse events include upper respiratory tract infections, nasopharyngitis, and folliculitis. It carries a black box warning for serious infections, malignancies and thrombosis and is contraindicated in people who are pregnant, hypersensitive to baricitinib or actively infected.

Delgocitinib

Delgocitinib (LEO Pharma and Japan Tobacco) is a pan-JAKi: JAK1 (1-fold), JAK2 (1-fold), JAK3 (4-fold) and TYK2 (19-fold).³⁶ Topical formulations of 0.25% or 0.5% delgocitinib ointment are under investigation in Japan for

adults and children aged ≥ 2 years of age with mild-to-moderate atopic dermatitis.^{37,38} Adverse events have been reported to include eczema herpeticum, nasopharyngitis, folliculitis, acne and skin papilloma.

Brepocitinib

Brepocitinib (Pfizer Inc.) is a TYK2 and JAK1 inhibitor.²¹ Early studies are being completed for plaque psoriasis, alopecia areata and cicatricial alopecia.

Conclusion and future directions

JAKi are finding increasing use in the dermatologic armamentarium. They are becoming valuable oral and topical treatments for immunological skin conditions such as atopic dermatitis, alopecia areata and psoriasis and may expand their use to other immune-mediated skin diseases such as graft-versus-host disease, cutaneous lupus, and dermatomyositis. Given the expansion of molecular libraries and rational designs from inhibitor-protein crystallography, JAKi can be tailored to target a specific JAK protein via a variety of mechanisms such as competitively, covalently, or allosterically.

In addition to modulating the immune system, JAKi are anti-proliferative.³⁹ This property has not been fully employed in dermatology, likely because the immune system is important in preventing malignancies and some JAKi have received a black box warning from regulators that includes the potential to induce malignancy. Nevertheless, JAKi have anti-proliferative effects on melanoma⁴⁰ and skin lymphomas⁴¹ in vitro and it is unknown whether these findings translate into improved outcomes if studied in model organisms or even patients. In fact, melanomas that acquire resistance to immunotherapy show loss-of-function mutations in the JAK-STAT pathway.⁴² The application of JAKi in dermatology is still in its nascent stages and there are a number of clinically relevant uses yet to be discovered.

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