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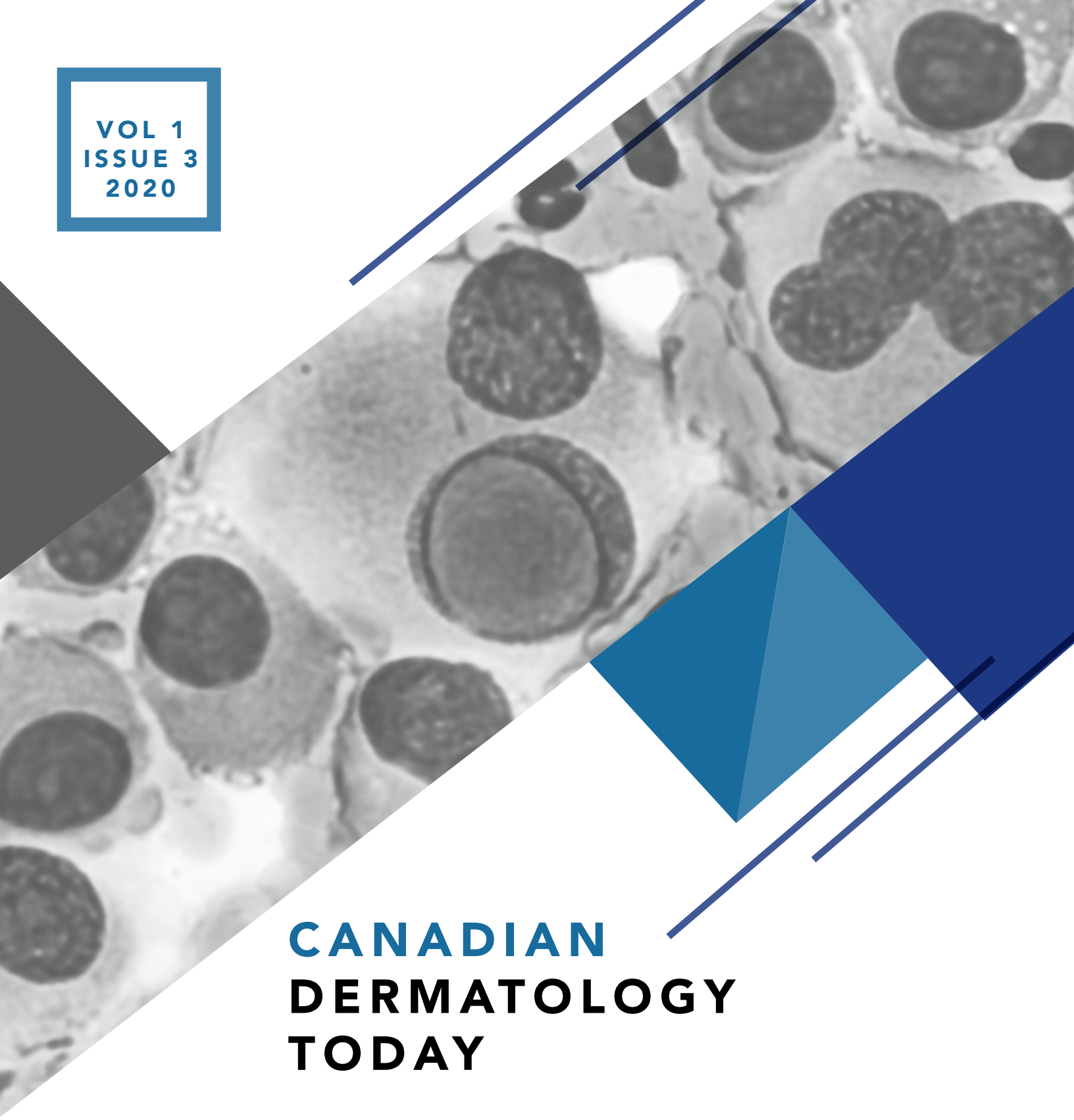

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Dear Canadian Dermatology Community,

Welcome to our 3rd issue of Canadian Dermatology Today in 2020! Since our last issue, we have seen tremendous progress in our battle against COVID-19 and many in the dermatology community and beyond are slowly starting to get back to a regular routine of patient care and follow up, for which we are tremendously thankful.

Our current issue discusses an update on existing and emerging treatments for vitiligo, provides an overview of AJCC staging and adjuvant treatment for melanoma, reveals some of the more common complications of fillers and elucidates the use of biologics to treat psoriasis in HIV patients, just to highlight a few of the articles you will find in the ensuing pages.

As always, we hope you find these articles informative and helpful. We are grateful for your continued readership. Please let us know how we are doing by suggesting topics and feel free to share our registration link at canadiandermatologytoday.com with your peers so that, they too, can subscribe to future issues!

Best wishes,

Kim Papp, MD Jensen Yeung, MD Melinda Gooderham, MD Chih-ho Hong, MD

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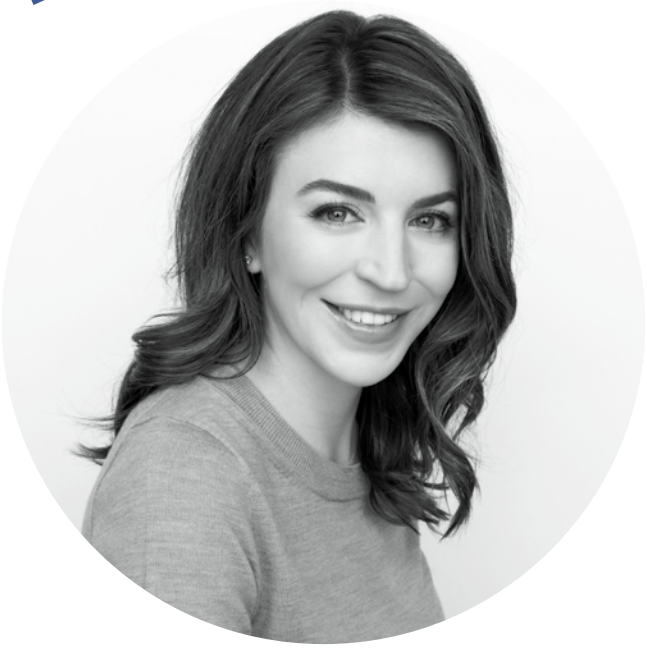

AN UPDATE ON COMPLICATIONS FROM FILLERS

Filler injections are one of the most popular cosmetic procedures performed worldwide in part due to their ease of use, as well as efficacy and safety. However, complications can occur, and it is important for injecting practitioners to have a thorough knowledge of these complications **(Table 1)** to both prevent and manage adverse events.

TYPE	DESCRIPTION
EARLY INJECTION SITE REACTIONS	SWELLING, ERYTHEMA, PAIN, AND BRUISING
TECHNIQUE AND PLACEMENT RELATED	NODULES, BEADING, TYNDALL EFFECT
DELAYED NODULES	INFECTIOUS, BIOFILMS, GRANULOMAS, INFLAMMATORY/IMMUNE-MEDIATED
VASCULAR	SKIN NECROSIS, BLINDNESS

Table 1: Filler Complications

Early Injection Site Reactions

Injection site reactions are common and include erythema, pain, swelling, and bruising. These reactions typically resolve within one to two weeks. Strategies to reduce these risks include minimizing the number of skin punctures and applying cool compresses or ice.[1] Bruising can be limited by avoiding blood-thinning medications or supplements for at least 7–10 days prior to injection. Using a small gauge needle, cannula, and injecting slowly with small volumes can further reduce bruising. However, bruising may occur despite the best techniques and can be treated with intense pulsed light, pulsed dye lasers or potassium titanyl phosphate (KTP) lasers, which target the extravasated hemoglobin as a chromophore.[2] Superficial bruising can lighten within a day following laser or light-based treatment.

Technique and Placement

Inappropriate or uneven placement of fillers may result in palpable nodules and papules. Injecting hyaluronic acid (HA) filler too superficially may lead to beading or a blue-grey discoloration secondary to the Tyndall effect.

Hyaluronidase

One advantage of HA fillers is that they are reversible, and hyaluronidase is an enzyme that can be used to dissolve filler to resolve papules, nodules, Tyndall effect, or vascular compromise. Different formulations are available, which makes it difficult to establish standardized dosing. An in vitro, dose–response study suggests that Juvederm® is more resistant to hyaluronidase compared to Restylane®.[3] A commonly articulated approach is 5-10 units of hyaluronidase are needed to dissolve 0.1 mL of filler and it should be noted that more hyaluronidase may be required for the highly cross-linked fillers. In the case of impending necrosis, a minimum of 500 units of hyaluronidase should be used.[4] Evidence has shown that degradation was similar when hyaluronidase was administered (10 U/0.1 ml of filler) at four days or four weeks post-filler injection, indicating that tissue integration did not impede the ability of hyaluronidase to degrade HA filler.[5]

The published incidence of allergic reaction to hyaluronidase is low at 0.05%.[6] Bee and wasp venoms contain hyaluronidase and there is a theoretical cross-reactivity in patients who have an allergy. For patients who have had severe reactions or anaphylaxis to bee or wasp stings, a skin test can be considered prior to treatment for non-urgent indications.[7]

Delayed Nodules

Delayed nodules secondary to filler have multiple possible etiologies and are difficult to diagnose without histopathology or culture results. Delayed nodules may result from infections, biofilms, foreign body granulomas, or inflammatory/immune-mediated causes.

Infection following filler treatment is uncommon but can occur with any procedure that breaks the surface of the skin. Potential infectious etiologies may be bacterial, fungal, or viral. To minimize the risk of infection, the skin should be cleansed prior to injection with an antimicrobial agent such as isopropyl alcohol, chlorhexidine or Techni-Care®. Infections may present as tender erythematous fluctuant abscesses or nodules. Systemic symptoms such as fever may occur but are rare. A lesion suspected of being an infection should be cultured or biopsied. Treatment options include incision and drainage and/or broad-spectrum antibiotics until the culture results are confirmed.[8] Trauma from the filler injection can also lead to reactivation of herpes virus infection. If the patient has a history of cold sores and is receiving treatment in the perioral area, prophylactic antiviral treatment should be considered.[2]

Biofilms have been implicated as one potential cause of delayed nodules after filler. Bacteria are thought to coat the filler when it is injected, forming a biofilm. Biofilms secrete a protective matrix that allows them to adhere to surfaces resulting in a low-grade chronic infection that is resistant to the immune system and antibiotics. Cultures are often negative as standard culturing techniques are not sensitive enough to detect the microorganisms.[2] To reduce the risk of acquiring biofilms, it is important to avoid any contamination during injection. The skin should be thoroughly cleansed prior to injection and makeup and any other potential contaminants on the skin should be removed. Sterile technique should be used when reconstituting or diluting fillers.[9]

Foreign body granulomas are another potential cause of delayed nodules. Synthetic fillers can act as foreign bodies, stimulating a host response and granulomatous inflammation. This presentation, though rare, has been reported and confirmed with histology.[2] Granulomatous reactions may be seen more commonly with permanent filler.

Inflammatory or immune-mediated causes of delayed nodules have become increasingly recognized in the literature. HA fillers are not typically considered immunostimulatory because HA is a natural component of the dermis and has no species specificity. However, both immediate and delayed hypersensitivity reactions have been described with HA fillers.[11] The time to onset of delayed nodules ranged from one month to three years after HA implantation.[12] It has been proposed that immune reactions could be due to residual proteins or impurities resulting from the manufacturing process; however, the manufacturing process has improved with time.[8] While HA injected on its own does not act as a foreign antigen, more recent data suggests that it has a larger role than an inert structural component. Data has also indicated that low-molecular weight HA (LMW-HA) may be pro-inflammatory and can trigger the immune system by direct interaction with cellular receptors or via inflammatory contaminants such as protein or endotoxins.[13] This may be a potential cause of some of the delayed reactions seen with fillers designed with Vycross® technology. The etiology of these delayed nodules is likely multifactorial. It is possible that as the filler breaks down, particularly over the three to five-month post-injection period, an increased exposure to LMW-HA fragments or catabolic by-products can stimulate an immune response. Having an inflammatory response to filler may be more common when the immune system is

primed after a triggering event, such as a recent infection like influenza or a dental procedure.[9]

Treatment of delayed nodules should be guided by any investigational results such as histopathology or culture. These nodules may resolve spontaneously; however, removal of HA filler by hyaluronidase, or incision and drainage can be considered. Treatments that have been used for delayed nodules include but are not limited to: intralesional hyaluronidase; topical, intralesional or oral corticosteroids; oral antibiotics; intralesional 5-fluorouracil; oral immunosuppressants; and lasers; or a combination of these treatments.[8] For suspected delayed inflammatory nodules from HA filler, treatment approaches include watchful waiting, intralesional hyaluronidase, oral prednisone (20–40 mg every morning for five to seven days), and/or intralesional triamcinolone acetonide (5–10 mg per ml, with repeat injections at two to four weeks as needed). If a biofilm is suspected, oral antibiotics for two to six weeks can be used.[9]

Vascular

The most serious potential complications from filler are vascular compromise with skin necrosis or blindness which may occur if filler is injected into the blood vessel resulting in an ischemic or embolic phenomenon. Blindness results from retrograde embolization of filler into the ocular vessels **(Figure 1)**.

Symptoms of vascular compromise include pain, blanching, duskiness, and reticulated violaceous erythema. This can progress to necrosis and scarring. Visual complications after filler may present with immediate vision loss, ocular pain, headache, nausea, or vomiting. Further, patients

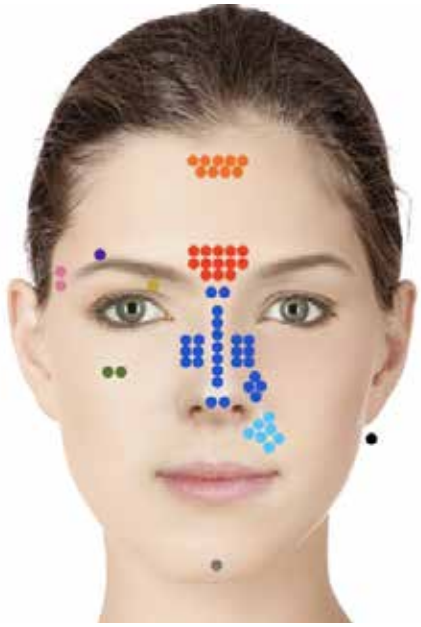

Figure 1. Location of filler injection resulting in visual complication. The single black dot represents a case where the anatomic location of injection was not specified. Originally published in Beleznay et al[22]; reprinted with permission.

may have central nervous system complications including infarction and hemiplegia in association with blindness. In our original review of the global literature, there were 98 cases of blindness reported. Autologous fat was the most common filler type to cause this complication (nearly 48%) followed by HA (23.5%). The sites that were high risk for complications were the glabella (38.8%), nasal region (25.5%), nasolabial fold (13.3%), and forehead (12.2%), but virtually every anatomic location where filler is injected in the face is at risk for vascular compromise.[14] Subsequently, we updated the review of blindness cases published in the literature and there were an additional 48 cases between 2015 and 2018. HA represented 81.3% of the cases in this review with the most common location being the nasal region (56.3%), glabella (27.1%), forehead (18.8%), and the nasolabial fold (14.6%).

Vascular Anatomy

Having an understanding the vascular anatomy prior to injection is critical to prevent these complications **(Figure 2)**. Most of the blood supply to the face is through the external carotid artery, except for a region of the central face encompassing the eye, upper nose, and central forehead. The ophthalmic artery, a branch of the internal carotid, provides the blood supply to this area.[15] The ophthalmic artery branches into various arteries including the supraorbital, supratrochlear, and dorsal nasal artery. The facial artery branches off the external carotid artery and passes over the jaw anterior to the masseter muscle and proceeds in a superior and diagonal direction. The facial artery becomes known as the angular artery in the region of the nasolabial fold and has variable patterns as it continues superiorly. It anastomoses with other facial vessels including the dorsal nasal artery connecting the external and internal carotid system.[16]

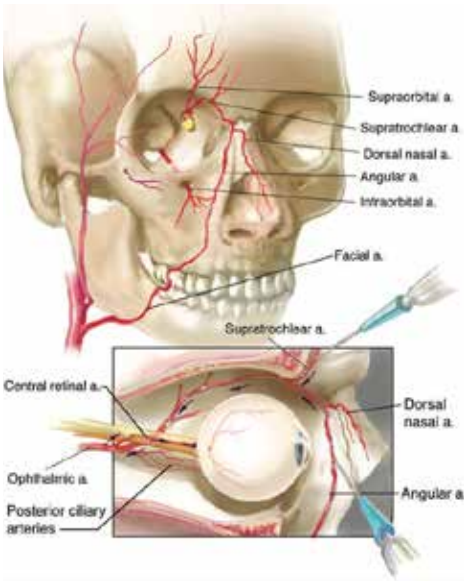

Figure 2. Vascular anatomy of the face. A selection of facial vessels are highlighted here. This is one depiction of the blood vessels of the face and there is individual anatomic variability. Inset demonstrates the mechanism of action of filler-induced blindness. In this diagram, filler is shown being injected directly into the supratrochlear artery or into the angular artery, which anastomoses with the supratrochlear artery. From here filler can travel retrogradely, as shown by the arrows, into the ophthalmic artery and its branches, blocking blood supply to the retina and causing visual complications. Originally published in Beleznay et al[22]; reprinted with permission.

It is important to understand the depth and location of vessels in high-risk sites. In the glabella and forehead, the two major arteries are the supratrochlear artery, which is typically found along the medial canthal vertical line, and the supraorbital artery, which is more lateral in the region of the medial iris. Both of these arteries start their course deep and become more superficial approximately 15–20 mm above the supraorbital rim. They remain in the subcutaneous plane as they travel superiorly on the forehead. Therefore, injections at the levels of the supraorbital rim or within 2 cm of that location should be quite superficial if attempted, keeping in mind this area is very high risk. However, injections more superiorly on the forehead should be deep in a supraperiosteal plane.[17] In the nasal region there are many anastomotic vessels and therefore several reports in the literature suggest that the safest plane to inject filler is deep in the more avascular supraperiosteal plane.[18] If the patient has had previous surgical procedures to the nose, filler injections should be avoided or carried out with extreme caution. In the medial cheek, periorbital area, and nasolabial fold the angular artery is the high-risk artery. The angular artery can have variable patterns after it branches off the facial artery and can be located in the subcutaneous layer, so caution is advised when injecting in this region. With the rich vascular supply of the face and multiple anastomoses, it is very important to understand the location of vessels and appropriate depth of injection.[14]

Prevention

Strategies to prevent vascular complications are critical. It is most important to have a firm understanding of the vascular anatomy and depth of injection, particularly in high-risk sites such as the glabella, nasolabial fold, and nose. Choosing a reversible HA filler allows for treatment with hyaluronidase and the possibility of reversing vascular occlusion if used in a timely manner. Other strategies to implement include using low volumes of product, injecting slowly, and using a small gauge needle or cannula. Cannulae are blunt tipped and many believe that they reduce the risk of vascular injury, particularly in high-risk areas. Key prevention strategies are highlighted in **Box 1**.

Box.1 Strategies to Prevent Vascular Compromise[14,19]

- Know the location and depth of facial vessels
- Inject slowly and with minimal pressure
- Inject in small volumes
- Move the needle tip while injecting to avoid injecting a large bolus in a vessel
- Consider aspiration prior to injection
- Use caution if injecting in a location where prior surgical procedure
- Consider using a cannula

Treatment

Treatment should be instituted immediately at the first sign of vascular compromise. It is important to recognize, however, that treatment recommendations are not based on a large body of evidence. The goal of treatment is rapid restoration of perfusion. Key management strategies for vascular compromise with skin sequelae **(Box 2)** and ocular complications will be discussed.

If blanching occurs while injecting filler, immediately discontinue the injection. If the complication occurs with an HA filler, injection of hyaluronidase is recommended. It has been shown that hyaluronidase can diffuse through the blood vessel walls without needing to be directly injected into the vessel.[20] A published protocol by DeLorenzi suggests the injection of 500 units of hyaluronidase every hour or so until the ischemia is resolved (skin colour has returned, and capillary refill time has returned to normal) for a single affected area. For two affected areas 1000 units should be used and 1500 units used for three areas. As long as treatment is completed within 72 hours of the onset of ischemia, successful resolution is common.[4] In addition, treatments that should be initiated include warm compresses and massage. Other potential therapies include topical nitroglycerin paste, aspirin, oral prednisone, hyperbaric oxygen, and low molecular weight heparin. A thorough individual assessment and treatment plan with close follow-up should be initiated for each patient to ensure optimal outcomes.[19]

Box 2. Treatment of Vascular Compromise with Skin Sequelae[19]

- Stop the injection immediately
- Inject hyaluronidase if an HA filler was used
- Apply warm compresses every 10 minutes for the first few hours
- Vigorous massage
- Consider administering aspirin, 325 mg under tongue immediately and 81 mg daily thereafter
- Follow patient daily until improvement. Provide them with clear written treatment instructions

Management of blindness from filler is more challenging as there are few reported successful treatments and no consistent evidence-based treatment

strategies. In addition, there is a strict timeline, ideally within 15 minutes, as the damage secondary to retinal ischemia is more likely to be irreversible beyond this timepoint.[21]

First and foremost, if the patient complains of ocular pain or vision changes, the injection should be stopped immediately. The patient should be immediately referred to an ophthalmologist. If an HA filler was used, hyaluronidase should be injected into the skin at the site of injection and along the path of anastomosing arteries. Injecting hyaluronidase into the area of the supraorbital or supratrochlear notch, in an attempt to cannulate the arteries, and push the hyaluronidase retrograde may also be considered. Retrobulbar or peribulbar injection of hyaluronidase has been described as a method of getting hyaluronidase closer to the area of blockage. It is controversial whether this technique is successful at salvaging vision loss and which clinician(s) should be attempting this technique. However, there have been several published and anecdotal reports of success from this technique. Other treatments that can be instituted in the office include topical timolol, rebreathing into a paper bag, ocular massage, and oral aspirin. Treatments that may be considered by the ophthalmologist to decrease intraocular pressure include anterior chamber decompression, mannitol, and acetazolamide. There have been many other treatments reported, but none have been consistently successful in restoring vision.[22]

Conclusion:

As the use of soft tissue fillers continues to rise, it is important to be aware of complications. To minimize any adverse events, a thorough understanding of facial anatomy and proper injection technique is critical. Injectors should be aware of both prevention and management strategies to minimize complications and improve patient outcomes.

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AN EVIDENCE-BASED REVIEW OF SYSTEMIC THERAPIES FOR MODERATE-TO-SEVERE PLAQUE PSORIASIS IN THE PEDIATRIC POPULATION

Introduction

Psoriasis is a chronic immune-mediated inflammatory condition of the skin that affects 2-3% of the general population.[1] Onset during childhood and adolescence occurs in up to one-third of cases.[2] The plaque subtype is most common.[3]

Moderate-to-severe plaque psoriasis can have a significant impact on quality of life for affected pediatric patients and their adult caregivers.[4,5] As a result, systemic therapy is often required. However, selecting the right treatment in this special population can be a challenge, given the paucity of data, standardized international guidelines, and approved options.

The aim of this article is to review the available evidence for systemic therapies used to treat moderate-to-severe plaque psoriasis in pediatric patients. In-depth discussion will be limited to the most rigorous studies only.

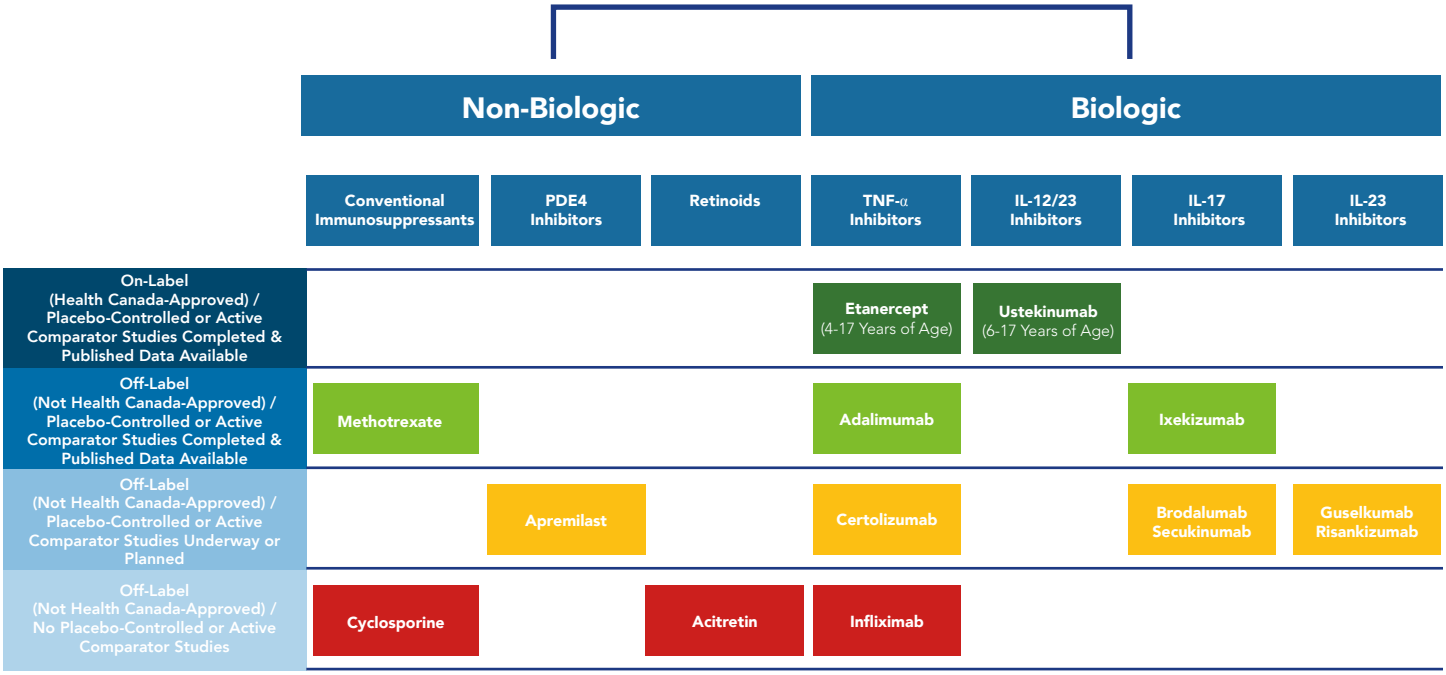

Figure 1. Systemic Therapies for Moderate-to-Severe Plaque Psoriasis in the Pediatric Population; developed by Prajapati, VH.

Overview

Systemic therapies for moderate-to-severe plaque psoriasis in pediatric patients can be classified into non-biologics and biologics. These are displayed in **Figure 1**. Despite an expanding therapeutic armamentarium, only etanercept and ustekinumab are approved by Health Canada for use in children and adolescents (etanercept: 4-17 years of age; ustekinumab: 6-17 years of age).[6]

In a multicentre, retrospective review of 390 pediatric patients with moderate-to-severe plaque psoriasis (mean age at diagnosis, 8.4 years; mean interval between diagnosis and initiation of systemic therapy, 3.0 years; 20 sites from several North American and European countries), the most frequently used treatment was methotrexate (69%), followed by etanercept (21%), acitretin (15%), and cyclosporine (8%).[7] Compared with methotrexate, more adverse events (AEs) occurred with cyclosporine and acitretin, while fewer AEs occurred with TNF-α inhibitors (only adalimumab, etanercept, and infliximab were included). Having one or more associated AEs (OR, 1.76; 95% CI, 1.06-2.92; p=0.03), gastrointestinal AEs (OR, 11.49; 95% CI, 3.31-39.88; p<0.001), AEs leading to discontinuation (OR, 5.69; 95% CI, 1.31-24.82, p=0.02), or abnormal laboratory test results (OR, 5.87; 95% CI, 1.81-18.99; p=0.003) was more likely with methotrexate than TNF-α inhibitors, but having one or more associated infections was less likely with methotrexate than TNF-α inhibitors. In addition, for those subjects who received methotrexate, the use of folic acid six days per week (OR, 0.16; 95% CI, 0.06-0.41; p<0.001) or seven days per week (OR, 0.21; 95% CI, 0.08-0.58; p=0.003) protected against gastrointestinal AEs more than folic acid one day per week, regardless of the total weekly dosage.

In a multicentre, retrospective review of 289 pediatric patients with moderate-to-severe plaque psoriasis (mean age, 11 years; four sites from a single European country), the most frequently used treatment was methotrexate (31%), followed by cyclosporine (29%) and acitretin (22%).[8] One-year drug survival rates for acitretin, methotrexate and cyclosporin were 36%, 21% and 15%, respectively. The most significant determinant of drug survival, which diminished over time, was treatment response. The *American Academy of Dermatology* and *National Psoriasis Foundation* recently published guidelines of care for psoriasis in pediatric patients.[9] Methotrexate, cyclosporine, acitretin, etanercept, adalimumab, infliximab, and ustekinumab were all considered effective systemic therapies for plaque psoriasis in children and/or adolescents; of these, only three (etanercept, adalimumab, and ustekinumab) had the highest level of evidence (I) and only two (etanercept and ustekinumab) received the strongest recommendation (A).

Non-Biologics

Methotrexate

Methotrexate is a conventional immunosuppressant. Use in children and adolescents for plaque psoriasis has not been approved by Health Canada, and, therefore, is considered off-label. The standard pediatric dosage is 0.2-0.7 mg/kg (up to a maximum of 25 mg) once weekly.[9]

It is available as an oral tablet or subcutaneous injection. Laboratory investigations are recommended before and during treatment.[9]

In a phase 3, multicentre, randomized, double-blind, active comparator study (n=114), methotrexate (0.1-0.4 mg/kg, up to a maximum dosage of 25 mg/week) was compared to adalimumab (0.4 mg/kg and 0.8 mg/kg, up to a maximum dosage of 40 mg/week) in pediatric patients with severe plaque psoriasis (≥4 to <18 years of age).[10] At week 16, the proportion of subjects achieving PASI 75 with methotrexate was significantly lower compared to 0.8 mg/kg adalimumab (32% versus 58%, p=0.027). In addition, methotrexate provided PASI 90, PASI 100, and PGA 0/1 responses in 22%, 3%, and 41% of subjects, respectively—these were numerically, but not significantly, lower compared to 0.8 mg/kg adalimumab (p=0.466, p=0.056, and p=0.083, respectively). The change in CDLQI score from baseline was -5.0 for methotrexate and -6.6 for 0.8 mg/kg adalimumab (p=0.304), while the change in PedsQL score from baseline was 1.9 for methotrexate and 10.8 for 0.8 mg/kg adalimumab (p=0.005). The most common AE associated with methotrexate was infection (57%), and none were deemed serious.

Apremilast

Apremilast is a phosphodiesterase-4 inhibitor. Use in children and adolescents for plaque psoriasis is not approved by Health Canada, and, therefore, is considered off-label. While a standard pediatric dosage has yet to be determined, both 20 mg twice daily and 30 mg twice daily were investigated in clinical trials.[11-13]

It is available as an oral tablet and laboratory investigations are not required as in adults.

In a phase 2, multicentre, open-label study, 42 patients with moderate-to-severe plaque psoriasis received weight-based dosing of apremilast (12-17 years and ≥35 kg: 20 or 30 mg twice daily; 6-11 years and ≥15 kg: 20 mg twice daily).[11] At week 16, improvements in mean PASI score were 70% (adolescents: 20 mg dosage), 67% (adolescents: 30 mg dosage), and 79% (children: 20 mg dosage). The most commonly reported AEs included nausea (52%), headache (45%), abdominal pain (43%), nasopharyngitis (38%), diarrhea (36%), and vomiting (31%). Nausea, nasopharyngitis, and diarrhea occurred more frequently in adolescents than children, while headache, abdominal pain, and vomiting occurred more frequently in children than adolescents. Nausea, headache, and diarrhea usually appeared during the first month of treatment and these generally resolved within three days of onset. Moderate weight loss developed in two adolescents, but this was transient and subsequently resolved. While the overall safety of apremilast in children and adolescents was generally similar to that observed in adults, this clinical trial did show a higher occurrence of the most commonly reported AEs. Dose titration was not part of the design and may have contributed to this finding. A phase 3, multicentre, randomized, placebo-controlled study with open-label long-term extension is underway.[12,13]

Other Non-Biologics

Cyclosporine is a conventional immunosuppressant, while acitretin is a retinoid. Although frequently used to treat plaque psoriasis in the pediatric population, neither has the Health Canada-approved indication for children and adolescents. The standard pediatric dosage is 1-5 mg/kg/day for cyclosporine and 0.1-1 mg/kg/day for acitretin.[9] Both cyclosporine and acitretin are available as oral capsules. Laboratory investigations are recommended before and during treatment.[9] At this time, there are no published data from rigorous placebo-controlled or active comparator studies to support the use of cyclosporine and acitretin for moderate-to-severe plaque psoriasis in pediatric patients; only case reports and case series exist.[9]

Biologics

Etanercept

Etanercept is a biologic that inhibits TNF-α. Use in children and adolescents for plaque psoriasis has been approved by Health Canada, and, therefore, is considered on-label (4-17 years of age). The standard pediatric dosage is 0.8 mg/kg (up to a maximum of 50 mg) once weekly, but 0.4 mg/kg twice weekly has also been investigated in clinical trials. It is available as a subcutaneous injection. Laboratory investigations are recommended before treatment, with annual rescreening for tuberculosis suggested in high-risk individuals.[9]

In a phase 3, multicentre, randomized, placebo-controlled study (n=211), etanercept (0.8 mg/kg once weekly, up to a maximum dosage of 50 mg/week) was compared to placebo in pediatric patients with moderate-to-severe plaque psoriasis (4-17 years of age).[14] At week 12, etanercept was superior to placebo (p<0.001) for PASI 50 (75% versus 23%), PASI 75 (57% versus 11%), PASI 90 (27% versus 7%), and PGA 0/1 (53% versus 13%).

Additionally, the mean improvement in CDLQI from baseline was greater with etanercept than placebo (52% versus 18%, p<0.001). In a subanalysis, significant differences (p<0.001) in CDLQI change from baseline were noted as early as week 2 when comparing etanercept to placebo (27% versus 8%).[15] At week 36, after 24 weeks of open-label treatment, PASI 75 was achieved in 68% and 65% with mean improvements in CDLQI of 63% and 59% in subjects initially assigned to etanercept and placebo, respectively.[14] During the final withdrawal-retreatment phase, intermittent treatment was also found to be effective, with 80% of subjects on etanercept maintaining or regaining PASI 75 at the end of the 12-week period.[14,16] The most common AEs were upper respiratory tract infection, headache, and nasopharyngitis.[14] Four serious AEs occurred in three subjects being treated with etanercept during the open-label period. This included three infections. All resolved without sequelae.

A long-term extension of the aforementioned clinical trial was conducted.[17,18] Of 182 enrolled subjects, 181 received treatment with 140 (77%) and 69 (38%) completing week 96 and week 264 of the study, respectively. At week 96, etanercept provided sustained responses for PASI 50 (89%), PASI 75 (61%), PASI 90 (30%), and PGA 0/1 (47%).[17] For this interim analysis, 80% reported at least one AE; five serious AEs occurred in three patients, none of which were treatment-related. At week 264, etanercept provided PASI 75, PASI 90, and sPGA 0/1 responses in ~60-70%, ~30-40%, and ~40-50% of subjects, respectively.[18] For this final analysis, 89% reported at least one AE. Upper respiratory tract infection (38%), nasopharyngitis (26%), and headache (22%) were most common. Eight serious AEs occurred in seven subjects; only one (cellulitis) was considered related to treatment. There were no cases of opportunistic infections or malignancy.

Adalimumab

Adalimumab is a biologic that inhibits TNF-α. Use in children and adolescents for plaque psoriasis has not been approved by Health Canada, and, therefore, is considered off-label. The standard pediatric dosage is 0.8 mg/kg (up to a maximum of 40 mg) at weeks 0, 1, and 2, then every 2 weeks thereafter.[9] It is available as a subcutaneous injection. Laboratory investigations are recommended before treatment, with annual rescreening for tuberculosis suggested in high-risk individuals.[9]

In a phase 3, multicentre, randomized, double-blind, active comparator study (n=114), adalimumab (0.4 mg/kg and 0.8 mg/kg, up to a maximum dosage of 40 mg/week) was compared to methotrexate (0.1-0.4 mg/kg, up to a maximum dosage of 25 mg/week) in pediatric patients with severe plaque psoriasis (≥4 to <18 years of age).[9] The proportion of subjects with PASI 75 at week 16 was significantly higher with 0.8 mg/kg adalimumab compared to methotrexate (58% versus 32%, p=0.027), a difference being noted as early as week 4 (24% versus 0%, p=0.002); in comparison to methotrexate, 0.8 mg/kg adalimumab also provided numerically, but not significantly, greater rates of PASI 90 (29% versus 22%, p=0.466), PASI 100 (18% versus 3%, p=0.056), and PGA 0/1 (61% versus 41%, p=0.083). Additionally, the change in CDLQI score from baseline was -6.6 for 0.8 mg/kg adalimumab and -5.0 for methotrexate (p=0.304), while the change in PedsQL score from baseline was 10.8 for 0.8 mg/kg adalimumab and 1.9 for methotrexate (p=0.005). The proportion of subjects achieving PASI 75, PASI 90, PASI 100, and PGA 0/1 with 0.4 mg/kg adalimumab at week 16 was 44%, 31%, 10%, and 41%, respectively. The most common AE of adalimumab was infection, reported in 45% (0.8 mg/kg adalimumab) and 56% (0.4 mg/kg adalimumab) of subjects; only one (food poisoning coded as gastrointestinal infection) was deemed serious. A total of three serious AEs were recorded and not judged to be related to treatment.

A long-term extension of the aforementioned clinical trial was conducted.[19] Of the 114 subjects randomized in the initial treatment period, 108 entered the long-term extension (n=36 in each group) with 90 (83%) completing the study through week 52. A total of 93 subjects received 0.8 mg/kg adalimumab. Efficacy in terms of PASI 75 was maintained or improved from entry to end of the long-term extension. At week 52, the overall proportion of subjects achieving PASI 75, PASI 90, PASI 100, and PGA 0/1 with adalimumab was 69%, 48%, 30%, and 60%, respectively. CDLQI and PedsQL also improved through week 52. For the final analysis, 79% reported at least one AE. Nasopharyngitis (26%), headache (21%), and nasopharyngitis (12%) were most common; five serious AEs occurred in five subjects with only one (eye nevus) being considered possibly related to treatment. There were no cases of malignancy, but two subjects (1.9%) did have latent (but not active) tuberculosis.

Ustekinumab

Ustekinumab is a biologic that inhibits IL-12 and IL-23. Its use in children and adolescents for plaque psoriasis has been approved by Health Canada, and, therefore, is considered on-label (6-17 years of age). The standard pediatric dosage is 0.75 mg/kg (≤60 kg), 45 mg (>60 kg but ≤100 kg), and 90 mg (>100 kg) at weeks 0 and 4, then every 12 weeks thereafter.[9] It is available as a subcutaneous injection. Laboratory investigations are recommended before treatment, with annual rescreening for tuberculosis suggested in high-risk individuals.[9]

In a phase 3, multicentre, randomized, double-blind, placebo-controlled study (n=110), weight-based dosing of ustekinumab, both standard (≤60 kg: 0.75 mg/kg; >60 kg and ≤100 kg: 45 mg; >100 kg: 90 mg) and half-standard (≤60 kg: 0.375 mg/kg; >60 kg but ≤100 kg: 22.5 mg; >100 kg: 45 mg), were compared to placebo in pediatric patients with moderate-to-severe plaque psoriasis (12-17 years of age).[20] At week 12, both ustekinumab standard and half-standard dosage were superior to placebo (p<0.001) for PGA 0/1 (69.4% and 67.6% versus 5.4%), PGA 0 (47.2% and 32.4% versus 2.7%), PASI 75 (80.6% and 78.4% versus 10.8%), and PASI 90 (61.1% and 54.1% versus 5.4%). These responses were maintained from week 12 to week 52 in subjects receiving ustekinumab at baseline. Through week 12, 44% and 51% of subjects in the ustekinumab standard and half-standard dosage groups, respectively, had at least one AE. Nasopharyngitis (3% and 14% for ustekinumab standard and half-standard dosages, respectively) and headache (8% and 11% for ustekinumab standard and half-standard dosages, respectively) were most common. Through week 60, 82% of subjects receiving ustekinumab reported at least one AE. Nasopharyngitis (35%) and upper respiratory traction infection (13%) were most common. Infections occurred in 67% of subjects receiving ustekinumab; only two (pyelonephritis and ear infection) were deemed serious. There were no cases of opportunistic infections or malignancy.

In a phase 3, multicentre, open-label study (n=44), pediatric patients (6-11 years of age) with moderate-to-severe plaque psoriasis received weight-based dosing of ustekinumab (<60 kg: 0.75 mg/kg; ≥60 kg and ≤100 kg: 45 mg; >100 kg: 90 mg).[21] At week 12, ustekinumab achieved PGA 0/1, PGA 0, PASI 75, PASI 90, PASI 100, and CLDQI 0/1 in 77%, 39%, 84%, 64%, 34%, and 62% of subjects, respectively, with a mean change in CDLQI of -6.3. These responses were maintained from week 12 to week 52. Through week 56, 77% of subjects had at least one AE, with nasopharyngitis (25%), pharyngitis (14%), and upper respiratory tract infection (14%) being most common. Infections occurred in 66% of subjects receiving ustekinumab. Three serious AEs occurred and were not judged to be related to treatment.

Ixekizumab

Ixekizumab is a biologic that inhibits IL-17, specifically IL-17A. Its use in children and adolescents for plaque psoriasis is not approved by Health Canada, and, therefore, is considered off-label. The standard pediatric dosage involves loading doses of 160 mg (>50 kg), 80 mg (≥25 kg and ≤50 kg), or 40 mg (<25 kg) followed by maintenance doses of 80 mg (>50 kg), 40 mg (≥25 kg and ≤50 kg), or 20 mg (<25 kg) every 4 weeks thereafter.[22] It is available as a subcutaneous injection and laboratory investigations are recommended before treatment, with annual rescreening for tuberculosis suggested in high-risk individuals.[9]

In a phase 3, multicentre, randomized, double-blind, placebo-controlled study (n=171), ixekizumab (<25 kg: 40 mg loading dose/20 mg maintenance dose; ≥25 kg and ≤50 kg: 80 mg loading dose/40 mg maintenance dose; >50 kg: 160 mg loading dose/ 80 mg maintenance dose) was compared to placebo in pediatric patients with moderate-to-severe plaque psoriasis (6-17 years of age).[22] At week 12, ixekizumab was superior to placebo (p<0.001) for PASI 50 (92% versus 38%), PASI 75 (89% versus 25%), PASI 90 (78% versus 5%), PASI 100 (50% versus 2%), sPGA 0/1 (81% versus 11%), sPGA 0 (52% versus 2%), Itch NRS≥4 (71% versus 20%), CDLQI/DLQI 0/1 (64% versus 23%), and PatGA 0/1 (79% versus 16%). In addition, significant differences between ixekizumab and placebo were noted as early as week 1 for PASI 50 (p<0.001), PASI 75 (p=0.032) and Itch NRS≥4 (p=0.008) and as early as week 4 (p<0.001) for PASI 90, PASI 100, sPGA 0/1, and sPGA 0. A higher proportion of subjects achieved clearance of scalp and genital psoriasis by week 12 with ixekizumab than placebo (p<0.001). Additionally, in comparison to placebo, ixekizumab resulted in significantly greater mean change from baseline at week 12 for Itch NRS (p<0.001), NAPSI (p=0.005), PSSI (p<0.001), and PPASI (p=0.006). Responses at week 12 with ixekizumab were sustained or further improved through week 48 for PASI 50 (92%),

PASI 75 (90%), PASI 90 (83%), PASI 100 (55%), sPGA 0/1 (81%), sPGA 0 (57%), Itch NRS≥4 (87%), CDLQI/DLQI 0/1 (76%), and PatGA 0/1 (86%), with complete clearance of special sites also noted, including nail (50%), scalp (74%), palmoplantar (76%), and genital (90%). Through week 12, 56% of subjects receiving ixekizumab reported at least one AE, with only one deemed serious. Infections occurred in 32%; none of these were serious. Through week 48, 82% of subjects receiving ixekizumab had at least one AE, with 13 deemed serious; infections occurred in 66% (two serious: acute otitis media and tonsillitis). A total of four subjects (2%) developed probable Crohn's disease (one during the double-blind treatment period and three during the maintenance period). There were no cases of opportunistic infections or malignancy.

In the aforementioned clinical trial, ixekizumab was also compared to etanercept in countries where etanercept had received approval for severe plaque psoriasis in pediatric patients.[22] At week 12, responses with ixekizumab were significantly greater than etanercept for PASI 90 (76% versus 40%, p=0.003), PASI 100 (61% versus 17%, p<0.001), and sPGA 0 (63% versus 17%, p<0.001). In addition, responses with ixekizumab were numerically, but not significantly, greater than etanercept for PASI 75 (84% versus 63%, p=0.089) and sPGA 0/1 (76% versus 53%, p=0.070).

Other Biologics

Despite their indication for plaque psoriasis in adults, other biologics that inhibit TNF-α (infliximab; certolizumab), IL-17 (brodalumab; secukinumab), and IL-23 (guselkumab; risankizumab) are not approved by Health Canada for use in children and adolescents. A phase 3 study has been completed for secukinumab, with the long-term extension ongoing.[23,24] Brodalumab, certolizumab, guselkumab, and risankizumab are also being investigated.[25-28]

Conclusion

Well-designed, randomized, placebo-controlled or active comparator studies have documented the efficacy and safety of methotrexate, adalimumab, etanercept, ixekizumab, and ustekinumab in pediatric plaque psoriasis with only methotrexate and adalimumab as well as ixekizumab and etanercept being compared head-to-head. Clinical trials investigating the use of secukinumab have been completed, while those for apremilast, brodalumab, certolizumab, guselkumab, and risankizumab are either underway or planned. As the therapeutic landscape continues to evolve and additional robust short- and long-term data become available, this will help fulfill the unmet need for more targeted Health Canada-approved systemic therapies to treat moderate-to-severe plaque psoriasis in the pediatric population.

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MELANOMA UPDATE AND REVIEW: AJCC STAGING AND ADJUVANT TREATMENT

In an era of rapidly changing medical guidelines it is important for dermatologists to be aware of the current recommendations for disease management. This summary article will highlight the 'need-to-know' information for the clinical dermatologist on staging, sentinel lymph node biopsy recommendations, and new therapeutic options including adjuvant therapy for the management of patients with melanoma.

AJCC Update

In 2016, the American Joint Committee on Cancer (AJCC) expanded its staging guidelines to incorporate additional evidence-based prognostic factors. In January 2018, the AJCC 8th Edition was implemented, and shortly thereafter, the National Comprehensive Cancer Network (NCCN) revised its management guidelines which were updated again in March 2019 (and more recently in May 2020).[2] New stage classifications were produced as the previous versions included patients from before sentinel lymph node biopsies were routine. The AJCC 7th Edition stage I and II patients likely included patients with occult microscopic regional disease, and therefore a worse survival. In the 8th edition, a new definition for T1a and T1b Tumor staging was introduced and there were significant changes to the Stage III data set.[1] Some of the 8th Edition AJCC changes are listed in **Table 1** below.

CATEGORY	CHANGE
T category	• T staging changes: o T1a <0.8 mm without ulceration o T1b<0.8 mm with ulceration or 0.8-1.0 mm with or without ulceration o Mitoses removed from staging • Pathology measurements of Breslow thickness measured to the nearest 0.1 mm instead of 0.01 mm
N Category	• Microsatellites, satellites, an in-transit metastases definitions dropped, and categorization based on number of lymph nodes involved • The terms "clinically occult" and "clinically detected" replace the descriptors "microscopic" and "macroscopic"
M category	• M1 category defined by anatomic site and LDH level o 0-LDH normal o 1-LDH elevated o non-visceral site M1a, lung M1b, visceral non-CNS M1c, CNS M1d • New M1d stage for distant CNS metastases
STAGE GROUPINGS	• Four Stage III groupings, increased from three • New Stage: IIID: for thick and ulcerated tumours (T4b+N3c-c)

Table 1. Notable 8th edition AJCC changes; adapted from Gershenwald et al., 2018

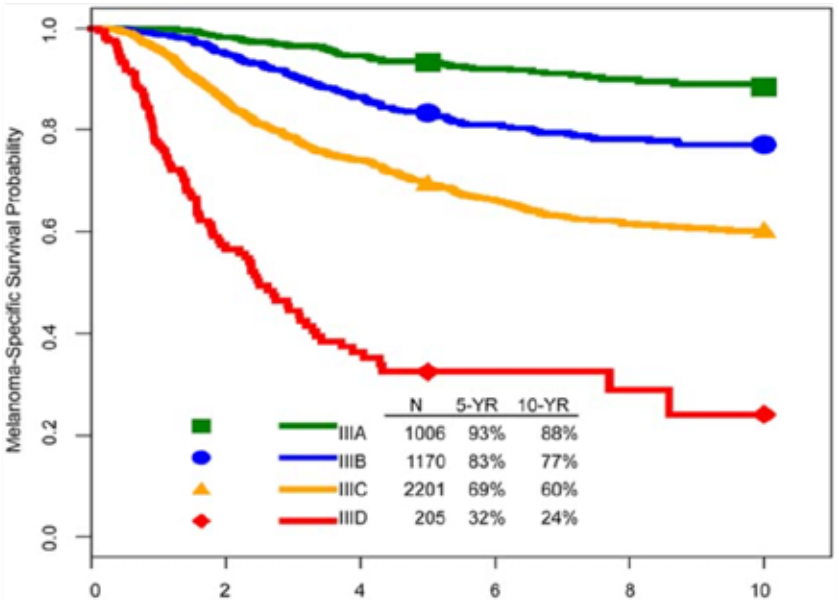

Figure 1. Kaplan-Meier Melanoma-Specific Survival Curves According to Stage III Subgroups; American Joint Committee on Cancer 8th Edition Cancer Staging Manual 1

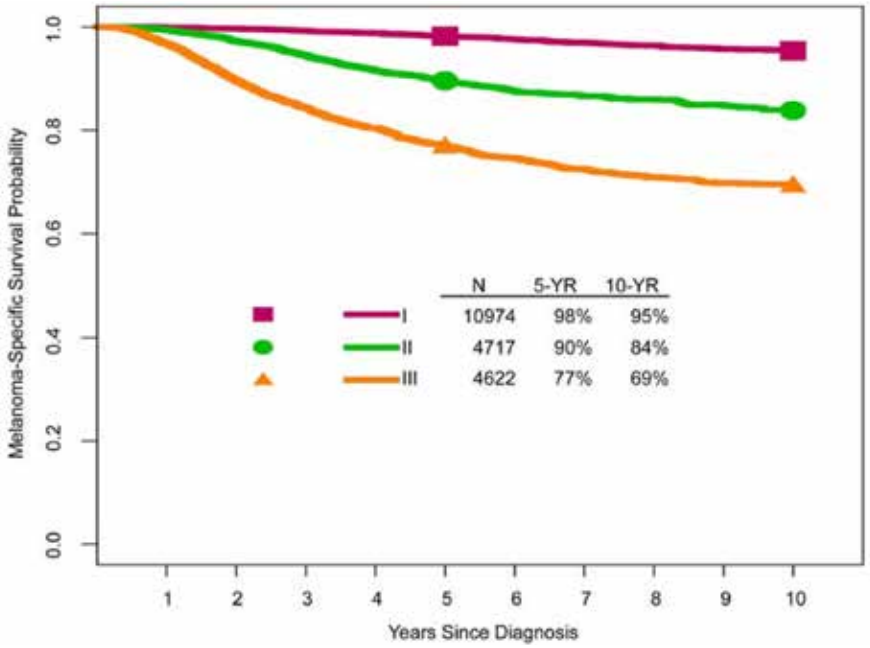

Figure 2. Kaplan-Meier Melanoma-Specific Survival Curves According to Stage in Patients With Stage I to III Melanoma From the Eighth Edition International Melanoma Database.

Importantly for dermatologists, it is now recommended to discuss a sentinel lymph node biopsy in every patient except those with T1a (<0.8mm and no ulceration) or in situ disease. Of note, histological regression is not noted in the AJCC 8th Edition Guidelines and is not felt to be an indication for a sentinel lymph node biopsy in a thin melanoma.[1]

With regard to the clinical workup for melanoma, there is no imaging indicated for Stage 0, Stage I, or Stage IIA disease, due to both the high rate of false positives and the lack of positive impact on treatment, progression, or survival.[1,2]

Additionally, the MSLT-2 trial (NCT00297895) demonstrated a lack of prognostic benefit for performing a complete lymph node dissection in patients with a positive sentinel lymph node biopsy.[3] Instead, these patients are largely observed with serial ultrasounds of the lymph node basins every 3 months for 2 years and then every 6 months for 3 years.

While sentinel lymph node biopsy itself has not been shown to improve disease-specific survival, a positive result upstages a patient to stage III. It is still recommended to conduct a sentinel lymph node biopsy (T1b or higher) to gain important staging and prognostication information and facilitate adjuvant therapy decision making. Adjuvant therapy has been shown to improve recurrence-free survival (RFS) and overall survival (OS) in selected high-risk stage III patients.[8-14]

As mentioned above, in the AJCC 8th Edition, Stage III was divided and a new category was added to include a group that had a worse prognosis: Stage IIID for thick and ulcerated tumours (T4b+N3c-c) with a 32% 5-year survival **(Figure 1)**.[1]

What does a dermatologist need to know about systemic treatment?

Systemic therapies can be broadly divided into 2 categories: targeted treatments (TT) or immuno-oncology (IO) agents. Despite several relatively recent Health Canada approvals for melanoma therapies, a large percentage of patients with advanced metastatic melanoma remain at significant risk of mortality. Thus, an unmet need remains for effective therapies in patients with melanoma **(Figure 2)**[1,4,5,6.]

Systemic therapies

In 2011, ipilimumab was approved for the treatment of unresectable metastatic melanoma as monotherapy. This was the first of 7 new agents that have

demonstrated improvement in overall survival in metastatic melanoma **(Table 2)**

TARGETED THERAPY (TT)	IMMUNO-ONCOLOGY AGENT (IO)
VEMURAFENIB (BRAF INHIBITOR)	IPILIMUMAB (ANTI-CTLA-4)
COBIMETINIB (MEK INHIBITOR)	PEMBROLIZUMAB (ANTI-PD-1)
DABRAFENIB (BRAF INHIBITOR)	NIVOLUMAB (ANTI-PD-1)
TRAMETINIB (MEK INHIBITOR)	

Table 2. Canadian approved therapies for the treatment of metastatic melanoma.

Adjuvant therapy

Adjuvant therapy is a strategy to prevent, and reduce recurrence of, metastatic disease.[5] The goal of adjuvant melanoma treatment is to provide a potential cure before disease recurrence and progression to an advanced stage. Most traditional chemotherapies have proven ineffective as adjuvant treatment, and systemic therapies (e.g. checkpoint inhibitors, targeted therapies) are now preferred options for adjuvant therapy in advanced melanoma.[7]

Surgery is the preferred treatment for localized melanoma, however, patients with lymph node involvement are at high risk of relapse after surgery. Patients with AJCC stages IIB or higher melanoma (TNM N > 0) have a high risk of recurrence and death when treated with surgical management alone. Adjuvant therapy is appropriate for patients with no evidence of macroscopic metastases, but who have a high risk for microscopic metastases. Adjuvant therapy is typically started within weeks of surgery.[2,6,7]

Systemic therapies such as targeted treatments and immuno-oncology agents were first studied and approved in patients with Stage IV disease. Currently,

STUDY NAME	COMBI-AD[9]	CHECKMATE238[10]	KEYNOTE-054[11]
NUMBER OF PATIENTS	870	906	1019
STUDY ARM	DABRAFENIB +TRAMETINIB (N = 438) VS PLACEBO (N = 432)	NIVOLUMAB (N = 453) VS IPILIMUMAB (N = 453)	PEMBROLIZUMAB (N = 514) VS PLACEBO (N = 505)
DISEASE STAGES INCLUDED (AJCC v7)	RESECTED STAGE IIIA (>1 MM METASTASIS), IIIB, IIIC	RESECTED STAGE IIIB/C OR STAGE IV	RESECTED STAGE IIIA (>1 MM METASTASIS), IIIB, IIIC
BRAF MUTATION-POSITIVE PATIENTS, %	100	41	48
PRIMARY ENDPOINT	➤ RFS	➤ RFS	➤ RFS
SECONDARY ENDPOINT	➤ OS ➤ DMFS ➤ Freedom from relapse ➤ Safety	➤ OS ➤ Safety & AE profile ➤ RFS by PD-L1 expression ➤ HR QoL	➤ DMFS ➤ OS ➤ Safety ➤ HR QoL
FOLLOW UP	5 YEARS AT ASCO 2020	3 YEARS AT ESMO 2019	3 YEARS AT ASCO 2020

Table 4. Pivotal adjuvant melanoma trials
DMFS= Distant Metastasis-Free Survival; OS= overall survival; RFS= relapse-free survival; AE= adverse event; HR QoL= Health- related Quality of Life

STUDY NAME	COMBI-AD[8,11,12] N=438	CHECKMATE238[9,10,13] N=453	KEYNOTE-054[11]
EFFICACY	Dabrafenib/ Trametinib	NIVOLUMAB (N = 453) VS IPILIMUMAB (N = 453)	PEMBROLIZUMAB
1-YEAR RFS, %	88%	70%	75%
2-YEAR RFS, %	67%	62%	68%
3-YEAR RFS, %	59%	58%	64%
4-YEAR RFS, %	55%	-	-
5-YEAR RFS, %	52%	-	-
RFS, HR VALUE (95% CI)	0.51 (0.42-0.61)	0.68 (0.56-0.82)	0.56 (0.47-0.68)
DISCONTINUATION DUE TO DISEASE RECURRENCE	5%	26%	21%
3-YEAR OS %	86%	-	-
SAFETY			
AEs (GRADE 3/4)	97 (41%)	96 (25%)	93 (31%)
AEs LEADING TO DISCONTINUATION	26%	9.7%	14%

Table 5. Pivotal melanoma trials: 5-year and 3-year data

most adjuvant trials are aimed at improving RFS and OS in patients with Stage III disease.[1,2,8] There are now 3 treatments approved by Health Canada for melanoma in adult patients with regional lymph node involvement as adjuvant therapy after complete resection: nivolumab, pembrolizumab and combination dabrafenib and trametinib **(Table 3)**.

High dose Interferon- alpha 2b is also currently approved for adjuvant treatment for high risk melanoma, but it is no longer

THERAPIES APPROVED IN CANADA FOR ADJUVANT THERAPY FOR MELANOMA:
NIVOLUMAB (ANTI-PD1 ANTIBODY)
PEMBROLIZUMAB (ANTI-PD1 ANTIBODY)
DABRAFENIB AND TRAMETINIB (BRAF INHIBITOR AND MEK INHIBITOR COMBINATION)

Table 3. Therapies approved in Canada for Adjuvant therapy for melanoma.

used due to low efficacy and high toxicity (15 RCTs and 3 meta-analyses, 7% absolute disease-free survival and 3% overall survival benefit). Radiation is used to decrease risk of recurrence locally if present: multiple lymph nodes, large lymph nodes, or extra-nodal extension. Recently at

the American Society of Clinical Oncology (ASCO) Annual Meeting in 2020, there were 3- and 5-year updates on pivotal adjuvant therapy trials **(see Table 4 and Table 5)**. The 5-year and 3-year adjuvant data shown at ASCO 2020 is reassuring, showing improvements in RFS and early evidence of improved OS.

Why should dermatologists know about adjuvant therapies?

The Breslow Paradox

It has been shown that more people die of thin melanomas than thick melanomas, due to sheer numbers, even though the absolute risk of dying is higher in thicker melanomas.

In addition, not all thin melanomas behave the same way as some are easily cured by surgery and some are biologically aggressive, metastasizing early.[15] In the future, clinicians may greatly benefit from companion diagnostics that can help determine which thin melanomas are biologically aggressive, so that these patients may benefit from adjuvant therapy early on, possibly in stage II or as early as stage I.

This may mean dermatologists could be prescribing these treatments more commonly in the future.

In summary, there is a rapid expansion of evidence-based information surrounding the diagnosis and management of melanoma including staging, the use of sentinel lymph node biopsy and the use of adjuvant systemic therapies. This review highlights the most important updates for daily clinical practice.

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AJCC Melanoma of the Skin Staging 8th Edition

Definitions

Primary Tumor (T)

TX Primary tumor cannot be assessed (for example, curettaged or severely regressed melanoma)

T0 No evidence of primary tumor

Tis Melanoma in situ

T1 Melanomas 1.0 mm or less in thickness

T2 Melanomas 1.1 - 2.0 mm

T3 Melanomas 2.1 - 4.0 mm

T4 Melanomas more than 4.0 mm

NOTE: a and b subcategories of T are assigned based on ulceration and thickness as shown below:

T CLASSIFICATION	THICKNESS (mm)	ULCERATION STATUS
T1	≤1.0	a: Breslow < 0.8 mm w/o ulceration b: Breslow 0.8-1.0 mm w/o ulceration or ≤ 1.0 mm w/ ulceration.
T2	1.1-2.0	a: w/o ulceration b: w/ ulceration
T3	2.1-4.0	a: w/o ulceration b: w/ ulceration
T4	>4.0	a: w/o ulceration b: w/ ulceration

Regional Lymph Nodes (N)

NX Patients in whom the regional nodes cannot be assessed (for example previously removed for another reason)

N0 No regional metastases detected

N1-3 Regional metastases based on the number of metastatic nodes, number of palpable metastatic nodes on clinical exam, and presence or absence of MSI[2]

NOTE: N1-3 and a-c subcategories assigned as shown below:

N CLASSIFICATION	# NODES	CLINICAL DETECTABILITY/MSI STATUS
N1	0-1 node	a: clinically occult[1], no MSI[2] b: clinically detected[1], no MSI[2] c: 0 nodes, MSI present[2]
N2	1-3 nodes	a: 2-3 nodes clinically occult[1], no MSI[2] b: 2-3 nodes clinically detected[1], no MSI[2] c: 1 node clinical or occult[1], MSI present[2]
N3	>1 nodes	a: >3 nodes, all clinically occult[1], no MSI[2] b: >3 nodes, ≥1 clinically detected[1] or matted, no MSI[2] c: >1 nodes clinical or occult[1], MSI present[2]

Distant Metastasis (M)

M0 No detectable evidence of distant metastases

M1a Metastases to skin, sub cutaneous, or distant lymph nodes

M1b Metastases to lung

M1c Metastases to all other visceral sites

M1d Metastases to brain

NOTE: Serum LDH is incorporated into the M category as shown below:

M CLASSIFICATION	SITE	Serum LDH
M1a-d	Skin/subcutaneous/nodule (a), lung (b) other visceral (c), brain (d)	Not assessed
M1a-d(0)	Skin/subcutaneous/nodule (a), lung (b) other visceral (c), brain (d)	Normal
M1a-d(1)	Skin/subcutaneous/nodule (a), lung (b) other visceral (c), brain (d)	Elevated

ANATOMIC STAGE/PROGNOSTIC GROUPS

	Clinical Staging[3]			Pathologic Staging			
Stage 0	Tis	N0	M0	0	Tis	N0	M0
Stage IA	T1a	N0	M0	IA	T1a	N0	M0
Stage IB	T1b	..	..		T1b	..	..
	T2a	..	..	IB	T2a	..	..
Stage IIA	T2b	N0	M0	IIA	T2b	M0	M0
	T3a	..	..		T2a	..	..
Stage IIB	T3b	..	..	IIB	T3b	..	..
	T4a	..	..		T4a	..	..
Stage IIC	T4b	..	..	IIC	T4b	..	..
Stage III	Any T	≥N1	M0	IIIA	T1-2a	N1a	M0
	..	..	..		T1-2a	N2a	..
	..	..	..	IIIB	T0	N1b-c	M0
	..	..	..		T1-2a	N1b-c	..
	..	..	..		T1-2a	N2b	..
	..	..	..		T2b-3a	N1a-2b	..
	..	..	..	IIIC	T0	N2b-c	M0
	..	..	..		T0	N3b-c	..
	..	..	..		T1a-3a	N2c-3c	..
	..	..	..		T3b-4a	Any N	..
	..	..	..		T4b	N1a-2c	..
	..	..	..	IIID	T4b	N3a-c	M0
Stage IV	Any N	Any N	M1	IV	Any T	Any N	M1

Notes

[1] Nodes are designated as 'clinically detectable' if they can be palpated on physical exam and are confirmed melanoma by pathology following excision/biopsy.

[2] MSI comprise any satellite, locally recurrent, or in transit lesions.

[3] Clinical staging includes microstaging of the primary melanoma and clinical/radiologic evaluation for metastases. By convention it should be used after complete excision of the primary melanoma with clinical assessment for regional and distant metastases.

[4] Pathologic staging includes microstaging of the primary melanoma and pathologic information about the regional lymph nodes after partial or complete lymphadenectomy.

ABOUT THE AUTHOR

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Dr. Vipul Jain is an allergist and immunologist who has independent practices in Niagara Falls and Stoney Creek, Ontario. He completed his Bachelor of Medicine and Bachelor of Surgery (MBBS) from Kasturba Medical College, India. He subsequently completed his internal medicine residency at Memorial University of Newfoundland. Thereafter, he completed his Royal College fellowship in clinical immunology and allergy from University of Manitoba. He has a specific interest in asthma, allergic rhinitis, atopic dermatitis, and food allergies. He is an adjunct professor at McMaster University in the department of Medicine and is also an investigator with Probity Medical Research.

ATOPIC COMORBIDITIES OF ATOPIC DERMATITIS

Introduction

Atopic dermatitis (AD) is a chronic, pruritic, inflammatory, multidimensional-burden skin disease. It is associated with numerous comorbidities, which have been summarized in the literature previously. This chronic inflammatory dermatosis is part of the atopic syndrome. This review will focus on atopic comorbidities of atopic dermatitis with specific attention to asthma, allergic rhinitis, and possible associated food allergies in the AD patient. We hope to help equip the dermatology outpatient practice with an economical, efficient, and validated tool which can be used to identify uncontrolled asthmatic patients who present with atopic dermatitis and to address questions commonly asked about the role of food allergies in atopic dermatitis.

Atopic Dermatitis and Asthma

Asthma is a complex, chronic inflammatory airway disease that manifests as inflammation and hyperresponsive airways. Approximately 3.8 million Canadians, 10 percent of the population, live with asthma.[1] Studies have indicated that AD and asthma may be correlated, with as many as 19 to 45 percent of asthmatic children having concomitant atopic dermatitis.[2] Atopic dermatitis in adults with asthma has been shown to be associated with a higher number of annual asthma exacerbations and more persistent asthma.[3]

The mechanism underlying AD's progression to asthma remains somewhat unknown, although recent findings suggest that defective epithelial barrier function plays a key role in the pathophysiology of airway inflammation in asthmatic patients.[4] The barrier consists of epithelial apical junctional complexes, which are multiprotein subunits known for their roles in cell-to-cell adhesion and barrier integrity.[4] These complexes can be compromised in asthmatic patients through numerous sophisticated pathways which are beyond the scope of this article. It should be noted that decades of studies suggest that the relationship between AD and asthma is more complicated than a direct causality.[5,6] A cluster analysis of 214 infants found that children with early-onset AD faced a higher risk of developing asthma if they had had multiple sensitizations to food allergens or a familial history of asthma.[7]

Uncontrolled asthma lowers health-related quality of life. A national survey of U.S. residents showed that children with uncontrolled asthma were rated by caregivers as having significantly lower physical and

psychological health, as well as missing significantly more school days than their controlled-asthma counterparts.[8] A large prospective cohort study corroborates these findings.[9]

The Asthma Control Test (ACT) may offer a convenient resource to detect and refer poorly controlled asthma patients in various clinical settings, such as dermatology outpatient clinics when evaluating atopic dermatitis patients. The ACT is a 5-item patient-completed questionnaire and asks about daytime and nighttime symptoms, medication use, and impaired productivity.[10] **(Figure 1)**. Scores range from 5 to 25, with well-controlled asthma yielding a score of 25. A score of 19 or lower indicates generally uncontrolled asthma; a score of 15 or lower is more concerning, as it indicates poorly controlled asthma[10]. Patients who score poorly should be referred to an allergist/immunologist or a respirologist. Schatz et al.[10] demonstrated that the ACT is reliable over time, internally consistent, and valid between baseline ACT scores, specialists' baseline asthma control assessments, Asthma Control Questionnaire scores, and percent predicted FEV[1] values. It was further found that ACT scores were lower in those with poorer asthma control (as judged by asthma specialists) than those with better asthma control, with percent predicted FEV[1] and therapy changes measuring "asthma control." The study additionally found that an ACT score of 19 indicated likely cause for concern; of patients with ACT scores lower than 19, only 27 percent were deemed to have well or completely controlled asthma. Conversely, of patients with ACT scores greater than 19, only 8 percent were deemed by an asthma specialist to have poorly controlled or not controlled asthma.

Asthma Control Test™

1. In the past 4 weeks, how much of the time did your asthma keep you from getting as much done at work, school or at home?

All of the time	Most of the time	Some of the time	A little of the time	None of the time
o	o	o	o	o
1	2	3	4	5

2. During the past 4 weeks, how often have you had shortness of breath?

More than Once a day	Once a day	3 to 6 times a week	Once or twice a week	Not at all
o	o	o	o	o
1	2	3	4	5

3. During the past 4 weeks, how often did your asthma symptoms (wheezing, coughing, shortness of breath, chest tightness or pain) wake you up at night or earlier than usual in the morning?

4 or more nights a week	2 to 3 nights a week	Once a week	Once or twice	Not at all
o	o	o	o	o
1	2	3	4	5

4. During the past 4 weeks, how often have you used your rescue inhaler or nebulizer medication (such as albuterol)?

3 or more times per day	1 or 2 times per day	2 or 3 times per week	Once a week or less	Not at all
o	o	o	o	o
1	2	3	4	5

5. How would you rate your asthma control during the past 4 weeks?

Not Controlled at All	Poorly Controlled	Somewhat Controlled	Well Controlled	Completely Controlled
o	o	o	o	o
1	2	3	4	5

Figure 1. Asthma Control Test (ACT); adapted from Schatz et al, 2006

As Schatz and colleagues remind us, "there is no gold standard for asthma control measurement".[10] Point-in-time measurements such as FEV[1] values often do not give a full picture of respiratory health and should not be used in isolation to diagnose asthma.[11] The ACT is a physician-tested screening tool that can be used to screen for uncontrolled asthma patients in the atopic dermatitis patient population.

Atopic Dermatitis and Allergic Rhinitis

Allergic rhinitis is an IgE-mediated reaction that, when triggered by aeroallergens, leads to sneezing, nasal pruritis, congestion, and rhinorrhea.[12] In a study of 2,270 children with physician-confirmed AD, Kapoor et al.[13] found that nearly two-thirds of subjects reported having either or both of allergic rhinitis and asthma. The presence of these comorbidities was found to correlate with poor AD control. These results indicate that when AD goes uncontrolled, respiratory health may decline.

A mouse-model study found that epicutaneous aeroallergen sensitization initiates T-helper Type 2 (Th2) immunity, priming for nasal hyperresponsiveness[14]. Akei et al. conclude that antigen sensitization can efficiently occur via skin.[14] Similarly, other mouse-model studies have demonstrated that epicutaneous sensitization to ovalbumin and peanut promotes Th2 immunity, as measured by increased Interleukin-4 secretion and high specific IgE and IgG1 levels.[15]

Exposure to aeroallergens can trigger AD-like symptoms[14]. House dust mites *Dermatophagoides pteronyssinus* and *farinae* are particularly pervasive and thus significant. In a multi-center, randomized, double-blind trial, Werfel et al.[16] administered subcutaneous immunotherapy (SCIT) to AD patients with Type I sensitization to house dust mite antigens over the course of one year. They found that SCORAD (SCORing atopic dermatitis) scores decreased, as well as the use of topical corticosteroids and oral antihistamines.

However, the triggers for AD are multifactorial and house dust mite allergy may be only one of several variables. It is thus unsurprising that other studies show little evidence to support the effectiveness of SCIT in treating AD patients. Therefore, desensitization of dust mite allergens in AD patients is an area of debate and higher quality research is required prior to drawing concrete conclusions.

Atopic Dermatitis and Food Allergies

Food allergy is defined by the National Institute of Allergy and Infectious Disease (NIAID) as an "adverse health effect arising from a specific immune response that occurs reproducibly on exposure to a given food"[17] and broadly comprises several types of reactions. Food allergies are commonly brought up by patients as potential triggers for their atopic dermatitis. Some patients describe anaphylaxis symptoms (immediate and IgE-mediated) while others report delayed dermatitis flares following ingestion. Generally, food allergies are more likely to develop in patients with earlier, more severe AD.[15]

Extensive literature review has demonstrated that 50 to 90 percent of presumed food allergies are not true allergies.[17] Self-reported food allergies can exceed true allergy incidence, as proven by an oral challenge, by a factor of 10.[18] The NIAID suggests that all suspected food allergies be confirmed using oral food challenges or further tests for sensitizations.[17] Patient history should only substitute for an oral challenge in the most unambiguous, clear-cut instances of acute and severe reactions. Further, patient history is often not clinically helpful when diagnosing delayed reactions to foods.[19]

With respect to IgE-mediated reactions, the suspected food allergen may be gradually re-introduced at home if the patient has a negative skin prick test (SPT), negative food-specific IgE test, and no history of immediate food allergy symptoms.[20] Those with a history of immediate food allergy symptoms, even in the presence of a negative SPT and food-specific IgE test, should undergo an oral challenge in a controlled clinical setting to confirm or exclude a true IgE-mediated reaction.[20]

Routine skin prick testing in the AD patient is generally not recommended for the purpose of diagnosing triggers. There is an approximately 40 percent chance of a false-positive reaction. If the patient has a false-positive reaction on a SPT, the patient should ideally undergo an oral challenge to confirm or rule out an IgE-mediated reaction.

Many patients and parents, however, are more frequently concerned with late eczematous reactions rather than IgE-mediated reactions. For this reason, this article will focus on late eczematous reactions.

The pathophysiology of these non-IgE mediated reactions is not fully understood. An oral food challenge in the AD patient can lead to 3 different outcomes:[18]

1. An immediate, IgE-mediated non-eczematous reaction
2. A delayed eczematous reaction (typically seen as an eczema flare 6-48 hours after ingestion)
3. A combination of an immediate non-eczematous reaction and a delayed eczematous reaction

Niggemann et al.[21] retrospectively analyzed the clinical outcome of 387 oral provocations using double-blind, placebo-controlled food challenges (DBPCFC) in 107 children with moderate to severe resistant AD. Of all positive challenges, 25 percent resulted in isolated, delayed reactions and 5 percent resulted in combined early and delayed reactions. Of all oral challenges with hen's egg, 70 percent resulted in positive reactions. This was followed by cow's milk, at 51 percent combined, cow's milk and hen's egg accounted for 83 percent of all positive oral challenges.

In a study by Breuer et al.[22], DBPCFC were administered to 106 children with AD. Food challenges included cow's milk, hen's egg, wheat gluten, and soy. Forty-six percent of all food challenges resulted in a positive reaction. Of these, 43 percent were immediate reactions, 12 percent were delayed eczematous reactions, and 45 percent resulted in combined immediate and delayed reactions. Hen's egg accounted for the highest proportion of positive reactions, at 62 percent, followed by cow's milk, at 47 percent. Isolated, delayed eczematous responses are generally seen 6 to 48 hours following ingestion and are thus not noted in many oral challenge studies.[23] Few studies have specifically observed these types of reactions and have found that 25 percent of delayed reactions occur 2 hours following ingestion, and 10 percent occur at least 16 hours following ingestion.[23]

Due to the delayed reaction, the patient's skin must be inspected by a physician for eczema area and severity index (EASI) and SCORAD scores both before the oral challenge and afterward. Patients who did not react after the first challenge should undergo further provocation with the same food for another 1 to 2 days.[18]

Food testing is not typically recommended with a new diagnosis of AD. However, testing may be helpful in certain types of patients. The NIAID expert panel suggests testing the following subsets:[17]

1. children <5 years of age who have intractable, moderate-to-severe AD despite optimal management and topical treatment
2. children who have experienced an immediate reaction following ingestion of a specific food

Testing processes should follow the diagnostic algorithm depicted in **Figure 2** below:

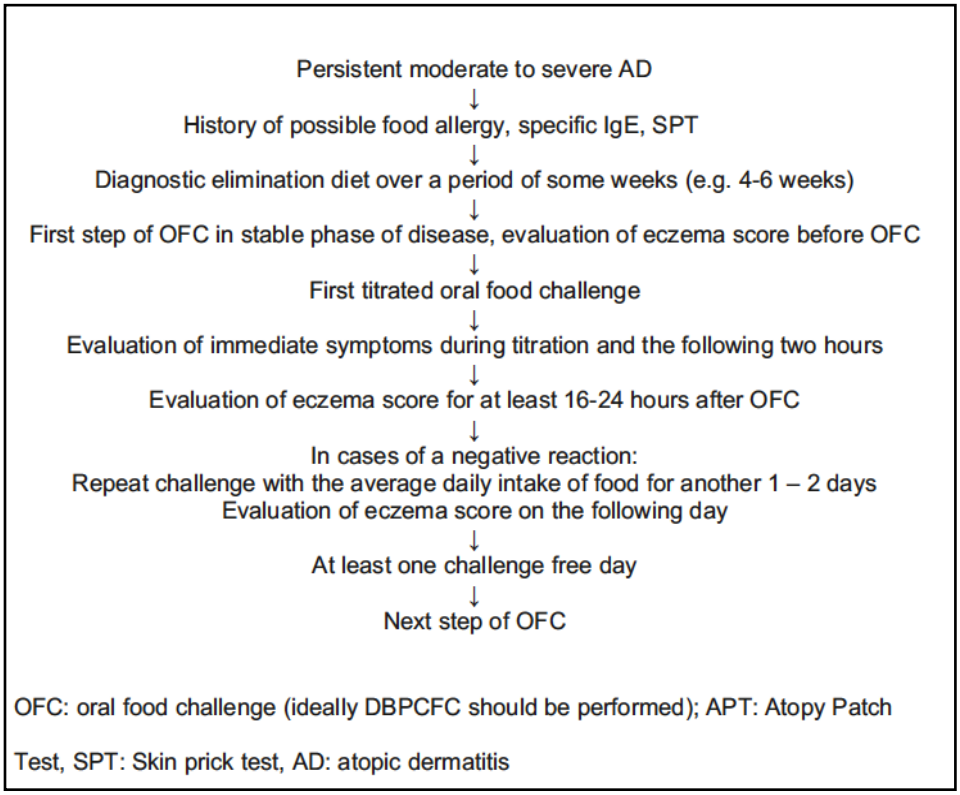

Figure 2. Diagnostic algorithm for the identification of food allergy in patients with AD; adapted from Sampson et al, 2012

Food elimination diets should not be recommended to all patients with AD. A review of 9 randomized, controlled trials measuring the effects of elimination diets on AD patients found that there was little evidence to support avoidance diets.[17] Furthermore, food elimination diets could introduce psychological and social burden, and acute, severe reactions upon re-introduction of food allergens.[24]

Oral challenges are still considered the gold standard for diagnosing IgE-mediated reactions. However, little quality data exists in diagnosing triggers for late eczematous reactions. This area is still developing and needs much research.

Conclusion

Atopic dermatitis is ultimately a complex and chronic inflammatory condition with many challenging comorbidities that impact patient quality of life, morbidity, psychological and economic burden. Although the mechanisms of AD correlation with asthma, food allergies, and allergic rhinitis are not entirely understood, AD patients see an increased likelihood of atopic comorbidities. Dermatologists are thus in the unique position to help screen and identify atopic comorbidities in AD patients to maximize AD control and improve patient outcomes.

Clinical pearls from our author

If a patient comes to us and is quite fixated that food allergies are triggering their atopic dermatitis, we carry forward with epicutaneous testing (i.e. skin prick testing) which is then followed by a supervised oral challenge. We strongly encourage most patients to avoid testing (unless history is suspicious for an IgE mediated reaction) because there is a risk of false positive reactions (~ 40%). If the patient still demands testing despite education AND if a patient has a positive skin test (in the setting of NON- IgE mediated symptoms), we follow through with a monitored 3- hour challenge. This helps us rule out immediate reactions (plus early delayed).

What about delayed reactions? Some of the newer clinics are certainly thinking about delayed reactions now but very few are actually carrying out delayed 6-12 hour challenges. Our practice is that patients get a call in the evening (6 hours after the initial challenge and we ask them to take pictures), then they come back 24 hours later, and then again 48 hours later for quick EASI scores, BSA, and IGA evaluation. This is cumbersome and resource intensive, but it seems to work and there is evidence in the literature to support this approach, though there are limitations even in the quality of literature. This is a new approach, however, there is certainly some merit and I am finding it is really convincing a majority of patients they don't have food allergies. The challenge is AD waxes and wanes and its course fluctuates many times. There are several triggers (i.e. heat, stress, sweat, irritants, etc.) and a controlled home setting is difficult to ensure. Almost all allergists are now carrying out immediate oral challenges in their clinics if the evaluation is being done right.

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USE OF BIOLOGICS TO TREAT PSORIASIS IN HIV

Background

Standard treatments for moderate-to-severe, refractory psoriatic disease generally involve immunosuppressant medications, which can complicate treatment in patients with concomitant immune suppression, including human immunodeficiency virus (HIV) infection. HIV is uniformly an exclusion criterion for clinical trials of biologic therapy, leaving dermatologists with scant evidence to support clinical treatment decisions for this subpopulation of patients. Patients with HIV also experience healthcare related inequality in disproportionately higher levels compared to the general population. It is important for dermatologists to have some degree of knowledge and comfort treating and managing patients with significant, refractory psoriatic disease and comorbid HIV infection.

Two sets of guidelines for the treatment of psoriatic disease in patients with HIV infection were published in 2010, each having similar recommendations.[1,2] For mild-to-moderate disease, topical therapy including corticosteroids, vitamin D analogues, tazarotene and tar derivatives are recommended as first-line treatment options. For moderate-to-severe disease, phototherapy and oral retinoids are subsequently recommended. In refractory moderate-to-severe disease, the use of cyclosporine, methotrexate and tumor necrosis factor (TNF) inhibitors can be considered. The paucity of evidence for methotrexate use in psoriasis and HIV makes informed and evidence-based clinical decisions difficult to incorporate into treatment management. Very few published cases exist in the literature. An article describing 9 published cases of patients with HIV (some with AIDS) receiving methotrexate therapy describes 8 developing infectious complications.[3] Six of the eight were not on concomitant antiretroviral therapy. The three receiving antiretroviral therapy were on zidovudine monotherapy, which is no longer the standard of care. It should also be noted that one of the patients was receiving high dose intravenous methotrexate as part of a treatment protocol for Kaposi sarcoma, the other

eight received standard doses for psoriasiform disease. The paucity of published cases, combined with the few patients who are described not matching the clinical context of the majority of North American patients with HIV today, make results difficult to interpret. It is unknown if patients would have experienced the same rate and extent of complications had their HIV been well controlled on antiretroviral therapy, which is the current recommendation for any patient with HIV being started on immunosuppressant therapy.

It is worth noting that since the above guidelines were published, apremilast has become available as an additional non-immunosuppressive option to treat psoriasis. Several case reports have been published illustrating effective and safe use of apremilast to treat psoriatic disease in patients with HIV.[4,5] Biologic agents with mechanisms of action not involving TNF inhibition have also become available.

TNF inhibitors – etanercept, adalimumab, infliximab

Current evidence for TNF inhibitors in patients with HIV consists mainly of case reports and small case series. As the TNF inhibitor class of biologics has been available to treat inflammatory dermatologic, rheumatologic and gastrointestinal diseases for over two decades, physicians understandably have developed the most experience and, by extension, comfort with their use. However, it is important to not automatically conflate the length of time a medication has been in use with superior efficacy or safety. The literature shows that individual patients have been followed for time ranges varying from months to almost 10 years.

Etanercept

Currently available evidence consists of 19 patients captured in 9 case reports.[6-14] All patients had clinical responses consistent with what would be expected in the general population, with five patients switching to alternate biologic therapy due to lack of efficacy. No significant changes in relevant laboratory parameters such as CD4 count and viral load were observed. One patient experienced multiple polymicrobial infections, which continued for 4 months after etanercept was discontinued, and eventually led to the patient's death. There were no other significant adverse events or opportunistic infections reported.

Adalimumab

Currently available evidence consists of 7 patients in 4 case reports.[7,8,15,16] Six patients had satisfactory clinical responses, and one being treated for psoriasis was switched to an alternate biologic therapy due to unsatisfactory response. No significant changes in relevant laboratory parameters were observed. There were no other significant adverse events or opportunistic infections reported.

Infliximab

Currently available evidence consists of 7 patients in 3 case reports.[8,17,18] All patients had clinical responses consistent with what would be expected in the general population. No significant changes in relevant laboratory parameters were observed. There were no other significant adverse events or opportunistic infections reported.

Other Anti-TNFs

No published evidence exists regarding the use of certolizumab in the treatment of patients with HIV. It is also worth noting that several patients in the case reports described above had concomitant hepatitis C virus (HCV) infection and none experienced elevations in alanine aminotransferase (ALT), HCV viral load or substantial changes on hepatic ultrasound.[7,10,12]

Another review looked at the rate of serious infection in patients with HIV treated with TNF inhibitors in a series of 24 patients.[19] Two cases of serious infection over 86.7 person years of follow up were identified. This equates to a serious infection rate of 2.3 per 100 patient years, which is comparable to the serious infection rate seen in registries of patients with rheumatoid arthritis treated with TNF inhibitors. The two cases were *Streptococcus pyogenes* pneumonia complicated by empyema and bacteremia, and methicillin-sensitive *Staphylococcus aureus* infection of a chest tube placed for pleural effusion of unknown etiology. The incidence of serious infection was not significantly different based on viral load and there were no cases of opportunistic infection.

IL-12/23 (ustekinumab)

Currently available evidence consists of 8 patients captured in 5 case reports.[7,14,16,20,21] All patients had clinical responses consistent with what would be expected in the general population. No significant changes in relevant laboratory parameters such as CD4 count and viral load were observed. There were no other significant adverse events or opportunistic infections reported. Of note, one patient with minimal and stable concomitant Kaposi sarcoma maintained stability while on ustekinumab therapy.[20]

IL-17 (secukinumab)

A single case report currently exists detailing secukinumab use in an

HIV positive patient.[22] A 48-year-old woman with a long history of psoriasis and psoriatic arthritis who was found to be HIV positive during screening for biologic therapy eventually went on to start both antiretroviral therapy and secukinumab, achieving control of her HIV, psoriasis and psoriatic arthritis. Her laboratory parameters remained stable and seven months into treatment she was found to have esophageal candidiasis which was successfully treated with fluconazole. Secukinumab therapy was not discontinued and her disease remained under good control at the 12-month follow up mark.

No published evidence exists regarding the use of ixekizumab or brodalumab in the treatment of patients with HIV.

IL-23 (guselkumab)

A single case report currently exists of guselkumab use in an HIV positive patient.[23] A 51-year- old-male with longstanding refractory psoriasis underwent successful treatment with guselkumab. No alteration in laboratory parameters, adverse events or opportunistic infections were reported.

No published evidence exists regarding the use of risankizumab in the treatment of patients with HIV. Several excellent review articles have been published which summarize sections of the evidence above.[24-28]

It is essential that we develop strategies to adequately treat HIV positive patients who suffer from psoriasis, psoriatic arthritis and other inflammatory skin conditions. As with any given segment of the population, some patients who happen to acquire HIV will have psoriatic disease that is refractory to non-immunosuppressant therapy. HIV infection itself can precipitate or exacerbate psoriasis which is perhaps due to the production of inflammatory cytokines including IL-17, IL-23, interferon and TNF by CD8+ and CD45RO+ T cells.[23] The cytokines which play roles in the pathogenesis of both psoriasis and HIV may serve as common targets for biologic agents.

The existing body of evidence outlined above demonstrates that biologic agents can be used safely and efficaciously in patients with HIV. It is important to realize however, that the current best level of evidence available to clinicians consists of case reports and small case series and that we lack randomized controlled trials. These descriptive data, such as case reports and case series, are prone to publication bias in that cases of biologic use in the context of HIV leading to a negative outcome are less likely to be published than those leading to a positive outcome. The prospective, deliberate study of HIV positive patients on biologic therapy, be that in the form of a registry or inclusion in clinical trials, would significantly add to our existing knowledge regarding this particular clinical scenario.

In terms of real-world clinical practice, dermatologists often consider efficacy, safety and the availability of existing published evidence when making treatment decisions. Etanercept, while perhaps relatively limited in terms of efficacy, has the largest body of evidence for use in HIV and the shortest half-life, making it the most easily discontinued therapy should complications occur. In contrast, biologics that have a longer half-life, such as ustekinumab and secukinumab, prohibit the drug being withdrawn quickly if complications occur--- a consideration which should be balanced against their greater efficacy, more targeted mechanism of action and subsequent theoretically reduced rate of infectious complications.

Important clinical considerations when treating patients with psoriasis and HIV include ensuring that patients are adherent to antiretroviral therapy, have stable CD4 counts and undetectable viral loads, and are followed regularly by their physician. Non-immunosuppressive therapies should be exhausted before immunosuppressive therapies are considered. Follow up and monitoring of HIV patients on biologic therapy do not differ greatly from that required for non-HIV patients on biologic therapy in general. Although no formal consensus exists, monitoring could include more frequent follow up visits, diligent education on how and when to report any possible symptoms of infection, ensuring relevant vaccinations are up to date, and the consideration of annual screening for tuberculosis infection. HIV parameters including CD4 count and viral load should be regularly monitored by the patient's physician.

Biologic therapies continue to play an important role in the management of moderate-to-severe psoriatic disease and HIV infection is not an absolute contraindication to the use of biologic therapy. These agents can be used safely when prescribed and monitored as part of a team-based approach to care which involves the patient, the HIV physician and the dermatologist.

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AN UPDATE ON EXISTING & EMERGING TREATMENTS FOR VITILIGO

Vitiligo is characterized by chronic depigmented patches due to selective loss of melanocytes. The estimated prevalence of vitiligo is about 0.5 to 2% worldwide and, in addition to its significant cosmetic effect, it may cause major psychological distress.[1,2]

Based on clinical distribution, vitiligo is divided into segmental vitiligo (SV) and non-segmental vitiligo (NSV). NSV is further sub-categorized based on the distribution of lesions into five distinct categories: vulgaris, generalized, acral, acrofacial and mucosal vitiligo.[3]

The pathogenesis of vitiligo involves a complex interplay of autoimmune factors, intrinsic melanocyte defects, neural and oxidative stress. Immunologically, a type I immune response is believed to be responsible for the development of vitiligo.[3, 4, 5]

In the last few years, there have been great strides made in understanding the pathogenesis of vitiligo at both the molecular and genetic level. In light of these developments, the future for vitiligo treatment looks promising as several new topical and systemic agents are in various phases of development. These future treatments may even prevent disease recurrence, once an unthinkable aim for vitiligo, as mechanistic models have elucidated targets by which memory T-cells can be altered in animal models.[3,6, 7]

Current treatment options
Current treatment modalities being used are primarily off-label, with the 3 main goals of treatment as follows:

1. Attaining stability of disease process and thereby limit spread of disease by using topical and /or systemic immunosuppressants / immunomodulators

2. Inducing re-pigmentation by stimulating melanogenesis (phototherapy, afamelanotide, and surgical treatments)

3. Reducing intrinsic stress on melanocytes by the use of oral anti-oxidants

Most treatment agents provide varying levels of impact in one or more of the above targets and current treatment modalities can broadly be classified into medical (topical & systemic agents), phototherapy, laser, and surgical methods. [3, 6, 8]

Topical medications
Topical corticosteroids
Corticosteroids are the most commonly used topical medications for vitiligo worldwide. Corticosteroids act by blocking cytotoxic T-lymphocyte activation. Among the various topical corticosteroids used, the literature has shown that mometasone has similar efficacy to clobetasol propionate but with the advantage of fewer side effects and a better safety profile in both the pediatric and adult population.[8-10]

Topical Calcineurin Inhibitors (TCI)
TCIs, such as tacrolimus, play an important role in the treatment of vitiligo by exerting an immunomodulatory effect through the blockade IL-2 and IFN- α, thereby inhibiting cytotoxic T-cells. Tacrolimus also helps in promoting melanogenesis by reducing systemic antioxidant stress. Tacrolimus 0.1% ointment has shown superior results to pimecrolimus 1% cream. TCIs are effective and safe, may be used long term and work best in the management of vitiligo when used in combination with other modalities of treatment.[3, 11, 12]

Latanoprost
When originally used as a treatment for glaucoma, topical prostaglandin analogues caused hyperpigmentation as a side effect which prompted studies in vitiligo. Their mechanism of action involves the induction of tyrosinase and an upregulation of melanocyte proliferation. Latanoprost has shown statistically superior results to placebo on both facial and non-facial skin but is likely more effective on the face and is safe for periocular vitiligo.[13, 14]

Phototherapy
Phototherapy is a first-line treatment modality for those with extensive vitiligo. Narrowband UVB (NBUVB) has mostly replaced PUVA as the primary phototherapy modality. Its mechanism of action is to induce tyrosinase enzyme and it has shown superior efficacy than PUVA in achieving disease stability and repigmentation.[6, 10, 15]

Lasers
A FDA-approved laser used for treating vitiligo is the monochromatic excimer light (MEL) 308nm laser with peer-reviewed results suggesting that the face responds better than other regions. Compared to NBUVB, the MEL laser may deliver superior clinical outcomes, but this treatment modality is more expensive and challenging to use for those with extensive vitiligo.[16,17] Another laser that has been tested for vitiligo is the Helium-neon laser (632.8nm). In use for head and neck segmental vitiligo, the HE-Ne laser has shown greater than 50% repigmentation in 60% of patients.[3]

Systemic treatments
Systemic Corticosteroids
For patients who have failed topicals and NBUVB, systemic immunosuppressants may be the next option to consider. The primary aim of systemic immunosuppressants is to attain disease stability (i.e. no newer / progressing lesions), and also to help with repigmentation. With this in mind, the most commonly used agents are systemic corticosteroids. Longer acting systemic corticosteroids used at a lower dose are commonly referred to as oral mini pulse (OMP) treatment, which involves giving either oral dexamethasone 2.5 mg or oral betamethasone 2.5 mg or 5 mg on 2 consecutive days in a week for up to 6 months. Several studies have shown the arresting of disease activity with OMP treatment in up to 90% of patients with recurrence upon discontinuation of the OMP regimen being noted in about 13% of patients. Compared to regular-dosed prednisone, much of the peer-reviewed literature suggests that OMP is better tolerated for arresting progressive unstable vitiligo with minimal adverse events. Adverse events reported were similar to those seen with corticosteroids including weight gain, acneiform eruptions, and lethargy.[18, 19]

Cyclosporine
As IL-2 is a major cytokine for recruitment of T-Cells, cyclosporine can be a therapeutic choice in the treatment of vitiligo for achieving stability in progressive and unstable disease. Taneja et al showed a significant improvement in the vitiligo area severity index (VASI) score with the use of cyclosporine at 3 mg/kg/day for 3 months.[20]

Methotrexate
In some patients with extensive disease that tends to follow a progressive unstable course over many years, immunosuppressants may be needed long term. In these patients, methotrexate is an option. A comparative study of low-dose methotrexate (10 mg weekly) demonstrated that it was well tolerated by patients and resulted in comparable outcomes to OMP with betamethasone.[3, 21]

Surgical methods
Surgical treatments in vitiligo involve reintroducing melanocytes harvested from pigmented skin of the same person. One of the most important aspects of utilizing surgical methods for the treatment of vitiligo is appropriate patient selection, with the specific aim of ensuring that the disease is stable for at least 1 year (i.e. no new or progressive lesions in the past 1-year period). In unstable / progressive disease, surgery may cause Koebnerization and induce new lesions. Two categories of surgical treatments are tissue grafting and cellular grafting with cellular grafting providing significantly better patient outcomes but requiring more expertise, and laboratory support.[22, 23]

Depigmenting treatment
In patients with extensive vitiligo not responding to treatment, the option of depigmenting remaining normal skin may give better cosmetic outcomes. Monobenzyl ether of hydroquinone (MBEH) 20% is a FDA-approved depigmenting agent for vitiligo. MBEH's mechanism of action involves the induction of lysosomal degradation and oxidative stress of melanocytes leading to immune destruction of the remaining melanocytes. The possible adverse events associated with the use of MBEH are rare but can include conjunctival melanosis and irritant contact dermatitis.[24]

Emerging treatment options in Vitiligo
Newer options currently in development include targeted immunotherapeutic agents such as JAK / STAT inhibitors, and newer phototherapy and laser options which will be reviewed below.

JAK Inhibitors
Janus kinases (JAKs) are a family of 4 proteins: JAK1, JAK2, JAK3, and TYK2. These proteins cause immunomodulation by activation of intracytoplasmic transcription factors called signal transducer and activator of transcription (STAT). Once activated, they dimerize and move to the nucleus where they modulate gene expression. Laboratory work in mice with vitiligo have helped illuminate the crucial role of the JAK/STAT pathway in the pathogenesis of vitiligo.[30] JAK inhibitors (JAKI) are broadly classified into first and second generation agents. First generation JAK inhibitors block more than 1 or all of the janus kinase family of proteins and have been the agents used with greatest frequency for vitiligo to date.[7, 25, 26]

Tofacitinib
Tofacitinib is a JAK 1/3 inhibitor. Both systemic and topical tofacitinib have been used in vitiligo. In various case series', the use of oral tofacitinib at doses of 5 mg po OD or BID for 3 to 6 months has demonstrated significant improvement in repigmentation.[26,27,28] Topical tofacitinib citrate 2% given for facial vitiligo achieved a mean improvement of 70% based on the difference in mean facial VASI at baseline and at follow-up (mean follow-up of 112 days).[29]

Ruxolitinib
Topical ruxolitinib 1.5% cream has shown great response in vitiligo, especially for facial vitiligo. In an open-label trial, a mean improvement of 92% was observed in facial lesions calculated as improvement in overall VASI for enrolled patients (n = 8) at week 52 from baseline. The results of a multicenter phase 2 study of topical Ruxolitinib cream in vitiligo has been recently published and shows significant improvement in vitiligo as measured by approximately 50% of patients on ruxolitinib cream achieving F-VASI50 (50% improvement in facial VASI) compared to only 3% of those on placebo.[30] A Phase 3 clinical trial is actively ongoing and results are expected in 2021. Transient acneiform eruption, worsening of acne, and mild erythema were the most commonly reported side effects.[30]

It is worth noting that there are better repigmentation rates in patients who received both JAK inhibitors and NBUVB at sites of chronic UV exposure such as the face and extensor forearms. Therefore, significant repigmentation in vitiligo using JAK inhibitors may also require photostimulation of melanocytes. Clinical trials examining this are ongoing with JAK inhibitors and NBUVB.

Alpha-melanocyte-stimulating hormone (α-MSH) analogue afamelanotide is a synthetic analogue of alpha-melanocyte-stimulating hormone (α-MSH) which induces melanogenesis. A clinical trial involving the use of afamelanotide with NBUVB vs NBUVB alone has shown that afamelanotide with NBUVB had superior repigmentation rates.[31]

Basic Fibroblast Growth Factor (b-FGF)

In vitro studies have shown that b-FGF is capable of stimulating melanogenesis and a recent phase IV double-blind randomized controlled trial has shown b-FGF with NBUVB to be superior to NBUVB alone with a very good tolerability profile.[32]

Bioskin evolution micro phototherapy

Bioskin evolution is a targeted 311-nm narrowband micro phototherapy device that is suitable for lesions involving <10% body surface area (BSA). The advantages of this device are that it can be used in patients with limited disease including sensitive areas such as eyelid skin and it is more convenient than having to expose the whole body to NBUVB treatment.[33]

311nm Titanium: Sapphire laser (TSL)

A 311nm TSL for vitiligo along with topical tacrolimus 0.1% ointment has shown significant benefit to complete repigmentation in 79% of patients. Results from TSL were similar to 308nm excimer laser (EL), but with better safety profile.[34]

UVA-1 lasers

The Laser Alba 355®, a UVA-1 laser with 355nm spectrum, has shown successful repigmentation in up to 75% of patients.[35] Utilization of a UVA-1 laser works well due to its deeper penetration and immunomodulatory properties.[35]

Oral Antioxidants

Oral antioxidants are now part of first line management of vitiligo in some countries, as they may help to decrease the oxidant stress on melanocytes. Oral gingko biloba, polypodium leucotomus, vitamin E, vitamin C, and alpha lipoic acid have all been shown to promote repigmentation.[36-38]

Future treatment prospects

Programmed cell death-1 ligand (PDL-1) is currently being studied for psoriasis and inflammatory bowel disease and might be beneficial for vitiligo as well, as it helps to maintain immune balance.

IL-15 causes oxidative stress mediated destruction of melanocytes; therefore inhibiting IL-15 may be explored as a future potential mechanism of action in the treatment of vitiligo. Inducing mi-RNA via a miR-155 agonist has also shown to improve melanocyte regeneration.[39] Hence mi-RNA induction may be a future treatment option for vitiligo.[3, 40-42]

Conclusion

The treatment of vitiligo cannot be addressed as one size fits all, but must be individualized to address patient expectations, impact of disease, and compliance. The effective treatment of vitiligo may require a multimodal approach including minimizing oxidative stress with anti-oxidants, implementing topical or systemic immunomodulatory agents, and initiating treatment modalities to regenerate melanocyte function by phototherapy and surgical methods. Future treatments, especially those involving the JAK-STAT pathway, hold promising potential.

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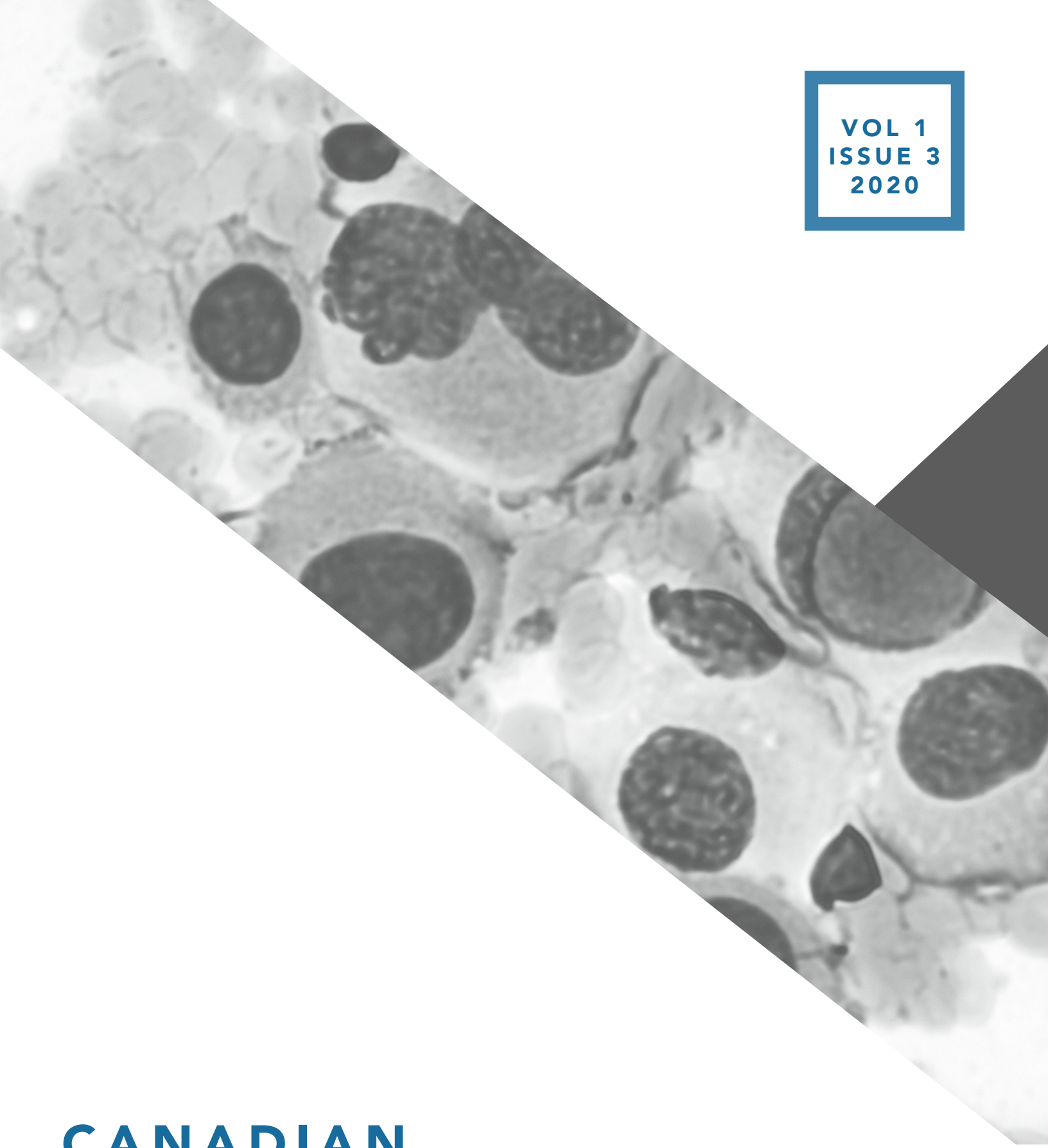

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