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EDITORS WELCOME

Dear Canadian Dermatology Community,

Welcome to our final issue of *Canadian Dermatology Today* in 2020! At the time this publication was first conceived in the summer of 2019, little did we know how much the world would change in 2020. Despite a difficult year behind us and much work ahead in the face of the COVID-19 pandemic, we are hopeful that 2021 will bring a return to some level of normal.

In this final issue of the year we discuss facial hyperpigmentation, present an article on frontal alopecia and examine the management of viral hepatitis in immunosuppressed patients. We also have wonderful contributions on future treatments for hidradenitis suppurativa, a look at photodynamic therapy treatment and a practical overview of skin picking for the Canadian dermatologist.

As always, we hope you find these articles informative and helpful. We are grateful for your continued readership and we look forward to another great year in 2021. 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!

Finally, as this year draws to a close, we wish you and your families a wonderful and peaceful holiday season.

Best wishes,

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



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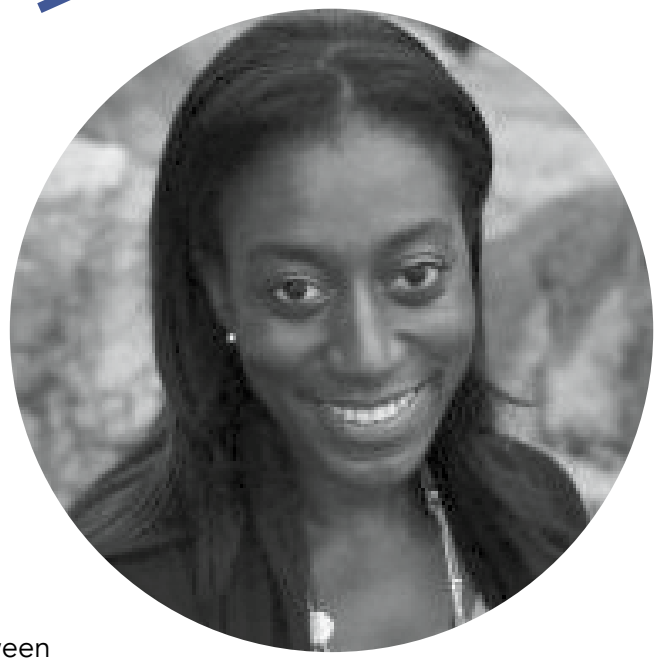


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AN UPDATE ON THE MANAGEMENT OF FACIAL HYPERPIGMENTATION: IS THERE ANYTHING TO USE OTHER THAN HYDROQUINONE?

The multicultural landscape of North America is changing. The visible minority population in the United States is expected to reach 50% by the year 2050.[1] Similarly, in Canada, it is projected that over the next decade, almost 1 in 3 Canadians will have Fitzpatrick skin types 4-6, with 60% of residents in Toronto and Vancouver being members of visible minority communities.[2]

Although common skin disorders such as acne and dermatitis are prevalent amongst all ethnic groups, certain conditions such as dyschromias are seen more readily in patients with darker skin. In a U.S. study comparing the top ten dermatological diagnoses between black and white patients, pigmentation disorders were the second most common reason for black patients to seek dermatological care.[3] This increased frequency of pigmentation disorders has also been observed in Asian, Latin American, African and in Afro-Caribbean communities.[4-6] Disorders of pigmentation in Caucasian patients however, were not listed in the top ten of dermatological diagnoses.[3]

There are two main types of dyschromia: melanotic and non-melanotic. Melanotic dyschromias are due to a disruption in melanocytic processes. Non-melanotic dyschromias result from other causes, such as vascular anomalies. Melanotic dyschromias can be further subdivided into disorders of hyperpigmentation and hypopigmentation.[5,7] In general, excluding vitiligo, disorders of hyperpigmentation such as melasma and post inflammatory hyperpigmentation make up the vast majority of pigmentation disorders in skin of color patients.[4] These conditions, particularly when affecting the face have been shown to decrease quality of life and cause significant psychosocial distress.[7,8] Therefore, a toolbox of effective options for treatment are essential to the practicing dermatologist.

Central to the understanding of therapeutic options for melanotic dyschromias is the complex process of skin pigmentation.[7] The steps involved are the primary targets for both traditional and emerging therapeutics. Skin pigmentation is genetically determined, however other factors such as hormonal status, exposure to ultraviolet radiation, trauma and age also play a role.[7] The steps and treatment targets in cutaneous pigmentation are outlined in **Figure 1**.[9,10]

The treatment of facial hyperpigmentation is extremely challenging, especially in patients with higher Fitzpatrick skin types. Concerns regarding the long-term efficacy, safety and cost of traditional treatments has led to the development of a variety of new and emerging alternatives for skin of color patients.[11]

1. Melanoblasts migrate from the neural crest to the dermis
2. Melanoblasts differentiate into melanocytes in the dermis
3. Melanocytes migrate to the epidermis (basal layer)
4. Mitotic division of melanocytes
5. Tyrosinase production in the rough endoplasmic reticulum and transfer to the golgi for modification
6. Formation of melanosomes with tyrosinase and tyrosinase related proteins
7. Melanogenesis (complex process of melanin production) within melanosomes
8. Transfer of melanosomes to keratinocytes
9. Eventual degradation of melanosomes within keratinocytes during differentiation

Figure 1. Stages in melanocyte development, melanosome formation and melanization, and melanin transfer to keratinocytes; adapted from Lambert et al, 2019

Disruption in specific steps leading to hyperpigmentation disorders

Melasma:
Steps:
5. Increased tyrosinase production
6. Increased melanosome formation
7. Increased melanin production
8. Increased transfer of melanosomes to keratinocytes

Post inflammatory hyperpigmentation:
Steps:
4. Increased production of melanocytes (melanocyte hyperplasia)
7. Increased melanin production
8. Increased transfer of melanosomes to keratinocytes

Steps targeted by specific treatments

Topical steroids
- Disrupt melanocyte secretory function (Step 6)

Hydroquinone, Arbutin, Licorice, Azelaic acid, Kojic acid
- Inhibition of tyrosinase (melanin production) (Step 7)

Tretinoin, Soy, Nicotinamide
- Disrupt melanosome transfer (Step 8)

Chemical peels: Glycolic acid, Salicylic acid, Trichloracetic acid, Tretinoin:
- Aid in keratinocyte removal (Steps 8-9)

Management

Behavioural Strategies:

Behavioural strategies are essential to the management of facial hyperpigmentation. Treating the underlying cause, avoidance of trauma from manipulation and/or picking the skin and camouflage make-up all play an important role in treating hyperpigmentation.[12] Avoidance of ultraviolet radiation has long been regarded as central to the management of melanotic dyschromias.[12] Visible light however, has also recently been shown to worsen facial hyperpigmentation. Protection from visible light with iron oxide containing (tinted or mineral) sunscreens has been shown to improve the appearance of hyperpigmentation.[13,14] Finally, the tincture of time is also an important concept to address with patients, especially those with post

inflammatory hyperpigmentation (PIH). Setting up the expectation that the resolution of pigmentation will take some time but is expected to fade is often encouraging for patients. In a study looking at PIH in acne, PIH resolved spontaneously in 57% of patients by 40 weeks.[15]

Topical therapies:

Hydroquinone

Hydroquinone is the gold standard topical agent for the treatment of facial hyperpigmentation. Hydroquinone is a tyrosinase inhibitor that works by preventing the production of melanin from tyrosine. The strongest evidence for its use has been in melasma at a concentration of 4%.[11] In combination with topical retinoids and corticosteroids, first popularized by Kligman,[16] its efficacy has been even higher than when it is used as monotherapy.[17] The most common side effects of hydroquinone are redness and irritation which, if they persist, can lead to the unwanted side effect of post-inflammatory hyperpigmentation. In such instances, it is best to ask the patient to discontinue its use. Another side effect of hydroquinone is the so called "hydroquinone halo."[17] This phenomenon is characterized by a rim of hypopigmentation surrounding a dark macule. These halos are thought to result from bleaching of the normal surrounding skin due to the fingertip application of hydroquinone to small pigmented macules. With prolonged use of hydroquinone, patients are at risk of the rare but significant consequence of exogenous ochronosis, or the paradoxical permanent pigmentation of the skin.[17] A number of studies have shown however, that hydroquinone can be used safely and continuously for at least six months and even up to one year without the development of ochronosis.[18-20] Beyond one year, the risk appears to be slightly increased and alternative therapies should be considered.[17]

Non-hydroquinone topical therapies for the management of hyperpigmentation

Prescription based agents:

Retinoids

Topical retinoids have been used as stand-alone therapy, and in combination with other agents to treat facial hyperpigmentation. Retinoids are vitamin A analogues which exert their effects on pigmentation in a variety of ways. Retinoids exhibit anti-inflammatory properties and modulate cell proliferation, differentiation, and apoptosis.[21] The most frequently prescribed topical retinoids are tretinoin, tazarotene and adapalene which have all demonstrated efficacy in treating facial hyperpigmentation.[22] Tretinoin is a first-generation naturally occurring metabolite of retinol. It is thought to inhibit the transcription of tyrosinase and to interrupt melanin biosynthesis. The most important effect of tretinoin in facial pigmentation is through its desquamative properties resulting in an overall reduction of melanin pigment.[15] Tazarotene and adapalene are both synthetic retinoids. In a blinded, randomized controlled study comparing the two agents in acne patients, tazorotene 0.1% cream was found to be superior in treating acne-associated PIH than adapalene 0.3% gel.[23] The main side effect of topical retinoids is retinoid dermatitis. This has been shown to occur in up to 50% of patients using these agents.[17] In skin of color patients, this is frequently associated with PIH. Minimizing this risk includes application of a moisturizing agent, slow upward titration, and selection of less irritating vehicles. Recently, tazarotene 0.045% lotion was approved for use in the United States. This new vehicle is promising as clinical trials demonstrate a reduction in skin irritation as compared to previous tazarotene formulations.[24]

Azelaic acid

Although, in Canada, azelaic acid is approved to use in rosacea, azelaic acid can also be used for melasma and PIH. Azelaic acid is a naturally occurring dicarboxylic acid obtained from cultures of *Malassezia furfur*. Azelaic acid improves hyperpigmentation by inhibiting tyrosinase.[22]

Kojic acid

Kojic acid is a metabolite of various fungal species including: *acetobacter, aspergillus* and *penicillium*. It is a potent inhibitor of tyrosinase activity and has primarily been studied in melasma. As monotherapy, it is inferior to hydroquinoine in improving facial hyperpigmentation but when combined with hydroquinone and/or topical corticosteroids, its efficacy is increased.[21,25] Kojic acid is a sensitizing agent, and contact dermatitis is not uncommon.[21]

Cosmeceuticals (Non-prescription)

Licorice root extracts, soybean derived proteins, niacinamide, rucinol and ascorbic acid have all been shown to have some efficacy in the treatment of facial hyperpigmentation. For patients seeking natural formulations, any of these well-tolerated agents could be considered.[17,21,26,27]

Alternatives to hydroquinone with equivalent efficacy and fewer side effects

Topical tranexamic acid

Tranexamic acid (TA) is gaining popularity in its ability to treat facial melasma. Both topical and systemic formulations have been studied. TA is an anti-fibrinolytic agent that has been successfully used to induce hemostasis in menorrhagia and has also been used successfully to treat angioedema and urticaria through the bradykinin pathway.[28,29] TA is a synthetic derivative of the amino acid lysine and its primary mechanism of action in the treatment of hyperpigmentation is through the inhibition of UV-induced plasmin activity in keratinocytes leading to a downstream decrease in the production of prostaglandins, which are known stimulators of tyrosinase activity.[30] Split face studies comparing topical TA to traditional hydroquinone-based melasma therapies have shown equivalent strong efficacy for topical TA when compared to hydroquinone. Currently, there is no standard dosing regimen or vehicle type recommended for topical TA. A number of small studies have shown statistically equivalent success with twice daily application of cream, gel, liquid and other formulations ranging from 2 to 5%.[31] Topical TA has been reported to be well-tolerated with few and mild side effects such as erythema scale, xerosis and irritation.[30,32] Thus, topical preparations of TA represent a possible first-line alternative to the current gold standard of hydroquinone in the treatment of melasma.

Cysteamine

Cysteamine hydrochloride (beta-mercaptoethylamine hydrochloride) is a molecule that is naturally produced by the body as a breakdown product of L-cystein. Its properties of potent depigmentation have been known for more than 50 years.[33] Production of commercial products up until recently has been limited due to an offensive odour associated with topical preparations.[34] Theories on how cysteamine reduces skin pigmentation include: inhibition of tyrosinase, scavenging of dopaquione, chelation of iron and copper ions, increasing intracellular glutathione and shifting eumelanogenesis to pheomelanin synthesis.[35] The efficacy and safety profile of cysteamine has been studied quite extensively. In vitro studies have reported cysteamine to be more effective than hydroquinone.[34] In human studies, the results have also been excellent. Reported side effects include: transient irritation and a residual sulfur odour following application.[33] Thus, for patients who have recalcitrant facial hyperpigmentation, cysteamine could be considered as a viable alternative to hydroquinone.

Physical/Procedural Therapies:

Chemical peels

The use of chemical peels can be helpful in treating facial hyperpigmentation.[17] Superficial chemical peels are generally well-tolerated in darker skin types, however care must be taken to reduce the risks of irritation, dyspigmentation and scarring through selecting the appropriate agent and carefully viewing the dermatologic history. Clinical improvement in facial pigmentation with the use of chemical peels in conjunction with traditional therapies has been reported in numerous studies.[21] In addition, pre-treatment with a course of topical hydroquinone 4% is thought to improve outcomes even further.[12]

Glycolic acid (GA) is a naturally occurring alpha-hydroxy acid found in sugar cane. It decreases pigmentation primarily through epidermolysis and dispersion of melanin in the basal layer. Standard treatment protocols include application of glycolic acid 20-70%, followed by a neutralizing agent.[12,21]

Salicylic acid (SA) is a beta hydroxy acid derived from willow tree bark and induces keratolysis which aids in the removal of melanin pigmentation.

Trichloroacetic acid (TCA) and Jessner's solution have also been used to treat facial pigmentation, however evidence to support their use in skin of color is lacking.[21]

Laser and light-based therapies

Durable improvement in hyperpigmentation can be achieved with laser therapy. Careful selection of appropriate devices to avoid scarring and dyspigmentation need to be employed in patients with richly pigmented skin. The use of low fluence Q-switched Nd:YAG lasers[36] and 1927nm thulium fiber fractional lasers[37] have shown convincing results in the treatment of recalcitrant melasma. Several case reports highlighting the success of other devices have been published, however there is a need for more data to determine the efficacy and safety of these devices in skin of color patients.[12,21]

Systemic agents

Oral Tranexamic acid

As previously mentioned, TA is an anti-fibrinolytic agent. In 1979, Sadako et al discovered that oral TA could help in the management of melasma.[38] Numerous studies have been performed since that

time. The largest study to date is a retrospective study published in 2016 by Lee et al.[39] in which 561 patients were treated with oral TA at a dose of 250 mg b.i.d. Most patients were also using concurrent topical depigmenting agents.The results of this study showed that 89.7% of patients had a clinically significant improvement after two months of treatment with reported side effects including abdominal pain, bloating and headache. One patient, who was later found to have protein S deficiency, had a deep vein thrombosis six weeks into therapy. TA is currently considered a safe and effective systemic agent in the treatment of melasma, and its use should be considered in refractory cases. TA is contraindicated in patients with a history of thromboembolic disease, with the use of other anticoagulant agents, and in patients who have renal, cardiovascular or respiratory disorders, as well as those with a history of malignancy.[38] A patient's lifestyle such as pregnancy, oral contraception use and long-distance travel should also be considering prior to initiating oral TA therapy. Despite studies showing rare or minimal adverse effects, a thorough history needs to be obtained to mitigate potential risks.[38]

Parenteral Glutathione and a Word About Skin Bleaching

An article featured in the *New York Times* in 2017 exposed the controversial use of IV glutathione in medical spas and aesthetic centres across the United States for the purpose of lightening one's natural skin tone.[40] The purposeful attempt to lighten skin tone is referred to as skin bleaching and it is a global phenomenon practiced in a variety of communities throughout the world especially in parts of Asia and Africa.[41] Its use stems from the perception that lighter skin equates with beauty and higher social status. As a result, the world market for skin whitening products is expected to reach $31.2 billion by the year 2024.[42] Glutathione is a sulfhydryl-containing antioxidant compound consisting of cysteine, glycine, and glutamate.[42] It has been marketed as a safe and effective treatment for skin whitening.[40] There are several postulated theories for the skin lightening effects of glutathione including: its antioxidant properties, its ability to switch production of eumelanin to pheomelanin, its inhibition of tyrosinase and its interference in tyrosinase transfer to premelanosomes.[41] Topical, oral and parenteral formulations of glutathione exist with studies on both oral and topical glutathione formulations elucidating conflicting data mainly due to limited absorption and bioavailability.[42]

Parenteral glutathione has therefore been gaining popularity. The safety and efficacy of intravenous glutathione has not been effectively studied, and dosing guidelines have not been established. Parenteral glutathione has been associated with brain, liver and kidney toxicity, as well as Stevens-Johnson syndrome and possible malignancy.[40,41] An increased risk of blood borne infections also exists as many individuals administering these 'treatments' are not medical professionals.[40] Given the lack of the available safety data, the Food and Drug Administration in the USA and regulatory authorities in the Philippines have issued warnings on its use.[41]

Summary

A combined approach to the treatment of facial hyperpigmentation is often required **(Figure 2)**.[27] Currently, first line therapies for treating facial hyperpigmentation include: sun protection, hydroquinone and hydroquinone-containing mixtures. Several topical alternatives have been studied both in combination with hydroquinone

Behavioural strategies for all patients:
- Avoidance of picking/manipulating the skin
- Emphasize treatment of underlying cause for post inflammatory hyperpigmentation
- Camouflage make-up
- Sun/visible light protection: consider recommending broad spectrum ≥ SPF30 iron oxide containing sunscreens

1st line:
- Hydroquinone 4% (modified Kligman formulations are preferred) **stop after 6-12 months**
- Sun avoidance and sunscreen consider recommending broad spectrum ≥ SPF30 iron-oxide containing sunscreens
- Tretinoin cream

2nd line: (1st line if prior prolonged use of hydroquinone, allergy to hydroquinone or patient preference)
- Tazarotene, Adapalene, Azelaic acid
- Other cosmeceuticals (Soy, vitamin C, Licorice extracts etc)
- Chemical peels (Gylcolic acid, salicylic acid, Trichloracetic acid, Jessner's solution)

3rd line:
- Topical cysteamine, topical tranexamic acid, kojic acid (warn about contact dermatitis)
- Consider oral tranexamic acid – avoid in patients with clotting disorders
- Niacinamide

Figure 2. General approach to facial hyperpigmentation[30]

and as monotherapy, with many of these having shown promising results. Procedural therapies such as chemical peels and laser devices may also be beneficial in improving facial dyschromias especially when used in combination with traditional therapies. Oral tranexamic acid is considered to be safe and effective in the treatment of facial melasma and its use should be considered in severe or difficult cases. Finally, the use of topical, oral and parenteral glutathione has not been studied enough to warrant recommendation for its use and, in addition, the promotion of glutathione for the purpose of skin bleaching brings up several ethical and safety concerns.

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THE MANAGEMENT OF VIRAL HEPATITIS IN IMMUNOSUPPRESSED PATIENTS: WHAT THE DERMATOLOGIST SHOULD KNOW

With a growing array of immunomodulatory and biologic therapies available for common and rare skin disorders, prescribing dermatologists increasingly need to be aware of the potential adverse effects of these medications. One serious potential adverse effect is the reactivation of viral hepatitis, which can lead to significant morbidity and mortality.[1] The reactivation risk of Hepatitis B virus (HBV) infection can be minimized by careful evaluation prior to initiating immunosuppressive therapy.

Case Example

A 46-year-old man of Chinese descent is referred for evaluation of psoriasis that is not responding to topical agents. After a detailed evaluation, you recommend adalimumab. The patient is sent for screening bloodwork prior to initiation of therapy, which demonstrates that he has chronic HBV infection (HBsAg positive, anti-HBs Ab negative, anti-HBc positive). How do you proceed?

Natural History of HBV Infection

Chronic HBV infection is most commonly acquired after exposure at birth. Globally, there are estimated to be close to 300 million infected persons, of whom only 10% are diagnosed.[2] After exposure at birth, the infection progresses to an immunotolerant stage characterized by high viral load, normal alanine aminotransferase (ALT), and no liver fibrosis. After the immunotolerant phase, patients will typically experience a phase of immune clearance characterized by fluctuating viral load and ALT, and possible accumulation of fibrosis.

Following immune clearance, patients may enter a phase of immune control characterized by low viral load, normal ALT and host immune response that prevents liver fibrosis.[3] Adult patients usually present in this latter stage.

Understanding HBV Reactivation

HBV is non-cytopathic, and the outcome of infection is determined by adaptive T and B cell responses.[4] Inflammation is the result of the immune response. Despite developing immune control, patients will retain a reservoir of persistent HBV, either as whole virus or as covalently closed circular DNA (cccDNA) which is sometimes called resolved or latent HBV. Medications that suppress general immune function or specific host pathways that alter the immune control of HBV can impair this immune control and result in clinical reactivation.

Reactivation is defined as a rapid increase in HBV DNA level by at least 100-fold in those with previously detectable DNA, or the reappearance of HBV viremia in those who did not previously have viremia. When this occurs, it can be followed by a rise in the ALT and aspartate aminotransferase (AST) and clinical outcomes include spontaneous resolution or persistent liver injury and acute liver failure. While most patients will spontaneously recover, the risk of acute liver failure and resultant death means that attention needs to be given to this serious event.

Screening Evaluation for Viral Hepatitis

All patients who receive immunosuppressive therapy should be screened for viral hepatitis prior to initiation of treatment. Screening should include HBsAg (Hepatitis B surface antigen), anti-HBs Ab (Hepatitis B surface antibody), anti-HBc Ab (Hepatitis B core antibody), and anti-HCV Ab (Hepatitis C antibody). Interpretation of the HBV screening test results is found in **Table 1.**

Patients who test negative for all HBV markers should be referred to their primary care provider or public health authority for vaccination. Patients who test positive for only Anti-HBc Ab have been previously exposed to HBV but do not have active infection. Patients who test positive for HBsAg have active infection and should be referred to specialty care for evaluation of the infection and determination of the need for therapy irrespective of immunosuppression.

HBV Clinical State	HBsAg	Anti-HBs Ab	Anti-HBc Ab
Infected	+	-/+	+
Immune (from vaccination)	-	+	-
Resolved (Natural Immunity)	-	-/+	+
Non-Infected Non-immune	-	-	-

Table 1. Interpretation of HBV screening tests

Patients who test positive for anti-HCV Ab should have a follow-up HCV RNA PCR performed and be referred on for treatment of HCV infection. While HCV RNA levels can slightly rise in a person taking immunosuppressive therapy, it does not cause clinical signs or symptoms.[5]

Risk Matrix for Decision to Prescribe Prophylactic Therapy to Prevent HBV Reactivation

Patients who test positive for HBsAg are high-risk patients for reactivation. These patients should receive prophylactic therapy to prevent reactivation when receiving medications that attribute any risk of reactivation.[6] High-risk patients receiving high-risk therapies have a possibility of reactivation that is higher than 10% and, in some studies, higher than 50%.

Patients who test negative for HBsAg but positive for anti-HBc Ab are low risk for reactivation. These patients should receive prophylaxis only when receiving medications that carry a very high risk of causing reactivation, as shown in **Table 2.**

Choice and Duration of Antiviral Prophylaxis

Patients who qualify for prophylactic therapy should have it initiated prior to, or when starting, immunosuppressive therapy. Baseline lab testing including ALT, AST, international normalized ratio (INR), bilirubin, albumin, hepatitis B e-antigen (HBeAg), anti Hepatitis B e-antibody (anti-HBe Ab), and HBV DNA should be obtained in all patients and HBV DNA should be monitored every 3-6 months while patients are on antiviral therapy.

The same nucleoside/nucleotide analogues used for the treatment of chronic HBV infection can be used for prophylaxis. In a published systematic review, the authors demonstrated that lamivudine can significantly reduce

Very high risk of reactivation	Rituximab, ofatumumab, ustekinumab, natalizumab
High risk of reactivation	High-dose corticosteroids Anthracyclines Potent TNF-α inhibitors including infliximab, adalimumab, golimumab
Moderate risk of reactivation	Systemic chemotherapy Etanercept Tyrosine-kinase inhibitors including imatinib Moderate-dose corticosteroids
Low risk of reactivation	Antimetabolites Azathioprine, 6-mercaptopurine, methotrexate Short-term low-dose corticosteroids

Table 2. Risk profile of common immunosuppressive therapies

the risk of reaction, HBV-related hepatitis, and HBV-related acute liver failure in patients receiving cancer chemotherapy.[7] The authors of this systematic review analyzed fourteen studies (2 randomized controlled trials; 8 prospective cohort studies; and 4 retrospective cohort studies) which met the predefined criteria for analysis. There were 275 patients in the preventive lamivudine group and 475 control participants for the primary end point of HBV reactivation. With preventive lamivudine, the relative risk for both HBV reactivation and HBV-related hepatitis ranged from 0.00 to 0.21. None of the patients in the preventive lamivudine group developed HBV-related hepatic failure (0 of 108 patients vs. 21 of 162 patients), and only 4 deaths were attributable to HBV (4 of 208 patients vs. 27 of 394 patients) in the preventive lamivudine group. Lamivudine was well tolerated, and no adverse effects were noted.[7]

Despite the accumulated evidence, lamivudine is generally not considered the preferred agent due its low potency and low barrier of resistance. More recently, entecavir and tenofovir have become the preferred agents.[8]

Specifically as it relates to the use of entecavir, a recent study comparing the efficacy of entecavir and lamivudine in preventing HBV reactivation in patients seropositive for the hepatitis B surface antigen with untreated diffuse large B-cell lymphoma receiving chemotherapy treatment with rituximab, cyclophosphamide, doxorubicin, vincristine, and prednisone (R-CHOP) was conducted. The primary efficacy endpoint was the incidence of HBV-related hepatitis. The secondary endpoints included rates of HBV reactivation, chemotherapy disruption due to hepatitis, and treatment-related adverse events. The results show that the incidence rates were significantly lower for the entecavir group vs the lamivudine group for HBV-related hepatitis (0% vs 13.3%, respectively; difference between groups, 13.3% [95% CI, 4.7% to 21.9%]; P = .003), HBV reactivation (6.6% vs 30%; difference, 23.4% [95% CI, 10.2% to 36.6%]; P = .001), and chemotherapy disruption (1.6% vs 18.3%; difference, 16.7% [95% CI, 6.4% to 27.0%]; P = .002). Of the 61 patients in the entecavir group, 15 (24.6%) experienced treatment-related adverse events. Of 60 patients in the lamivudine group, 18 (30%) experienced treatment-related adverse events (difference between entecavir and lamivudine groups, 5.4% [95% CI, -10.5% to 21.3%]; P = .50).[8]

While prophylaxis can start just prior to the initiation of immunosuppression, it should continue for at least 6 months after the last dose of immunosuppression. Since the risk of reactivation is highest during the immune reconstitution phase following immunosuppression, the patient must receive prophylaxis through this period to be protected. Clinicians should note that there is some evidence that reactivation risk after rituximab can persist for 2 years, so in the case of this therapy, prophylaxis must be given for a longer period of time.[6]

Follow-up and Monitoring of Patients

The risk of reactivation is not eliminated by prophylactic therapy. All patients should be monitored for serologic evidence of reactivation with laboratory testing every 3-6 months that includes HBsAg, HBV DNA and ALT. Patients who are HBsAg positive should also be assessed for fibrosis and there is need for ultrasound surveillance of hepatocellular carcinoma.

Conclusion

Reactivation of viral hepatitis is an uncommon event but can cause severe morbidity and even death when it does occur. It is essential to screen all patients receiving immunosuppression for HBV and HCV and manage them appropriately with collaboration from liver specialists where needed.

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HIDRADENITIS SUPPURATIVA: WHAT'S ON THE HORIZON?

Hidradenitis suppurativa (HS) is a chronic inflammatory skin condition that has a paucity of effective therapeutic options. In recent years, progress has been made in the understanding of HS pathophysiology which has led to the development of new therapeutic options.

The current HS management algorithm has been outlined in North American treatment guidelines and includes a combination of medical and surgical treatment modalities.[1] The guidelines focus on helping clinicians make optimal treatment decisions while taking an individualized approach in each particular patient case. Medical management recommendations include topical and intralesional therapies, systemic antibiotics, hormonal agents, retinoids, immunosuppressants, and biologics. Immunomodulation has adopted a solid place in HS management and will be the focus of this review.

Various tools have been used for disease assessment and monitoring in clinical practice and clinical trials. Hurley staging[2] has been used to assess disease severity focusing on scarring but lacks in its assessment of disease dynamics. The Hidradenitis Suppurativa Clinical Response (HiSCR) has been validated in clinical trials[3, 4] and is used in clinical practice to assess treatment effectiveness. HiSCR50 is defined as at least a ≥ 50% reduction in total abscess and inflammatory nodule count, with no increase in abscess or tunnel (fistula) count relative to baseline.[3] HiSCR75 is defined as at least a ≥ 75% reduction in total abscess and inflammatory nodule count, with no increase in abscess or tunnel (fistula) count.[4] HiSCR90 is defined as at least a ≥ 90% reduction in total abscess and inflammatory nodule, with no increase in abscess or tunnel (fistula) count.

The HS ALLIANCE working group conducted a systematic review of the literature and provided evidence-based recommendations for disease assessment and monitoring.[5] They suggested that while Hurley staging is useful to assess baseline disease severity, HiSCR is recommended as the dichotomous outcome measure in inflammatory areas under treatment. Additionally, patient-reported outcome measures (e.g. dermatology life quality index [DLQI] and the visual analog scale [VAS]) may provide important insight into patient functioning, quality of life and symptoms and should be included in the disease assessment.[5] Adalimumab is currently the only Health Canada and FDA-approved treatment for HS. The efficacy and safety of adalimumab has

been investigated in two parallel double-blind placebo-controlled phase 3 trials, PIONEER 1 and PIONEER 2[6] with concomitant use of tetracycline class antibiotics permitted in PIONEER 2. The primary endpoint of HiSCR response (HiSCR50) at week 12 was achieved by 42% of patients treated with adalimumab vs 26% of patients treated with placebo (P=0.003) in PIONEER 1 and 59% vs 28%, respectively, in PIONEER 26 **(Figure 1)**. Adalimumab was dosed 160 mg at week 0, 80 mg at week 2 and then 40 mg weekly starting at week 4. Forty percent of patients who failed to achieve the primary endpoint at week 12 achieved HiSCR at week 36 with continuous treatment.[6]

The long term efficacy and tolerability of adalimumab was evaluated by pooling the results of the PIONEER 1 and PIONEER 2 phase 3 studies and the open-label extension (OLE) study.[7] After screening, the patients entered period A and were randomized to receive adalimumab 40 mg weekly or placebo for 12 weeks. In period B, patients who were randomized to receive adalimumab in Period A were reassigned to receive adalimumab 40 mg weekly, adalimumab every other week, or placebo for 24 weeks. Patients who were randomized to receive placebo in period A were reassigned to continue receiving placebo (PIONEER 2) or to receive adalimumab 40 mg weekly in period B (PIONEER 1). In the OLE trial, all patients received adalimumab 40 mg weekly for at least 60 weeks. At week 12 of the pooled analysis, HiSCR was achieved by 52.3% of patients receiving adalimumab weekly who entered the OLE and 73% of patients defined as responders plus partial responders (PRRs) which included those who did not achieve HiSCR but did achieve at least a 25% reduction in abscess and nodule count relative to

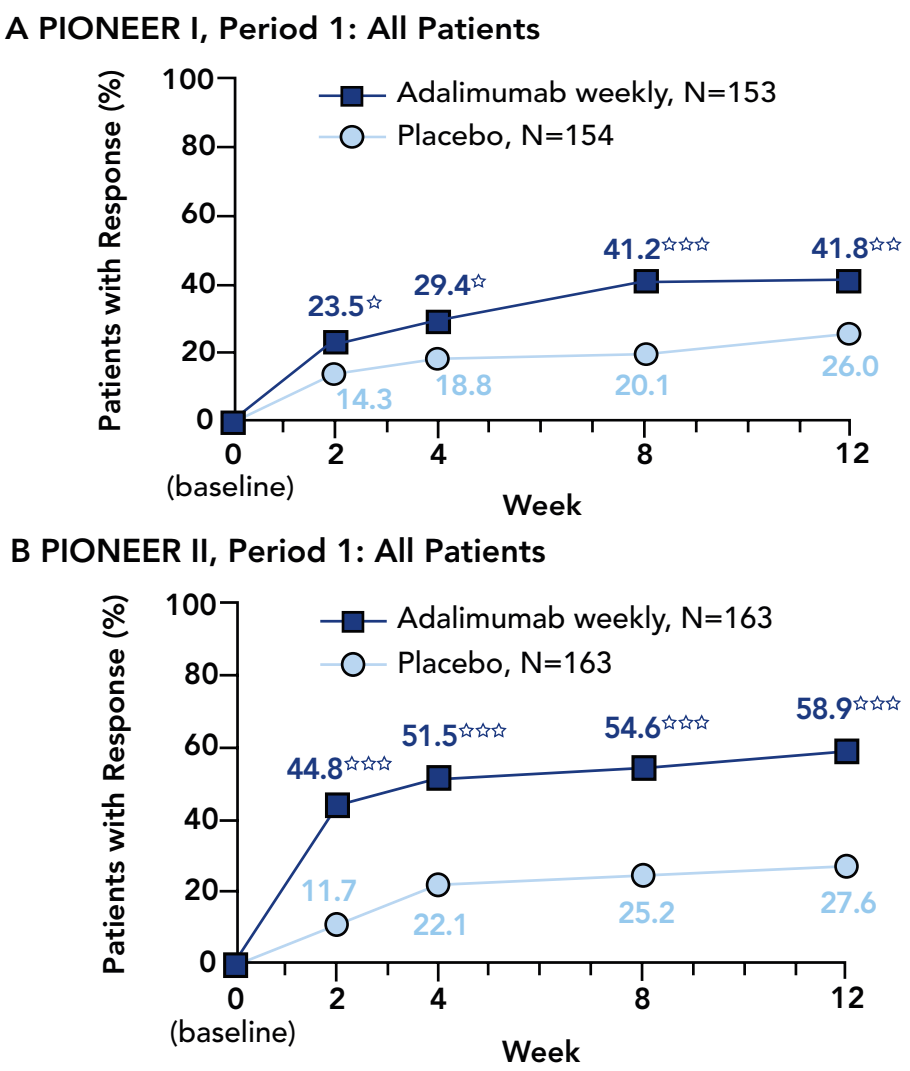


Figure 1. PIONEER 1 (A) and PIONEER 2 (B) results for all patients at Week 12; adapted from Kimball et al, 2016

baseline. HiSCR was maintained through week 168 in 52.3% receiving adalimumab weekly and 57.1% of patients defined as PRRs. Inflammatory lesion count, draining fistula count, total fistula count and pain, all improved from baseline in both populations. Sustained improvement was seen through week 168.[7]

The Canadian Humira Post Marketing Observational Epidemiological Study: Assessing Humira® Real-life Effectiveness and Impact on Moderate to Severe HS Burden of Illness and Health Care Resources Utilization (SOLACE) evaluated adalimumab efficacy and safety in a prospective cohort of patients with moderate-to-severe HS in a real-world clinical setting.[8] Overall, 69% of patients achieved HiSCR at week 24 (primary endpoint) which was maintained out to week 52. The HARMONY study is another real-world prospective, multicenter, post-marketing observational study conducted in Europe and Middle East that included patients with moderate- to-severe HS. In the HARMONY study, 70.2% of patients achieved HiSCR at week 12 (the primary endpoint) which was maintained out to weeks 24 (HiSCR 75.7%) and 52 (HiSCR 72.1%).[9] These studies confirm adalimumab's efficacy in a real-world clinical setting and suggest that treatment optimization with the addition of medical and surgical therapeutic modalities achieve further improvements in HS management.

Other TNF-α inhibitors have been investigated as potential therapeutic options and are currently used off label.[1] Infliximab has the most published experience with the most benefit seen in higher dosing regimens (5-10 mg/kg every 4 -8 weeks).[10-12] Etanercept (50 mg twice weekly) was evaluated in 20 patients in a single center, randomized, prospective, double-blind, placebo controlled study and failed to achieve its primary endpoint of physician global assessment clear or mild at week 12. There were also no statistical differences between the active arm and placebo in patient global assessment and DLQI.[13] Certolizumab pegol has also been reported to be beneficial in achieving clinical response in case reports.[14-16]

Anakinra, an IL-1 inhibitor has been shown to achieve HiSCR in a small randomized controlled trial of 20 patients and an open label study of 6 patients.[17,18] Anakinra was dosed at 100 mg daily. The North American clinical management guidelines recommend considering anakinra only after failure to TNF inhibition.[1] Unfortunately, the use of anakinra for HS is limited in Canada due to accessibility issues.

Ustekinumab, an IL-12/23 p40 inhibitor was investigated in a small open label study in 17 patients with moderate-to-severe HS and demonstrated improvements in Sartorius scores and inflammatory lesion count.[19] There is no robust evidence confirming ustekinumab's efficacy in this patient population and no data evaluating its efficacy using higher doses similar to Crohn's disease. However, ustekinumab has been successful in achieving clinical response in case reports and small case series[19-22] and might be a useful therapeutic option for patients with HS and other comorbidities or HS patients with inadequate response to TNF-α inhibitors.

New therapeutic targets in HS management include inhibition of IL-17 and IL-23 pathways. IL-17 cytokines have been shown to be elevated in serum[23] as well as lesional and perilesional HS skin.[24] Several case reports and case series utilizing secukinumab[25-30], ixekizumab[31-32] and brodalumab[33] have demonstrated improvements in HS clinical outcomes. Therapeutic agents in clinical development for the treatment of HS are outlined in **Table 1**.

A recent bimekizumab phase II clinical trial (NCT03248531) had demonstrated clinically meaningful improvements across all outcome measures.[34] This trial included patients with diagnosis of HS for 1 year, abscess and inflammatory nodule count of 3 and inadequate response to a 3 month course of oral antibiotics (used for HS treatment) and HS lesions presents in 2 distinct anatomical areas (one of which must be at least Hurley stage II or III) and excluded patients with prior anti-IL-17 or anti-TNF experience. Eighty-eight patients were randomized 2:1:1 to bimekizumab 320mg (q2w; 640 loading dose), placebo, or adalimumab (as per product monograph). Primary endpoint was HiSCR50 at week 12. Exploratory endpoints included: HiSCR75, IHS4, PGA skin pain, DLQI.

At 12 weeks, 56.9% of patients treated with bimekizumab achieved HiSCR response compared to 23.7% of patients treated with placebo. In this study, 59.8% of patients treated with adalimumab had achieved a HiSCR response, similar to the proportion of patients achieving HiSCR50 on bimekizumab. More patients treated with bimekizumab achieved HiSCR75 compared to placebo (50% vs 11.1%), and adalimumab (38.9%) at week 12. In addition, at week 12, bimekizumab performed better than placebo and adalimumab in exploratory endpoints of PGA skin pain. Bimekizumab performed similar to adalimumab in quality of life measures (DLQI) and IHS4 and better than placebo. The overall incidence of treatment emergent adverse events at week 12 was similar between placebo, adalimumab and bimekizumab with no unexpected safety findings.

In addition, the IL-23/Th17 pathway has been shown to be an important player in the inflammatory milieu in HS lesions.[35] A small retrospective chart review and 2 case reports[36-38] of HS patients treated with guselkumab (using psoriasis dosing of 100 mg q 8 weeks) suggest that it might present a new therapeutic option for HS. Guselkumab and risankizumab are currently being investigated in clinical trials as potential HS therapies.

Other emerging HS therapeutic options include Janus kinase (JAK) inhibitors and bermekimab. JAK inhibitors are made up of a family of intracellular tyrosine kinases that transduce cytokine-mediated signals to further activate transcription. Inhibition of JAK can simultaneously block transcription of multiple cytokines. The JAK family includes JAK1, JAK2, JAK3, and tyrosine kinase 2 (TYK 2). Most cytokine receptors use a combination of JAKs. Therapeutic agents inhibiting JAK can possess high or low selectivity for a particular JAK target and some earlier compounds may possess multi-JAK inhibition. Pan-JAK inhibition is not clinically desirable due to a higher risk of severe adverse events. JAK inhibition is of particular interest in management of HS due to various cytokines involved in disease pathogenesis and the lack

of one therapeutic target.[39] In this instance a phase 2 clinical trial is currently underway to investigate three different kinase inhibitors (PF-06650833, PF-06700841 and PF-06826647) as potential therapeutic targets in adults with HS. Bermekimab, an IL-1α inhibitor represents a novel therapeutic option showing efficacy in a phase II open label study.[40] Bermekimab efficacy was assessed in both HS patients who had previously failed TNF-α therapy and patients who were TNF-naïve. Regardless of the patient's prior TNF failure history, 61% of TNF-naïve patients and 63% of TNF-failed patients achieved HiSCR at week 12, suggesting that the bermekimab therapeutic target is of interest in HS management.

In conclusion, HS is a complex inflammatory condition with an established therapeutic algorithm, yet there exist a paucity of effective approved therapeutic options. Many therapeutic agents currently used in the management of other inflammatory conditions like psoriasis are of high clinical interest as potential therapeutic options for HS. Immune modulation remains an area of high scientific and clinical interest with many agents being investigated in ongoing clinical trials.

Compound	Mechanism of action	Phase in development	Registered trials
Anakinra	IL-1 antagonist	2	NCT01558375, NCT01516749
Bermekimab	IL-1α antagonist	2	NCT03512275, NCT04019041
PF-06650833	IL-1 receptor associated protein kinase 4 (IRAK4) inhibitor	2	NCT04092452
Secukinumab	IL-17 antagonist	3	NCT03099980, NCT03713632 NCT03713619, NCT04179175
Brodalumab	IL-17 antagonist	1, 2	NCT03960268, NCT03910803
Bimekizumab	IL-17 antagonist	2	NCT03248531, NCT04242498 NCT04242446
CJM112	IL-17 antagonist	2	NCT02421172
Guselkumab	IL-23 antagonist	2	NCT04061395, NCT03628924
Risankizumab	IL-23 antagonist	2	NCT03926169
INCB054707	JAK-1 inhibitor	2	NCT03569371, NCT03607487 NCT04476043
Upadacitinib	JAK-1 inhibitor	2	NCT04430855
Ruxolitinib 1.5% Cream	JAK1/JAK2 inhibitor	2	NCT04414514
PF-06700841	Dual JAK1/TYK2 inhibitor	2	NCT04092452
PF-06826647	TYK2 inhibitor	2	NCT04092452
IFX-1	C5a inhibitor	2	NCT03487276 NCT03001622
Apremilast	PD-4 inhibitor	2	NCT03049267 NCT02695212
CSL324	Granulocyte colony-stimulating factor (G-CSF) receptor antagonist	1	NCT03972280
Iscalimab (CFZ533)	CD-40 antagonist	2	NCT03827798
LYS006	Not reported	2	NCT03827798
LY3041658	Not reported	2	NCT04493502

Table 1. Therapeutic agents under investigation for the treatment of HS (clinicaltrials.gov, accessed 04-October-2020)

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PRACTICAL PHOTODYNAMIC THERAPY FOR THE CANADIAN DERMATOLOGIST

Introduction

Photodynamic therapy (PDT) is used in dermatology for the treatment of malignant and non-malignant cutaneous diseases. PDT utilizes a photosensitizing agent and visible light in the presence of oxygen to produce reactive oxygen species (ROS). ROS then induce apoptosis of cellular components leading to cell death.[1] PDT is approved in Canada for the treatment of non-hyperkeratotic actinic keratoses (AK)[2,3] and superficial basal cell carcinoma (BCC) outside the H-zone of the face.[2] In addition, some European countries have approved its use in the treatment of squamous cell carcinoma *in-situ* (SCCis) and thin nodular BCC.[4]

Off-label uses of PDT include acne, photoaging, infectious dermatoses, and malignancies such as cutaneous T cell lymphoma (CTCL), and extra-mammary Paget's disease.[5] This review will focus on the practical use of PDT for the treatment of premalignant and malignant lesions.

Mechanism of Action

For dermatologic conditions, PDT is carried out by topical application of precursors of the heme biosynthetic pathway, specifically 5-aminolaevulinic acid (5-ALA) or its ester, methyl aminolaevulinate (MAL). In Canada, there are two photosensitizers approved to treat AK: Levulan®Kerastick (5-ALA) (DUSA Pharmaceuticals Inc.) and Metvix (MAL) (Galderma Canada Inc). Only Metvix is approved for the treatment of superficial BCC in Canada. During an incubation period, these precursors are converted within target cells into protoporphyrin IX (PpIX).[1] PpIX has major absorption peaks in the visible spectrum of light, particularly in the blue (410-420nm) and red (630-635nm) wavelengths **(Figure 1)**. After incubation, visible light in the blue (5-ALA) or red (MAL, 5-ALA) spectrum is used to activate the photosensitizer. Light sources used include narrowband LED devices, metal halide lamps, fluorescent lamps, filtered intense pulsed light (IPL), and lasers.[4]

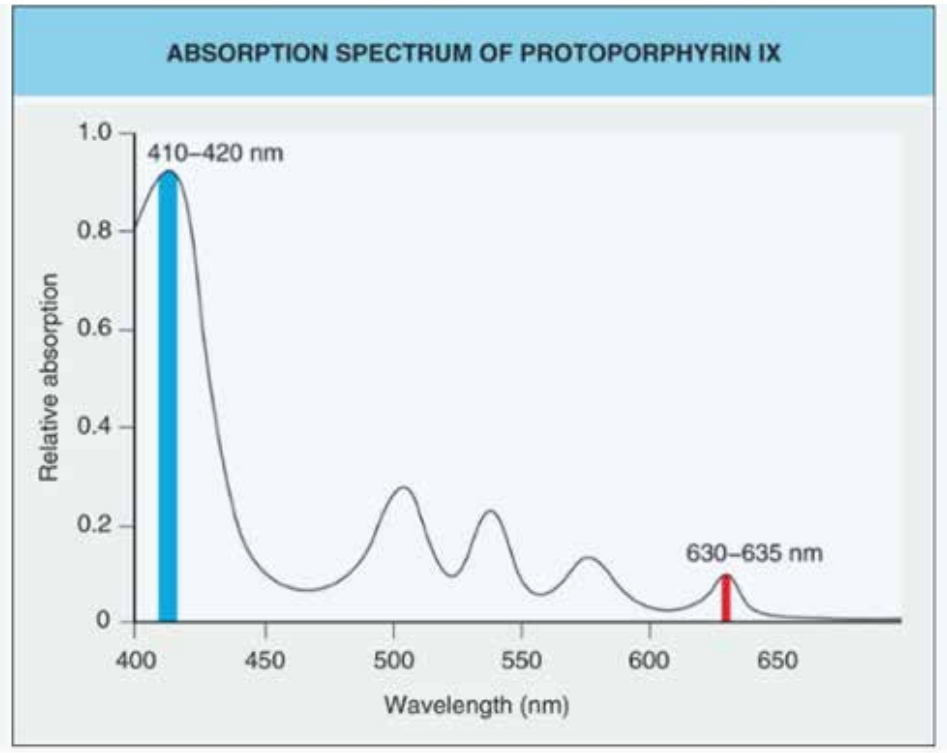


Figure 1: Absorption spectrum of protoporphyrin IX; adapted from Liu and Richer, 2018

When light at the appropriate wavelength is absorbed by PpIX, it excites the PpIX to a higher energy "singlet" state. This singlet state molecule can then transfer its energy to oxygen, producing singlet oxygen and other reactive oxygen species. It can also release energy as photons, which is seen as fluorescence when a Wood's lamp is shined on the treated field.[6] The ROS interact with components of the cell, leading to apoptosis and cellular necrosis. Tumour destruction is kept localized by several factors: preferential accumulation of porphyrins in both malignant and pre-malignant cells, the targeted application of the photosensitizer, limiting the area of light exposure to only the specific skin target, and photobleaching (deactivation) of the photosensitizing chemical with continued light exposure.[7]

Methods of Administration

Patient selection is important prior to performing PDT. Contraindications to PDT include hypersensitivity to the photosensitizing agent (MAL or 5-ALA) or ingredients in the formulation (peanut and almond oil in Metvix), a history of photosensitive disorders, history of porphyria, and morpheaform basal cell carcinoma.[2,3]

Conventional PDT (c-PDT) involves the application of the 5-ALA or MAL photosensitizer followed by occlusion for 3-4 hours, then exposure to the appropriate activating wavelength of light. Protocols for current approved indications are summarized in **Table 1**. For AK, clinical trials have demonstrated a lesion clearance rate of 83-92% at 3 months and a one-year sustained clearance of up to 78-80%.[11,12] In comparative studies, c-PDT was superior to cryotherapy[13], diclofenac[14], and 50% trichloroacetic acid[15] in the clearance of AK. It has comparable clearance rates to topical 5-fluorouracil (5-FU)[16], imiquimod[17], and ingenol mebutate.[18] However, patients rate the cosmetic outcome of PDT higher than other AK treatments, with the exception of imiquimod, which was equivalent.[4,19]

Superficial BCC has a primary clearance rate of 92-97% at 12 weeks using MAL-PDT, with a 1-year recurrence rate of 9% and 5-year recurrence rate of 22%.[20] While some European countries approve the treatment of nodular BCC with c-PDT, the response rates are lower and recurrence rates higher than with superficial BCC. Conventional MAL-PDT is also approved for SCCis in many countries, with lesion clearance rates of 86-93% and a 2-year sustained clearance rate of 68-71%.[21] Nodular BCC and SCCis treatment with PDT is off-label in Canada. PDT is not recommended for other subtypes of BCC or invasive squamous cell carcinoma (SCC).

Daylight PDT

Daylight PDT (d-PDT) involves the application of sunscreen to the entire face, followed by MAL application to the affected areas, and a short 30-minute incubation time. Ambient outdoor light is then used to activate the MAL over a longer period of time (2 hours) than c-PDT.[10] This approach allows for the exposure of large surface areas and minimizes pain. However, d-PDT requires certain environmental criteria to be met in order to be effective. The mean outdoor temperature must be above 10°C, or an insufficient amount of PpIX may be generated. Also, patients need a sufficient light-dose to ensure complete activation of the photosensitizer. At northern latitudes such as Canada this typically restricts d-PDT to the months between April-October.[22,23] D-PDT is approved for the treatment of actinic keratoses, and is as effective as c-PDT, but is much less painful.[24,25] The original Australian and European studies demonstrated 70-89% clearance of AK after treatment. D-PDT is

not approved for the treatment of BCC, SCCis or SCC.

Technique Variations of PDT

There are several techniques used to enhance the efficacy of PDT, though all are considered off-label. Pretreatment of lesions to improve penetration of the photosensitizer can be done chemically with topical keratolytics such as retinoids, salicylic acid, and a-hydroxy acids. Physical modalities such as tape-stripping, fractional CO2 laser[26], and microneedling[27] have also been used. Laser-assisted PDT was found to be significantly more effective than PDT alone, with no difference in pain intensity, especially for clearance of AK on difficult sites such as the extremities.[26]

The use of combination field therapies such as imiquimod, 5-FU, and calcipotriol prior to PDT also increases efficacy, with combination treatment showing higher clearance rates when compared with PDT alone.[28] Pretreatment with topical 5-FU cream, applied twice daily for 6–7 days prior to PDT, led to a mean improvement in lesion clearance of 11–30% compared with PDT alone. Imiquimod, when used either pre-or post-PDT, led to higher rates of complete clearance than PDT monotherapy.[28] However some combined treatment regimens trade increased efficacy for increased pain and local side effects, such as with calcipotriol pretreatment.[29] Elevating skin temperature after ALA/MAL application has also been shown to increase short- and long-term efficacy of AK clearance by up to 90%.[30] This is based on the fact that PpIX creation is a temperature-dependent process, so an increase in PpIX conversion and accumulation may lead to increased clearance of AK.[30] This technique does not lead to increased pain, and has the benefit of shortening incubation time.

Adverse Effects and Complications

PDT is not without adverse effects. First and foremost is photosensitivity. Patients must be aware that they will develop a phototoxic reaction during PDT treatment.[31] This presents as pain, erythema, edema, exudation and crusting. Patients must avoid sunlight for 48 hours after PDT is performed, allowing any residual photosensitizer to be slowly photobleached by indoor visible light. The use of conventional sunscreens is insufficient to protect treated areas after PDT, as residual photosensitizer can be activated by visible light, and most sunscreens do not protect in this wavelength. D-PDT typically generates milder local inflammation that resolves faster than c-PDT. These reactions resolve over 1-3 weeks, and any wounds heal by secondary intention. Scarring is a rare, uncommon side effect, and PDT is being investigated as a treatment option for hypertrophic and keloid scars. As mentioned above, the ultimate cosmetic outcome after PDT is preferred over other field therapies by patients in many studies.[4]

Pain or discomfort is a common adverse effect of c-PDT, and many strategies have been used to mitigate this. There is a large variation in the intensity of PDT-induced pain between patients, but up to 16-20% of patients report experiencing severe pain.[32] Once the treated area is exposed to light, patients experience a range of symptoms from a prickling sensation, to burning, or a "stabbing" sensation. This typically builds with the length of exposure and varies with the rate of light delivery. D-PDT has a lower irradiance of light exposed over a longer period of time, leading to significantly less pain.[24] Effective techniques to mitigate pain include treatment interruption, talking and distraction, fans or cold forced air directed at the site, application of ice packs or cold sprayed water, and anesthesia through local infiltration or nerve blocks.[31] Topical agents such a lidocaine, eutectic mixture of local anesthetics (EMLA), tetracaine, or capsaicin are ineffective at mitigating the pain of PDT.[31] Many guidelines recommend using multiple options for pain mitigation simultaneously. Although pain is frequently reported during PDT treatment, only 2% of PDT treatments are discontinued due to pain.[33]

Lastly, less common adverse reactions to PDT include flaring of latent herpes simplex infections, and open wounds may rarely lead to a secondary bacterial or viral infection. Rarely, urticaria, purpura, alopecia, dyspigmentation or milia may develop to treatment sites. Contact hypersensitivity may develop in patients who have undergone multiple PDT treatments, had large areas treated, or in staff administering the treatment. As such, gloves are recommended for healthcare providers handing MAL and ALA to avoid contact sensitization.[34]

Conclusion

In summary, topical PDT is a widely used therapy which is generally well-tolerated by patients. It offers efficacy similar to other standard treatments, combined with excellent cosmetic results. While pain and discomfort are the main adverse effects of c-PDT, effective strategies have been developed to manage discomfort. This includes the development of d-PDT, which is a relatively pain-free treatment option allowing treatment of larger surface areas with equivalent results. Careful patient selection and thorough counselling, both pre-procedure

	C-PDT with 5-ALA[8]	C-PDT with MAL[9]	D-PDT with MAL[10]
Indication	Single and multiple non-hyperkeratotic actinic keratoses of the face and scalp	1) Thin or non-hyperkeratotic AK on face and scalp. 2) Superficial BCC 3) SCCis (Europe)	Thin or non-hyperkeratotic, non-pigmented AK on face and scalp
Lesion Preparation/ Photosensitizer application	Curettage of hyperkeratotic lesions. Apply solution to AK and let dry. Incubate for 14-18 h overnight. Treatment site not occluded, but protect from sun/bright light. Off-label use: incubate 3h with occlusion[9]	Curettage of hyperkeratotic lesions. Remove scales/crusts, roughen surface. Apply layer of cream ~1 mm thick via spatula to lesion and surrounding 5–10 mm of skin. Cover with occlusive dressing for 3 h.	Apply mineral sunscreen (SPF 30-50). Once dry, remove scales and crusts, roughen skin. Apply thin layer of Metvix to treatment area. No occlusion
Photosensitizer	ALA 20% hydroalcoholic solution (Levulan Kerastick)	MAL 16.8% cream (Metvix/Metvixia)	MAL 16.8% cream (Metvix/Metvixia)
Light Source	Blue, fluorescent light (417nm wavelength)	Red LED light (630nm wavelength)	Ambient daylight
Illumination Protocol	Rinse and pat dry prior to light exposure. Irradiate treated area for 1000 seconds (16 minutes 40 seconds) to achieve total dose of 10 J/cm^2	Rinse with saline. Irradiate using red light of spectrum 630-635nm to a total dose of 37 J/cm^2	Patient goes outside within 30 min of application. Dry day, temperature >10°C, exposure time of 2 hours
Cream Removal and Aftercare	Avoid sun for 30-48 hours	Wipe clean with saline.	Remove MAL with warm water and washcloth. Avoid sun for 24 hours
Treatment Frequency and Follow up	One treatment. Follow up in 8-12 weeks.	1) AK: one treatment 2) BCC: 2 treatments, 1 week apart 3) SCCis: 2 treatments, 1 week apart	Single treatment. Follow up in 7 days and reassess at 12 weeks.

Table 1: Treatment protocols for approved indications

and post-procedure, are key to the successful delivery of PDT. Topical PDT has an important place in the management of patients with precancerous lesions and superficial nonmelanoma skin cancer, with further research ongoing to increase its efficacy and broaden its successful clinical usage.

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A TALE OF TWO FRONTAL ALOPECIAS: TRACTION ALOPECIA AND FRONTAL FIBROSING ALOPECIA – CLINICAL PEARLS AND PROMISING THERAPIES

Introduction

Traction alopecia (TA) is a form of hair loss caused by repetitive tension and pulling of the hair.[1] TA most commonly occurs in women of Afro-Caribbean descent with afro-textured hair due to the higher prevalence of high-tension hairstyles such as braids and weaves.[2] However, it has also been reported in other patient demographics including ballerinas[3], gymnasts, and patients with certain head coverings.[4] TA typically occurs

in a biphasic nature, starting with an early stage that is non-cicatricial (without scarring) which can progress to cicatricial and permanent alopecia with prolonged tension.[5] Conversely, frontal fibrosing alopecia (FFA) is a variant of lichen planopilaris (LPP) that presents as an inflammatory cicatricial alopecia. FFA is clinically characterized by permanent alopecia, an unpredictable clinical course, and a band-like pattern of involvement in the frontal and temporal hairline.[6] FFA mainly affects post-menopausal women as described by Kossard,[7] although there have been cases reported in premenopausal women and in men.[8]

When hair loss involves the frontotemporal region, it can sometimes be difficult to distinguish between TA and FFA. Marginal or frontal hairline TA can especially mimic the band-like pattern of hair loss seen in FFA. As such, delineation of the clinical presentations and distinguishing features of each condition is important. This paper outlines clinical parameters for each diagnosis to enable accurate diagnosis and therapy.

Clinical Examination

Traction alopecia (TA) is directly related to mechanical trauma and repetitive pulling from high-tension hairstyles, therefore it is crucial to elicit haircare practices during history-taking. Women with afro-textured hair are at highest risk due to the increased prevalence of high-risk hairstyles such as twists, braids, cornrows, weaves which are installed with tension and involve added hair, and dreadlocks which can be heavy as they mature and lengthen.[9,10] Chemical relaxation/ hair straightening products coupled with artificial extensions are also strongly associated with increased risk of TA.[10] This increased risk occurs because the existing hair is permanently weakened, and tension-based styles or added hair further strain the hair strands. It is important to note that although TA is more prevalent in Afro-Caribbean patients, this is more related to common haircare practices rather than afro-textured hair types, as similar haircare practices yield symptomatology in other groups. Examples include tight buns and ponytails, religious practices (e.g. hair twisting in Sikh boys and men), tight scarf styles, extensions,[11] curlers, and chignon.[3]

The clinical features of traction alopecia depend heavily on the level of mechanical trauma and the stage of the disease. The most common presentation of TA is marginal alopecia which affects the frontal and temporal scalp, while the less common nonmarginal alopecia results in hair loss in other areas like the interior scalp.[1] In the earliest stages, patients will admit to sustaining pain or a headache after hairstyle installation. TA is non-scarring and may present as a slight decrease in hair density or small alopecic patches. Among the earliest clinical signs is the presence of traction folliculitis, producing perifollicular erythema, papules, and pustules in areas with the highest tension.[12] The 'fringe sign' is typically present, which is characterized by fine or miniaturized hairs remaining at the margin of the frontal hairline with hair loss posterior to the fringe.[13] There may also be hair casts, which are thin, white-hued cylindrical concretions that surround the hair shaft.[14] Permanent alopecia may occur with persistent mechanical trauma.

Unlike the mechanical pathogenesis of TA, frontal fibrosing alopecia (FFA) is a primary cicatricial alopecia. The pathogenesis of FFA is poorly understood, but LPP in general is believed to occur via an inflammatory process.[15] Overall, LPP seems to be more common in women than in men.[16] The classic presentation of FFA is a band-like hair loss in the frontotemporal hairline in post-menopausal women.[17-19] FFA can also affect premenopausal women, and rarely, men.[6] Multiple studies have also demonstrated a strong association between thyroid disease (especially hypothyroidism) and FFA.[21,22]

Although, the band-like distribution of FFA predominantly occurs in the frontal hairline, scarring can extend to the preauricular and retro-auricular regions of the scalp.[23] It can also affect other areas including the occipital region and the auricular margins.[24] While TA affects only the area of the scalp under tension, FFA commonly causes hair loss in eyebrows as well. In male patients affected by FFA, there may be hair loss in the frontal hairline, eyebrows, beard area and sideburns.[25] Clinicians may also notice a small number of isolated or solitary hairs within the band of alopecia, often referred to as the 'lonely hair sign.'[26] Other clinical features include erythematous and hyperkeratotic follicular openings, hypopigmentation,[27] and trichodynia[28] in patients with white skin. Interestingly, patients with brown skin and afro-textured hair generally display less erythema and may show perifollicular hyperpigmentation instead.

Histopathology

Since TA has a biphasic course, histopathological findings differ based on the severity and stage of alopecia. Early TA is characterized by a normal number of vellus hairs,

trichomalacia, and a decrease in telogen and catagen follicles.[29] Late-stage TA results in scarring with reduced follicular density, retained sebaceous glands, and a decrease in terminal follicle count (follicular 'drop out').[29] Conversely, primary cicatricial alopecias such as FFA feature the replacement of destroyed follicular units with fibrous tissues[30] as well as loss of follicular ostia.[31] FFA is a lymphocytic primary cicatricial alopecia with perifollicular inflammation and lymphocytic cell infiltrate at the infundibulum and isthmus.[32]

Therapeutic Management

Both types of alopecia can be managed according to their clinical severity and progression, as well as patient preference for non-prescription versus prescription-based management **(Table 1)**.

Behavioural Management

For both forms of alopecia, minimizing damage to the frontal scalp is critical. In TA, minimization, if not avoidance, of hair styles with tension or pulling is paramount. Varying scalp parts for typical hairstyles or wearing the hair in a looser style, such as a low bun is helpful.[33] For women and men who wear headgear for religious observance, adjustments like applying a cotton band to the hairline, then the turban or hijab afterwards will help relieve tension. In FFA, there is some association of its provocation following mechanical or thermal trauma to the scalp.[34] Australian dermatologists have proposed an association between FFA and the application of sunscreen to the hairline, including hair regrowth following its stoppage.[35] Therefore, avoidance of these potential triggers at these scalp sites is preferred.

	TA	FFA
Behavioural Measures	Hair style modification Loosen hairstyles or head coverings if painful	Avoid trauma (thermal or chemical burns) to the hairline Apply cosmetic products 2cm away from the hairline
Topical Therapy	minoxidil 5% foam* corticosteroid therapy (medium potency)	minoxidil 5% foam* calcineurin inhibitors* corticosteroid therapy (medium – high potency)
Procedural Therapy	Kenalog injections 5 mg/mL (consider 3 sessions 4 - 8 weeks apart to gauge response)	Kenalog injections 2.5 – 5 mg/mL (performed at 6 – 12 week intervals)
Oral Treatment	Sub-acute duration 3 – 6 months Minoxidil 1.25 – 2.5 mg qhs*	Acute duration ~ 3 mth course with stoppage if clinically stable Doxycycline 100mg twice daily* Sub-acute duration ~ 3 – 6 month course Cyclosporine 150mg twice daily* Chronic duration ~ 6 month course with reassessment of need of prescription continuation Methotrexate 20 – 25mg weekly* Mycophenolate mofetil 1g twice daily* Mycophenolic acid 720mg twice daily* Hydroxychloroquine 5mg/kg/day body weight* Acitretin 10 - 20mg daily Pioglitazone 15mg daily* Finasteride 5 mg daily*
Surgical Treatment	Hair transplant with permanent adoption of low tension hair-styling	Hair transplant if clinically stable and asymptomatic x 12 months or more

Table 1: Management of traction alopecia (TA) and frontal fibrosing alopecia (FFA)
**Off-label therapy*

Topical therapy

In TA and FFA, topical therapy can be used to limit inflammation, particularly in the early stages of the condition, or if there are symptoms of erythema, tenderness, and edema. Use of medium potency steroids like betamethasone valerate 0.1% lotion can help abate clinical symptoms in TA and FFA. Removal of the inciting hairstyle and use of topical minoxidil preparations can stimulate hair regrowth in TA.[36]

Procedural therapy

Reports of hair regrowth following injection of triamcinolone acetonide 5 mg/mL (Kenalog) to the affected scalp in TA make it a feasible in-office therapy at 6-8-week intervals.[37] However, patients risk pain and injection site atrophy. Also, it must be emphasized that this is not curative or a substitution for adaptation of tension-free hairstyling. In FFA, the use of Kenalog therapy at 8–12 week intervals is considered a cornerstone of management. It is postulated to help negate the presence and activity of inflammatory cytokines.[38] There are limited reports of platelet rich plasma (PRP) showing success in FFA for cessation of symptoms and hair regrowth.[39] Patients should be informed of its out-of-pocket cost and potential to require ongoing maintenance sessions to maintain its effect.

Oral Therapy

Although not the cornerstone of therapy, there is evidence that off-label use of oral minoxidil 1.25 – 2.5 mg at night can result in hair regrowth in non-scarred TA patients.[40] Results are noted after 3-6 months of consistent use. Patients should be advised of the risk of extra-scalp hypertrichosis.

There are a range of oral therapies for FFA, many of which are similar to LPP. In the acute phase, short courses of tetracycline antibiotic doxycycline may be helpful in diminishing scalp erythema and inflammatory symptoms. Successful treatment of LPP with immunomodulators such as cyclosporine, methotrexate, and mycophenolate mofetil has been reported and each yield better clinical improvement than hydroxychloroquine.[41] Given its relation to lichen planus, therapy with the retinoid acitretin can be a therapeutic option which also avoids immunosuppression. However, patients should be educated about the potential for telogen effluvium with this treatment. Finasteride treatment can be helpful, perhaps due to concurrent androgenetic alopecia activity. Finally, use of immune-modifiers like pioglitazone have a therapeutic role, particularly for patients who have clinical symptoms associated with their hair loss.[42]

Surgical Treatment

There are successful reports of TA correction with hair transplant in patients with afro-textured hair and straight hair.[43,44] While FFA, if stable for 12 months, can undergo hair transplant, scalp surgery has also been associated with inciting FFA,[45] and thus must be considered as a last resort therapy with a patient who fully understands the potential for a paradoxical result.

Conclusion

These two forms of hair loss, TA and FFA, share a predilection for the frontal scalp and overlapping therapeutic options. Dermatologists' clinical acumen and therapeutic experience are best suited to confirm their diagnoses and optimize therapy. The descriptions of their clinical findings, histological features, and management options provided here are a framework to help provide comprehensive clinical management and improvement.

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SKIN PICKING: A PRACTICAL APPROACH FOR THE BUSY DERMATOLOGIST

There is often a sense of dread when a dermatologist receives a referral for skin picking or excoriations. Due to the nature of our practices, these referrals typically suggest a longer visit, a frustrated patient, and ultimately, a less-than-satisfying visit for all parties involved. How can this be minimized?

There are many reasons why a patient might manipulate their skin including an underlying dermatologic condition or neurologic abnormality, pruritus without a rash, medication or drug abuse, and psychiatric illness. As a practicing dermatologist, a patient who presents with an underlying dermatologic condition is relatively easy to identify and diagnose as these cases of skin picking are usually related to an underlying inflammatory dermatosis, infection, or infestation. Similarly, systemic illnesses leading to pruritus without a rash and underlying neurologic abnormality are equally easy to identify and diagnose. An important neurologic condition to rule out, which may lead to skin picking is dementia. The dermatologist should also be familiar with identifying medications and/or recreational drugs of abuse that may lead to itching and subsequent picking. This, then, leaves the category of psychiatric illnesses. Excoriation (skin picking) disorder is listed in the DSM-V as follows[1]:

A. Recurrent skin picking resulting in skin lesions.
B. Repeated attempts to decrease or stop skin picking.
C. The skin picking causes clinically significant distress or impairment in social, occupational, or other important areas of functioning.
D. The skin picking is not attributable to the physiologic effects of a substance (e.g., cocaine) or another medical condition (e.g., scabies).
E. The skin picking is not better explained by symptoms of another mental disorder (e.g., delusions or tactile hallucinations in a psychotic disorder, attempts to improve a perceived defect or flaw in appearance in body dysmorphic disorder, stereotypes in stereotypic movement disorder, or intention to harm oneself in non-suicidal self injury).

For the practicing dermatologist, the above criteria can be difficult to remember. Instead, it may be easier to approach the patient according to the primary psychopathology: delusional, depressive, anxious, or obsessive-compulsive, which may help guide the management approach. It is important for the dermatologist to be reminded that one of the most important aspects to the successful management of these patients involves the building of rapport. Recognizing that there is no single "right" way, it is important to develop one's own style of interacting with these patients. For example, empathic listening while the patient details their difficulties may be very therapeutic for many of these patients who can feel as though their concerns may not have always been previously heard. At the same time, it is important to remain neutral and avoid speculation pertaining to the potential underlying cause of the patient's lesions.

A thorough physical examination is critical to ensuring an accurate diagnosis. All skin lesions should be reviewed, specifically looking for primary lesions suggesting an alternative diagnosis. Patients with delusions of parasitosis often display the "matchbox" or "baggy" sign containing collected samples, often containing keratinaceous debris or bits of dried blood. This is thought to be pathognomonic of this condition. However, it is important that the dermatologist actually review these samples to ensure there are not samples of arthropods that can actually cause a bite reaction, such as a bedbug.

Sometimes, a patient will bring in an insect that is thought to represent the culprit organism. If a specimen is sent off for identification, it is important to stipulate on the lab requisition that you are looking for an organism known to bite/infest humans.

As practices are busy, it is important to arrange short, but frequent visits for these patients. Although there may be a desire to refer these patients out for psychiatric assessment, it is critical to have an established relationship with mental health clinicians within your network. This is particularly important in delusional patients. The majority of our mental health colleagues have not seen these types of patients and their lesions and it is quite easy for unfamiliar mental health professionals to mistake the lesions as being infectious in nature. A single psychiatric assessment suggesting the lesions are "infected" can significantly delay the care some of these patients need.

The key to identifying a delusional patient is that they often articulate a firm belief that something is causing their lesions. Unfortunately, management of these patients is particularly challenging as they lack insight with respect to any underlying psychiatric condition. For patients who agree to a course of medication, antipsychotics are the recommended first-line treatments. Pimozide is a first-generation antipsychotic which has limited peer-reviewed data to support its use in patients with delusions of infestation, however, due to concerns with potential side effects, second generation antipsychotics are suggested.[3] Risperidone and olanzapine are the most commonly prescribed second-generation antipsychotics for this condition with risperidone being favored over olanzapine given that the latter has greater documented risk of weight gain and metabolic syndrome.[4] Aripiprazole, a newer third-generation antipsychotic, has also demonstrated some success in these patients as evidenced by several case reports supporting its use.[5,6]

Non-delusional patients are usually easier to identify and treat as they are able to provide significant insight as to the underlying cause of their lesions and they are also usually agreeable to treatment. These patients may often present with an overlap of various other psychiatric conditions such as depression with anxiety, anxiety with depression, depression and anxiety with obsessive-compulsive traits, obsessions and/or compulsions leading to depression and anxiety due to frustration, to name a few. These patients will often require combination treatment modalities.[7] Clinicians should select a therapy that addresses the most prominent psychiatric symptom as a starting point. For example, antidepressants when depressive symptoms predominate, anxiolytics when anxiety symptoms predominate; and anti-obsessional and/or anti-compulsion agents for obsessive-compulsive symptoms. After a few weeks, depending on patient response, the addition of adjunctive agents may be warranted.

For patients with depression necessitating pharmacotherapy, selective serotonin reuptake inhibitors (SSRIs) are still recommended as first-line agents, however clinicians may also wish to consider noradrenaline and dopamine reuptake inhibitors (NDRIs) as an alternative first-line agent.[8] These agents may also be used as anxiolytics. Clinicians should be mindful that since the time between initiation of therapy and optimal response may take some time with these classes of drugs, patients with significant

anxiety issues may be candidates for benzodiazepines while bridging to these agents. SSRIs are very versatile agents and at higher doses, these agents may also be useful in patients with obsessive-compulsive disorders. At our combined psychiatry-dermatology clinic, however, we have found clomipramine, at lower, non-antidepressant dosages, to be very useful.[9] This agent was the first drug used in the treatment of obsessive-compulsive disorders and is indicated for patients ten years of age and older.[10]

In summary, many patients present with excoriations to the dermatologist with the majority of these patients having an underlying dermatologic condition or systemic illness that can be identified as the trigger for their skin picking. Clinicians treating these patients should be reminded that medications and recreational drugs can also contribute to this problem. In order to help the busy clinician manage these rare patients who present with a psychiatric cause for their excoriation disorder, it is important to identify the major psychiatric symptom. Once that has been identified, a targeted therapy will allow for appropriate management of these patients and aid in ensuring an optimal outcome.

Antipsychotics*

Drug	Start	Range	Monitoring	Notes
Aripiprazole	5 mg daily	5-30 mg daily		Lower risk of extrapyramidal side effects and weight gain
Olanzapine	2.5 mg at bedtime	20 mg daily		High risk of weight gain and metabolic syndrome
Pimozide	1 mg daily	1-6 mg daily	Pre-treatment EKG	Higher risk of extrapyramidal side effects; risk of cardiac death with prolonged QTc
Risperidone	0.25-0.5 mg daily	1-6 mg daily	Consider prolactin levels	Lower risk of extrapyramidal side effects; may increase prolactin levels

** For antipsychotics in general, it is important to obtain baseline lipid, body mass index, waist circumference, and hemoglobin A1c*

Antidepressants†

Drug	Start	Range	Notes
Escitalopram	5 mg daily	10-20 mg daily	Cannot use with tricyclic antidepressants or monoamine oxidase inhibitors; few side effects; few drug interactions
Sertraline	25-50 mg daily	50-200 mg daily	Cannot use with tricyclic antidepressants or monoamine oxidase inhibitors; few side effects; few drug interactions
Venlafaxine	37.5-75 mg daily	75-225 mg daily	May be activating; watch blood pressure

† Like most antidepressants, it may take several weeks before benefits show; start low, go slow

Anxiolytics§

Drug	Start	Range	Notes
Escitalopram	5 mg daily	10-20 mg daily	Cannot use with tricyclic antidepressants or monoamine oxidase inhibitors; few side effects; few drug interactions;
Sertraline	25-50 mg daily	50-200 mg daily	Cannot use with tricyclic antidepressants or monoamine oxidase inhibitors; few side effects; few drug interactions;

§ Like most anxiolytics, it may take several weeks before benefits show; start low, go slow

Anxiolytic (acute management)

Drug	Start	Range	Notes
Clonazepam	0.25 mg daily	0.25 mg b.i.d. to t.i.d.	Max dose is 4 mg, but for dermatologists, given the addiction potential, I would suggest keeping max dose at 2 – 3 mg daily; t1/2= 30-40 hours

Anti-OCD

Drug	Start	Range	Monitoring	Notes
Clomipramine	12.5-25 mg daily	12.5-150 mg daily	None; routine	Assess overdose risk as may be lethal; mostly anticholinergic side effects: dry mouth, sleepiness, and weight gain; cannot use in combination with SSRIs; average dose 75 mg daily, titrate by 25 mg every 1-2 weeks
Escitalopram	5 mg daily	Closer to 20 mg daily	None; routine	Cannot use with tricyclic antidepressants or monoamine oxidase inhibitors; few side effects; few drug interactions; same range for anxiety management
Sertraline	25-50 mg daily	Closer to 200 mg daily	None; routine	Cannot use with tricyclic antidepressants or monoamine oxidase inhibitors; few side effects; few drug interactions; same range for anxiety management

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