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# **CANADIAN DERMATOLOGY TODAY**

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FOR UNRESECTABLE  
OR METASTATIC  
UVEAL MELANOMA IN  
HLA-A\*02:01-POSITIVE  
PATIENTS**

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# TEBENTAFUSP: A NEW SYSTEMIC TREATMENT FOR UNRESECTABLE OR METASTATIC UVEAL MELANOMA IN HLA-A\*02:01-POSITIVE PATIENTS

## Introduction

Uveal melanoma (UM) is the most common intraocular cancer in adults. It is distinct from cutaneous melanoma in terms of its mutations, metastatic pattern and treatment response. UM commonly metastasizes to the liver. Tebentafusp is a new systemic treatment approved for unresectable or metastatic UM in HLA-A\*02:01-positive adult patients.<sup>1</sup> Tebentafusp is a bispecific protein consisting of an affinity-enhanced T-cell receptor fused to an anti-CD3 effector that can redirect T cells to target glycoprotein 100 (gp100) positive cells.<sup>1</sup> Tebentafusp is administered intravenously weekly. For UM, it is superior to immune checkpoint inhibitors with superior overall survival (OS) and progression-free-survival (PFS).<sup>1</sup> Tebentafusp commonly induces dermatological toxicities.

## Uveal Melanoma

Between 3.7% and 5% of melanomas occur in the eye.<sup>2,3</sup> Ocular melanomas originate from melanocytes situated in various parts of the eye and

are subdivided into UM, conjunctival melanoma (CM), orbital melanoma, and eyelid melanoma. The vast majority of ocular melanomas are primary; however, they can also represent an ocular metastasis from a distant cutaneous melanoma. UM is the most common primary ocular melanoma subtype, with an 83% incidence; in addition, it is the most common primary intraocular malignancy in adults.<sup>3</sup> UM originates from melanocytes within the choroidal plexus (90%), the ciliary body (6%), or the iris (4%).<sup>4</sup> UM is distinct from its cutaneous counterpart in terms of genetic mutations, metastatic spread, tumour-immune microenvironment, and response to treatment. UM is distinct from conjunctival melanoma. CMs share more similarities with cutaneous melanoma than with UM.

The mean age at diagnosis for UM is 58-years-old.<sup>5</sup> Risk factors include older age; Caucasian population; fair skin colour; inability to tan; propensity to sunburn; light eye colour; oculodermal melanocytosis (nevus of Ota); atypical cutaneous nevi; cutaneous freckles; and uveal nevus.<sup>4-6</sup> The role of solar UV exposure in

the development of UM is uncertain; the clinical data is inconclusive.<sup>5</sup> Artificial UV exposure from welding is a well-known risk factor for UM.<sup>5</sup> Patients with BAP1 tumour predisposition syndrome are at higher risk of UM, in addition to cutaneous melanomas, basal cell carcinoma (BCC), malignant mesothelioma, and renal cell carcinoma (RCC).<sup>4</sup> Patients with xeroderma pigmentosum (XP) are also at increased risk of ocular melanoma, including melanoma originating from the iris and the choroid.<sup>7</sup>

UM lacks typical cutaneous melanoma mutations (BRAF, NRAS, KIT) but commonly harbors GNAQ and GNA11 mutations,<sup>8,9</sup> such as benign blue nevi and malignant blue nevi. Mutations in GNAQ or GNA11 result in constitutive activation of the MAPK pathway. Inactivating somatic mutations in BAP1 and decrease or complete loss of PTEN have also been found in UM.<sup>5</sup> The BAP1 and SF3B1 mutations are associated with a higher risk of metastatic spread.<sup>5</sup>

Fewer than 4% of patients have detectable metastatic disease at the time of diagnosis; however, approximately 50% of patients with UM will develop metastases.<sup>5</sup> Poor prognostic factors for metastatic risk include increasing age; larger tumour diameter; greater tumour thickness; UM arising from the ciliary body; loss of chromosome 3 in the tumour; mutations in the *BAP1* and *SF3B1* gene; and UM in a patient with BAP1 tumour predisposition syndrome.<sup>5</sup> In addition, posterior UM has a worse prognosis vs the anterior type. Patients with high-risk UM need regular follow-up for the early detection of metastases, with a liver MRI every six months and chest x-rays or a chest CT scan every 12 months.

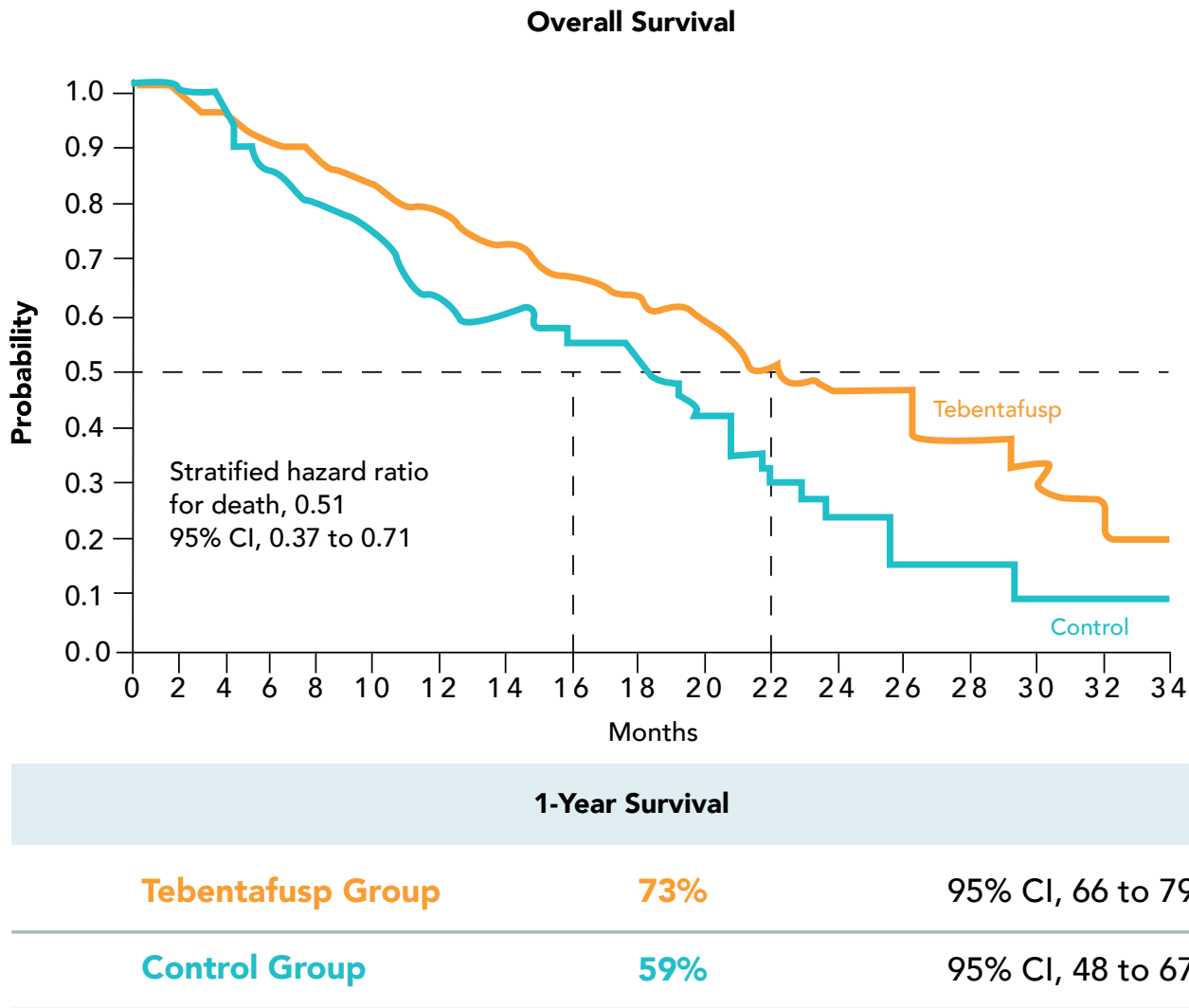
UM disseminates hematogenously and has a very strong propensity to metastasize to the liver.<sup>5</sup> Ninety-three percent of patients with metastatic UM have disease in the liver, followed by 24% in the lungs and 16% in the bones.<sup>10</sup> UM can also spread to the brain and the skin.<sup>5</sup> UM typically does not metastasize to the lymph nodes due to a lack of lymphatic spread, except when UM perforates the sclera and infiltrates the conjunctival lymphatics; however, this rarely occurs.<sup>5</sup> Metastatic spread confers a very poor prognosis with a median overall survival (mOS) of 10.2 months.<sup>11</sup> UM is a deadly cancer. In a cohort of 289 patients with UM, UM-related mortality was 31% by five years, 45% by 15 years, 49% by 25 years, and 52% by 35 years.<sup>12</sup>

Local treatments for primary uveal malignant tumours include transpupillary thermotherapy; photodynamic therapy; plaque brachytherapy; proton beam

radiotherapy; local resection; and enucleation.<sup>4</sup> Most patients are treated with plaque brachytherapy or enucleation. Systemic treatments for metastatic UM include tebentafusp, immunotherapy and conventional chemotherapy.<sup>13</sup> Immunotherapy has revolutionized the treatment of many cancers including Stages III and IV cutaneous melanoma, with significant survival benefit. However, response to immunotherapy in metastatic UM is disappointing, due to a different tumour-immune microenvironment and UM low tumour mutational burden. Survival is not increased with the use of single-agent ipilimumab, nivolumab or pembrolizumab.<sup>13</sup> Combination immunotherapy using ipilimumab plus nivolumab benefits patients with metastatic UM, with increased overall survival up to 18–19 months; however, this double immunotherapy is significantly more toxic than the single-agent form, with frequent Grade 3 and Grade 4 immune-related adverse events.<sup>13</sup> Stage IV UM, like cutaneous melanoma, tends to be chemo-resistant. Dacarbazine, fotemustine and temozolomide can be used, but represent a last option. Metastases can also benefit from local treatments using surgical excision, intra-arterial liver chemotherapy, hepatic arterial chemoembolization, liver radioembolization, and stereotactic radiosurgery.<sup>13</sup>

## **Tebentafusp Mechanism of Action, Indications and Dosing**

Tebentafusp has been Health Canada and United States Food and Drug Administration (FDA)-approved since 2022 for HLA-A\*02:01-positive adult patients with unresectable or metastatic UM. Forty-five percent of individuals in the United States and Europe are HLA-A\*02:01-positive and HLA testing is conducted via serology prior to initiating tebentafusp.<sup>1</sup> For UM, tebentafusp is superior to immune checkpoint inhibitors (ICIs) and chemotherapy with superior OS and PFS. A recent Phase 3 trial compared patients receiving tebentafusp to patients receiving the investigator's choice of treatment with single-agent pembrolizumab, ipilimumab or dacarbazine.<sup>1</sup> The estimated OS at one year was 73% (95% confidence interval [CI], 66–79) in the tebentafusp group and 59% (95% CI, 48–67) in the control group (**Figure 1**). There was a survival benefit in patients with cancer progression receiving tebentafusp vs patients with cancer progression in the control group. The estimated PFS at six months was 31% in the tebentafusp group vs 19% in the control group (stratified hazard ratio for disease progression or death, 0.73; 95% CI, 0.58–0.94; P=0.01). Forty-six percent (95% CI, 39–52) of patients receiving tebentafusp had disease control (complete response,



**Figure 1.** Estimated 1-year survival in tebentafusp group vs control group; adapted from Nathan, P et al, 2021.

partial response or stable disease for  $\geq 12$  weeks) vs 27% (95% CI, 20-36) in the control group.

Tebentafusp is a bispecific protein comprised of a soluble T-cell receptor fused to an anti-CD3 single-chain variable fragment-activating domain.<sup>1</sup> The high-affinity, high-specificity T-cell receptor targets a nine-amino-acid peptide derived from proteasomal degradation of the intracellular gp100 protein, presented by HLA-A\*02:01 molecules on the surface of target cells, including skin melanocytes and tumours derived from melanocytes (UM). The anti-CD3 domain engages and activates CD3+ cells. By targeting a specific shared tumour-associated antigen, these T-cell receptor bispecific molecules can recruit T cells to target tumours independent of the presence of tumour antigen-specific T cells or of the tumour mutational status.<sup>1</sup> In summary, tebentafusp redirects the immune system to target and kill gp100-expressing UM tumour cells.

Tebentafusp is an intravenous infusion administered weekly. Doses are escalated over the first three weeks to reduce toxic effects: 20  $\mu\text{g}$  on Day 1, 30  $\mu\text{g}$  on Day 8, 68  $\mu\text{g}$  on Day 15, and 68  $\mu\text{g}$  weekly thereafter. Patients are admitted to hospital for overnight monitoring following their first infusions. Following several weeks of treatment, if treatment is well-tolerated, patients are transitioned to weekly infusions administered in an outpatient setting.

Since its approval tebentafusp has been used as a first-line treatment for HLA-A\*02:01-positive patients with unresectable or metastatic UM. In patients who are HLA-A\*02:01-negative, combination immunotherapy using ipilimumab and nivolumab remains the treatment of choice. If patients progress on tebentafusp, the typical subsequent treatment phase is the use of combined ipilimumab and nivolumab. As discussed previously, conventional chemotherapy remains a last option as melanomas are refractory to chemotherapy.

## Tebentafusp-related Adverse Events

Tebentafusp-related adverse events are subdivided into two main categories: cytokine-mediated and skin-related adverse events. In the majority of patients, toxicities occur in the initial four weeks of treatment during inpatient dose escalation. The incidence and severity of acute adverse events decrease with repeated dosing. Only 2% of patients permanently discontinue tebentafusp due to treatment-related adverse events.<sup>1</sup>

Many patients develop cytokine-mediated adverse events in the initial weeks of treatment; 76% have pyrexia, 47% experience chills and 38% have hypotension (**Table 1**).<sup>1</sup> A cytokine release syndrome, described by the combination of pyrexia, hypotension and hypoxia, commonly occurs within a few hours following the initial three infusions of tebentafusp. Patients are treated with antipyretics, intravenous fluids and systemic steroids.

Regarding dermatological adverse events, 69% of patients receiving tebentafusp experience pruritus and 83% of patients develop a “rash”,<sup>1,14,15</sup> likely due to cytotoxic T cells attacking gp100-expressing normal melanocytes.<sup>15</sup> Patients typically develop the characteristic eruption in the initial four weeks of treatment in association with tebentafusp dose escalation. The eruption is clinically morbilliform to erythrodermic. Some patients develop impetigo-like superficial bullae and superficial erosions.<sup>15</sup> Two patients with a photo-distributed eruption were also described with erythema and edema in sun-exposed areas (face, neck, ears and dorsum of the hands) following the fourth treatment cycle.<sup>17</sup> The typical acute eruption and pruritus occur in the initial 24 hours following the infusion, last for 24–72 hours following each infusion, and lead to superficial exfoliative desquamation in the following week. Superficial desquamation can involve sites of resolving inflammation, as well as previously uninvolved skin. The eruption tends to increase in severity following each dose up to the second to fourth infusions. After the third infusion, tebentafusp doses remain stable and the acute skin toxicities diminish in incidence and severity following each subsequent infusion, possibly due to gp100-expressing normal melanocytes being destroyed. Acute cutaneous adverse events eventually cease beyond the first three to six infusions. The early cutaneous eruption is associated with longer survival.<sup>14,15</sup>

The treatment of tebentafusp-associated acute skin toxicities is symptomatic. Pruritus is managed with cold compresses, oral or intravenous first-generation antihistamines (diphenhydramine), and oral second-generation antihistamines. Typical eruptions are managed using emollients, topical steroids and topical steroid wet wraps.

Tebentafusp is a new treatment and there is no guideline for the treatment of acute cutaneous adverse events. Treatment interruption is typically not indicated for cutaneous toxicities. The expert opinion is that treatment interruption may lead to a recurrence of the same skin toxicity with a similar severity when tebentafusp is re-introduced.

Fifty-seven percent of patients also develop late dermatological adverse events occurring after a median of 2.7 months: vitiligo-like hypopigmentation and depigmentation, hyperpigmentation, and leukotrichia.<sup>14,18</sup> Patients who experienced late pigmentary adverse events have 72% lower odds of mortality vs those who did not.<sup>18</sup>

## Conclusion

Tebentafusp is approved for unresectable or metastatic UM and acts by redirecting T cells to target gp100-positive cells. It commonly induces early (rash/pruritus) and late (pigmentary changes involving the skin and hair) cutaneous toxicities. Dermatologists have most likely been diagnosing and managing a greater number of tebentafusp-induced cutaneous toxicities since its approval by Health Canada and the FDA in 2022.

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| Treatment-Related Adverse Events (Safety Population).* |                                     |                |                          |                |
|--------------------------------------------------------|-------------------------------------|----------------|--------------------------|----------------|
| Event                                                  | Tebentafusp Group<br>(N=245)        |                | Control Group<br>(N=111) |                |
|                                                        | Any Grade                           | Grade $\geq 3$ | Any Grade                | Grade $\geq 3$ |
|                                                        | <i>number of patients (percent)</i> |                |                          |                |
| Any treatment-related adverse event                    | 243 (99)                            | 109 (44)       | 91 (82)                  | 19 (17)        |
| Cytokine release syndrome <sup>&gt;&gt;</sup>          | 217 (89)                            | 2 (1)          | 3 (3)                    | 0              |
| Rash <sup>&lt;&lt;</sup>                               | 203 (83)                            | 45 (18)        | 27 (24)                  | 0              |
| Pyrexia                                                | 185 (76)                            | 9 (4)          | 3 (3)                    | 0              |
| Pruritus                                               | 169 (69)                            | 11 (4)         | 23 (21)                  | 0              |
| Chills                                                 | 114 (47)                            | 1 (<1)         | 3 (3)                    | 0              |
| Nausea                                                 | 105 (43)                            | 2 (1)          | 21 (19)                  | 0              |
| Fatigue                                                | 101 (41)                            | 7 (3)          | 29 (26)                  | 1 (1)          |
| Hypotension                                            | 93 (38)                             | 8 (3)          | 0                        | 0              |
| Dry Skin                                               | 72 (29)                             | 0              | 4 (4)                    | 0              |
| Vomiting                                               | 64 (26)                             | 1 (<1)         | 7 (6)                    | 0              |
| Erythema                                               | 56 (23)                             | 0              | 1 (1)                    | 0              |
| Headache                                               | 53 (22)                             | 1 (<1)         | 3 (3)                    | 1 (1)          |
| Aspartate aminotransferase increased                   | 47 (19)                             | 11 (4)         | 9 (8)                    | 0              |
| Alanine aminotransferase increased                     | 43 (18)                             | 7 (3)          | 8 (7)                    | 2 (2)          |
| Lipase increased                                       | 32 (13)                             | 9 (4)          | 7 (6)                    | 6 (5)          |
| Diarrhea                                               | 31 (13)                             | 2 (1)          | 16 (14)                  | 3 (3)          |
| Lymphopenia                                            | 22 (9)                              | 6 (2)          | 2 (2)                    | 0              |
| Hyperbilirubinemia                                     | 21 (9)                              | 5 (2)          | 2 (2)                    | 0              |
| Hypophosphatemia                                       | 19 (8)                              | 7 (3)          | 1 (1)                    | 0              |
| Hypertension                                           | 15 (6)                              | 9 (4)          | 2 (2)                    | 1 (1)          |

**Table 1.** Treatment-Related Adverse Events (Safety Population); courtesy of Dr. Cynthia Fournier.

\* Shown are treatment-related adverse events that were reported in at least 20% of patients (any grade) or in at least 2% of patients (grade  $\geq 3$ ) in either group.

» Cytokine release syndrome was graded according to the 2019 recommendations of the American Society for Transplantation and Cellular Therapy for consensus grading for cytokine release syndrome.<sup>21</sup>

» Rash is a composite term for a list of skin-related adverse events of any grade.

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Dr. Asfandiyar Mufti attended medical school at the University of Ottawa graduating in 2017. He then completed his dermatology residency at the University of Toronto in 2022. During his residency, he also completed the Master of Science in Community Health (Health Practitioner Teacher Education) at the University of Toronto. He was awarded the Women's College Hospital F.M. Hill Resident Mentorship Award, PARO Trust Fund Resident Teacher Award for the University of Toronto, and the Canadian Dermatology Association Resident Teacher Award in his final year of residency. His clinical and research interests include medical dermatology, therapeutics, wound care, immunobullous disorders and cutaneous lymphomas. He has published numerous peer-reviewed manuscripts and has a mixed academic-community practice, working at Sunnybrook Health Sciences Centre and medical dermatology clinics in the GTA.



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# PSORIASIFORM AND ECZEMATOUS PARADOXICAL REACTIONS TO BIOLOGIC AGENTS

## Introduction

Biologics, a class of therapeutic monoclonal antibodies (mAbs), have formed the cornerstone for treatment of many systemic diseases and conditions in the fields of rheumatology and dermatology.<sup>1,2</sup> These agents have demonstrated strong efficacy profiles in clinical trials, with numerous new agents being approved in the past few years. However, it is important to note that some patients being treated with biologics may experience paradoxical reactions (PRs), which refers to the new occurrence or worsening of pre-existing immune-mediated conditions following initiation of the drug.<sup>1</sup> True paradoxical reactions involve the development of immune-mediated diseases with the use of biologic agents that are typically utilized to treat the idiopathic form of the drug-induced reaction.<sup>2</sup> This article aims to summarize the literature on psoriasiform and eczematous PRs to biologics.

## Psoriasiform Paradoxical Reactions

### *TNF-alpha inhibitors*

Psoriasiform PRs are commonly reported in association with tumor necrosis factor (TNF) therapy, which is widely used for the management of inflammatory conditions such as moderate-to-severe psoriasis and inflammatory bowel disease (IBD).<sup>3</sup> The incidence of paradoxical psoriasis in patients receiving anti-TNF- $\alpha$  treatment varies from 3.8% to 10%, with infliximab (>50%), adalimumab (30%) and etanercept (11%) accounting for the majority of the cases respectively. Onset time between initiation of the treatment and emergence of the PR is extremely variable and can range from one month to 10 years from the start of treatment, with an average of 16.4 years.<sup>4</sup> A summary of paradoxical psoriasis incidence with biologic agent exposure appears in **Table 1**.

While most cases represent new-onset development of psoriasis, paradoxical exacerbations and morphological transitions have been reported with

| Drug Classes            | General Information                                                                                                     | Presentation and Morphology                                                                                                                                                                                                                                        | Relative Latency                                                                 | Management                                                                                                                                                                                                                                                                                                                                                                                                                 |
|-------------------------|-------------------------------------------------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|----------------------------------------------------------------------------------|----------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| TNF- $\alpha$ inhibitor | Incidence varies from 3.8% to 10%<br><br>Cases associated with infliximab (>50%), adalimumab (30%) and etanercept (11%) | May resemble plaque, palmoplantar pustular, guttate, inverse and generalized/pustular psoriasis<br><br>Higher incidence of palmoplantar involvement compared to classical form of psoriasis                                                                        | 1-10 months range, average of 16.4 years.                                        | Systematic review of IBD patients: majority of patients who switched to different drug class (e.g., ustekinumab) reported complete clearance. Less resolution in patients who switched to a different anti-TNF- $\alpha$ agent.<br><br>Retrospective cohort study in pediatric patients: majority of patients continued treatment with topical corticosteroid and steroid-sparing adjuvant therapies for management of PR. |
| IL-17 inhibitor         | Most cases associated with secukinumab, followed by brodalumab and ixekizumab treatment respectively.                   | May resemble plaque psoriasis, palmoplantar psoriasis, generalized pustular psoriasis, and inverse psoriasis.                                                                                                                                                      | 1-16 months range, average of 4.9 months.                                        | Most patients were resistant to topical treatments.<br><br>Varying responses to systemic treatments (e.g., brodalumab, cyclosporin A, methotrexate).<br><br>In some cases, secukinumab treatment was discontinued due to the adverse reaction, with successful resolution. <sup>8</sup>                                                                                                                                    |
| IL-12/23 p40 inhibitor  | Most cases associated with secukinumab, followed by brodalumab and ixekizumab treatment respectively.                   | Common morphological presentations were plaque psoriasis and palmoplantar psoriasis<br><br>Generalized pustular psoriasis also observed                                                                                                                            | Average time to onset of 3 months                                                | Targeted treatments and ustekinumab discontinuation in most cases, leading to resolution. <sup>8</sup>                                                                                                                                                                                                                                                                                                                     |
| IL-4Ra inhibitor        | Dupilumab is currently the only approved IL-4Ra inhibitor                                                               | Most cases presented as plaque psoriasis and palmoplantar psoriasis lesions<br><br>Some resembled guttate, erythrodermic, scalp and pustular psoriasis<br><br>Lesions identical to idiopathic disease; described as well-demarcated and erythematous scaly plaques | Average of 4.3 months and 3.3 months for new-onset and exacerbation respectively | Patients received topical corticosteroids, vitamin D analogues with successful resolution.<br><br>In severe or refractory cases, dupilumab was discontinued in favour of other immunomodulating agents and systemic treatments (e.g., JAK inhibitors).                                                                                                                                                                     |

**Table 1.** Paradoxical psoriasis with biologic agent exposure; courtesy of Asfandiyar Mufti, MD.

the use of anti-TNF- $\alpha$  treatment for psoriasis. With respect to morphology, psoriasiform PRs seen with these agents typically resemble plaque, palmoplantar pustular and guttate lesions, but other reactions such as inverse and generalized/pustular psoriasis may also occur.<sup>5</sup> A systematic review analyzing 207 published cases of TNF- $\alpha$  inhibitor-induced psoriasiform eruptions observed that these drug-induced PRs involved a higher incidence of palmoplantar involvement compared to the classical idiopathic form of psoriasis. Moreover, multiple concomitant morphologies may be present in individual patients, with 15% of cases presenting with more than one type of lesion.<sup>5,6</sup> Histologically, anti-TNF- $\alpha$ -associated psoriasiform PRs have generally demonstrated the typical findings of classical psoriasis, which are characterized by epidermal hyperplasia and lymphocyte infiltrates, dilated capillaries and

parakeratosis.<sup>6</sup> However, there have been reports of uncharacteristic findings such as spongiosis and the presence of eosinophils and plasma cells, which may be used to distinguish from primary psoriasis.<sup>7</sup>

With respect to management, a systematic review of TNF- $\alpha$ -induced paradoxical PR treatment outcomes in IBD patients who switched to different biologic therapies reported several key findings. Among the patients who switched to a different anti-TNF- $\alpha$  agent, only 39.2% reported resolution of symptoms. However, when switching to a different class of biologic therapy, such as ustekinumab or vedolizumab, the majority of patients experienced complete resolution.<sup>7</sup> Conversely, in a retrospective study, in a cohort of children under the age of 18 who developed new-onset PR while taking a TNF inhibitor for a non-dermatologic disorder, the majority of

patients were able to continue TNF inhibitor therapy with topical corticosteroids and non-corticosteroid adjuvant therapies for the management of symptoms.<sup>8</sup> Further research is needed to explore management and treatment outcomes in the context of patients receiving anti-TNF- $\alpha$  agents for inflammatory skin diseases such as psoriasis.

### ***IL-17 inhibitors***

The therapeutic potential of anti-IL-17 agents has been explored in recent clinical trials and studies. Although there is limited literature reporting the development of psoriasiform PRs in response to anti-IL-17 treatment, the few cases that have been described are primarily associated with secukinumab, followed by brodalumab and ixekizumab treatment respectively. The average onset time to presentation of paradoxical psoriasis is 4.9 months and ranges from 1–16 months following initiation of anti-IL-17 treatment.<sup>4</sup>

Secukinumab selectively binds to and neutralizes IL-17A, a pro-inflammatory cytokine that is believed to play a key role in driving the pathogenesis of psoriasis. However, despite being approved for the treatment of psoriasis, several cases of new-onset development and exacerbation of psoriasis have been observed in patients treated with this agent. Clinical presentation manifested in a range of morphological phenotypes including plaque psoriasis, palmoplantar psoriasis, generalized pustular psoriasis, and inverse psoriasis. Larger-scale studies are needed to draw comparisons regarding the frequency of morphological presentations between IL-17-associated PRs and idiopathic psoriasis.<sup>9</sup>

Most patients were resistant to topical treatments and had varying responses to systemic treatments such as infliximab, brodalumab, cyclosporin A and methotrexate. In some cases, secukinumab treatment was discontinued due to the adverse reaction.<sup>9</sup>

### ***IL-12/23 p40 inhibitors***

Given that ustekinumab is currently the only approved p40 inhibitor,<sup>1</sup> there is limited literature available on the association of paradoxical psoriasis with IL-12/23 inhibitors. This agent blocks the shared p40 subunit on IL-12 and IL-23 cytokines, both of which contribute to the inflammatory symptoms seen with psoriasis. Although ustekinumab has been in use since 2009 and is approved for the treatment of psoriasis, psoriatic arthritis and IBD, only nine reported cases of associated psoriasiform PR have been described. Among these patients, four cases involved the new-onset development of psoriasis, and five cases involved the exacerbation of pre-existing

psoriasis.<sup>9</sup> Although it is difficult to draw conclusions from a small body of data, the average onset time to the presentation of psoriasiform PR was within three months of ustekinumab treatment initiation.<sup>1</sup>

Similar to the psoriasiform PRs associated with other biologic treatments, ustekinumab-induced paradoxical psoriasis manifested as various clinical phenotypes. Along with the common morphological presentations such as plaque psoriasis and palmoplantar psoriasis, generalized pustular psoriasis was observed in five cases and two of these had new-onset development. In the majority of the patients, ustekinumab treatment was discontinued along with targeted treatments for the PR, leading to improvement in or resolution of the psoriasiform lesions.<sup>9</sup>

### ***IL-4Ra inhibitors***

As with ustekinumab, dupilumab is the first and, currently, the only approved agent in its drug class. It has been associated with marked symptomatic improvement in clinical trials focusing on atopic dermatitis (AD), asthma and other indications. Dupilumab targets the alpha-subunit of IL-4 receptor, subsequently inhibiting the IL-4 and IL-13 signalling pathways, which are implicated in the pathogenesis of AD.<sup>10</sup>

In a review summarizing all known cases of dupilumab-associated psoriasis, the average time to onset of psoriasiform PRs was 4.3 months and 3.3 months post-treatment initiation for new-onset and exacerbation of pre-existing psoriasis respectively. Similar to cases of classical psoriasis, most cases of dupilumab-associated psoriasis presented as plaque psoriasis and palmoplantar psoriasis lesions.<sup>1</sup> The presentation of the lesions have been described as well-demarcated and erythematous scaly plaques, which is identical in appearance to the idiopathic form of the disease.<sup>10</sup> A smaller proportion of dupilumab-induced cases manifested as guttate, erythrodermic, scalp, and pustular psoriasis.<sup>1,10</sup> Interestingly, although dupilumab is not typically employed for the treatment of psoriasis, in three patients with pre-existing psoriasis, a flare of the disease was observed. In these patients, the exacerbation was severe in nature and was characterized by a shorter time to onset.<sup>10</sup> Upon skin biopsy, histological findings resembled features characteristic of classical psoriasis such as parakeratosis and lymphocyte infiltration of the dermis. However, mild spongiosis and the presence of eosinophils were also observed and may serve as distinguishing features between the two causes of psoriasis.<sup>1,10</sup> Approximately half of the patients in this

| Drug Classes            | General Information                                                                                         | Presentation and Morphology                                                                                                                                                                                      | Relative Latency             | Management                                                                                                                                                                                                                                                                                                                                                                            |
|-------------------------|-------------------------------------------------------------------------------------------------------------|------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------------------------------|---------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|
| TNF- $\alpha$ inhibitor | Cases associated with infliximab (70%), followed by adalimumab (24.5%) and other agents                     | Clinical morphology included erythematous plaques, papules and excoriations affecting the face, neck, trunk and limbs                                                                                            | Average time of 22.7 months  | Anti-TNF treatment was rarely discontinued, and eczema was successfully managed with emollients as well as topical corticosteroids in more severe cases                                                                                                                                                                                                                               |
| IL-17 inhibitor         | Overall incidence of 72.55%, majority associated with secukinumab (52.94%), followed by ixekizumab (19.61%) | Range of clinical presentations: classic generalized AD, facial dermatitis and dyshidrotic eczema                                                                                                                | 4 months                     | Eczematous PRs were managed primarily with topical corticosteroids<br><br>In severe or refractory cases, anti-IL-17 treatment was discontinued<br><br>Case series including patients receiving brodalumab for psoriasis: all patients were switched to risankizumab directly or received cyclosporin and apremilast prior to risankizumab, and achieved complete clearance of lesions |
| IL-23 p19 inhibitor     | 4 identified cases: 2 associated with guselkumab and risankizumab respectively                              | Clinical presentation consistent with eczema: erythematous plaques, scaling and excoriations<br><br>Histological findings consistent with eczema: acanthosis, spongiosis and perivascular lymphocytic infiltrate | Range of 3 weeks to 4 months | Severe case was unresponsive to topical corticosteroid treatment, and required discontinuation of guselkumab and administration of tar preparation<br><br>One risankizumab case was switched to alternative anti-psoriatic agent ustekinumab and received topical corticosteroids with successful improvement of lesions                                                              |
| IL-4Ra inhibitor        | Dupilumab is currently the only approved IL-4Ra inhibitor                                                   | Commonly appeared as a localized dermatitis reaction affecting the face and/or neck regions                                                                                                                      | Insufficient data available  | Discontinuation of dupilumab led to improvement in and resolution of symptoms in majority of cases                                                                                                                                                                                                                                                                                    |

**Table 2.** Paradoxical eczema with biologic agent exposure; courtesy of Asfandiyar Mufti, MD.

review continued with dupilumab treatment. They received primarily topical corticosteroid treatments and experienced improved clearance of skin symptoms. In severe or refractory cases, dupilumab use was discontinued with recourse to other immunomodulatory agents and systemic treatments, including Janus kinase (JAK) inhibitors such as baricitinib and upadacitinib.<sup>10</sup>

## Eczematous Paradoxical Reactions

### TNF- $\alpha$ inhibitors

Following psoriasis, eczematous reactions are the second most common PR associated with anti-TNF- $\alpha$  treatment and have been observed in the management of various rheumatological conditions.<sup>1,5</sup> Within this drug class, infliximab was responsible for the largest proportion of cases (70%), followed by adalimumab (24.5%) and other agents. The average

time to onset of eczematous PR was 22.7 months following the initiation of anti-TNF- $\alpha$  treatment.<sup>4</sup>

It is worth noting that there have also been several reports of a phenotypic switch to eczema in patients receiving biologic agents such as TNF-inhibitors for psoriasis. In this study, a prior history of eczema/AD was described in 11 of the 24 cases (46%). Similar to cases of eczema development in patients being treated with TNF-inhibitors for indications other than psoriasis, the clinical morphology included erythematous plaques, papules and excoriations affecting the face, neck, trunk and limbs.<sup>11</sup>

Data specific to treatment outcomes of eczematous lesions from different management strategies is scarce as information regarding eczema PRs is often pooled with a broader range of dermatologic complications of anti-TNF agents. Regardless, in

these studies, eczematous reactions were successfully resolved with topical treatments such as emollients and topical corticosteroids while continuing use of the initial anti-TNF agent in most patients.<sup>12</sup>

### *IL-17 inhibitors*

Unlike other biologic drug classes which are primarily associated with psoriasiform PRs, eczematous reactions are the most commonly reported PR with anti-IL-17 treatment.<sup>1</sup> A systematic review of patients receiving biologics for psoriasis found that eczematous PRs are more common with IL-17A inhibitors vs other biologics, with an overall incidence of 72.55%; secukinumab accounted for most cases (52.94%), followed by ixekizumab (19.61%) and other agents. All patients in this study responded well to biologic treatment prior to the onset of paradoxical eczema.<sup>12</sup> A summary of paradoxical eczema incidence with biologic agent exposure appears in **Table 2**.

With respect to time to onset, eczematous PRs typically occurred within four months of initiating anti-IL-17 treatment. The clinical spectrum included a range of presentations such as classic generalized AD, facial dermatitis and dyshidrotic eczema. IL-17 inhibitor treatment was discontinued in half of the cases and the eczematous PR was managed primarily with topical corticosteroids.<sup>1</sup>

In a case series reporting on three patients who received brodalumab treatment for psoriasis refractory to topical and/or systemic treatments and subsequently developed eczematous reactions, their treatment was either switched to risankizumab directly or they received cyclosporin and apremilast initially before recourse to risankizumab. All of the patients in this study achieved full clearance of skin symptoms.<sup>13</sup> Eczema was diagnosed clinically in two patients and one patient showed histological findings consistent with eczematized psoriasis upon skin biopsy.

### *IL-23 p19 inhibitors*

IL-23 p-19 inhibitors have rarely been reported in the literature in association with eczematous eruptions, possibly because they have only recently been approved for psoriasis. Of the four identified cases, two involved guselkumab and two involved risankizumab. Of all four cases, three patients had a history of atopy, suggesting that an underlying atopic predisposition increases the risk of eczematous eruptions following treatment.<sup>5</sup> Among these patients, time to onset of eczematous PR ranged from three weeks to four months. The clinical presentation and histological findings were relatively consistent with eczema: erythematosquamous

plaques, scaling and excoriations upon physical examination, as well as biopsy showing acanthosis, spongiosis and perivascular lymphocytic infiltrate.<sup>14-16</sup> The case reports explicitly mentioned that guselkumab and risankizumab treatment was discontinued in two patients respectively. One patient's eczematous PR was markedly severe, recalcitrant to topical corticosteroids, and required hospitalization for treatment with tar preparation composed of betamethasone dipropionate and salicylic acid, leading to successful resolution. The other patient was switched to ustekinumab for psoriasis management and received topical corticosteroids to treat eczematous symptoms with successful clearance.

### *IL-4Ra inhibitors*

Although dupilumab has been approved for the treatment of AD based on overall efficacy and a positive safety profile, Phase 3 trials of dupilumab have described an exacerbation of AD in 10% to 18% of patients. Eczematous PRs most commonly appear as a localized dermatitis reaction, commonly affecting the face and/or neck regions. Discontinuation of dupilumab led to improvement in and resolution of symptoms in the majority of cases.<sup>1</sup>

## **Conclusion**

The mechanism implicated in the development of PRs has not been fully elucidated and may vary depending on the class of biologics used. Anti-TNF- $\alpha$  treatment is the most well-studied in the context of PRs and there are several hypotheses underpinning the pathogenesis of PRs associated with TNF- $\alpha$ -inhibitors. For example, blocking TNF- $\alpha$  may lead to the overproduction of Type 1 interferons by plasmacytoid dendritic cells (pDCs), which can result in the induction or worsening of psoriasiform lesions.<sup>17,18</sup> With respect to eczematous PRs, several studies have hypothesized that inhibition of TNF alters the cytokine balance and shifts T cell polarization from Th-17/Th-1 subsets to Th-2 mediated signalling. As psoriasis is an inflammatory skin disease that is predominantly Th-1/Th-17 mediated and AD is a Th-2 mediated disorder, this hypothesis explains why many of the patients with psoriasis who received anti-TNF treatment developed paradoxical eczematous reactions.<sup>5</sup>

The primary objective in the management of PRs is to maintain symptomatic relief and control of the underlying disease while treating the emerging PR.<sup>18</sup> As there are no well-established guidelines for managing PRs with biologic treatment, clinicians should closely monitor patients and may refer to

treatment guidelines for classical psoriasis and AD. In the case of TNF-inhibition-associated psoriasis, a study proposed a treatment algorithm initiating the referral of patients to a dermatologist for clinical and histological confirmation of psoriasis.<sup>6</sup> In mild-to-moderate PRs that present solely as cutaneous symptoms and affect less than 5% of the body surface area, the PR may be managed with topical treatments such as corticosteroids and vitamin D analogues. If more than 5% of the body surface area is affected, phototherapy and systemic treatments such as methotrexate or acitretin may be added to the treatment regimen.<sup>1</sup> However, with severe psoriasiform lesions, involvement of internal organs, erythrodermic presentation, and/or significant detriment to the patient's quality of life (QOL), discontinuation of the biologic agent should be considered given that most PRs have shown to resolve with treatment interruption.<sup>20</sup> Additionally, if the underlying disease is not well managed, a switch to a different class may also be beneficial.<sup>1,6</sup> An understanding of risk factors, such as increased risk of psoriasiform PRs with adalimumab and decreased risk with advanced age, a history of atopic diseases, and other risk factors may be beneficial to clinicians in informing their management plan.<sup>21</sup> Similar guidelines can be applied to the management of eczematous PR.

Further study of psoriasiform and eczematous PRs with biologic treatment is needed to better understand their pathogenesis, develop more comprehensive treatment guidelines, and facilitate early recognition of these reactions for more effective management.

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## **Financial Disclosures**

**None.**

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## USE OF NEUROMODULATORS AS AESTHETIC TREATMENT IN THE LOWER FACE

### Introduction

Neuromodulator treatment is one of the most common non-invasive aesthetic treatments in dermatology. Botulinum toxin A has been established as a safe and effective treatment for the upper face. It is increasingly used beyond the forehead, glabella and peri-ocular region. The purpose of lower face neuromodulator use is to soften dynamic rhytids, improve facial expression at rest and with animation, and provide facial contouring. There is significant interplay between the muscles of the lower face for expression and function; therefore, careful administration of botulinum toxin A is necessary to avoid adverse effects. This article reviews off-label botulinum toxin A treatments to the peri-oral region, chin and masseter. For the purposes of the article, all dosing provided is for onabotulinum toxin A.

### Peri-oral Region

The peri-oral region is a facial cosmetic unit, extending from the base of the nose to the labiomental crease. Muscles in this area include: levator labii superioris alaeque nasalis (LLSAN); orbicularis oris; depressor anguli oris (DAO); depressor labii inferioris (DLI); risorius; zygomaticus major; and zygomaticus minor.

### LLSAN – “Gummy Smile”

The LLSAN enables flaring of the nostril and elevation of the upper lip. A hyperactive LLSAN can lead to excessive gingival show when smiling, colloquially known as a “gummy smile” (**Table 1**). This is clinically defined as maxillary gingiva exposure > 2 mm above the dental line during a smile.<sup>1,2</sup>

Treatment to the LLSAN with botulinum toxin A reduces muscle activity, thereby decreasing gingival show with smiling. Various treatment protocols exist, with dose ranging from 2–5 units per side.<sup>3</sup> The injection point is located 3 to 5 mm lateral each nostril (**Figure 1**).<sup>1</sup> Dosing should be adjusted to account for any asymmetries in gingival show; the side with greater upward pull will require a higher dose of botulinum toxin A.

### Orbicularis Oris – “Smoker’s Lines and Lip Flip”

The orbicularis oris is a circular muscle surrounding the opening of the mouth. It is responsible for closing and projecting the lip outwards. This muscle plays a role in mastication, expression, phonation, whistling, and kissing. The formation of radial peri-oral rhytids, often referred to as “smoker’s lines,” can partially be due to repeated contraction of the orbicularis oris. Relaxation of this muscle can lead to reduced dynamic peri-oral rhytids. It can also lead to a slight

| Colloquial name/phrase       | Target muscle  | Verbal cues for examination          | Pertinent examination findings                             |
|------------------------------|----------------|--------------------------------------|------------------------------------------------------------|
| "Gummy smile"                | LLSAN          | Smile                                | >2 mm maxillary gingival show with smiling                 |
| "Smoker's lines"             | Orbicular oris | Make a kiss and hold it              | Dynamic perioral rhytids                                   |
| "Lip flip"                   |                | Smile                                | Inversion of upper lip with smiling                        |
| "Saggy mouth corners"        | DAO            | Stick out your bottom teeth          | Downward turned oral commissures at rest                   |
| "Chin cellulite"             | Mentalis       | Roll your bottom lip out             | Deep labiomental crease and pebbled appearance at the chin |
| "Jaw pain," "teeth grinding" | Masseter       | Bite down without opening your mouth | Square facial shape at rest; bulge with clenching          |

**Table 1.** Lower face muscles commonly treated with botulinum toxin A; courtesy of Malika Ladha, MD. LLSAN = levator labii superioris alaeque nasalis; DAO = depressor anguli oris.

increase in upper lip eversion; this technique is known on social media as a "lip flip" (Table 1).

A maximum total dose of 6 to 10 units is recommended. Six injection points are recommended: four to the upper lip and two to the lower lip. The lateral injection points should be medial to the oral commissures to avoid diffusion to the levator anguli oris.<sup>4</sup> The upper medial injection points should not be directly over the philtral columns, to prevent flattening of Cupid's bow. Injections should be superficial and on the vermilion border. To ensure safety and preservation of muscle function, a lower dose should be used. The dose can then be gradually titrated upward until the desired effect is achieved.

Possible side effects include: decreased ability to drink out of a straw, decreased ability to whistle, and difficulty enunciating the letters F, M, O and P. Treatment of the orbicular oris with botulinum toxin A should not be performed on individuals whose professions and/or hobbies require full function of the mouth, such as saxophone players.

### DAO – "Downward Mouth Corners"

The DAO is a triangle-shaped muscle that originates at the inferior border of the mandible and inserts at the angle of the mouth, fusing with the orbicularis oris and risorius. With aging, a melomental fold, or Marionnette line, can emerge from the oral commissure to the jawline. The etiology is multifactorial: loss of collagen; mandible and maxillary bone resorption; and, hyperactive DAO muscles. The combination of these factors creates a sad expression

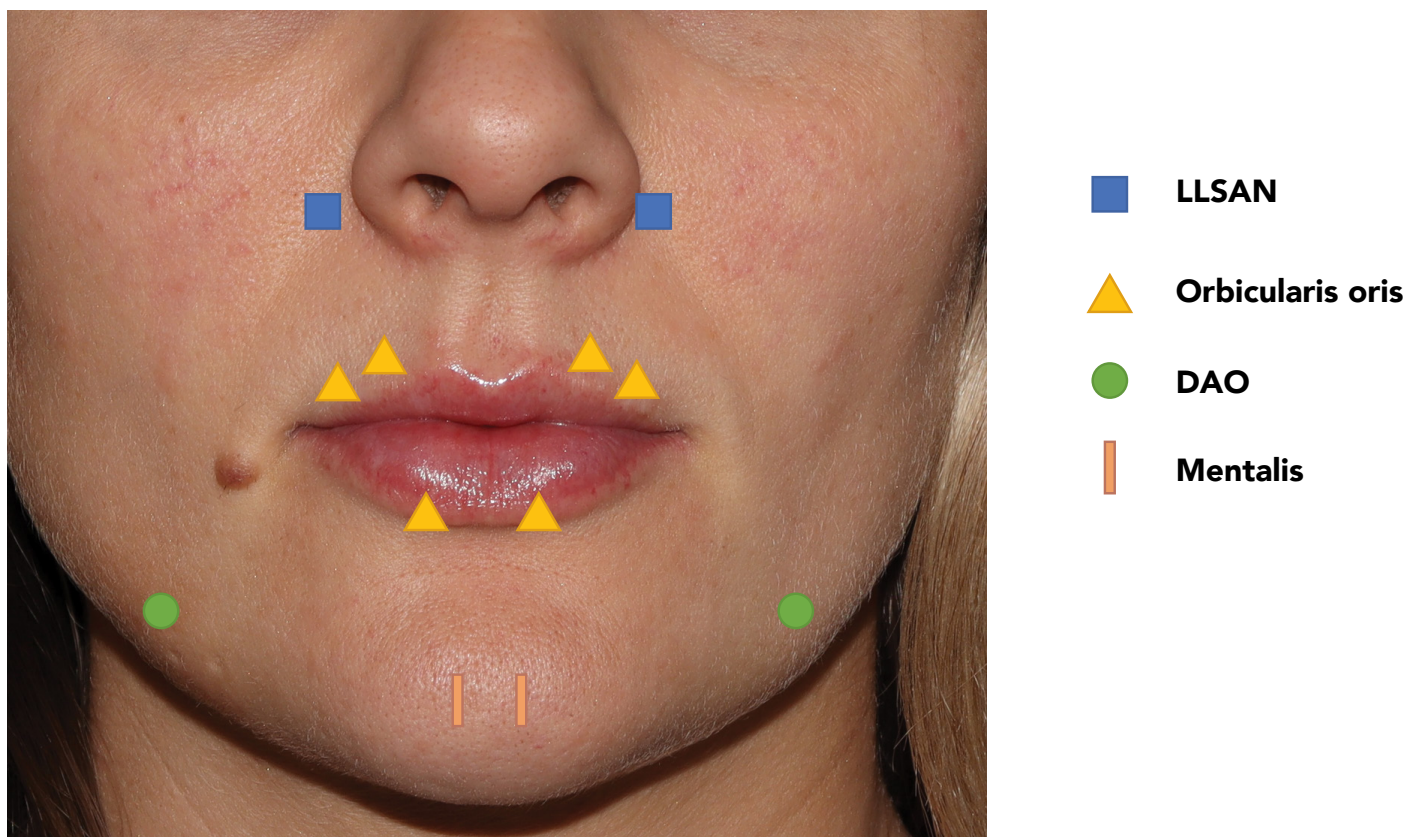
at rest. It can be elicited on examination by asking patients to "stick out their bottom teeth" (Table 1, Figure 2).

A dose of 2 to 5 units per side can be used. The injection site has been variably reported.<sup>5</sup> The author's preferred location is near the jawline, at least 1 cm away from the corners of the mouth. A pearl is to direct the needle laterally to avoid diffusion into the DLI. The DLI is responsible for depressing and everting the lower lip. If inadvertently injected with botulinum toxin A, the affected DLI will not equally depress the lower lip, resulting in an asymmetric smile.<sup>5</sup>

### Chin – "Peau d'orange"

The mentalis is the major muscle of the chin. Contraction of the mentalis raises the chin and contributes to the labiomental fold. With maturity, overactivity of the mentalis, in combination with loss of fat and collagen, leads to a cobblestone – or "peau d'orange" – appearance of the skin. This is colloquially known as "chin cellulite." This can be further accentuated on examination by asking patients to "roll their bottom lip out" (Table 1, Figure 3).

A total dose of 4 to 10 units of botulinum toxin A can be used. The single injection technique involves one injection at the midline point 0.5 to 1.0 cm above the most inferior aspect of the chin.<sup>5</sup> Another technique is two lateral injections parallel to the midline. The injections should be directed medially to avoid displacement of the neurotoxin to the DLI muscle, as above.



**Figure 1.** Injection points for various lower face muscles; courtesy of Malika Ladha, MD.



**Figure 2.** Examining the depressor anguli oris by asking patients to “stick out their bottom teeth.”; courtesy of Malika Ladha, MD.



**Figure 3.** Examining the mentalis by asking patients to “roll their bottom lip out.”; courtesy of Malika Ladha, MD.

## Masseter

The masseter is an important mastication muscle; its primary role is to elevate the mandible with chewing. The surface anatomy of the masseter muscle includes the zygomatic arch and the inferior border of the mandible. The anterior and posterior borders can be observed and palpated by asking patients to clench their teeth. This muscle consists of three layers; the maximum bulk is at the overlapping point of these layers.<sup>6</sup>

Masseter hypertrophy can be genetic or related to jaw clenching or bruxism. The former is more common in East Asian patients.<sup>7</sup> The latter may be associated with pain, headaches and damage to teeth. Masseter hypertrophy also leads to squaring of the facial shape. Treatment of masseter hypertrophy with botulinum toxin A will therefore provide relief of symptoms, as well as facial contouring.

Careful patient selection is required. A masculine appearance is associated with sharp angles. Treating hypertrophic masseters with botulinum toxin A will decrease the size of the muscle and will soften well-defined jawline contours. Therefore, patients who prefer to maintain a square jawline are not ideal candidates for this treatment. In addition, decreasing the masseter muscle mass can make jowls appear larger by contrast. While this treatment may provide relief of symptoms, patients with prominent jowls and pre-jowl sulci may not achieve ideal aesthetic facial contouring results.

Three deep injections in a triangular pattern can be delivered to each masseter. A range of 4 to 10 units can be injected at each site.<sup>5</sup> Dosing will be dependent on the size of the masseters; gender (males require a higher dose than females due to their larger muscle bulk); amount of desired facial tapering; and the presence of jowls and lower face sagging.<sup>8</sup> A lower initial dose should be used, and then gradually titrated upward until the desired effect is achieved. Unlike botulinum toxin A injections for rhytids, full effect on the masseters requires four to six weeks post-treatment; duration of the effect is up to six months.

It is recommended that clinicians counsel patients on the following possible treatment side effects: difficulty chewing foods that require powerful biting or grinding, such as steak; increased appearance of jowl and lower facial sagging; intramuscular or subcutaneous hematoma; and paradoxical masseter bulging.

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## Financial Disclosures

**Consultant/Advisory Boards:** Allergan, Galderma, L'Oreal, NAOS, Neutrogena

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## ABOUT THE AUTHOR

### Rachel Asiniwasis, MD, MS(HS), FRCPC

Dr. Rachel Asiniwasis is a dermatologist and early-career clinician-researcher with a special interest in inflammatory dermatoses, remote outreach, virtual care, skin of color, Indigenous health, dermatologic health disparities, and translational research. She has been practicing in her hometown of Regina since 2014, after graduating residency at the University of Toronto. Recently, she graduated with a Master's of Science in Health Sciences in clinical and translational research. She is Plains Cree and Saulteaux on her father's side, and provides outreach dermatology clinics in the form of virtual care, teledermatology and in-person to various remote and northern Indigenous communities around Saskatchewan.



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## A PRACTICAL GUIDE TO NON-INSURED HEALTH BENEFITS (NIHB) FOR DERMATOLOGISTS CARING FOR STATUS FIRST NATIONS AND INUIT PEOPLES OF CANADA

### Historical Contexts and Health Disparities

Canadian Indigenous peoples (First Nations, Metis and Inuit) represent approximately 5% of the total Canadian population, with ancestry and archeological evidence tracing back to the original inhabitants of what is now known as North American land. Indigenous populations of America may have represented more than 100 million individuals prior to colonization, although devastating population losses resulting from multiple impacts such as virgin soil epidemics have been recorded. Recognizing that individual and community variation exists among the diverse population of Canadian Indigenous peoples, together they share common historical, legal and systemic injustices that have led to inequities and health disparities. These have continued to endure, embedded in complex layers of overlapping determinants of health. Many of these impacts have affected generations alive to this day, who have faced lack of opportunities from disproportional systemic

effects. Specific examples include Indian reserves as a form of legislated racial segregation, and the government-run pass system that was repealed only in 1951 under the 'Indian Act'. The reserves prohibited Indigenous peoples from attaining economic and personal freedom, including strict limitations on buying, selling and owning property, such as farming produce. The last residential school closed its doors only in 1996 in southern Saskatchewan. Indigenous peoples were not allowed to vote until 1960 without losing their Indigenous status. Numerous other examples of inequalities exist. Many of these legacies, both past and recent, originate from the impact of colonization, which is considered a health determinant.<sup>1-4</sup> Extensive documentation of increased morbidity and mortality among Indigenous Canadians, including dermatologic conditions, substantiates the comprehensive impact of colonization. However, it is beyond the scope of this article.

Historically, the Numbered Treaties have represented oral and written negotiations between the Crown and Indigenous peoples. The “*Medicine Chest*” provision clause of Treaty 6 represents supplementary healthcare provision in consideration of the impact of non-Indigenous land settlement and is constitutionally protected. Details and controversies surrounding the initiation and implementation of such negotiations are beyond the scope of this paper; however, further information can be found in Craft & Lebihan’s 2021 document *The Treaty Right to Health* published by the National Collaborating Centre for Indigenous Health.<sup>5</sup> First Nations and Inuit are supposed to receive healthcare equivalent to that provided to other Canadian citizens. However, the reality is that high-quality health-care is concentrated in urban centres, making it difficult to access for many Indigenous individuals.

## What is NIHB and who is Eligible?

In the realm of dermatologic health, Canadian and North American Indigenous peoples continue to be broadly under-represented as dermatologists, researchers, mentors, and program participants. One component of improving healthcare and raising awareness of Indigenous health in Canada is understanding coverage programs for status Indigenous patients. The purpose of this article is to provide an overview of the features and coverage of the NIHB (Non-insured Health Benefits) program.

NIHB is a national, federally administered program that provides coverage to registered First Nations and Inuit in order to promote equitable healthcare status comparable to other Canadians. Eligibility includes Canadian residents who are First Nations or Inuit/Inuk persons registered under the Indian Act (commonly referred to as “having status”).

Of note, Metis and non-status First Nations are not considered eligible for NIHB. If a therapy is not covered by the NIHB, and is declined, an appeal process can be accessed.

Broadly, coverage includes medical supplies and equipment (pressure garments, dressings, bandages, orthotics, and custom footwear); prescription and over-the-counter (OTC) medications (lowest cost equivalent/generic; may require prior approval); medical transportation; and basic vision and dental care. Prescription medication may be prescribed by a physician, nurse, nurse practitioners or pharmacist within their provincial/territorial scope of practice.

## Topical Therapies

Insurance coverage information for topical dermatologic therapies appears in **Table 1**.

**Table 1** is excerpted from the most recent version (September 2020) of the NIHB Drug Benefit list.<sup>6</sup> However, an online search tool for updated formulary content can be found at <https://nihb-ssna.express-scripts.ca/en/040212>.<sup>7</sup> The NIHB formulary can be accessed online through Express Scripts Canada (<https://nihb-ssna.express-scripts.ca/>). On-label and off-label uses are not indicated in this table, and medical use is at the judgement and discretion of the licensed prescriber.

## Compounding

Basic compounding is covered by the NIHB under some circumstances. Miscellaneous and limited use external compound mixtures are listed. To be eligible, the prescription must contain one ingredient listed on the formulary but it must not be a duplicate formulation of commercially available treatments. More detailed information on compounding can be found in Appendix E, Extemporaneous Mixtures, of the NIHB formulary.<sup>6</sup>

## Systemic Therapies and Phototherapy

Due to the broad range of systemic medications, including those frequently used off-label in dermatology, a summary table is not included. General comprehensive coverage for all antibiotics (anti-bacterial, viral, fungal, others); antiandrogens; oral retinoids (e.g., isotretinoin brands, acitretin); traditional systemic immunosuppressants and other anti-inflammatories; anti-pruritics; and antihistamines exists. In-home phototherapy units are not covered by the NIHB.

## Biologic Therapies

### Moderate-to-severe atopic dermatitis

With regard to coverage of biologics for moderate-to-severe atopic dermatitis, dupilumab is the only agent on the formulary. As of 2023, the coverage for oral JAK inhibitors and IL-13 inhibitors are not yet defined. For dupilumab, the current coverage criteria in Canada is not consistent with that of the FDA and Health Canada, which approved dupilumab in 2023 for use in children aged 6 months and over. Of note, cyclosporine and methotrexate are not required for approval. The following criteria for dupilumab for NIHB clients is summarized in **Table 2** (NIHB, 2023).

| TOPICAL THERAPIES          | Name (generic)<br>(alphabetical order)          | Trade names                         | Percentages<br>(if applicable)* | Formulation        | Notes |
|----------------------------|-------------------------------------------------|-------------------------------------|---------------------------------|--------------------|-------|
| <b>Topical Antibiotics</b> |                                                 |                                     |                                 |                    |       |
|                            | Bacitracin zinc                                 | N/A                                 | N/A                             | ointment           |       |
|                            | Clindamycin                                     | N/A                                 | 1%, 2%                          | cream,<br>solution |       |
|                            | Fusidic acid                                    | Fucidin                             | 2%                              | cream,<br>ointment |       |
|                            | Metronidazole                                   | Metrogel,<br>Noritate               | 0.75%, 1%                       | cream, gel         |       |
|                            | Mupirocin                                       | Bactroban                           | 2%                              | cream,<br>ointment |       |
|                            | Polymyxin B +<br>Bacitracin +/-<br>Gramcidin    | Polysporin,<br>Polytopic,<br>others | N/A                             | cream,<br>ointment |       |
| <b>Topical Antivirals</b>  |                                                 |                                     |                                 |                    |       |
|                            | Acyclovir                                       | Zovirax                             | 5%                              | cream,<br>ointment |       |
|                            | Sinecatechins                                   | Veregen                             | 10%                             | ointment           |       |
| <b>Topical Antifungals</b> |                                                 |                                     |                                 |                    |       |
|                            | Ciclopirox                                      | Loprox                              | 1%                              | cream, lotion      |       |
|                            | Clotrimazole                                    | Canesten,<br>Clotrimaderm           | 1%, 2%                          | cream              |       |
|                            | Clotrimaderm +<br>Betamethasone<br>dipropionate | Lotriderm                           | 1%/0.05%                        | cream              |       |
|                            | Ketoconazole                                    | Ketoderm,<br>Nizoral                | 2%                              | cream,<br>shampoo  |       |
|                            | Miconazole                                      | Monistat                            | 2%                              | cream              |       |
|                            | Nystatin                                        | Mycostatin,<br>Nyaderm,<br>others   | 25,000 IU,<br>100,000 IU        | cream,<br>ointment |       |

**Table 1.** Topical dermatologic therapies insurance coverage; courtesy of Dr. Rachel Asiniwasis. Continues on next page.

\* If more than one agent is included, percentages are stated according to ingredient order

\*\* Agents may also contain zinc, pramoxine, urea or counter-irritants (e.g., menthol, camphor), varying by brand

| TOPICAL THERAPIES                          | Name (generic) (alphabetical order)         | Trade names                           | Percentages (if applicable)*   | Formulation             | Notes |
|--------------------------------------------|---------------------------------------------|---------------------------------------|--------------------------------|-------------------------|-------|
|                                            | Terbinafine                                 | Lamisil                               | 1%                             | cream                   |       |
|                                            | Tolnaftate                                  | Tinactin, DrScholl's, Zeasob          | 1%                             | aerosol, cream, powder  |       |
| <b>Scabicides and Pediculicides</b>        |                                             |                                       |                                |                         |       |
|                                            | Crotamiton                                  | Eurax                                 | 10%                            | cream                   |       |
|                                            | Dimethacone                                 | Nyda                                  | 50%                            | solution                |       |
|                                            | Isopropyl myristate                         | Resultz                               | 50%                            | solution                |       |
|                                            | Permethrin                                  | Nix, Nix Dermal, Kwellada-P           | 1%, 5%                         | Cream and lotion        |       |
|                                            | Piperonyl butoxide/Pyrethrins               | RID shampoo, others                   | 3%/0.3%                        | shampoo                 |       |
| <b>Miscellaneous local anti-infectives</b> |                                             |                                       |                                |                         |       |
|                                            | Isopropyl alcohol                           | Duonalc                               | 70%                            | liquid                  |       |
|                                            | Povidone-Iodine                             | Betadine                              | 10%                            | solution                |       |
|                                            | Selenium sulfide                            | Selsun, Versel                        | 2.5%                           | shampoo, lotion         |       |
|                                            | Silver sulfadiazine                         | Flamazine                             | 1%                             | cream                   |       |
| <b>Topical Anti-Inflammatory</b>           |                                             |                                       |                                |                         |       |
|                                            | Amcinonide                                  | Cyclocort                             | 0.1%                           | cream, lotion, ointment |       |
|                                            | Beclomethasone dipropionate                 | Propaderm                             | 0.025%                         | cream                   |       |
|                                            | Betamethasone dipropionate                  | Diprosone, Topisone, Topilene, others | 0.05%                          | cream, lotion, ointment |       |
|                                            | Betamethasone dipropionate + salicylic acid | Diprosalic                            | 0.05%/2%, (lotion)<br>0.05%/3% | ointment, lotion        |       |

**Table 1 (Cont.).** Topical dermatologic therapies insurance coverage; courtesy of Dr. Rachel Asiniwasis.

\* If more than one agent is included, percentages are stated according to ingredient order

\*\* Agents may also contain zinc, pramoxine, urea or counter-irritants (e.g., menthol, camphor), varying by brand

| TOPICAL THERAPIES | Name (generic) (alphabetical order)       | Trade names                                                                             | Percentages (if applicable)* | Formulation                    | Notes                                                                                                      |
|-------------------|-------------------------------------------|-----------------------------------------------------------------------------------------|------------------------------|--------------------------------|------------------------------------------------------------------------------------------------------------|
|                   | Betamethasone valerate                    | Betaderm, Celestoderm, Ectosone, others                                                 | 0.05%, 0.1%                  | cream, lotion, ointment        |                                                                                                            |
|                   | Calcipotriol                              | Dovonex                                                                                 | 50mcg/g                      | Cream, ointment                |                                                                                                            |
|                   | Calcipotriol + Betamethasone dipropionate | Dovobet, Enstilar                                                                       | 50mcg/0.5mg                  | gel, ointment, foam            |                                                                                                            |
|                   | Clobetasol butyrate                       | Spectro EczemaCare Medicated Cream                                                      | 0.05%                        | cream                          |                                                                                                            |
|                   | Clobetasol propionate                     | Dermovate                                                                               | 0.05%                        | cream, lotion, ointment        |                                                                                                            |
|                   | Desonide                                  | Tridesilon                                                                              | 0.05%                        | cream, ointment                |                                                                                                            |
|                   | Desoximetasone                            | Topicort                                                                                | 0.05%, 0.25%                 | cream, ointment, gel           |                                                                                                            |
|                   | Fluocinonide                              | Lyderm, Lidex, Synalar                                                                  | 0.01% (solution), 0.05%      | cream, ointment, gel, solution |                                                                                                            |
|                   | Halobetasol propionate                    | Ultravate, Bryhali                                                                      | 0.01 (lotion), 0.05%         | cream, ointment                |                                                                                                            |
|                   | Halobetasol + Tazarotene                  | Duobrii                                                                                 | 0.01%/0.045%                 | lotion                         |                                                                                                            |
|                   | Hydrocortisone acetate                    | Cortate, Cortoderm, EmoCort, Hyderm, Prevex-HC*, Sarna-HC*, Cortoderm, Anusol*, others* | 0.5%, 1%, 2.5%               | cream, lotion, ointment        | *Agents may also contain zinc, pramoxine, urea or counterirritants (eg. menthol, camphor) varying by brand |
|                   | Hydrocortisone acetate + urea             | Dermaflex HC                                                                            | 1%/10%                       | cream, lotion                  |                                                                                                            |

**Table 1 (Cont.).** Topical dermatologic therapies insurance coverage; courtesy of Dr. Rachel Asiniwasis.

\* If more than one agent is included, percentages are stated according to ingredient order

\*\* Agents may also contain zinc, pramoxine, urea or counter-irritants (e.g., menthol, camphor), varying by brand

| TOPICAL THERAPIES                                            | Name (generic) (alphabetical order)     | Trade names                      | Percentages (if applicable)* | Formulation             | Notes                                                                                  |
|--------------------------------------------------------------|-----------------------------------------|----------------------------------|------------------------------|-------------------------|----------------------------------------------------------------------------------------|
|                                                              | Hydrocortisone acitrate + fuscidic acid | Fucidin H                        | 1%/2%                        | cream                   |                                                                                        |
|                                                              | Hydrocortisone valerate                 | Hydroval                         | 0.2%                         | cream, ointment         |                                                                                        |
|                                                              | Mometasone furoate                      | Elocom                           | 0.1%                         | cream, lotion, ointment |                                                                                        |
|                                                              | Pimecrolimus                            | Elidel*                          | 1%                           | cream                   | *Limited use benefit; those failing topical steroids or have experienced side effects. |
|                                                              | Triamcinolone acetonide                 | Aristocort                       | 0.1%, 0.5%                   | cream, ointment         |                                                                                        |
|                                                              | Triamcinolone acetonide                 | Kenalog                          | 10mg/mL, 40mg/mL             | suspension (injection)  |                                                                                        |
|                                                              | Tacrolimus                              | Protopic                         | 0.03%, 0.1%                  | ointment                | *Limited use benefit; those failing topical steroids or have experienced side effects. |
|                                                              | Tarazotene (psoriasis)                  | Tazorac                          | 0.05%, 0.01%                 | cream or gel            |                                                                                        |
| <b>Antipruritics and local anesthetics, counterirritants</b> |                                         |                                  |                              |                         |                                                                                        |
|                                                              | Capsaicin                               | Zostrix                          | 0.025%, 0.075%               | cream                   |                                                                                        |
|                                                              | Lidocaine                               | Jampocaine, Xylocaine, Lidocaine | 2% (solution), 5%            | ointment, solution      |                                                                                        |
|                                                              | Lidocaine + Prilocaine                  | EMLA                             | 2.5%/2.5%                    | cream, patch            |                                                                                        |

**Table 1 (Cont.).** Topical dermatologic therapies insurance coverage; courtesy of Dr. Rachel Asiniwasis.

\* If more than one agent is included, percentages are stated according to ingredient order

\*\* Agents may also contain zinc, pramoxine, urea or counter-irritants (e.g., menthol, camphor), varying by brand

| TOPICAL THERAPIES                                   | Name (generic) (alphabetical order)       | Trade names                                            | Percentages (if applicable)*                  | Formulation            | Notes                                                                         |
|-----------------------------------------------------|-------------------------------------------|--------------------------------------------------------|-----------------------------------------------|------------------------|-------------------------------------------------------------------------------|
| <i>Basic ointments, Demulcents, and Protectants</i> |                                           |                                                        |                                               |                        |                                                                               |
|                                                     | Emollient creams indicated for eczema*    | Eg. Glaxal Base, Emulsifying ointment, CeraVe, Eucerin | Over-the-counter                              | various formulations   | *Coverage limited to 450g per month. Prior approval not required for children |
|                                                     | Dimethicone                               | Barriere                                               | 20%                                           | cream                  |                                                                               |
|                                                     | White petrolatum                          | Critic-Aid Clear, Prevex                               | 67%, 71.5%                                    | barrier ointment       |                                                                               |
|                                                     | Zinc oxide                                | N/A                                                    | 15% (cream), 25% (paste), 40% (ointment)      | cream, paste, ointment |                                                                               |
| <i>Keratolytic/keratoplastic agents</i>             |                                           |                                                        |                                               |                        |                                                                               |
|                                                     | Coal tar                                  | Target, Neutrogena T-gel                               | 0.5%, 1% (shampoo), 10% (gel), 20% (solution) | gel, shampoo, solution |                                                                               |
|                                                     | Coal tar, salicylic acid                  | Target SA, Sebcur-T                                    | 10%/3% (gel), 10%/4% (shampoo)                | gel, shampoo           |                                                                               |
|                                                     | Urea                                      | Uremol, Uremol10, Uresec10, Urisec12 and 22            | 10%, 20%, 22% (cream), 10%, 12% (lotion)      | cream, lotion          |                                                                               |
| <i>Warts</i>                                        |                                           |                                                        |                                               |                        |                                                                               |
|                                                     | Cantharadin                               | Canthacur, Cantharone                                  | 0.7%                                          | liquid                 |                                                                               |
|                                                     | Cantharadine, Podophyllin, Salicylic acid | Cantharone Plus                                        | 1%/2%/30%                                     | liquid                 |                                                                               |
|                                                     | Salicylic                                 | Compound W, Clear Away, Soluver, Occlusal              | 20%, 26%, 27% (liquid), 40% (plaster)         | liquid or plaster      |                                                                               |

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\* If more than one agent is included, percentages are stated according to ingredient order

\*\* Agents may also contain zinc, pramoxine, urea or counter-irritants (e.g., menthol, camphor), varying by brand

| TOPICAL THERAPIES       | Name (generic)<br>(alphabetical order) | Trade names                 | Percentages<br>(if applicable)*        | Formulation                          | Notes |
|-------------------------|----------------------------------------|-----------------------------|----------------------------------------|--------------------------------------|-------|
| <b>Genital warts</b>    |                                        |                             |                                        |                                      |       |
|                         | Podofilox                              | Condyline                   | 0.5%                                   | solution                             |       |
|                         | Podophyllin                            | Podofilm                    | 25%                                    | liquid                               |       |
| <b>Acne and Rosacea</b> |                                        |                             |                                        |                                      |       |
|                         | Adapalene                              | Differin                    | 0.1% (cream),<br>0.1% or 0.3%<br>(gel) | cream, gel                           |       |
|                         | Adapalene +<br>Benzoyl peroxide        | Tactupump                   | 0.1%/2.5%                              | gel                                  |       |
|                         | Adapalene +<br>Benzoyl peroxide        | Tactupump<br>Forte          | 0.3%/5%                                | gel                                  |       |
|                         | Azelaic acid                           | Finacea                     | 15%                                    | gel                                  |       |
|                         | Benzoyl peroxide                       | Benzagel,<br>Panoxyl        | 4% (lotion), 5%                        | gel, liquid<br>wash, bar,<br>lotion, |       |
|                         | Clindamycin                            | Dalacin-T,<br>others        | 1%                                     | solution                             |       |
|                         | Clindamycin +<br>Benzoyl peroxide      | Clindoxyl,<br>Clindoxyl ADV | 1%/3% or 5%                            | gel                                  |       |
|                         | Clindamycin +<br>Tretinoin             | Biacna                      | 1.2%/0.025%                            | gel                                  |       |
|                         | Erythromycin +<br>Benzoyl peroxide     | Benzamycin                  | 3%/5%                                  | gel                                  |       |
|                         | Metronidazole                          | Metrogel,<br>Noritate       | 0.75%, 1%                              | cream, gel                           |       |
|                         | Tretinoin                              | Retin-A,<br>Stieva-A        | 0.01%,<br>0.025%, 0.05%                | cream or gel                         |       |
|                         | Tretinoin                              | Arazlo                      | 0.045%                                 | lotion                               |       |

**Table 1 (Cont.).** Topical dermatologic therapies insurance coverage; courtesy of Dr. Rachel Asiniwasis.

\* If more than one agent is included, percentages are stated according to ingredient order

\*\* Agents may also contain zinc, pramoxine, urea or counter-irritants (e.g., menthol, camphor), varying by brand

| TOPICAL THERAPIES                                    | Name (generic) (alphabetical order) | Trade names | Percentages (if applicable)* | Formulation | Notes |
|------------------------------------------------------|-------------------------------------|-------------|------------------------------|-------------|-------|
| <i>Antineoplastics and immune response modifiers</i> |                                     |             |                              |             |       |
|                                                      | Flurouracil                         | Efudex      | 5%                           | cream       |       |
|                                                      | Flurouracil + salicylic acid        | Actikerall  | 0.5%/10%                     | solution    |       |
|                                                      | Imiquimod                           | Aldara      | 5%                           | cream       |       |

**Table 1 (Cont.).** Topical dermatologic therapies insurance coverage; courtesy of Dr. Rachel Asiniwasis.

\* If more than one agent is included, percentages are stated according to ingredient order

\*\* Agents may also contain zinc, pramoxine, urea or counter-irritants (e.g., menthol, camphor), varying by brand

### Patients aged 12 years and older with chronic moderate to severe atopic dermatitis

Initial coverage criteria (6 months):

- ✓ patient has a score greater than or equal to 16 on the Eczema Area and Severity Index (EASI) or when the face, palms, soles or genital area are severely affected; AND
- ✓ patient has a score greater than or equal to 8 on the Dermatology Life Quality Index (DLQI) or Children's Dermatology Life Quality Index (cDLQI); AND
- ✓ body surface area (BSA) of 10% or more is affected (except in cases where the face, palms, soles or genital area are severely affected); AND
- ✓ the disease is insufficiently controlled despite the use of topical treatments including at least two medium or high-potency topical corticosteroids and one topical calcineurin inhibitor; AND
- ✓ intolerance or lack of response to phototherapy or inability to access phototherapy.

Renewal coverage criteria (12 months):

- ✓ patient has an improvement of at least 75% in the EASI score compared to the baseline level; OR
- ✓ patient has an improvement of at least 50% in the EASI score and a decrease of at least five points on the DLQI or cDLQI questionnaire compared to the baseline level; OR
- ✓ patient has an improvement of lesions on the face, palms, soles or genital area compared to pre-treatment assessment and a decrease of at least five points on the DLQI or cDLQI questionnaire compared to the baseline level

**Table 2.** NIHB criteria for dupilumab for atopic dermatitis; adapted from NIHB Online Drug Benefit List, 2023.<sup>7</sup>

### Moderate-to-severe psoriasis

For moderate-to-severe psoriasis, the following biologic agents are covered when prescribed by a dermatologist: TNFα inhibitors (e.g., adalimumab), IL12/23 (ustekinumab), IL-23 inhibitors (risankizumab, tildrakizumab), and IL-17 pathway inhibitors (secukinumab, ixekizumab, bimekizumab). The coverage criteria are summarized in **Table 3.**<sup>7</sup> **Chronic Idiopathic Urticaria (CIU)/Chronic Spontaneous Urticaria (CSU)**

Omalizumab is available under the criteria stated in **Table 4.**<sup>7</sup>

### Conclusion

This practical guide is aimed at increasing awareness of NIHB coverage. Familiarity with coverage may not only reduce treatment delays, but also paperwork burdens. It is worth noting that certain Indigenous peoples of Canada, in particular Metis and non-status Indigenous peoples, are not eligible for NIHB coverage. Limitations of this article include that in British Columbia, many Indigenous clients are no longer covered by NIHB, but rather by the First Nations Health Authority (FNHA), a self-governing health authority. However, differing access to certain dermatologic therapies is observed between the two programs, as Indigenous peoples covered

For the treatment of patients with moderate to severe psoriasis who meet all of the following criteria:

- ✓ body surface area (BSA) involvement greater than 10% and/or significant involvement of the face, hands, feet or genital region; AND
- ✓ intolerance or lack of response to phototherapy; OR
- ✓ inability to access phototherapy; AND
- ✓ intolerance or lack of response to methotrexate (MTX) weekly oral or parenteral at 20 mg or greater (15 mg or greater if patient is > 65 years of age) for more than 8 weeks; OR
- ✓ a contraindication to methotrexate.

Coverage beyond 16 weeks will be based on significant reduction in body surface area (BSA) involved and improvements in the psoriasis area severity index (PASI) score and the dermatology life quality index (DLQI):

- ✓ a 75% reduction in PASI; OR
- ✓ a  $\geq 50\%$  reduction in the PASI score with a  $\geq 5$ -point improvement in the DLQI; OR
- ✓ a significant reduction in BSA involved, with consideration of important areas such as face, hands, feet or genital regions.

**Table 3.** NIHB criteria for biologic therapy for moderate-to-severe psoriasis; adapted from NIHB Online Drug Benefit List, 2023.<sup>7</sup>

Coverage is provided for an initial period of 24 weeks at a maximum dose of 300 mg every 4 weeks (6 injections over a 24 week period) for the treatment of adults and adolescents (12 years of age or older) with moderate to severe chronic idiopathic urticaria (ciu) who:

- ✓ remain symptomatic (presence of hives and/or associated itching) despite optimum management with h1 antihistamines; AND
- ✓ Prescriber is experienced in the treatment of ciu (allergist, dermatologist, immunologist, or other authorized prescriber experienced in the treatment of ciu).

**Table 4.** NIHB Criteria for moderate-to-severe CIU/CSU; adapted from NIHB Online Drug Benefit List, 2023.<sup>7</sup>

under the FNHA in British Columbia have disparate access to modern therapies compared to NIHB clients. Examples of this include lack of access to advances in topical therapy for chronic inflammatory skin disease. Multistakeholder initiatives are required to engage policy- and decision-makers. Exploring and recognizing the needs of these patients, and the impact of chronic skin disease among Indigenous patients under the FNHA, would reduce gaps in populations facing disproportional barriers to attaining optimal care. Consultation and cooperation will become increasingly necessary as Indigenous peoples assert greater control over provision of their healthcare.

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## ABOUT THE AUTHOR

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Dr. Vincent Richer practices medical and cosmetic dermatology at Pacific Derm in Vancouver. He holds the position of Clinical Assistant Professor at the University of British Columbia's Department of Dermatology and Skin Science. He trained at Université de Montréal in Medicine and Dermatology and completed a fellowship in Photobiology and Cutaneous Laser Surgery at UBC.

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# STRATEGIES TO OPTIMIZE OUTCOMES AND PREVENT COMPLICATIONS WITH LASERS

## Introduction

The world of device-based treatments of the skin is unregulated, with minimal enforcement of laser operator training and credentials, combined with an often purposeful “gray zone” in terms of qualifications communicated to patients.<sup>1</sup> Dermatologists and the staff they directly supervise are at an advantage when it comes to appropriately diagnosing conditions of the skin, as well as delivering effective and safe treatments. Light-and laser-based devices are one of the many tools in the dermatologist's armamentarium and optimizing their use has the potential to provide superior outcomes for patients. We share herein pearls from nearly ten years of experience in the field to refine your laser dermatology practice.

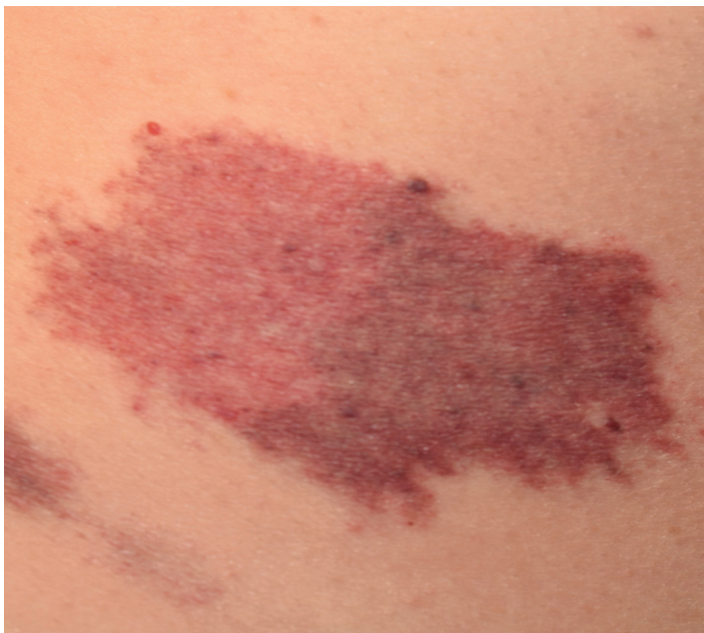
### 1. Treat to effective biological endpoints with your vascular- and pigment-targeting lasers

Lasers can target various chromophores within the skin, such as DNA, hemoglobin, melanin, water, sebum or fat. Hemoglobin and melanin, in particular, can be effectively targeted while minimizing risks of treatment by treating to biological endpoint.<sup>2</sup>

When targeting hemoglobin with a vascular laser, endpoints can be non-purpuric or purpuric.

Non-purpuric endpoints include the persistent contraction of a telangiectasia, temporary blanching (edema) to treat background erythema or the persistent contraction of a vein (sometimes accompanied by a faint pop). To shorten the “social recovery,” purpura is often considered undesirable and can in certain circumstances be considered a side effect. However, in many instances, such as treating cherry angiomas or treating a dark capillary malformation, it can be the desired biological endpoint (**Figure 1**).

When targeting melanin with a nanosecond or picosecond range pigment-targeting laser, the preferred biological endpoint is an immediate whitening reaction (**Figure 2**). Depending on the degree of contrast of the lesion and on the device, this may be quite stark or very faint. When using a millisecond range pigment-targeting laser to perform laser hair removal, the ideal biological endpoint is perifollicular erythema/edema.



**Figure 1.** A purpuric endpoint is observed on the right side of this capillary malformation. Treatment was interrupted to show the contrast with the untreated lesion (left); photo courtesy of Vincent Richer, MD.



**Figure 2.** Immediate whitening reaction as a favourable biological endpoint following Q-switched alexandrite laser exposure of a solar lentigo; photo courtesy of Vincent Richer, MD.

## 2. Be aware of biological endpoints that may signal a potential complication

Laser operators would do well to use conservative fluences initially and exercise patience to monitor the skin for the desired biological endpoint. Special attention should be given to the development of undesirable biological endpoints that may suggest excess tissue damage.<sup>3</sup> In the context of vascular laser treatment, gunmetal gray discoloration or persistent pallor should prompt the laser operator to halt treatment and stop or scale back treatment. When using a nanosecond or picosecond range melanin-targeting laser, excess fluence can cause epidermal damage beyond the immediate whitening reaction. This may be associated with epidermolysis which is also a sign to deliver more conservative treatment fluences.

## 3. Prevent and manage pain and anxiety pro-actively

Considering that exposure to most laser beams is associated with some pain, pain management is a critical element of treatment planning and delivery. Many laser devices are equipped with a cooling mechanism such as contact cooling, forced cool air or cryogen spray, both for pain control and to limit epidermal damage from laser exposure. These typically provide partial pain control. When treating small areas such as the face, compounded lidocaine up to 30% will provide more pain relief

than commercially available topical anesthetic preparations. Occlusion with cling wrap is a simple and inexpensive way to potentiate the process and can be particularly useful over larger, flat surfaces (i.e. scalp, dorsal hands). There is some controversy regarding the use of topical anesthetics in the context of IPL or vascular laser treatment. Astute clinicians have noticed that topical anesthetics have a degree of vasoactivity, leaving the skin more blanched or erythematous after topical anesthetics have been used. This has led to the concern that topical anesthetics may mask the hemoglobin chromophore, rendering treatment less effective. A recent review<sup>4</sup> highlighted that other vasoconstrictors (such as oxymetazoline) may increase the effectiveness of vascular lasers, and that the limited published evidence on pulsed-dye laser comparing topical anesthesia to vehicle or no anesthesia does not support a difference. This suggests there is insufficient evidence to recommend against the use of topical anesthetics in the context of vascular laser treatments.

For more aggressive procedures such as fractional ablative resurfacing, nerve blocks and local anesthesia can be used. Patient anxiety should be managed in a case-by-case basis. Nitrous oxide is increasingly being used in cosmetic dermatology clinics. If benzodiazepines or opioid derivative drugs are used for pain control, it should be confirmed that patients can be driven home by a relative or other individual.

#### 4. Ensure appropriate eye protection for both the patient and the laser operator

Laser eye injury is arguably one of the most devastating potential complications of laser surgery. A recent review<sup>5</sup> revealed that the majority of eye injuries occurred in the setting of laser removal of facial hair and that in 73% of cases, improper eye protection was used. Operators are advised to consider the optical density on the goggle they are donning to ensure they are protected for the wavelengths used. Special attention is required in rooms where multiple devices (and consequently goggles providing varying levels of protection) are present. For patients, “black-out” anodized metal goggles are recommended when treating the face. Alternatively, disposable laser-safe stickers have been designed to grant appropriate protection. If treatment over the orbit is required (upper eyelid, lower eyelid not overlying bone), a well-lubricated metal corneal shield should be placed after use of an anesthetic drop prior to any treatment (**Figure 3**).



**Figure 3.** Disposable laser-safe stickers (left) and Cox II metal corneal shields (right); photo courtesy of Vincent Richer, MD.

#### 5. Do not delay treatment of acne scars until at least six months following isotretinoin therapy

In 2017 a consensus paper<sup>6</sup> was published highlighting that there is insufficient evidence to delay most acne scar treatments (apart from aggressive dermabrasion and full-field ablative resurfacing), effectively challenging the accepted protocol that one should wait at least six months after a course of isotretinoin was completed before initiating acne scar treatment. This has allowed

more prompt treatment of acne scarring in our patients with severe acne requiring isotretinoin treatment. In addition, several articles have been published exploring the use of laser devices during treatment with isotretinoin, for example to treat post-inflammatory erythema/red scars (**Figure 4**) or to begin resurfacing as soon as inflammatory lesions were cleared. This is also relevant to our patients on low-dose, suppressive isotretinoin treatment who are seeking to improve their complexion with laser treatments.



**Figure 4.** Post-inflammatory erythema from acne that was cleared with isotretinoin was treated with vascular laser to hasten clinical improvement; photo courtesy of Vincent Richer, MD.



**Figure 5.** Seborrheic keratoses of the scalp treated with CO2 laser resurfacing. Notice hair growth at the site of treatment as seborrheic keratosis is a superficial lesion that does not need deep ablation to remove, as well as post-inflammatory erythema from the procedure; photo courtesy of Vincent Richer, MD.



**Figure 6.** Treatment of dermatosis papulosa nigra with long-pulse KTP laser. Notice the response was not as effective for solar lentigines present within the treatment area; photo courtesy of Vincent Richer, MD.

## 6. Consider laser therapy when treating benign epidermal lesions

It is common for clinicians to initially consider cryotherapy, electrocautery or traditional shave excision to remove benign epidermal lesions; however, sometimes the precision of a laser can make a difference. There is a paucity of clinical data confirming the superior nature of ablative lasers when treating benign epidermal lesions. In the

treatment of seborrheic keratoses, erbium YAG laser treatment led to longer post-inflammatory erythema, but less post-inflammatory pigment alteration when compared to cryotherapy (**Figure 5**).<sup>7</sup>

There is room for creativity in the use of lasers to treat benign epidermal lesions. For instance, we have reported on the efficacy and safety of pull-stacking the long-pulse KTP laser for treatment of dermatosis papulosa nigra (**Figure 6**).<sup>8</sup>



**Figure 7.** Medical treatment of acne followed by six sessions of combination subcision + 1550 nm non-ablative fractional resurfacing; photo courtesy of Vincent Richer, MD.

## 7. Discuss laser treatments with your medical dermatology patients when it is relevant to their condition

Many of our medical patients can benefit from laser treatments, and they may seek treatment outside of your office with less qualified providers. Vascular lasers can help our patients with vascular rosacea, post-inflammatory erythema from acne, red scars, and capillary malformations. Millisecond range pigment-targeting lasers can help our patients with hirsutism, whereas nanosecond and picosecond range pigment-targeting lasers can help our patients with solar lentigines and tattoos, for example. Resurfacing can treat multiple aspects of chronic sun damage, including actinic keratoses. A recent small retrospective cohort study has shown the development of fewer keratinocyte carcinomas in patients undergoing non-ablative fractional resurfacing.<sup>9</sup> Despite this, in general, ablative resurfacing is considered to have superior efficacy in clearing actinic keratoses.<sup>10</sup>

## 8. Administer combination or serial treatments, even low-tech ones

While in many cases a single device can be sufficient to treat a focal issue, full-face treatments often require treating multiple conditions and may require more than one treatment modality. Lasers can be combined in the same session – however, clinicians should also consider low-tech tools such as cryotherapy, electrocautery, chemical peels, and subcision.

This is a partial list of my preferred combination treatments:

- Focal vascular or pigment-targeting laser followed by full-face IPL
- Focal vascular laser for telangiectasias + full-face 1927 nm laser fractional resurfacing for solar lentigines, actinic keratoses and textural changes
- Pigment-targeting laser for solar lentigines and light cryotherapy for thin seborrheic keratoses
- TCA CROSS + cannula subcision + 1550 nm laser fractional resurfacing or TCA CROSS + cannula subcision + CO<sub>2</sub> laser fractional resurfacing for acne scars to target different morphologies (icepick, boxcar, rolling) (**Figure 7**).

This is a partial list of my preferred sequential treatments:

- CO<sub>2</sub> laser ablation of benign epidermal lesions (such as sebaceous hyperplasias) followed by vascular laser for post-inflammatory erythema and erythema/telangiectasias
- Hyaluronic acid dermal fillers to rapidly improve acne scars, followed by a series of non-ablative resurfacing laser treatments for long-term correction

## 9. Establish appropriate patient expectations

Certain skin conditions can be improved dramatically with one or several treatments, while others require multiple treatments or respond unpredictably. Since as dermatologists we can establish a proper diagnosis, we are in an excellent position to discuss the expected response to treatment with our patients and to let them decide if they see value in initiating a treatment plan.

For example, the vast majority of spider angiomas and venous lakes respond to one treatment session or may require only a subsequent touch-up treatment, which represents great value for our patients. Non-ablative fractional resurfacing of rolling and boxcar acne scars, for example, requires several sessions to provide noticeable improvement, while icepick scars do not respond well to this treatment modality. Some conditions, such as melasma, are usually not well managed with monotherapy using lasers.

## 10. Consider performing spot-tests

Laser test spots refer to the treatment of a small, focal area involved by the skin condition. They can serve numerous purposes:

- Test the clinical response in a condition that is either difficult to treat or in which the clinical response is unknown/unpredictable
- Test recovery or side effect development in a patient who may be at risk of a complication

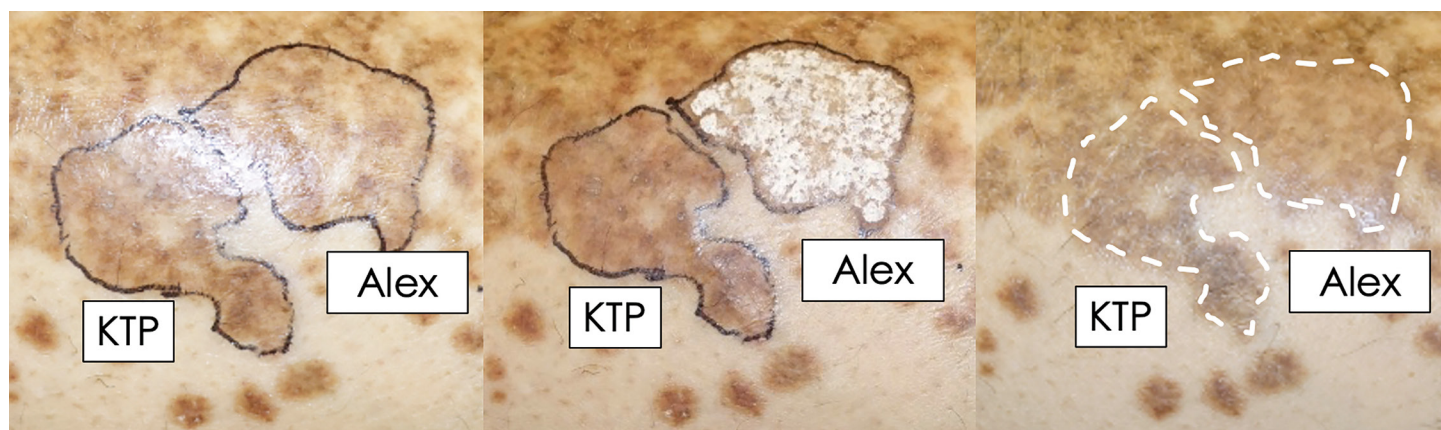
(for instance, due to their skin type or previous experience with other providers/devices)

- Establishment of a therapeutic window, by testing various settings (fluence, pulse duration, spot size) of a single device
- Establishment of a preferred wavelength/device for treatment, by using various devices over adjacent areas (**Figure 8**).

Although time-consuming, spot-tests can provide valuable information that is customized to the patient's skin. A cautious approach is often appreciated by patients when the scenario warrants it, for instance if they have had a negative experience with another provider/device but are still motivated to treat their skin condition.

## Conclusion

Dermatologists are in a privileged position to provide their patients with the best that laser devices can provide. By treating to biological endpoint; anticipating patient pain/anxiety; ensuring appropriate eye protection; not rejecting patients with recent isotretinoin treatment; exposing medical dermatology patients to laser treatment options; performing combination treatments; setting expectations; and performing spot-tests when relevant, we can maximize treatment outcomes while minimizing complications for our patients.



**Figure 8.** Spot-test sequence representing the evaluation of two wavelengths (KTP 532 nm and QS Alexandrite) for the treatment of hemosiderin staining from pigmented purpura. In the first panel, the treatment areas are outlined. In the second panel, immediate whitening reaction is observed as a biological endpoint for the alexandrite laser, while only erythema is observed with the KTP laser. On the third panel, which represents six-week follow-up, there is lightening of the lesional area where the alexandrite laser was used, and no change in the KTP laser area; photo courtesy of Vincent Richer, MD

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## Financial Disclosures

None.

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