Onychomycosis Diagnosis and Emerging Therapy
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Introduction
Onychomycosis is a common nail disorder for which successful treatment can be clinically challenging. The prevalence of onychomycosis is estimated at 2-8% of the global population. A number of medical conditions can also increase the risk of co-morbid onychomycosis infection including diabetes, peripheral vascular disease, HIV, immunosuppression, obesity, smoking, and increased age.1-5 Onychomycosis has traditionally been treated by oral and topical antifungals that often yield low to moderate efficacy.6 Even when pharmacotherapy initially results in a mycological cure, the relapse and/or reinfection rate ranges between 16-25%.7-8 Efinaconazole, a sterol 14α-demethylase inhibitor, is an emerging antifungal therapy for the topical treatment of onychomycosis, which has shown greater efficacy in vitro than terbinafine, itraconazole, ciclopirox and amorolfine against dermatophytes, yeasts and non-dermatophyte molds.9 Further, it may be a useful adjunct to oral and device-based therapies, during the main course of treatment, and as a subsequent maintenance therapy to prevent reinfection.

Background
• Onychomycosis is a fungal infection of the nail apparatus.10 It is primarily caused by dermatophytes, yeasts and non-dermatophyte molds.
• Keratinolytic dermatophytes infect and colonize the nail plate, bed, and matrix.11 This may cause symptoms such as onycholysis, discoloration, and thickening of the nail plate.11
• Onychomycosis needs to be treated for both cosmetic and medical purposes. Left untreated, the infection can spread to other nails and potentially cause further complications, especially in at-risk populations like diabetics and the immunosuppressed.2,12
• The treatment of onychomycosis poses a number of challenges due to the nail plate's lack of intrinsic immune function and the poor accessibility of drugs into the nail plate.
• The current gold standard therapy for onychomycosis is oral antifungals because their systemic distribution allows them to penetrate the nail apparatus and to a certain extent, the nail plate via the circulatory system.13
• Problematically, all of the oral drugs suffer from a potential for systemic adverse events and drug interactions.14
• This potential for negative side effects and drug interactions is often higher in the very populations who are at the greatest risk for onychomycosis, such as diabetics and the immunosuppressed; however, these individuals are the most susceptible to health complications if left untreated.
• Existing topical antifungals are not associated with adverse events to the same extent as oral therapy, as they rarely penetrate the systemic circulation and gain a significant concentration in the body.
• The topical antifungals available in the past were less widely used because their poor penetration into the nail plate results in correspondingly poor mycological and complete cure rates.15
• The ideal topical antifungal would have a higher nail plate penetration than existing drugs but maintain the advantage of minimal systemic uptake.15,16

Diagnosis of Onychomycosis Caused by Dermatophytes
• Diagnosing onychomycosis on clinical grounds alone is challenging; therefore, correlation with mycological evidence remains critical for an accurate diagnosis.17
• Definitive laboratory criteria include positive microscopic evidence of septate hyphae and/or arthroconidia (KOH preparation, Calcofluor white, Sigma-Aldrich, St Louis, Mo), periodic acid

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Schiff, and/or biopsy, and positive fungal culture findings for dermatophytes (Trichophyton, Epidermophyton, or Microsporum species) or certain nondermatophyte nail pathogens (eg, Scytalidium dimidiatum and S lyalii).17

- The primary criteria for clinical diagnosis are17
  - White/yellow or orange/brown patches or streaks
  - Secondary criteria are
    - Onycholysis
    - Subungual hyperkeratosis/debris
    - Nail-plate thickening
    - *Tinea pedis* often occurs concomitantly with pedal onychomycosis, and *tinea manuum* with infected fingernails.
- Laboratory diagnostic criteria are17
  - Positive microscopic evidence
  - Positive culture of dermatophyte
  - If onychomycosis is suggested based on clinical observation, diagnostic laboratory tests should be performed. If these produce negative findings, they should be repeated.

**Treatment**

- The primary aim of treatment is to eradicate the organism as evidenced on microscopy and culture.16

**Oral Therapies Approved in Canada**

- There are two oral therapies currently approved for use in Canada:
  1. Terbinafine 250mg/day for 12 weeks
  2. Itraconazole pulse therapy; for dermatophyte onychomycosis
     - 1 pulse = 200mg twice daily for 1 week on, 3 weeks off.
     - 3 pulses are standard for toenail onychomycosis.
- Oral therapies provide access to the nail bed and matrix of all toes; both terbinafine and itraconazole may persist in nails for long periods after treatment.
- Oral therapy can also treat concomitant skin infections such as *tinea pedis*.
- Current prescribing information should be consulted for contraindications and monitoring requirements.
- Liver function testing should be done prior to therapy, and periodically during therapy.

**Topical Therapies Approved in Canada**

- Ciclopirox nail lacquer 8%, once daily for 48 weeks.10
- Adverse events are few, with mild localized reactions at the application site.
- It may not provide adequate penetration where nails are thick or severe onycholysis is present.
-Efinaconazole 10% topical triazole antifungal was approved by Health Canada in October 2013.

**Efinaconazole, A New Topic Antifungal**

- Efinaconazole is a topical triazole antifungal developed specifically for the topical treatment of distal and lateral subungual onychomycosis (DLSO).19
- Efinaconazole expands on the success of the existing triazole antifungals, while being intentionally formulated to more effectively penetrate the nail plate.20
- Additionally, because it is a solution, there is no product build-up and removal time.

**In Vitro Efficacy**

- Efinaconazole is an inhibitor of sterol 14α-demethylase (14-DM).21
- In broth dilution tests *in vitro* against reference strains, efinaconazole was more potent than terbinafine, ciclopirox, itraconazole and amorolfine.9
- The efficacy of efinaconazole was comparable in clinical isolates of *T. mentagrophytes* and *T. rubrum* from Canada, the USA and Japan.
- The high *in vitro* efficacy of efinaconazole against the reference strains suggests that the agent would be effective in onychomycosis should the formulation provide sufficient nail penetrance.

**Clinical Efficacy**

- A randomized, parallel-group, double-blind, vehicle-controlled, Phase II clinical trial of efinaconazole was conducted at 11 sites in Mexico.22 This initial trial compared the use of 10% solution, 5% solution and 10% solution with semi-occlusion in a 2:2:1 ratio with placebo. The treatment period was 36 weeks with a 4 week wash-out period prior to the evaluation of the outcome measures.
- The efficacy variables reported were mycological cure, complete cure, clinical efficacy, and effective treatment (Table 1). Efinaconazole 10% solution without semi-occlusion was the most effective treatment for all outcomes measured.
- Recently, two parallel, double-blind, randomized, controlled, Phase III trials of efinaconazole 10% nail solution (ENS) were completed.19 Trial participants applied ENS daily for 48 weeks followed by a 4-week wash-out period. Trial outcome measures were evaluated at week 52. Results demonstrated that ENS was superior to vehicle for all outcome measures. The primary outcome measure, complete cure for efinaconazole, was 17.8% and 15.2% respectively in the two parallel studies.
- The mycological cure rates were 55.2% and 53.4% respectively. Table 1 shows a comparison of the mycological cure rates for efinaconazole, itraconazole, terbinafine and ciclopirox.23-24 The mycological and complete cure rates for efinaconazole were comparable to oral itraconazole.

**Safety and Adverse Events**

- In Phase II, 76.9% of the ENS group experienced treatment associated adverse events (TEAEs) compared with 63.6% of vehicle.22
- The main TEAEs associated with efinaconazole were blisters, contact dermatitis, erythema and ingrown nail, none of which resulted in study discontinuation.
- In the duplicate Phase III studies, the reporting rates for a single adverse event during treatment with efinaconazole were comparable to vehicle (S1: 66.0% vs. 61.0%; S2: 64.5% vs. 58.5%).20
- The reported primary TEAEs were application site dermatitis and vesicles; however, the rates for localized skin reactions were comparable to vehicle.
- Discontinuation as a result of TEAEs was low, with 3.2% and 1.9% vs. 0.5% and 0% of participants in the efinaconazole and vehicle groups respectively.
- Overall, efinaconazole showed low rates of treatment emergent adverse events.

**Other Therapies**

- Mechanical or chemical debridement lessens the burden of infection and may benefit any degree of onychomycosis; it can be performed in office, or by other healthcare professionals.

**Combination Therapy**

- Dual therapies: oral/topical, oral/debridement, or topical/debridement.26
- Triple therapies: oral/topical/debridement: Oral therapy combined with topical therapy can provide penetration of the nail plate from inside and out, which may increase the overall amount of antifungal medication reaching the infection, particularly where the nail is thickened, shows extensive onycholysis, has lateral or matrix involvement, or is a dermatophytoma.26
- Debridement may increase access to the infection by topical medications.
Table 1: Comparison of Phase III trial outcomes between efinaconazole and comparator drugs. (-) not reported

<table>
<thead>
<tr>
<th>Assessment Timepoint</th>
<th>Efinaconazole</th>
<th>Itraconazole</th>
<th>Terbinafine</th>
<th>Ciclopirox</th>
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<tbody>
<tr>
<td></td>
<td>52 weeks</td>
<td>-</td>
<td>48 weeks</td>
<td>60 weeks</td>
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Factors Affecting Treatment Failure and Recurrence

- Poor adherence
- Poor absorption
- Immunosuppression
- Dermatophyte resistance
- Zero nail growth
- Concomitant disease
- Age >60 years
- Trauma/faulty biomechanics
- Moisture exposure
- Poor patient hygiene/footwear

Recurrence

- Patient education on recurrence is recommended, specifically.
- One course of treatment may not produce the optimum results.
- May require multiple courses of antifungals.
- Recurrence of onychomycosis is very common.
- If the patient experiences any signs of onychomycosis recurrence or tinea pedis, they should be treated immediately.
- Proper foot care may minimize the chance of recurrence.
- Due to the high rate of recurrence and relapse, even in completely cured individuals, long-term topical therapy is often recommended concurrently or following oral therapy.
<table>
<thead>
<tr>
<th>Nail Presentation</th>
<th>Assumptions</th>
<th>Treatment Option</th>
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<tbody>
<tr>
<td><strong>Distal/Lateral Subungual Onychomycosis (DLSO)</strong></td>
<td></td>
<td></td>
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<tr>
<td>Mild DLSO (&lt;25% affected area)</td>
<td>Minimal thickening; minimal onycholysis</td>
<td>No matrix or lateral involvement</td>
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<td></td>
<td>&gt; 5 nails</td>
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<td></td>
<td>Matrix/lateral involvement</td>
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<tr>
<td>Moderate DLSO (25%-75% affected area)</td>
<td>25%-&lt;50%</td>
<td>5 nails or fewer; minimal thickening; minimal onycholysis; no matrix or lateral involvement</td>
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<tr>
<td></td>
<td>&gt; 5 nails</td>
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<tr>
<td></td>
<td>50%-75%</td>
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<tr>
<td>Severe DLSO (&gt;75% affected area)</td>
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<td><strong>Any DLSO involving:</strong></td>
<td>Nail matrix</td>
<td></td>
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<tr>
<td></td>
<td>Thick nails</td>
<td>&gt;2mm</td>
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<tr>
<td></td>
<td>Extensive onycholysis</td>
<td></td>
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<td></td>
<td>Nail spikes (dermatophytoma)</td>
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<tr>
<td><strong>Superficial White Onychomycosis (SWO)</strong></td>
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<tr>
<td><strong>Proximal Subungual Onychomycosis (PSO)</strong></td>
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Table 2: Simple treatment algorithm for dermatophyte toenail onychomycosis
An Update on Medical Therapies for Chemical Exfoliation

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Introduction
Chemical exfoliation has been used for decades to reverse the signs of aging skin and provide a cosmetic benefit. Alpha Hydroxy Acids (AHAs) have been at the forefront in revolutionizing the skin care industry, particularly glycolic acid-based therapies. Daily low dose glycolic acid formulations have been proven safe and effective for at-home use and have become widely popular amongst consumers. Recently, a new product line containing either 5% Encapsulated Glycolic Acid (GA) or 10% GA with the Amphoteric System, has been added to the market. It offers options for those with sensitive skin to benefit from GA therapy, while also providing those familiar with GA regimens to further benefit their skin’s appearance.

Background
- The application of chemicals to the skin in the pursuit of aesthetic improvement can be traced back to ancient times.1 Alabaster, grape skins, sour milk, salt, and animal oils are just some examples of chemicals used four thousand years ago to rejuvenate the skin.1,2
- The Romans rubbed the skins of fermented grapes on themselves to enhance their beauty, while Cleopatra allegedly would bathe in sour milk to have smoother skin.2 It would later be discovered that tartaric acid in grapes and lactic acid in sour milk, the chemicals responsible for skin enhancement, are both alpha hydroxy acids.1,2
- The use of alpha hydroxy acids is now well established by dermatologists in products such as chemical peels,1 a form of skin resurfacing or exfoliation that benefits conditions such as acne and melasma, and improves overall skin tone.
- Additionally, initial signs of aging skin begin to appear after the age of 28.4 The skin undergoes intrinsic changes which results in atrophy of particular skin components.4
- Further, sun exposure, smoking and other environmental factors can greatly accelerate changes in the skin.4,5
- Consequently, a variety of skin exfoliation technologies containing GA have been developed to reverse the various signs of aging skin, which can be broadly broken down into mechanical and chemical modalities.2,4
- With any of these approaches an accurate assessment of an individual’s baseline skin condition is crucial for success of the treatment and preventing complications, such as hypertrophic scarring.6

Mechanical Exfoliation
- Mechanical exfoliation uses physical or “mechanical” means to abrade the skin and achieve the desired effect.5,7
- Microdermabrasion and dermabrasion are two examples of mechanical exfoliation and their difference lies in the depths to which they abrade the skin.8,9
- Microdermabrasion is a non-surgical technique that uses abrasive substances, such as aluminum oxide crystals, to act at the outermost layer of the epidermis, or the stratum corneum.8,7
- The ablation of the most superficial layer of the skin reveals the underlying healthy skin.6,7 It is best suited to patients with minimally photo-aged skin that are looking for cosmetic improvements to their skins texture and tone, with minimal inconvenience.6,7
- Dermabrasion, a more aggressive form of resurfacing, acts at the level of the dermis.6 Since this mechanical exfoliation penetrates into the dermis, completely removing the epidermis, it promotes re-epithelialization and collagen remodeling.6
- In turn, this technique, when performed by a qualified professional, leads to significant clinical improvements in skin architecture, although more recovery time is usually required.8
- Dermabrasion can be used to improve a much wider range of skin conditions than microdermabrasion.6
- Various scars, facial rhytides, tattoos, rhinophyma, and actinic keratosis can all be treated with dermabrasion.6

Chemical Exfoliation
- Chemical exfoliation, such as chemical peels, abrade the skin at a desired depth to achieve a cosmetic effect.2,4-10
- Chemical peels can be classified into three groups: superficial, medium and deep, based on the depth to which they penetrate the skin.2,4,9
- The depth of peeling is dependent not only on the particular chemical used but also on the concentration at which it is used.8,9
- The deeper the peel, the more discomfort and potential side effects may occur, and consequently, the greater the recovery time. However, deeper peels also provide better cosmetic results. For example, trichloroacetic acid (TCA; also sometimes referred to as dichloroacetic acid) can be used for deep peels, medium-deep peels, or superficial peels depending on the concentration at which it is used.8
- By knowing the depth to which a chemical penetrates into the skin, dermatologists are better able to predict which skin abnormalities will benefit the most from a particular exfoliation.7
- In order to achieve the best results, a chemical peel must extend as deep as the skin abnormality to be corrected.2

Superficial Peels
- These peels penetrate into the epidermis and do not extend further than the dermal-epidermal interface.2,8,9
- Typically, superficial peels are associated with a sensation of heat.8 Examples of superficial peels include GA, beta hydroxyl acids, tretinoin, low concentration TCA, and B- lipohydroxy acid.11
- Skin dyschromias, actinic keratosis, active acne, and improvement of skin tone are the predominant clinical indications for superficial peels.8
- Since superficial peels are minimally abrasive, they are suitable for all skin types.9

Medium-depth Chemical Peels
- These peels penetrate through the epidermis and into the papillary dermis.2,8,9
- A topical anaesthetic is sometimes required.8
Glycolic Acid

- Alpha-hydroxy acids (AHA) are naturally occurring acids found in organic materials such as fruit, milk, and wine.12
- Many of these acids are utilized in topical preparations to exfoliate the skin and yield a cosmetic benefit.13
- In addition, these acids possess comedolytic effects when used at a particular pH and thus are beneficial in acne-prone patients.18
- By gently removing the top layers of skin, other concurrent active ingredients will penetrate deeper and provide enhanced effects.
- GA is an AHA originating from sugarcane, and is the most commonly used acid in AHA peels, due to its natural origin and ability to easily penetrate the skin.1
- The use of GA peels on skin yields cosmetic as well as therapeutic benefits attributed to its antioxidant, anti-inflammatory and keratolytic effects.1
- The depth to which the GA penetrates the skin is dependent on its concentration, pH, and amount of time left on the skin.
- A lower pH and increasing concentrations of GA results in deeper exfoliation.5
- Typically, GA peels are superficial in depth, resulting in very little recovery time for patients.1

Deep Peels

- These peels penetrate through the epidermis, papillary dermis and into the reticular dermis.2,8,9 As a result, they typically require general anesthesia.8
- Deep peeling solutions are comprised of varying concentrations of phenol and croton oil.9
- Fine and coarse wrinkling, actinic keratoses, acne scars, and dyschromia are the main indications for a deep chemical peel.9
- These peels are the most effective in generating new collagen and deposition of glycosaminoglycans.2,9
- Inflammation, common to all chemical resurfacing, stimulates the healing process.4
- The amount of inflammation is correlated to the depth to which the chemicals penetrate into the skin.9
- The inflammatory reaction is characterized by erythema, desquamation, and edema.11
- With superficial peels, inflammation last 1-3 days, whereas with medium to deep peels, inflammation can last 5-10 days.11 These deeper peels can require longer periods of recovery time.2,11

Side Effects

- Side effects of chemical peels include acneiform eruptions, post-inflammatory hyperpigmentation, hypopigmentation, scarring, infection, and persistent erythema.9
- Different ethnicities may not respond in a predictable manner with chemical peels.11 Therefore, a thorough individual history is quite important, with particular attention paid to instances of post-inflammatory hyperpigmentation.12,2
- To minimize complications, it is important to select the most appropriate peel accurately for each patient, and it is critical that any kind of chemical peel be administered by a trained skin professional.
- In general, the deeper a chemical peel penetrates the greater the risk of complications.8 However, the deeper a peel extends the greater the potential cosmetic benefit.4
- In the care of a trained professional, the outcome with any chemical peel is mostly predictable, and ensures that patients receive the greatest cosmetic benefit possible with minimal chance of adverse reactions.2

Conclusion

The skin care industry underwent a dramatic transformation when AHAs were introduced in the early in the 1970s.19 Today, AHAs, such as GA, are widely used in cosmetic dermatology to reverse many signs of aging skin, and offer benefit to a wide array of skin diseases.1,13 GA peels have been researched for decades, and are proven to be a simple, effective, and evidence-based method of providing significant cosmetic and therapeutic benefits to the skin of appropriately selected patients.1,19 Continued innovation with GA skin care products has resulted in improved delivery systems, reduced adverse effects and better cosmetic benefits.3,18 NeoStrata’s two new formulations, the glycolic renewal cream and lotion, utilize encapsulated GA and the amphoteric system to provide patients of all skin types with the benefits of AHA therapy. References on Page 9
New Developments in the Science Behind Anti-Aging Skin Care Products

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Introduction
The cosmeceutical industry has undergone phenomenal growth over the past decade, and much of this expansion can be attributed to an aging population wanting to sustain a youthful appearance. The availability on drug store shelves of biologically active compounds that exhibit both cosmetic and drug-like effects has created a new group of agents, whose degree of efficacy, in many cases, has been unsubstantiated by science, and they remain unregulated. As such, acquiring a basic knowledge of the major classes of active ingredients that are found in cosmeceuticals will enable healthcare professionals to provide accurate and educational information to consumers. Consumers and physicians are looking for more than hydration in topical anti-aging creams. This article will talk about three active ingredients found in new skin care products that utilize new and innovative plant stem cell technology, specifically.

Background
Albert Kligman coined the term “cosmeceutical” and defined it in 1984 as a formulation that is used to improve the appearance of skin, but is not for therapeutic purposes. 1

Major Classes of Cosmeceuticals
Retinoids
Natural and synthetic derivatives of vitamin A
Drugs:
• Retinoic acid (tretinoin), adapalene, and tazarotene
• Substantial scientific data confirm their anti-aging and anti-acne benefits. 2
• Retinoic acid is considered by dermatologists to be the anti-aging gold standard.
• It is available only through a doctor’s prescription
• Cosmeceuticals: retinol, retinaldehyde, retinyl propionate, retinyl palmitate
• In many cases, bioavailability and activity are unproven when formulated.

Moisturizers
• Include emollients, occlusives and humectants.
• Considered to be the most useful product for the management of various skin conditions (e.g., atopic dermatitis, psoriasis, pruritus, aging skin).

Other Vitamins and Minerals
Antioxidants:
• Include vitamins A, C, and E; alpha lipoic acid; ubiquinone (coenzyme Q-10); idebenone; polyphenols (e.g., catechins, flavonoids); kinetin; botanicals (e.g., teas, grapeseed, grape skins and stems, coffeeberry).
• Enhance the skin’s natural antioxidant protection system with topical application.
• Reduce free-radical damage by blocking the oxidative processes in cells.
• Inhibit inflammation that causes collagen depletion.
• Protect against photodamage and skin cancer.
• Do not reverse signs of photo-aging.

Hydroxy acids (alpha, beta, poly)
• Include glycolic acid, lactic acid, citric acid, tartaric acid, pyruvic acid, and malic acid.
• Can improve skin texture and dyspigmentation.
• Can induce actual structural changes in skin, so the potential exists for regulatory scrutiny.

Botanicals/ Plant Extracts
• Have experienced a rapid rise due to the popularity of “natural” compounds.
• Represent the largest group of additives found in marketed products.
• Limited scientific data to support efficacy and safety.

Epidermal Growth Factors
• Naturally occurring chemicals in the body that influence cellular proliferation and differentiation.
• Potential applications include regeneration of damaged or aged skin.

Proteins/Peptides
• These can trigger skin repair as needed. There are some indications that they can reduce the signs of aging and accelerate the skin’s healing processes. 3, 4

Plant Stem Cells
• Stem cells are of significant interest in the anti-aging field because they are essential for cellular repair, and this repair capacity is known to diminish with age.
• Epidermal turnover decreases with time and the skin gradually becomes thinner and more fragile, with impaired wound healing. 5
• 2-7% of the cells in the basal layer of the epidermis are adult stem cells, with the capacity to regenerate the rest of the skin. There are also reservoirs of stem cells in the hair bulge. Epidermal stem cells renew themselves slowly. Fewer divisions mean fewer opportunities to accumulate damaging DNA mutations and less telomere loss.
• Cells have a finite capacity to divide, so the slower the process, the longer the capacity is preserved.
• Epidermal stem cells are able to do their work because they generate transient amplifying cells, which divide more rapidly and produce the epidermal turnover. 6
• Epigenetic signals regulate the turning on and off of genes. These signals are tags on the DNA or the surrounding histone proteins. It is theorized that the beneficial effects observed in human stem cells in the presence of the stem cells of the Uttwiler Spatlauber apple are related to epigenetic factors from the apple stem cells. 6

PhytoCellTec Malus Domestica
• PhytoCellTec Malus Domestica contains fruit stem cells derived from the Uttwiler Spatlauber apple. This is a rare heritage variety of Swiss apple which had been cultivated for superior storage over the winter as it did not tend to wizen when stored for long periods.
• The apple stem cells are incorporated into lecithin liposomes which enhance the colony forming efficiency of human stem cells.
in vitro and the capacity to form 3D epidermis in older stem cells which would otherwise become senescent.7,10

- The stem cells are obtained by first cutting the plant, and then culturing the cells of the callus which appears as the plant attempts to repair itself.
- The cells can be propagated in the lab so that sterile preparations are available regardless of the season.
- There have been several in vitro studies of the PhytoCellTec apple stem cell preparations. In one, fibroblasts were stressed for 2 hours by exposure to hydrogen peroxide, then incubated for 72 hours either with or without 2% Malus Domestica stem cell extract.7

The fibroblasts were then analyzed for genetic upregulation or downregulation. The control groups showed downregulation of 5 genes by 63–89%. These same genes were upregulated by 117–211% in the PhytoCellTec group.

- The genes affected were cyclin B1, which induces proliferation, cyclin E1, a cell cycle regulator, p53, a tumour suppressor gene, insulin like growth factor II, a cell proliferation enhancer, and heme oxygenase I, an antioxidant enzyme.
- Another in vitro study on umbilical cord derived stem cells showed that incubation with 0.01% and 0.1% PhytoCellTec gave a progressive concentration dependent increase in cell counts from 70,000 in the control group to over 120,000 at the higher concentration.8

There was also protection against ultraviolet damage. In the control group over 40% of the cells were lost after UV exposure whereas that number was less than 10% in the treated group.

- Research on PhytoCellTec using a special cell culture medium designed to select for epidermal progenitor cells showed that keratinocytes cultured in this medium had a 10 fold increase in the CD34/alpha 6 integrin doublet labeled cells by the fourth passage.

When these cells are then cultured with 0.01% and 0.04% Malus Domestica there is a progressive and concentration dependent increase in colony forming efficiency, which is a proxy for concentration and activity of progenitor stem cells, to 92% above control for the higher concentration.9

- Lengthening the hair growth cycle is an important mechanism for lash enhancement, and 0.2% PhytoCellTec kept hairs in culture growing well past the 14 days when they typically senesce.

- A similar effect was noted in vitro on 3D epidermis produced by epidermal progenitor cells. Epidermis, produced by young progenitor cells after 5 passages, grows well in regular culture medium. Epidermis produced by old progenitor cells which have undergone 14 passages, grows to day 14, but is noticeably thinner and less developed. It will not grow to day 21, but if incubated with PhytoCellTec it is still growing at 28 days and producing thicker better differentiated epidermis.10

Data from a study of 2% PhytoCellTec cream using plant stem cells incorporated into lecithin liposomes have shown beneficial effect. In the study, 20 women applied the cream twice daily to the crow’s feet for 28 days and wrinkle depth was compared before and after.15

Wrinkle depth was found to have decreased by 15%, however there was no control cream, making it difficult to ascertain how much benefit could be attributed to the vehicle.15

- Another study involved 37 women, 21 of whom applied a placebo serum followed by a placebo cream twice daily. The other 16 used a treatment serum twice daily, with a treatment day cream and a treatment night gel. A qualitative survey revealed that patients in both groups were very positive about their creams and found them cosmetically appealing. Hydration was evaluated by corneometer and improved in both groups with no difference between them.10

- Skin colour analysis showed some improvement in evenness of skin tone over the course of treatment but this did not differ between the groups. Profiometry to assess skin wrinkles at day 56 did show a 12.1% decrease in total wrinkles in the treatment group which was statistically significant compared to the placebo group.11

**Survixyl IS**

- Survixyl IS (Vincience Biofunctionals (Lucid Inc.)), is a peptide that provides a supportive environment for epidermal stem cells. In vivo, on confocal reflectance microscopy, Survixyl IS was found to decrease sunburn cells by 33.8% after ultraviolet light exposure.12

- It also provides a 30% increase in active dermal papillae as evidenced by confocal microscopy after 29 days of twice-daily use in vivo.12

- The complex consists of survivin, which prevents apoptosis due to loss of cell adhesion, p63, which maintains the self-removal potential of epidermal stem cells, and 3 proteins which influence anchoring- beta 1 integrin, alpha 6 integrin and keratin 15, a cytoskeletal protein found in stem cells and progenitor cells.12

- There are ex-vivo studies documenting the effect of Survixyl IS on all three of these proteins. For example, survivin shows a 20.5% increase in staining of the epidermis at the base of the rete ridges in skin biopsy specimens after incubation with 0.5% Survixyl IS and a 55% increase after incubation with 1% Survixyl IS.12

- In vivo data come from a double blind, placebo controlled study of 10 patients who applied 1% Survixyl IS twice daily to the thigh for two weeks. On day seven there was UV exposure sufficient to elicit sunburn cells. The sunburn cells were counted using the confocal microscope in vivo on days 8, 9 and 13.12

- Compared to control areas where Survixyl IS had not been used, the treated areas had 24 - 34% fewer sunburn cells at day 8, and 33.8% fewer sunburn cells at day 13.12

- A similar double blind placebo controlled study, with twice-daily application of 1% Survixyl IS to the thigh for 29 days used the confocal reflectance microscope to assess dermal papillae in vivo. They found a 30% increase in the number of active dermal papillae with the product.12

**Quintescine IS**

- Quintescine IS is a peptide dimer which mimics glutathione and increases the enzymes which remove reactive oxygen species. It also decreases glycation so that collagen fibers do not stiffen as much.13

- Culture with Quintescine IS increases levels of both manganese super oxide dismutante (MnSOD) and catalase, especially in the presence of a stressor like UVA.13

- MnSOD is a free radical scavenger that catalyzes the breakdown of harmful reactive oxygen species like superoxide dismutase into hydrogen peroxide, which in turn is broken down to water and oxygen with catalase as the required enzyme.

- Fibroblasts produce 33% more MnSOD and 23% more catalase when Quintescine IS is present.13

- Protein carbonylation is also decreased when Quintescine IS is present- 36% if there is no UVA stress and 137% if there is UVA stress.13

- Lipid peroxidation is decreased 44% with Quintescine IS under UVA stress.13

- DNA damage induced by UVB is decreased by 73% in this fibroblast culture model when Quintescine IS is added to the culture medium.13

- Glycation produces cross links which stiffen collagen fibers and decrease tissue elasticity. Quintescine IS decreases glycation by 33% in the in vivo fibroblast culture model. Benefit was also shown on 6 mm punch biopsies of skin ex vivo, using methylglyoxal as the stress: it increased protection by 30-33%.13
Conclusion

Taken together, these data are encouraging and suggest a worthwhile adjunct to sunscreen. The benefits one might hope to obtain from preserving and enhancing stem cell function, decreasing damage due to reactive oxygen species and decreasing glycation would all accrue over far extended time periods. While these newest skin care products will not take the place of rejuvenating procedures like lasers, botulinum toxin and fillers, they do give patients the opportunity to get more than simple hydration from their skin care routines. Clinically, it is important that patients have realistic expectations when they are applying topical anti-aging creams.

References

12. Vincience Survixyl IS Presentation
13. Vincience Quintescine IS Presentation
Background

**Chronic idiopathic urticaria (CIU)** is a common autoimmune skin condition characterized by spontaneously recurring hives for six weeks or longer. The new terminology used for CIU in most countries including Canada is chronic spontaneous urticaria (CSU). CSU is associated with significant psychosocial morbidity with a markedly negative impact on overall quality of life. Conventional approaches with antihistamines even at high doses is effective in about 50% of cases. A new treatment option, omalizumab, (Xolair ™) a humanized monoclonal antibody against the Fc domain of IgE, has undergone randomized research studies evaluating its efficacy in CSU. Here, we review the mechanisms of action of omalizumab, efficacy, cost and potential side effect profile.

**Introduction**

Chronic idiopathic urticaria (CIU) is a common autoimmune skin condition characterized by spontaneously recurring hives for six weeks or longer. The new terminology used for CIU in most countries including Canada is chronic spontaneous urticaria (CSU). CSU is associated with significant psychosocial morbidity with a markedly negative impact on overall quality of life. Conventional approaches with antihistamines even at high doses is effective in about 50% of cases. A new treatment option, omalizumab, (Xolair ™) a humanized monoclonal antibody against the Fc domain of IgE, has undergone randomized research studies evaluating its efficacy in CSU. Here, we review the mechanisms of action of omalizumab, efficacy, cost and potential side effect profile.

**Background**

- CSU is a common autoimmune skin disease characterized by spontaneously recurring hives or welts, which may also be accompanied by deeper cutaneous swelling termed angioedema.
- The primary symptom causing significant disability is itchiness or pruritus.1
- The diagnosis is defined as urticarial skin lesions occurring intermittently or continuously for more than six weeks.
- A fairly common condition, urticaria occurs across all age groups and has a lifetime prevalence of about 20% with about 1% of the population suffering from the chronic form.2
- CSU occurs largely in young women between 20 and 40 years old.3,4
- Notably, 70% of patients diagnosed with CSU (CIU) report symptoms lasting more than one year and a significant 14% report non-remitting symptoms which have lasted for more than 5 years.5
- Although most CSU patients have no identifiable allergy triggers, and there is not necessarily an increased incidence of atopy or high IgE levels, chronic urticaria may develop due to many stimuli; including NSAIDS use, certain foods and emotional stress.
- This condition has been associated with significant psychosocial impairment; specifically impacting emotional and physical health-related quality of life indices; resulting in substantial disability and diminished productivity.6-8
- Notably, the negative impact on quality of life measures reported by patients with CSU is on par with the severity reported by patients with triple vessel ischemic coronary disease. Specifically, patients in both clinical populations report similar levels of emotional distress, social isolation and lethargy.9,10

**Treatment of Chronic Spontaneous Urticaria**

- Current practice guidelines for management of CSU describe a stepwise approach with non-sedating H1 oral anti-histamines as the initial agents: these can be given in up to four times the FDA recommended dose.11
- However, close to half of all CSU patients do not achieve adequate symptom relief with H1 antihistamines alone.12
- Second line therapies can involve addition of H2 blockers although these are not recommended as first, second or third line treatment because of low evidence supporting their clinical efficacy.
- The H2 blocking agents and anti-leukotriene medications are often tried because of their excellent safety profiles.
- If remission does not occur, third-line treatments may be initiated; this includes use of immune modulators.
- To date, cyclosporine is the single most studied agent with demonstrated efficacy based on adequately powered studies of good quality. Its significant toxicity profile, however, has limited its widespread use in many patients, especially in the older population dealing with other comorbidities.11
- Other immune modulators used in refractory CSU include tacrolimus, mycophenolate, hydroxychloroquine, sulfasalazine and even intravenous immunoglobulin. In addition to the limited data supporting use of these agents in managing CSU, many of them are associated with substantial and often unacceptable toxicities.
- Systemic glucocorticoids have also been used in refractory cases and while consensus guidelines recommend their use to be limited to exacerbations, clinical practice has often necessitated their long term use; again posing less than desirable side effects.13
- Treating CSU is challenging as there are often no identifiable indicators as to the responders to specific treatments.

**Pathophysiology**

- Cutaneous mast cell degranulation with release of histamine and other mediators are ascribed to urticaria, however, non-IgE and non-immunologic mast cell activation is responsible for ongoing urticaria.14
- In up to 50% of patients, an autoimmune mechanism is thought to mediate the disease process; this involves autoantibodies to the alpha chain of the high affinity IgE receptor or intrinsic IgE immune modulation is believed to account for the pathophysiology.15,16
- Research-based assays have been developed to isolate an autoimmune etiology; however at the present time, these are not readily available nor practical in a clinical setting.17

**Omalizumab: Mechanism of Action**

- In the last few groups, there has been a burgeoning interest in expanding the use of omalizumab beyond its originally approved use as adjunctive therapy for refractory asthma to CSU.
- Recently approved in Canada for CSU management, omalizumab is a fully humanized recombinant monoclonal antibody which binds to the Fc region of the IgE molecule which itself binds to FcεRI.18,19
- In theory, this structure precludes anaphylactogenic potential since the drug does not interact directly with IgE which is already bound to cell surfaces. Therefore, mast cell or basophil degranulation would not be inducible.20,21
- Functionally, omalizumab binds to circulating IgE, irrespective of allergen specificity. This results in circulating IgE-anti-IgE complexes, which are biologically inert and have specifically been shown not to activate the complement system.19,20,25
- Notably, reductions in circulating IgE reaching up to 99% have been reported in studies (that is free IgE not bound to omalizumab).22,23

Interestingly, these serologic changes are seen within the very first administrations of the drug and are typically maintained throughout the duration of treatment; although the precise doses in CSU have not yet been established.

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**Chronic Idiopathic Urticaria: Treatment with Omalizumab**

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Omalizumab has also been shown to down regulate FcεRI on basophils, mast cells, and dendritic cells. A reduction in the expression of FcεRI on basophils and mast cells decreases the binding of circulating IgE, thus preventing the release of inflammatory mediators.

Omalizumab has also been shown to reduce the expression of FcεRI on dendritic cells; thereby attenuating the degree of allergen presentation and processing.

**Evaluation of Efficacy**

- In addition to initial observation studies, case reports and one proof-of-concept study, there have been four prospective randomized clinical trials which have directly evaluated the clinical efficacy of omalizumab in treatment of refractory CSU, and one multicenter double blinded placebo-controlled study.

- Omalizumab has been evaluated using a total pool of 15,000 patients across all studies to date.

- Results have demonstrated clinically significant efficacy of omalizumab in decreasing pruritus and Urticaria Activity Scores (UAS - a widely used patient-reported outcome measure for patients with CSU) in comparison with conventional treatments.

- Specifically, studies have demonstrated symptom attenuation and improvement on quality of life measures in adult patients treated with omalizumab for 6-20 months.

- In one study, which enrolled patients presenting with moderate to severe CSU who were unresponsive to antihistamines, omalizumab was associated with clinically relevant decreases in severity of hives and associated pruritus, as well as meaningful improvement on quality of life questionnaires.

- Notably, omalizumab demonstrated onset of action within one week of drug initiation and there did not appear to be a rebound increase in symptoms to baseline levels once the drug was discontinued for the duration of the study.

- Though patients in that study were allowed to take antihistamines; the effect of this regimen appeared to work better after omalizumab was started compared to when the antihistamines were taken alone prior to study entry.

- Also of relevance is the demonstrated utility of this drug in a particularly challenging subset of patients with cold induced urticaria for whom treatment options have generally been rather limited and outcomes unsatisfactory.

- In real life studies omalizumab generally induces remissions in 50% of patients after the first dose.

- Overall, more than 70% of patients achieve complete remission at some point within their treatment course. About 80% have a clinically significant response overall.

- The dose interval is generally between 4-8 weeks in most patients. More research is needed to more fully evaluate the dose interval and complete remission rate. The 300 mg dose was superior to the 150 mg dose in randomized clinical trials.

**Treatment Cost**

- Omalizumab is substantially more expensive than mainstream therapies that have been traditionally used to treat CSU.

- Depending on the dose frequency, treatment cost may reach upwards of $20,000 annually. This compares with approximate costs per year of $1,280 for cetirizine, $924 for desloratadine, $712 for doxepin, and $190 for hydroxyzine.

- Despite its high cost at the present time, it can be argued that using omalizumab in selected patients with refractory and chronic urticaria may in fact defray the potential long term financial costs associated with conventional therapies; in addition to alleviating the psychosocial burden associated with loss of productivity.

**Side Effect profile**

- Use of omalizumab in the asthmatic population is more extensive compared to CSU. In asthma there are reports of anaphylactic reactions in about 1 in 50,000 injections. It should be noted, however, that omalizumab is designed to interact with the Fc region of the IgE molecule making its anaphylactogenic potential very low and clinical experience confirms that it is safe.

- There is still a recommendation for all patients to be observed for 2 hours after the first injection as well as carry epinephrine auto injectors as some anaphylactic reactions have been reported as being delayed.

- The malignancy warning has been removed from the product monograph as patients with undiagnosed cancer were enrolled in one early trial.

- The most common adverse side effects reported by patients include viral infections, headaches, sinus inflammation; however, these did not reach statistical significance when compared to patients enrolled in the placebo group.

- Notably, omalizumab is approved for children under 12 years of age.

- The data available on its safety in children showed that after one year of use, there was a slight increase in frequency of headaches and upper respiratory tract infections in the omalizumab group compared to placebo.

**Conclusion**

Omalizumab has emerged in recent years as a very effective treatment for refractory CSU. Future research should aim at investigating its mechanism of action and optimal dose schedule and treatment duration required for long term remission. To date, the longest trial duration has been 24 months.

**References**
