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Human Skin Equivalent, **Apligraf[®]** — Cellular technology benefits wound repair

In April 1997, *Apligraf[®]* (Novartis), an *in vitro* construct of human skin (human skin equivalent HSE¹), gained approval from the HPB in Canada for use in healing venous leg ulcers. This was the first major regulatory body to approve HSE for this indication. Awaiting approval in several other countries, *Apligraf[®]* is the first bilayered (epidermal-dermal), *in vitro*-engineered, skin tissue commercially available for clinical use. *Apligraf[®]* is also under investigation in clinical trials for various cutaneous surgical wounds, burns, and diabetic foot ulcers.²

Apligraf[®] is the most recent addition to a family of bioengineered skin healing agents which includes *Dermagraft-TC[®]* (Advanced Tissue Sciences, Smith & Nephew) and *Integra Artificial Skin[®]* (Integra Life Sciences Corp.).

Indications for Use

- Venous leg ulcers' Canadian approval was granted April 1997. Approval was based on safety and efficacy data from the largest multicentre, parallel group, randomized clinical trial ever conducted in venous leg ulcers.³ Studies in North America suggest that 1-3% of the population suffer from venous leg ulcers, particularly the population over age 60. Other causes of leg ulcers include diabetic or other neuropathies and arterial insufficiency.

Preparation^{2,4}

Apligraf[®] represents the culmination of several recent advances in tissue culture techniques.² It has been

engineered using serially passaged human epidermal keratinocytes and human dermal fibroblasts, cells obtained from neonatal foreskin, with a matrix of acid dissociated type I bovine collagen. The overlying epidermis is developed on the surface of the dermal matrix and when a monolayer of epidermal cells is formed, the HSE is raised to the air-liquid interface to generate a protective cornified layer. Serum is not necessary for the development of the epidermis. HSE is strong and has handling characteristics similar to split-thickness skin allowing it to be meshed, stapled, and sutured.⁴

Clinical Studies in Venous Ulcers

Interim results from a prospective, controlled, parallel group, multicentre trial in 233 patients with venous ulcers are interesting.¹ All patients entered into this trial had failed on previous venous ulcer treatments, the median duration of ulcers was approximately one year, and the median size of the treated ulcers was approximately 400 mm.⁴

Treatment

Weekly visits for eight weeks with one mid-week visit the first week. Patients received up to five applications to their venous ulcers during the first three weeks of treatment. The *Apligraf[®]* was held firmly in place with a multilayered compression wrap and the active control group also received a multilayered compression bandage. After eight weeks, patients were placed in elastic stockings. If healing had not occurred, the bandaging technique was continued for up to six months. All patients were followed for one year with visits scheduled at three-month intervals.^{2,4} *Practical details on how best to use this new product are important and will be detailed in Part II of this article in the next issue of the Letter.*

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Preliminary Results

Median time to 100% wound closure was 57 days with active treatment versus 181 days for standard care (P=0.0066). Of the 127 actively treated patients, 78 (64.1%) achieved complete wound closure, while only 47 of 109 (44.3%) of the control patients achieved 100% closure (P=0.012).¹

Mechanism of Action

Unknown, but contact between the wound bed and human fibroblasts in the dermal layer of HSE seems to send out physiologic signals for wound repair.³ In many patients, HSE promotes new tissue growth at the wound edge. In others, it appears to take like any graft, rapidly integrating into surrounding tissue. Over time, HSE is replaced by the patient's own skin cells.³

Side Effects

Clinical trials have found no sign of toxicity in over 352 HSE treated patients, and there have been no reports of allergic reactions or immunological responses with initial or repeated use.³ This product is said to have a safety profile similar to traditional wound-healing methods. Both the maternal donor blood and donor cells from neonatal foreskin are meticulously screened and certified free of CMV, hepatitis A, B and C, Epstein-Barr virus, and other infectious agents.³

Availability

Novartis have worldwide marketing rights. The cost of a 7.5 cm round disk will be approximately \$950 Canadian. Usually only one treatment is needed.

Clinical Assessment

HSE has a number of clinical advantages. Unlike much autografting, treatment with HSE does not necessitate hospitalization,³ and unlike other bioengineered skin alternatives, HSE has a well-defined stratum corneum. HSE contains both dermal fibroblasts and an epidermal sheet, with their commensurate cytokine and growth factor capabilities and natural biologic interaction. It also provides a collagenous matrix and a natural protective covering, the stratum corneum. It therefore has the potential to not only promote healing via different mechanisms (primary take, protective covering, growth factors²) but also serve as a source of new tissue.⁴

Preliminary results suggest that Apligraf® will improve the treatment of venous ulcers. It is also undergoing clinical trials to assess its benefit in other areas of wound care (burns, diabetic ulcers) and following dermatological surgery procedures (post-micrographic surgery wounds, etc.).²

"Apligraf® is ideal for patients whose leg ulcer has persisted for more than three months. Once the underlying cause of ulceration is corrected, HSE provides the structural and physiological properties of human skin that promote healing in chronic leg wounds."

Dr G. Sibbald, Toronto

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Current Approaches to the Management of Post Herpetic Neuralgia: Part 2 — Non-Systemic

In the last issue of Skin Therapy Letter, we described oral therapies which are useful in the management of post herpetic neuralgia (PHN), a common manifestation of herpes zoster (shingles) in the elderly¹. These therapies included the nucleoside analogue antiviral agents, acyclovir (Zovirax®, Glaxo Wellcome), valaciclovir (Valtrex®, Glaxo Wellcome) and famciclovir (Famvir®, SmithKline Beecham); corticosteroids; tricyclic antidepressants; and anticonvulsants.

In this article, we examine the other approaches to PHN management. Claims have been made for products ranging from vitamins to snake venom for patients who develop PHN. However, few controlled clinical trials have been conducted and, of non-oral approaches to the treatment of PHN, only topical lidocaine, capsaicin, and various nonpharmacologic techniques have been shown to be effective². This article describes these approaches to the treatment of PHN.

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Update on Sunscreens

Review by Dr. Robert Bissonnette, Vancouver

Sunscreens have been in use for nearly 70 years. Originally designed to protect against sunburn, enable longer sun exposure and promote tanning, sunscreens are now often promoted as a method for preventing skin cancer and skin aging. Although there is experimental evidence in animals suggesting that used adequately, sunscreens can prevent skin cancer, no prospective study has shown a decrease in incidence of skin cancer in sunscreen users, and sunburn prophylaxis is currently the only FDA-approved use of sunscreens. Preliminary studies suggest that new-generation sunscreens could prevent photodermatoses like polymorphous light eruption.¹

The regular and adequate use of sunscreens, avoiding the sun around mid-day, staying in the shade, wearing hats with brims which can shade the head, face and neck, and wearing clothes made from tightly woven fabrics, are all important factors that could prevent the deleterious effects of sunlight.

Table 1 lists some sunscreen agents available with their corresponding spectral photoprotection. Chemical

agents protect by absorbing light, whereas physical agents act mainly by reflecting and scattering light. The recent development of micronized preparations of physical agents has improved the cosmetic acceptability of physical sunscreens. We will review some key factors to consider when selecting a sunscreen and will compare some commercially available sunscreens, including new sunscreens made recently available in North America (Table 2).

Factors to consider when selecting a sunscreen

- **UVB protection** UVB (290-320nm) is the most erythemogenic solar radiation reaching the surface of the earth. It is also a potent skin carcinogen in animal studies. *Sun Protection Factor (SPF)* indicates the degree of protection against UVB induced erythema. It is measured in the laboratory by applying 2 mg/cm² of sunscreen to the skin of volunteers and irradiating with an artificial light source. Studies have shown that people use an average of 0.5 to 1 mg/cm² of sunscreen,^{4,5} and that the SPF may overestimate the actual protection against sunlight.⁶

TABLE 1.
Protection wavebands of sunscreens^{2,3}

Sunscreen	Protection (nm)
Chemical sunscreens	
<i>Aminobenzoic acid and derivatives</i>	
- PABA	260-313
- Lisadimate (Glyceryl PABA)	264-315
- Padimate O	290-315
- Roxadimate	280-330
<i>Anthranilates</i>	
- Menthyl anthranilate	260-380
<i>Benzophenones</i>	
- Dioxybenzone	250-390
- Oxybenzone	270-350
- Sulisobenzene (Eusolex 4360)	260-375
<i>Camphor derivatives</i>	
- Benzoate-4 methylbenzylidene camphor	290-300
- Mexoryl SX	290-400
<i>Cinnamates</i>	
- Octocrylene	250-360
- Octyl methoxycinnamate (Parsol MCX)	290-320
<i>Dibenzoylmethanes</i>	
- Avobzone (Parsol 1789)	320-400
<i>Salicylates</i>	
- Homosalate	295-315
- Octyl salicylate	280-320
- Trolamine salicylate	260-320
<i>Others</i>	
- Phenylbenzimidazole	290-340
Physical sunscreens	
Titanium dioxide	290-700
Zinc oxide	290-700

TABLE 2.
Comparison of Some Sunscreens Available in North America

Product	Sunscreen Agents	Long wave UVA protection
<i>Anthelios L Cream^a</i> SPF 60 Water resistant	Benzoate-4 methylbenzylidene camphor 5% Mexoryl SX 3.3% Parsol 1789 3.5% Titanium dioxide 4.2%	Yes. Parsol 1789, Mexoryl SX and physical agents
<i>Bain de Soleil 25 Lotion^b</i> SPF 25 Waterproof 8 hours	Titanium dioxide 9.6% Zinc oxide 1.5%	Yes. Physical agents
<i>Durascreen Lotion 15</i> SPF 15 Waterproof 8 hours	Benzophenone-3 6% Octyl methoxy cinnamate 7.5% Octyl salicylate 5% Titanium dioxide 1.6%	Yes. Physical agents.
<i>Ombrelle Extreme</i> SPF 30 Waterproof	Benzophenone-3 6% Octyl methoxy cinnamate 7.5% Parsol 1789 2.5% Titanium dioxide 2%	Yes. Parsol 1789 and physical agents.
<i>Pre Sun 30 Cream</i> SPF 30	Octyl methoxy cinnamate 7.5% Octyl salicylate 5% Oxybenzone 3% Parsol 1789 3%	Yes. Parsol 1789.

a Could prevent polymorphous light eruption¹

b Contains no chemical sunscreen

The real protection against sun-induced erythema of a self-applied SPF 15 sunscreen is thus lower than 15, probably not much more than half this figure. By applying a sunscreen with a SPF of 30 or higher, most people should get a SPF protection equivalent to at least 15. UVB also induces immunosuppression, which in animal studies is not totally prevented by sunscreens.^{7,8} One consequence of high SPF sunscreens is that, by preventing sunburn, some people may stay under the sun for long periods of time and thus receive high total daily UVA exposures.

• **UVA protection** In animal models, UVA (320-400 nm) has been implicated in skin sagging, skin cancer and immunosuppression. UVA protection is now offered in most sunscreens, but unfortunately the labels usually provide no indication of the level or wavelengths of UVA protection. Most UVA protecting sunscreen agents only offer protection against short wave UVA (Table 1). Relative protection against long wave UVA can be achieved by Avobenzone (Parsol 1789), and physical agents. Mexoryl SX is a new sunscreen agent with maximal absorption in the mid-UVA that also offers some UVB protection. Spectral protection, including UVA protection, from micronized physical agents varies according to the size of the micronized particles, with smaller particles providing more UVB and less UVA protection.⁹

• **Children** Sun exposure in the first 20 years of life is a strong determinant for the risk of skin cancer.¹⁰ Therefore sun protection throughout childhood and teenage years is probably crucial to preventing such carcinogenesis. Direct sun exposure should probably be minimized in children, and if they must spend periods of time outside during the day, physical blockers such as clothing should be used; failing that, sunscreens. Sprays and gels should be used with caution in young children as they can irritate the skin and exacerbate atopic dermatitis. Sunscreens are not recommended for use in children less than 6-12 months of age in order to discourage unnecessary sun exposure. However, there is no strong reason to suggest that sunscreens are harmful in this age group.

• **Substantivity** Substantivity is the ability of a sunscreen to resist its removal by physical means such as sweating or contact with water. If the SPF of a sunscreen stays unchanged after 40 minutes of contact with water, it is said to be *water resistant*, whereas if it stays unchanged for 80 minutes or more, it is said to be *waterproof*. Thus a person staying outside in a pool for six hours may wish to reapply a waterproof sunscreen at least four times to

ensure that the SPF remains unchanged. Some manufacturers state the actual time their product remains waterproof, and products which are waterproof for six hours or more should be used if prolonged exposure to water or prolonged sweating is anticipated.

• **Allergic potential** The prevalence of allergic reactions to sunscreens is low and most reactions reported by patients are of the irritant type. PABA and its derivatives, benzophenone and fragrances are among the most allergenic ingredients in sunscreens, explaining why many commercial products no longer contain PABA. Physical sunscreen agents do not cause allergic contact dermatitis.

• **Photodegradation** Certain sunscreen agents like avobenzone (Parsol 1789) have been shown to isomerize and lose part of their sun protection properties when exposed to light, whereas others like the newer agent Mexoryl-SX are especially photostable.¹¹ *In vitro studies have shown that certain sunscreen formulations can lose more than half their SPF value after one hour of artificial light exposure, suggesting that photodegradation is an important factor to consider when evaluating sunscreens.*¹² *In vivo studies are needed comparing the photostability of sunscreens to both UVA and UVB.* ☞

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Topical Therapy

• Idoxuridine

Idoxuridine dissolved in dimethylsulfoxide (DMSO) is available in many European countries for the treatment of herpes zoster. This product may reduce the time to rash healing and duration of acute pain, but its effect against the development of PHN is inconclusive.^{3,4}

• Capsaicin

Capsaicin cream (Zostrix[®], GenDerm), which depletes the peptide neurotransmitter substance P, is approved by the US FDA for the treatment of PHN. Capsaicin, applied 3-4 times daily for four weeks, was shown to reduce the duration of PHN by 21%, compared to 6% with placebo ($p < 0.05$), in patients who had suffered from PHN for at least six months. However, 61% of patients in the capsaicin group experienced burning on application of the cream, compared with 33% of placebo recipients. This burning can be intolerable for up to one-third of patients who receive the product in clinical practice.²

Other Topical Therapies

Topical lidocaine was tested in one trial and found to confer short-term benefit in patients with PHN. Ethyl chloride spray has also been found to provide some relief.² Topical acyclovir was found to be ineffective against herpes zoster.¹

Electrical Stimulation and Surgical Procedures

Electrical stimulation of the thalamus and transcutaneous electrical nerve stimulation (TENS) have provided relief in patients with intractable PHN.² TENS has been used for over 20 years, but there is still a controversy over its utility, with some studies showing only a transient effect and others showing a prolonged benefit.³

Anterolateral cordotomy has provided relief in some patients, as have other surgical approaches. However, none have shown consistent benefit against PHN.^{2,3}


Vaccination

Herpes zoster is caused by a reactivation of the latent varicella zoster virus (VZV), the causative agent of chickenpox. A VZV (live Oka-strain) vaccine is approved

for inoculation against chickenpox, although it is not 100% effective.⁵ However, if chickenpox could be prevented for life then zoster would eventually become a disease of the past.

Furthermore, a VZV vaccine may also be useful in reinvigorating the humoral and cellular responses to the virus in the elderly. An exploratory study with the Oka vaccine on 200 healthy adults over 60 years of age suggested that enhancement of cell mediated immune response (CMIR) in the elderly can lead to a decrease in the incidence and/or severity of reactivated zoster. The vaccine elevated CMIR to the levels seen in 40-year-olds and, after four years, none of the subjects had experienced true cases of zoster when at least eight cases would have been expected. A large, double-blind, placebo-controlled clinical trial of the vaccine in an elderly population is currently underway.⁶

Recommendation

As we recommended in the last article, the prevention of PHN is the best strategy in herpes zoster. Oral antiviral therapy offers patients the best opportunity to minimize zoster pain, particularly if initiated within 72 hours of rash onset. In patients who develop PHN, however, tricyclic antidepressants are the mainstay of therapy in patients who do not respond to conventional analgesics.^{7,8} Topical lidocaine-prilocaine cream, or lidocaine gel (5%) have also been recommended. Non-pharmacologic approaches can be used to complement the medical treatment. For very severe pain, patients may need to be referred to pain-management specialists.² 

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Update on Drugs

Class	Name/Company	Approval Dates and Comments
<i>Anti-acne</i>	Tretinoin gel 0.1% Retin-A Micro® <i>Ortho</i>	Approved by the FDA for acne treatment. Reported to cause less irritation than the original Retin-A® formulation.
<i>Anti-HIV</i>	Delavirdine Rescriptor® <i>Pharmacia & Upjohn</i>	Approved by the FDA April 7, 1997 as an added potency enhancement agent of HIV drug cocktails. It is a non-nucleoside reverse transcriptase inhibitor, which is not as powerful as protease inhibitors. <i>Skin reaction is the main side effect of delavirdine.</i>
	Nelfinavir Viracept® <i>Agouron Pharmaceuticals</i>	Indication(s): Approved by the FDA March 14, 1997 for treatment of HIV infection when therapy is warranted Nelfinavir is the first protease inhibitor approved simultaneously for adults and children. In trials, it was combined with zidovudine (Retrovir®) or lamivudine (Epivir®).
<i>Antipsoriasis</i>	Calcipotriene ointment Dovonex® <i>Bristol Myers Squibb</i>	<i>The efficacy claim for once daily dosing of plaque psoriasis was approved by the FDA March 20, 1997.</i>
<i>Antiviral</i>	Valacyclovir tablet Valtrex® <i>Glaxo Wellcome</i>	Labelling amendment approved FDA April 30, 1997. The contraindication in immunocompromised patients has been removed and reference to “in immunocompetent adults” has been removed from the indication statements.
<i>Laser system</i>	Pulsed Er:Yag laser system Derma 20® <i>Esc Medical Systems Ltd.</i>	Approved by the FDA April 15, 1997. This laser system is used for general dermatologic applications, including skin resurfacing applications.
<i>Skin Substitute</i>	Human skin equivalent Apligraf® <i>Novartis</i>	Approved in Canada April 1997 for use in healing venous leg ulcers. See article on page one of this issue.
<i>Wart removal</i>	Podofilox gel 0.5% Condylox® <i>Oclassen</i>	Approved by the FDA March 13, 1997 for the treatment of perianal warts and external genital warts. The topical solution was previously approved for external genital warts only.

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