Hormone Tans Fair Skin, Screens Sun

BY BETSY BATES
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SAN FRANCISCO — Fair-skinned volunteers injected with synthetic α-melanin-stimulating hormone readily acquired tans and showed minimal epidermal damage following exposure to ultraviolet light, in a study unveiled at the annual meeting of the American Academy of Dermatology.

Dr. Ross Barnetson, the Raymond E. Purvess Professor of Dermatology at the University of Sydney (Australia) and the Royal Prince Alfred Hospital, both in Camperdown, New South Wales, reported on the experimental approach to sun protection during a special session highlighting exciting new trial data.

In his presentation, Dr. Barnetson explained that 79 Australian subjects, most of them fair-skinned women, were enrolled in a 3-month trial comparing subcutaneous abdominal injections of Melanotan, which is an analog of α-melanocyte-stimulating hormone (α-MSH), with a placebo.

Melanin density, which was measured in the skin of subjects by using spectrophotometry, was found to increase significantly in patients who received the α-MSH injections for 10 days a month for 3 months.

"What was fascinating was that … the patients with low baseline MED [minimal erythema dose]—that is, [Fitzpatrick] skin type I or skin type II—had much better responses than those with high MED," Dr. Barnetson said during the session.

"It was a big surprise to us that, suddenly, people with red hair were getting a tan," he added.

The patients who had low baseline MED scores demonstrated a 40% increase in melanin density over eight separate skin sites after being administered the hormone, compared with a 12% increase in those with high baseline MED scores.

Melanin density increases were seen not only in skin that was exposed to the sun but also in skin that was unexposed.

The investigators went on to measure epidermal changes following exposure of subjects to three times their baseline MED of solar-simulated ultraviolet rays, 90 days into the trial.

Compared with placebo, individuals with low baseline MED who were administered the hormone demonstrated a 50% reduction in epidermal sunburned (apoptotic) cells and nearly a 60% reduction in DNA damage, as measured by thymine dimer formation.

"Melanotan results in an increase in skin pigmentation, with the greatest increases in those with low MED, [for example] type I and II skin types," Dr. Barnetson said in his conclusion.

"Clearly, it has the propensity to prevent cellular damage, as measured by sunburned cells and thymine dimers."

In the short term, he said that the synthetic hormone may prove to be useful as a means of preventing photosensitizing diseases such as polymorphic light eruption. Early studies of the effect of the synthetic hormone on those diseases have been "very encouraging," he noted.

Although that has not proven to be an issue, 'there is some suggestion [Melanotan] could be immunosuppressive, so we have to think of the long term.'

In the long term, a product might be developed that could be used to prevent the development of skin cancer in individuals who are fair-skinned.

There are wrinkles that must be worked out before a commercial product can become a reality in the marketplace, however.

Dr. Barnetson noted that 12 of 59 patients assigned to the active treatment arm of the investigation dropped out because of flushing and nausea, which were adverse events associated with the Melanotan injections. A depot form of injection that was administered to subjects in a subsequent study appears to have ameliorated those side effects, he said.

An audience member asked Dr. Barnetson about the possibility of melanocyte proliferation in response to the injections.

Although that has not proven to be an issue, "there is some suggestion [Melanotan] could be immunosuppressive, so we have to think of the long term," Dr. Barnetson replied.

In trials involving "quite a lot of subjects" who were administered the synthetic hormone, no case of melanoma has been diagnosed.

Melanotan is manufactured by the Melbourne (Australia)–based company Clinuvel Pharmaceuticals Ltd. (formerly Epitan Ltd.). Dr. Barnetson disclosed that he serves on the firm's medical advisory board. ■

ALTERNATIVE MEDICINE

AN EVIDENCE-BASED APPROACH

Polypodium leucotomos for Skin Protection

History of Use

The rhizomes and leaves of ferns have been used for a variety of medicinal purposes at least since the days of the Greek physician and botanist Dioscorides. The prominent Elizabethan herbalist John Gerard noted in his 1633 *Herbal, or General History of Plants* that Dioscorides described the fern polypody as having the "power to purge and to draw forth choler and flegme," and that it was "very good for members out of joint, and for chaps betweene the fingers." Gerard also reported that in the region around the Rhine River, the root of polypody was considered a remedy for arthritis.

► *Extracts of a tropical fern have anti-inflammatory and immunomodulating effects in the skin, suggesting a possible role as a skin protectant.*
► *The extracts also may have clinical benefits in skin disorders such as vitiligo.*

Maud Grieve wrote in *A Modern Herbal* in 1931 that common polypody was used as a mild laxative and expectorant and was valuable in early consumption. She also said it was "perfectly safe and reliable" for skin diseases.

Many tropical species of the genus *Polypodium* grow throughout mountainous areas of South and Central America, and are used medicinally by indigenous peoples for treating rheumatoid arthritis, tumors, and psoriasis, and as a cough remedy. Descriptions of the tropical fern were first recorded in diaries kept by Spanish botanist Hipolito Ruiz during his travels through Chile and Peru in 1777-1788.

Mechanisms of Action

At a meeting at New York University, Dr. James M. Spencer summarized the various in vivo and in vitro effects that researchers have identified for *Polypodium leucotomos* since an initial report of its effects (Nature 1967;214:1256-8). The extract increases circulating CD8+ suppressor cells in humans, prolongs survival of skin allografts in mice, and suppresses effector and memory T cells in rats, he said.

The fern extract also is strongly photoprotective, exerting antioxidant effects including scavenging of superoxide anions, hydroxyl radicals, and singlet oxygen (Toxicol. In Vitro 2006;20:464-71).

A proprietary extract of *P. leucotomos* (Fernblock, Industrial Farmacéutica Cantabria, Madrid) also was found to inhibit photoisomerization of transurocanic acid, which is a photoreceptor found in the stratum corneum, and to inhibit UV-induced depletion of Langerhans cells (J. Photochem. Photobiol. B. 2006; 82:173-9). Langerhans cell depletion induces local immunodeficiency in the skin, which is thought to contribute to the long-term risk of skin cancer following high-dose PUVA therapy.

Human Studies

According to Dr. Spencer, the ability of *P. leucotomos* to prevent ultraviolet-induced skin damage was discovered serendipitously. Clinicians at Harvard Medical School, Boston, using the extract for treatment of vitiligo in combination with PUVA, noticed that it prevented the expected phototoxic reaction to the phototherapy, and they presented their observations at the annual meeting of the American Academy of Dermatology in 1994, he said.

P. leucotomos decreases dermal mast cell infiltration, inhibits the expression of matrix metalloproteinases in UVB-exposed fibroblasts and keratinocytes, and ameliorates the histologic damage associated with photoaging of the skin, explained Dr. Salvador Gonzalez of the Wellman Laboratories of Photomedicine, Massachusetts General Hospital, Harvard Medical School.

Later, researchers from Wellman Laboratories and from Malaga and Santiago de Compostela universities in Spain collaborated on human studies. In one study, 10 healthy volunteers with skin types II and III were exposed to PUVA plus either 0.6 mg/kg oral 8-methoxypsoralen or 7.5 mg/kg oral *P. leucotomos* extract. Those who received the herbal extract rather than the conventional psoralen had significantly less acute phototoxicity, with a lower grade of erythema and edema—a decrease that "should make PUVA considerably more tolerable and comfortable for patients." The histologic response, which in the psoralen group included microvesiculation and vacuolization of keratinocytes, also was decreased in subjects receiving the extract (J. Am. Acad. Dermatol. 2004;50:41-9).

Several of these researchers also published the first report establishing the ability of an oral antioxidant to decrease DNA damage in dermal cells, noting that their findings suggest a possible role for *P. leucotomos* in skin cancer prevention (J. Am. Acad. Dermatol. 2004;51:910-8).

Experimental use as a treatment for vitiligo also continues. In a double-blind pilot study, 19 patients with generalized vitiligo were randomized to receive PUVA plus *P. leucotomos* extract or placebo for 12 weeks. The percentage of subjects who achieved greater than 50% skin repigmentation was significantly higher in the *P. leucotomos* group than in the placebo group. Moreover, the active treatment normalized the expression of activation markers by T cells and significantly decreased the proliferative response to T-cell mitogens (J. Dermatol. Sci. 2006;41:213-6).

Better Than Sunscreen?

A significant proportion of the population does not use sunscreen at all, and those who do use it apply it insufficiently, said Dr. Spencer, professor of clinical dermatology, Mount Sinai School of Medicine, New York. He suggested that oral *P. leucotomos,* currently available as Heliocare (IVAX Dermatologicals Inc., Miami) might make sun protection more convenient and more widely used by the public.

But the National Institutes of Health's online MedlinePlus resource offers a caveat, noting that experiments with a related fern species, *P. vulgare,* showed that it affected cardiac function and lowered blood pressure in animal studies. "In theory, the use of *Polypodium leucotomos* extract with medications that affect heart function or lower blood pressure may cause the effects of these drugs to increase," the report states (www.nlm.nih.gov/medlineplus/druginfo/natural/patient-polypodium-leucotomos.html).

—Nancy Walsh