

Emerging Treatments for Vitiligo Offer Hope

BY KERRI WACHTER

Senior Writer

PARIS — Vitiligo can be a psychologically devastating disorder, but there are several effective therapies that can improve skin pigmentation and reduce the burden of this disease, according to Dr. Pearl Grimes.

"Pigmentation significantly influences the paradigm of psychosocial interactions. . . . Any aberration or any deviation from normal causes enormous distress for patients," Dr. Grimes said during a plenary session at the annual congress of the European Academy of Dermatology and Venereology.

Vitiligo is associated with depression, stigmatization, low self-esteem, social embarrassment, and impaired interpersonal relationships. The disease is particularly problematic for children in their formative years, and some quality of life studies have shown that negative childhood experiences are significantly associated with impairment in early adulthood, said Dr. Grimes, who is the director of a practice that specializes in vitiligo and pigmentation in Los Angeles.

During the last 10-15 years, several studies have also shown that severity of vitiligo correlates with quality of life, that impairment is greatest in women, and that counseling may help improve body image, self-esteem, and quality of life for children and adults.

The message for physicians: "Be sensitized and aware of these issues for patients, and refer them for counseling to cope with the despair caused by this disease," Dr. Grimes said.

She discussed recent advances in vitiligo assessment and therapy that have offered hope to these patients:

► **Definition and assessment.** Historically, there has been no common grading scale for vitiligo that could be used to compare the results of clinical studies.

In 2007, the Vitiligo European Task Force published a consensus report on the definition of vitiligo and methodologies for assessing treatments for this skin disease (*Pigment Cell Res.* 2007;20:27-35). The assessment is based on body surface area, disease stage, and progression.

"I think the European task force has done a wonderful job in addressing some of the issues that we face as physicians in addressing this disease," she said.

► **Topical calcineurin inhibitors.** In recent years, multiple studies have documented the efficacy and safety of calcineurin inhibitors as repigmentation tools in the treatment of vitiligo.

These topical immunomodulators "are now the No. 1 treatment that is prescribed for patients who have limited involvement," Dr. Grimes said.

Calcineurin inhibitors work by inhibiting T-cell activation, deactivating calcineurin, and inhibiting the formation of proinflammatory cytokines. These agents also decrease tumor necrosis factor- α levels following treatment, and stimulate melanocyte growth.

Calcineurin inhibitors offer several advantages, she continued. These agents are well tolerated. They do not cause atrophy or telangiectasia, as steroids do. Pigmentation is homogeneous. And calcineurin inhibitors work especially well for the face and neck.

They are the optimal treatment for patients with limited involvement over the body surface area, Dr. Grimes said.

However, in the United States these agents carry black box warnings regarding long-term use. Rare cases of cancer have been reported in patients who were treated with topical calcineurin inhibitors, although no causal relationship has been established. Physicians are encouraged to avoid continuous long-term use of these agents for their patients and to limit application to areas of involvement, she said.

Despite the black box warning, the evidence for an association with cancer is not clear. In a nested case-control study published in 2007, researchers looked at the



Vitiligo is associated with depression, stigmatization, low self-esteem, and social embarrassment.

possible association between topical immunosuppressives and lymphoma in more than 290,000 patients with atopic dermatitis. Based on logistic regression analysis, there was no increase in lymphomas in patients who were treated with calcineurin inhibitors (*J. Invest. Dermatol.* 2007;127:808-16).

"At the end of the day, as clinicians . . . you have to decide how you will situate these combination protocols/combination uses in your practice," Dr. Grimes said.

She added that she relies on calcineurin inhibitors tremendously in her practice, but does not use them with ultraviolet light. Instead, she treats patients on the basis of a rotational algorithm, starting with tacrolimus/pimecrolimus, then targeted phototherapy, then steroids/calcipotriol, then steroids/tacrolimus, and back to tacrolimus/pimecrolimus.

► **Vitamin D analogues.** Another treatment that is being considered for vitiligo is vitamin D. "There are exciting new data in the literature on the role of vitamin D in the autoimmune process," Dr. Grimes said. The immunomodulatory effects of vitamin D include suppression of T-cell activation, induction of regulatory T cells, and modulation of the production of proinflammatory cytokines from activated T cells and keratinocytes. Vitamin D also has antioxidant and photoprotective effects.

Vitamin D stimulates the differentiation of immature melanocyte precursors and plays a regulatory role in melanocyte development and melanogenesis. Vitamin D also increases tyrosinase activity.

However, in terms of using vitamin D analogues as repigmentation therapies, results have been varied. Response is poor when these agents are used as monotherapy. The best results are achieved with sunlight, phototherapy, or topical mid- to high-potency steroids.

The use of vitamin D analogues may decrease the cumulative UV dose and number of phototherapy treatments required for repigmentation. The fact that vitamin D analogues are degraded by UV light may account for some of the variability seen in the studies, Dr. Grimes said.

► **Narrow-band UVB.** Narrow-band UVB (NB-UVB) phototherapy, which affects both peripheral blood and lesional skin, has moved to the forefront as a treatment for vitiligo. In peripheral blood, narrow-band UVB decreases natural killer-cell activity, cytokine response, and lymphoproliferative responses. In lesional skin, this therapy decreases Langerhans cell activation and increases apoptosis, melanocyte proliferation, and melanogenesis.

NB-UVB has no systemic side effects, requires no posttreatment ocular protection, and has a good safety profile for adults and children. A good response can be achieved even in patients with extensive involvement. "We know that narrow-band [UVB phototherapy] is tremendously well tolerated and easier for the patient," Dr. Grimes said.

NB-UVB appears to provide a better response than

does psoralen with UVA (PUVA). In a recent study, 25 patients with vitiligo were treated with PUVA and 25 with NB-UVB (*Arch. Dermatol.* 2007;143:578-84). At the end of therapy, 64% of the NB-UVB patients had a greater-than-50% improvement in affected body surface area, compared with 36% of the PUVA group. The color match of the repigmented skin was excellent in all patients in the NB-UVB group, but in only 44% of those in the PUVA group.

On the down side, NB-UVB therapy may require three treatments per week for maximum efficacy. In addition, the long-term carcinogenic effects—as well as the long-term stability of NB-UVB repigmentation—are not known.

"We need more data on the stability of the treatments that we do, as well as [on] the need for maintenance treatment once you achieve repigmentation," she said.

► **Polypodium and phototherapy.** *Polypodium leucotomos* (PL), a fern plant grown in Central America that was used in the 1980s as a repigmenting agent, is enjoying a resurgence in interest. The plant has been found to have antitumor and anti-inflammatory effects. It has immunosuppressive properties, reducing CD4 and CD8 levels.

In one study, researchers explored the effects of PUVA plus PL in a pilot randomized, double-blind, placebo-controlled trial with 19 patients who had generalized vitiligo. Skin repigmentation greater than 50% was achieved by a significantly higher percentage of patients in the PUVA-plus-PL arm than in the PUVA-plus-placebo arm (*J. Dermatol. Sci.* 2006;41:213-6).

"I think that we're going to be seeing more on this combination of *Polypodium* plus light in the future," Dr. Grimes said.

► **Targeted light therapy.** Excimer laser-targeted light therapy is another effective option for treating vitiligo. This therapy targets affected skin with a high-intensity light, but avoids exposure to normal skin. Rapid therapeutic responses are seen; cumulative UV exposure is limited.

In addition, targeted light therapy can have a synergistic effect with certain topical agents. Studies suggest that the fastest repigmentation occurs with treatment two to three times per week.

This therapy is a good choice for patients with areas of depigmentation on the genitalia. "Typically in my practice, I tend to avoid treating these areas. But I do have a cohort of gentlemen who are absolutely devastated by genital depigmentation," Dr. Grimes said. She said she has had good results using targeted light therapy in these patients.

► **Imatinib mesylate.** Imatinib mesylate (Gleevec) is a tyrosine kinase inhibitor that is used for the treatment of chronic myeloid leukemia. "One of the most common side effects is that it induces hypopigmentation and depigmentation," Dr. Grimes said, so this may be a future depigmenting agent for vitiligo.

► **Surgical options.** Surgical therapy for vitiligo is indicated for stable disease that is focal or segmental and does not respond to medical treatment. It is contraindicated in patients with keloids and hypertrophic scars.

Available procedures include autologous suction blister grafts, autologous melanocyte transplants, autologous punch grafts, sheet grafts, and co-cultures of melanocytes and keratinocytes. "Using these grafting procedures, we actually have the ability to cure some patients who have segmental vitiligo," Dr. Grimes said.

One new surgical option is a technology called Re-Cell (Avita Medical Ltd.). This is a single-use, battery-operated, autologous cell harvesting system. The cell suspension is sprayed onto the affected areas of skin.

Dr. Grimes reported that she had no relevant conflicts of interest. ■