INTRODUCTION

Despite recent significant therapeutic advances, vitiligo remains a clinical problem and many patients are abandoning hope of successful treatment. Topical immunotherapy has been extensively tested in the treatment of various dermatologic disorders, especially those believed to have an immunologic basis. Aim: To evaluate the role of topical diphenylcyclopropenone (DPCP) in the treatment of vitiligo. Methods: Nineteen patients with limited vitiligo lesions were enrolled in this study. After sensitization with 2% lotion of DPCP in acetone, progressively higher concentrations beginning at 0.001% up to 2% were applied weekly for 6 months to the depigmented skin lesions. Results: Thirteen of the 19 patients were evaluated at the end of 6 months. Four patients with focal vitiligo, one patient with vitiligo vulgaris, and three patients with segmental vitiligo showed marked (grade 3) repigmentation. Conclusion: Marginal and central repigmentation with hyperpigmented borders was seen in the majority of lesions. Further controlled trials should be undertaken to evaluate the use of topical DPCP in vitiligo.

KEY WORDS: Diphenylcyclopropenone, Immunotherapy, Treatment, Vitiligo

METHODS

Nineteen patients with vitiligo, attending the Department of Dermatology, Jahrom School of Medicine, Jahrom, Iran, were enrolled in this study. Written informed consent was obtained from all patients. Before starting therapy, the patients were evaluated clinically to record the duration and progression of the disease, the sites of the lesions, and the extent of the cutaneous involvement. Patients showing evidence of spontaneous repigmentation in any of the lesions were not included in this trial. Patients with rapidly progressive disease or patients with any changes in lesions during the last 3 months were also excluded. Individuals with vitiligo were ineligible for DPCP treatment if they presented with more than 10% skin involvement; also those aged less than 10 years or who had significant cardiovascular disease or were pregnant or had serious intercurrent medical illnesses were excluded. The different DPCP lotion concentrations were achieved by dissolving the 98% pure powder (Acros Organics, New Jersey, USA) in acetone.

Primary sensitization was performed with the application of 2% solution of DPCP to an area of 4×4 cm on the medial side of the non-dominant arm. Two weeks following sensitization, treatment was started by weekly applications.
of incremental concentrations of DPCP (between 0.001% and 2%) adjusted to the patient’s reactivity to the contact allergen. The aim was to maintain mild contact eczema and itchiness for about 48 hours after application. Patients were instructed to avoid direct sun exposure of the involved area and not to wash it for 48 hours after each application. The overall duration of therapy was 6 months. Treatment was discontinued if the patients did not show any improvement or if there was worsening at 3 months.

The response to treatment was evaluated by keeping photographic records of all or some representative lesions and repeating the photographs at intervals of 4 to 6 weeks. Based on previous studies, repigmentation was graded on a 6-point scale depending upon the extent of repigmentation in the existing lesions (0 indicated no repigmentation; 1, repigmentation of 1%-24%; 2, repigmentation of 25%-49%; 3, repigmentation of 50%-74%; 4, repigmentation of 75%-99%; and 5, total repigmentation). The surface area was compared after all the photographs were taken by a digital camera (S60, Canon, Japan) with similar conditions of place, light, and magnification.

RESULTS

Thirteen patients were evaluated at the end of 6 months, as 3 patients withdrew the course for reasons unrelated to the study and treatment was discontinued in 3 other patients because of worsening of the disease. The basic data pertaining to age, sex, duration of the disease, and the type of vitiligo are summarized in Table 1. Of the 13 patients, 5 patients had a history of thyroid disease and 4 patients had a positive family history of diabetes mellitus in their first-degree relatives. Seven out of 13 patients had family history of vitiligo.

Of the 13 patients, 1 patient revealed grade 1 (1%-24%) repigmentation; 4 patients, grade 2 (25%-49%); and 8 patients, grade 3 (50%-74%). Three patients with segmental vitiligo, 4 patients with focal vitiligo, and 1 patient with vitiligo vulgaris showed marked (grade 3) repigmentation [Figures 1 and 2]. All patients showed perilesional hyperpigmentation which disappeared on stopping the treatment. Some
patients showed repigmentation which was darker than the surrounding normal skin. All patients tolerated the drug well, except for 3 patients who complained of mild irritation on exposure to sunlight. The irritation and itching was mild to moderate in nature; but in 4 patients, there was a need for systemic medication (hydroxyzine) to relieve the itching during DPCP treatment.

**DISCUSSION**

Vitiligo is supposed to be a disorder with a flaw in the immune system. Basically, a lower total number of lymphocytes, an elevated percentage of memory T cells, and a lower percentage of NK-T cells and naïve T cells were recorded in peripheral blood T cells. These findings probably reflect an increased antigen-mediated activation and subsequent activation-induced cell death, resulting in a lower overall lymphocyte count in vitiligo. Also, the preceding findings reiterated the earlier observations of Grines et al and Halder et al, who had documented a decrease in the CD4+ T cell count and a perceptible decrease in the ratio of CD4+/CD8+.

Le Poole et al, had an occasion to comprehensively dwell on autoimmune aspects of depigmentation in vitiligo, where it was highlighted that pigment might be lost in vitiligo as a function of reduced melanocyte numbers in the epidermis, and that depigmentation might be accompanied by a T cell influx into the skin in a large majority of patients. The cells were characterized as infiltrating T cells and further classified as type I pro-inflammatory cytokine-secreting cells reactive with melanocyte-specific antigen, a major step toward effective therapy. In accordance with these findings, immunosuppressive treatment or bursectomy in Smyth chickens has been shown to reduce depigmentation.

An obvious variation in current opinions and recommended strategies for management of vitiligo has existed. Up to now, vitiligo has remained a difficult disease to treat. Currently therapeutic options are available that include administration of oral and topical psoralen photochemotherapy, topical corticosteroid and phototherapy (solar exposition, and narrowband UV-B therapy), and depigmenting methods. However, no treatment provides truly satisfactory results. Historically, topical and systemic psoralen photochemotherapy with UV-A (PUVA) was considered the gold standard for repigmenting vitiliginous skin lesions, though PUVA-induced repigmentation rates are too varied. Indeed, adverse effects could be substantial, including phototoxic reactions, nausea, vomiting, pruritus, and elevated liver transaminases. The distinct mechanisms of these treatments are not clear, but recent studies emphasize the probable implication of the immunosuppressive action of UV therapy in the repigmentation of vitiliginous patches. This immunomodulating photobiological action of UV therapy involves the withdrawal of Langerhans cells and the decrease of their antigen presentation function, the keratinocytic cytokines, and moreover, the apoptosis of the activated T lymphocytes.

 Additionally, tacrolimus, a new topical immunosuppressive drug developed for the treatment of atopic dermatitis, has been utilized for the treatment of vitiligo in various combinations with natural sunlight or 308-nm excimer laser.

DPCP (2,3-diphenylcyclopropenone-1) was described in the chemical literature in 1972 as provoking allergic reactions but was not noticed by dermatologists until 1980. The immunomodulatory mechanism of DPCP remains to be clarified. Happle’s ‘antigenic competition’ view suggests that DPCP may redirect the immune response away from the antigen responsible for alopecia areata (AA). The postulation that IL-10 may be responsible for the effectiveness of DPCP in alopecia totalis treatment by inhibiting lesional T lymphocytes. Moreover, it is postulated that IL-10 may be responsible for the effectiveness of DPCP in alopecia totalis treatment by inhibiting lesional T lymphocytes. DPCP induces a striking over-expression of transforming growth factor-β1 mRNA in successfully treated patients.

Based on the previously discussed mechanisms, we
hypothesized that DPCP may improve vitiligo lesions through immunomodulatory effects. Although a few studies report vitiligo as a side effect after DPCP treatment,[15] in most of the published studies, vitiligo was not a side effect even after long-term therapy.[11] In keeping with this finding, vitiligo[15] was found to occur in about 7% of treated patients, similar to the 4%-9% incidence of vitiligo in untreated alopecia areata patients. It may represent a Koebner phenomenon in predisposed individuals.[14] In our study, in 3 patients with vitiligo vulgaris, the treatment was discontinued because of worsening of the disease. We suppose that it was due to Koebner phenomenon, which is positive in vulgaris type. Moreover, electron microscopic studies have confirmed that the hypopigmentation is not post-inflammatory, and so the vitiligo occurring during treatment of alopecia areata may not be due to distant spreading of DPCP.[15] Also vitiligo has not been reported in patients treated for warts with this agent,[2,17] perhaps because the duration of treatment is much shorter and such individuals are intrinsically less susceptible.

It is true that this is a small uncontrolled pilot study and further controlled trials are warranted to evaluate the use of topical DPCP in vitiligo, notwithstanding the fact that the trend toward significant clinical improvement in vitiligo with the use of DPCP was evident for the first time in our study.

REFERENCES