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Triple Combination of Systemic Corticosteroids, Excimer Laser, and Topical Tacrolimus in the Treatment of Recently Developed Localized Vitiligo

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Dear Editor:

The treatment of localized vitiligo usually involves a stepwise strategy; the first-line treatment is topical corticosteroids or calcineurin inhibitors, and a combination strategy has been proposed for patients with refractory lesions[1]. However, these schemes require many months to years of treatment and can result in disappointing outcomes. Moreover, previous studies have demonstrated that the longer the duration of the disease, the worse the prognosis were for the treatment, including surgical treatment[2]. Therefore, delay in treatment initiation may make treatment more difficult, and thus there is a strong need for early intervention for a successful treatment. Multiple combination modalities have been suggested, including topical agents and phototherapy, or systemic corticosteroid and surgery[3]. In this open pilot study, we investigated the efficacy of a triple combination treatment, consisting of systemic corticosteroids, excimer laser, and topical tacrolimus, in patients with recently developed localized vitiligo.

Fourteen patients (eight men, six women; mean age, 28.9 years) were enrolled in this study. Five patients had segmental vitiligo, whereas nine had focal vitiligo. All patients had recent-onset vitiligo lesions that had been evident for at least 6 months. The average duration of the vitiligo was 6.6 weeks. The mean body surface area of the vitiligo was $<3\%$. None of the patients had a family history of vitiligo or had received another additional therapy for the disease before entry or during the study. One patient had Hashimoto's thyroiditis. This study was approved by the institutional review board of Ajou University Hospital (AJIRB-MED-MDB-12-158). All patients were treated with low-dose oral prednisolone (0.3 mg/kg/day) for 4～8 weeks, 0.1% topical tacrolimus (Protopic; Fujisawa Healthcare Inc., Deerfield, IL, USA) twice daily, and excimer laser twice a week for 12 weeks. The excimer laser (Xtrac; Photomedex, Radnor, PA, USA) was initiated at 100～200 mJ/cm^2, and the dose was increased by 50 mJ/cm^2. The size of the treated lesions was documented at study entry and every 4 weeks thereafter, by using digital photography. The endpoint of primary efficacy was the repigmentation rate of the lesion after 12 weeks, whereas the endpoint of secondary efficacy was complete repigmentation. Treatment efficacy was classified by using a visual grading system: weak effect, 0%～25% repigmentation; moderate effect, $>25\%$～50% repigmentation; good effect, $>50\%$～75% repigmentation; excellent effect, $>75\%$～99% repigmentation; and complete effect, 100% repigmentation. Repigmentation was confirmed by the examination of treated lesions under a Wood's lamp; three dermatologists performed the photographic assessments. The treatment was ceased early in patients who showed complete repigmentation before 12 weeks. All patients were followed for 7 months to assess the stability of the pigmentation. Safety profiles were assessed simultaneously throughout the study.

All patients completed the 12-week treatment period. The

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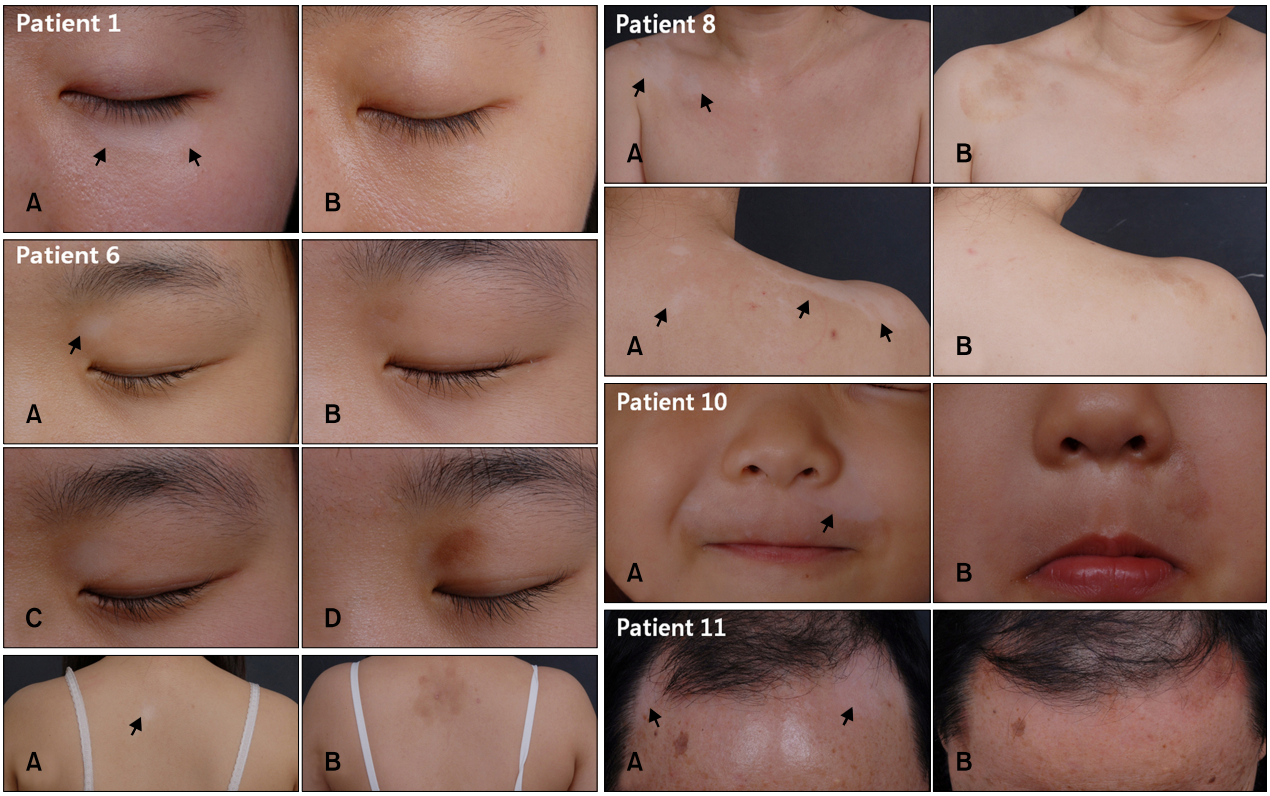

Fig. 1. Complete repigmentation. (A) Before treatment and (B) after 3 months of triple combination treatmentin patients 1, 8, 10, and 11. (C) At the end of the 7-week follow up, patient 6 with Hashimoto's thyroiditis had developed some areas of depigmentation over the repigmented sites. (D) However, this lesion was also completely repigmented after 1 month of combination treatment with excimer laser and topical tacrolimus. The black arrows indicate depigmented lesions.

lesions were located on the head and neck (n=12) and on the trunk (n=3). Among the 14 patients, repigmentation was scored as complete in five (35.7%) (Fig. 1), excellent in four (28.6%), good in one (7.1%), moderate in two (14.3%), and weak in two (14.3%) patients. There was no difference in treatment efficacy between the focal type and the segmental type. Complete repigmentation was achieved in 3 of 10 lesions in the focal type and in 2 of 5 lesions in the segmental type.

Initial repigmentation was noted within 2 weeks in most of the patients. Among the five patients with complete repigmentation, two showed complete repigmentation within 1 month (patients 10 and 11). The response to treatment was generally poor in lesions accompanied by poliosis (good in one, moderate in two, and weak in two). At the 7-month follow-up, patient 6 (with Hashimoto's thyroiditis) had developed some areas of depigmentation over the repigmented sites, whereas the pigmentation remained stable in the other patients. Three patients complained of adverse effects, including slight pain and bulla due to laser therapy, and abnormal menstruation, which may be due to the systemic steroid. However, the adverse effects were not serious and were reversible, and therefore did not affect the treatment schedule. The demographics of the patients and a summary of the treatment results are presented in Table 1.

Previous studies have consistently reported that combination interventions of topical therapy and phototherapy were superior to monotherapies[1]. Phototherapy induces a predominantly perifollicular pattern of repigmentation, whereas topical agents exhibit a diffuse type, acting synergistically when combined[4]. A significant finding of this study is that complete repigmentation occurred in 35.7% of the patients, which was much higher than that reported for other modalities of current vitiligo therapy. One previous study revealed that the combination of excimer laser and topical 0.1% tacrolimus ointment achieved >75% repigmentation in 70% of patients. However, complete repigmentation occurred in only 2 of 23 lesions within 2 months[5]. When excimer laser was combined with topical hydrocortisone for the treatment of vitiligo of the face and neck, >75% repigmentation was observed in 42.8% of the patients and complete repigmentation occurred in 21.4% of the patients[6]. Therefore, the higher rate of com-

Table 1. Demographics and treatment results in 14 patients with recent onset vitiligo

Patients	Sex/age (y)	Disease duration (wk)	Type	Affected site	Associated features	Treatment response*	Stability of pigmentation	Side effects
1	Female/18	4	Focal	Left infraorbital area		Complete		Slight pain
2	Male/79	1.5	Focal	Forehead and scalp		Excellent		-
3	Female/10	4	Focal	Left frontal scalp	Poliosis	Weak		-
4	Male/11	2	Focal	Right eyebrow	Poliosis	Good		-
5	Female/45	2	Segmental	Right neck and perioral area	Poliosis	Weak		-
6	Female/13	4	Focal	Left eyelid and upper back	Hashimoto's thyroiditis	Complete	Recurred by 7 months	-
7	Male/18	4	Focal	Left eyebrow	Poliosis	Moderate		Bulla
8	Female/45	24	Segmental	Right shoulder, chest, and forearm		Complete		Abnormal menstruation
9	Male/43	4	Focal	Left eyebrow and scalp	Poliosis	Moderate		-
10	Male/3	3	Segmental	Left nasolabial fold		Complete		-
11	Male/57	24	Focal	Both forehead and scalp		Complete		-
12	Male/35	4	Segmental	Left neck		Excellent		-
13	Female/10	4	Segmental	Right nose and nasolabial fold		Excellent		-
14	Male/17	8	Focal	Right temple and neck		Excellent		-

*No or weak effect, 0%～25% repigmentation; moderate effect, ＞25%～50% repigmentation; good effect, ＞50%～75% repigmentation; excellent effect, ＞75%～99% repigmentation; complete effect, 100% repigmentation.

plete repigmentation in this study is meaningful, as most patients do not favor inhomogeneous repigmentation. In addition, complete repigmentation was more rapid and was achieved within 1 month in two patients. The rapid onset of repigmentation improved the patients' motivation and their compliance to therapy.

We added a systemic corticosteroid that had been suggested to suppress disease activity or progression without any noticeable adverse effects[7,8]. It was suggested that early dynamic events in vitiligo, including for the segmental type, are characterized by the infiltration of inflammatory cells on histological examination, which is implicated in the development of vitiligo[9]. The combination of a systemic corticosteroid and topical tacrolimus was also reported in two cases of recent-onset vitiligo[10]. These cases were treated successfully and suggest the necessity of early intervention.

The limitation of this study was the small population size.

In conclusion, we propose that the triple combination treatment with systemic corticosteroids, excimer laser, and topical tacrolimus is effective for recent-onset vitiligo as a first-line therapy. It is likely that early intervention with this combination treatment can prevent disease progression, and achieve a more rapid and complete repigmentation.

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Prayer Mark on the Forehead: Hyperpigmentation

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Dear Editor:

Muslims develop prayer marks on the skin due to the practice of praying for long periods[1]. Sharma et al.[2] also called them the Naamaj sign. In the Muslim religion, praying requires four different positions, namely Waquf (standing), Ruku (bowing), Sajda (prostration), and Julus (sitting). The resulting prayer marks are mainly distributed on the forehead, elbows, knees, and ankles (Fig. 1A)[3]. In one reported case, the mark was on the nasal bridge[4]. During Sajda, the forehead repeatedly comes into contact with the ground (especially with the prayer rug). These repeated and long periods of friction leads to skin changes such as thickening, hyperpigmentation, and lichenification[1-4].

A 75-year-old man presented to our clinic with a 7-year history of vitiligo. His dermatological examination revealed multiple depigmented macules on the scalp. Also, a hyperpigmented macula was seen on the middle of the forehead and on both knees (Fig. 1B). The patient's history revealed that he has been praying 5 times a day for 50 years and that he developed the lesions 10 years ago.

In the study by Abanmi et al.[1] in 349 Muslims, prayer marks were noted to be more common in men than in women. Hyperpigmentation of the forehead was more frequent in men, and lichenification of the forehead was seen in only one man in their study. In this study, the common histological findings of the lesions were orthokeratosis, hypergranulosis, and dermal papillary fibrosis. In some cases, increased dermal capillaries lined with endothelial cells and cytoplasmic pigmentation were seen. Other reported histological changes were basal cell hyperpigmentation, hyperkeratosis, and acanthosis.

Cangiano et al.[3] published a case report in which prayer marks were associated with the worsening of an underlying chronic disease. Sharma et al.[2] also reported a case in which prayer marks appeared 2 months before an acute myocardial infarction. At the time of presentation, our patient did not

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