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Original Article

Efficacy of combination therapy of pimecrolimus 1% cream and mometasone cream with either agent alone in the treatment of childhood vitiligo

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Abstract

Objective To evaluate the efficacy of the combination therapy of mometasone and pimecrolimus in the treatment of vitiligo in children.

Methods In this double-blind randomized controlled trial, 50 patients were enrolled. Based on the planned treatment protocol, three lesions with approximately identical size at similar anatomic sites were selected in each patient. Lesions were divided to three groups: pimecrolimus cream 1 % (twice a day), mometasone furoate ointment 0.1 % (every night), and combined therapy group (pimecrolimus twice a day on weekdays and mometasone every night on weekends), all being applied for three months. They were followed up for three months.

Results Forty patients (with 46% of cases being male) with a mean age of 10.6 years completed the study. There was no significant difference in response rate between three groups at the end of the treatment.

Conclusion Our study results did not demonstrate significant difference in the response rate and adverse effects between combined treatment group and either alone.

Key words
Pimecrolimus, Mometasone; Vitiligo; Children

Introduction

Vitiligo is the most common pigmentary dermatologic disease caused by the destruction of melanocytes.[1-3] Different studies have reported a prevalence of 0.1-2% for this condition.[4] Although, pathogenesis of the vitiligo is not well-known exactly, but genetic predisposition, autoimmunity and neurological theories have been proposed.[5-8] Although vitiligo is not life-threating or symptomatic, it can alter the individual's quality of life and may lead to mental and psychological problem in childhood, and interfere with the treatment adherence process.[3]

Different treatment methods are in hand with different efficacy such as phototherapy (particularly narrow-band UVB), topical corticosteroids, topical calcineurin inhibitors, and surgery.[5] Treatment associated complications and recalcitrant lesions are among

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the most important limitations of the current used medication for vitiligo. So, searching for new treatments is always required.[8,9]

Although the topical steroids such as clobetasol have had positive therapeutic effects on pediatric vitiligo, their numerous side effects have limited their use.[10]

Considering the main possible role of humoral and cellular immune dysfunction in the pathogenesis of vitiligo, recently several studies have assessed calcineurin inhibitors (topical tacrolimus and pimecrolimus) as a safe and efficient therapy for vitiligo in children. Calcineurin inhibitors act as topical immunomodulators (TIM) by inhibiting the activity of T cells.[9,11]

A study compared the therapeutic effects of clobetasol and topical tacrolimus on vitiligo, reported the equal efficacy of both medications, while more complications were mentioned in those treated with clobetasol.[6] In another study, the therapeutic effects of mometasone with pimecrolimus were compared, both treatments led to nearly similarly decrease in size of vitiligo lesions.[9]

Due to the high cost of pimecrolimus and in order to achieve a more efficient treatment response, and to reduce the complications and duration of treatment, combination of pimecrolimus with other treatment methods such as phototherapy and excimer laser and microdermabrasion is recommended which in turn leads to less rate of relapse.[12]

According to studies showing that combining pimecrolimus and corticosteroid on a weekday/weekend basis enhances the therapeutic efficacy and reduced complications in skin diseases such as psoriasis,[13] we decided to evaluate the efficacy of the combination therapy of mometasone and pimecrolimus in the treatment of vitiligo in children.

Methods

This clinical trial was done during two years, in dermatology clinics and Afzalipour Hospital, Kerman, Iran. The study was approved by the Ethics Committee of Kerman University of Medical Sciences (approval code K/88/45) and also registered in *Australian New Zealand* Clinical Trials Registry (registration code ACTRN12611001165976).

The participants included were children with vitiligo between 2-18 years old, with washout period of three month. Exclusion criteria were patients with any other systemic or autoimmune diseases, history of allergy to pimecrolimus and macrolides, unstable vitiligo.

The calculated sample size for this study was 50 lesions in each group based on previous studies[14] (α=5%, β=20%, 60% response to pimecrolimus and clobetasol weekend/weekday treatment, and d=23% [the minimum value of difference between groups]). Participants were randomized based on the inclusion criteria by Mini Tab 16 software® (Mini Tab Inc.). Patients were diagnosed clinically and suspected cases were excluded from the study.

Written informed consent was obtained from all patients and for those under 12 years from their parents. Data were collected regarding the following variables: age, sex, location of lesions, duration of disease, mucosal involvement, leukotrichia, existence of koebner phenomenon, family history, prior treatment history, type of lesions (limited, extensive, etc.), existence of lesions on acral areas and bony prominences, size of the lesions, and type of repigmentation (follicular vs. diffuse). At the beginning of the therapy blood tests (CBC, urea, creatinine, ESR,

liver function tests [alanine and aspartate aminotransferase and alkaline phosphatase and bilirubin), and thyroid peroxidise autoantibody were checked.

In each patient, three lesions with approximately identical size at similar anatomic sites were selected. The lesions were divided into three treatment groups using the block randomization method. Topical pimecrolimus cream 1% (Novartis®, England) was applied to the first lesion twice daily, topical mometasone 0.1% ointment (Schering-Plough®, Istanbul-Turkey) was applied to the second lesion every night, and on the third lesion, topical pimecrolimus cream 1% was applied twice/daily for the weekdays and topical mometasone ointment 0.1% was used at nights for the weekends. Daily treatment was continued for 12 weeks. Patients were assessed at the end of each month for complications including itching, irritation, erythema, desquamation, atrophy, and telangiectasia.

Patients whose vitiligo changed to an unstable condition were excluded from the study. Response rate was assessed by measuring the size of the lesions in each visit. The lesions were checked for the follicular pigmentation at baseline, once a month until the end of the treatment period, and then once a month for three months after the end of the treatment protocol by an observer blinded to the treatment options, who was not involved in the study. The treatment response was divided into 6 categories: unfavorable response (an increase or <25% reduction in the size of the lesions), moderate response (25-49% reduction in the size of the lesions), acceptable response (50-74% reduction in the size of the lesions), excellent response (75-99% reduction in the size of the lesions), complete response (complete disappearance of the white lesion and replacement with pigmented skin), response without lesion size reduction (only with follicular repigmentation). The therapeutic response was considered as a 50% reduction in size of the lesion from baseline.

Data were analyzed using SPSS version 16. Appropriate descriptive, scatter plot and Chi-square tests were used to compare repigmentation percent in three groups. Test power was considered equal to 80% (P<0.05).

Results

Of fifty patients enrolled in the study, 40 (80%) completed the treatment period, because 10 individuals refused to continue the treatment protocol (they did not respond to the treatment). Mucosal involvement, leukotrichia, and Koebner phenomenon were not observed in any of the patients. All laboratory tests were within normal ranges in all patients and none of the patients had thyroid disorders. Demographic features of patients at baseline visit have been shown in **Table 1**. Patients were assessed in two different periods of time: the first 3 months (intervention period), and the second 3 months (follow-up period). The reduction in the size of the lesions over time was significant in each group (P<0.0001). Although reduction of size of the lesions was observed over the follow-up period, it was not significant (P=0.3), and there was no difference between the three treatment groups (**Figure 1**). **Table 2** shows the repigmentation of the lesions in the 3rd month of the treatment period and the 3rd month of follow-up. Follicular repigmentation in lesions treated with pimecrolimus, mometasone, and combination therapy in the 3rd month of treatment was 29.3%, 14% and 20%, respectively; and at the end of the treatment it was 8%, 10% and 16% respectively.

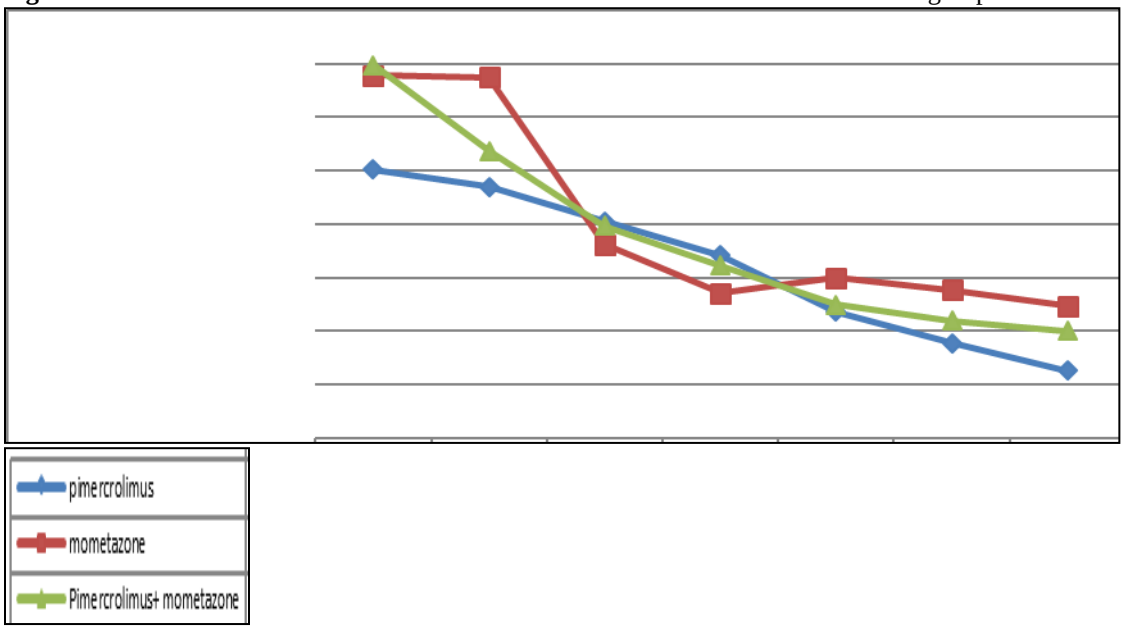
Table1 Demographic features of patients at baseline visit.

Variables		*N (%)*
Sex	Male	23(46)
	Female	27(54)
Previous history of treatment	Yes	29(58)
	No	21(42)
Family history	Yes	16(32)
	No	34(68)
Type of vitiligo	Generalize	9(18)
	Localize	36(72)
	Segmental	1(2)
	Acrofacial	3(6)
	Universal	1(2)
Site of involvement	Head & Neck	19(38)
	Trunk	12(24)
	Upper Limb	3(6)
	Lower limb	12 (24)
	Acral	4 (8)
Age (year)	Mean (SD)	10.6 (4.5)
Duration of disease (months)		18.8 (26.6)

Table 2 Repigmentation rate at the end of the treatment and follow-up.

Repigmentation rate	*3 months after treatment*			*3 months after follow-up*		
	Pimecrolimus	*Mometasone*	*Pimecrolimus + mometasone*	*Pimecrolimus*	*Mometasone*	*Pimecrolimus + mometasone*
	N (%)	*N (%)*	*N (%)*	*N (%)*	*N (%)*	*N (%)*
<25%	4 (10)	12 (30)	8 (20)	3 (7.5)	4 (10)	6 (15)
25%-49%	18 (45)	2 (5)	10 (25)	4 (10)	6 (15)	3 (7.5)
50%-74%	5 (12.5)	10 (25)	9 (22.5)	7 (17.5)	8 (20)	5 (12.5)
75%-99%	8 (20)	12 (30)	3 (7.5)	21 (52.5)	8 (20)	7 (17.5)
100%	5 (12.5)	4 (10)	10 (25)	5 (12.5)	14 (35)	19(47.5)

Figure 1 Mean size of the lesion in relation to duration of treatment in three treatment group.



Discussion

In our study, at the end of treatment there was no difference in the mean size of the lesions between the three treatment groups. However, the decrease in the size of the lesions was significant over time in each group.

In two studies,[8,14] the efficacy of pimecrolimus or tacrolimus was evaluated in comparison with clobetasol, and it was concluded that both drugs were as effective as clobetasol in reducing the size of lesions, while more complications were reported in those treated with clobetasol. In our study atrophy, telangiectasia and erythema were seen in 2 (10%) patients in the mometasone group and itching in 2 (10%) patients treated with pimecrolimus.

Silverberg and colleagues[15] found that tacrolimus was very effective in treating pediatric vitiligo particularly for lesions on the head and neck with treatment response of 89% over three months. Moreover, 63% of the patients with lesions on other sites responded to the treatment. In their trial tacrolimus had higher response rates in comparison with pimecrolimus in our study (45% at the end of the first period and 72.5% after 3 months follow-up).

In a study on the efficacy of pimecrolimus,[16] better response rate was seen in face area treated with pimecrolimus along with NB-UVB (64.3%), compared with NB-UVB alone (25.1%) and in other sites there was no meaningful difference between these two groups; however, we found no significant difference regarding the site of involvement.

In another study,[17] the researchers treated 40 patients with topical mometasone cream daily or topical pimecrolimus 1% cream twice daily. Both treatments reduced the size of lesions effectively, and there was no difference in treatment response between the two medications. At the end of the study, repigmentation rate was 65% and 42% in the mometasone group and pimecrolimus group respectively, which is relatively compatible with our results (65% and 45%, respectively at the end of the intervention period).

The combination of pimecrolimus with other therapeutic modalities has been evaluated in order to enhance and accelerate treatment response. Farajzadeh and colleagues[12] conducted a study on the efficacy of combination therapy of pimecrolimus and microdermabrasion in childhood vitiligo. Treatment response was observed in 60.4% of patients who received the combination therapy (pimecrolimus along with microdermabrasion), 32.1% receiving pimecrolimus only, and 1.7% treated with placebo. In our study, combination therapy of pimecrolimus with mometasone had higher response rate (77.5% in combined group, at the end of 3 months of follow-up) than the mentioned study. These differences may be attributed to the shorter treatment periods in their study as well as differences in sample size.

In other survey in Iran,[18] the efficacy of excimer laser with or without pimecrolimus was evaluated in the eyelid, and at the end of the treatment 78% of the patients receiving combined therapy achieved at least 75% repigmentation. Although this result was comparable to our results in the combined group, but in that study 100% of patients had acquired some degree of repigmentation in comparable with our survey it was 77.5% in combined group. This can be attributed to the greater absorption of pimecrolimus in the eyelid than other areas of treatment.

Topical calcineurin inhibitors including pimecrolimus and tacrolimus have immunomodulatory effects and inhibit T cell

activation and TNF-α production by T-cells that increase in vitiligo lesions. Furthermore, both tacrolimus and pimecrolimus lead to proliferation and migration of melanocytes and increase melanin biosynthesis due to activation of matrix metalloproteinase 9 and stem cell factors. These drugs also have the ability to decrease autoimmune-induced destruction of melanocytes due to their effects on TNF-α and downregulation of ICAM-1 in melanocytes and decreased attachment of lymphocytes to melanocytes. The addition of pimecrolimus to other treatments such as corticosteroids may improve the efficacy of pimecrolimus in modulating the immune response without increasing the associated side effects. Pimecrolimus can be a safe option for treating particular sites of the body such as facial and flexural, where other therapies may lead to adverse effects.[17,19]

The limitations of our study were the small sample size and short period of follow-up.

Conclusion

In our study, combination therapy had no advantage over treatment with each medication (pimecrolimus and mometasone) *per se*; although at the end of the study the number of the patients with complete treatment response (100% repigmentation) was higher in the group with using combination therapy. However, due to the limited number of the patients further studies with larger sample size are needed to evaluate the efficacy of this type of combination therapy. In our study increased treatment response trend continued in three months of follow-up. It can be concluded that some treatment modalities need some latency to show their maximum efficacy. So, we recommend increasing the wash out period from 1 month to 3 months.

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