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The Efficacy of Topical Immunomodulators in Treating Vitiligo

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Abstract
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Hypothesis: Topical Immunomodulators are an effective treatment for repigmentation of vitiligo patches.

Study Design: A systematic review of literature.

Methods: A literature search was performed using the National Library of Medicine (MEDLINE), EMBASE, CINAHL, International Pharmaceutical Abstracts, Current Contents, and search databases. Articles included those from 2006-2009, in English-language literature, that were human studies, and with the search term using the key word below.

Results: Out of forty eight articles were found in data base, only six articles have the criteria to be included in this review. The criteria were controlled trial, and using topical immunomodulators (tacrolimus and pimcrolimus) alone for treating vitiligo patches. All six articles are included in this review.

Conclusion: Topical immunomodulator ointment is an effective and well-tolerated therapy for vitiligo especially involving the head and neck. Larger placebo-controlled studies using calcinerurin inhibitors in combination therapy or alone are required to determine the exact role of these drugs in vitiligo treatment.

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A Clinical Graduate Project Submitted to the Faculty of the

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Biography

Mahkameh Mehdianrad is a native of Iran where she received her medical degree from Kerman Health and Sciences University. After completion of her degree, as a General Practitioner, she worked full time in variety of clinical and hospital positions, then continued her education as a Forensic Medicine, in Tehran University. Shortly after, she married and moved to Portland, Oregon. Then she selected to pursue Physician Assistant program due to her interests and similarity of prior experience as a General Practioner.

Abstract

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To *my beloved family*: Thank you for helping me to succeed and for supporting me when began to question why I was putting myself through this much work. The end is worth it.

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The Efficacy of Topical Immunomodulators in Treating Vitiligo

Introduction

Vitiligo is an acquired idiopathic hypomelanotic disorder characterized by circumscribed depigmented macules. Histologically, involved skin shows a loss of functional melanocytes and melanin within the epidermis. Vitiligo affects people of all races, with an incidence of 1–2% without gender predilection.[1] Vitiligo usually begins in childhood or young adulthood: approximately one-half of those with vitiligo, acquire the disease before the age 20.[2] The course of the disease is usually unpredictable, but it is often slowly progressive. In some patients the lesions may remain static, at other times vitiligo may progress rapidly. Depigmented patches may be present in a localized asymmetric form with a focal or segmental distribution or in a generalized symmetric form with an acrofacial, disseminated or universal distribution. [3] Although the disease is asymptomatic and does not adversely affect mortality and physical morbidity, depigmentation in visible area leads to severe cosmetic disfigurement and may be a source of considerable psychological distress.[4] Patients with vitiligo have numerous treatment options available to them, but not all patients respond to current treatment methods. Even among patients who respond to treatment there is a high potential for relapse. [5] The development of effective treatment for vitiligo is dependent on an understanding of the event leading to depigmentation. However, at present, pathogenesis of vitiligo is not fully understood. There are several hypotheses as to the pathogenesis of the disease, but not a single one is fully explanatory. [6] There was subtended research in this area prior to 2006 which yield some interesting results which appear in Tables 2 and 3. These studies were excluded for purposes of this review but may be useful background information.

Autoimmune hypothesis

Autoimmune hypothesis is one of the most important and popular. This hypothesis suggests that abnormality of the immune system results in destruction of melanocytes. Substantial new data implicate immune mechanisms in the pathogenesis of vitiligo and indicate that vitiligo may share common linkages with other autoimmune diseases. Historically, vitiligo has been reported in association with a number of autoimmune diseases. Thyroid disorders, in particular Hashimoto thyroiditis and Graves's disease, are most commonly associated with vitiligo. Other associated disorders include diabetes mellitus, alopecia areata, pernicious anemia, rheumatoid arthritis, autoimmune polyglandular syndrome, and psoriasis. The presence of antibodies on the surface, and cytoplasmic melanocyte antigens in the area of vitiligo on the patients, lends additional support to the autoimmune hypothesis. These antibodies can induce the destruction of melanocytes grown in culture by complement-mediated lyses and antibody-dependent cellular cytotoxicity. In addition, melanocyte antibodies, when passively administered to nude mice grafted with human skin, have a destructive effect on melanocytes within the skin graft. Recent studies have provided additional insights into the role of cell-mediated immunity in the destruction of melanocytes, suggesting that cytotoxic T lymphocytes may play a significant role in melanocyte destruction in vitiligo. [8]

Medical therapies for vitiligo

Vitiligo has been and remains a difficult disease to treat. Previously, therapeutic options have included administration of oral and topical psoralen photochemotherapy, topical steroids, and depigmentation therapies. At best, none of these treatment options have been optimal. [9] Study outcomes have varied considerably given differences in inclusion criteria and scoring systems used to assess repigmentation. Recently, a vitiligo Area Scoring Index was developed as a quantitative tool to evaluate vitiligo responses parametrically. [7] The scale is based on the degree of macular repigmentation within lesions over time and was validated against physician and patient global assessments. Additional studies will

be necessary to validate this scoring system. During the past six years, there have been several new advances in the treatment of vitiligo. These new treatment options include narrowband UV-B phototherapy, targeted light therapy, topical immunomodulators, and calcipotriol in combination with UV light.

Topical Immunomodulators

Topical Immunomodulators are novel therapeutic agents that act via immunologic pathways either to suppress or to enhance immune and inflammatory reaction in the skin. The inhibitory topical immunomodulators, tacrolimus and pimecrolimus, are used for treatment of vitiligo. The primary mechanism of action in these drugs for the treatment of vitiligo involves calcineurin inhibition (calcineurin inhibitors are drugs that were primarily developed for use in transplantation medicine), which leads to downregulation of antigen-specific T-cell reactivity and interruption of the transcription of genes for a range of proinflammatory cytokines important in the pathophysiology of the early immune response.[10] Additional mechanisms may include actions on other important cells in the pathophysiology of vitiligo such as dendritic cells, mast cells, keratinocytes, basophils and eosinophils. Unlike topical corticosteroids, these drugs do not interfere with collagen synthesis or induce skin atrophy. Tolerance for these drugs is good because there is minimal systemic absorption from the ointment; topical tacrolimus 0.03% or 0.1% is not associated with the adverse events that have been observed with the oral administration of the drug. Treatment with ointment was generally well tolerated in short-term (3- to 12-week) and long-term (12- and 24-month) clinical trials. Related adverse events were mostly associated with the application site (skin burning or pruritus), were mild or moderate and tended to diminish during the first week of, or early in, treatment as the lesions healed. [11]

Methods

A literature search was performed using the National Library of Medicine (MEDLINE), EMBASE, CINAHL, International Pharmaceutical Abstracts, Current Contents, and Search databases from 2006-

2009 , English-language literature, Human study, with the search term using the key word “Vitiligo”, “Pimecrolimus”, “Tacrolimus”, “monotherapy”. Articles reporting the use of pimecrolimus or tacrolimus, monotherapy for treating vitiligo in all ages were reviewed. Selected studies comprised randomized, vehicle-controlled trials, and pilot studies of topical pimecrolimus and tacrolimus for treating vitiligo.

Results

Six studies were found which included in this review. These studies were presented based on the recent publish year.

The first study was conducted by Ai.-E Xu Department of Dermatology Third Hospital of Hangzhou Hangzhou China, (2009). [12] They sought to assess the efficacy of topical tacrolimus ointment in the treatment of vitiligo. This prospective pilot study was performed of 30 patients with vitiligo. Patients were treated with tacrolimus ointment for at least four months. Clinical responses were documented during clinic visits, and by pretacrolimus and post-tacrolimus photography. Twenty five (83.3%) patients showed some repigmentation at the end of 4 months. Patients with vitiligo for more than five years also responded well to tacrolimus ointment. Repigmentation in active vitiligo was superior to that in stable vitiligo. 80% of patients with segmental vitiligo of the head and neck showed some response to tacrolimus, but there was no statistical significance between segmental and vulgaris vitiligo. The mean percentage of repigmentation on the head and neck was greater than that on the trunk and extremities. Four patients initially experienced burning on application. The study concluded that topical tacrolimus ointment is an effective and well-tolerated alternative therapy for vitiligo especially involving the head and neck area.

The second study was done by Hartmann A. Department of Dermatology University of Wurzburg, Germany. [13] They evaluated efficacy of tacrolimus 0.1% ointment in adult patients with vitiligo in a placebo-controlled 12-month prospective study. They appraised the placebo-controlled application of

tacrolimus 1% ointment for up to 12 months in 30 adult patients with vitiligo. By the end of the treatment, 17 of the 21 patients with facial lesions (81%) showed repigmentation on the face and neck areas (a mean response of 79.4% of surface area). On the extremities, there was almost no effect when applying tacrolimus ointment without dressing. However, when using polyurethane foil or hydrocolloid dressing for overnight occlusive treatment, moderate to excellent repigmentation could be achieved. In discussion, they showed for the first time that occlusion therapy can enhance the effect of topical tacrolimus therapy in vitiligo.

The third study was conducted by Beom Joon Kim, M.D., Department of Dermatology, Chung-Ang University, Seoul, Korea. [14] They reviewed the treatment of vitiligo with topical immunomodulators and topical steroids, to evaluate the efficacy of immunomodulators in treatment of vitiligo. They reviewed 52 patients treated with topical immunomodulators and 27 patients with topical steroids. A total of 79 patients were recruited; 38 men and 41 women. The mean age of the 79 patients was 37 years (range, 2–76). The mean disease duration was 58.8 months (range, 1 month–40 years). Fifty-nine patients had lesions on the face, and 53 and 23 patients had lesions on the hand and foot, respectively. Fifty-two patients were treated with topical immunomodulators (51 patients were treated with tacrolimus ointment, one with pimecrolimus cream) and 27 patients were treated with steroids (23 patients used a class III topical steroid and four patients were treated with intralesional steroid injections). Between gender, mean age, mean disease duration and distribution of lesions, they could not find any significant differences in either group. Seventy-nine patients were also divided into three groups according to the location of vitiligo lesions. Fifty-nine patients had lesions on the face, and 53 and 23 patients had lesions on the hand and foot, respectively; 38 patients showed repigmentation on the face, 31 on the hands and nine on the foot. However, they could not find any statistically significant differences in the ratio of lesions which showed response among these three groups. Between the two treatments, the duration from the start of treatment to onset of repigmentation was

significantly shorter in the topical immunomodulator group (P = 0.002). However, no statistically significant differences were found in gender, age, and mean disease duration, sites of vitiligo lesion and ratio of patients who showed response. They suggested topical immunomodulator as an alternative to topical steroids for treatment of vitiligo.

The fourth study was been done by N. Sendur, Department of Dermatology, Faculty of Medicine, Adnan Menderes University, Turkey.[15] The purpose of their study was to assess the efficacy of pimecrolimus cream 1% in vitiligo and to evaluate the effects of age at the patients, age of onset and duration of disease on response rate. Twenty-three patients with vitiligo were enrolled in their study; 19 patients (seven male, 12 female) completed the six-month study period.Patients were treated with topical pimecrolimus 1% cream once daily. The response was evaluated as excellent (76–100%), moderate (51–75%), mild (26–50%), minimal (1–25%), or no response. The mean age of the 19 patients was 29.3 (range 7–62 years) and the mean duration of vitiligo was 68.4 months. Three patients demonstrated an excellent response to the therapy. Four patients had moderate, six patients had mild and five patients had minimal responses; one patient had no response to the treatment. Side effects were noted as a burning and stinging sensation in only three patients. The correlations between response rate and duration of the disease (r=0.02, p=0.95), onset age (r=-0.17, p=0.48), and age of the patients (r=-0.16, p=0.53) were not significant. In conclusion, they found Pimecrolimus has a mild therapeutic effect on vitiligo without significant side effects and can be an alternative therapy agent.

The fifth study was conducted by Klaus Wolff, MD, FRCP Department of Dermatology Medical University of Vienna, Austria. [16] They performed a double-blinded, intrapatient comparison of pimecrolimus cream 1% with placebo cream. They recruited twenty adult Caucasians with symmetrical vitiligo predominantly on their extremities, none on the face and treated them twice a day for six months left/right with pimecrolimus/vehicle (N = 10) or vehicle/pimecrolimus (N = 10),

respectively. Primary efficacy endpoint was the size of the target lesion at month six and secondary efficacy endpoint was re-pigmentation. The treatment with pimecrolimus cream 1% or vehicle resulted in no significant change in the mean target lesion size. Modest repigmentation (1–25%) was noted with pimecrolimus at month 2 in 12 of 17 patients (vehicle: 9 of 17 patients). Afterwards, the number of patients who experienced an improvement of pigmentation steadily decreased (3 of 14 patients with pimecrolimus and 2 of 14 with placebo at month 6).Treatment was well tolerated. There were no treatment-related adverse events, no induction of skin atrophy nor any other application site side effects. In this group of adult patients with symmetrical vitiligo, treatment of body lesions (except the face) with pimecrolimus cream 1% could not be shown to be effective.

The sixth study has been done by Boone B. Institution Department of Dermatology, University Hospital of Ghent, Belgium. [17] They performed an open pilot study in 26 patients to evaluate the efficacy and safety of 1% pimecrolimus in the treatment of vitiligo lesions in the head and neck region. In 13 of 26 (50%) evaluated target lesions, repigmentation was noted after a six month treatment period with a median percentage of repigmentation of 72.9% (interquartile range: 30.5-98.3%). The duration of vitiligo and the total affected body surface area tended to be inversely correlated with the success rate of treatment. Side effects were mainly limited to a burning sensation at the application site.

Discussion

In this systemic review study, recent trials (2006-2009) on monotherapy of vitiligo with topical immunomodlators such as tacrolimus (Protopic) or pimcrolimus (Elidel) were reviewed. Each of the studies examined a different area or population based on their specified study, so no comparison between studies can be made and also, each study has strong and negative points which are discussed separately below.

The first study was a prospective pilot study of response to treatment with tacrolimus ointment in 30 vitiligo patients. The mean age of the 30 patients was 22.3 ± 7.8 years (range 7–40 years). Forty target lesions were selected on which to apply 0.1% ointment twice a day. The majority of the 25 patients used tacrolimus ointment to treat only involvement of the head and neck; two patients used the tacrolimus ointment to treat vitiliginous sites only on the trunk and/or extremities, and three patients applied the tacrolimus ointment for involvement both of head/neck and body/extremities. Twenty-five (83.3%) patients showed some repigmentation at the end of four months and the other five patients had showed no response. Although this is a good study it has some draw backs. The number of patients was small and the duration of treatment was only four months, so definite conclusion cannot be made. Clinical studies usually define a successful treatment as when more than 75% repigmentation has been achieved and in this study it is not clear what percent reach the point of successful treatment. The other issue is number of lesions treated with tacrolimus on the trunk; face and neck were not equal. From forty lesions, 25 patient lesions were located in head and neck area and fewer lesions were treated in the extremities or trunk.

The second study was a prospective placebo-controlled right-left comparison study. They investigating the efficacy and safety of tacrolimus 0.1% ointment twice a day for up to 12 months in 30 adult patients aged between 19 and 65, with vitiligo and also tested the influence of additional occlusive treatment. By the end of treatment, 17 of the 21 patients with facial lesions (81%) showed repigmentation on the face and neck areas .On the extremities there was almost no effect when applying tacrolimus ointment openly. However, when they used polyurethane foil or hydrocolloid dressing for overnight occlusive treatment moderate to excellent regimentation occurred. Based on the therapeutic appraisal form in placebo-right and left comparison, this study is validated. Unfortunately, this study is not blind study so patient knowledge can cause bias. The number of patients was small, so definite statics cannot be obtained. A weakness in this study is that since the age range in those tested was 19-65, hell of the population at risk for vetiligo, those under 19 were ignored.

In the third study, a retrospective review, 52 patients were treated with topical immunomodulators for six months and 27 patients with topical steroids, to evaluate the efficacy, of topical immunomuodulators compare to topical steroid in treatment of vitiligo. Between the two groups, the duration from the start of treatment to onset of repigmentation was significantly shorter in the topical immunomodulator group (P = 0.002). However, no statistically significant differences were found in as to gender, age, and mean disease duration, sites of vitiligo lesion and ratio of patients who showed response. So at six month the result would look alike applying topical immunomodulators or topical steroids for more than six months without repigmentation was considered treatment failure. Their results showed that topical immunomodulators are as effective as topical steroids in repigmentation. This study has a lot of drawbacks; first, they didn't measure the repigmentaion as mild, moderate or excellent and used no measurement scale for repigmentation. They could not unify topical immunomodulators and topical steroids, and they could not review side-effects of treatment. Moreover, they evaluated efficacy only by repigmentation of vitiligo lesions; they could not evaluate the area of repigmentation. Despite these limitations, on the basis of their study, they may suggest topical immunomodulators as an alternative for treating vitiligo.

The fourth study is prospective a review; the purpose of this study was to assess the efficacy of pimecrolimus cream 1% in vitiligo and to evaluate the effects of age of the patients, age at onset and duration of disease, on response rate. Twenty-three patients with vitiligo were enrolled in their study; 19 patients completed the six-month study period. Patients were treated with topical pimecrolimus 1% cream once daily. They found that pimecrolimus has a mild therapeutic effect on vitiligo without significant side effects and can be an alternative therapy for treating vitiligo and there were no significant correlations between response rate and duration of the disease (r=0.02, p=0.95), age at onset of the disease (r=20.17, p=0.48), nor age of the patients (r=20.16, p=0.53). This study has a lot of

limitation; first, the number of patients was small, so absolute conclusion cannot be drawn. The limited number of patients for clinical type as of vitiligo was the main limitation of their study. It restricted the comparison rates for each clinical type the efficacy of therapy alternatives is variable in vitiligo and mostly depends on the clinical type of the disease which was unspecified. The therapeutic response is known to be poor in segmental and acrofacial forms. They also had four who patients were lost to follow-up which is quite damaging in such a small study; furthermore no clear explanation of their loss is given.

In the fifth study which is a randomized, double blinded, vehicle-controlled study; the purpose of the study was to assess the efficacy of pimecrolimus cream 1 % in adult patient with vitiligo. Twenty adults with symmetrical vitiligo (predominantly on extremities, none on the face) were treated twice a day for six months left/right comparison with pimecrolimus/vehicle (N = 10) or vehicle/pimecrolimus (N = 10), respectively. Primary efficacy endpoint was the size of the target lesion at month six and secondary efficacy endpoint was repigmentation. They found that in this group of adult patients with symmetrical vitiligo, treatment of lesions on the body (except face) with pimecrolimus cream 1% could not be shown to be effective, although there were no treatment-related adverse events, no induction of skin atrophy nor any application site side effects. This study as with the others has drawbacks. The number of patient was small, so definite statics cannot be made. Also, four of the 20 patient didn't complete the treatment. Pimecrolimus cream 1% is known to be highly effective in children and infants with atopic dermatitis with superior results in lesions on the face and neck as compared to lesions on the total body surface [18-20]. The comparably poor effect on pigmentation observed with pimecrolimus in the present study might, therefore, be explained by the fact that it was conducted in adult patients and that almost all lesions treated were localized on the extremities with 9/20 on the back of the hands. It is likely therefore, that, this study is neither representative true of the affected actual population nor the site of the vitiligo.

The last study was an open pilot study in 26 patients to evaluate the efficacy and safety of 1% pimecrolimus in the treatment of vitiligo lesions in the head and neck region. Subsequently, the percentage of area reduction or repigmentation in the reference lesion during the trial was calculated. This percentage of repigmentation was the main parameter to measure treatment efficacy. Changes in pigmentation were evaluated with a Wilcoxon Ranked Sign test with a p-value less than 0.05 indicating statistical significance. Clinical assessment revealed repigmentation of the target lesion on the face or neck in 38.5% of patients after three months and in 50.0% of patients after six months. Objective measurement of the target lesion showed a median relative area reduction of 26.2% and 72.9% after three and six months respectively. They suggest that using pimecolimus for vitiligo on the head and neck is promising shows results but, due to the small sample size of the pilot study no statistically significant predictors of response rate could be identified. However, some tendencies were noted. Duration of vitiligo and total affected body surface area influenced treatment outcome. The shorter the duration of vitiligo and the smaller the total affected body surface area, the better the probability of repigmentation.

A summary of reviewed studies is appears in Table 1 and also a summary of case reports and clinical studies on tacrolimus and pimcrolimus in the treatment of vitiligo before 2006 is in table 2-3. In general data from case reports and pilot studies investigating the use of topical calcineurin inhibitors in the treatment of vitiligo are promising.

Conclusion

Substantial strides have been made in uncovering of the pathogenesis of vitiligo in pursing an effective treatment. New, more effective therapies provide renewed hope for patients affected by this disease. Until now, many therapies have been used to treat vitiligo; topical and oral steroids, topical and oral psoralen photochemotherapy, narrow-band and broad-band ultraviolet-B, calcipotriol, tar and vitamins/antioxidants. Despite many kinds of therapies, none are satisfactory completly. After Grimes et al and others [21, 22] reported repigmentation induced by tacrolimus in patients with vitiligo, topical immunomodulators were widely used to treat it. Moreover, the lack of atrophogenic potential and lack of risk of induction of ocular cataracts or glaucoma with topical immunomodulators make these new topical agents appropriate agents for treating vitiligo of children and face or neck lesions or adult vitiligo patients. Also, topical immunomodulators induced faster repigmentation than steroids, and this could be an advantage over steroids in treatment of vitiligo. The size of the studies looked at in this review was so small as to render their conclusions unreliable. The sample size will be the key to future, successful studies. Each of the studies examined a different area or population and made tentative finding based on their specified study. If all of the parameters were combined a conclusive, valid study may result. While this is a condition which has mostly psychological repercussions for those suffering from outbreaks, it is still vital to address what might be a relatively simple and cost effective solution. Larger placebo-controlled studies using calcinerurin inhibitors in combination therapy or alone are required to determine the exact role of these drugs in vitiligo treatment.

Table 1: Summary of Review Studies

Author/ Title/ Journal	Yr. published	Patients / Population	Intervention	Comparison	Outcome(s)	Study type	Validity (Jadad score)	Comments/ result
Ai-E.Xu/Efficacy and safety of tacrolimus cream 0.1% in the treatment of vitiligo/International Journal of Dermatology	2009	30 Pt	Using Topical tacrolimus 0.1% for four months	None	repigmentation	Prospective pilot study	Zero	Study one/ 83.3% Pt repigmentation after four months on head and neck
Anke Hartmann/Occlusive Treatment Enhances Efficacy of Tacrolimus 0.1% Ointment in Adult Patient With Vitiligo: results of a Placebo controlled prospective study/Acta Derm Venereol 88	2008	30 Pt	Using Topical tacrolimus 0.1% for 12 months	Not using tacrolimus	repigmentation	Prospective Placebo-controlled Right and left camparison study	zero	Study two/ 81% Pt showed repigmentation after 12 months in facial and neck area, no effect on the extremities lesion
Beom Joon Kim, M.D., Topical immunomodulators are effective for treatment of vitiligo/The journal of dermatology,volume35,issue8	2008	52 Pt	Using topical immunomoduator for six months	compare to steroid therapy	repigmentation	A retrospective review	zero	Study three/ topical immunomodulator are as effective as topical steroids in repigmentation
Markus dawid/Efficay and safety of pimercrolimus cream 1% in adult patient with vitiligo: Results of randomized double-blind, vehicle-controlled study/JDDG	2006	23 Pt	pimercrolimus cream 1% for six months	none	repegmentation	Prospective study	Zero	Study four//68.5% Pt achieved mild to moderate repigmentation in focal vitiligo
Neslihan Sender/Topical pimecrolimus: A new horizon for vitiligo treatment/Journal of Dermatological Treatment	2006	20 Pt	pimercrolimus cream 1% for six months	Placebo cream	repigmentation	Double-blind-intra patient	2	Study five/no effect showed on symmetrical vitiligo lesion in body
Barbara BOONE /Topical pimecrolimus in the treatment of vitiligo/Eur J Dermatol 2007; 17 (1): 55-61 EJD, vol.	2007	26 Pt	Pimcrolumus cream 1% for six months	none	repigmentation	Open pilot study	Zero	Study six/ 50% Pt showed moderate repigmentation in face and neck area

Table 2: Case reports and clinical studies on tacrolimus in the treatment of vitiligo [23]

			Tacrolimus				
Reference	**Study Design**	**Number of Patients**	**Study Duration**	**Treatment Regimen**	**Materials and Methods**	**Results**	**Adverse Effects**
Mehrabi D [42] 2006	Randomized, placebecontrolled , double-blind trial	9	12 weeks	0.1% tacrolimus + UVB vs. placebo + UVB	2 paired vitiligo patches, digital photography, computerized area measurement	No statistically significant difference	Redness, pruritus, burning (most likely related to light therapy)
Ostovari N [43] 2006	Comparative prospective, non blind, pilot study	9	12 weeks	0.1% tacrolimus + UVB vs. 0.1% tacrolimus	2 paired vitiligo patches,digital photography, 6-point scale for grading repigmentation by 2 investigators	No repigmentation with tacrolimus monotheraphy	Erythema (most likely related to light therapy)
Almeida P [44] 2005	Open pilot study	12	8 months	0.1% tacrolimus twice daily	Digital photography, 3-point, scale tor grading repigmentation	Good to excellent repigmentation in 50% of patients	Pruritus at initial application
Kanwar AJ [45] 2004	Open pilot study	12 children	12 weeks	0.03% tacrolimus twice daily	Digital photography, serial mapping of body lesions, 3-point, scale tor grading repigmentation	Complete repigmentation in 57.9% of patients, best results in face and hear bearing sites	Pruritus and burning
Silverberg N [46] 2004	Retrospective review	57 children	3 months	0.03% or 0.1% tacrolimus once or twice daily	Digital photography, 3- points scale for grading repigmentation	At least partial repigmentation in 84% of patients, best results in head and region	Burning at initial application
Passeron T [17] 2004	Comparative, prospective, randomized, intra-individual study	14	12 weeks	0.1% tacrolimus + excimer laser vs. excimer laser	2 to 5 paired lesions, digital photography, 6- points scale for grading repigmentation	Combination therapy is superior to excimer laser mootheraphy	Erythema, bullae (most likely related to light therapy)

Table 2: Case reports and clinical studies on tacrolimus in the treatment of vitiligo [23] Continue:

Reference	Study Design	Number of Patients	Study Duration	Treatment Regimen	Materials and Methods	Results	Adverse Effects
Kawalek A [18] 2004	Prospective, doubleblind, plaeebocontrolled study	8	10 weeks	0.1% tacrolimus + excimer laser vs. placebo + excimer laser	24-symmetric patches,photography, 4-point scale forgrading repigmentation	Significantly greater degree ofrepigmentation when treatmentwith combination therapy	Excimer: erythema, blisteringTacrolimus: tingling, burning,erythema
Grimes P [10] 2004	Open prospective study	23	24 weeks	0.1% tacrolimus twice daily	6-points disease severity scale	Varying levels in 89% of patients, best result head and neck region	Burning, stinging, pruritus, verruca vulgaris
Lepe V [14] 2003	Randomized, double-blind, comparative trial	20 children	2 months	0.1% tacrolimus vs. 0.05% clobetasol propionate	2-symmetrical lesions, color slides, morphometric digitalized computer program	Tacrolimus almost as effective as clobetasol propionate	Clohetasol propionate: atrophy, telangiectasia Tacrolimus: burning
Travis L [47] 2003	Case report	3	2 - 4 moths	0.1% tacrolimus twice daily	Lesions on face and eyelids	Complete repigmentation in 100% of patients	None
Castanedo-Cazares [48] 2003	Case report	1	4 months	0.1% tacrolimus + UV-B	Lesions on face	Percentage of repigmentation area: 95%	Not mentioned
Tanghetti E [49] 2003	Open pilot study	15	1.5 - 9.5 months	0.1% tacrolimus twice daily [+ sunlight exposition in some pateints]	4-points scale for grading overall repigmentation	At least partial repigmentation in 87% of patients	None
Grimes P[50] 2002	Open pilot study	6	1 - 5 months	0.03% or 0.1% tacrolimus twice daily	Application on all vitiliginous lesions, 4-points scale for grading overall repigmentation	Moderate lo excellent repigmentation in 83% of patients	Burning and stinging at initial application, tinea corporis
Smith D P[51] 2002	Case report	1	18 months	0.1% tacrolimus twice daily	Lesions on face	90% repigmentation in face and scalp region	Not mentioned

Table 3: Case reports and clinical studies on pimecrolimus in the treatment of vitiligo [19]

			Pimecrolimus				
Reference	**Study Design**	**Number of Patients**	**Study Duration**	**Treatment Regimen**	**Materials and Methods**	**Results**	**Adverse Effects**
Coskun B [16] 2005	Comparative prospective, non-blind trial	10	2 months	1% Pimecrolimus vs. 0.04% Clobetasol propionate	2-paired vitiligo patches, digital photography, 4-points scale for grading repigmentation	Comparable rate of repigmentation	Clobetasol propionate: telangiectasia, atrophy Pimecrolimus: burning
Mayoral F[15] 2003	Case report	1	5 months	1% Pimecrolimus	Lessions on the face, scalp, trunk (+atopic dermatitis)	Percentage of repigmentation: >90%	None

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