

# We are IntechOpen, the world's leading publisher of Open Access books Built by scientists, for scientists

**4,800**

Open access books available

**122,000**

International authors and editors

**135M**

Downloads

Our authors are among the

**154**

Countries delivered to

**TOP 1%**

most cited scientists

**12.2%**

Contributors from top 500 universities



**WEB OF SCIENCE™**

Selection of our books indexed in the Book Citation Index  
in Web of Science™ Core Collection (BKCI)

Interested in publishing with us?  
Contact [book.department@intechopen.com](mailto:book.department@intechopen.com)

Numbers displayed above are based on latest data collected.

For more information visit [www.intechopen.com](http://www.intechopen.com)



## Topical Calcineurin Inhibitors in the Treatment of Vitiligo

Cristina Caridi, Andrew Sohn and Rita V. Patel  
*Department of Dermatology, Mount Sinai School of Medicine, New York  
USA*

### 1. Introduction

Vitiligo is the most common depigmenting disorder, with a prevalence of approximately 0.5% in the world population. Almost half of the patients with vitiligo present before 20 years of age. The two sexes are affected equally, and there are no apparent differences according to skin type or race.<sup>1,2</sup> On histology, vitiligo is identified by the loss of epidermal melanocytes with absence of inflammation.

Commonly used repigmentation therapies whose efficacy is supported by data from randomized controlled trials include ultraviolet light (for whole body or targeted lesions) and topical agents (corticosteroids and calcineurin inhibitors). Narrow-band ultraviolet B radiation (NB-UVB), which delivers peak emission at 311nm, is currently the preferred treatment for adults and children with vitiligo. Topical therapies may be effective in cases of localized disease. Combination therapy is often considered when there has been no response to phototherapy alone after three months or when the goal is to accelerate the response and reduce cumulative exposure to UV light.<sup>3</sup> This chapter will review the literature on the topical use of pimecrolimus and tacrolimus in the treatment of vitiligo alone as well as when combined with other common therapies.

### 2. Pimecrolimus

Topical calcineurin inhibitors have shown promise in the repigmentation of affected areas in patients with vitiligo without causing the adverse effect profile associated with other common treatments for this disease.<sup>4</sup> Pimecrolimus has been approved for the treatment of atopic dermatitis and has shown a very low incidence of side effects. In comparison, corticosteroids can cause thinning of the skin as well as epidermal atrophy at the application site, and PUVA has an associated skin cancer risk.<sup>5</sup> Thus far, pimecrolimus has shown a very low incidence of mild, temporary adverse effects including erythema and irritation at the application site,<sup>6</sup> which makes this modality a safe treatment option. It appears that pimecrolimus may offer a considerable advantage in cases where the side effects of other therapies are of greater concern as in vitiligo occurring in pediatric patients or disease affecting facial, intertriginous, and genital regions, as neither epidermal atrophy nor telangiectasia are major concerns.<sup>2</sup>

There are several hypotheses about the pathogenesis of vitiligo, but there is increased evidence of an auto-immune mechanism involving both humoral and cellular immunity.

This has been supported by the frequent detection of circulating auto-antibodies, cytoplasmic antigens of melanocytes, and activated T-cells in the periphery of actively progressing lesions in vitiligo patients.<sup>7</sup> An analysis of 19 vitiligo patients for 24 weeks showed that, at baseline, patients expressed a significant increase in the expression of interferon- $\gamma$ , tumor necrosis factor alpha (TNF- $\alpha$ ) expression, and IL-10 in involved and uninvolved skin as compared to healthy patients. After treatment, TNF- $\alpha$  expression decreased in involved and adjacent uninvolved skin, illustrating a relationship between cytokine imbalance and the depigmentation process of vitiligo.<sup>8</sup>

Pimecrolimus inhibits the production of T-cells and prevents mast cells from releasing pro-inflammatory mediators.<sup>9</sup> The structure of pimecrolimus has higher lipophilicity than that of tacrolimus and binds to macrophilin 12 with high affinity.<sup>10</sup> This complex inhibits calcineurin resulting in the suppression of pro-inflammatory cytokine<sup>1</sup> secretion by activated T-cells, specifically that of interferon- $\gamma$ , IL-1, IL-2, IL-3, IL-4, IL-5, GM-CSF, and TNF- $\alpha$ <sup>11,12</sup> which are believed to be responsible for the damage to melanocytes that results in vitiligo. *In vitro* research on the effect of calcineurin inhibitors on melanocytes affected by vitiligo may further support the hypothesis that the pathogenesis of vitiligo involves an auto-immune response as well as autocytotoxic components. It has been observed *in vitro* that the interaction between calcineurin inhibitors and keratinocytes induces the release of stem cell factor and enhancing matrix metalloproteinase-9 activity, allowing melanocytes to grow.<sup>13</sup>

A study evaluating the efficacy of topical 0.05% clobetasol propionate versus 1% pimecrolimus ointment indicated that pimecrolimus is just as effective as clobetasol propionate in repigmenting skin without producing the side effects that often result in the discontinuation of steroid treatment. The study group included 10 patients ranging in age from 12-66 years old with generalized vitiligo ranging in duration from two to 40 years. Affected regions varied from extremities, trunk, or acral regions. There was no statistically significant difference in the degree of repigmentation resulting from pimecrolimus versus clobetasol propionate, but atrophy and telangiectasia were reported in the clobetasol propionate treatment group, indicating that pimecrolimus has a more favorable safety profile than clobetasol. Two patients being treated with pimecrolimus reported experiencing a mild burning sensation that was not severe enough to result in the discontinuation of treatment.<sup>14</sup> Topical corticosteroids are indicated in the treatment of vitiligo and have been a common treatment for approximately 30 years.<sup>15</sup> Recurrence of symptoms of vitiligo and the relatively high incidence of adverse effects including atrophy, telangiectasia, striae, and contact dermatitis are limiting factors particularly for children and sensitive areas of the skin.<sup>10,16</sup>

Because of the low-toxicity of pimecrolimus, it may be a treatment of particular interest in more sensitive areas affected by vitiligo such as the periocular and genital regions and in pediatric patients. In a case study conducted by Leite et al.<sup>7</sup> an eight-year old patient showed near-complete remission of symptoms of vitiligo in the periocular area after four months of treatment and with no relapse one year thereafter. In another case study presented in Leite et. al. study, an eleven-year-old boy achieved almost complete repigmentation of all vitiligo lesions in the genital region after three months of treatment. Both patients showed good tolerability to the treatment regimen indicating that pimecrolimus may be a safer option for the skin of children and adolescents whose skin shows greater predilection for local side-effects.<sup>7</sup>

In a study conducted by Mayoral et al., eight adults presenting with facial vitiligo were treated with pimecrolimus 1% cream twice a day for at least three months. The average length of the study was eleven months from baseline to the final follow-up visit. Patients showed a statistically significant response, averaging 72.5% improvement in pigmentation of the facial region. Every patient showed a response to study treatment regardless of length of disease, extent of disease, or previous treatment regimen, including patients who had not responded to previous therapies including PUVA and Melagenina®. It was observed that the greatest improvement in surface area correlated with the longest duration of disease at baseline and had no significant association with longer treatment duration. Treatment was well tolerated.<sup>8</sup>

The combination of pimecrolimus with other common treatment modalities for vitiligo has been studied to determine whether the degree of response to treatment could be improved or the response time could be accelerated. Esfandiarpour et al. conducted a double-blind, placebo-controlled study to determine the efficacy of pimecrolimus 1% cream combined with NB-UVB in the treatment of vitiligo.<sup>1</sup> NB-UVB has been recently introduced as a similar, safer treatment option than PUVA. Although these photochemotherapy (NB-UVB and PUVA) do have some local immunomodulatory effects, these treatment methods are effective most likely because of the stimulation of melanocyte proliferation.<sup>17,18</sup> It was hypothesized that the addition of pimecrolimus 1% cream to treatment with NB-UVB would better address the autoimmune components of the disease. In this study, 68 patients were randomized into one of two groups: NB-UVB plus pimecrolimus 1% cream or NB-UVB plus placebo for three months. After 12 weeks of treatment, statistically significant repigmentation occurred in more than 50% of facial lesions in 64.3% of patients in the group that received NB-UVB plus pimecrolimus 1% versus 25.1% of patients in the group that received NB-UVB plus placebo. There was no significant difference in the repigmentation rate of other body areas between the two groups.<sup>1</sup>

Another study explored the addition of microdermabrasion in the treatment of nonsegmental vitiligo in children with pimecrolimus 1% cream. It is believed that microdermabrasion may modulate the immune response and autoinoculation of melanocytes as well as enhance the absorption of topical immunomodulators through the inflammation and erosion of the skin. The purpose of this study was to determine if microdermabrasion would be effective in enhancing the efficacy and decreasing the treatment time. Results indicated a positive response to treatment, as 60.4% of lesions treated by combined therapy showed a clinical response, with 43.4% of lesions treated by combined therapy showing complete repigmentation after a three month treatment period, compared with 32.1% repigmentation of lesions treated with pimecrolimus alone, and 1.7% for placebo.<sup>19</sup>

### 3. Tacrolimus

Topical tacrolimus is a potential therapeutic option for the management of vitiligo. Despite this drug's clinical efficacy, the underlying mechanism of topical tacrolimus in the management of vitiligo is not well understood and has been rarely studied. Tacrolimus is a non-steroidal anti-inflammatory agent used in the treatment and management of many skin disorders and was initially formulated for atopic dermatitis. Similarly to pimecrolimus, tacrolimus exerts its therapeutic effects by targeting and inhibiting calcineurin in the skin, which regulates T-cell division and activation, and in turn inhibits

pro-inflammatory cytokines.<sup>20</sup> Systemically administered tacrolimus is an effective immunosuppressant that is used as an anti-rejection agent in organ transplantation, and due to its effective immunosuppression, systemic tacrolimus increases the risk for skin cancer.<sup>21</sup> Topical tacrolimus, however, has not been associated with systemic immunosuppression or increased risk for malignancies in long-term clinical research.<sup>22,23,24</sup> The avoidance of natural and/or artificial light during tacrolimus therapy and application of sunscreen daily is advised.

Multiple studies have documented the stimulatory effects of UV light on melanogenesis and melanocyte proliferation.<sup>25,26</sup> The therapeutic effects of psoralen photochemotherapy and phototherapy with NB-UVB for the repigmentation of vitiliginous skin have also been documented.<sup>27,28</sup> The suppression of pro-inflammatory cytokines via tacrolimus may facilitate the stimulatory effects of ultraviolet light on the repigmentation of vitiliginous skin. Evidence suggests a suppression of TNF- $\alpha$  after application of tacrolimus, which may play a role in repigmentation.<sup>21</sup> TNF- $\alpha$  has been shown to inhibit melanocyte proliferation and melanogenesis, which has allowed for speculation that epidermal cytokines may be a part of a negative feedback that negates the stimulus of melanocytes.<sup>29</sup> Additionally, a number of cytokines, including TNF- $\alpha$  are shown to up-regulate the expression of intercellular adhesion molecule-1 (ICAM-1) on melanocytes, which may trigger a lymphocyte-melanocyte attachment and play a role in the destruction of melanocytes.<sup>30,31</sup> Because tacrolimus inhibits T-cells and therefore cytokines, including TNF- $\alpha$ , tacrolimus may help prevent the aforementioned negative feedback loop as well as the expression of ICAM-1 on melanocytes.

Studies have shown that topical corticosteroids and topical tacrolimus are similarly efficacious in the repigmentation of both facial and nonfacial vitiliginous lesions.<sup>32,33</sup> However, long-term use of topical corticosteroids is contraindicated due to their serious side effects. Therefore, topical tacrolimus offers many advantages over topical corticosteroids for the management of chronic skin disorders including vitiligo. In contrast to topical corticosteroid treatment which results in a predominantly diffuse pattern of repigmentation,<sup>34</sup> topical tacrolimus often induces follicular repigmentation. This indicates the involvement of melanoblast in the repigmentation process, namely the proliferation of inactive melanocytes (melanoblasts), which migrate to the nearby epidermis to differentiate and form perifollicular pigment islands.<sup>35,36,37</sup> Topical tacrolimus induces follicular repigmentation better in sun-exposed anatomical sites. Keratinocytes are known to secrete endothelin, a prodifferentiation factor of melanoblasts, after exposure to UVB radiation.<sup>38</sup> Therefore, sun-exposed keratinocytes most likely provide the necessary endothelin for optimal melanoblast differentiation effect induced by topical tacrolimus.<sup>10</sup>

Topical tacrolimus has been reported to promote melanoblast differentiation and growth. Additionally, topical tacrolimus promotes a favorable environment that fosters the proliferation of melanocytes/melanoblasts through an interaction with keratinocytes, and thereby repopulating vitiliginous skin lesions.<sup>10</sup> In another study by Kang et. al.,<sup>39</sup> topical tacrolimus was seen to induce tyrosinase, which eventually leads to melanin biosynthesis, activity, and expression.

Studies have shown mixed results for combination therapy, consisting of topical tacrolimus and UVB.<sup>40,41,42,43</sup> The use of topical tacrolimus in association with phototherapy gives rise to concern about the possibility of an increased risk to skin malignancies.<sup>44</sup> However, the results of a 2005 study on hairless mice suggest that topical



tacrolimus prevents DNA photodamage due to a filter effect of both active and vehicle components in topical formulation but does not affect the clearance of DNA photoproducts.<sup>45</sup> Fai et. al., employed combined therapy, and indicated a rapid and relevant improvement of facial vitiligo, followed by lesions on the limbs and trunk (including the neck), whereas the overall response of vitiligo in other skin areas (extremities and genital areas) was poor.<sup>46</sup> This fact has been attributed to the greater density of hair follicles in the head and neck areas, and thus, greater melanocyte reservoirs.<sup>47</sup> Further long-term efficacy and safety data and randomized controlled trials on a large number of study participants are required.

Combined therapy of topical tacrolimus and 308-nm excimer laser in the management of vitiligo has been evaluated as well. Unlike topical tacrolimus and UVB phototherapy, combination treatment of topical tacrolimus and 308-nm excimer laser has been reported to be more effective and faster than that of excimer laser in monotherapy.<sup>48,49</sup> In comparison with NB-UVB, phototherapy with excimer laser has the advantage of a targeted treatment, thereby limiting the delivery of radiation only to affected vitiligo skin areas. However, NB-UVB may be more useful for the treatment of extensive vitiligo and is more advantageous than excimer phototherapy with regards to cost, session duration, and patient compliance.<sup>42</sup>

Occlusive treatment has been reported to enhance topical tacrolimus efficacy in treating vitiligo. As mentioned earlier, it has been shown that when applying tacrolimus openly on extremities, there was negligible effect. However, Hartmann et. al.<sup>50</sup> used polyurethane foil or hydrocolloid dressings for overnight occlusive treatment, and moderate to excellent repigmentation was achieved, depending on the dressing utilized. It was suggested that since hydrocolloid dressings lead to higher stratum corneum water holding capacity compared with polyurethane foil<sup>51</sup>, the hydrocolloid dressings may be more suitable for enhancing the transcutaneous penetration of the topically applied agent. Moreover, the Hartmann et. al. study had also measured serum concentrations of tacrolimus. All study subjects had tacrolimus serum levels below the detection limit after 12 months, indicating the long-term topical treatment with additional long-term occlusion of areas up to 150 cm<sup>2</sup> does not lead to accumulation of tacrolimus in the blood.<sup>47</sup> Still, larger placebo-controlled studies using topical tacrolimus in combination with occlusion, penetration enhancers, or phototherapy, or in higher concentrations, are required to determine the exact role of topical tacrolimus in the treatment of vitiligo and its optimal mode of use.

#### 4. Conclusion

In conclusion, topical pimecrolimus and tacrolimus are effective and well tolerated treatment options for both adults and children with vitiligo. Moreover, it has been documented that topical tacrolimus has better outcomes for the treatment of vitiligo in children<sup>52</sup> and in patients of skin of color.<sup>53</sup> Topical calcineurin inhibitors are a great alternative for persons with vitiligo but with poor compliance to phototherapy and/or with fear of the side-effects of using topical corticosteroids long-term. Further randomized controlled studies are needed to enhance the understanding of how these topical medications work. Additionally, combination therapy utilizing NB-UVB or excimer laser with topical calcineurin inhibitors should be evaluated in larger trials so that safety and efficacy data can help guide clinicians in managing vitiligo when presented with refractory cases.

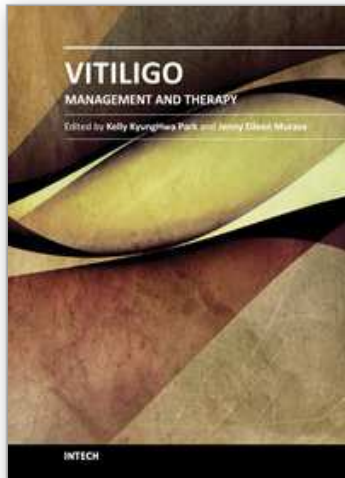
## 5. References

- [1] Howitz J, Broadthagen H, Swartz M et al. Prevalence of vitiligo: epidemiological survey on the Isle of Bornhold, Denmark. *Arch Dermatol* 1977; 113: 47-52.
- [2] Boisseus-Garsaud AM, Garsaud P, Cales-Quist D et al. Epidemiology of bitiligo in the French West Indies. *Int J Dermatol* 2000; 39: 18-20.
- [3] Taieb A and Picardo M. Vitiligo. *New Engl J Med* 2009; 360: 160-169.
- [4] Esfandiarpour I, Ekhlasi A, Farajzadeh S, Shamsadini S. The efficacy of pimecrolimus 1% cream plus narrow-band ultraviolet B in the treatment of vitiligo: A double-blind, placebo controlled clinical trial. *Journal of Dermatological Treatment*. 2009; 20:1; 14-18.
- [5] Sendur N, Karaman G, Sanic N, Savk E. Topical pimecrolimus: A new horizon for vitiligo treatment? *Journal of Dermatological Treatment*. 2006; 17: 338-342.
- [6] Ashcroft DM, Dimmock P, Garside R, Stein K, Williams HC. Efficacy and tolerability of topical pimecrolimus and tacrolimus in the treatment of atopic dermatitis: meta-analysis of randomized controlled trials. *BMJ*. 2005 Mar 5;330(7490):516.
- [7] Nordlund JJ. The epidemiology and genetics of vitiligo. *Clin Dermatol* 1997; 15: 875-8
- [8] Grimes PE, Morris R, Avaniss-Aghajani E, et al. Topical tacrolimus therapy for vitiligo: therapeutic responses and skin messenger RNA expression of proinflammatory cytokines. *J Am Acad Dermatol* 2004; 51: 52-61.
- [9] Dawid M, Veensalu M, Grassberger M, Wolff K. Efficacy and safety of pimecrolimus cream 1% in adult patients with vitiligo: Results of a randomized, double-blind, vehicle-controlled study. *JDDG*;2006 4:942-946.
- [10] Billich A, Aschauer H, Aszodi A, Stuetz A. Percutaneous absorption of drugs used in atopic eczema: pimecrolimus permeates less through skin than corticosteroids and tacrolimus. *International Journal of Pharmaceutics*. 2004; 269:29-35.
- [11] Seifari H, Farnaghi F, Firooz A, Vasheghani-Farahani A, Alirezaie N-S, Dowlati Y. Pimecrolimus cream in repigmentation of vitiligo. *Dermatology*. 2007;214:253-259.
- [12] Mayoral FA, Vega JM, Stavisky H, McCormick CL, Parneix-Spake A. Retrospective analysis of pimecrolimus cream 1% for treatment of facial vitiligo. *J Drugs Dermatol*. 2007 May;6(5):517-21.
- [13] Lan CCE, Chen GS, Chiou MH, Wu CS. FK506 promotes melanocyte and melanoblast growth and creates a favourable milieu for cell migration via keratinocytes: possible mechanisms of how tacrolimus ointment induces repigmentation in patients with vitiligo. *Br J Dermatol*. 2005; 153:498-505.
- [14] Coskun B, Saral Y, Turgut D. Topical 0.05% clobetasol propionate versus 1% pimecrolimus ointment in vitiligo. *Eur J Dermatol* 2005 Mar-Apr;15(2):88-91.
- [15] Mosher DB, Fitzpatrick TB, Ortonne JP, Hori Y. Hypomelanoses and hypermelanoses. In: Freedberg IM, Eisen AZ, Wolff K, et. al., eds. *Dermatology in General Medicine*. 5th ed. New York: McGraw Hill, 1999: 949-60.
- [16] Kostovic K, Nola I, Bucan Z, Situm M. Treatment of vitiligo: current methods and new approaches. *Acta Dermatovenerol Croat* 2003; 11:1633-70.
- [17] Borderé AC, Lambert J, van Geel N. Current and emerging therapy for the management of vitiligo. *Clin Cosmet Investig Dermatol*. 2009; 2: 15-25.
- [18] Fitzpatrick TB. Mechanisms of phototherapy of vitiligo. *Arch Dermatol*. 1997 Dec;133(12):1525-8.
- [19] Farajzadeh S, Daraei Z, Esfandiarpour I, Hosseini SH. The efficacy of Pimecrolimus 1% cream combined with microdermabrasion in the treatment of nonsegmental

- childhood vitiligo: a randomized placebo-controlled study. *Pediatric Dermatology* 2009 May-Jun;26(3):286-91.
- [20] Nghiem P, Pearson G, Langley RG. Tacrolimus and pimecrolimus: From clever prokaryotes to inhibiting calcineurin and treating atopic dermatitis. *J Am Acad Dermatol*. 2002; 46:228-41.
- [21] Woodle ES, Thistlethwaite JR, Gordon JH, Laskow D, Deierhoi MH, Burdick J, et al. A multicenter trial of FK506 (tacrolimus) therapy in refractory acute renal allograft rejection. A report of the Tacrolimus Kidney Transplantation Rescue, Study Group. *Transplantation* 1996;62:594-9.
- [22] Kang S, Lucky AW, Pariser D, Lawrence I, Hanifin JM, Tacrolimus Ointment Study Group. Long-term safety and efficacy of tacrolimus ointment for the treatment of atopic dermatitis in children. *J Am Acad Dermatol* 2001;44:S58-64.
- [23] Paller AS, Caro I, Rico MJ, and the Tacrolimus Ointment Study Group. Long-term safety and efficacy of tacrolimus ointment monotherapy in atopic dermatitis patients: open-label study results. *Ann Dermatol Venereol* 2002;129(Suppl 1):S247.
- [24] Koo JYM, Prose N, Fleischer A, Rico MJ, Tacrolimus Ointment Study Group. Safety and efficacy of tacrolimus ointment monotherapy in over 7900 atopic dermatitis patients: results of an open-label study. *Ann Dermatol Venereol* 2002; 129(Suppl 1):S415.
- [25] Jimbow K, Uesugi T. New melanogenesis and photobiological processes in activation and proliferation of precursor melanocytes after UV-exposure ultrastructural differentiation of precursor melanocytes from Langerhans cells. *J Invest Dermatol* 1982;78:108-15.
- [26] Friedmann PS, Gilchrist BA. Ultraviolet radiation directly induces pigment production by cultured human melanocytes. *J Cell Physiol*13321198788-94.
- [27] Grimes PE. Vitiligo an overview of therapeutic approaches. *Dermatol Clin* 1993;11:325-38.
- [28] Grimes PE. Therapeutic trends for the treatment of vitiligo. *Cosmetic Dermatol* 2002;15:21-5.
- [29] Swope VB, Abdel-Malek Z, Kassem LM, Nordlund JJ. Interleukins 1a and 6 and tumor necrosis factor-a are paracrine inhibitors of human melanocyte proliferation and melanogenesis. *J Invest Dermatol* 1991;96:180-5.
- [30] Yohn JJ, Critelli M, Lyons MB, Norris DA. Modulation of melanocyte intercellular adhesion molecule-1 by immune cytokines. *J Invest Dermatol* 1990;90:233-7.
- [31] Morelli JG, Norris DA. Influence of inflammatory mediators and cytokines on human melanocyte function. *J Invest Dermatol* 1993;100(Suppl):191S-5S.
- [32] Ho N, Pope E, Weinstein M, et. al. A double-blind, randomized, placebo-controlled trial of topical tacrolimus 0.1% vs.clobetasol propionate 0.05% in childhood vitiligo. *Br J Dermatol* 2011; doi: 10.1111/ j.13652133. 2011. 10351.x [Epub ahead of print].
- [33] Lepe V, Moncada B, Castanedo-Cazares JP, et. al. A double-blind randomized trial of 0.1% tacrolimus vs 0.05% clobetasol for the treatment of childhood vitiligo. *Arch Dermatol* 2003;139(5):581-5.
- [34] Parsad D, Pandhi R, Dogra S, Kumar B. Clinical study of repigmentation patterns with different treatment modalities and their correlation with speed and stability of repigmentation in 352 vitiliginous patches. *J Am Acad Dermatol* 2004; 50:63-7.
- [35] Silverberg NB, Lin P, Travis L et al. Tacrolimus ointment promotes repigmentation of vitiligo in children: a review of 57 cases. *J Am Acad Dermatol* 2004; 51:760-6.



- [36] Kenwar AJ, Dogra S, Parsad D. Topical tacrolimus for treatment of childhood vitiligo in Asians. *Clin Exp Dermatol* 2004; 29:589–92.
- [37] Fitzpatrick TB. Mechanisms of photochemotherapy of vitiligo. *Arch Dermatol* 1997; 133:1591–2.
- [38] Imokawa G, Miyagishi M, Yada Y. Endothelin-1 as a new melanogen: coordinated expression of its gene and the tyrosinase gene in UVB-exposed human epidermis. *J Invest Dermatol* 1995; 105:32–7.
- [39] Kang HY, Choi YM. FK506 increases pigmentation and migration of human melanocytes. *Br J Dermatol* 2006; 155(5):1037–40.
- [40] Castanedo-Cazares JP, Lepe V, Moncada B. Repigmentation of chronic vitiligo lesions by following tacrolimus plus ultraviolet-B-narrow-band. *Photodermatol Photoimmunol Photomed* 2003; 19:35–36.
- [41] Mehrabi D, Pandya AG. A randomized, placebo-controlled, double-blind trial comparing narrow-band UV-B Plus 0.1% tacrolimus ointment with narrow-band UV-B plus placebo in the treatment of generalized vitiligo. *Arch Dermatol* 2006; 142:927–929.
- [42] Stinco G, Piccirillo F, Forcione M, et. al. An open randomized study to compare narrow band UVB, topical pimecrolimus and topical tacrolimus in the treatment of vitiligo. *Eur J Dermatol* 2009; 19(6):588–93.
- [43] Nordal E, Guleng G, Ronneviq J. Treatment of vitiligo with narrowband-UVB (TL01) combined with tacrolimus ointment (0.1%) vs. placebo ointment, a randomized right/left double-blind comparative study.
- [44] Yarosh DB, Pena AV, Nay SL *et al.* Calcineurin inhibitors decrease DNA repair and apoptosis in human keratinocytes following ultraviolet B irradiation. *J Invest Dermatol* 2005; 125: 1020–1025.
- [45] Tran C, Lubbe J, Sorg O *et al.* Topical calcineurin inhibitors decrease the production of UVB-induced thymine dimmers from hairless mouse epidermis. *Dermatology* 2005; 211: 341–347.
- [46] Tran C, Lubbe J, Sorg O *et al.* Topical calcineurin inhibitors decrease the production of UVB-induced thymine dimmers from hairless mouse epidermis. *Dermatology* 2005; 211: 341–347.
- [47] Cui J, Shen LY, Wang GC. Role of hair follicles in the repigmentation of vitiligo. *J Invest Dermatol* 1991; 97:410–416.
- [48] Kawalek AZ, Spencer JM, Phelps RG. Combined excimer laser and topical tacrolimus for the treatment of vitiligo: a pilot study. *Dermatol Surg* 2004; 30: 130–135.
- [49] Passeron T, Ostovari N, Zakaria W *et al.* Topical tacrolimus and the 308-nm excimer laser: a synergistic combination for the treatment of vitiligo. *Arch Dermatol* 2004; 140:1065–1069.
- [50] Hartmann A, Brocker EB, Hamm H. Occlusive treatment enhances efficacy of tacrolimus 0.1% ointment in adult patients with vitiligo: results of a placebo-controlled 12-month prospective study. *Acta Derm Venereol* 2008; 88(5):474–9.
- [51] Berardesca E, Vignoli GP, Fideli D, Maibach H. Effect of occlusive dressings on the stratum corneum water holding capacity. *Am J Med Sci* 1992; 304:25–28.
- [52] Udompataikul M, Boonsupthip P, Siriwattanagate R. Effectiveness of 0.1% topical tacrolimus in adult and children patients with vitiligo. *J Dermatol*. 2011; 38(6):536–40. doi: 10.1111/j.1346-8138.2010.01067.x. Epub 2010 Nov 2.
- [53] Silverberg JL, Silverberg NB. Topical tacrolimus is more effective for treatment of vitiligo in patients of skin of color. *J Drugs Dermatol*. 2011; 10(5):507–10.



## **Vitiligo - Management and Therapy**

Edited by Dr. Kelly KyungHwa Park

ISBN 978-953-307-731-4

Hard cover, 174 pages

**Publisher** InTech

**Published online** 14, December, 2011

**Published in print edition** December, 2011

Vitiligo: Management and Therapy is a practical guide to vitiligo that reflects current research related to the fundamentals of vitiligo and its management. Vitiligo experts and researchers from all over the world have contributed to this text, accounting for its comprehensive nature and diverse array of topics. The recent advances in medicine and technology have led to a better understanding of the disease and have broadened available treatment options. The essentials are captured in this book and are complemented by useful clinical photographs and reference tables. This concise tool will serve as an invaluable resource for clinicians in daily practice.

### **How to reference**

In order to correctly reference this scholarly work, feel free to copy and paste the following:

Cristina Caridi, Andrew Sohn and Rita V. Patel (2011). Topical Calcineurin Inhibitors in the Treatment of Vitiligo, Vitiligo - Management and Therapy, Dr. Kelly KyungHwa Park (Ed.), ISBN: 978-953-307-731-4, InTech, Available from: <http://www.intechopen.com/books/vitiligo-management-and-therapy/topical-calcineurin-inhibitors-in-the-treatment-of-vitiligo>

**INTECH**  
open science | open minds

### **InTech Europe**

University Campus STeP Ri  
Slavka Krautzeka 83/A  
51000 Rijeka, Croatia  
Phone: +385 (51) 770 447  
Fax: +385 (51) 686 166  
[www.intechopen.com](http://www.intechopen.com)

### **InTech China**

Unit 405, Office Block, Hotel Equatorial Shanghai  
No.65, Yan An Road (West), Shanghai, 200040, China  
中国上海市延安西路65号上海国际贵都大饭店办公楼405单元  
Phone: +86-21-62489820  
Fax: +86-21-62489821

© 2011 The Author(s). Licensee IntechOpen. This is an open access article distributed under the terms of the [Creative Commons Attribution 3.0 License](#), which permits unrestricted use, distribution, and reproduction in any medium, provided the original work is properly cited.

IntechOpen

IntechOpen