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Topical mycophenolate mofetil in the treatment of vitiligo: a pilot study

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ABSTRACT

Background: Vitiligo is a multifactorial disease that is characterized by circumscribed depigmented macules and patches. Autoimmune reactions may play an important role in the pathogenesis of the disease. Mycophenolate mofetil is a drug that inhibits DNA synthesis in lymphocytes and has been used in autoimmune diseases such as immunobullous skin diseases, lupus erythematosus, and autoimmune hepatitis.

Objectives: The objective of this study was to show the efficacy of topical mycophenolate mofetil in the treatment of vitiligo.

Methods: Thirty patients with limited vitiligo were enrolled in this study. The patients applied a topical preparation of mycophenolate mofetil 15% twice daily for three months and at the end of every month, repigmentation was assessed using the Vitiligo Area Scoring Index (VASI).

Results: At the end of the third month, 36.6 % (n=11) of the patients showed about 25% repigmentation of the lesions. No side effects were observed throughout the study.

Conclusion: This study showed that topical mycophenolate mofetil can be somewhat effective in the treatment of vitiligo; however, it seems to be inferior to potent topical steroids in inducing repigmentation.

Introduction

Vitiligo is characterized by circumscribed depigmented macules and patches of skin. It is a multifactorial disorder due to genetic and environmental factors. Vitiligo affects approximately 0.5-2% of the general population worldwide [1]. The disease can affect all age groups, but studies have shown that most patients seem to develop the disease about the age of 20. It also occurs more often in individuals with dark or tanned skin [2].

Different theories have been proposed for the pathogenesis of vitiligo in which autoimmunity in genetically suscep-

tible individuals is considered to play an important role [3,4]. The autoimmune mediated destruction of melanocytes is a well accepted theory and currently is the leading hypothesis in vitiligo pathogenesis. This immune reaction is mediated by cellular and humoral immunity and cytokines [5].

Various treatment modalities, including topical therapy, phototherapy and systemic therapy have been used [6-10], but no single treatment has been shown to be successful in all cases, hence a search for a new drug continues.

Mycophenolate mofetil (MMF) is a purine antagonist that selectively inhibits proliferation of activated lymphocytes. MMF is converted to mycophenolic acid in the human body which then inhibits inosine monophosphate dehydrogenase. This enzyme converts inosine monophosphate to guanosine monophosphate. In fact, MMF inhibits DNA synthesis in lymphocytes, and inhibits the production of antibody by B-cells. The drug prevents glycosylation and expression of binding molecules and the summoning of lymphocytes and monocytes into sites of inflammation [11]. MMF can induce apoptosis of activated lymphocytes and decrease the recruitment of lymphocytes (both CD4 and CD8) and monocytes into inflammation sites [12]. Lee YF et al showed that the recruitment of CD8 lymphocytes to the skin was significantly decreased after MMF therapy [13]. Therefore, the use of it could theoretically help in the management of vitiligo.

Objective

The objective of this study was to assess the efficacy of topical MMF in the treatment of vitiligo. To our knowledge, there is no such study in the literature to date.

Methods

This study was conducted at the department of dermatology, Shahid Faghihi University Hospital, Shiraz, Iran over a 14-month period. Thirty patients were enrolled in this pilot study. All patients had limited vitiligo (less than 5% of total body surface area) and had either received no previous treatment or three months had elapsed since their last treatment plan. Patients with mucosal vitiligo, pregnant and lactating women, children and neutropenic patients were excluded due to probable side effects of MMF on these patients.

The patients were instructed to apply topical MMF 15% preparation twice daily for three months, and at the end of every month repigmentation was assessed using the Vitiligo Area Scoring Index (VASI) for every patient.

The reason for choosing a 15% concentration of MMF was that this was the maximum concentration that could be obtained by dissolving the MMF tablets (500 mg tablet, Actoverco Company, Iran) in Eucerin®. This study was approved by the Ethical Committee of Shiraz University of Medical Sciences and all patients signed the informed consent form. Statistical analysis was performed with the SPSS 19.0 statistical package (SPSS Inc., Chicago, IL, USA), using paired t-test and descriptive methods. The criterion for statistical significance was at $\alpha = 0.05$.

Results

Thirty patients were included in this study with a mean age of 32.8 years (with an age range from 17 to 51 years). Eight of them were male (27%) and the rest were females (73%). The mean duration of the disease was 9.4 months (ranging from 1 to 48 months). Nine patients had acrofacial vitiligo and the rest had the segmental type of the disease. Most of lesions were located on the hands (41.2%), followed by the face (32.3%), while the remaining lesions were located in other regions of the body (26.5%).

At the end of third month, 36.6 % (n=11) of patients achieved approximately 25% repigmentation. At the end of first month, only one patient had dramatic response with 40% repigmentation, but at the end of second month, five patients (16.6%) had achieved 25% repigmentation.

Thirteen patients had a history of previous treatment with topical corticosteroids and/or topical calcineurin inhibitors. Five of them had shown a good response to previous treatment but had presented with new lesions. One of the patients which had shown a good response to previous treatments, showed no response to MMF therapy, whereas the other four showed some repigmentation (28.8%).

There were eight patients who were resistant to previous topical therapy, who also showed no response to MMF therapy. Two of them had a positive family history of vitiligo in their first- or second-degree relatives. One patient with a positive family history of vitiligo in her mother had a good response to MMF therapy, while the other patient with history of vitiligo in his aunt did not respond to therapy. This patient was also resistant to previous topical steroid therapy.

All lesions that responded to MMF therapy were in sun-exposed areas, except for one lesion, which was on the thigh area.

Comparing the overall pigmentation at the end of the second month with the first month showed a statistically significant difference (P.value= 0.027).

Comparing the overall pigmentation at the end of the third month with the first month showed a statistically significant difference (P.value= 0.0.005) (Table 1).

None of the patients presented with any adverse side effects while using the topical medication.

Discussion

This study was a pilot study investigating the therapeutic effects of topical MMF on vitiligo patients.

TABLE 1. Overall pigmentation at the end of each month with MMF Therapy. [Copyright: ©2017 Handjani et al.]

Time (at the end of each month)	Pigmentation (mean +/- SD)
1st month	1.33+/- 1.33
2nd month	4.16+/- 2.19
3rd month	10 +/- 2.82

Autoimmune destruction of melanocytes is currently the leading hypothesis in vitiligo pathogenesis. The immune system involved in this destruction includes the cellular and humoral immunity and various cytokines. The presence of several antibodies against different melanocyte-associated antigens was confirmed in vitiligo. Elimination of melanocytes by cytotoxic T cells is also another mechanism involved in vitiligo. Cytokines also play an important role in vitiligo. Increased levels of tumor necrosis alpha (TNF-α) and interferon-gamma (IFN-γ) are important arms in vitiligo pathogenesis [5].

MMF inhibits DNA synthesis in lymphocytes, and inhibits the production of antibody by B-cells. The drug prevents glycosylation and expression of binding molecules and the infiltration of lymphocytes and monocytes into sites of inflammation [11].

In this study, the maximum concentration of topical MMF, using its 500 mg tablet, was utilized. At the end of first month, only one patient had dramatic response with 40% repigmentation, but at the end of second month 16.6% of the patients had achieved 25% repigmentation, and in the third month, 36.6 % of patients achieved 25% repigmentation. This study showed that MMF may be an alternative and safe topical drug therapy for vitiligo.

Topical MMF is also used in plaque type psoriasis with success. Pure MMF 2% was compared to 0.1% betamethasone-17-valerate cream. No difference was seen between the therapeutic efficacies of both topical drugs in psoriasis [14].

Nearly all the lesions that showed a good response to MMF therapy were in sun-exposed areas; this may be due to the synergistic effects of natural ultraviolet light in the repigmentation of vitiligo lesions.

There are some limitations in this study. Firstly, because it was a pilot study, the number of cases was few and there was no control group. Further studies with larger sample sizes and in the form of randomized clinical trials are needed to assess the efficacy of topical MMF in the treatment of vitiligo. Secondly, because of the difficulty in skin penetration of topical drugs, using skin permeation enhancers, such as eucalyptol (EUL) and N-methyl-2-pyrrolidone (NMP) suggested by Amnuaikit et al may increase the therapeutic efficacy of topical MMF [15].

It seems that although the use of topical MMF in the treatment of vitiligo can be effective, its use may not be warranted in cases resistant to topical steroids. However, due to its safety, it can be considered in cases where the use of topical steroids is contraindicated or can cause significant atrophy.

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