Low dose Methotrexate for the treatment of generalized lichen planus

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Background: Lichen planus is a common inflammatory disease that can involve the skin, nails, mucous membrane, and hair follicles. There is a long list of topical and systemic therapies for its treatment. Methotrexarte has some characteristics that make it a good choice for generalized lichen planus.

Aim: The goal of this study was to assess the effect of low dose methotrexate in generalized lichen planus.

Method: Eighteen patients (8 male and 10 female, mean age: 51.1, range: 22-80, SD: 14.9) with generalized lichen planus were enrolled in the study. After basic evaluations, low dose methotrexate (7.5-10 mg weekly) initiated. The response rate was appraised after 2, 4 and 8 weeks. Six-month follow-up was done for evaluating the recurrence rate.

Result: At the end of the 8th week, 75% of the patients had more than 75% improvement. After six months, no case of recurrence was reported. Adverse effects were limited to laboratory abnormalities in two patients (abnormal liver function tests in one case and decreased hemoglobin in the other case).

Conclusion: Low dose methotrexate is a very good and safe treatment for generalized lichen planus, especially when there is concern regarding the steroids undesired effects or when the disease is resistant to corticosteroids.

Keyword: lichen planus, Methotrexate, corticosteroids

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INTRODUCTION

Lichen planus (LP) is a common pruritic, inflammatory disease that may involve the skin, mucous membranes, nails, and hair follicles.Topical treatments are associated with a good response in limited lesions but in patients with widespread disease, these treatments are usually unsatisfactory.

Systemic corticosteroids have long been the treatment of choice for generalized LP but their use is limited in several conditions like old age, systemic diseases such as diabetes mellitus and osteoporosis.

Additionally, despite the good results with corticosteroids, recurrence is quite common and sometimes leads to long-term use of such medications.

Other systemic treatments that have been tried in cutaneous LP with variable response rates include oral retinoids, azathioprine, Tetracycline, cyclosporine, mycophenolate mofetil, thalidomide, low molecular weight heparin, PUVA or UVB, metronidazol, and biologic agents [1-15].

A treatment with a good response rate and safety comparable to corticosteroids but with a lower recurrence rate can be a very good substitute for systemic corticosteroids, especially in old ages and patients with systemic diseases. Methotrexate (MTX) inhibits the action of Dihydrofolate reductase which is a necessary enzyme in the synthesis of

thymidylate and purine nucleotides required for DNA/RNA synthesis.

The most important side effects of MTX include pancytopenia and hepatotoxicity. Pancytopenia typically develops earlier, as compared to hepatic fibrosis and cirrhosis which take years to develop. Therefore, in the case of lichen planus, the risk of liver fibrosis is low because of the short period of consumption.

MTX is not difficult to use and oral administration achieves reliable blood levels unaffected by food intake.

There have been few reports regarding the effectiveness of low dose methotrexate alone for the treatment of lichen planus. Therefore, the aim of this study was to investigate the effect of low dose methotrexate (MTX) for the treatment of generalized lichen planus.

PATIENTS AND METHODS

Eighteen patients (8 male and 10 female, mean age: 51.1, range: 22-80 years, SD: 14.9) with generalized lichen planus who were referred to our dermatology clinic between September 2009 and September 2010 were enrolled in the study. The diagnosis had been proven histologically in all patients. Seven patients had typical lesions of oral LP and three had concomitant lichen planopilaris of the scalp or beard. There was no erosive form and no genital or nail involvement.

Our exclusion criteria were age less than 18 or more than 80 years, pregnancy and lactation, chronic liver or kidney disease, use of systemic corticosteroids in the previous 6 months or application of topical steroids in the previous month and inability to attend the clinic for follow-up visits.

Before treatment, all patients were thoroughly informed of the treatment and each one signed a detailed informed consent form.

Laboratory data including blood counts and liver and kidney function tests were collected at base line and photographs were taken from all patients at the first visit. The tests and photos were repeated at the 2nd, 4th, and 8th weeks and the 6th month for the evaluation of the response, compliance, and adverse effects.

Methotrexate (MTX)was initiated at the dose of 7.5 mg weekly in 12 patients and 10 mg weekly in six patients, together with 1 mg folic acid daily except for the day of MTX administration. Patients were strongly advised to avoid any other treatment except eucerin cream as emollient and H1 blocker drugs if necessary. They were also strongly advised to use a good contraception during the administration and 3 months after the cessation of MTX.

The results were assessed 2, 4, and 8 weeks after starting the treatment. Treatment results were sorted into four categories as follows:

No response (less than 25% improvement), mild response (25%-50% improvement),

moderate response (50%-75% improvement) and excellent response (more than 75% improvement). Treatment was tapered after the 8th week or whenever a complete response was achieved. A response rate less than 75% at 8th week was regarded as treatment failure; in this case, MTX was discontinued and switched to another treatment. Patients who attended follow-up sessions were visited at the 6th month for the evaluation of recurrence. Adverse events, treatment compliance, and laboratory abnormalities were also noted at each visit.

RESULT

Eighteen patients with generalized lichen planus entered the study. Demographic characteristics of the patients are listed in Table 1.

Two of them left the study after 2 weeks because of laboratory abnormalities (abnormality in liver function tests in one and anemia in the other) and 16 patients continued their participation in the study for the total of 8 weeks.

After 2 weeks, 7 out of 18 patients (38.8%) had mild improvement, one patient (5.5%) had moderate improvement while 10 patients (55.5%) showed no changes in their lesions. There was no case of excellent response after 2 weeks.

After 4 weeks, 5 out of 16 patients (31.2%) had mild improvement, six patients (37.5%) had moderate and four patients (25%) had excellent improvement. One patient (6.2%) showed no improvement after 4 weeks.

At the end of the 8th week, three patients (18.7%) had mild improvement and 12 (75%) had excellent improvement. One patient remained unresponsive after 8 weeks.

Table 1. Demographic characteristics and final response of patients with generalized lichen planus treated with low dose methotrexate.

Patients no.	Sex	Age	Duration of disease (month)	Extracutaneous involvement	MTX dose (weekly)	Response after 8 weeks
1	M	45	6	Lichen planopilaris of scalp & beard	10 mg	Mild
2	M	50	1	Mucosal disease	7.5 mg	Excellent
3	M	80	3	----------	7.5 mg	Exit because of Hb↓
4	F	29	9	----------	7.5 mg	Excellent
5	M	46	6	Lichen planopilaris of scalp	10 mg	Mild (no response in LPP)
6	M	40	1	Mucosal disease Lichen planopilaris of scalp	10 mg	Excellent
7	F	72	18	----------	7.5 mg	Excellent
8	F	52	6	----------	7.5 mg	Mild
9	F	69	24	----------	7.5 mg	Excellent
10	M	47	48	Mucosal disease	7.5 mg	Excellent
11	M	39	8	----------	10 mg	Excellent
12	F	55	12	----------	10 mg	Excellent
13	F	50	36	----------	7.5 mg	Excellent
14	F	45	4	Mucosal disease	7.5 mg	No response
15	F	59	6	----------	7.5 mg	Exit because of LFT↑
16	F	50	1	Mucosal disease	7.5 mg	Excellent
17	M	22	2	Mucosal disease	10 mg	Excellent
18	F	71	12	Mucosal disease	7.5 mg	Excellent

Patients with an excellent response were followed for 6 months to monitor the recurrence rate. Four other patients were swithched to another drug and left the study.

In the six-month follow up, none of the 12 patients (with more than 75% response) experienced recurrence.

We did not find any significant correlation between sex, age or disease duration with response rate.

As mentioned before, three cases had lichen planopilaris in addition to their cutaneous generalized LP. The first one was a 45-year-old man who showed mild improvement in both cutaneous and follicular LP after 8 weeks, the second one was a 40-year-old man with excellent improvement in cutaneous disease but mild in his follicular disease and the third one was a 46-year-old man with mild improvement in his cutaneous lesions and no change in his follicular lesions.

No case of intolerable general complications (nausea, vomiting, abdominal pain, fatigue, or headache) was noted, but treatment led to adverse laboratory changes in two patients (11.1%). One was an 80-year-old with generalized LP since 3 months ago. He was treated with 7.5 mg methotrexate weekly. Two weeks later, he showed a decrease in hemoglobin concentration and therefore stopped the treatment.

The other one was a 59-year-old woman with generalized LP treated with 7.5 mg MTX weekly. She also left the study because of a rise in liver function tests (Alanin transfrase and aspartat transfrase) after two weeks.

Furuncles on the buttocks and thighs occurred in two patients; both had lichen planopilaris together with their generalized cutaneuos LP. It is not obvious whether their development was due to MTX treatment or other personal factors.

DISCUSSION

There are few published reports regarding the efficacy of methotrexate in generalized lichen planus. As we know, only one study has evaluated the effect of methotrexate for the treatment of generalized lichen planus. Turan et al conducted this survey in Turkey in 2009 using methotrexate in 11 patients with generalized LP ten of whom (more than 90%) were completely cured after the first month and only one case of recurrence was reported during tapering MTX. Only one of their patients discontinued treatment because of intolerable nausea and fatigue [16]. In Turan's study, methotrexate was used at the dose of 15-20 mg weekly, almost similar to the doses used for psoriasis patients. They reached higher response rates in their study when compared to our findings

(>90% complete response after one month vs. 75% after 8 weeks). This difference is even higher after 4 weeks when only 25% of our patients achieved more than 75% improvement. Our experience in psoriatic patients is that methotrexate needs several weeks to show its effects and its maximum effect usually does not commence before 4 weeks. This may explain why only one fourth of our patients achieved an excellent response after 4 weeks and most of them (68.7%) only experienced mild and moderate responses.

There are also four important reports of successful use of methotrexate in combination with several topical therapies such as potent corticosteroids, tacrolimus, or pimecrolimus for the treatment of refractory types of erosive oral or genital LP [17,18,19,20]. All of them reported an acceptable response with minimal adverse events.

Although the aetiology of LP is unknown, an autoimmune pathogenesis is postulated with activated T-cells directed against basal keratinocytes [21]. On this basis, methotrexate would be helpful in the treatment of this condition through down-regulation of an immunologically mediated mucosal response. Its efficacy may also be related to its effect on epidermal cell proliferation. However, in vitro studies demonstrate that MTX has a more significant effect on lymphoid cells [22].

Our study has some characteristics. First, it is the largest study of its kind to date because of its appropriate sample size. Second, we used methotrexate alone for generalized lichen planus; therefore, we could reduce the confounding effects of other variables and third, we used lower doses of MTX rather than what is usually used in psoriatic patients.

Thus, methorexate can be a very reliable treatment for generalized lichen planus. It has some superiority over corticosteroids such as safety in diabetic, hypertensive, or old patients. Moreover, MTX may be associated with lower recurrence rates. Its major disadvantage is its delayed onset of action that is unacceptable for some patients.

Finally, we conclude that low dose methotrexate can be a good and safe treatment for generalized lichen planus, especially when there is concern regarding steroids undesired effects or when the disease is resistant to corticosteroids.

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