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Efficacy And Safety Of Low-Dose Methotrexate In Generalized And Recalcitrant Lichen Planus: A Retrospective Study At A Tertiary Care Center

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ABSTRACT

Introduction: Methotrexate (MTX) acts by suppressing multiple immune pathways involved in the pathogenesis of lichen planus (LP). Trials assessing the efficacy and relapse rates of methotrexate in LP are lacking.

Objectives: Our objective was to analyze the efficacy and safety of low-dose methotrexate in generalized and recalcitrant LP patients retrospectively and to assess the relapse rates in patients after stopping MTX therapy.

Methods: We analyzed clinical and therapeutic details of LP patients treated with low-dose MTX at our center. The cumulative dose and duration of MTX was calculated, and the time to achieve disease control was noted. We analyzed duration of remission and time after which recurrences were seen post-treatment.

Results: Records of 42 generalized and recalcitrant LP patients treated with MTX were analyzed. The starting dose of MTX was 7.5 mg (n=7) or 10 mg (n= 35) once weekly, increased to 10/15 mg weekly in patients with inadequate response. Ten patients were lost to follow-up. Complete resolution was achieved in 30/32 (93%) patients within a mean duration of 14.76 weeks (4-32 weeks), and the cumulative dose of MTX to achieve remission was 153.58 mg (50-375 mg). Only minor side effects were noted in 12/32 (37.5%) patients, and none required treatment discontinuation. The mean duration of remission was 29.43 months (5-60 months).

Conclusion: MTX demonstrated high efficacy and a good safety profile in extensive cutaneous LP and may be a safer alternative to steroids for this condition.

Introduction

Lichen planus (LP) is an idiopathic inflammatory disorder with a relapsing and remitting course. Most often the disease is localized and subsides with topical therapy; however, severe and recalcitrant lesions can be seen in up to 20% patients [1]. A meta-analysis on interventions for LP which analyzed 21 different treatment modalities reported low or very low quality of evidence for all systemic drugs except oral steroids [2].

Oral corticosteroids (OCS) are often prescribed for moderate to severe cutaneous LP, but frequent recurrences are noted after stopping therapy, and steroid related adverse effects consistently develop. The latter are also frequently seen with the use of long-acting steroids as part of "oral mini pulse" [3]. Other drugs in the therapeutic armamentarium for the management of extensive LP include metronidazole, acitretin, cyclosporine, thalidomide [4], leflunomide [5], griseofulvin, sulfasalazine, enoxaparin, methotrexate, dapsone, mycophenolate mofetil, azathioprine, phototherapy, and most recently, JAK inhibitors, but most have limited and low-level evidence to their credit [6,7].

Methotrexate (MTX) has a significant inhibitory effect on lymphoid cells [8]. In an open trial, four patients with severe erosive LP were treated with combination of MTX (10-15 mg/week) and topical corticosteroids for 17 months and the drug was found to be safe and effective for the condition [9]. Our objective was to analyze the efficacy and safety of low-dose MTX in lichen planus patients retrospectively and to assess the relapse rates in patients after stopping MTX therapy.

Methods

We retrospectively analyzed records of generalized recalcitrant lichen planus cases who were treated with low-dose methotrexate (7.5-15 mg/week) at our tertiary center during the period August 2018–April 2023, after obtaining ethical clearance from our institution [vide letter number 631 (74/2022)/IEC/ABVIMS/RMLH/1134].

The outpatient department record proformas of patients with LP treated with methotrexate were scanned for clinical and therapeutic data. The baseline and follow-up clinical assessment details were noted, and laboratory evaluations performed at baseline and follow-up were also scanned. The cumulative dose and duration of MTX was calculated. Times to achieve disease control in terms of resolution of pruritus, cessation of new lesions, and flattening of lesions were noted. Finally, we also analyzed the duration of remission and time after which recurrences were seen post-treatment, wherever records for the same were available.

Results

A total of 42 LP patients presenting with papules and plaque lesions managed on low-dose methotrexate were analyzed in this study. Demographic and baseline clinical parameters of the patients are detailed in Table 1. The mean age of patients was 32.66 years (6–79 years), and the male-to-female ratio was 0.75:1. The mean duration of disease was 17.25 months (1–240 months). The majority of the patients (35/42) had failed or showed partial response to other medications, including topical/intralesional/oral steroids, dapsone, and doxycycline. Also, most of the patients had extensive LP with > 20% body surface area involvement (31/42, 73.8%).

The diagnosis of LP was made based on clinical presentation in all cases. All patients had undergone a baseline assessment consisting of complete hemogram, liver function tests, kidney function tests, hepatitis serology, HIV, chest radiograph, and Mantoux test prior to starting MTX. The starting dose of MTX was 7.5 mg (n=7) or 10 mg (n= 35) once weekly. Patients were also co-prescribed folic acid (5 mg) supplementation once weekly, while no topical steroids were prescribed for any patient. In those who had inadequate response (no decrease in pruritus, appearance of new lesions, or no flattening of existing lesions) to the starting dose, the dose was increased to 10/15 mg weekly. A total of 12 patients were prescribed a dose of 15 mg/week, while 17 received a maximum of 10 mg/week, and three received only 7.5 mg/week throughout the treatment course. No patient was prescribed a dose higher than 15 mg. Ten patients were lost to follow-up.

Two patients were given concomitant isoniazid for latent tuberculosis detected on baseline investigations, while another patient with a history of treated pulmonary tuberculosis five years prior, with radiological sequelae of treated infection but a negative Mantoux test, was given MTX without any anti-tubercular drugs following medical consultation. MTX was tapered down and stopped in four patients and abruptly discontinued in rest of the patients when complete response was achieved.

Complete resolution was achieved in 30/32 (93%) patients. The mean time to achieve complete resolution of the disease was 14.76 weeks (4-32 weeks), and the cumulative dose of MTX to achieve remission was 153.58 mg (50-375 mg) (Table 2). Side effects were noted in 12/32 (37.5%) patients, including headache (n=1), nausea (n=2), fatigue (n=2), fever (n=1), decreased appetite (n=1), diffuse hair loss (n=3), vomiting (n=1), abdominal pain (n=1), dyspepsia (n=3), elevation of transaminases (n=1), mood disturbances (n=1), plantar erythema and burning (n=1), and thrombocytopenia (n=1). No serious adverse effect was observed, and no patient discontinued treatment due to a drug-related adverse event.

Table 1. Demographic and baseline clinical parameters of 42 lichen planus patients.

Age (years)	32.66 (6-79)
Sex	
Males	18 (42.85%)
Females	24 (57.14%)
Mean disease duration (months)	17.25 (1-240)
Lesions at site of trauma	10 (23.8%)
Number of new lesions over previous 2 weeks	
<20	17 (40.47)
20-50	23 (54.76%)
50-100	2 (4.76%)
Pruritus score (0-10)	
<5	7 (16.66%)
≥5	35 (83.33%)
Distribution of lesions	
Localized	11 (26.19%)
Generalized	31 (73.8%)
Morphology of lesions	
Papules	35 (83.33%)
Micropapules	3 (8.57%)
Plaques	29 (69%)
Annular	2 (4.7%)
Koebnerization present	15 (35.71%)
Secondary changes (Excoriations/erosions/scaling/crusting)	11 (26.19%)
Hair involvement	1 (2.38%)
Nail involvement	1 (2.38%)
Mucosal involvement	15 (35.71%)
Previous treatment	
Topical/Intralesional Corticosteroids	20
Oral corticosteroids	7
Dapsone	7
Isotretinoin	1
Apremilast	1
Doxycycline/Minocycline	3
Others (ayurvedic/homeopathic/antihistamines/permethrin/salicylic acid)	11
None	7

The mean duration of remission was 29.43 months (5-60 months). Recurrence of lesions was observed in 13/30 (43.3%) patients after a mean duration of 17.33 months (5-36 months) of stopping MTX (Table 2).

Discussion

LP is a chronic inflammatory disorder involving skin, mucosae, nails, and scalp. The disease is often associated with pruritus of varying intensity. It runs an unpredictable course, and prognosis depends on the subtype of LP. While spontaneous resolution is seen in two-thirds of patients within 18 months, oral LP may take longer to subside [10,11]. The pathomechanism of LP involves a complex interplay between genetic, environmental and immunological factors.

The immunopathogenesis is largely cell-mediated, with T lymphocytes playing a pivotal role. Among T cell lines, T helper1 (Th1) and T cytotoxic 1(Tc1) and Th 17 and Tc17 lymphocyte subpopulations play important roles [12]. The key cytokines that play a role include Interferon-gamma (IFN-γ)

Table 2. Therapeutic parameters.

Mean initial dose of methotrexate (mg)	9.46 (5-10)
Mean highest dose of methotrexate (mg)	11.64 (10-15)*
Duration of treatment (weeks)	
To achieve pruritus score 0	7.96 (2-32)
To achieve cessation of appearance of new lesions	4.45 (2-18)
To achieve 50% improvement in disease	5.43 (2-12)
To achieve grade 4 flattening of lesions[#]	9.5 (2-24)**
To achieve complete resolution (n= 29/32)	14.76 (4-32)
Cumulative dose of methotrexate (mg)	153.58 (50-375)
Side effects	12/32 (37.5%)
Transient exacerbation (while on treatment)	3 (9.37%)
Relapse	13 (40.6%)
Mean time to relapse post-treatment (months)	17.33 (5-36)
Mean duration of remission (months)	29.43 (5-60)
Physician Global Assessment (16 weeks)	
Poor	2 (4.76%)
Average	4 (9.52%)
Good	10 (23.8%)
Excellent	16 (38%)

*10 patients lost to follow-up. #grading of flattening of lesions (grade 1- 20%; 2- 20-50%; 3-50-90%, 4->90%). **2 patients failed methotrexate (did not achieve complete flattening of lesions and developed new lesions while on treatment).

and Interleukin-17 (IL-17) while the key effector cells CD8+ lymphocytes (Tc1 and Tc17 lines) mediate epidermal injury primarily by engaging cytotoxic mechanisms through granule exocytosis and also by the Fas-FasL and TNF-α-TNF-α receptors interaction. The release of cytotoxic molecules such as perforin, granzyme B, and granulysin causes keratinocyte apoptosis, with consequent epidermal and dermal changes and the development of specific LP lesions. Other inflammatory cells such as dendritic cells, macrophages, and natural killer cells also initiate and maintain the inflammatory process. Regulatory T (Treg) cells are defective and hence unable to control the inflammatory process, while tissue-resident memory cells (Trm) are responsible for reactivations and flares [12]. MTX is mechanistically a rational choice for LP owing to its profound effects on T lymphocytes [13]. MTX suppresses Th1 cell line, with simultaneous increase in Treg cell differentiation, both actions causing attenuation of the ongoing inflammation [13-15]. IFN-γ induced chemokine CXCL10 is strongly expressed in serum of patients with LP as well as in both skin and mucosal lesions [16]. CXCL10 is a major mediator of chronic cytotoxic inflammation which is downregulated by MTX [16]. Interestingly, MTX also has an inhibitory effect on JAK STAT pathway, which has been shown to be relevant to the immunopathogenesis of LP in recent reports [17].

We found low-dose MTX to produce a satisfactory response in most patients, with complete clearance in 93% patients over a mean of 14.76 weeks. Similarly, Kanwar et al. [18] reported a mean improvement of 79% over 12 weeks of MTX in 24 patients and a complete remission in 58% patients by 24 weeks. The cumulative dose of MTX used was, however, much higher than in our study (306 mg versus 153 mg). Similar findings were noted in a small retrospective study by Turan et al. [19] investigating the efficacy and safety of MTX (15-20 mg/week) in 11 generalized LP patients, with improvement in mucocutaneous lesions as early as the first month of treatment initiation. Our patients achieved control in pruritus within a mean duration of 7.96 weeks, cessation of new lesions within 4.45 weeks, and complete resolution of lesion within 14.76 weeks (in 93% patients) (Table 2). Post-discontinuation recurrences were, however, noted in 43.3% patients after a mean duration of 17 months. Relapses post-cure is an important concern in clinical practice; however, there is only limited literature documenting the same. Kanwar et al. [17] and Turan et al. [18] reported relapses in none [17] and one [18] patient, respectively, after three months and six months post-treatment discontinuation. These follow-up periods are notably short and hence may have led to estimation of falsely low relapse rates.

Notably, MTX has been shown to achieve a comparable response to oral steroids. Hazra et al. [3] compared 12 weeks of oral mini-pulse (oral betamethasone 5 mg twice a week) with MTX 10 mg weekly in 44 patients and found

no significant difference in response rates between the two groups. Similarly, Bakhtiar et al. [20] found an insignificant difference in efficacy of oral steroids (72%; with 40 mg daily for eight weeks followed by tapering) and MTX (80%; with 10 mg weekly for eight weeks). We observed only minor side effects in 37% of patients, and the drug was not discontinued due to adverse events in any patient. The adverse effect profile of MTX is much more favorable than daily or even twice-weekly oral steroids (oral mini-pulse), as is evident from existing literature [3] and from our results as well.

Recurrence remains an important concern with any treatment given the role of tissue resident memory T cells in pathogenesis of LP [20]. Notably, seven patients in our study had previously been treated with oral steroids, and 5/7 patients reported prompt relapse on stopping steroids. Relapses post-dose lowering/stopping of steroids is a well-established clinical phenomenon, and requirement of re-treatment exposes patients to cumulative adverse effects [19].

Conclusions and Limitations

We demonstrate the high efficacy and good safety profile of MTX for extensive recalcitrant LP, although the retrospective nature of the study and a significant loss to follow-up in analyzed records are significant limitations. Reasonably high efficacy, in addition to the low cost, makes MTX a desirable treatment option for extensive cutaneous LP. However, larger head-to-head trials with other potentially effective systemic drugs in LP are urgently required to firmly establish the role of MTX in management of extensive LP.

Ethics Approval: Ethical clearance obtained from institutional ethics committee [vide letter number 631 (74/2022)/IEC/ABVIMS/RMLH/1134].

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