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A comparative study of methotrexate & low molecular weight heparin for the treatment of generalized lichen planus

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Abstract

Background: Lichen planus is a difficult condition to treat and is often disappointing for dermatologist. Many a times it's associated with relapse. There is long list of topical & systemic therapies for its treatment.

Aim & Objectives: the objective of this study was to compare the efficacy and safety of methotrexate and low molecular weight heparin in generalized lichen planus patients along with 6 months follow up. In this study 40 patients with generalized lichen planus were enrolled after basic evaluation 20 patients(11 males, 9 females) were started on low dose methotrexate & 20 patients(11 males, 9 females) on low molecular weight heparin. The response rate were appraised after once a week for 16 to 24 weeks for both methotrexate & low molecular weight heparin. Six month follow up was done for evaluating the recurrence rate.

At the end of 16 to 24 weeks of treatment with methotrexate 19 of 20 patients showed 90% improvement, 1 patient did not tolerate methotrexate after 4 weeks because of its adverse effects. Only 3 patients were showed relapse after discontinuation of therapy at 3, 2.6, 2 months respectively.

At the end of 16 to 24 weeks of treatment with low molecular weight heparin complete remission of skin lesions in 13 of 20 patients with 80% improvement. Also 7 patients showed relapse after discontinuation of therapy at 2, 3, 3.6, 1.6, 4, 2, 6 months respectively.

Conclusion: Overall we want to emphasized that low dose oral methotrexate is effective & is a reasonably safe option for generalized LP. There was better tolerance by patients with low recurrence rate than subcutaneous low molecular weight heparin.

Keywords: Generalized Lichen planus, Methotrexate, Low molecular weight Heparin

Introduction

Lichen planus (LP) is a chronic inflammatory disease affecting skin, mucosae (oral and /or genital), nail, scalp. Although the pathogenesis of LP is unclear & the target antigens are still elusive, there is some evidence that T lymphocytes infiltrating the epidermis and dermis act as effector agents against keratinocytes.(1)

Short course of systemic corticosteroids is usually recommended as first line treatment for generalized LP, but recurrences are frequently seen after treatment withdrawal. A wide range of systemic drugs like metronidazole, acitretin, cyclosporine, griseofulvin, itraconazole, mycophenolatemofetil, azathioprine and phototherapy have been used in its management besides topical therapies.(2) However, most of these are case studies using either oral methotrexate in generalized LP or Low molecular weight Heparin in generalized LP. To the best of our knowledge this is first study to compare the efficacy of this both drugs in generalized LP.

Methotrexate is a gold standard in management of psoriasis, but it has rarely been used for generalized LP. Given its low cost oral administration, proven efficacy & safety with regular monitoring after chronic use in psoriatic patients, it could prove to be a safe option for LP also. Recently, Turan et al, in retrospective review of 11 cases of LP treated with methotrexate, found it to be a useful agent.(3)

LP may represent a type IV hypersensitivity response to an antigenic stimulus residing within the epithelium.(4) Heparin CD4+ lymphocytes have been shown to produce endoglycosidase (heparanase), which allows them to penetrate into subendothelial basal lamina. Low molecular weight Heparin (clexane) has been shown to inhibit expression of heparanase. Heparin has been shown to inhibit delayed type hypersensitivity response at very low doses & proven effective in various types of LP.(5-9)

The aim of this study to compare the efficacy, safety and therapeutic response to both drugs in generalized LP.

Patients & Methods

Patients clinically diagnosed to have generalized to have generalized lichen planus with papular and plaque lesions involving at least 5% body surface area involvement were included into the study after taking informed consent. The study period was 4 years. Institute ethics committee approval was taken. The diagnosis of lichen planus was done solely on the clinical basis. Baseline investigations for both group patients included complete blood count, liver and renal function tests, chest x ray, hepatitis B surface antigen and hepatitis C antibody. Following were exclusion criteria: pregnant or lactating women, hemoglobin <9gm%, leukocyte count <4000/mm^3, platelet count <100000/mm^3, liver enzymes >2 times the upper

reference range, active tuberculosis, hepatitis B surface antigen and hepatitis C antibody positive status. Subsequent investigations included hemogram repeated every 2 weeks for 1 month and monthly thereafter, liver and renal function tests repeated after 1 month of methotrexate & Enoxaheparin initiation & every 2 months thereafter. Methotrexate was stopped in patient who developed significant derangement in the haemogram and biochemical parameters anytime during the follow up visits.

Adult patients were treated with once weekly dose of 15 mg for children and adolescents, the dose was estimated according to body weight (0.25mg/kg). Folic acid tablets were given on the day before & after methotrexate intake in a dose of 5 mg/day irrespective of body weight. Enoxaheparin was administered subcutaneously at a dose of 5 mg once a week. Oral anti histamines & emmolients were allowed as & when necessary. However topical corticosteroids were not allowed.

On every follow up visit, they were asked to assess by themselves, the overall improvement in disease severity & express it in percentages. The assessment was based on the following parameters: reduction in the appearance of new lesions, elevation of lesions & pruritus. The improvement was graded as complete improvement (>90%) or partial improvement (<90%). Any side effects that occurred were also noted at each follow up visit. All patients follow up done for 1 year.

The objectives of this study was to assess percentage decrease in disease severity after 24 weeks of both treatment. Another objective to assess the time taken for complete clearance of disease & incidences of side effects after both drugs. The treatment was continued till complete clearance of lesions or maximum duration 6 months whichever occurred earlier. Post treatment follow up was carried out up to 1 year of treatment completion to detect any relapse. Relapse was defined as appearance of any new lesions during post treatment follow up.

Results

A total of 45 patients were screened for the study. 5 patients were excluded due to chronic hepatitis B, hepatitis C, & Alcoholic liver disease. We made two groups for this study Group A contains 20 patients who were treated with methotrexate & Group B contains 20 patients who were treated with Enoxaheparin. Demographic characteristics, clinical data & final response rate with follow up of patients with generalized lichen planus treated with methtrexate showed in Table 1 & treated with Enoxheparin showed in Table 2.

Table 1: Clinical data and treatment results of patients treated with methotrexate

Pt no	Age (yrs)	Sex	Duration of disease (months)	Extracutaneous involvement	Previous treatment	Initial dose of Heparin (mg/SC)	Total dose (mg)	Total no of doses		Adverse drug reaction	Relapse	Status of treatment	Duration of treatment (wks)
								CR	NC				
1	12	M	18	-	Anitihistamin ics and emollients	5	80			-	2 m	Complete	16
2	38	F	6	Oral	Topical CS	5	120			-	-	Complete	24
3	32	F	8	-	-	5	120			-	3m	Complete	24
4	38	M	9	-	-	5	120			-	3 ½ m	Complete	24
5	30	F	18	Oral, genital	Topical CS	5	120			-	1 ½ m	Complete	24
6	58	M	24	Oral, genital	-	5	120			-	4 m	Complete	24
7	40	F	3	-	-	5	100			-	2 m	Complete	20
8	65	M	12	-	-	5	120			-	6 m	Complete	24
9	20	F	9	-	-	5	120			-	-	Complete	24
10	24	M	6	-	-	5	120		+	-	-	Complete	24
11	39	M	12	-	-	5	120		+	-	-	Complete	24
12	45	F	6	-	-	5	100		+	-	-	Complete	20
13	49	F	11	Oral	Topical CS	5	100		+	-	-	Complete	20
14	63	M	4	-	-	5	120		-	-	-	Complete	24
15	55	M	10	Genital	Topical CS	5	100		+	-	-	Complete	20
16	25	F	2	-	-	5	120		+	-	-	Complete	24
17	35	F	3	Oral	Topical CS	5	100		+	-	-	Complete	20
18	69	M	18	-	-	5	120		-	-	-	Complete	20
19	51	M	9	-	-	5	120		-	-	-	Complete	24
20	45	M	8	-	-	5	20		-	-	-	complete	24

Table 2: Clinical data and treatment results of patients treated with low molecular weight heparin

Pt no	Age (yrs)	Sex	Duration of disease (months)	Extracutaneous involvement	Previous treatment	Initial dose of Heparin (mg/SC)	Total dose (mg)	Total no of doses		Adverse drug reaction	Relapse	Status of treatment	Duration of treatment (wks)
								CR	NC				
1	12	M	18	-	Anitihistaminics and emollients	5	80			-	2 m	Complete	16
2	38	F	6	Oral	Topical CS	5	120			-	-	Complete	24
3	32	F	8	-	-	5	120			-	3m	Complete	24
4	38	M	9	-	-	5	120			-	3 ½ m	Complete	24
5	30	F	18	Oral, genital	Topical CS	5	120			-	1 ½ m	Complete	24
6	58	M	24	Oral, genital	-	5	120			-	4 m	Complete	24
7	40	F	3	-	-	5	100			-	2 m	Complete	20
8	65	M	12	-	-	5	120			-	6 m	Complete	24
9	20	F	9	-	-	5	120			-	-	Complete	24
10	24	M	6	-	-	5	120		+	-	-	Complete	24
11	39	M	12	-	-	5	120		+	-	-	Complete	24
12	45	F	6	-	-	5	100		+	-	-	Complete	20
13	49	F	11	Oral	Topical CS	5	100		+	-	-	Complete	20
14	63	M	4	-	-	5	120		-	-	-	Complete	24
15	55	M	10	Genital	Topical CS	5	100		+	-	-	Complete	20
16	25	F	2	-	-	5	120		+	-	-	Complete	24
17	35	F	3	Oral	Topical CS	5	100		+	-	-	Complete	20
18	69	M	18	-	-	5	120		-	-	-	Complete	20
19	51	M	9	-	-	5	120		-	-	-	Complete	24
20	45	M	8	-	-	5	20		-	-	-	complete	24

In Group A 20 patients(11 male & 9 female), the age of patients ranges from 12 years to 69 years the mean 47.35±14.81 years. And Group B 20 patients(11 male & 9 female), the age of patients ranges from 6 years to 68 years the mean 41.65±15.56 years paired "*t*" at 1.186 d.f. = 38, *P* value =0.243, which was statistically not significant. Similar with duration of disease in group A ranges from 2 months to 24 months mean was 7.85±4.70 months, with group B ranges from 2 months to 24 months mean was 9.5±5.56 months, paired "*t*" at 1.102, d.f. = 38, *P* value =0.318, which was statistically not significant.

Total doses of methotrexate required to cleared the disease ranges from 120mg to 360mg, median 330, Q1 255, Q3 360 n± sd 300±79.67 and with enoxheparin ranges from 20 to 120 median 120, Q1 100, Q3 120 n±sd 108± 23.75. According to Mann Whitneys U test is statistically significant p value <0.001 at Z5.405.

Duration of treatment for group A (methtrexate) was ranging from 4 weeks to 24 weeks the mean 20.73weeks±3.95 And for group B (heparin) ranging from 4 weeks to 24 weeks mean 22.4=2.39 paired t test =1.598 at d.f.=37, p-value=0.119 which was not statistically significant.

Adverse drug reaction for group A noted for 1 patient & for group B no adverse reaction noted According to fishes exact test p value=1.

Relapse of disease in patients who were taking methotrexate was 3/20(15%) and with heparin 7/20(35%) according to chi square test =2.133 at d.f.=1, pvalue=0.144 which was statistically not significant.

Complete clearance of disease in patients who were taking methotrexate was 19/20 and with heparin 13/20 according to Fischers exact test pvalue=0.043 which was statistically significant. In our study we want to emphasized that methotrexate is a better drug in generalized lichen planus for complete clearance of disease, with lesser relapse rate.

Discussion

Lichen planus represents T-cell mediated autoimmune damage to basal keratinocytes that may express altered self-antigen or in cases trigged by exogenous agents, processed antigens present on keratinocyte surface.[10] When precipitating factor is known, removal of such an agent may be helpful. Spontaneous remission of cutaneous lesion has been observed in up to one third of patients after 1 year of onset.[11] Lichen planus may be completely asymptomatic or associated with significant pruritus. Even though it subsides spontaneously or is not associated with symptoms, post-lichen planus violaceous or brownish pigmentation may persist for long time and it's associated with significant cosmetic disability, particularly in pigmented races like ours. Therefore, early aggressive treatment of LP is reasonable approach.

Methotrexate is an antimetabolite used to treat various malignancies and autoimmune inflammatory diseases. It is a competitive inhibitor of dihydro folate reductase, which is involved in conversion of folic acid to reduce folate cofactors, required for 1- carbon unit transfers in DNA synthesis. Thus, it inhibit replication of T & B lymphocytes. Methotrexate possesses both immunomodulatory & anti-inflammatory properties. Other potential mechanisms of methotrexate activity in skin diseases are suppression of inflammatory cell chemotaxis, inhibition of monocyte/ macrophage activation, and inhibition of histamine release from basophils.[12]

The beneficial role of methotrexate in lichen planus, cutaneous,[3] oral[13,14] and erosive valvo-vaginal,[14-16] has recently been established. Lundqvist et al.(2002) assessed the role of weekly methotrexate (10-15mg) in addition to topical corticosteroids in severe mucosal LP involving oral & genital mucosa of their 4 patients after 17 months of treatment, they found methotrexate to be effective and safe in LP.[14] Similarly in our study 7/20 patients having oral and genital LP al are responded well with 6 months of methotrexate treatment. All patients are follow up upto 1 year only one patient had recurrence after 3 months.

Tauran et al., in a retrospective review of 11 patients of generalized LP treated with methotrexate (weekly 15-20mg), observed improvement of mucocutaneous lesions after first month of initiation of treatment.[3] Complete resolution of pruritus & disappearance of skin lesions was observed in 10 patients at the end of 1 month. Their treatment regimen were well tolerated by 10 while in one, it had to be discontinued after 4 weeks due to intolerable nausea & fatigue. Their treatment period spanned between 5 to15 weeks with total cumulative dose required varied between 65 to 260 mg. within 6 month post treatment follow up, one patient had recurrence after 2.5 months.

Our study findings are also in concordance with these studies. By the end of 24 weeks of treatment, 85% of our patients had complete remission and only 3 patients had relapse after 3, 2.5, 2 months respectively. We only included patients with generalized LP with papular and plaque lesions as in other forms of cutaneous LP, the treatment is less defined. Provided that it requires lower doses of methotrexate for shorter duration and given the fact that LP is not as chronic or relapsing as psoriasis, we recommend that weekly methotrexate can be used as alternative to oral corticosteroids in treatment of generalized LP, both in children and adults. Regular monitoring of haematological & biochemical parameters are, however, imperative as recommended for treatment of psoriasis.

The infiltrating cells in LP are predominantly T lymphocytes with very few B lymphocytes More than 90% are activated T lymphocytes expressing HLA-DR antigen & some interleukin-2 receptor.[17] At the early

stage of the LP, the number of Langerhen's cells is increased in the epidermis. Specific conjunction between CD4+ T lymphocytes, Langerhen's cells, CD8+ T-cell lymphocytes & macrophages have been shown in LP lesions with immunoelectron microscopy.[18] It probably represents a cell-mediated immunological response to an induced antigenic change in the skin and mucosa.[3] The ability of activated T lymphocytes to penetrate into the extracellular matrix & migrate to target tissue was found to be related to the expression of this heparanase enzyme.[19] In vitro &in vivo studies in animal model showed that heparin molecules inhibited expression of T- lymphocytes heparanase and, in low doses in mice, inhibited T- cell migration & delayed type hypersensitivity.[20]

Enoxaparin is a low-molecular-dose heparin. It have been evaluated in a number of clinical trials & have been shown to be safe and effective anticoagulants.

Previous studies have shown that a small dose of enoxaparin(3 mg/week subcutaneously) is effective in the treatment of LP.[7-9] Our results are similar with these study results. There are two studies that failed to demonstrate a beneficial effect of enoxaparin in the treatment of LP.[21,22]

As shown in the present study, the administration of 3-mg/week enoxaparin in subcutaneous injection for the treatment of LP is effective, safe & harmless. Complete remission was observed in 13 of 20 patients(65%) who had generalized LP.

The rapid improvement of skin and oral, genital lesions in 6 patients after enoxaparin treatment suggest that enoxaparin could be effective for mucosal lesions. And 7 of 20 patients had relapse after stopping the treatment. Although spontaneous remission may occur in LP, the rapid improvement of skin, oral and genital lesions in 6 patients after enoxaparin treatment suggest that it is safer alternative therapy for LP where we cannot use methotrexate.

Conclusion

To summarize the findings of our study metrhotrexate works wonderfully in generalized LP with mucosal involvement and lesser relapse rate than enoxaparin.

References

1. Rebora A.Hepatitis virus and lichen planus. Arch dermatol 1994;130:1328-29.
2. Criber B, Frances C, Chosidow O. Treatment of lichen planus: an evidence based medicine analysis of efficacy. Arch Dermatol 1998;134:1521-30.
3. Turan H, Baskan EB, Tunali S, Yazici S, Saricaoglu H. Methotrexate for the treatment of generalized lichen planus. J Am Acad Dermatol 2009;60:164-66.
4. Akasu R, From L, Kahn HJ. Lymphocyte and macrophage subsets in active and inactive lesions of lichen planus. Am J Dermatopathol 1993;15:217-23.
5. Boyd AS, Nelder KH. Lichen planus. J Am Acad Dermatol 1991;81:294-319.
6. Farmer ER, Hood AF, Graft – versus – host disease. In: Fitzpatrick TB, Eisen AZ, Wolff K et al, eds. Dermatology in General Medicine, 4th edn. New York: McGraw- Hill, 1993:1510-9.
7. Hodak E, Yosipovitch G, David M et al. Low-dose low-molecular weight heparin (enoxaparin) is beneficial in lichen planus: a preliminary report. J Am Acad Dermatol 1998;38:564-68.
8. Stefanidou MP, Ioannidou DJ, Panayiotides JG, Tosca AD. Low molecular weight heparin; a novel alternative therapeutic approach for lichen planus. Br J Dermatol 1999;141:1040-45.
9. Pacheco H, Kerdel F, Successful treatment of lichen planus with low-molecular-weight heparin: a case series of seven patients. J Dermatolog treat 2001;12:123-26.
10. Sugerman PB, Savage NW, Zhou X, Walsh LJ, Bigby M. Oral lichen planus. Clin Dermatol 2000;18:533.
11. Tompkins JK. Lichen planus: statistical study of 41 cases. Arch Dermatol 1995;71:515-19.
12. Cassetty CT, Shupack JL, Washenik K. Cytotoxic and antimetabolite agents. In Freedberg IM, Eisen AZ, Wolff K, Austen KF, Goldsmith LA, Katz SI, eds. Fitzpatrick's Dermatology in General medicine. McGraw-hills, New York, 2003:2398-2408.
13. Torti DC, Jorizzo JL, McCarty MA. Oral lichen planus- a case series with emphasis on therapy. Arch Dermatol 2007;143:511-15.
14. Nylander LundqvistE, Wahlin YB, Hofer PA. Methotrexate supplemented with steroid ointments for the treatment of sever erosive lichen ruber. Acta Derma Venereol 2002;82:63-64.
15. Jang N, Fischer G, Treatment of erosive valvovaginal lichen planus with methotrexate. Australas J Dermatol 2008;49:216-19.
16. Kortekangas-Savolainen O, Kilholma P. Treatment of valvovaginal erosive and stenosing lichen planus by surgical dilatation and methotrexate. Acta Obstet Gynecol Scand 2007;86:339-43.
17. Sundqvist KG, Wanger L. Expression of lymphocyte activation marker in benign cutaneous T cell infiltrates. Discoid lupus erythematosus versus lichen ruber planus. Acta Derm Venereol 1989;69:292-95.
18. Hirota J, Osaki T. Electron microscopy study on cell-to-cell interaction in lichen planus. Pathol Res Pract 1992;188:1033-41.
19. Fridman R, Lider O, Naparstek Y, Fuks Z, Vlodavsky I, Cohen IR. Soluble antigen induces t lymphocytes to secrete an endoglycosidase that degrades the heparin sulphate moity of subendothelial extracellular matrix. J Cell Physiol 1987;130:85-92.
20. Lider O, Mekori YA, Miller T et al. inhibition of T lumphocyte heparanase by heparin prevents T cell migration and T cell mediated immunity. Eur J Immunol 1990;20:493-95.
21. Ria R, Kaur I, Kumar B. Low-dose low-molecular-weight heparin in lichen planus. J Am Acad Dermatol 2002;46:141-3.
22. Ferahbas A, Uksal U, Kutlugun C, Kontas O. Low-molecular-weight heparin (enoxaparin) in lichen planus. J Eur Acad Dermatol Venereol 2003;17:604-5.