
Low-dose low-molecular-weight heparin (enoxaparin) is beneficial in lichen planus: a preliminary report

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Background: Low-dose heparin devoid of anticoagulant activity inhibits T-lymphocyte heparanase activity, which is crucial in T-cell migration to target tissues.

Objective: The purpose of this study was to assess the efficacy of low-dose enoxaparin (Clexane), a low-molecular-weight heparin, as monotherapy in lichen planus.

Methods: Included in the study were 10 patients with widespread histopathologically proven lichen planus (LP) associated with intense pruritus of several months' duration. Patients were given 3 mg enoxaparin, subcutaneously once weekly; three patients received four injections, and seven patients received six injections.

Results: In nine patients the itch disappeared within 2 weeks. Within 4 to 10 weeks in eight of these patients, there was complete regression of the eruption with residual postinflammatory hyperpigmentation; in one patient, there was marked improvement. In one patient, no effect was observed. Of the four patients who also had oral LP, only one showed improvement. No side effects were observed in any of the patients.

Conclusion: These findings indicate that enoxaparin may be a simple, effective treatment for cutaneous LP.

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Evidence suggests that lichen planus (LP) is a T-cell-mediated skin disorder. The dermal infiltrate consists largely of T cells that attach to keratinocytes,¹ abnormally expressing HLA-DR and intercellular adhesion molecule-1 antigens on their surface. This lymphocyte-keratinocyte apposition is believed to lead to the destruction of the epidermis.² Clinical evidence also supports the role of cell-mediated immunity in LP. A clinical and histologic picture resembling LP is often seen in chronic graft-versus-host reaction.³ Cyclosporine, the primary target of which is the T helper/inducer cell, is an effective therapy for LP.^{4,5}

Administration of low doses of heparin devoid

of anticoagulant activity inhibits experimental T lymphocyte-mediated autoimmune disease and allograft rejection in mice.⁶ Furthermore, in humans, low-dose, low-molecular-weight heparin, enoxaparin (Clexane; Rhone Poulenc, France), inhibited the elicitation of allergic contact dermatitis.⁷ These observations provided a rationale for the present study, the purpose of which was to assess the possible therapeutic effect of enoxaparin in LP.

PATIENTS AND METHODS

Included in the study were 10 patients (nine women and one man; aged 33 to 72 years) with widespread histopathologically proven cutaneous LP associated with intense pruritus for 2 to 36 months (Table I). One patient also had palmoplantar involvement (patient 9). Oral lesions were also present in patients 1, 6, 8, and 10. None of the patients was taking any medication known to induce LP-like reactions. Other criteria for exclusion from the study included all the known contraindications for heparin therapy in general: congenital or acquired hemostatic defect, risk of hemorrhage from uncontrolled hypertension, simultaneous use of

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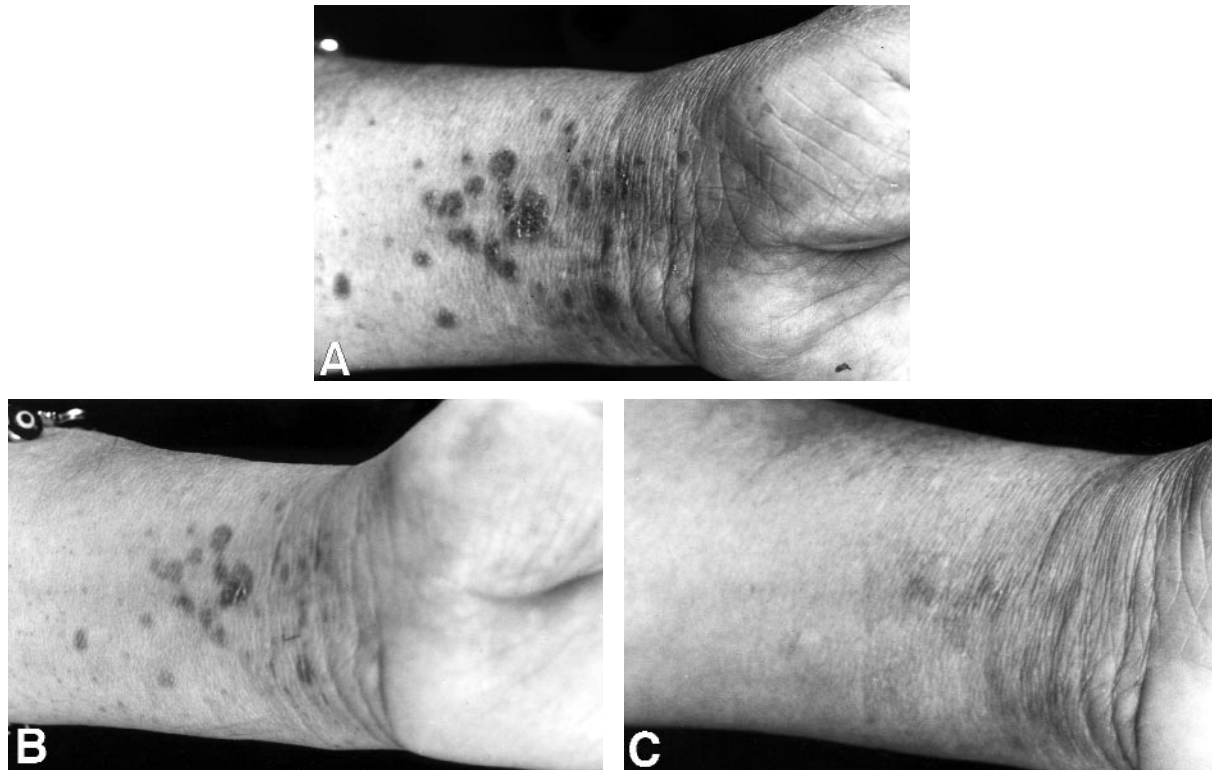


Fig. 1. Lichen planus: Patient 3. **A**, Before therapy. **B**, One week after completion of therapy. **C**, Six months after completion of therapy.

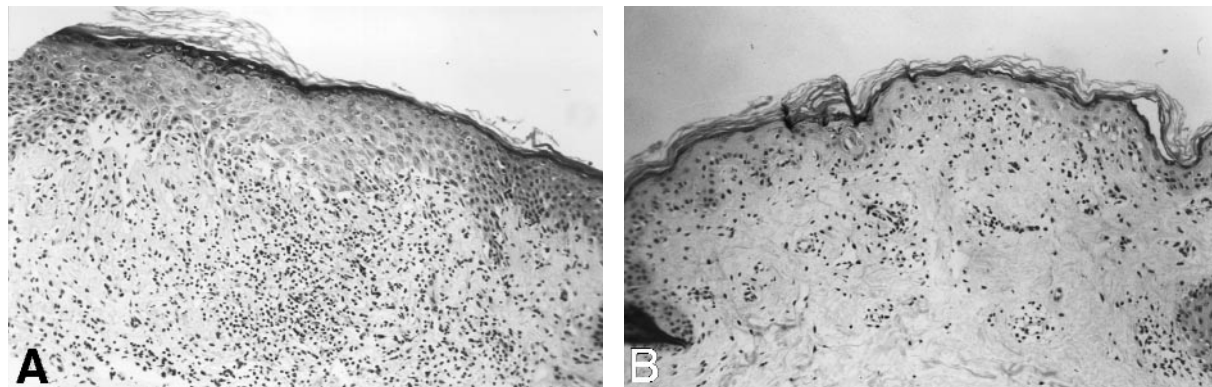


Fig. 2. Biopsy specimens obtained from patient 3. **A**, Pretherapy: Typical LP. **B**, Posttherapy: The epidermis is thinned with slight focal vacuolar changes at the dermoepidermal junction and sparse superficial perivascular lymphocytic infiltration. (Hematoxylin-eosin stain; original magnification $\times 160$.)

nonsteroidal antiinflammatory drugs, active peptic ulcer or recent cerebrovascular accident, and severe liver disease.⁸ In all patients, the results of laboratory tests including complete blood count, liver and renal function, and coagulation function were normal. All sera were negative for hepatitis B or C virus antibodies.

Previous treatment with oral H₁ blockers and topical corticosteroids had been ineffective; these were discontinued, respectively, 4 weeks and 2 weeks before com-

mencement of enoxaparin therapy. Informed consent was obtained from all patients after the study had been approved by the ethics committee of our institution.

Enoxaparin was administered at a dose of 3 mg subcutaneously, once each week. The heparin used in this study was derived from a selected batch, for which immunomodulatory activity was confirmed,⁹ because not all batches of low-molecular-weight heparin preparations contain this activity. Moreover, the dose of the

Table I. Case summaries of patients with lichen planus who were treated with enoxaparin

Patient No.	Age (yr)/Sex	Duration before treatment (mo)	Disappearance of itch (days)	Skin status after 4 injections
1	33/F	4	5	Hyperpigmented macules
2	55/F	12	—	No improvement
3	55/F	4	7	Marked improvement
4	40/F	10	14	Marked improvement
5	60/F	3	3	Hyperpigmented macules
6	47/F	2	3	Marked improvement
7	61/F	11	7	Marked improvement
8	72/F	36	5	Hyperpigmented macules
9	44/M	2	14	Marked improvement
10	60/F	3	10	No improvement

NR, Not relevant.

*Remission was achieved 2 to 4 weeks after termination of therapy.

low-molecular-weight heparin preparation is critical because the dose-response curve of the immunomodulatory effect is bell-shaped.⁹ Patients 1, 2, and 3 received a total of four injections, and patients 4, 5, 6, 7, 8, 9, and 10 received a total of six injections. The clinical response was evaluated once weekly. One week after completion of therapy, a thorough cutaneous examination was made. A posttherapy biopsy specimen was obtained from a lesion adjacent to the pretherapy biopsy site in four patients.

RESULTS

Nine patients showed a clinical response; eight patients achieved a complete remission, and one patient showed marked improvement. One patient showed no change (Table I).

CLINICAL RESPONSE

Antipruritic effect

Nine patients reported the disappearance of the itch, six within week 1 of therapy and three within week 2. There was no recurrence of the itch either during the course of the treatment or in the follow-up period, except in patient 7, in whom a mild itch recurred 5 months later.

Effect on skin lesions

In patients 1, 3, 4, 5, and 6, onset of regression was observed roughly concurrent with the disappearance of the itch; in patients 7, 8, 9, and 10, this was noted 1 to 3 weeks after the disappearance of the itch. Complete clinical remission with postinflammatory hyperpigmented macules was observed in patients 5 and 8 two weeks before

completion of therapy; in patients 1, 4, and 7 at the end of therapy; and in patients 3, 6, and 9 two weeks to one month after cessation of therapy (Fig. 1).

Effect of oral lesions

Of the four patients with oral LP, only patient 10 showed improvement, which was observed roughly concurrent with the improvement of the skin lesions.

Duration of remission

Patients 1, 3, 4, 5, 6, 7, and 9 remained in remission from 5 to 18 months. In patient 1 a few nonpruritic lichenoid papules were observed on the abdomen 4 months after the completion of the therapy, but these disappeared within 2 weeks and did not reappear. In patient 8, three months of remission was followed by a clinical relapse. In patient 9, there has been a sustained marked improvement for 2 months.

Side effects

No side effects were observed in any of the treated patients.

HISTOPATHOLOGIC FINDINGS

In the four patients from whom a posttherapy biopsy specimen was obtained, there was histopathologic improvement. In three patients the epidermis was thinned with only slight focal vacuolar alteration at the dermoepidermal junction; there was a marked decrease in the lymphocytic infiltration with prominent pigment-laden

Skin status after 6 injections	Response of oral lesions	Posttherapy skin biopsy	Duration of remission to present time (mo)
NR	No improvement	Regressing LP	18
NR	NR	LP	—
NR	NR	Regressing LP	11*
Hyperpigmented macules	NR	Postinflammatory	12
Hyperpigmented macules	NR	Regressing LP	12
Marked improvement	No improvement	Not done	7*
Hyperpigmented macules	NR	Not done	5
Hyperpigmented macules	No improvement	Not done	3 and then relapse
Marked improvement	NR	Not done	5*
Marked improvement	Sustained marked improvement for 2 mo	Not done	Sustained marked improvement for 2 mo

macrophages (Fig. 2). In one patient there was mainly postinflammatory hyperpigmentation (Fig. 3).

DISCUSSION

The ability of activated T lymphocytes to negotiate through vascular barriers, penetrate the extracellular matrix, and migrate to target tissues is related to their expression of a heparanase enzyme. This enzyme degrades the heparin-sulfate moiety of the proteoglycan of the extracellular matrix.¹⁰⁻¹² In vitro and in vivo studies in animals showed that low-dose heparin suppressed the expression of T-lymphocyte heparanase activity and concurrently inhibited T-cell migration and delayed-type hypersensitivity.¹³ In rats, once-daily treatment with low-dose heparin, devoid of anticoagulant activity, led to inhibition of allograft rejection and ameliorated adjuvant arthritis or experimental autoimmune encephalomyelitis; higher doses of heparin, possessing anticoagulant activity, were less effective.⁶ The ability of heparin to inhibit these immune reactions was associated with its ability to inhibit expression of T-lymphocyte heparanase.⁶

It appears that the immunomodulatory molecules in heparin might be sulfated disaccharides, which seem to inhibit the production of the key proinflammatory cytokine tumor necrosis factor- α .^{9,14} Low-molecular-weight heparin preparations are produced by fractionation of standard heparin; therefore certain batches may contain active disaccharide molecules. Each batch

of low-molecular-weight heparin must be tested for immunomodulatory activity because the presence of the effective molecules are not detected in the standard anticoagulation and antithrombotic assays used to define and calibrate heparin and low-molecular-weight heparin.

Enoxaparin, a low-molecular-weight heparin, is widely used to prevent and treat thromboembolic disorders. Like other low-molecular-weight heparins, it shows improved pharmacodynamic properties and a better safety profile than nonfractionated heparins. It shows a decreased ability to prolong the activated partial thromboplastin time while still possessing an antithrombotic property through its potentiation of the inhibition of anti-factor A.¹⁵

The recommended daily dose ranges from 20 to 80 mg subcutaneously. Recently, it was found that a small dose (3 mg subcutaneously) of a selected batch of enoxaparin, suppressed the standard patch test reactions in patients with allergic contact dermatitis.⁷ In the present study, we found that this same batch of enoxaparin given subcutaneously once weekly led to remission in 8 of 10 patients with widespread LP.

This study was open and the number of patients was small. Furthermore, the self-limiting course of LP often makes it difficult to evaluate the efficacy of therapy. Spontaneous resolution, however, is usually a slow and gradual process. The rapid improvement and sustained remission observed in our patients strongly suggest that enoxaparin could be effective for cutaneous LP. Oral LP is

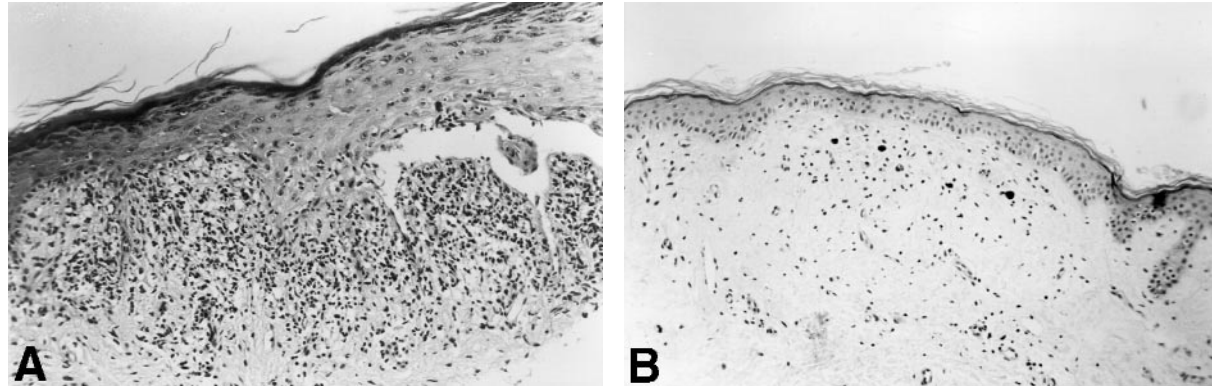


Fig. 3. Biopsy specimens obtained from patient 4. **A**, Pretherapy. **B**, Posttherapy: The epidermis is thinned, and the papillary dermis contains mainly prominent pigment-laden macrophages. (Hematoxylin-eosin stain; original magnification $\times 160$.)

known to be more chronic and recalcitrant than cutaneous LP.^{16,17} It is therefore not surprising that only one of the four patients with mucocutaneous LP showed improvement of the oral lesions. Because the duration of therapy in our study was short, it is conceivable that a longer period of therapy could also have induced improvement of the oral lesions. No side effects were observed, suggesting that low-dose, low-molecular-weight heparin is safe. Some side effects of low-molecular-weight heparin, such as bleeding, are dose dependent and are a direct result of its therapeutic action.⁸ However, other reactions, such as heparin-induced skin necrosis, are idiosyncratic and rare.

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