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The Efficacy of Low-Dose Enoxaparin in Psoriasis

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ABSTRACT

Psoriasis is a frequently encountered inflammatory skin disease with unclear etiology and no curative therapy. Enoxaparin is a low-molecular weight heparin analogue. Heparin and its analogues in low doses have antiproliferative and immunomodulatory effects. Low-dose enoxaparin has inhibitory effects on T cell-mediated immune reactions. T lymphocytes play a key role in the immunopathogenesis of psoriasis. The aim of this study was to evaluate the efficacy of low-dose enoxaparin in the treatment of psoriasis. Twenty-three patients with chronic plaque and guttate psoriasis were enrolled in an open study. Patients were given subcutaneous injections of 5 mg enoxaparin once weekly for a total of 6 weeks. There was a statistically significant difference between the PASI (Psoriasis Area and Severity Index) scores at the beginning and at the 6th week follow up (p=0.008). Four out of 23 patients (17%) showed marked improvement (≥50% reduction in PASI score), 8 patients (35%) showed moderate improvement (25-49% reduction in PASI score), 5 patients (22%) were unchanged (<25% reduction in PASI score). Six patients (26%) experienced worsening with a corresponding increase in the PASI scores. Based on these findings, 52% of patients were considered to get benefit from enoxaparin treatment. No systemic side-effects due to enoxaparin were observed. The only local side-effect recorded in 7 patients (30%) was ecchymosis at the injection site. Low-dose enoxaparin, which appears to be safe, is a candidate to become a future alternative in the treatment of psoriasis. Further studies assessing the optimum dose and duration of treatment, as well as patient subgroups that will benefit most from enoxaparin treatment are warranted. In addition, efficacy of enoxaparin in psoriasis should be compared to those of standard therapeutic modalities.

Keywords: Enoxaparin, psoriasis, treatment, low-molecular-weight heparin

Psoriazis Hastalarinda Düşük Doz Enoksaparinin Etkinliği

ÖZET

Psoriazis sık görülen, etyolojisi aydınlatılmamış ve kesin tedavisi olmayan inflamatuvar bir deri hastalığıdır. Enoksaparin düşük moleküler ağırlıklı bir heparin türevidir. Heparin ve türevleri düşük dozlarda antiproliferatif ve immünomodülatör etkilere sahiptir. Düşük doz enoksaparin özellikle T hücre aracılı immün reaksiyonları bloke etmektedir. T lenfositler psoriazis immünpatogenezinde temel rol oynayan hücrelerdir. Bu çalışmanın amacı, düşük doz enoksaparinin psoriazis tedavisindeki etkinliğini araştırmaktı. Bu amaçla, tek merkezli, tek kollu ve prospektif bir çalışma planlandı. Kronik plak ve guttat tip psoriazisli toplam 23 hastaya, haftada 1 kez, 5 mg emoksaparin subkutan enjeksiyon şeklinde uygulandı. Hastaların başlangıç PASI (Psoriazis Alan ve Şiddet İndeksi) skorları ile 6 haftalık tedavi sonundaki PASI skorları arasında istatistiksel olarak anlamlı fark saptandı (p=0,008). Dört hastada (%17) belirgin düzelme (PASI skoru azalması ≥ %50), 8 hastada (%35) orta dereceli düzelme (PASI skoru azalması %25-49) izlendi. Beş hastada (%22) PASI skorundaki azalma %25'ten az idi. Altı hastada (%26) ise PASI skorunda başlangıca göre artış mevcuttu. Bu bulgulara göre hastaların %52'sinde PASI skorundaki azalma anlamlı idi. Hiçbir hastada enoksaparine bağlı sistemik yan etki gözlenmedi. Tek lokal yan etki, 7 hastada (%30) enjeksiyon bölgesinde ekimoz oluşumu idi. Düşük doz enoksaparin, güvenli yan etki profiliyle psoriazis tedavisinde alternatif bir tedavi seçeneğidir. Etkinlik açısından ise, enoksaparinin psoriazisde uygun doz ve kullanım süresinin, hedef hasta alt grubunun belirlenmesine ve standart psoriazis tedavileri ile karşılaştırılmasına yönelik çalışmalara ihtiyaç vardır.

Anahtar Kelimeler: Enoksaparin, psoriazis, tedavi, düşük moleküler ağırlıklı heparin

Psoriasis is a frequently encountered, chronic inflammatory skin disease. The etiopathogenesis of the disease remains unclear. Clinical presentation and severity of psoriasis may vary in different patients and during different life periods in the same patient. Although not considered a mortal disease, psoriasis has a great negative impact on the affected patients' quality of life, because it creates psychological stress, feelings of shame and physical discomfort.

Current modalities of treatment consist of topical agents, phototherapy, and systemic medications; however, none of these options offers a cure for the disease. Routinely available systemic treatment alternatives have potential serious side effects, which limit their long-term use in a lifetime chronic disease. Research continues to elucidate safer systemic treatment methods with fewer side effects.

The two main events in the pathogenesis of psoriasis are keratinocyte hyperproliferation and dermal inflammation. In recent years, the pivotal role of cellular immune system, especially T lymphocytes, in the immunopathogenesis of psoriasis has been firmly established (1,2). In the light of this information, novel therapeutics with immunomodulatory effects have been developed (3).

Enoxaparin is a low molecular weight (LMW) heparin derivative. It is widely used as an anticoagulant in the prophylaxis and treatment of venous thrombosis. Studies have shown that heparin has immunomodulatory effects at low doses, where it cannot exert an anticoagulant effect. It can inhibit T lymphocyte-mediated reactions, especially due to its negative effects on T lymphocytes (4-6). Heparin and its derivatives also have suppressive effects on keratinocyte proliferation (7). It has recently been reported that low-dose enoxaparin is effective in the treatment of lichen planus, a T-cell-mediated dermatosis (8,9).

The present study aimed to assess the possible clinical efficacy of low-dose enoxaparin in the treatment of psoriasis, grounded on encouraging results from previous studies and considering the fundamental role of T cells in the pathogenesis of psoriasis.

PATIENTS AND METHODS

Patients who applied to Hacettepe University School of Medicine Department of Dermatology Clinic between March 2001 and August 2001 and diagnosed with psoriasis were recruited in this study. The study was planned as a single-center, single-arm, and prospective study.

Inclusion Criteria

Patients with psoriasis, who met the following criteria were enrolled:

1. Age 18 and above
2. Diagnosis of plaque or guttate type psoriasis
3. Involvement of more than 20% of the body surface
4. Diagnosis of psoriasis confirmed by biopsy and histopathological examination
5. No systemic (oral, parenteral, photobiological) treatment for psoriasis within the last 3 months
6. No topical treatment for psoriasis within the last month
7. Patient approval to participate in the study and signing the "Patient Consent Form"

Exclusion Criteria

Patients with psoriasis, who met the following criteria were excluded:

1. Pregnancy or lactation
2. History of bleeding diathesis, uncontrolled hypertension, cerebrovascular accident, peptic ulcer
3. Hypersensitivity to heparin and heparin derivatives and a history of heparin-induced thrombocytopenia
4. History of major surgery within the last 3 months
5. Having a family history of bleeding diathesis, or cerebrovascular accident
6. Concomitant use of oral anticoagulants, acetylsalicylic acid, or other nonsteroidal anti-inflammatory drugs
7. Liver disease and/or abnormal liver function tests
8. Abnormal kidney function tests.

Study Plan

Before starting the treatment, each patient's age, gender, duration of the disease, the presence of psoriasis in the family, and previous treatment methods were questioned and recorded in the pre-prepared forms. Detailed systemic inquiry, particularly questioning of the exclusion criteria, systemic physical and dermatological examination were performed. The clinical type of psoriasis was determined and recorded.

Before the treatment, the extent and severity of the disease were calculated by two different observers using the PASI (Psoriasis Area and Severity Index) scoring method, and the mean of the two values was accepted as the initial PASI score. The patients' lesions were marked on a diagram representing the human body and photographed. Before treatment, laboratory tests including complete blood count, liver and kidney function tests, prothrombin time and active partial thromboplastin time were ordered in all patients.

To avoid possible drug interactions, patients were warned not to use any medications (including painkillers) concurrently without the knowledge of the physician. Also, they were not allowed to use any concomitant topical agents (including moisturizers) during the period of enoxaparin therapy.

During treatment, patients received 5 mg enoxaparin (Clexane®; Eczacıbaşı-Rhone-Poulenc) as a subcutaneous injection once a week for 6 weeks. A 5 mg injection dose was prepared as 0.05 ml in a 26 Gauge insulin syringe, drawn from 20 mg/0.2 ml commercial enoxaparin preparation.

The abdomen was used as the subcutaneous injection site. The injection was administered to the abdominal wall, approximately 10 cm lateral to the midline. The site of injection was alternated every week, i.e., if one dose was given to the right side, the other was administered to the left.

Before each injection, patients were questioned for possible local and systemic side effects. Physical examination and local examination of the previous injection site were performed. Complete blood count and activated partial thromboplastin time were ordered weekly; liver function tests were repeated at the end of the treatment (after the 6th dose). Three weeks and 6 weeks after the start of treatment, PASI scores were calculated by two different observers and the average of the values was recorded. At the end of the treatment, the patients were photographed again.

Evaluation Criteria

Pre-treatment psoriasis area (involved body parts) and severity and response to treatment of the patients in the study group were evaluated using the PASI scoring system (10). In this scoring system, the area is determined by dividing the body into 4 main regions: head, upper extremities, trunk, and lower extremities. These regions were considered to constitute 10%, 20%, 30% and 40% of the total body surface, respectively. For each of the four regions, the area affected by psoriasis was scored with a number value between 0 and 6 according to the percentage of surface area involved. For each site, erythema (E), induration (I), and desquamation (D) were seperately evaluated with a score range of 0-4.

Response to enoxaparin treatment was determined according to changes in PASI scores. After 6 weeks of enoxaparin treatment, 50% or more reduction in PASI score was accepted as "significant improvement", and a decrease of 25-49% was considered as "moderate improvement". Significant and moderate improvement outcomes were accepted as positive responses to enoxaparin. Less than 25% reduction in PASI score was evaluated as "no significant change".

Statistics

Due to limited number of patients in the study group and the non-normal distribution of PASI scores, Wilcoxon test, which is a non-parametric method, was used to compare the PASI values of patients before and after the 6th week of treatment. The Mann-Whitney U test, which is also a non-parametric test, was used to investigate the relationship between the presence of a family history and the age of onset of psoriasis. In comparison of other parameters, cross tables were created and the difference between the groups was tested with the chi-square method.

All statistical evaluations were made using SPSS (Statistical Packages for Social Sciences) for MS Windows Release 10.0.

RESULTS

Twenty-three patients with chronic plaque and guttate psoriasis, 13 males and 10 females, completed the study. The mean age of the patients participating in the study was 36 ± 11 years. The youngest patient was 19 years old, and the oldest patient was 57 years old. The age of onset of the disease ranged from 6 to 38 years, with a mean age of onset of 23 ± 8 years. The mean disease duration was 12.8 ± 9.6 years, and the median disease duration was 12 years (range 0-35 years). The shortest duration of disease was 1 month. Family history of psoriasis was positive in 16 patients (70%) and negative in 7 patients (30%). The age of onset was statistically significantly different in patients with a positive and negative family history (p=0.048). Family history was positive in all 5 patients whose age at onset was 15 years or younger. Demographic characteristics and treatment outcome in enrolled patients are summarized in Table 1.

Table 1. Demographic Characteristics of the Study Group and Response to Enoxaparin

#	G	A	AD	D	F	Ty	PrTx	$PASI_0$	$PASI_6$	$PASI_c$	CR
1	M	52	22	30	+	Pl	T, PUVA, UVB, C, R, M	19.0	23.6	24% ↑	Wor
2	M	35	25	10	+	Pl	T, UVB	24.6	18.0	27% ↓	Moderate
3	M	29	9	20	+	Pl	T, PUVA, M	18.9	16.3	14% ↓	NC
4	M	45	30	15	-	Pl	T, M	11.8	7.0	41% ↓	Moderate
5	M	44	21	23	+	Pl	T, PUVA	29.7	20.1	32% ↓	Moderate
6	M	41	29	12	+	Pl	T	22.2	21.4	4% ↓	NC
7	F	45	21	24	+	Gu	T, PUVA, UVB	18.3	20.1	9% ↑	Wor
8	F	23	6	17	+	Gu	T, UVB	8.8	3.6	59% ↓	Significant
9	M	19	15	4	+	Pl	T	12.3	11.5	7% ↓	NC
10	M	20	14	6	+	Pl	T, PUVA, UVB, C	29.7	32.2	8% ↑	Wor
11	M	40	31	9	+	Pl	T, PUVA, UVB, C, R	25.0	30.2	21% ↑	Wor
12	F	57	22	35	-	Pl	T, PUVA, UVB, C, R M	15.2	8.9	41% ↓	Moderate
13	M	26	20	6	-	Gu	T	20.8	13.5	35% ↓	Moderate
14	F	46	33	13	-	Pl	T, M	28.2	15.3	46% ↓	Moderate
15	F	22	19	3	+	Pl	T	11.7	7.3	38% ↓	Moderate
16	F	44	28	16	-	Pl	T, C, SS	26.1	22.1	15% ↓	NC
17	M	19	14	5	+	Pl	T, UVB	16.0	11.2	30% ↓	Moderate
18	F	41	29	12	+	Pl	T	16.2	15.6	4% ↓	NC
19	M	44	19	25	+	Pl	T, UVB	13.5	14.5	7% ↑	Wor
20	F	37	34	3	+	Pl	T	25.4	30.2	19% ↑	Wor
21	F	38	38	0.08	-	Gu	T	15.2	0	100% ↓	Moderate
22	F	28	24	4	+	Gu	T	12.0	2.8	77% ↓	Moderate
23	M	29	26	3	-	Gu	T, SS	43.2	18.3	58% ↓	Moderate

Abbreviations: #: Patient no.; **G**: gender (***M***: male; ***F***: female); **A**: age; **AD**: age at diagnosis; **D**: duration (years); **F**: family history; **Ty**: Type of psoriasis (***Pl***: Plaque versus ***Gu***: Guttate); **PrTx**: Previous therapies (***T***: topical corticosteroids and/ or calcipotriol; ***C***: cyclosporine; ***R***: oral retinoid; ***M***: Methotrexate; ***SS***: systemic steroids); **$PASI_0$**: PASI score at baseline; **$PASI_6$**: PASI score at the end of treatment; **$PASI_c$**: Change in PASI score (percent) with enoxaparin; **CR**: clinical response (***Wor***: worsening; ***Moderate***: moderate response; ***Significant***: significant response; ***NC***: no change).

The mean pre-treatment PASI score of patients was 20.2 ± 8.0 (range 8.8 to 43.2). After the 6th dose of enoxaparin treatment, the mean post-treatment PASI score was 15.81 ± 8.73. There was a statistically significant difference between the initial and final PASI scores (p=0.008).

A reduction in PASI scores was detected at the end of the treatment in 17 (74%) of 23 patients included in the study: significant improvement in 4 patients (17%); and moderate improvement in 8 patients (35%). In five patients (22%), there was no significant change in PASI scores. Six patients (26%) had an increase in PASI scores ranging from 7.4% to 24% at the end of treatment compared to baseline values. The outcome of enoxaparin therapy according to the changes in PASI scores, is shown in Figure 1. Photographs of two demonstrative patients, before and after the 6th dose of enoxaparin, are shown in Figures 2-5.

In 3 of 17 patients who had a decrease in PASI score after the sixth dose of injection, there was initially an increase in the PASI score of 5-7.5% compared to the baseline after the third dose. The decrease in PASI scores after the sixth dose was less than 25% in all 3 patients.

There was no significant correlation between the change (decrease or increase) in the PASI score at the end of the treatment and gender, age of onset of the disease, duration of the disease, clinical form of psoriasis and previous treatments for psoriasis (p>0.05). A statistically significant correlation was found between family history and the change in PASI score (p=0.06). Family history was positive in all 6 patients whose PASI scores were increased at the end of the treatment.

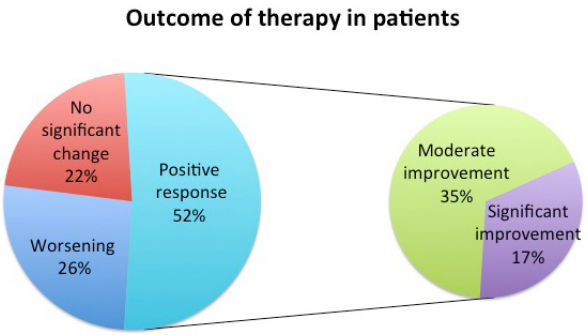

Figure 1. Outcome with enoxaparin treatment in patients with psoriasis. Positive response: PASI score reduction ≥25% (significant improvement: PASI score reduction ≥50%, moderate improvement: PASI score reduction 25-49%). Negative response: no significant change: PASI score reduction <25%.

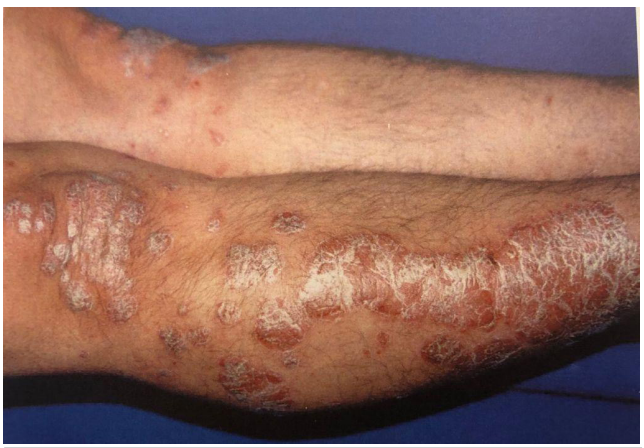

Figure 2. A demonstrative patient with psoriasis before enoxaparin treatment.

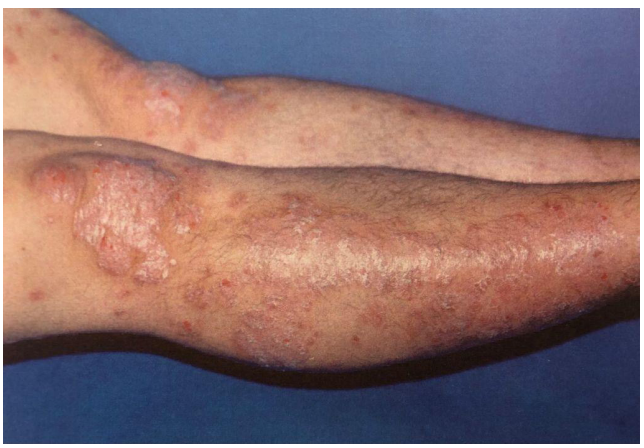

Figure 3. Patient in Figure 2 after enoxaparin treatment.

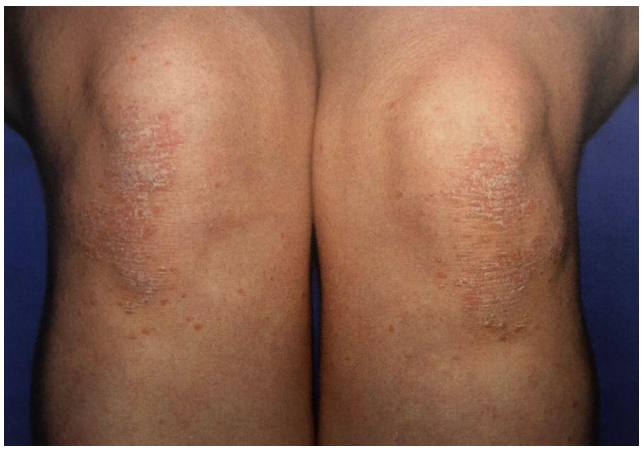

Figure 4. Another demonstrative patient with psoriasis before enoxaparin treatment.

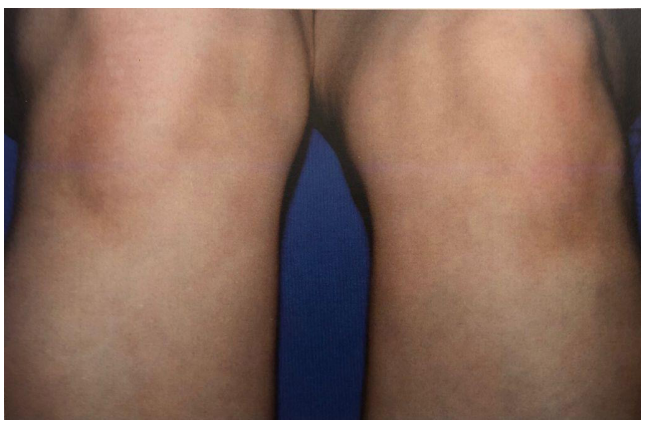

Figure 5. Patient in Figure 4 after enoxaparin treatment.

Weekly complete blood count and activated partial thromboplastin time during the treatment and liver function tests repeated at the end of the treatment were within normal limits in all patients. No systemic side effects or complications related to enoxaparin that required discontinuation of treatment were observed in any of the patients. Ecchymosis formation at the injection site, as the only local side effect related to treatment, was observed in 7 patients (30%). The ecchymoses spontaneously regressed within 2 weeks in all patients.

DISCUSSION

Psoriasis is a common, chronic autoinflammatory and autoimmune disease, that especially affects young adults. Currently, there is no treatment method that provides a complete cure for the disease. Therefore, there is a need for novel, systemic, more effective, and safer therapeutics, appropriate for long-term use.

In the past, the target of systemic treatments for psoriasis has been hyperproliferative keratinocytes. Today, it is known that many of the traditional systemic treatment methods not only harbor antimitotic effects, but immunosuppressive and immunomodulatory effects as well. Immunological studies conducted in recent years have revealed the importance of T-lymphocyte-mediated immunological reactions in the development of psoriasis. Activated T lymphocytes in psoriatic lesions secrete heparin-binding epidermal growth factor (EGF)-like growth factor, which causes epidermal hyperplasia, in conjunction with T helper cell type-1 and type-2 cytokines (11,12).

Activated T lymphocytes harbor a heparinase enzyme, that assists these cells in crossing vascular barriers, entering the extracellular matrix, and reaching their target tissues. This enzyme can degrade heparin sulfate side chains of extracellular matrix proteoglycans (13,14). Lider et al. (5), has shown that low-dose heparin suppresses T lymphocyte heparinase activity and simultaneously inhibits T cell migration and delayed-type hypersensitivity reactions. This effect is observed only at low doses where heparin does not exert an anticoagulant effect. The absence of these positive effects at high heparin doses with anticoagulant effect suggests that heparinase inhibition occurs independent of the anticoagulant effect and is not a competitive bioeffect. The negative effect of heparin on heparinase expression by T cells is thought to devise from a direct interaction between heparin and T lymphocytes (4,15). Through animal studies, it was interpreted that the dose at which heparin can exert an immunomodulatory effect on humans should be approximately 1-2 mg (150-300 units) per day (5).

Heparin has a heterogeneous structure consisting of many polysaccharides. Sulfated disaccharide groups in the heparin structure are presumed to exert immunomodulatory effects (6,16). LMW heparins are obtained by chemical degradation of standard heparin. Therefore, only certain LMW heparins contain active disaccharide molecules with immunological action.

Enoxaparin is a widely used LMW heparin that conveys the immunomodulatory effects of heparin (16). The recommended daily dose for anticoagulant effect is 20-80 mg. Its immunomodulatory effects arise at much lower doses.

The first study on the immunomodulatory effects of enoxaparin in humans was performed by Ingber et al. (17). The authors investigated the effects of low-dose enoxaparin on patch test results in patients with allergic contact dermatitis and found that 8 (38%) of 21 positive reactions converted to negative after a single dose of 3 mg enoxaparin.

The first preliminary study on the therapeutic use of low-dose enoxaparin in dermatology arena was published by Hodak et al. (8). In their study, 3 mg enoxaparin was administered subcutaneously once a week for 4-6 weeks to 10 patients with extensive lichen planus, and complete remission was observed in 8 of 10 patients at the end of the treatment period. Histopathological improvement was also noted in biopsy samples of 4 clinical responders. In another study, Stefanidou et al. (9) explored the therapeutic efficacy of enoxaparin in patients with lichen planus and reported complete remission in 11 of 18 patients and significant improvement in 2 patients. In their study, patients were administered 3 mg of enoxaparin weekly subcutaneously for a total of 6-13 weeks. No local or systemic side effects were observed in any of the patients. These encouraging early preliminary studies were followed by other international research in the succeeding years. In the literature, there are mostly open-ended and non-randomized studies involving a small number of patients and investigating the efficacy of subcutaneous enoxaparin in lichen planus (18-22). In the single randomized study, Iraji et al. (23) compared the efficacy of low-dose enoxaparin with oral prednisolone and concluded that, although its therapeutic efficacy is lower than that of oral prednisolone, low-dose enoxaparin has therapeutic efficacy in lichen planus and that it may be a safer treatment alternative with fewer side effects.

It is not known exactly by which mechanism(s) enoxaparin improves lichen planus. In active lichen planus lesions, there is accumulation of fibrin and fibrin degradation products in the dermoepidermal junction area, around the lymphocytic infiltration. Although fibrin deposition is not pathognomonic for lichen planus, it is a very characteristic finding. This finding might implicate that lymphokines released in lichen planus are responsible for activation of

the coagulation system. However, the dose of enoxaparin utilized in studies is low and does not exert an anticoagulant effect. It may therefore be deduced that the efficacy mechanism of enoxaparin in lichen planus is not through its effects on the coagulation system. It is plausible that its efficacy mechanism could be through inhibition of the heparinase enzyme, involved in T lymphocyte recruitment and accumulation in target tissues. In addition, large amounts of proinflammatory cytokines such as TNF-α, granulocyte/macrophage colony simulating factor, IL-1β, IL-6, and chemokines are produced by keratinocytes in lichen planus (24). Keratinocytes, through these cytokines, chemokines, and adhesion molecules, can interact with fibroblasts, endothelial cells, and lymphocytes; the outcome is inflammation and cytotoxic destruction of keratinocytes by T lymphocytes. It is known that heparin inhibits TNF-α, which is one of the key molecules in the emergence of inflammation (9). Thus, inhibition of TNF-α might represent another alternative mechanism in enoxaparin's efficacy in lichen planus. TNF-α is also an important cytokine in the pathogenesis of psoriasis and TNF-α levels are increased in lesional and nonlesional skin and serum of patients with psoriasis (25). Considering that T lymphocytes and keratinocytes are the cells that play pivotal roles in the pathogenesis of psoriasis as well as lichen planus, it can be extrapolated that enoxaparin may also be effective in the treatment of psoriasis. However, there is no published study on the efficacy of enoxaparin in psoriasis hitherto.

In our preliminary study, we investigated the efficacy of low-dose enoxaparin in the treatment of psoriasis. For this purpose, we administered subcutaneous weekly injections of 5 mg enoxaparin to 23 patients with chronic plaque and guttate type psoriasis for 6 weeks. The injected dose was high enough to exert immunomodulatory effects, yet low enough to avoid anticoagulant effects. We evaluated the clinical efficacy of enoxaparin in psoriasis, using the PASI scoring system. There was a statistically significant difference between the PASI scores of patients at the baseline (before treatment) and PASI scores at the end of the treatment (after the 6th dose of enoxaparin) ($p=0.008$). At the end of the treatment, 74% of the patients had a decrease in the PASI scores: significant and moderate responses were noted in 17%, and 35% of patients, respectively. There was no significant reduction in PASI scores in 22% of treated patients. Based on these findings, there was a positive response (significant or moderate improvement) to enoxaparin in 52% of patients with psoriasis.

In our study, there was no correlation between the alteration (decrease or increase) in PASI scores and gender, age of onset of psoriasis, duration of psoriasis, clinical form of psoriasis (plaque or guttate) and previous treatments. However, the positivity rate of family history of psoriasis was 70% in our study group, which was rather higher than the normally expected 1/3 rate within the psoriasis population. It was remarkable that all 6 patients, whose PASI scores increased at the end of the treatment, had a positive family history. Three of these 6 patients had previously received both systemic therapy and phototherapy. Familial psoriasis is intractable and typically refractory to therapy. We believe that higher family history positivity rate in our study may have negatively influenced the response to enoxaparin treatment.

The dose of enoxaparin (5 mg/week) used in our study was far below the dose exerting an anticoagulant effect. We reflect that its possible mechanism of action in psoriasis is through immunomodulatory effects, as in other T cell-mediated dermatoses such as allergic contact dermatitis and lichen planus. Inhibition of heparinase enzyme or inhibition of TNF-α might account for enoxaparin's beneficial therapeutic efficacy in psoriasis.

A potential pathogenetic mechanism in T-cell-mediated disorders with epidermal proliferation and Koebner phenomenon is autocrine dysregulation. Abnormal epithelial proliferation occurs because of endogenous production of various polypeptide growth factors and activation of their corresponding receptors. It is assumed that part of immunomodulatory effects of heparin and its derivatives could arise from binding to some growth factors and inhibiting them from binding to their own receptors.

Amphiguline is a growth factor from the epidermal growth factor family, like EGF and TGF-α, and stimulates fibroblast and keratinocyte proliferation. EGF, TGF-α, amphiregulin and heparin-binding EGF-like growth factor act by binding to a common receptor in the tyrosine kinase structure, named the epidermal growth factor receptor (EGFR). While EGF and TGF-α do not require any cofactor to bind to the receptor, amphiregulin and heparin-binding EGF-like growth factor need a heparin sulfate proteolytic as an essential cofactor to bind to the receptor. It is thought that exogenous heparin-like glycosaminoglycans competitively inhibit this proteolytic cofactor and block the binding of growth factors to their receptors, thereby inhibiting autonomous keratinocyte proliferation (7,26). Thus, blockage of growth factor function might represent a third mechanism for enoxaparin's efficacy in psoriasis.

No systemic side effects related to treatment were observed in our study group. No abnormality was detected in the laboratory tests performed during and after the treatment. As the only local side effect, ecchymosis at the injection site was observed. Although these findings suggest that low-dose enoxaparin therapy is quite safe, it should be kept in mind that rare side effects such as hypersensitivity reactions may develop independent of the dose.

In conclusion, low-dose enoxaparin represents a candidate novel therapeutic alternative in psoriasis and has a favorable side-effect profile. In terms of efficacy, further large-scale studies are warranted to determine the appropriate dosage and duration of therapy, the target psoriasis subgroup, and comparison of enoxaparin with standard psoriasis treatments.

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