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Enoxaparin in the treatment of psoriasis

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Abstract
Psoriasis is a chronic, immune-mediated inflammatory disease with diverse clinical manifestations and significant systemic burden. While current treatments, including biologics, offer effective control, limitations such as high cost, adverse effects, and resistance necessitate alternative options. Enoxaparin, a low-molecular-weight heparin, has shown promising anti-inflammatory and immunomodulatory effects at low, non-anticoagulant doses, particularly through its inhibition of T-cell activity, cytokine signaling, and keratinocyte proliferation. These mechanisms suggest its potential as an adjunct or alternative therapy in psoriasis management, warranting further clinical research to confirm its efficacy and safety in long-term use.

Keywords: Psoriasis, enoxaparin, immunomodulatory

Introduction

Psoriasis (Ps) is a chronic, immune-mediated, multisystem disorder predominantly driven by T-cell-mediated inflammation, characterized by a broad spectrum of clinical manifestations and a substantial disease burden. It is a lifelong dermatological condition with considerable clinical variability, presenting in diverse forms such as plaque, inverse (flexural), guttate, pustular, erythrodermic, among others [1].

The most prevalent clinical variant of Ps is plaque Ps, which is typified by sharply demarcated, erythematous plaques overlaid with thick, silvery-white scaling [2]. Common anatomical sites of involvement include the extensor surfaces of the elbows and knees, the lumbosacral region, the scalp, palms, soles, genitalia, and nail apparatus; nonetheless, any cutaneous area can be affected [3].

Given its systemic nature, Ps is frequently accompanied by a range of comorbidities that contribute to the overall disease burden. These include psoriatic arthritis (PsA), cardiovascular diseases (CVD), inflammatory bowel diseases (IBD), and psychiatric disorders such as depression [4].

Conventional therapeutic strategies for Ps encompass the use of topical formulations, phototherapy, and systemic agents including methotrexate and cyclosporine. In recent years, the advent of biologic therapies targeting precise immunologic pathways particularly interleukin-17 (IL-17) and interleukin-23 (IL-23) inhibitors has markedly transformed disease management by offering enhanced efficacy and favorable safety profiles [5]

Despite these advancements, biologic treatments are associated with certain drawbacks, notably high cost, potential loss of therapeutic response over time, and the occurrence of adverse effects in some individuals [1]. Consequently, ongoing research is directed toward the development of alternative or adjunctive therapies capable of overcoming these challenges [6].

Enoxaparin, classified as a low-molecular-weight heparin (LMWH), has been shown to possess anti-inflammatory capabilities. Experimental evidence indicates its potential utility in modulating immune function, particularly through the inhibition of T cell-mediated inflammatory pathways, thus offering promise as a therapeutic option in chronic inflammatory diseases such as Ps [6].

Enoxaparin

Heparins are biological agents derived from mast cells and are primarily employed in clinical settings as anticoagulants. They are most commonly extracted from porcine intestinal mucosa [7]. These agents, which are administered parenterally, act rapidly and are classified

into two major categories: unfractionated heparin (UFH), which has a long history of clinical use, and LMWHs. Over the past few decades, LMWHs have largely supplanted UFH due to their enhanced efficacy, improved safety profile, and the advantage of not requiring routine laboratory monitoring to assess therapeutic efficacy. Complications such as bleeding and heparin-induced thrombocytopenia, which are more commonly linked to UFH, occur infrequently with LMWHs [8]

LMWHs are derived through either enzymatic or chemical depolymerization processes applied to UFH, which is originally extracted from porcine intestinal mucosa or bovine lung tissue. Currently, eight chemically distinct LMWHs have been officially recognized and approved for clinical use: bemiparin, dalteparin, enoxaparin, parnaparin, nadroparin, reviparin, certoparin, and tinzaparin. These agents were initially developed for the prevention of thromboembolic events and the treatment of acute myocardial infarction. At present, numerous clinical investigations are underway to explore the potential of LMWHs in treating a broader spectrum of diseases [9]

FDA approved enoxaparin (Lovenox, Sanofi-Aventis U.S.), a LMWH, in 1993. Subsequently, various generic formulations of enoxaparin have also gained regulatory approval. In general, LMWHs demonstrate comparable therapeutic efficacy to UFH in the treatment of conditions such as deep vein thrombosis (DVT) and pulmonary embolism (PE), and they have increasingly replaced UFH in several clinical contexts for pragmatic reasons. LMWHs consist of fragments of UFH, a heterogeneous ensemble of sulfated glycosaminoglycans, and possess approximately 1/3 the molecular weight of UFH. This reduced molecular size, due to the presence of a shorter pentasaccharide sequence, limits the formation of the ternary complex required for effective thrombin inhibition [10]

Structure of enoxaparin

Enoxaparin is composed of a heterogeneous mixture of structurally intricate, highly negatively charged oligosaccharide fragments, ranging in size from disaccharides (dp2) to approximately 22-saccharide chains (dp22). These fragments lack a fully defined structure and exhibit inherent variability. Importantly, enoxaparin contains both anticoagulant and non-anticoagulant components. A growing body of evidence suggests that the non-anticoagulant fractions are primarily responsible for the observed anti-inflammatory properties attributed to enoxaparin [11]

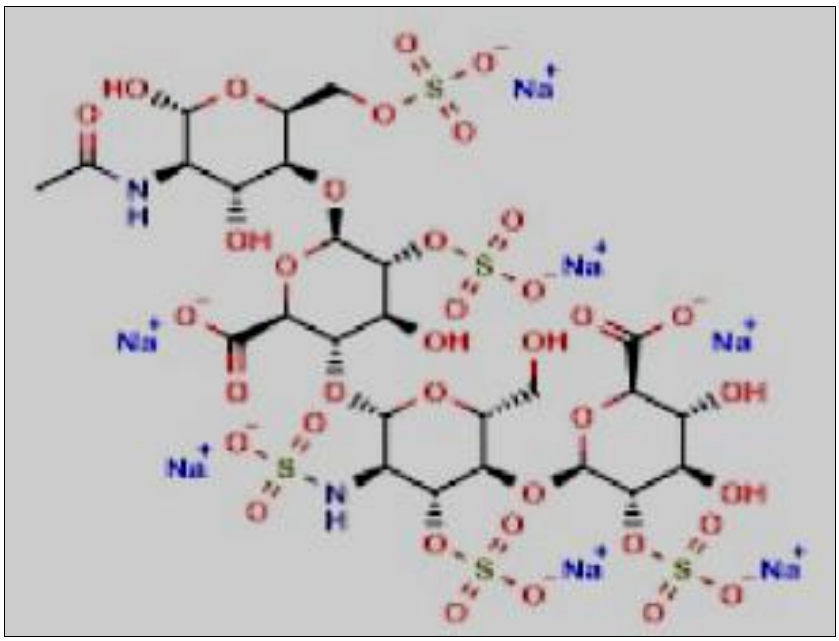

Fig 1: Structural formula of enoxaparin sodium [12]

Pharmacokinetics

Rote of administration: LMWH including enoxaparin, are administered subcutaneously. This route has significant implications for the long-term selection of anticoagulant agents, particularly in the context of thromboprophylaxis [13]

Absorption: Enoxaparin reaches its peak pharmacodynamic activity approximately four hours post-administration. The plasma presence of anti-Factor Xa activity, a surrogate marker for enoxaparin efficacy, persists for approximately 12 hours following injection [14].

Distribution: Based on anti-Factor Xa activity measurements, the apparent volume of distribution for enoxaparin is estimated to be approximately 4.3 liters [15].

Metabolism: Hepatic metabolism of enoxaparin involves desulfation and depolymerization processes, resulting in lower molecular weight fragments that exhibit diminished biological activity [16].

Excretion: Enoxaparin exhibits first-order elimination kinetics and is predominantly cleared via renal excretion. After a single dose, the elimination half-life ranges from 3 to 4.5 hours. With repeated administration, this half-life extends to approximately 7 hours. Given that renal clearance is the principal route of elimination, there is heightened concern regarding drug accumulation and increased bleeding risk in individuals with impaired renal function [14].

Mechanism of Action: Enoxaparin, a type of LMWH, possesses an average molecular weight ranging between

4,000 and 5,000 Daltons. It functions as an indirect anticoagulant by binding to and enhancing the activity of antithrombin III, a serine protease inhibitor. This interaction occurs via a specific pentasaccharide sequence, leading to the formation of a complex that irreversibly inactivates coagulation factor Xa. The principal distinction between UFH and LMWHs such as enoxaparin lies in their differential inhibitory effects on thrombin (factor IIa) and factor Xa. Smaller heparin fragments lack the necessary chain length to simultaneously bind both thrombin and antithrombin III. Consequently, LMWHs, due to their reduced molecular size, exhibit enhanced selectivity for factor Xa inhibition and comparatively diminished activity against thrombin. Enoxaparin, therefore, demonstrates a lower degree of factor IIa inhibition than UFH. The ratio of anti-factor Xa to anti-factor IIa activity among LMWHs typically ranges from 2:1 to 4:1 [17].

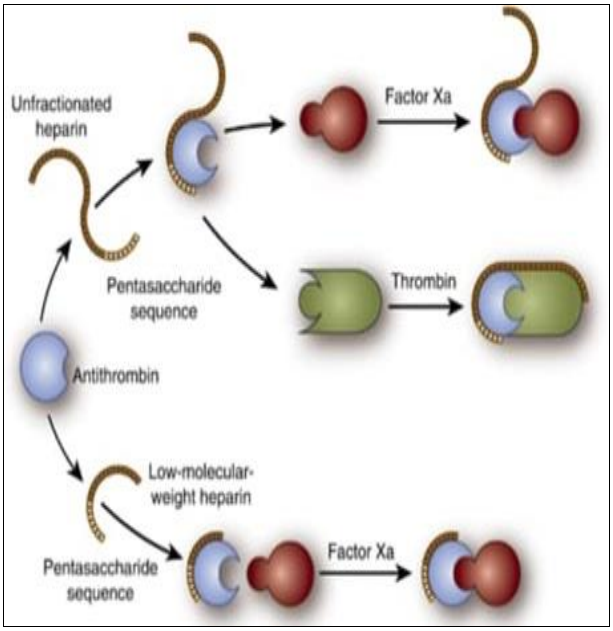

Fig 2: Mechanism of Action of Enoxaparin [18]

The immunomodulatory effect of enoxaparin

TThe anti-inflammatory properties of LMWH are primarily attributed to its modulatory effects on two pivotal cytokines: interferon-gamma (IFNγ) and interleukin-6 (IL-6). The molecular interaction between heparin and these cytokines, along with the resultant inhibition of their biological activity, has been elucidated through extensive molecular dynamics simulations. The impact of LMWH on IFNγ signaling was further evaluated using Wilm's Tumor 1 (WT1) Inducible Stably Human (WISH) cells, where the assessment focused on antiproliferative effects and the nuclear translocation of phosphorylated signal transducer and activator of transcription 1 (p-STAT1). LMWH exhibits high-affinity binding to IFNγ, effectively blocking its interaction with the cellular receptor. It also interferes with IL-6 signaling by binding either directly to IL-6 or to the IL-6/IL-6Rα complex, thereby preventing the assembly of the IL-6/IL-6Rα/gp130 signaling complex required for downstream activity [19].

Furthermore, research has demonstrated that heparin interacts with various components of the complement system. Specifically, it can inhibit both the classical and alternative complement pathways by binding to and functionally inhibiting key complement factors, such as the activated C1 complex and C3 convertase, as well as by disrupting the formation of membrane-bound terminal complexes, ultimately impeding cytolytic activity [20].

Heparin also plays a role in modulating leukocyte behavior during inflammation. It has been shown to suppress neutrophil chemotaxis and leukocyte migration. Additionally, heparin binds to selectins, including platelet/leukocyte selectin (P/L-selectin), which mediate leukocyte adhesion to the endothelial surface. It also interacts with integrin-type adhesion molecules, thereby inhibiting the activation and firm adhesion of leukocytes to endothelial cells [21].

Low molecular weight heparin in psoriasis

Heparin-binding epidermal growth factor-like growth factor (HB-EGF) and amphiregulin (AREG) are ligands within the epidermal growth factor (EGF) family that engage the epidermal growth factor receptor (EGFR) in the epidermis. HB-EGF has been identified as an autocrine mitogen for human epidermal keratinocytes. Notably, the transcription levels of both HB-EGF and AREG are significantly elevated in psoriatic epidermis relative to healthy skin [19]. This upregulation implies a potential pathogenic role for these growth factors in hyperproliferative dermatologic conditions such as Ps. Experimental data indicate that neutralizing antibodies targeting AREG attenuate keratinocyte proliferation *in vitro* and diminish epidermal hyperplasia *in vivo* in a human skin graft model using severe combined immunodeficient mice [22].

Psoriatic plaques are characterized by a dense infiltration of immune cells, including T lymphocytes, macrophages, and neutrophils. Among these, contemporary studies and emerging therapeutic approaches have predominantly emphasized the functions of T cells, particularly their transendothelial migration and cytokine secretion profiles. The majority of T lymphocytes present in psoriatic plaques are known to produce type 1 T-helper (TH1) cytokines, such as tumor necrosis factor-alpha (TNF-α), interleukin-2 (IL-2), and interferon-gamma (IFN-γ) [20].

LMWH when administered in sub-anticoagulant doses, exhibits immunomodulatory effects. These effects are primarily mediated through inhibitory actions on T lymphocyte-driven responses. Moreover, both unfractionated heparin and its derivatives have demonstrated the capacity to suppress keratinocyte proliferation [6].

Recent investigations have shown that low-dose enoxaparin can be therapeutically beneficial in lichen planus, an inflammatory dermatosis driven by T-cell activity. Unlike EGF and transforming growth factor-alpha (TGF-α), which are capable of receptor engagement without auxiliary molecules, both AREG and HB-EGF require heparan sulfate proteoglycans as essential cofactors to facilitate receptor binding. It is hypothesized that exogenously administered heparin-like glycosaminoglycans act in a competitive manner against these proteoglycans, thereby obstructing the interaction between growth factors and their receptors. This interference may lead to the inhibition of autocrine keratinocyte proliferation. Consequently, the interruption of growth factor signaling pathways might constitute a 3rd mechanism through which enoxaparin exerts therapeutic efficacy in Ps [6].

References

1. Raharja A, Mahil SK, Barker JN. Psoriasis: a brief overview. Clin Med (Lond). 2021;21(2):170-173.
2. Michalek IM, Loring B, John SM. A systematic review of worldwide epidemiology of psoriasis. J Eur Acad Dermatol Venereol. 2017;31(2):205-212.
3. Yan B-X, Chen X-Y, Ye L-R, Chen J-Q, Zheng M, Man X-Y. Cutaneous and systemic psoriasis: classifications and classification for the distinction. Front Med (Lausanne). 2021;8:649.
4. Strober B, Karki C, Mason M, Guo N, Holmgren SH, Greenberg JD, *et al.* Characterization of disease burden, comorbidities, and treatment use in a large, US-based cohort: results from the Corrona Psoriasis Registry. J Am Acad Dermatol. 2018;78(2):323-332.
5. Kofoed K, Skov L, Zachariae C. New drugs and treatment targets in psoriasis. Acta Derm Venereol. 2015;95(2):133.
6. Demircioğlu D, Atakan N. The efficacy of low-dose enoxaparin in psoriasis. Acibadem Univ Saglik Bilim Derg. 2022;13(3):352-359.
7. Shute JK. Heparin, low molecular weight heparin, and non-anticoagulant derivatives for the treatment of inflammatory lung disease. Pharmaceuticals (Basel). 2023;16(5):584.
8. Adya KA, Inamdar AC, Palit A. Anticoagulants in dermatology. J Dermatol Venereol Leprol. 2016;82(6):626.
9. Hao C, Sun M, Wang H, Zhang L, Wang W. Low molecular weight heparins and their clinical applications. Prog Mol Biol Transl Sci. 2019;163:21-39.
10. Shaikh SA, Regal RE. Dosing of enoxaparin in renal impairment. P T. 2017;42(4):245.
11. Patel RP, Shastri MD, Ming LC, Zaidi STR, Peterson GM. Therapeutic potential of enoxaparin in lichen planus: exploring reasons for inconsistent reports. Front Pharmacol. 2018;9:586.
12. Sahu S, Lariya NK. Development and validation of spectrophotometric method for the estimation of enoxaparin sodium in marketed formulation. J Drug Deliv Ther. 2019;9(4):1236.
13. Seaman S, Nelson A, Noble S. Cancer-associated thrombosis, low-molecular-weight heparin, and the patient experience: a qualitative study. Patient Prefer Adherence. 2014;8:453-461.
14. Febbraro S, Martínez-Bujanda JL, Magro CN, Bettica P. Bioavailability study of Enoxaparin Sodium Chemi (80 mg/0.8 mL) and Clexane (80 mg/0.8 mL) subcutaneous injection in healthy adults. Int J Clin Pharmacol Ther. 2021;59(11):734.
15. Dawes J. Comparison of the pharmacokinetics of enoxaparin (Clexane) and unfractionated heparin. Acta Chir Scand Suppl. 1990;556:68-74.
16. Fareed J, Hoppensteadt D, Walenga J, Iqbal O, Ma Q, Jeske W, *et al.* Pharmacodynamic and pharmacokinetic properties of enoxaparin: implications for clinical practice. Clin Pharmacokinet. 2003;42(12):1043-57.
17. Nutescu EA, Burnett A, Fanikos J, Spinler S, Wittkowsky A. Erratum to: pharmacology of anticoagulants used in the treatment of venous thromboembolism. J Thromb Thrombolysis. 2016;42(2):296-311.
18. Lai S, Coppola B. Use of enoxaparin in end-stage renal disease. Kidney Int. 2013;84(3):433-436.
19. Litov L, Petkov P, Rangelov M, Ilieva N, Lilkova E, Todorova N, *et al.* Molecular mechanism of the anti-inflammatory action of heparin. Int J Mol Sci. 2021;22(20):10730.
20. Shi C, Wang T, Li J-P, Sullivan MA, Wang C, Wang H, *et al.* Comprehensive landscape of heparin therapy for COVID-19. Carbohydr Polym. 2021;254:117232.
21. Vitiello A, Ferrara F. Low molecular weight heparin, anti-inflammatory/immunoregulatory and antiviral effects, a short update. Cardiovasc Drugs Ther. 2023;37(2):277-281.
22. Zhou X, Chen Y, Cui L, Shi Y, Guo C. Advances in the pathogenesis of psoriasis: from keratinocyte perspective. Cell Death Dis. 2022;13(1):81.

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