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Recommendations on biosimilar low-molecular-weight heparins

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Summary. Based on the results of large clinical trials, several low-molecular-weight heparins (LMWHs) have been approved for prophylaxis and the treatment of venous and arterial thromboembolism. As a result of expiration or pending expiration of patent protection of the originator LMWHs, many generic or biosimilar LMWHs have been approved in some countries and more are likely to be approved elsewhere. Their greater availability may reduce the treatment costs. The Working Party on Requirements for Development of Biosimilar LMWHs of the Subcommittee on Control of Anticoagulation, Scientific and Standardization Committee of the International Society on Thrombosis and Haemostasis has reached a consensus on recommendations to ensure the quality of biosimilar LMWHs as compared with the originator LMWHs.

Keywords: biogeneric, biosimilar, clinical trial, low-molecular-weight heparin, thromboembolism.

Introduction

Low-molecular-weight heparins (LMWHs) have received regulatory approval as individual biological medicines for many indications [1–3]. The patents for LMWHs have expired or will expire. Therefore biosimilar LMWH preparations are

currently under development and have been approved for clinical use in some countries.

The terms ‘generic’, ‘biosimilar’ and ‘biogeneric’ LMWHs may have different meaning in different jurisdictions. In the US, where LMWHs are regarded as individual drugs, the term ‘generic LMWHs’ may be more appropriate, whereas LMWHs are regarded as biological medicines in Europe and therefore copies of branded LMWHs may be considered to be ‘biosimilars’ or ‘biogenics’. There is no entirely satisfactory term to describe these drugs, but we have arbitrarily chosen the term ‘biosimilar’.

The widespread availability of biosimilar LMWHs may reduce the treatment costs associated with LMWHs. However, biosimilar LMWHs may also raise some new concerns related to the presence of inactive, uncharacterized, less and/or more active moieties not found in the originator products. Differences between the biochemical and biological activities of biosimilar and originator LMWHs may have significant clinical consequences. The present expert group defined specific characteristics of originator LMWHs that should be demonstrated for biosimilar LMWHs. Some of these recommendations have been already included in United States Pharmacopeia (USP) and European Pharmacopoei monographs for heparin and LMWHs.

Physicochemical characterization of biosimilar LMWHs

LMWHs can be produced from heparin isolated from animal tissues. The heterogeneity of the starting material may lead to relevant changes in the LMWH preparations. Some tissue-derived impurities may remain in purified LMWH preparations. The tests to define the identity, potency,

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impurities and other safety characteristics of an individual originator LMWH are described in the respective monograph. However, many reliable methods have become available after the release of the patents to define the LMWHs in more detail. Nuclear magnetic resonance (NMR) spectra provide highly specific profiles for each type of LMWH [4]. In addition, several established methods adequately describe the molecular mass distribution of LMWHs [5].

Recommendation of the working party (1)

The lack of significant differences between the biosimilar and originator LMWH should be demonstrated using an adequate study design. All results obtained *in vitro*, *ex vivo* and in clinical settings should adequately demonstrate the similarity or non-inferiority of the biosimilar LMWH relative to the originator LMWH and the confidence intervals should be defined using adequate statistical methods. The number of *in vitro* experiments can be lower and the size of the preclinical and clinical study designs can be smaller for head-to-head comparison of the biosimilar to the originator LMWH than those required for the development of the originator-patented LMWHs. The origin of the starting material (animal tissue and country of origin) of the originator and the biosimilar LMWH should be specified.

The characteristics of a biosimilar LMWH should be described exactly as in the monograph of the originator product and it should be produced exactly in the same way. Tests establishing lot-to-lot variations should be performed, to show that these variations are not larger than in the originator. Point estimate and statistical dispersion should be shown for all data. Similarity testing should be performed on all experimental settings for the biosimilar compared with the originator LMWH [6].

Quantification of a biosimilar LMWH should include an analysis of the internal disaccharide sequences, the terminal 2, 5-anhydromannose residues (nitrous acid degradation method) 1,6-anhydroglucose or unmodified N-sulfated glucosamine end-groups (heparinase treatment method), the average molecular weight and the dispersion of molecular weight.

The content of sulfate and carboxyl groups should be described for the originator and the biosimilar LMWHs by measuring their charge density as expressed by molar ratios of >2 for sulfate/carboxyl groups using conductimetric or potentiometric titration. LMWHs contain 12–20% of antithrombin-binding chains. This should be compared for the biosimilar LMWHs with the originator LMWH using an antithrombin affinity chromatography technique. Heparin cofactor II activity should be comparable for the biosimilar and originator LMWH.

Up to 3% of the natural accompanying dermatan sulphate could be tolerated. Other glycosaminoglycans or impurities detected by NMR and other techniques should not be allowed. No significant differences between biosimilar and originator LMWHs should be found by repeated analysis of one lot of the LMWHs as well as for different lots of both LMWHs.

***In vitro* anticoagulant activities**

The anticoagulant activity of LMWH is determined by various coagulation assays. The methods for inhibition of factor (F)Xa, FIIa and the activated partial thromboplastin time (aPTT) have been standardized in international collaborative studies [7]. They are used by the manufacturers to define the amount of LMWH per milligram dry substance and the activity of one lot and for lot-to-lot variations.

Neutralization of LMWHs may be crucial in patients with bleeding complications. Binding of LMWH to platelet factor 4 (PF4) may induce HIT type II reactions and the generation of antibodies directed against the heparin/PF4 complex. Reliable methods to analyze these effects of LMWHs are neutralization/titration assays [8].

Recommendation of the working party (2)

The ability (biological activities) of a biosimilar LMWH to catalyze inhibition of FXa and thrombin and to prolong the aPTT of pooled human plasma should be in the same range as the originator LMWH. Lot-to-lot variations should not be different for the two products. Appropriate statistical analysis of the data should be performed.

The protamine neutralization or titration and PF4 binding should be assessed with different lots of the biosimilar and originator LMWH. No differences should be allowed for the two LMWHs as demonstrated by appropriate statistical analysis.

Pharmacological studies

Pharmacodynamic and toxicologic studies were performed according to standard procedures. The efficacy of LMWHs was determined in thrombosis models and the bleeding potency in bleeding models. The pathophysiology of thrombosis and bleeding differs in arterial and venous systems. Many thrombosis and bleeding models are available and the thrombosis growth models and ear bleeding time models are best standardized. Such data serves to determine the safety of LMWHs before administration to humans. The number of experiments can be reduced for the development of a biosimilar LMWH compared with development of the originator LMWH. An estimate of the reduction of experiments depends entirely on the statistical design of the studies.

Recommendation of the working party (3)

Studies assessing acute and chronic toxicity should be performed in appropriate settings comparing the biosimilar with the originator LMWH. Acute and repeated toxicity studies in accordance with the GLP (good laboratory practice) guidelines should be available in two animal species using different dosages comparing the biosimilar and the originator product. The number of animals and experiments should be

sufficient to demonstrate no statistically significant difference between the originator and the biosimilar LMWH.

The effects of the biosimilar and originator LMWH should be compared in animal thrombosis models of the venous and the arterial system and in a bleeding model. The lack of difference between the two compounds should be demonstrated.

Pharmacodynamic investigations in human

The pharmacodynamic profiles of LMWHs are investigated in healthy volunteers using different dosages and duration of administration. The design of the studies is based on animal pharmacology results. The parameters of the coagulation system include the anti-FXa, anti-FIIa and aPTT assays. From these data, the anti-FXa/anti-FIIa or the anti-FXa/aPTT ratios can be calculated. Many other new parameters may be of scientific interest but are not standardized at present [9].

Recommendation of the working party (4)

Phase I clinical trials in human volunteers should be performed using the typical dose for prophylaxis of venous thromboembolism over 5–7 days and separately one therapeutic dose twice daily for 5–7 days. The effect on anti-FXa activity, anti-FIIa activity, aPTT, release of tissue factor pathway inhibitor and on the interaction with PF4 should be investigated. The anti-FXa/anti-FIIa ratio of the area under the activity-time curve is calculated from these experiments. The lack of statistically significant differences should be demonstrated for all parameters between the biosimilar and the originator LMWH.

Pharmacodynamics in patients with renal dysfunction

The elimination half-lives of UFH and LMWHs decrease with increasing impairment of renal function. Dose adjustment is necessary to avoid bleeding complications. Anti-FXa, anti-FIIa and aPTT methods are the best, standardized methods for determination of the anticoagulant effects in patients with renal impairment [10].

Recommendation of the working party (5)

It may be relevant to obtain pharmacodynamic data for a biosimilar LMWH. In this case, patients with renal impairment should be investigated using the dose for prophylaxis of venous thromboembolism comparing the originator and biosimilar LMWH once daily subcutaneously for 5–7 days. Parameters are the same as in the phase I study in healthy volunteers. The lack of differences of the biosimilar and the originator LMWH should be demonstrated.

Clinical trials for biosimilar LMWHs

Despite advanced knowledge of the pharmacological and biological actions of LMWHs, whether and how these activities

are related to the antithrombotic and safety properties in patients are not yet established. Therefore, the clinical development of a new LMWH requires appropriate clinical trials comparing its efficacy and safety to that of the originator LMWH for prophylaxis of thromboembolic diseases.

The pathophysiology of thrombus formation in venous and arterial vessels differs. Different dosing regimens with LMWHs are used for prophylaxis of venous thromboembolism postoperatively and in medical patients hospitalized for acute diseases, for treatment of acute venous thromboembolism and acute coronary syndromes [3]. Artificial surfaces are in contact with blood in several clinical situations, e.g. intracoronary stenting, extracorporeal circulation and hemodialysis, where LMWHs routinely are used.

The European Medicines Agency (EMA) has published (London, April 24, 2008) a 'Guideline (Draft) on similar biological, medicinal, products containing low-molecular-weight-heparins.' They recommend at least one double-blind clinical trial to demonstrate the efficacy of a biosimilar LMWH compared with the originator LMWH for the prevention of venous or arterial thromboembolism. The safety data of these trials should include information on the incidences of HIT type II, effect on liver enzymes and on osteoporosis [11].

Recommendation of the working party (6)

The efficacy and safety of a biosimilar LMWH should be demonstrated in comparison to the originator LMWH in clinical trials for every indication for which regulatory approval is sought. This contrasts to the development of new LMWH preparations, which are compared with UFH for efficacy and safety in clinical trials. However, if biosimilar LMWHs claim to be as effective and safe as the originator products, a head-to-head comparison of the two LMWH preparations should also be performed in clinical trials. Thus, a prospective, randomized, double-blind trial should be performed to show the non-inferiority of a biosimilar LMWH compared with the originator LMWH. The most relevant indications are prophylaxis of post-operative venous thromboembolism, treatment of acute deep vein thrombosis and pulmonary embolism, and prevention of acute coronary events in patients with unstable or stable angina.

Conclusion

Based on the heterogeneity of LMWHs, biosimilar LMWHs have to demonstrate their non-inferiority compared with the originator products in preclinical and clinical investigations. Simplified pharmacological, pharmacokinetics and clinical studies may be required for biosimilar LMWHs whose compositional profiles and physicochemical properties are similar to those of the originator.

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