Critical Analysis of Criteria for the Evaluation of Low-Molecular Weight Heparin Biosimilars

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Biological products are pharmaceutical products, of which active ingredients are obtained from biotechnological processes and differ from conventional medications as they are constituted of a mix of complex molecules, of difficult chemical characterization, which are very often incomplete. For this class of medication, the classic concept of generics does not apply and the term "biosimilars" is used to qualify products developed to be similar to the original ones that can be considered clinically equivalent within an established margin.

The low-molecular weight heparins (LMWH) are classified as biological products, of which molecular complexity is due to the diverse origin of the extraction material (unfractionated heparin of animal origin) and to the heparin fractionation and production processes. The clinical usefulness of the LMWH is well established in the treatment and prevention of arterial and venous thrombosis. The International Society on Thrombosis and Hemostasis (ISTH) acknowledges that LMWH biosimilars contribute to reduce the cost of treatment, but are also a source of concern, as biochemical and biological differences can affect the effectiveness and safety of these products.

With the objective of defining characteristics of the original product that must be demonstrated in biosimilars, the ISTH established a consensus to ascertain the quality of LMWH biosimilars[1]. They recommended performing prospective, randomized, double-blind clinical trials in order to demonstrate the non-inferiority of biosimilars when compared to the original product.

Specific and more detailed guidelines on this subject have been published by the European Medicines Agency (EMEA), through the Committee for Medicinal Products for Human Use (CHMP)[2]. It is important to emphasize in these recommendations: the poor correlation between pharmacodynamic markers and clinical effectiveness; and the recommendation of studies on prevention in orthopedic surgeries presenting high risk of thromboembolism (knee and hip arthroplasty), as a clinical model of higher sensitivity to detect potential effectiveness differences. The incidence of events in these indications is higher and reasonably well known, which allows a better study planning. It is estimated that in major orthopedic surgeries, the risk of venous thromboembolism without prevention is around 40 to 70%[3] and that the use of LMWH decreases this risk by about 60%[4]. Thus, it can be estimated that in prevention studies in these cases, the incidence of events must be around 15 to 25% and that in these conditions, studies of non-inferiority with a margin of 5 to 10% must require clinical studies with 600 to 1,200 patients. If the expected incidence of events is decreased to, for instance, 5%, as it occurs in low-risk interventions, the sample size necessary for the study, while maintaining the same statistical properties, will be around 3,700 patients.

Another guideline on the same subject was issued by the South Asian Society on Atherosclerosis & Thrombosis (SASAT)[5]. This organization basically endorses the EMEA position, being, however, more stringent regarding the clinical studies, stipulating the need to include two randomized and double-blind studies - one on venous thromboembolism and another on arterial thromboembolism.

In Brazil, there is no specific official guideline to evaluate LMWH, but, in general, the Brazilian National Health Surveillance Agency (ANVISA) regulates the registration of biological products through the Resolução da Diretoria Colegiada (RDC) #315 of October 26, 2005[6]. This document gives detailed instructions on how to submit a registration request for a biological product and concisely, albeit very clearly, indicates the clinical and pre-clinical requirements. It establishes the need for a therapeutic trial report, containing data on toxicity, mutagenic and oncogenic activity and phase I, II and III clinical trials.

Moreover, it specifies that, in case of non-new biological products (i.e., biosimilars), the individual requesting the registration can alternatively present non-inferiority clinical trials to demonstrate therapeutic activity and safety. Recently, three LMWH that are biosimilar to enoxaparin received regulatory approval by ANVISA. The clinical data that supported this submission were made public, which allows their analysis considering the aforementioned guidelines.

Apparently, the first product[7] had its approval based on a single pharmacodynamic study, in which 59 patients, with chronic kidney disease undergoing dialysis, were treated with the biosimilar and the standard enoxaparin during 12 hemodialysis sessions. The assessment was carried out through the measurement of two markers, aPTT and anti-Xa. This study report does not contain the evaluated marker results, but only

Key words

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mentions that "statistical tests of clinical interchangeability between the formulations were used", without providing further details. The study declares equivalence or non-inferiority, although it was not planned for this type of comparison; moreover, it uses an inadequate clinical model with surrogate markers, which are known not to constitute a demonstration of clinical effectiveness.

The second product[8] was also approved with a clinical documentation based on a pharmacodynamic study, with the primary variable being anti-Xa. The study evaluated the treatment and prophylaxis of arterial and venous thromboembolism in 100 patients with different clinical conditions in intensive care units. Fifty patients were allocated to the prophylaxis regimen and 50 to the treatment regimen. For each one of them, the patients were randomized into two groups of 25 patients, who received either the biosimilar drug or standard enoxaparin. The evaluated marker results did not show any significant difference between the groups, and erroneously, the equivalence was assumed. Only one patient in each group presented deep venous thrombosis, an insufficient total number of events to evaluate the treatments. As well as in the previous case, the anti-Xa measurements should not have been used as an alternative to demonstrate clinical effectiveness.

A third product[9] was evaluated by a clinical trial carried out with 200 patients submitted to unspecified abdominal and pelvic surgeries, but which were certainly low-risk, as the end of the study the incidence of thromboembolic events was very low, of around 1% (2/200). It was a comparative, multicenter open study, in which the patients were allocated by a deterministic, non-random procedure (systematic alternation) in two study groups, standard enoxaparin and biosimilar. Treatment duration lasted seven to ten days, hence compatible with low-risk procedures. The clinical outcomes were inaccurately defined and tolerability was evaluated by the occurrence of major or minor hemorrhages, although they lacked a clear characterization.

Signs and symptoms of deep venous thrombosis were reported in two patients from the standard enoxaparin group (2% in intention to treat) and in none of the patients from the group that received the biosimilar (0%). Adverse events classified as severe were reported in six patients from the standard enoxaparin group and in seven patients from the biosimilar group. Minor bleeding was reported in 4 patients from the standard enoxaparin group and in 3 patients from the biosimilar group. These differences between the groups were not statistically significant.

The study was inconclusive mainly because it included an insufficient number of patients and had a very low incidence of events. Additionally, the study was incorrectly reported as of non-inferiority - there was no definition of the non-inferiority margin, there was no assay sensitivity control and the sample size for this type of study was not calculated.

As mentioned before, a study of non-inferiority in prophylaxis of venous thromboembolism in a high-risk surgery, with an acceptable margin of non-inferiority, would require a minimum number of patients three to six-fold higher than the number recruited in this study. Moreover, patient selection was incorrectly carried out (very low risk of venous thromboembolism), as patients were allocated to the groups using a deterministic procedure and the sample size was insufficient, which resulted in lack of study sensitivity and low statistical power. The majority of the evaluation criteria for LMWH biosimilars were not observed.

The studies analyzed herein present a basic inference error by assuming the lack of statistical significance as a demonstration of equivalence[10]. In a clinical study, the non-rejection of the null hypothesis does not imply in its support of being true. Proving that two treatments are equivalent is actually much more difficult than demonstrating a difference between them[11]. The present analysis suggests more caution is required in the regulatory approval of biological products.

Potential Conflict of Interest

No potential conflict of interest relevant to this article was reported.

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Study Association

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