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EDITORIAL

Biosimilars: Is absence of proof of difference, proof of absence of difference?

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Biosimilars have been available for a short period of time in hematology-oncology, and prescribing physicians have been wondering about their similarity in terms of safety and efficacy compared with standard comparator. In general, the market penetration in various countries is very similar to that of generic drugs, following prescription habits of the medical profession, variously dependent on the financial and administrative pressures of the country's environment.

A major difference compared to generics is that for biosimilars, before marketing, the European Medicines Agency (EMEA) and the US Food and Drug Administration (FDA) require producers to carry out additional clinical trials for efficacy and safety, as well as formal post-marketing surveillance. These requirements are therefore fulfilled at the time of marketing, at least in those countries dependent on these regulatory authorities. The European Union (EU) has developed a legal basis for biosimilars. EMA regulations require that the reference product be authorized in the EU. If this is also the case for other non-EU countries, it could require duplication of studies for each region. International guidelines can facilitate bringing to market and approvals. The World Health Organisation (WHO) has and is developing EU-similar procedures, as are many countries. It is interesting that Australia more or less adopted EMA regulations for biosimilars in 2008.

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With regards to the original natural human product, standard drugs produced by genetic engineering are already biosimilars. Over time, due to technical changes in cell cultures and other changes, these have also changed and are not necessarily identical to the initially marketed product (various insulins, erythropoietin [EPO], granulocytopoietins, thrombopoietins, etc.).

Standard generic drugs were accepted a few years ago, albeit with some difficulties, and the discussion of biosimilars is a different one. In this issue of "Targeted Oncology", a panel of international authors explores various regulatory, clinical and economic aspects.

The topics are of direct interest to hematologists and oncologists. The area of biosimilars started in other medical areas with insulin, human growth hormone, etc., and will develop more in hematology and oncology in the near future with monoclonal antibodies and others. For presently available biosimilars, a measurable endpoint is, for the most part, proof of efficacy. For instance, for EPO, the standard parameter of response is the hemoglobin level, and the other aspects of this cytokine's effects on angiogenesis, apoptosis, cellular differentiation, etc., are clinically less marked. Nevertheless, lately the association with thromboembolic disorders, possibly secondary to the effect on vascular endothelium has been widely discussed. The same applies to an effect on tumor progression that is still not fully settled. Long-term follow-up is necessary, due to the fact that, as seen in the present example, years after usage an unexpected adverse effect in relation to a production change, such as antibody-mediated pure red blood cell aplasia, has been noted.

The example of low molecular weight heparins (LMWH) demonstrates other practical and conceptual difficulties. Heparins have a pleotrophic effect. Measuring the effect of LMWH is not limited to pharmacokinetics or pharmacodynamics laboratory parameters. It is not enough to determine

the anti-Xa or anti-IIa effect but, in addition to the patient's profile, the clinical effect on thrombosis and embolism is dependent on other biological aspects of the LMWH. This problem is addressed in the article by L. Drouet.

Other problems will have to be resolved with future biosimilars such as monoclonal antibodies and others, where the endpoint is not a direct laboratory measurement such as the hemoglobin level, but clinical endpoints such as survival.

What will the regulatory authorities require for approval? Will interim endpoints such as progression-free survival or other surrogate markers of overall survival be acceptable in the hemato-oncology area?

For some of these new drugs, it is probably appropriate to change the question in the subtitle of this editorial to a statement: "absence of proof of difference is not absence of difference."

I hope you will enjoy reading this issue.