Biosimilars require scientifically reliable comparative clinical data

In Brazil, the Law 9787 of February 10, 1999, authorized the commercialization by any pharmaceutical company of drugs, whose patent protection expired, in a standardized packaging with a yellow band and a 'G' of 'generic'. Generic drugs are usually cheaper, because, after the expiration of the patent protection of their brand-name pharmaceutical products, manufacturers need neither to invest in clinical research, nor to redo the trials that confirm the efficacy and safety of a certain drug. Such costs are inherent to certain phases of the process of research and discovery of new pharmaceutical drugs, and have already been conducted by the innovator company that had first obtained patent on a certain drug. Thus, manufacturers of generic drugs can sell their copies with the same quality of the brand-name pharmaceutical product at a lower price. However, biological drugs differ between themselves regarding complexity and cannot be approved in the same way of synthetic generic drugs or with the same criterion used for synthetic generics.[1]

There is worldwide consensus that a similar biotherapeutic product is a biopharmaceutical product approved via a regulatory pathway, which comprises biological and clinical comparison with the brand-name product counterpart, in addition to a strict assessment of its immunogenic potential.[2] These requirements for a biological molecule to be named 'similar biotherapeutic product' is included in the World Health Organization (WHO) guidelines on evaluation of similar biotherapeutic products, and are considered the minimum conditions required for approval for market and selling.[2,3]

Similarly to other emerging countries, from the economic viewpoint, Brazil has a promising market of similar biotherapeutic products to manufacturers and/or traders of copies, patients and payers, including the Federal Government. However, the approval for marketing and selling similar biotherapeutic products, unlike generic drugs, without the conduction of quality clinical trials, represents a real threat to patients. The Brazilian Sanitary Surveillance Agency (ANVISA) has established a review of its previous normalization to approve similar biotherapeutic products by use of the RDC 55, published at the end of 2010.[4] However, that normalization diverges in certain aspects from the WHO guidelines, particularly in establishing two regulatory pathways for approval, individual and comparative, in the extrapolation of therapeutic indications and in differences in the emphasis given to the design and statistical considerations of the trials; nevertheless, the practical application of the latter has not yet been completely clarified by that agency to the scientific community.[5]

An interesting exercise recently published in the medical literature, and conducted in a meeting sponsored by the WHO in Seoul, South Korea, illustrates the relevance of the need for a case-to-case approach when comparing clinical data between similar biotherapeutic products and their brand-name pharmaceutical counterparts.[6] That is the only way to ensure the adequate efficacy and safety of similar biotherapeutic products to any studied indication.

The fact that small biochemical and biological differences might cause significant clinical differences makes us believe that one biosimilar product must at least be as effective and safe as its brand-name pharmaceutical counterpart. Comparative randomized clinical trials are currently considered the best experimental design to assess treatment-related questions.

In a phase 3 study, a similar biotherapeutic product can be assessed by use of statistical designs, such as the equivalence and non-inferiority approaches comparing them with controls. The former has the greatest affinity with the nature of the biosimilarity process (to ensure that a similar biotherapeutic product is neither more nor less effective than a brand-name pharmaceutical product counterpart at the same dose and for the same route of administration).[7] Non-inferiority studies are justified and accepted mainly when the innovative product already has a large safety margin, and they are aimed at determining whether the similar biotherapeutic product is at least as effective as its brand-name pharmaceutical product counterpart, or even a little less effective, but within a certain

pre-established limit, that is, within an acceptable range.[8] In addition, one copy might have a better efficacy profile, above that range, but the non-inferiority result will be equally valid. Theoretically, a similar biotherapeutic product could be better assessed by use of equivalence studies, which are more restrict, implying that neither better nor worse results should exist within the pre-established range. The non-inferiority margin is based on previous studies performed with the brand-name pharmaceutical product counterpart, preferably in comparison with a placebo.

It is worth noting that in the non-inferiority study, the populations studied and the outcomes should be equal to those of the study providing the characteristics of the brand-name pharmaceutical product counterpart. Superiority studies, as shown in Figure 1, are not meant to comparison between biological innovations and copies, but might be used to demonstrate the better efficacy profile of molecules known as biobetters. Another important aspect relates to the size of the sample that should be included in the comparative study between an innovation and its copy. That sample size will depend mainly on the value stipulated for the non-inferiority margin and data variability.[9] Very wide non-inferiority or equivalence margins usually require small sample sizes, while narrower margins require a larger number of patients. Unfortunately, so far the sample sizes of non-inferiority or equivalence studies involving similar biotherapeutic products have been very small. In addition, it is worth noting that occasional losses of patients per group in a study, mainly due to flaws in the interpretation of tests and patient's withdrawal, should be replaced to maintain the statistical power of the project. In Brazil, copies of recombinant erythropoietin have been approved after an open study with 25 patients in phase 1–2a studies.[10] Studies like those would not be adequate for the current approval of copies of fusion proteins or monoclonal antibodies, whose patents expire.

The choice of a clinical trial design depends on several factors, and the specific design selected for a particular trial should be explicitly justified in the protocol of that trial. The selection of the endpoints of primary efficacy and of the statistical design of the main study, as well as the calculation of the appropriate sample size to ensure statistical power, is a multi-step process. To be properly assessed, that process requires clear understanding of the comparability margins (sometimes called comparability limits or, simply, margins) for a certain endpoint, which ultimately translates better efficacy. According to the WHO, the selected margin should represent the largest difference in efficacy/safety that matters in clinical practice.

Similarly, regarding the treatment of individuals with rheumatoid arthritis, only margins properly defined to detect significant differences between a certain anti-TNF biosimilar and its brand-name pharmaceutical product counterpart, based on the efficacy measured by the impact of both treatments on the ACR20 index, could be accepted. By definition, any difference in result contained within that variation would have no clinical relevance. By nature, the comparability margins for a certain endpoint result from clinical reasoning, being frequently neither well established nor universally accepted. Thus, the choice of the sample size should be well justified by the sponsors of the study, being usually a combination of the opinion of experts and previously published analyses.

In addition, ANVISA representatives should also agree with those margins before the study is initiated. Thus, it is understandable that experts of the Brazilian Society of Rheumatology, with a large experience in managing patients with rheumatoid arthritis and spondyloarthritides, be previously consulted by the sponsors of the study to provide an opinion about and agree on the size of those margins, in cases in which the endpoints are related to rheumatic disorders. The combination should not be based on 'guesses', requiring a deep search in the literature about the most impacting clinical outcomes related to the current treatment of rheumatic disorders.

The scientific community of Brazilian rheumatology waits for the results of high-quality clinical trials developed by manufacturers responsible for new biosimilars of biological molecules used in their clinical practice.

The author declares receiving no incentive for this article's publication; he reports being part of the advisory boards of the Janssen, Abbott and Pfizer pharmaceutical companies.

Valderílio Feijó Azevedo

PhD in Health Sciences, Pontifícia Universidade Católica do Paraná - PUC-PR;
Professor of Rheumatology, Universidade Federal do Paraná - UFPR;
Coordinator of the Spondyloarthritis Ambulatory, Hospital de Clínicas, UFPR

aceitável.[8] É possível, inclusive, que uma cópia tenha melhor perfil de eficácia, acima dessa variação, havendo um bônus, mas o resultado de não inferioridade será igualmente válido. Por conceito, um biossimilar poderia ser mais bem avaliado por estudos de equivalência, pois são mais restritos e implicam que não deveria haver resultado nem melhor nem pior, dentro da variação preestabelecida. A margem de não inferioridade tem base em estudos prévios feitos com o medicamento original, de preferência em comparação a placebo.

No desenho do estudo de não inferioridade, devemos lembrar que as populações estudadas e os desfechos devem igualmente ao estudo que forneceu as características do comparador original. Estudos de superioridade, como demonstrado na Figura 1 não se prestam à comparação entre inovadores e cópias biológicas, mas podem ser empregados para a demonstração de melhor perfil de eficácia de moléculas conhecidas como *biobetters*. Outro aspecto importante diz respeito ao tamanho da amostra de pacientes que devem ser incluídos no estudo comparativo entre um inovador e sua pretensa cópia. Esse tamanho amostral dependerá, sobretudo, do valor estipulado para a margem de não inferioridade e da variabilidade dos dados.[9] Margens de não inferioridade ou de equivalência muito amplas requerem, muitas vezes, pequenos tamanhos amostrais, enquanto margens mais estreitas requerem maior número de pacientes. Infelizmente, os tamanhos amostrais de estudos de equivalência ou não inferioridade entre biossimilares, até aqui, têm sido frequentemente muito pequenos. Além disso, é preciso salientar que eventuais perdas de pacientes por grupo, principalmente por conta de falhas na interpretação de exames, desligamentos da pesquisa etc., devem ser repostas, de modo a manter o poder estatístico do projeto. No Brasil, cópias de eritropoetinas recombinantes foram aprovadas após estudo aberto com tamanho amostral de 25 pacientes em estudos de fase 1–2a.[10] Certamente, estudos nesse molde seriam inviáveis para a atual aprovação de cópias de proteínas de fusão ou anticorpos monoclonais que perdem suas patentes.

A escolha do desenho de um ensaio clínico é dependente de muitos fatores, e o desenho específico selecionado para um estudo particular deve ser explicitamente justificado no protocolo do ensaio proposto. A seleção dos *endpoints* de eficácia primária e o desenho estatístico do estudo principal, bem como o cálculo do tamanho amostral apropriado para assegurar seu poder estatístico, são um processo de muitas etapas. Esse processo requer claro entendimento sobre o que são as margens de comparabilidade (algumas vezes chamadas limites de comparabilidade ou somente margens), para que determinado *endpoint* particular, que traduza melhor eficácia em última análise, seja adequadamente avaliado. A OMS muito bem explicitou em seus guias que "a margem selecionada deve representar a mais larga diferença em eficácia/segurança que importa na prática clínica".

De forma analógica, somente margens adequadamente definidas para detectar diferenças significantes no tratamento de portadores de artrite reumatoide entre um determinado biossimilar de um agente anti-TNF e seu comparador, tomando por base a eficácia medida por impacto de ambos os tratamentos no índice ACR20, poderiam ser aceitas, porque, por definição, não haveria relevância clínica de qualquer diferença de resultado que estivesse contido dentro dessa variação. Por natureza, as margens de comparabilidade para um dado *endpoint* são em última análise um juízo clínico e frequentemente não estão bem-estabelecidas ou universalmente aceitas. Portanto, a escolha do tamanho dessa margem deve ser bem-justificada pelos patrocinadores do estudo, usualmente uma combinação da opinião de *experts* e de análises prévias publicadas.

Além disso, representantes da ANVISA também devem concordar com elas antes que se inicie o estudo. Dessa forma, faz sentido que especialistas da Sociedade Brasileira de Reumatologia, com grande experiência no tratamento de portadores de artrite reumatoide e espondiloartrites, sejam previamente consultados pelos patrocinadores para opinar e concordar com o tamanho dessas margens, nos casos em que os *endpoints* estejam relacionados a tais enfermidades. A combinação não deveria ser pautada somente por "achismos", sem um estudo aprofundado da literatura sobre os desfechos clínicos mais impactantes relacionados ao tratamento atual de enfermidades reumatológicas.

A comunidade científica da reumatologia brasileira aguarda os resultados de ensaios clínicos de alta qualidade desenvolvidos por fabricantes responsáveis pela entrada de novos biossimilares de moléculas biológicas usadas em nossa prática clínica.

O autor declara não ter recebido qualquer incentivo para a publicação deste artigo; declara fazer parte de *advisory boards* dos laboratórios Janssen, Abbott e Pfizer.

Valderílio Feijó Azevedo

Doutor em Ciências da Saúde, Pontifícia Universidade Católica do Paraná - PUC-PR; Professor de Reumatologia, Universidade Federal do Paraná; Coordenador do Ambulatório de Espondiloartrites, Hospital de Clínicas, UFPR

REFERENCES

REFERÊNCIAS

1. Azevedo VF, Felippe LR, Machado DM. Opinião de uma amostra de reumatologistas brasileiros sobre biossimilares. Rev Bras Reumatol 2011; 51(6):.662–71.

2. World Health Organization. Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs), 2010. Available from: http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf
3. Expert committee on biological standardization Geneva, 19 to 23 October 2009. Guidelines on evaluation of Similar Biotherapeutic Products (SBPs).Adopted by the 60th meeting of the WHO Expert Committee on Biological Standardization.
4. ANVISA. Registro de Produtos Biológicos. Baes Legais e Guias – Coletânea. Resolução – RDC n 55, de 16 de dezembro de 2010. Available from: http://portal.anvisa.gov.br/wps/wcm/connect/935aed0048bd2755a7cdaf9a6e94f0d0/Registro_Produtos_Biologicos_Hemoterapicos_10102011_WEB.pdf?MOD=AJPERES.
5. Castanheira LG, Barbano DB, Rech N. Current development in regulation of similar biotherapeutic products in Brazil. Biologicals; 2011; 39(5):308–11.
6. Fletcher MP. Biosimilars clinical development program: confirmatory clinical trials: a virtual/simulated case study comparing equivalence and non-inferiority approaches. Biologicals 2011; 39(5):270–7.
7. Njue C. Statistical considerations for confirmatory clinical trials for similar biotherapeutic products. Biologicals 2011; 39(5):266–9.
8. Piaggio G, Elbourne DR, Altman DG, Pocock SJ, Evans SJ, CONSORT Group. Reporting of non inferiority and equivalence randomized trials: an extension of the CONSORT statement. JAMA 2006; 295:1152–60.
9. Chow SC, Shao J, Wang H. Sample size calculations in clinical research. 2. ed. Boca Raton: Chapman & Hall/CRC Biostatistical series; 2008.
10. Bio-Manguinhos, Fundação Oswaldo Cruz. Eritropoietina Humana Recombinante – Monografia do produto. Available from: http://www.fiocruz.br/bio_eng/media/monografia_epo.pdf. Accessed on Feb 28, 2012.