Editorial

The Explosion of Biosimilars in Immune Mediated Chronic Inflammatory Diseases

The approval of biosimilars for the treatment of immune-mediated diseases has heated the debate around this class of biopharmaceutical drugs. The first biosimilars were similar versions of previously approved hormones and growth factors, with simple chemical structures, low molecular weights and predictable pharmacodynamic profiles. The endorsement of Omnitrope™ (somatropin) by the European Medicines Agency in 2006 was a landmark and paved the way for biosimilar regulation, development and widespread use. However, fusion proteins and monoclonal antibodies used to treat inflammatory and oncolgic conditions are incomparably more intricate, with tertiary and quaternary protein structures, post-translational modifications and multiple mechanisms of action. They bind both soluble and membrane-bound targets and have Fc and Fab-mediated functions. Furthermore, it is common for rheumatic and oncologic patients to have comorbidities and co-medications that influence pharmacokinetics and immunogenicity of biological drugs. For these reasons, and despite the previous good experience with smaller biosimilars, the approval of such complex biosimilars was surrounded by uncertainty. In 2013, the European Union endorsed CT-P13 as the first biosimilar of infliximab and, since then, etanercept, rituximab, trastuzumab and other infliximab biosimilars have followed. Prospective and retrospective evidence on efficacy, safety and extrapolation of these biosimilars was reassuring. However, the future poses further challenges. By the time this issue of Current Pharmaceutical Design was prepared, there were close to 45 biosimilars in different stages of development for the treatment of inflammatory diseases. This explosion of biosimilars means that, in the upcoming years, several versions of the same reference biological will be concurrently available. It is likely that pharmacovigilance and traceability will become increasingly difficult, especially if these drugs are used as interchangeable and automatic substitution takes place; the assessment of long-term immunogenicity will be troublesome in patients submitted to multiple transitions from one biosimilar to another; and debate around new concepts, such as consistency and divergence, will rise. To facilitate making informed decisions about therapeutic substitution with biosimilars, healthcare providers are encouraged to gather pharmacovigilance data in registries about the outcome of such switches made in the context of clinical practice.

This issue of Current Pharmaceutical Design was elaborated with the contribution of several experts in the field of biopharmaceutical drugs. It aims to provide a comprehensive review and contribute to reduce residual uncertainty about the use of biosimilars for the treatment of immune mediated chronic inflammatory diseases. These manuscripts raise awareness about biosimilars and discuss the key issues that healthcare providers must consider when using biosimilars to treat their patients. This group of experts has a high level of agreement about the evaluation of biosimilars and their use to treat inflammatory and autoimmune diseases. The manuscripts in this issue carry the message that biosimilars approved by authorities in highly regulated areas are unlikely to differ from their bio-originators in clinically meaningful ways. The information gathered shows that there is sufficient evidence about safety and efficacy of biosimilars to allow for extrapolation of indications, and also growing evidence to support the transition from an originator biologic, no longer protected by patent, to its biosimilar. Biosimilars now provide the opportunity to expand access to effective but otherwise expensive medications at more affordable costs, increasing the number of available treatment choices and contributing to containment of rapidly increasing drug expenditures.

In the first article of this issue, Perez et al. [1] discuss the nature, the development and the regulatory frameworks concerning bio-originators and biosimilars. The structural complexity of a biotechnological agent is such, and there are so many variables involved in the manufacturing process, that one might consider that the process becomes the product. As a consequence, all biological drugs have inherent structural variability, even between batches of the same product. A biosimilar must demonstrate similar physicochemical, biological and clinical properties to its originator counterpart, and this requires an extensive and highly regulated stepwise comparability exercise. Throughout the manuscript, the authors address: the differences between the assessment of biocompatibility and the assessment of comparability of pre and post-manufacturing changes; the need for a risk-based approach when comparing biological drugs; and the clinical implications of consistency, evolution, drifting and divergence for both originators and biosimilars.

All biologicals have the potential to elicit immune responses. Biosimilar immunogenicity may arise from either structural differences to the originators or product- or process-related impurities. The assessment of immunogenicity is mandatory during the comparability exercise and only similar immunogenic profiles with no impact on safety and efficacy will grant a biosimilar candidate approval. In the first part of their manuscript, Detre et al. [2] summarize the preclinical and clinical data leading to the marketing authorization of infliximab, etanercept and adalimumab biosimilars in Europe. In the second part, they review current methodologies used to assess immunogenicity of monoclonal antibodies; the clinical implications of antidrug antibodies in efficacy and safety; and propose a general strategy for assigning immunogenicity risk levels to biosimilars and respective risk level–based schemes for assessing antidrug antibodies.

In the manuscript by Zhao et al., the concept of extrapolation of clinical indications is discussed and its potential implications addressed [3]. Once biosimilarity to a reference product is demonstrated, the biosimilar may be used in all clinical indications for which the reference product was approved, without the need for additional expensive clinical trials. Extrapolation is a common pharmacological principle and has been used with smaller biosimilars for several years. However, in the context of large and intricate protein structures such as monoclonal antibodies, there are concerns about the best clinical model to extrapolate biosimilarity from; the immunogenic consequences of biosimilar/originator structural discrepancies in the different clinical indications; and the effect of biosimilar molecules in the disease process of extrapolated indications. In the context of off-label treatments, the authors suggest that biosimilars may increase both investigational interest and patient access in uncommon conditions for which approved drugs are scarce.

Azevedo et al. performed a review on biosimilars of infliximab for the treatment of rheumatic diseases [4]. The first biosimilar of a monoclonal antibody approved by an agency of a regulated market was the infliximab biosimilar CT-P13. Based on extensive physicochemical, preclinical and clinical studies, the latter on ankylosing spondylitis and rheumatoid arthritis patients, biosimilarity with reference product was demonstrated and confirmed in the long-term extensions, in which no significant difference in efficacy, safety, immunogenicity and radiographic damage was found. Although currently available studies on switch from reference infliximab to CT-P13 are reassuring, the authors consider that no definite conclusions can be made on interchangeability as these studies are not designed to assess multiple switches. The second infliximab biosimilar to be approved was SB2, following an identical comparability exercise as CT-P13. Similar efficacy, safety and
immunogenicity to reference product were demonstrated in rheumatoid arthritis patients. Other infliximab biosimilars, such as PF-06438179, ABP710 and BOW015 are currently in different stages of development and are also mentioned in this manuscript.

Infliximab biosimilars were approved for the treatment of inflammatory bowel diseases (IBD) based on the extrapolation of data from rheumatoid arthritis and ankylosing spondylitis trials. The complexity of the manufacturing process, the specificities of IBD and the absence of direct clinical evidence in these patients raised efficacy and safety concerns among gastroenterologists. Ávila-Ribeiro et al. performed a systematic literature review of infliximab biosimilars in IBD [5], finding two systematic reviews, one randomized clinical trial and 23 observational studies, all regarding CT-P13. Despite heterogeneity in study design, results were overwhelmingly favorable to the similarity between originator and biosimilar in both treatment induction and treatment switch, yielding comparable safety, efficacy and immunogenicity. The authors stress that biosimilars will play an important role in the treatment of IBD and, despite growing acceptance of extrapolation of clinical indications, randomized controlled trials are ongoing to further confirm biosimilarity in IBD and reassure both patients and physicians.

Biosimilars were developed with the sole purpose of cost-containment and access improvement. The review by Péntek et al. provides a comprehensive economical perspective of biosimilars in chronic inflammatory diseases, which are expected to reduce the burden of treatment-associated costs [6]. Cost-utility analysis and budget impact models suggest that biosimilars will improve treatment strategies (such as patient eligibility and drug sequence) and will contribute to significant budget savings, respectively. However, the authors consider that many country specific variables (like local treatment recommendations, reimbursement policies and regulatory framework) negatively influence biosimilar penetration and hamper the fulfillment of their economical potential. Policies that support interchangeing from the reference product seem to be important drivers of biosimilar uptake.

The discussion about the hurdles to the use of biosimilars by Péntek [6] is broadened in the manuscript by Chapman et al. [7]. They consider that these barriers not only prevent the achievement of the much-needed expenditure reduction, but also impair wider use and improved access for patients suffering from inflammatory conditions. In many countries, physicians are using biosimilars in treatment-naïve patients, but oppose interchangeability and automatic substitution in patients already on biological treatment. This conduct is justified by the absence of robust and consistent data showing long-term efficacy and safety in a large number of patients, especially after multiple switching, and also by the fact that interchangeability in one clinical indication cannot be extrapolated to another nor between distinct biosimilars. The authors stress that non-medical switching, which is driven by cost containment, may hypothetically result in the paradoxical effect of increasing direct and indirect health expenditure, if efficacy or safety complications emerge from indiscriminate switching and interchanging. For the purpose of pharmacovigilance and traceability, biosimilar naming is crucial, but there is still no worldwide consensus on the most appropriate naming convention. Patient associations acknowledge the potential of biosimilars to increase access to biological therapies and praise their use, even in switching situations, as long as the decision involves both physician and patient, and the switch is made on clinical and not only economical grounds.

REFERENCES