

Letters to the Editor

New contributions to consensus on biosimilars

Key words: Biosimilar. EMA. Inflammatory bowel disease.

Dear Editor,

Following the initial publication by the Multidisciplinary Working Group on Biosimilars and Inflammatory Bowel Disease (IBD) of Sociedad Española de Patología Digestiva (SEPD) and Sociedad Española de Farmacología (SEF) of a position statement regarding the anticipated launch of biosimilars approximately one year ago in *Revista Española de Enfermedades Digestivas* (REED) (1), and after the publication of some other position statements on this subject by other societies, including the Canadian Association of Gastroenterology (2) and ECCO (3) (along the same lines as ours), the European Medicines Agency (EMA) has now authorized the first such monoclonal antibodies for use in the management of IBD (4). This has led our Group to review the aforementioned statement.

The EMA provides an extensive document assessing the comparability between the new biosimilar drug and Remicade®. This biosimilar is a single molecule with two brand names (Inflectra® and Remsima®). The paper discusses its pharmacological, pharmacodynamic, and clinical aspects, and finally its safety profile. According to this report and the evidence provided by the manufacturer, the physical, chemical, and biological characteristics of this biosimilar drug are comparable to those of Remicade®. The EMA Committee observed a small difference in the amount of fucosylated (glycosylated) infliximab, which translates into a lower binding affinity for specific Fc receptors, and reduced *ex vivo* activity on antibody-dependent cell-mediated cytotoxicity (ADCC). This difference is not considered clin-

ically significant by the EMA, as it does not impair biosimilar activity in the experimental models deemed most relevant for the pathophysiological conditions seen in patients.

The clinical data demonstrating the similarity of the biosimilar product and Remicade® derive from two clinical trials: One is a pivotal pharmacokinetics study in patients with ankylosing spondylitis (AS), and the other is an equally pivotal efficacy and safety study in patients with rheumatoid arthritis (RA). The assessment of the biosimilar product's safety profile was supported by the findings of these two clinical trials. This research showed no statistically significant differences between the new biosimilar drug and Remicade®, hence the EMA concludes that they both may be used in the same indications, both for rheumatic conditions and inflammatory bowel disease. However, as of today, no studies have been carried out in patients with Crohn's disease (CD) or ulcerative colitis (UC), and yet the EMA has approved this biosimilar for use patients with inflammatory and fistulizing CD, pediatric CD, and both adult and pediatric UC. Furthermore, the biosimilar product was used in doses of 3 mg/kg, lower than those approved for CD and UC (5 mg/kg). We deem it necessary to recall that lower doses showed no effectiveness for CD.

On the other hand, according to the EMA report, a higher incidence of infectious diseases was identified in the group receiving the biosimilar product. Therefore, it is concluded that serious infections, including tuberculosis, will be carefully monitored longer-term and in bigger patient cohorts as part of the post-marketing follow-up through a number of registries for different patient populations. The identification of any adverse events is thus warranted.

In this respect, recently reported news indicate that some non-European agencies, such as the Canadian one, have considered a partial acceptance of this biosimilar product with only some of the EMA-authorized indications, approving its indication for rheumatic conditions alone, and inviting the manufacturer to perform some study in the setting of inflammatory bowel disease.

However, regardless of the above, we are satisfied that—at least apparently—there is consensus that the anticipated regulations in our country will guarantee non-interchangeability,

brand monitoring, and clinical leadership as regards therapy indications.

Without doubt, we miss here further clinical research in the IBD setting and, while it is true that the demonstration of biosimilarity predicts at least likely results (5), only adequate, stringent post-marketing surveillance under the direction and coordination of the EMA and through the national agencies may ensure those still undemonstrated results and, above all, safety.

Federico Argüelles-Arias, Manuel Barreiro-de-Acosta,
Fernando Carballo, Joaquín Hinojosa
and Teresa Tejerina

*Multidisciplinary Working Group on Biosimilars and
Inflammatory Bowel Disease of the Spanish Society of
Gastroenterology and Spanish Society of Pharmacology*

References

1. Argüelles-Arias F, Barreiro-de-Acosta M, Carballo F, Hinojosa J, Tejerina T. Joint position statement by Spanish Society of Gastroenterology and Spanish Society of Pharmacology on biosimilar therapy for inflammatory bowel disease. *Rev Esp Enferm Dig* 2013;105:37-43.
2. Devlin SM, Bressler B, Bernstein CN, Fedorak RN, Bitton A, Singh H, et al. Overview of subsequent entry biologics for the management of inflammatory bowel disease and Canadian Association of Gastroenterology position statement on subsequent entry biologics. *Can J Gastroenterol* 2013;27:567-71.
3. Danese S, Gomollon F; Governing Board and Operational Board of ECCO. ECCO position statement: The use of biosimilar medicines in the treatment of inflammatory bowel disease (IBD). *J Crohns Colitis* 2013;7:586-9.
4. http://www.ema.europa.eu/ema/index.jsp?curl=pages/regulation/general/general_content_000408.jsp
5. Choy E, Allen Jacobs I. Biosimilar safety considerations in clinical practice. *Semin Oncol* 2014;41(Supl. 1):S3-S14.