

POINT OF VIEW

Joint position statement by “Sociedad Española de Patología Digestiva” (Spanish Society of Gastroenterology) and “Sociedad Española de Farmacología” (Spanish Society of Pharmacology) on biosimilar therapy for inflammatory bowel disease

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ABSTRACT

Biological drugs or biopharmaceutical products, manufactured with or from living organisms using biotechnology, have represented a therapeutic revolution for the control of inflammatory bowel disease (IBD). At present, in this indication and in our country, only two biologicals are approved, infliximab (IFX) and adalimumab (ADA), both of them monoclonal antibodies against tumor necrosis factor alpha. Effectiveness data are strong for both therapies, with maximum levels of scientific evidence.

The upcoming expiry date for these biologicals' patents has allowed the potential marketing of so-called biosimilar agents for the IBD indication. While biosimilars are conceptually for biologicals what generics are for chemical drugs, the structural complexity of biosimilars and their biological and manufacturing variability lead to consider validation processes for these two types in humans as highly differential. Thus, in our setting, under the coverage of “Agencia Española del Medicamento y Productos Sanitarios (AEMPS)” (Spanish Agency of Medicines and Medical Devices), guidelines issued by the European Medicines Agency (EMA) are to be applied, which states that a number of stages or steps must be overcome in order to obtain approval for a biosimilar agent.

However, despite the presence of these recommendations by EMA, which must be met by a biosimilar in order to be licensed in our marketplace, relevant uncertainties persist that only future decisions by EMA and AEMPS may clarify. The present stance by our task force is that biosimilar development should be undertaken according to established regulations, thus certifying their efficacy and safety. Similarly, this task force considers that results obtained from studies in rheumatoid arthritis (RA) should not be extrapolated to IBD since the biological variability of these complex structures will not ensure a lack of noticeable changes in efficacy and safety.

Key words: Inflammatory bowel disease. Crohn's disease. Ulcerative colitis. Biosimilars. Infliximab. Adalimumab. Spanish Society of Gastroenterology.

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INTRODUCTION

Biological therapies, particularly anti-TNF treatments, have represented a revolution in the management of patients with Crohn's disease (CD) ever since they showed up in the market over 13 years ago. Tumor necrosis factor alpha (TNF α) is a proinflammatory cytokine that induces cell proliferation and differentiation, and also modulates gene expression and increases adhesion molecule numbers via their signaling pathways (1). TNF α favors an inflammatory response in various conditions, including RA, ankylosing spondylitis, psoriasis, ulcerative colitis (UC) and CD, the symptoms of which improve when on treatment with anti-TNF drugs.

Currently in our country for the treatment of IBD we only have two drugs available: infliximab (IFX) and adalimumab (ADA). The remaining biologics, some of which are regularly used for rheumatic and dermatological conditions, may only be used compassionately in our setting.

The proximity of patent expiry for infliximab (Remicade[®]) and adalimumab (Humira[®]), and hence regulatory approval for the development of so-called biosimilar molecules, requires that scientific societies involved in using this type of drugs report their positioning about it. In this respect “Sociedad Española de Patología Digestiva (SEPD)” (Spanish Society of Gastroenterology), together with “Sociedad Española de Farmacología (SEF)” (Spanish Society of Pharmacology), has developed this paper to publicly report their institutional stance regarding this subject.

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CURRENT KNOWLEDGE ON THE USE OF BIOLOGICALS FOR IBD

Crohn's disease

Luminal Crohn's disease

- *Remission induction in luminal CD.* The first study, which allowed its introduction into clinical practice, was performed by Targan et al. (2) in 1997. The study by Lemann et al. (3) included 113 corticoid-dependent patients with CD who were receiving immunomodulators. Finally, the SONIC study (4) compared the efficacy of azathioprine, infliximab, and their combination in naïve patients. On the other hand 2 clinical trials (CD) have assessed response induction following 2 doses of adalimumab: CLASSIC I trial (5) in anti-TNF-naïve patients and GAIN trial (6) in patients losing response to or intolerant of infliximab.
- *Response maintenance in luminal CD.* In 1999 Rutgeerts confirmed that re-treatment with more than one infusion improved results *versus* single infusions (7). The ACCENT I study (8) was a placebo-controlled study in over 500 patients with luminal CD. Similarly, ADA has been shown in controlled clinical trials to be superior to placebo. The CHARM study (9) is a controlled clinical trial with an open-label phase for patients anti-TNF-naïve or otherwise. A group of 276 patients who completed 1 month on treatment in the CLASSIC-I trial were started on an extension phase (CLASSIC-II). All were treated with ADA 40 mg in week 0 (week 4 for CLASSIC-I) and week 2.

Another biologic agent used subcutaneously in the United States, certolizumab pegol (CDP-870), characterized by a pegylated, humanized antigen-binding fragment that binds TNF, has also been shown to be superior to placebo both for remission induction (10) and maintenance in patients with CD (11).

Fistulizing Crohn's disease

Patients with fistulizing CD, particularly those with perianal involvement, make up a subgroup for whom hardly any effective drug therapies existed prior to the launching of biological products; early studies of biologicals in these patients meant an advance as relevant as in inflammatory forms with even a greater impact.

In the first placebo-controlled clinical trial that assessed the short-term response to IFX in patients with fistulizing CD 68% of subjects receiving IFX 5 mg/kg had more than 50% of fistulas closed, as compared to 26% of those on placebo ($p = 0.002$), and 55% of those on the active drug had all their fistulas closed, as compared to 13% of the placebo group ($p = 0.001$) (12). As regards remission maintenance in fistulizing CD, major conclusions may be

extrapolated from the double-blind, placebo-controlled ACCENT II study (13).

The effectiveness of ADA in patients with fistulizing CD has not been analyzed in any studies with fistula closing as their primary endpoint. The study by Colombel et al. (14) shows that ADA is superior to placebo both for fistula closure induction and its maintenance over time (33% vs. 13% for placebo).

Ulcerative colitis

It is only recently that we may use both drugs (IFX and ADA) in our patients with UC. They were introduced later than for CD because of a number of both immune (it was considered a Th2 disease from the immunology standpoint, with a greater role for IL-10 and IL-5 and a lesser role for TNF- and IL-12) (15) and clinical reasons (availability of cyclosporine for severe illness).

Remission induction

Since its early use for CD IFX began to be prescribed for compassionate use in UC, and thus a number of small randomized, placebo-controlled clinical trials were reported (16-18). The results from the ACT studies have allowed IFX to be used in UC (19).

Early data about ADA for UC came from clinical case reports (20) or highly limited studies which included only patients with loss of response or intolerance to IFX (21). The results from an induction study comparing ADA effectiveness in moderate-to-severe UC (Mayo > 6) *versus* placebo have been recently reported. The authors conclude that ADA 160/80 is safe and effective to induce clinical remission in patients with moderate-to-severe UC (22).

Remission maintenance

The level of evidence for this recommendation is lower. It depends on the drug the patient used previously and on flare severity. Thus, GETECCU guidelines regarding UC (23) recommend that IFX be carried on for patients having initially responded to induction doses following a severe or moderate flare, and who took no azathioprine. When this latter drug was not taken, it should be prescribed and the response assessed.

ACT studies, and the long-term study of ACT studies with results after 3 years, confirmed the efficacy of IFX, with sustained remission above 75% (24). The extension of ADA induction studies to week 52 showed that ADA is effective for response maintenance (25).

In the light of these results and of a recently reported meta-analysis (26) scientific evidence for the use of these drugs is obviously far-reaching and strong. Just as wide and robust is its now widespread use for patients with IBD,

with a stringent post-marketing surveillance of adverse effects. Once this evidence is assessed, it is necessary that the use of biosimilar molecules (see below) be based on equally consistent scientific evidence.

FUTURE PROSPECTS

After reviewing the current status of biological therapies it seems unlikely that new drugs will be available for clinical practice by 2013. Ustekinumab, a human monoclonal antibody also targeted against the p40 subunits of IL-12 and IL-23 that is already used in our country for compassionate use, would be nearest to approval for CD. A phase-2b, multicenter, randomized, double-blind, placebo-controlled study was recently reported in which over 500 patients with CD previously treated with another biological drug received this medication and were assessed for efficacy (27). Higher remission rates were seen at week 22 *versus* placebo (41.7 vs. 27.4%, $p = 0.03$). While we have evidence available on the efficacy of natalizumab (28), an inhibitor of cell adhesion molecules used for the management of multiple sclerosis, regarding remission induction and maintenance in patients with CD, the finding of multifocal leukoencephalopathy cases associated with JC virus reactivation has limited its use, and the drug is now only licensed for very specific patients by the FDA (29).

As regards UC, with encouraging results only reported as an abstract, the biologicals seemingly nearer licensed availability would be vedolizumab (anti- $4\alpha7\beta$ integrin agent) (30) and golimumab (an anti-TNF drug with a human sequence that is already approved for rheumatoid arthritis) (31).

However, we should envisage the future of CD management beyond anti-TNF agents (32,33) since 10% of patients are not primary responders and around 30% lose their response to them. Primary non-responders require an agent with a different mechanism of action, and response losses are managed by switching to another anti-TNF; however, 40% will not respond and one third of the remaining 60% will lose response, which represents that nearly two thirds of patients will ultimately require a therapeutic option involving the use of agents with different mechanisms of action, or researching other inhibition pathways.

A better understanding of IBD pathogenesis is facilitating the research of novel therapeutic targets not only focused on the inhibition of inflammation mediators but also intended to enhance cell repair mechanisms. Of the potential pathways, possibly three enjoy better prospects: a) oral inhibitors of small molecules, namely Janus kinases (JAKS), which play a relevant role in the signal transduction of cytokines regulating lymphocyte survival, proliferation, differentiation, and apoptosis (34); b) antiinflammatory pacemakers that stimulate local acetylcholine release via the activation of cholinergic pathways (35); and c) human enterome changes, as many susceptibility genes for CD are clearly involved in the interaction between the immune system and the microbiota (36,37).

In summary, the final goal of therapy in IBD is inflammation suppression plus complete mucosal healing in order to prevent structural damage and restore normal intestinal function (38) and improve the quality of life of these patients (39), facts that often go hand in hand (40). Today deep remission is obtained in a limited percentage of patients, hence therapy is intended to extend this goal to most patients. Our better understanding of the pathogenesis of this disease will allow the targeting of different molecules with probably a greater role -or at least a different one- in the inflammation framework. So, the understanding of the interaction microbiota-immune system, the identification of neuromediator-linked anti-inflammatory pathways, and an enhanced development of mechanisms clearly targeting cell repair processes forebode a future beyond anti-TNFs.

BIOSIMILARS - WHAT ARE WE TALKING ABOUT? DEFINITIONS AND REGULATIONS

One of the initial definitions for "biological drug or product" was that of preparations designed for the diagnosis, prevention, and treatment of diseases caused by specific infectious agents (41). Already then there was talk of restrictions not only in its selling but also in environmental safety and storage conditions during manufacturing. A more encompassing definition for biological product appeared subsequently that included any vaccine, complex product from a biological source, product derived from recombinant DNA technology, protein or peptide regardless of source, and antibody or antibody fragment used to develop drugs (42). The most widely accepted definition today states that a "biological drug" is a medicinal product of biotechnological origin that is developed from DNA-derived proteins and hybridation processes, which require living organisms as a key component in the production process, hence its designation of biotechnological drug (43).

The backbone of biotechnological drugs are glycoproteins, since amino acids necessary for their production are linked into sequences that are key for correct function, and minimal changes in their folding would therefore result in impaired effectiveness and tolerability. The main known changes in glycosylation occur in producing cells, hence it is recommended that potential differences in results between pre- and post-change products be established by means of analytical testing, and functional testing may also be required to determine the biological or clinical significance of the observed difference (44).

The concept of "biologically similar" or "bioequivalent" drugs was introduced into the European regulatory framework in 2005, when the basic concepts of biological drugs, biosimilars, and products to be used as reference for assessment were defined (45):

1. *Biological drug*: a drug whose active principle is a biological substance (recombinant DNA, attenuated virus, blood or plasma derivatives, monoclonal antibodies, etc.) and is defined as a biological substance

produced by or extracted from a physico-chemically characterized biological source, via a fully developed production process.

2. *Biosimilar drug*: a drug developed by a new manufacturer who states is similar to a known biological drug ("reference"). It contains the same active product as the reference drug, and is targeted to be used for the treatment of the same disease(s), at the same doses, and using the same administration route.
3. *Reference drug*: a biological drug previously approved and marketed in the European Union.

These definitions are currently in use. What has made a difference is the notion of "similar" or "very similar", since such consideration cannot be granted until a lack of clinically significant differences is demonstrated between a biosimilar and its reference product in terms of tolerability, purity and power; therefore a so-called biosimilar will have to prove its bioequivalence primarily based on analytical studies and trials in animals and then humans. Fortunately in our setting, besides the assurance provided by "Agencia Española del Medicamento y Productos Sanitarios (AEMPS)" (Spanish Agency of Medicines and Medical Devices), rules issued by the European Medicines Agency (EMA) are to be implemented, wherein a number of stages or steps must be overcome to gain approval for a biosimilar (46). Table I lists these stages regarding recommendations for the development of biosimilar monoclonal antibodies (mAb) (47). In this specific regulation the EMA first states that the clinical research stage should never commence before the conclusion of non-clinical studies. The first step in this preclinical stage includes *in vitro* studies. Should comparability not be deduced from this stage, the mAb obtained cannot be considered a biosimilar and thus requires a full, independent development research. The second preclinical step is decision-making on whether *in vivo* studies are needed, which -if performed- make up the third and last step in the preclinical stage. The clinical stage is mandatory for EMA. The first formal step in the clinical phase includes pharmaco-

kinetics (PK) and pharmacodynamics (PD). PK may be initiated using healthy volunteers except when foreseeable toxicity suggests patients should be used instead. At any rate, when in patients, PK studies should be performed in a population group unlike that to be used for efficacy and safety trials. The selection of biomarkers for pharmacodynamic studies should be as encompassing as feasible. PD studies may only be considered pivotal when a clear dose-response relationship is demonstrated and at least one of the selected markers is an accepted surrogate for clinical outcome (47).

The second clinical step is to establish comparability for clinical efficacy, which must be proven by means of randomized, parallel-group, preferably double-blind clinical trials (CTs) with adequate statistical power. Clinical safety must be similarly assessed with great care, particularly regarding immunogenicity, a detailed plan for post-marketing surveillance being also particularly relevant (47).

CURRENT SITUATION

In this context, growth hormone, erythropoietin, and human granulocyte colony stimulating factor biosimilars are now available in Europe. In recent years, of a total of 18 attempted registrations 14 were approved and 4 rejected for suboptimally meeting mandatory quality standards (43).

Even with the aforementioned recommendations by EMA, which must be met for a biosimilar mAb to be approved in our market, relevant uncertainties persist that only future EMA and AEMPS decisions may clarify. Various laboratories, Asian all of them, are now performing studies with IFX biosimilars in order to obtain an indication for rheumatic diseases, mainly ankylosing spondylitis and rheumatoid arthritis, and Crohn's disease. Celltrion is the most advanced company in this regard since phase-III clinical trials have already been developed. Other laboratories include Sanofi, BioXpress, Harvest Moon Pharmaceuticals, and Cosmo Pharmaceuticals. Two proposals

Table I. A summary of the stages required by the European Medicines Agency (EMA) for the approval of a biosimilar monoclonal antibody (47)

Phase	Description
Non-clinical studies	
Step 1. <i>In vitro</i> studies	Proven comparability with high sensitivity
Step 2. Decision-making on the need for <i>in vivo</i> studies	Judgment on whether <i>in vivo</i> studies should complement <i>in vitro</i> studies
Step 3. <i>In vivo</i> studies	Additional studies in animals potentially needed for PK, PD or safety-related purposes
Clinical studies	
Step 1. Pharmacokinetics	Studies in healthy volunteers (or in patients if toxicity criteria are met)
Step 1. Pharmacodynamics	Required as additional support for comparability
Step 2. Clinical studies	Randomized, adequately powered, parallel-group, preferably blind equivalence clinical trials

for an IFX biosimilar have been currently filed at EMA. The first one, already mentioned, has just completed phase-III clinical trials, and so it seems that the process followed from the preclinical stage through the initial steps in the clinical stage is of sufficient quality. At any rate, it is reassuring that the EMA required wide efficacy and safety clinical studies. Presuming these clinical trials will eventually yield fully convincing results, and the EMA approves this biosimilar, uncertainty would remain regarding whether such approval refers only to the indication wherein it was tested, RA, or results would be extrapolated to the remaining indications. Thus, in the field of rheumatology, given that Enbrel[®]'s patent expiry date is 2012 in the USA and 2015 in Europe, two highly advanced clinical studies for biosimilars are under development. A study has already been reported (48) that demonstrates the new biosimilar's PK is comparable to that of Enbrel[®] in healthy subjects. Nevertheless, the American health agency (FDA) has extended the patent term for an additional 17-year period of time, hence research on these biosimilars has been halted.

EMA recommendations on a possible extension of indications to areas not directly researched are anyway inconclusive; while a door remains open to this possibility, it is only considered for cases based on sound scientific reasoning. Although an antecedent exists when the Korean agency primarily approved this IFX biosimilar for multiple indications, there is nothing to suggest that the EMA will follow suit. Various scientific societies, particularly in the field of rheumatology (49,50) have taken up a stance in this regard and manifested their refusal to extrapolate results in a condition to a different one. They even advocate for the performance of specific studies in each indication. Our position is aligned with that reported by these societies because of our need to maintain and watch over the safety of our patients.

INSTITUTIONAL POSITION OF SEPD AND SEF

Within the framework of the present European legislation, "Sociedad Española de Patología Digestiva" and "Sociedad Española de Farmacología" manifest the following position regarding biosimilars:

1. A biosimilar is a drug that, using molecular biology techniques, is intended to provide an action equivalent to that of the product it attempts to copy.
2. Obtaining these biosimilars requires a complex process that does not ensure their being identical to their originals. Therefore, according to the present regulatory framework in Europe, deep research is needed both in animals and humans, across all phases, and using comparison with the original, in order to consider the drug under development as "similar" to the original. Thus, approval of a biosimilar should be based on all the preclinical and clinical trials demanded by European Law.

3. In no case does a license obtained for the management of a certain disease allow an extrapolation of results to a different disorder. In this way, results obtained from studies in RA should not be extrapolated to IBD because the above-mentioned biological and manufacturing variability that characterizes these complex structures does not guarantee an absence of noticeable changes in efficacy and safety.
4. As with originals, in order to obtain a given indication a biosimilar should be tested in a clinical trial specifically designed to that end.
5. Substituting a biosimilar for the original drug cannot be an accepted practice.
6. Each product's label should clearly emphasize it is a biosimilar drug so that the drug a patient is in fact taking may be always identified.
7. The appropriate use of biosimilar drugs requires interaction by physicians, pharmacists, and regulatory agencies with the aim of favoring the right to health of patients by offering quality, effective, and safe products.
8. This task force favors the development of biosimilar drugs and therefore their approval by regulatory agencies provided they are subjected to quality standards as supported by said agencies in terms of production and development, as well as an assessment of their efficacy and safety. Similarly, a stringent post-marketing surveillance program is also necessary.
9. This position should be regularly updated in the light of new evidence approximately every two years.

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