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Progress Report

Use of biosimilars in inflammatory bowel disease: Statements of the Italian Group for Inflammatory Bowel Disease

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ABSTRACT

The introduction of biological therapies, particularly anti-TNFα agents, has revolutionized the management of inflammatory bowel disease in those cases which are refractory to conventional treatment; however these drugs are not risk-free and their use has substantially increased the cost of treatment. As marketing protection expires for original, first-generation biopharmaceuticals, lower-cost "copies" of these drugs produced by competitor companies—referred to as biosimilars—are already entering the market. In September 2013, the European Medicines Agency approved two infliximab biosimilars for treatment of adult and paediatric inflammatory bowel disease patients, a decision based largely on efficacy and safety data generated in studies of patients with ankylosing spondylitis and rheumatoid arthritis. For many clinicians, extrapolation practices and the general question of interchangeability between biosimilars and reference biologics are cause for concern. In the present paper, the Italian Group for inflammatory bowel disease presents its statements on these issues, with emphasis on the peculiar clinical characteristics of inflammatory bowel disease and the importance of providing physicians and patients with adequate information and guarantees on the safety and efficacy of these new drugs in the specific setting of inflammatory bowel disease.

1. Introduction

Biological medicinal products (or biologics) are characterized by active substances derived from living cells or organisms with the aid of biotechnology methods (recombinant DNA, controlled gene expression, antibody technologies) [1]. The first-generation biologics were launched in the late 1970s and early 1980s, and this innovative class of drugs is now one of the fastest growing sectors of the pharmaceutical industry [2]. In the field of inflammatory bowel diseases (IBD), the therapeutic use of monoclonal antibodies (mABs), particularly those directed against tumour necrosis factor α (TNFα), has allowed physicians to set and achieve more ambitious therapeutic targets [3,4], however these drugs are not without risk [5], and their use has also markedly increased the direct costs of medical treatment of IBDs [6]. Data exclusivity and market protection for many of the original biologics (e.g., erythropoietins, gonadotropins, human insulins) are currently expiring in various parts of the world, and competitors are already seeking authorization to market "copies" of these agents. Referred to collectively as *biosimilars*, *follow-on biologicals*, or *subsequent-entry biologicals*, these new drugs are expected to be considerably less expensive than the originals [2]. In the European Community, marketing authorization for biosimilars is granted in accordance with guidelines established in 2005 by the European Medicines Agency's (EMAs) Committee for Human Medicinal Products (CHMP) [7,8] and integrated in 2012 with specific guidance for biosimilar mAbs [9]. Biosimilar drugs have also been identified as a topic for regular exchange of information and collaborative meetings by the EMA and United States Food and Drug Administration (FDA) [10].

The anti-TNFα mAb infliximab was the first biologic agent used to treat Crohn's disease (CD) and ulcerative colitis (UC), and it is still the one most widely used for this purpose. Its patent protection expires in Europe between 2013 and 2015, depending on the country [11], and in September 2013 the EMA approved two infliximab

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biosimilars that had been licensed for use in India and South Korea in 2012 [12]. Although infliximab biosimilars are expected to reduce the cost of IBD treatment, questions are being raised regarding the degree to which biosimilars can be considered interchangeable with their respective reference biologics. Particular concern has been expressed over the authorization for treatment of IBD based on data extrapolated from studies conducted in autoimmune diseases [13–15].

In this paper, the Italian Group for the study of Inflammatory Bowel Disease (IG-IBD) outlines its official position on the use of biosimilar agents in the treatment of IBD. Emphasis is placed on the peculiar characteristics of IBD (see statements #5, 6, 8, and 9), and the current lack of validated biomarkers for assessing disease activity, responsiveness to treatments, and the efficacy of therapy.

2. Biosimilars

Unlike chemical generics, biosimilars cannot be considered mere copies of the original reference drug. The characteristics and properties of drugs containing biotechnology-derived proteins depend largely on the type of cell in which they are produced, the production and purification processes, and the methods used to transform them into drugs. Subtle differences involving a single step in the production process—even the plant location can translate into major differences in terms of pharmacokinetics, treatment efficacy, and/or safety. Some degree of divergence between the reference drug and biosimilar manufacturing processes is inevitable because, even after patent expiration, the reference agent manufacturer is not obliged to reveal details of its production practice. However, the same caveat applies to post-marketing changes/improvements in the process used to manufacture any given biologic. The production process for the original version of infliximab (Remicade™), for example, has undergone over 30 major or minor modifications since the drug was first licensed, and each has had to be assessed by the EMA and other regulatory authorities to ensure the comparability of the pre- and post-change products [16]. Verification of comparability is especially important for mAbs, which are high-molecular-weight proteins with complex secondary and tertiary structures that often undergo post-translational modifications, such as glycosylation. Indeed, covalent modifications of these complex proteins, including phosphorylation, SUMOylation, O-GlcNAcylation, and ubiquitylation, represent key mechanisms for regulating the protein's stability and transcriptional activity.

For these reasons, marketing authorization for a biosimilar is granted only after the applicant has reliably demonstrated the innovator product's equivalence with the reference biological agent in terms of quality, efficacy, and safety. For the EMA, this is generally accomplished with a step-wise comparability exercise, which includes in vitro experiments followed, when necessary, by in vivo studies. Only when these pre-clinical studies have generated sufficient evidence of the two drugs' pharmaco-toxicological comparability (including structural characteristics, physicochemical properties, purity and impurities, biological activity) is clinical testing undertaken to ensure comparability at the levels of pharmacokinetics, pharmacodynamics, efficacy, and safety, with special emphasis on potential immunogenicity [2]. Full equivalence cannot be demonstrated without the aid of extremely large clinical trials, but the innovator drug must display comparability with the reference drug that falls within pre-specified and well-justified clinical margins established by the EMA [17].

Authorization of biosimilars—as for all drugs—must be based on data generated in clinical studies large enough to provide a comprehensive profile of the new agent's safety profile. This entails comparison of the nature, severity, and frequency of the biosimilar's adverse effects with those of the reference product. Collection of post-approval safety data is also essential for these drugs. Both the EMA and FDA require pharmacovigilance programmes for biosimilars, with continuous monitoring of safety issues to ensure timely, appropriate responses if problems arise [18].

Once a biosimilar has been approved by the EMA for use in a given indication, efficacy and safety data may be extrapolated to other indications approved for the reference drug, even though the biosimilar agent has not been formally tested in that setting [7]. This practice is more common when the drug's mechanism of action in the different diseases is the same or similar (i.e., immunosuppression). However, additional data may well be needed to justify the extrapolation if, for example, the reference drug's actions in the two diseases involve different sites of the molecule or of the target cells or if its safety profiles in the two settings are different [7]. In addition, a potential concern with the practice of data extrapolation is that use of a biopharmaceutical may be associated with different risks in different patient populations (e.g., patients with different diseases, different age groups).

It is important to note that the EMA's assessment of biosimilar medicines is done exclusively to the purposes of marketing authorization. The agency takes no stance on the question of whether or not the biosimilar should be used interchangeably with its reference medicine. Indeed, it suggests that such decisions be made by qualified healthcare personnel on the basis of national or local guidelines [14]. The Italian Drug Agency (Agenzia Italiana del Farmaco, AIFA) has recently taken a step further, recommending that the decision to prescribe a biosimilar drug or its reference drug be made exclusively by the specialist managing the specific disease [19]. Clinicians must thus be aware of the basis of a biosimilar drug's approval for a given indication, and they must be free to make informed treatment choices with their patients on the use of such drugs.

3. Biologics in inflammatory bowel disease

Therapeutic mAbs have become a fundamental tool for the management of numerous diseases. Over 300 products of this type are currently under development, and approximately 30 others have already been approved in the United States [20]. One of the most effective and widely used classes of therapeutic mAbs are the anti-TNFα agents, which are used in the treatment of rheumatic diseases (e.g., rheumatoid arthritis [RA], ankylosing spondylitis [SA]), as well as for IBD. Indeed, four of the biologics currently approved by the EMA and FDA for the treatment of IBD are anti-TNFα mABs (infliximab, adalimumab, golimumab, and certolizumab, which has only FDA approval). The other two are anti-integrin mABs (natalizumab, which is directed against integrin α4β1 and was authorized by the FDA in 2004, and the new anti-α4β7-integrin vedolizumab, which has been recently approved for treatment of IBD in both Europe and the United States).

Table 1 summarizes the results of the American College of Gastroenterology's recent meta-analysis and systematic review of placebo-controlled studies on the efficacy of anti-TNFα and natalizumab therapy in adults with IBD [21]. Data are expressed as failure to achieve remission at 4–12 weeks.

Significant heterogeneity has emerged between anti-TNFα agents ($P = 0.007$) in terms of their efficacy in active CD: the best results were achieved with infliximab (number needed to treat, NNT = 4) and adalimumab (NNT = 7), whereas the difference between certolizumab and placebo displayed only borderline statistical significance. However, for preventing relapse of quiescent luminal CD, two trials found that adalimumab was not significantly better than placebo. The benefit of infliximab in fistulizing CD was documented only in the single trial in which fistula healing was