

Position paper of Italian rheumatologists on the use of biosimilar drugs

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ABSTRACT

The recent availability of biosimilars as a result of the expiry of the patents of first-generation biotechnological drugs may theoretically reduce the direct costs of such treatments, making their use accessible to a larger number of patients. However, the currently available clinical data refer to a relatively small number of patients, and do not provide sufficient information concerning long-term efficacy and safety or the frequency of rare adverse events. Given the importance of the introduction of biosimilar drugs and the limitations of our current knowledge of their efficacy and safety profiles, we believe it is mandatory to draw up a position paper for Italian Rheumatologists. Moreover, in order to guarantee their safety, it is mandatory to indicate behavioural rules for the involved specialists and competent authorities, and perform ad hoc clinical trials and appropriate drug surveillance.

Introduction

Biological and biotechnological drugs are medicinal preparations whose active component is produced by, or extracted from, a biological system by means of a biotechnological process (1). Biological drugs may include hormones, enzymes, blood derivatives, and immunological drugs such as sera, vaccines, immunoglobulins and monoclonal antibodies. These therapeutic tools have revolutionised the treatment of a large number of rheumatic, neurological and neoplastic diseases, and benefited millions of patients throughout the world. Unfortunately, the development process from early research to the clinical phases is expensive, and raises the issue as to whether such drugs are economically sustainable by National Health Services (NHS) (1).

The recent availability of biosimilars, as a result of the expiry of the patents of first-generation biotechnological drugs, may theoretically reduce the direct costs of such treatments, making their use accessible to a larger number of patients. Given the importance of the introduction of biosimilar drugs and the limitations of our current knowledge of their efficacy and safety profiles, we believe

it is mandatory to draw up a position paper for Italian Rheumatologists.

Methodology

The Italian Society of Rheumatology (SIR) and the Italian Group for the Study of Early Arthritis (GISEA) nominated a multidisciplinary panel of expert rheumatologists, regulatory affair experts, biostatisticians and patients' representatives to make a systematic review of the literature in order to finalise a series of statements concerning the use of biosimilars in clinical practice. These statements will be used as a basis for training courses dedicated to rheumatologists involved in prescribing and monitoring biological and biosimilar drug treatments. Six points were identified on the basis of the existing literature, the FDA and EMA guidelines, and the experts' opinions, and then discussed at a Consensus Conference held in Rome on 11 April 2014 in the presence of 40 experts chosen among Professors of Rheumatology, Directors of Rheumatology Units, specialists with experience in prescribing and monitoring biological drugs, and representatives of the Association of Patients with Rheumatic Diseases (APMAR).

The discussion led to the drawing up of six statements approved on the basis of the agreement of at least 80% of the attendees.

Definition of biosimilars

Although similar, the FDA and EMA definitions of biosimilar drugs are slightly different: for the FDA, a biosimilar drug is a biological product displaying minimal differences with the reference product already registered in the USA in terms of its clinically active components, safety, purity and efficacy (2). For the EMA, a biosimilar drug is a new version of an already registered original product (the reference product), whose qualitative characteristics, biological activity, and safety and efficacy profiles have been shown to be similar to those of the reference product by means of comparability studies (3).

The criteria for the marketing authorisation of a biosimilar are rigorous and designed to guarantee adequate production and safety standards.

Comparability exercise

Comparability is not only the gold standard for evaluating the similarity between a biosimilar and its reference molecule, but is also used to check whether the reference product is modified during its production. The aim is to demonstrate that the safety and efficacy profile of a given drug is not changed during manufacturing. Clinical data are generally unnecessary in a comparability exercise. Biosimilar drugs should pass comparability tests with their reference product, before being formally approved (3).

The production processes of all of the currently marketed biological drugs (monoclonal antibodies and receptors) have been modified over the years. It is known that even small changes can give rise to significant variations in the characteristics of a drug; hence, every modification must be evaluated by means of comparability testing in order to highlight any difference, and monitored by means of post-marketing surveillance.

Approved biosimilars

CT-P13 is the first biosimilar of infliximab that was marketed in Europe in 2014. Two randomised and controlled clinical trials were carried out: one involving patients with rheumatoid arthritis (RA) (PLANETRA) and the other patients with ankylosing spondylitis (PLANETAS). They were both designed to compare the efficacy, safety and pharmacokinetics of the new drug and infliximab.

The 30-week PLANETAS trial did not find any statistically significant difference between infliximab and CT-P13 in terms of efficacy (evaluated on the basis of thoracic expansion and ASDAS-CRP, BASDAI, BASFI and BASMI scores) or safety (the frequency of adverse events was 64.8% with CT-P13 and 63.9% with infliximab, and there was no difference in severe adverse events). The data from the PLANETAS trial were also compared with those from the infliximab registration trial (ASSERT), and there was no substantial difference in terms of clinical efficacy and adverse events.

The primary aim of the PLANETRA

trial was to evaluate the efficacy of infliximab and CT-P13 in combination with methotrexate (MTX) in 606 patients unresponsive to MTX who were randomised 1:1. The primary endpoint was the achievement of ACR20 after 30 weeks, and the secondary endpoints were the CDAI and SDAI scores. The *intention-to-treat* analysis showed that ACR20 was achieved by 60.9% of the patients treated with CT-P13 and 58.6% of those treated with infliximab, and the changes in the CDAI and SDAI were also comparable. Adverse events were observed in respectively 60.1% and 60.8% of the patients.

The results of the PLANETRA study were also compared with those of the registration studies of infliximab in RA: the ACR 20 results were better than those observed in the ATTRACT trial and similar to those observed in the START trial. The safety results were similar to those of the ATTRACT and ASPIRE studies (4-8).

However, the currently available data refer to a relatively small number of patients, and do not provide sufficient information concerning long-term efficacy and safety or the frequency of rare adverse events.

Extrapolation of indications

Both the EMA and FDA are theoretically favourable to transferring the clinical prescriptions of the reference drug to the biosimilar automatically: the so-called extrapolation of indications. This is a very critical point since there is no scientific evidence supporting such a conclusion, and particularly because of the complex and different pharmacological mechanism(s) of action of a given biological in the differently approved clinical indications (*e.g.* TNF inhibitors in Crohn's disease and RA) (9).

Furthermore, the non-inferiority evaluation of two drugs should be calculated on the basis of the difference in efficacy between the reference product and placebo: the smaller is the difference, the narrower the margin of error. In this regard, RA is certainly the least sensitive model for highlighting a difference in efficacy between CT-P13 and infliximab, since the latter displays the less high response rate compared to pla-

cebo. In addition, given the small difference in responses, the studied populations should have been much larger than that of the PLANETRA study in order to support that the non-inferiority does not fall within the range of a placebo response (6, 10).

Particular caution is required concerning the paediatric use of biosimilars because clinical manifestations, side effects, comorbidities and concomitant therapies are different in children and adults. Furthermore, little is known about the pediatric pharmacokinetics of biosimilars (and biological drugs in general), and further investigations should be carried out (10).

Immunogenicity

Immunogenicity is another characteristic of biological drugs since non-self proteins can trigger an immune response even when completely humanised. Immunogenicity can be influenced by several factors (for example, a different pattern of glycosylation can expose or hide antigenic epitopes, alter solubility or affect protein degradation). Immunogenicity is related to the appearance of anti-drug antibodies which are associated with the development of adverse events and/or loss of efficacy and can be evaluated by means of comparability testing. According to the *World Health Organisation*, it should be assessed in cohorts of patients at highest risk of developing an anti-drug immune response or treatment-related adverse events (11).

The PLANETRA and PLANETAS studies evaluated the immunogenicity of CT-P13 after 30 weeks, but published data suggest that longer observation periods are necessary. For example, anti-drug antibodies generally appear in RA patients after the fourth infusion, and sometimes even after one year (4, 6, 12-14).

Interchangeability and replaceability

The interchangeability and replaceability of chemically synthesised drugs is beyond doubt, but the same is not true of biological drugs.

The Biologics Price Competition and Innovation Act in the United States lays

down that, before a biosimilar drug can be declared interchangeable with its reference product, the manufacturer must be capable of demonstrating not only its biosimilarity, but also its similar clinical efficacy. Furthermore, in the case of a switch from the reference to its biosimilar (or *vice versa*), the risk in terms of safety or diminished efficacy must be the same as that of the starting treatment. Currently, the FDA and EMA have neither identified any interchangeable drug nor suggested any criteria for supporting interchangeability. It is also worth pointing out that *interchangeability* includes the possibility that a physician or pharmacist can dispense the innovator drug rather than the biosimilar in the USA. Differently in Italy, *interchangeability* indicates the possibility for a physician to prescribe either of the two drugs, and *replaceability* the possibility for a pharmacist to dispense one drug instead of the other without the physician's consent.

The EMA *Guidelines on biosimilar biological drugs* state that the uncontrolled replaceability of a biological drug could complicate drug surveillance negatively by affecting safety profiles. Replacement should only be allowed in the case of the explicit consent of the prescribing physician and patient. Accordingly, the EMA Medicines Evaluation Board states that (15):

- naïve patients can be treated with a biosimilar;
- patients treated with a biological drug should avoid switching to a biosimilar (or *vice versa*);
- repeated switches between the original drug and biosimilar (or *vice versa*) should be avoided.

Consequently, replaceability should not be applicable to biological drugs without the prescriber's knowledge. Whereas interchangeability should be evaluated for any given biosimilar and therapeutic indication, and approved only after *ad hoc* clinical trials have been carried out.

Traceability

As stated above, automatic replacement could complicate drug surveillance insofar as repeated switches of different biosimilars could make it difficult (if

not impossible) to determine the attribution of side effects, leading to inappropriate therapeutic discontinuations (16). It is essential to distinguish a biosimilar from the original drug, and any adverse event report should include the trade name (brand), international non-proprietary name (INN), and batch number of the involved drug. Although not all authors agree, the majority of the member States of the European Pharmaceutical Commission believe that biosimilars should have the same INN as their reference biological drug (15). The new European regulations governing drug surveillance also lay down that patients should be able to report adverse events directly to their national authorities, and has also introduced a new approach aimed at publishing a list of drugs undergoing additional monitoring. These drugs, which include the currently marketed biosimilars and monoclonal antibodies, are identified by a downward-pointing black triangle printed on their packages (17-19). Finally, it is necessary to collaborate with scientific societies in establishing a registry of all biotechnological drugs with a marketed biosimilar in order to monitor them and identify any differences, with particular attention to their efficacy, adverse events and immunogenicity.

In conclusion, the availability of biosimilars will allow the treatment of more patients with severe diseases and at the same time will offer greater economic sustainability to the NHS, particularly in the case of naïve patients. However, in order to guarantee their safety, it is mandatory to indicate behavioural rules for the involved specialists and competent authorities, and perform *ad hoc* clinical trials and appropriate drug surveillance.

Consensus statements

1. Replaceability and interchangeability

The interchangeability between a biosimilar and its reference drug, or two biosimilars, should be evaluated for each biosimilar drug and each therapeutic prescription, and approved only after *ad hoc* clinical trials have been carried out.

The automatic replaceability of a bio-

logical drug may affect post-marketing drug surveillance. Automatic replaceability should not apply to biological/biosimilar drugs.

Replacement should be agreed with a specialist physician and patients should give their informed consent.

2. Traceability and drug surveillance

It is essential to trace a drug so that it is possible to identify rare or delayed side effects, as well as immunogenicity. In order to associate adverse events with a given drug, reports should contain the trade name of the drug, the international non proprietary name of the active ingredient, and the batch number.

Furthermore, collaboration with scientific societies would be useful to establish a registry of all biotechnological drugs with a marketed biosimilar, for the purposes of monitoring and identifying any difference, particularly regarding efficacy, adverse events and immunogenicity.

3. Immunogenicity

Immunogenicity is an important factor that can be evaluated by means of comparability testing because of anti-drug antibodies (ADA) production and the related adverse events and/or loss of efficacy. According to the WHO, drug immunogenicity should be investigated in patients at highest risk of developing an anti-drug immune response or related adverse events.

In the PLANETRA study the prevalence of ADA was 27.4%, whereas in PLANETAS it was 48.4% at 30 weeks. These data underline that immunogenicity linked to replaceability and interchangeability should be carefully evaluated in the real practice in different clinical settings.

Repeated switches between a biosimilar and its reference drug may favour the appearance of ADAs.

4. Extrapolation of indications

Since the mechanism(s) of action of biologicals is complex, not only related to Fab/antigen interaction, and diverse for different diseases, extrapolation to indications not included in the comparability exercise should be carefully evaluated. This is particularly true in

the case of extrapolation to inflammatory bowel diseases and the paediatric population, from both the efficacy and the safety points of view. Clinical trials involving specific targets are strongly encouraged.

5. Efficacy and safety

The currently available data come from studies with a relatively small number of patients, and do not provide sufficient information concerning long-term efficacy and safety or rare adverse events.

Further information from appropriate post marketing clinical trials is therefore necessary to improve patient safety. Like all biologicals, biosimilar drugs should only be prescribed by trained specialists on the basis of clinical safety and efficacy data, including those from national and international registries.

6. Informed consent

Patients should be adequately informed about the advantages and the possible adverse effects of biotechnological therapy before starting treatment. In the same way, they should be informed about any drug change.

Clinically well controlled patients should not be switched from an original drug to its biosimilar, or *vice versa*.

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