

REVIEW ARTICLE

Biosimilars for Healthcare Professionals

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Safety assessment of biosimilars in Europe: a regulatory perspective

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Clinical safety is important during the development of a biosimilar. This paper provides an overview of the main aspects related to the safety assessment of biosimilars. The European Medicines Agency's 'Guideline for similar biological medicinal products containing biotechnology-derived proteins as active substances: non-clinical and clinical issues', which is currently under revision, forms the basis for the topics discussed in this paper. Topics discussed include adverse events related to an exaggerated pharmacology, immunogenicity including assay development, extrapolation of indications in relation to safety assessment and pharmacovigilance.

Keywords: Biosimilar, clinical safety, immunogenicity, pharmacovigilance

Introduction

The safety profile of biologicals can often be attributed to: a) adverse events related to an exaggerated pharmacology, and b) immunological reactions, including immunogenicity and infusion-related reactions [1, 2].

Adverse events related to an exaggerated pharmacology can be illustrated by the occurrence of infections during the use of biologicals with a strong immunosuppressive mode of action. Patients treated with tumour necrosis factor alpha (TNF-alpha) inhibitors should, for example, be tested for latent tuberculosis before treatment is initiated due to an increased risk of tuberculosis related to treatment with these agents. TNF-alpha plays an important role in human immune defence against the *Mycobacterium tuberculosis* bacterium. Patients with latent tuberculosis should, therefore, receive anti-tuberculosis treatment before starting treatment with a TNF-alpha inhibitor [1-6].

Immunological reactions are varied, and can include the formation of antibodies, allergic reactions, and administration-site conditions, which are inherent to the biological nature of these agents and the parenteral route of administration. If antibodies are formed they often have no clinically relevant effect, but in some cases they are directed against the administered biological, neutralizing the agent's effect and in some cases antibodies are not only directed against the administered biological but also against the endogenous available protein. Neutralizing anti-drug antibodies (ADAs) result in a diminished clinical response to the biological, and their presence is reflected in clinical practice by the administration of higher doses and/or more frequent dosing over time. A study by Bartelds et al. found that about one third of patients treated with adalimumab for rheumatoid arthritis developed neutralizing antibodies within three years after the start of treatment [7].

Testing for the presence of neutralizing antibodies is receiving more and more attention in clinical practice, partly as a result of available tests and trained staff able to use them. In addition, ADA has been associated with severe infusion reactions following treatment with monoclonal antibodies [8]. The development of antibodies directed against both the administered biological

and the endogenous available protein can be illustrated by the well-known Eprex[®] case. After a change in the formulation of epoetin-alfa, patients developed antibodies against both the administered epoetin and also against the endogenous available erythropoietin, resulting in a complete depletion of erythropoietin and a serious condition: pure red cell aplasia. As illustrated by the Eprex[®] case, a change in the production process of a biological might influence the immunogenic potential of that biological, and any change in the production profile should, therefore, be clearly evaluated during the production of all biologicals [9-13]. Several factors are known to influence immunogenicity in clinical practice, including the presence of impurities and/or leachables, and protein aggregation. The subcutaneous route of administration is in general more immunogenic than the intravenous route of administration, and the concomitant use of other immunosuppressive agents is known to reduce the formation of antibodies. Alongside these factors, an individual patient's genetics and age are known to influence immunogenicity [10, 14]. Adverse events related to the parenteral mode of administration are often reflected in adverse reactions at the site of administration.

Clinical safety is important during the development of a biosimilar. This paper provides an overview of the main aspects related to the safety assessment of biosimilars. The European Medicines Agency's 'Guideline for similar biological medicinal products containing biotechnology-derived proteins as active substances: non-clinical and clinical issues', which is currently under revision, forms the basis for the topics discussed in this paper [15].

Clinical safety during biosimilar development

Data related to the clinical safety of the biosimilar should be collected during the complete clinical development programme and should be captured during initial pharmacokinetics and/or pharmacodynamics studies and also as part of the pivotal clinical efficacy study [15]. A complete overview of all safety data collected should be submitted to the regulatory authorities for assessment.

Safety related to an exaggerated pharmacology

Adverse events related to an exaggerated pharmacology known for the reference product will also occur during use

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of the biosimilar. Differences in adverse events related to an exaggerated pharmacology, which can be related to the biosimilar and not to a chance finding, may preclude registration as a biosimilar and should be carefully evaluated in relation to the totality of evidence obtained for the biosimilar.

The safety data available for the reference product should specifically be taken into account and should form the basis for the safety evaluation of the biosimilar [15]. For the infliximab biosimilars Inflectra® and Remsima®, safety issues of special interest were identified which are known safety concerns for the reference product, Remicade®. These safety issues included heart failure, serious infections, serious infusion reactions, delayed hypersensitivity reactions (serum sickness), systemic lupus erythematosus/lupus-like syndrome, hepatobiliary events, demyelinating disorders, haematologic reactions and lymphoma [16-18]. Due to a relatively limited number of patients, the pivotal clinical efficacy study is in general not capable of detecting differences in rare adverse events between the biosimilar and the reference product. However, the equivalence design used for the pivotal clinical efficacy trial of the biosimilar is usually much larger than the superiority trials against placebo that formed the basis for the approval of the reference product. This results in a safety database which is usually sufficient for the assessment of the biosimilar. In addition, adverse events should be compared by type, severity and frequency in order to provide as complete as possible a comparison between the safety profile of the biosimilar and the reference product [15]. A thorough evaluation of the particular cases, in light of the totality of evidence as regards biosimilarity, is needed in case differences are observed between the biosimilar and the reference product; in other words, is a more adverse safety profile scientifically plausible? For the biosimilar infliximab, a numerical imbalance was found in serious adverse events in the pivotal clinical efficacy trial, with a higher incidence of serious infections, including tuberculosis. A thorough review of all the available data suggested that the difference was most likely a chance finding and that this should be further evaluated as part of the risk management plan (RMP). The following arguments were considered:

- Four cases of tuberculosis in the biosimilar arm did not fulfill adequate diagnostic criteria of tuberculosis and/or had pre-existing suspicious pulmonary lesions.
- The total rate of infections was comparable in both treatment arms.
- The tuberculosis rate in patients treated with the biosimilar was comparable to those reported in historical studies with the reference product, whereas it was unexpectedly low in patients treated with the reference product.
- Seroconversion in the interferon-gamma release assay was equally frequent in both treatment arms.
- From a mechanistic point of view there is no plausible explanation for a difference in host defence between the two products.

This example illustrates a challenge in the safety assessment of a biosimilar and the need for a thorough post-marketing follow-up, especially if differences are observed during the assessment of safety data collected throughout clinical development [15, 16].

Immunogenicity assessment

Immunogenicity and other immunological reactions, e.g. infusion and hypersensitivity reactions, are especially important during the development of a biosimilar. As already mentioned in the introduction, a change or a difference in production process might influence the characteristics of the biological and potentially its immunogenic potential – notably, in either an adverse or beneficial way. Since the production process of a biological is proprietary knowledge of a company, biosimilar companies should develop their own production process [9-12]. Assessment of immunogenicity, therefore, already starts during the quality assessment of the biosimilar, where the physicochemical characteristics of the biosimilar and the reference product are extensively assayed, assessed and compared. If differences are found, for example, differences in glycosylation, companies are advised to clearly evaluate these differences in relation to the immunogenic potential of the biosimilar [14].

Immunogenicity assessment is an important part of the clinical development programme and should also be investigated in a comparable way between the biosimilar and the reference product. The amount of immunogenicity data needed will depend on experience gained with the reference product and/or the product class. Immunogenicity data for chronically administered biosimilars should normally be collected pre-licensing for up to one year. However, shorter follow-up might be justified based on the immunogenicity profile of the reference product. If, for example, it is known that immunogenicity for the reference product mostly develops within six months after the start of treatment, collection of immunogenicity data for the biosimilar less than one year pre-licensing may be justified. Immunogenicity data for the additional period, up to one year, could then be submitted post-authorization, if considered necessary by the regulatory authorities [15]. In addition, other aspects related to immunogenicity, e.g. route of administration and/or type of disease; should be included and preferably tested in the most sensitive patient population [10, 14].

Immunogenicity testing of the biosimilar and the reference product should be conducted within the biosimilar comparability exercise by using the same assay format and sampling schedule. The assay used to detect antibodies is an important consideration during the clinical development of a biosimilar and should meet all current standards. Comparison of data obtained for the biosimilar with historical data obtained for the reference product is generally not considered appropriate due to continuing developments in this field.

Assays have over time evolved to be much more sensitive. If one were to directly compare the immunogenicity of a biosimilar measured using a current assay with historical data of the reference product using an outdated assay, then it could appear that the biosimilar exhibits a much higher immunogenicity since the current assay is much more sensitive. This would not result in comprehensive data. Preferably, two assays should be used which are capable of detecting antibodies against both the biosimilar and the reference product. However, if only one assay is used, the assay should be capable of detecting antibodies to the biosimilar. This will provide a conservative comparison between the biosimilar and the reference product, and biosimilar companies should take into consideration that the

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one assay approach may result in higher antibody levels for the biosimilar as compared to the reference product. Differences found between the biosimilar and the reference product need to be justified in the application dossier. In principle, the incidence of antibodies and antibody titres should be measured and presented [14]. Assessment and interpretation of antibodies in relation to the potential effect on clinical efficacy and safety is important, as illustrated by the development of the infliximab biosimilar. Development of antibodies to infliximab was associated with an increase in the frequency of hypersensitivity/infusion-related reactions in patient groups treated with both the biosimilar and the reference product [16, 17].

In principle, the safety profile of the biosimilar and the reference product should be comparable. This also relates to immunogenicity. However, one exemption might be possible: if a lower immunogenicity is found for the biosimilar, this might not preclude approval as a biosimilar. Reduced development of neutralizing antibodies to the biosimilar could erroneously suggest that the biosimilar is more efficacious than the reference product when analysing the entire study population (since efficacy is less antagonized). The biosimilar company is therefore recommended to perform a subgroup analysis of patients treated with both the biosimilar and the reference product which did not mount an ADA response during the clinical trial. This subgroup analysis could be helpful to establish that the efficacy of the biosimilar and the reference product are in principle similar if not impacted by an immune response. [15].

Extrapolation of indications

Extrapolation of indications is a key aspect in the development and approval of biosimilars in Europe. Safety of the biosimilar should also be taken into account in relation to the mode of action of the biological in different indications. Adverse events related to an exaggerated pharmacology will apparently also occur in different indications of the biological. Immunogenicity is related to different aspects as discussed in the introduction, which might differ between indications, e.g. differences in concomitant medication and/or duration of treatment. Extrapolation of immunogenicity data from one indication to the other should, therefore, be justified based on the knowledge obtained with the reference product and/or product class. In case differences exist, there might be a need for additional immunogenicity studies in one or more specific indications [15].

Pharmacovigilance

The safety profile of the biosimilar should be evaluated on an ongoing basis during use in clinical practice. The same rules and obligations apply for biosimilars as for any other biological medicinal product, which means that a RMP must be submitted as part of the application procedure as well as Periodic Safety Update Reports (PSURs) and the collection of adverse events identified and reported after approval.

The RMP of the biosimilar should, as a starting point, be based on the RMP and knowledge obtained with the reference product and should take into account identified and potential risks associated with the use of the reference product. Immunogenicity and infusion-related reactions should specifically be addressed in the RMP and, if needed, additional pharmacovigilance activities to

identify these reactions should be described. It is expected that spontaneous reporting of adverse events will generally not be able to detect effects of neutralizing antibodies and therefore other activities should be considered, e.g. measuring neutralizing antibodies in a subset of the population as part of a post-marketing obligation, where deemed necessary. Any specific safety monitoring for the reference product should, in principle, also apply to the biosimilar. In some instances there will be a need to compare certain adverse events of interest between the biosimilar and the reference product. With very rare events, e.g. progressive multifocal leukoencephalopathy during use with rituximab, any case will contribute to the general knowledge about this very rare condition and a comparison will not be possible due to the limited number of cases. Biosimilars are, therefore, encouraged to participate in already existing registries of the reference product.

Several registries are in place in Europe, particularly with biologicals used for rheumatoid arthritis, which have contributed greatly to the general knowledge on the safety and efficacy of the agents during use in clinical practice [1, 15]. The biosimilar infliximab will, for example, perform several post-marketing studies in already existing registries used for RA [16, 17].

Risk minimization measures in place for the reference product should generally also apply to the biosimilar, e.g. a patient alert card for serious infections related to the use of Remicade® is also included in the risk minimization programme of the biosimilar infliximab [16-18]. One exemption to this approach is risk minimization activities in place for the reference product which are specific for the device by which the reference product is administered [15]. The device by which the biological is administered might differ between biosimilar and reference product and might consequently need different educational measures to realize correct use in clinical practice [15].

An important issue related to pharmacovigilance is traceability of the administered biological, which applies to all biologicals and is not specific to biosimilars. Therefore, all appropriate measures should be taken to identify clearly any biological medicinal product which is the subject of a suspected adverse reaction report, with due regard to its brand name and batch number. This not only applies to the collection of spontaneously reported adverse events, but also during pharmacoepidemiological studies, including registries [15].

Conclusion

Safety assessment is an important part of the development of a biosimilar. Safety data should be collected throughout the complete clinical development programme and should be compared between the biosimilar and the reference product. Assessment of immunogenicity is especially important in this context due to the potential impact of changes in the production process and consequently on clinical safety. Differences in the safety profile will question biosimilarity and will require appropriate in-depth assessment and evaluation. A lower immunogenicity of the biosimilar might, however, be acceptable. Extrapolation of safety data from one indication to the other is possible and should be justified, especially with regard to immunogenicity and potential differences in the characteristics of the patient population and the disease in which the biological is used.

The same pharmacovigilance rules apply for biosimilars as for any other biological. Within the RMP the knowledge obtained with the reference product should be the basis for the content of the RMP and the obligatory post-marketing requirements, including risk minimization measures. Traceability is important and measures should be implemented to improve traceability.

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