Immunogenicity assessment of monoclonal antibodies

The most critical safety concern relating to biologicals (including biosimilars) is immunogenicity. This is especially important for monoclonal antibody (mAb) biologicals, which are large molecules with complex structures and functions and which represent the largest class of biologicals.

Immunogenicity is the ability to induce a humoral and/or cell-mediated immune response. Most biologicals induce immune responses, because they are polypeptides or proteins and might therefore be recognized by the immune system as foreign. However, in most cases, the presence of antibodies is harmless and has little clinical consequence. The problem is that some cases of immunogenicity can cause problems or even be fatal, such as in the case of pure red cell aplasia [1]. Such cases raise concerns about the potential clinical consequences of extensive use of biologicals and biosimilars. Given that biologicals may induce such unwanted immune responses it is essential to investigate the immunogenicity of a biological prior to marketing approval. This is especially important when considering that the problem with immunogenicity is that it is impossible to predict.

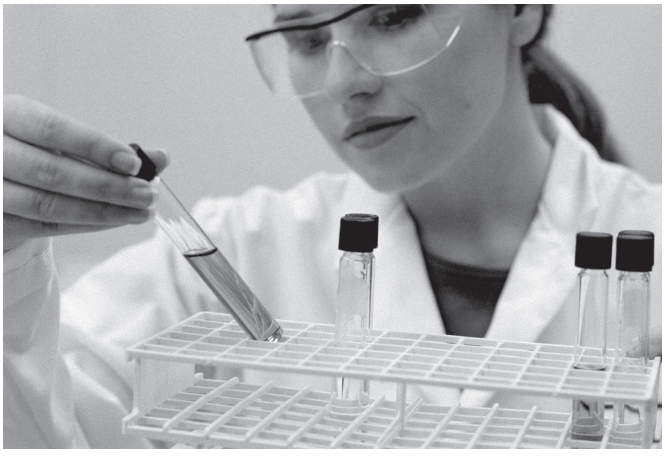
The immune response is influenced by many factors and data generated in pre-licensure studies may prove difficult to assess for regulators. Immunogenicity can be influenced by the product itself, e.g. structure, aggregation, dose, duration, but can also be affected by the patient, e.g. age, gender, ethnicity, immune status, genetic make-up [2]. The knowledge and expertise required for assessment of immunogenicity requires a thorough understanding of animal and human immunology as well as specific product characteristics, including mechanism of action, antibody assays and assessment of results in a given clinical context. The appropriate interpretation of immunogenicity data is of critical importance for defining the safety profile of an mAb.

At the World Health Organization (WHO) implementation workshop on Evaluation of Biotherapeutic Products, held in Seoul, Republic of Korea, in May 2014, regulators and manufacturers participated in a workshop evaluating two case studies mimicking a real situation evaluating immunogenicity studies for two fictitious mAb products [3].

It was expected that after completing the workshop, participants would have an understanding of how immunogenicity studies are conducted and assessed. In addition, how the information obtained is used to make decisions relating to the appropriateness of the studies and how the observed immunogenicity impacts on the clinical use of the mAbs was also covered.

Predictive immunogenicity modelling algorithms, such as *in silico* and T cell studies, are showing promise for identification of potential immunogenic T cell epitopes. However, despite the promise of these predictive tests, human clinical data is still needed for determining immunogenicity. This cannot be replaced by use of animal or *in vitro* or *in silico* tools [4].

Suitability of the assays for immunogenicity assessment was highlighted as a topic of critical importance for conducting the case studies. In the case of biosimilars, the methods used to measure the incidence of immunogenicity and the immunogenic potential of biosimilars and reference biologicals can significantly impact the comparability of the two molecules, and therefore great care must be taken in the development and execution of assays to measure immunogenicity [5]. The value of reviewing raw data for each individual subject in order to assess the impact of immunogenicity on efficacy and safety was also clearly demonstrated in the case studies.



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ABSTRACTED SCIENTIFIC CONTENT

WHO guidelines [6] state that the monitoring period for immunogenicity assessment depends on the intended duration of treatment and the expected time of antibody development. However, one of the examples in the case studies illustrated that a longer period of observation may be necessary to increase accuracy in assessing immunogenicity.

Discussion on additional indications and the need for additional immunogenicity studies revealed that the expectations in terms of the size and design of such studies differ among regulators and manufacturers. However, there was a consensus that the original case studies were limited and that additional data needed to be generated.

When it comes to biosimilar mAbs, it becomes an even more sophisticated exercise, and includes the challenge of addressing correlation between bioanalytical signals and clinical endpoints.

The case studies highlighted the need to assess the methods used for appropriateness for use for their intended purpose and to interpret the data generated, taking into account their limitations.

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