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Review

Immunogenicity assessment of monoclonal antibody products: A simulated case study correlating antibody induction with clinical outcomes

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ABSTRACT

Monoclonal antibodies are large molecules with complex structure and functions. They have a wide application for treatment of a broad range of chronic diseases and represent the largest class of biotherapeutic products. Given that biotherapeutic products may induce unwanted humoral and/or cellular immune responses in recipients, it is essential to investigate the immunogenicity of a product prior to licensure. The immune response is influenced by many factors and data generated in the pre-licensure studies are usually somewhat difficult for regulatory review. The knowledge and expertise required for this 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 a monoclonal antibody.

Two case studies described in this paper were prepared to mimic a real situation in which regulators need to evaluate immunogenicity studies conducted by manufacturers of monoclonal antibody products. The specific objective of the case studies was to illustrate assessment of unwanted immunogenicity and the important factors that need to be considered in this context. Regulators and manufacturers who attended the World Health Organization (WHO) implementation workshop on Evaluation of Biotherapeutic Products, held in Seoul, Republic of Korea, in May 2014, participated in the case studies and provided valuable input. This article outlines the main aspects of immunogenicity discussed in these case studies and a summary of the lessons learned at this occasion.

1. Introduction

Monoclonal antibodies (mAbs) have very considerable potential for therapeutic use and are the largest class of biotherapeutic products. Although most are potent products with clear clinical efficacy, some are associated with adverse effects. A potential problem with the in-vivo use of mAbs is induction of unwanted immunogenicity, usually most clearly manifest as production of antibodies against the mAb. This can cause safety issues such as anaphylactoid problems of varying severity and also impact on efficacy, rendering the product less or non-efficacious. Assessment of immunogenicity is now regarded as an essential part of product development. Evidence shows that the incidence of immunogenicity, its characteristics and clinical consequences vary considerably and this is affected by many different factors [1–4]. However, prediction of whether a product will be immunogenic and how this will affect safety and particularly efficacy is difficult, if not impossible [5]. In view of this, it is necessary to assess unwanted immunogenicity directly by carrying out immunogenicity studies. Such studies involve screening patients for antibody development normally as part of clinical trials. It is also important that immunogenicity studies include an assessment of how antibody development impacts on clinical efficacy and safety, and appropriate methods for this must be adopted [1–6]. Immunogenicity studies need to be evaluated to assess whether immunogenicity is a problem for the clinical use of a product and results need to be taken into account when using the product.

In 2013, the WHO Expert Committee on Biological Standardization (ECBS) adopted WHO guidelines on the quality, safety and

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efficacy of biotherapeutic protein products prepared by recombinant DNA technology [5]. During this meeting, members proposed that WHO provides further assistance on immunogenicity assessment including screening/confirmation/neutralizing assays and data interpretation in implementation workshops. Furthermore, some regulators have expressed the opinion that they find various problems with assessing immunogenicity studies. These are problems with assessing the strategy adopted, with evaluating the types of assays used, with evaluating the data generated, with assessing the meaning of the results obtained and with assessing how the findings impact on the clinical safety and efficacy of the product.

The 1st WHO implementation workshop for the newly adopted guidelines was held from 13 to 14 May 2014 in Seoul, Republic of Korea, and two case studies were intentionally developed for the purpose of training for a better understanding of principles relating especially to immunogenicity assessment as outlined in section C.6 of the Guidelines [5]. Since monoclonal antibody products were identified as the most complex and difficult biotherapeutics for evaluation, mAbs were selected as subjects for these case studies.

The strategy adopted for assessing unwanted immunogenicity normally involves a stepwise application of methods. As described in the WHO guidelines [5] a "highly sensitive screening assay should be used for antibody detection and a confirmatory assay should be used to confirm the presence of antibodies and eliminate false positive results". Also, a "neutralization assay should be available for further characterization of antibodies". Although no single strategy is mandatory and details of this may differ according to products assessed etc., some general principles apply and a tiered approach for this is normally adopted. A screening immunoassay is usually used to assess all samples from all individuals for the presence of antibodies and then a confirmatory assay is used to confirm positives i.e. eliminate false positives. Confirmed positive samples are then normally assessed for neutralizing activity using a bioassay or surrogate for this. The clinical consequences of induced antibodies also need to be assessed [1,2,5–10].

Tumour necrosis factor (TNF)-alfa is a cytokine with potent pro-inflammatory activity. Not only is it involved in inflammation, but is also a stimulatory immunomodulator, and is involved in the development of immune responses e.g. against infectious agents. Inappropriate production of TNF-alfa (usually along with other inflammatory substances) can result in inflammatory disorders such as Rheumatoid Arthritis, Irritable Bowel Disease (IBD), Crohn's disease, some forms of psoriasis etc. Undesirable involvement of TNF-alfa in these diseases clearly identifies anti-TNFs as a therapeutic option for their treatment and mAbs which neutralize the activity of TNF are currently used for such clinical intervention. Some examples of these are infliximab (Remicade), adalimumab (Humira), certolizumab pegol (Cimzia), golimumab (Simponi).

CD20 is a cell-surface marker expressed on mature B cells and most malignant B cells.

It is involved in B cell maturation, but seems to have no natural ligand. Targeting CD-20 for treatment of numerous B-cell leukaemias has been shown to be effective and several mAbs have been used for this e.g. rituximab (Rituxan, MabThera and Zytux), ofatumumab (Arzerra), tositumomab (Bexxar) and ibritumomab tiuxetan (Zevalin). The mechanism for action of such mAbs in this is binding of the mAb to CD-20 followed by killing/clearing of malignant cells expressing the antigen.

2. Methodology

Two case studies were prepared for the WHO implementation workshop in order to understand the principles for evaluation of immunogenicity studies aimed at assessing the unwanted immunogenicity of mAbs outlined in WHO Guidelines [5].

Immunogenicity studies for two different mAbs are considered. These mAb products, called mAbX and mAbY are produced taking account of the WHO guidelines [5] and are intended for in vivo clinical use in humans. The information and data in these case studies are fictitious and do not represent products approved or under development. The scenarios of case studies are intended to outline evaluation principles in immunogenicity assessment and data interpretation of immunogenicity of biotherapeutics, in particular monoclonal antibody products. In addition, the assay methods used in these case studies are limited, so other methods should be considered in the actuality of immunogenicity assessment.

In order to practice the case studies through group discussions, workshop participants including 40 regulators from 22 countries and 20 manufacturers (see acknowledgements section) took part in the case study exercise during the workshop. Their expertise covered the quality, nonclinical and clinical parts of the development and regulation of biotherapeutic products. Participants were divided into 8 groups, i.e. 8 persons/group, comprising even distribution between WHO regions, regulators vs. manufacturers, gender ratio and expertise in quality and clinical assessment. Two facilitators per group were appointed. Four groups (group 1–4) were asked to focus on assessment of mAbX and the remaining four (group 5–8) to focus on mAbY. Two questions were given to each group to allow at least 2 groups to work on the same questions. The plan for the group-work was sent to all participants 10 days before the workshop.

2.1. Questions asked of participants

After considering the case studies, participants were asked to address/answer the following questions:

1. Study design:
   a. if you are a regulator, would you approve study design for mAbX/mAbY? Explain the pros and cons;
   b. if you are manufacturer, would you proceed with such study design for mAbX/mAbY? Explain the pros and cons.
2. Are the assays appropriate for immunogenicity assessment of mAbX/mAbY?
3. On the basis of the results would you consider that the immunogenicity profile of mAbX/mAbY:
   a. is acceptable for the intended use?
   b. should be further investigated?
   c. is not acceptable for the intended use?
4. Following application submission using the stand-alone approach for mAbX, the product was approved for treatment of rheumatoid arthritis (RA). Sometime later, the manufacturer wishes to increase the indications for treatment to include Crohn's disease and IBD. Would you consider the current immunogenicity study suitable for that purpose? Elaborate on this.
5. The manufacturer of mAbY is considering conducting clinical trials to evaluate the product for use in inducing immunosuppression in patients suffering from autoimmune diseases. Will new immunogenicity studies be needed with these or would the existing studies with leukaemia patients be sufficient? Explain the pros and cons.

3. Description of case studies

3.1. mAbX

MAbX is a human mAb specific for human TNF-alpha. It was made using phage display technology followed by production as an