European Guidance for the Assessment of Unwanted Immunogenicity of Biologicals: An Update.

Robin Thorpe PhD.,FRCPath. 
Head, Biotherapeutics Group, NIBSC.,UK. 
email: Robin.Thorpe@nibsc.hpa.org.uk
Unwanted Immunogenicity - The Most Challenging Issues

• It is impossible to predict
  - the incidence of unwanted immunogenicity
  - the characteristics of the immune response
  - the clinical consequences & significance of such immunogenicity

• THE ABOVE NEED TO BE ASSESSED IN APPROPRIATE STUDIES
Current Position

Testing for unwanted immunogenicity is integral to product development (clinical & post-marketing phase) for ensuring:

– The clinical safety of a biotherapeutic
– Product Comparability
– When a Biosimilar product is developed.
Executive Summary

Introduction

Scope

Legal Basis

Main Guideline Text

Factors that may influence the development of an immune response against a therapeutic protein

- Patient and disease related factors,
- Product related risk factors of immunogenicity

Non-clinical assessment of immunogenicity and its consequences

Development of assays for detecting and measuring immune responses in humans.

- Assay strategy
- Antibody assays
- Assay validation
- Characterization of antibodies to a therapeutic protein

Potential clinical consequences of immunogenicity

- Consequences on Efficacy
- Consequences on Safety

Immunogenicity and Clinical Development

- Rationale for sampling schedule and kinetics of the antibody response
- Consequences on pharmacokinetics of the product
- Methodology aspects to assess comparability of immunogenicity potential as part of a comparability exercise
- Immunogenicity in paediatric indications

Risk Management Plan

References

ANNEX 1 - Further details on methods for assessment and characterisation of immunogenicity

ANNEX 2 - An example of a strategy for antibody detection and characterisation.
Immunogenicity studies need to be carefully and prospectively designed to ensure all essential procedures are in place before commencement. This includes –

- the selection, assessment, characterisation and validation of all assays,
- identification of appropriate sampling points, duration of testing,
- sample volumes and sample processing/storage and
- selection of statistical methods for analysis of data.

This applies to assays used to measure and characterise antibodies and to methods employed for assessing clinical responses to antibodies if they are induced. Much of this needs to be established on a case-by-case basis, taking account of product, patients, expected clinical parameters.
There is to be a new CHMP guideline: ‘IMMUNOGENICITY ASSESSMENT OF MONOCLONAL ANTIBODIES INTENDED FOR IN VIVO CLINICAL USE’.

- Concept paper agreed by BMWP Feb 2009.
- Sent for external consultation.
- Consultation completed/comments received June 2009.
- Drafting underway.
Time line

- Drafting group was convened in October’09
- Comprises members from different member states
- Rapporteur – Robin Thorpe, NIBSC
- First draft to be prepared for
  - Biosimilar medicines working party meeting in Feb 2010
  - Draft finalised by March end final draft considered by BMWP end of June.
  - Sent out for Consultation (mid-late 2010 ?)
Concept Paper: Main Topics

- Points specifically relating to immunogenicity of mAbs which are not covered in the guideline on immunogenicity assessment

- Variability of immunogenicity of mAbs and its consequences.

- Particular problems experienced with screening and confirmatory assays used in assessing immunogenicity of mAbs.

- Appropriate strategies to be adopted for assessing the neutralizing capacity of antibodies induced against mAbs.

- Approaches which may be helpful in predicting unwanted immunogenicity of mAbs.

- Assessment of the clinical consequences of immunogenicity of mAbs, including a risk-based assessment of immunogenicity of mAbs and its problems. This could include also issues relating to immunogenicity of biosimilar mAbs.
Comments from Consultation

• Guideline for immunogenicity of Mabs
  
  – Conflicting views received; majority are supportive
  
  – Some said the new guideline should be an Annex rather than a guideline by itself but this is not possible in the EMEA framework.
• Variability in immunogenicity of abs and their clinical consequence:
  
  – Since mAb products vary in size, structure & species of origin, degree of humanisation, categorisation into different ‘classes’ of mAbs, according to molecular structure etc has been suggested.

  – Also consider various factors
    • Patient and disease
    • Product – sequence, modifications, impurities, aggregates, route
    • Target expression
• Consider benefit-risk-based assessment of immunogenicity of mAbs and its challenges.
  
  – Consider improvements in benefit/risk offered by mAbs and other treatments
  
  – Provide evidence-based examples of immunogenicity, including new or severe safety issues
  
  – Clarification on type of clinical sequelae expected to be associated with antibodies directed against therapeutic mab; e.g., whether main clinical consequence is diminution in efficacy (other than the rare hypersensitivity or other immune complex reactions)
• Risk-based Approach — varied views
  – Stratify risk of immunogenicity that reflects the clinical experience with respect to molecular features of product class and the nature of the therapeutic indication.
  – BUT, this is only feasible, in some cases and a full understanding of the incidence and consequences of immunogenicity can only be determined from appropriate clinical trials. Some have taken the view that an accurate ‘risk level’ cannot be determined at the outset.
  – Case-by-Case approach needed.
Comments (cont)

• Prediction of immunogenicity - consensus
  – In-silico and T cell methods are promising but information on the true clinical utility of these approaches in a prospective manner is lacking
  – While progress in this area is supported, it is premature to endorse the adoption of these approaches.

  – Approach advocated:

    Human clinical data needed for all relevant indications of all mAb products – these data cannot be replaced by use of animal or in vitro or in-silico tools
• Detailed testing strategy needed:
  – Use of assays that are appropriate for detecting all of the specific human anti-mAb antibody response. Issues relating to sensitivity, false-positive results also important.
  – The issue of drug interference and strategies for measuring abs in the presence of residual therapeutic e.g., acid treatment is very important.
  – Sampling strategies & Sample handling critical as is the distinction between transient vs persistent antibody responses.
  – Appropriate positive controls needed.
  – Need for confirmatory assays.
• Detailed testing strategy:
  – Assessment of neutralizing activity crucial—Clarification of what is meant by ‘neutralizing antibody’
    - abs directed against antigen binding site alone or also those interfering with immunobiological mode of action.
  – Requirement for Neutralization assays needs to be considered—Pros & Cons of Bioassays vs Competitive ligand binding (CLB) assays. In some cases CLB assays may be the method of choice.
  – Relevance of neutralizing antibody for safety and efficacy needs to be considered. Integration of ab data with PK/PD assessments required.
Comments (cont)

- Biosimilar mAbs – varied views
  - Specific reference to ‘biosimilar mAbs’ needed?
  - Comparative studies with innovator mAb should be conducted to assess relative immunogenicity.
Assay Validation

Assays need to be validated for their intended purpose.

Validation studies must be conducted to establish that the assays show appropriately linear responses to relevant analytes as well as appropriate accuracy, precision, sensitivity, specificity and robustness.

Problems encountered include matrix effects, selection of appropriate antibody controls and other reagents, residual product in samples, presence of pre-existing antibodies.
Immunogenicity Testing

- So far, there is no perfect assay for determining the immunogenicity of therapeutics. Each assay has its own relative merits and weaknesses.
- May need to evaluate more than one assay platform, assay depends on therapeutic, assay conditions also vary.
- Select appropriate antibody controls
- Assess sera – normal donors, patient sera
- Consider possibility of interference from residual therapeutic, implement strategies if needed
- Regulatory obligation to validate assays
In some cases development of (neutralizing) antibodies in patients clearly can reduce the clinical response to the mAb.

Examples of this are Remicade (anti-TNF alpha), Tysabri (anti-alpha 4 integrin), Humira (anti-TNF alpha).

In other cases there is less clear correlation e.g. Rituximab (anti-CD20).

This makes interpretation and particularly prediction of the clinical effects of antibody development difficult, and generalizations concerning this dangerous.
The frequency of antibody development may differ significantly in different patient groups suffering with different clinical problems.

For example, Rituximab (anti-CD20) produced antibodies in 65% of SLE patients, but was non-immunogenic in non-Hodgkin lymphoma patients.
Frequency of Antibody Development in Different Patient Groups

The frequency of antibody development may differ significantly in different patient groups suffering with the same clinical problem, but which differ in some other way.

For example, Infliximab (anti-TNF alpha) shows a higher incidence of immunogenicity in children than in adults.
Frequency of Antibody Development in Different Patient Groups

The frequency of antibody development may differ significantly in different patient groups suffering with the same clinical problem, but which differ in some other way.

For example, Cimzia (pegylated anti-TNF alpha) induced antibodies in 12% of non-immunosuppressed patients, but only in 2% of immunosuppressed patients.
Pre-existing Antibodies

Patients may have pre-existing antibodies which react with product which may cause clinical problems and/or affect immunogenicity assessment.

For example, antibodies against gal-alpha-1,3-gal are present in most humans and can react with this antigen on mouse cell expressed mAbs. This has caused hyposensitivity reactions in patients treated with Erbitux (anti EGF receptor). In this case the antibodies responsible were IgE.
Conclusions

Immunogenicity issues occur all along the life cycle of a product and particularly when:

- a new therapeutic protein is developed and used for various clinical indications
- a change is introduced e.g. process, formulation, storage conditions etc
- a biosimilar product is proposed

Assessment requires

- an optimal antibody testing strategy
- validated methodologies and reference standards

‘Risk’ assessment may be more problematical for mAb products than other products because of their complexity.

Risk may be variable, even for the same antibody used differently.
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