Immunogenicity of Biological Therapeutics

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Who are we?

Office of Pharmaceutical Science
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Division of Monoclonal Antibodies
Kathleen Clouse, Ph.D., Director
- Monoclonal Antibodies
- Fc - Fusion Proteins

Division of Therapeutic Proteins
Amy Rosenberg, Ph.D., Director
- Growth factors
- Toxins
- Enzymes
- Cytokines
Why is FDA concerned about immune responses to therapeutic proteins?

- Got me! It only seems like a theoretical problem and most therapeutics do not seem to induce problematic immune responses.

- There have been real life examples in which immune responses to therapeutic proteins have had devastating consequences for healthy volunteers and patients.
Immune Responses to Recombinant Human Therapeutic Proteins: Devastating Consequences for Healthy Volunteers and Patients.

- rhuMGDF
- Erythropoietin
- Glucocerebrosidase
- α-glucosidase (Pompe’s)
- Factor VIII
- Insulin
Clinical Concerns for Antibodies to Therapeutic Proteins

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<tr>
<th>Clinical Concern</th>
<th>Clinical Outcome</th>
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| Safety                  | • Neutralize endogenous counterpart with unique function causing deficiency syndrome  
                         | • Hypersensitivity reactions                                            |
| Efficacy                | • Inhibition or enhancement of product efficacy                       |
| Pharmacokinetics        | • Changes in dosing level due to PK changes.                           |
| None                    | • Despite generation of antibodies, no discernable impact              |
Evaluation immunogenicity: A tiered approach

Sensitive screening immunoassay

- IgG
- IgM
- IgE
- IgA

Epitope Specificity

Confirmatory assay (immunodepletion)

- Negative
- Positive

Bioassay (neutralizing)

- Negative
- Positive
Regulatory Considerations
NEW SUBMISSIONS

Provide a background
   Product attributes
   Difference between product and endogenous counterpart
   Literature reference (e.g. knockout animal)

Provide Data
   Preclinical animal data
   How well animal modeling reflects clinical situation
   How “good” is the assay for immune monitoring

Provide a plan
   Monitoring patient immune response
   Monitoring potential sequelae to immune response (e.g. immune complexes, hypersensitivity)
   Where there is known significant risk eg. EPO then well qualified if not fully validated assays are required for phase 1
LATER STAGES OF DEVELOPMENT

• REVIEW PATIENT IMMUNOGENICITY DATA
  Was immune monitoring adequate?
  Predict immune mediated events?

• HYPERSENSITIVITY REACTION
  Consider development of IgE specific assay

• NEUTRALIZING ANTIBODIES AND EFFECTIVE DOSE

• IMPROVEMENTS IN IMMUNE ASSAY
  Sensitivity
  Determination of cutoff
  Appreciation of confounding factors
THE LICENSE APPLICATION: APPROVAL AND LABELING

• A SOUND, FULLY VALIDATED ASSAY
  Science grounded
  Labeling will NOT be based on poor assays

• PERCENTAGE WITH IMMUNE RESPONSE
• PERCENTAGE WITH NEUTRALIZING RESPONSE
• RELATIONSHIP TO ADVERSE EVENTS
  Hypersensitivity
ELEMENTS OF ASSAY VALIDATION

• ICH DOCUMENT
• SENSITIVITY
• SPECIFICITY
• CUTOFF
• REPRODUCIBILITY (PRECISON)


Immunogenicity and Animal Studies
Why are FDA pharmacologists and toxicologists worried about immunogenicity?

- Because protein therapeutics are usually heterologous to the animal model it is very common to develop antibodies.
- As with humans, the antibodies can affect PK, PD, neutralize efficacy or be benign.
- The antibody status of the animal model must be known in order to interpret pharmacology and toxicology data.
- This has sometimes required performing studies with autologous animal counterpart to the drug.
What else do we learn from the animal models?

- Immunogenicity in animals is not predictive of immunogenicity in humans.
- The impact of immunogenicity in animals can provide information on potential impact of immunogenicity in humans.
- Other animal models (KO mice etc.) can also provide information on the impact of immunogenicity in humans.
- This information can be useful in monitoring subjects for adverse effects of immunogenicity.
Special Cases
When should I perform an immunocomparability study?*

- When changes to the manufacturing process have clearly altered the drug substance/product in ways for which there is no clinical experience (e.g., introduction of a new glycoform)
- Manufacturing changes that are reasonably expected to impact the drug substance/product in ways that cannot be adequately understood by comparability studies using physico-chemical and bioassay methods (e.g., certain types of formulation changes, new master cell bank)
- Risk based – what are the consequences to product immunogenicity
- Upon discussion with the FDA

*This definition reflects personal thoughts and does not reflect consensus within the agency
What is immunocomparability?*

- Comparable spectrum and incidence of adverse clinical events pertaining to immunogenicity,
- Comparable incidence and duration of Nabs to product
- Comparable incidence and duration of non-neutralizing antibody;
- Comparability of target epitopes and antibody isotypes

*This definition reflects personal thoughts and does not reflect the consensus within the agency
What is the appropriate comparison to demonstrate immunological equivalence?

- In vitro evaluations
- Animal Studies: Are they relevant?
- Human Studies

Recommendation:
- Discuss study designs with the FDA
Issue #2  Competitor Products and and Immunogenicity

- Generally cannot compare across assays
- Potential value of reporting sensitivity in label???
- Development of antibody standards???
- Development of standardized assay methods???
- Value of a validated, sensitive assay
Issue #3 Fusion Proteins and Immunogenicity

- Multi-Domains
  - Ig Domain
  - His Tag
  - Other Proteins

- Immunogenicity Against Which Domains?
  - Problems with RF
  - Problems with common serum proteins
Tolerance Induction
Lysosomal Storage Disorders
Enzyme Replacement Therapy

- Over 40 different lysosomal storage disorders that collectively occur in ~1/7000 live births
- Gaucher’s: ~13% of patients develop Ab to glucocerbrosidase and 90% of patients tolerate over time. A few patients develop neutralizing Ab that is associated with either a plateau in improvement or disease progression. Non-neutralizing Ab are associated with infusion reactions. These disappear over time as well but have been known to return years later. The development of Ab is associated with the severity of the genetic lesion.
- Pompe’s disease: All patients developed Ab on acid β glucosidase replacement therapy. CRIM (Cross Reactive Immunological Material) negative status was associated with high titer Nab generation.
- Fabry’s disease: Patients with α-galactosidase A activity < 0.5 nmol/mg protein/hr developed Nab (10/12) than patients with > 1.1 nmol/mg protein/hr (1/4)
Factor VIII

- 25 – 30% hemophilia A patients (Factor VIII deficiency) develop inhibitory Ab that complicates disease management.
- The severity of the genetic lesion and lower levels of protein are associated with increased incidence of BAb and Nab.
- Gene deletion of factor VIII accounts for 75% of NAb responses in hemophilia A patients.
- Other factors include HLA type, number and pattern of exposures, genetics.
Tolerance induction strategies

- Evidence that NAb generation in hemophilia A is T cell driven:
  - Decrease in Ab formation in HIV patients.
  - In murine studies show that blockade of T cell activation reduces Ab formation.
  - T cell epitopes have been identified that stimulate PBL from both patients and healthy donors.
  - Neutralizing Ab are class switched (mostly IgG1 and IgG4).
5 yr old patient with type III Gaucher’s disease developed neutralizing Ab to infused ERT that reversed clinical improvements and led to disease progression.

Received plasmapherisis, IVIG treatment and cyclophosphamide treatment on day 1 and daily oral doses of cyclophosphamide on days 2 – 10 along with ERT. Resulted in improvement that relapsed after a number of months.

Received plasmapheresis on day, IVIG on days 1 and 4 – 8, cyclophosphamide IV days 1 and 2 and oral doses for 30 days.

Ab status was stable for 4 months then decreased months 33 – 42. At 60 months Ab levels remained greatly reduced.
Non-depleting anti-CD4 has been shown to induce tolerance to soluble proteins and aggregated horse Ig in non-human primates.

Cyclosporine A and azathioprine plus antigen (a-L-iduronidase or a-glucosidase) for 60 days induced tolerance in a canine models of mucopolysaccharidosis.

Methotrexate short course reduced Ab titers to ERT in a-galactosidase KO and normal Balb/c mice.
Conclusions

- Use scientifically (including statistically) sound approaches when designing assays and studies to evaluate product immunogenicity.
- Have assays qualified early in development.
- Provide rationale for study designs (e.g. acceptance criteria in validation assays).
- Consider tolerance induction therapy when the presence of NAb is catastrophic to patients.