Biotherapeutic Immunogenicity Risk Factors – the science, reliability, and concepts for implementing predictive tools to improve their reliability

Mastering Immunogenicity, Cambridge, MA 12 Sep 2011

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Concepts:

• All biotherapeutics potentially immunogenic under some circumstances

• Risk varies considerably among products, patient populations and treatment regimens.

• Immunogenicity risk & mitigation planning well established, intended to focus resources where needed, continuing to evolve as does biotherapeutics field.

• Although based on immunological science, predictive value of risk factors needs improvement in order to improve and refine management and mitigation strategies.
4 Decades in Biotechnology: Evolution of Protein Therapies

- rDNA expression of human proteins
- Humanized Antibodies
- FC fusion proteins
- Antibody-conjugates
- Human Antibodies
- Novel scaffolds
- Biosimilars
- “Biobetter” proteins

- IV injection/infusions
- Subcutaneous administration
- Alternative delivery routes/forms
4 Decades in Biotechnology: Evolution of Protein Therapies

- rDNA expression of human proteins
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IV injection/infusions Subcutaneous administration Alternative delivery routes/ forms
BTx Immunogenicity Assessment

Tiered Anti-Drug Antibody Testing

Pre- and Post-dose Samples

Screening Assay
  positive

Confirmatory Assay
  positive

Titer Assay

Neutralizing Ab Assay

Other Characterization

negative: report result
negative: report result
positive: report titer result
Immune response to a therapeutic protein

Protein

Innate immune signals

Antigen presenting Cell

Epitope recognized by Ab

CD40

TCR

CD4

CD40L

Activated T helper cell

Activated T helper cell

Target cell

Resting B cell

CD40

Secreted ADA

Clonal deletion

Memory cell

Plasma cell

Secreted ADA

T reg

Anergized

CD27

CD86

CD25

CD44

CD69

CD40L (CD154)
Risk-Based Approach

~ 1999-2002 adverse event reports (rErythropoeitin, rThrombopoietin)
  • Pure Red Cell Aplasia & Thrombocytopenia reports related to Erythropoeitin and Thrombopoietin NAb development
  • Epo traced to changes in administration route, removal of HSA, Tween 80 in manufacturers’ process

•~ 1993 adverse events (plasma-derived Factor VIII)
  • Reports of increased pdFVIII inhibitor (NAb) in low risk population traced to manufacturing change (viral inactivation step)
What factors may influence development of an immune response?

<table>
<thead>
<tr>
<th>Risk Category</th>
<th>Risk Factor</th>
</tr>
</thead>
<tbody>
<tr>
<td>Product-related</td>
<td>Presence of foreign amino acids, structures</td>
</tr>
<tr>
<td></td>
<td>Unusual post-translational modification</td>
</tr>
<tr>
<td></td>
<td>Level of aggregates/impurities/degradants</td>
</tr>
<tr>
<td></td>
<td>Presence of promiscuous MHC epitopes</td>
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<tr>
<td></td>
<td>Self-protein in non-tolerizing environment</td>
</tr>
<tr>
<td></td>
<td>Product Biology/Pharmacology</td>
</tr>
<tr>
<td>Patient/Subject Population-related</td>
<td>Immune status of patients</td>
</tr>
<tr>
<td></td>
<td>Genetic profile (incl. HLA)</td>
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<tr>
<td></td>
<td>Underlying disease</td>
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<tr>
<td></td>
<td>Target biology</td>
</tr>
<tr>
<td></td>
<td>Pre-existing antibodies</td>
</tr>
<tr>
<td>Treatment-related</td>
<td>Route of administration</td>
</tr>
<tr>
<td></td>
<td>Dosing frequency</td>
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<tr>
<td></td>
<td>Concomitant medications</td>
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</tbody>
</table>
What factors may influence consequences of an immune response?

<table>
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<tr>
<th>Risk Category</th>
<th>Risk Factor</th>
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<tbody>
<tr>
<td>Product-related</td>
<td>Presence of endogenous counterpart</td>
</tr>
<tr>
<td></td>
<td>Unique activity of counterpart</td>
</tr>
<tr>
<td>Patient/Subject Population-related</td>
<td>Compounding effect of existing deficiency</td>
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<tr>
<td></td>
<td>Life-threatening disease</td>
</tr>
<tr>
<td></td>
<td>Non-reversible/treatable AEs</td>
</tr>
<tr>
<td></td>
<td>Replacement therapy</td>
</tr>
<tr>
<td>Treatment-related</td>
<td>Availability of alternative treatment</td>
</tr>
<tr>
<td></td>
<td>Multiple/chronic treatment needed</td>
</tr>
<tr>
<td></td>
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</table>

Neutralization of non-redundant endogenous counterpart?

Anaphylaxis? Other hypersensitivity? Immune complex disease?

Loss of effect?

Mild infusion rxn?
Immunogenicity Risk and Mitigation Planning

Pre FIH

Risk assessment

Product-

Patient-

Treatment-related

Mitigation Strategy

Product

Pre FIH

Mitigation Strategy

Patient/Treatment

Assays

Sampling Strategy

Clinical Management Strategy

Pre FIH

Implementation

Analysis Results

Study Results

Post-FIH Refinement

Clinical results (analytical, AEs, PK, PD, efficacy)

Product/process changes
Implementation of Risk Based Approach

Use risk assessment to support design clinical analysis strategy. Examples:

Selection of study population
- Patients with lower risk in earlier studies
- Different populations depending on risk category (development vs consequences)

Type of testing to be conducted
- Sensitivity of assays, orthogonal/characterization methods

Timing of sample collection & analysis
- More samples early vs frequency
- Drug levels cleared
- Monitor for transience/persistence
- Rapid turn-around of results
Stage-Related Risk Questions

Candidate selection:
- Is any candidate likely to induce immunogenicity; which has highest risk?
- Will presence of foreign sequences (or other risk factor) result in increased immunogenicity; what mitigation strategy is most likely to decrease risk?

Nonclinical Development:
- Will ADA development limit the interpretability of my study; is the immunogenicity seen in nonclinical studies based on a translatable risk factor; findings relevant to humans?
- Will aggregates/post-translational mods/impurities result in increased immunogenicity?
- What mitigation strategies are most likely to decrease risk?

Early Clinical Development:
- If pre-existing x-reactive antibodies are present, are they likely to increase after dosing?
- Is ADA observed after a single dose likely to increase or decrease after repeat dosing?
- What consequences are likely to occur? What mitigation strategies are most likely to decrease/maintain risk profile?

Later Clinical Development
- Will a change in (manufacturing, dosing regimen, indication, patient population, assays), result in a change in immunogenicity profile?
Protein x is an Fc fusion protein
Fc contains mutations x, y, x
Linker has unique sequence
Non-Fc portion has endogenous counterpart
Subcutaneous route of administration
Intended for chronic treatment of inflammatory disease

ADA development multiple dose toxicity studies
Hypersensitivity reactions

Low titer ADA development single dose FIH study
No clinical sequelae observed
Goal: Mitigation Strategies Focus on Factors Predicted to Generate Highest Risk

Proteins stimulate immune signals

Reduce inflammation/modify route of administration

Epitope recognized by Ab

Reduce aggregation

T-independent Ag

Target cell

Antigen presenting Cell

Antigenic peptide recognized by TCR

Remove T cell epitopes

Helper cell

Memory cell

Activated T helper cell

Activated B cell

Secreted ADA

Plasma cell,

Concomitant meds

CD40

CD86

CD27

CD25

CD44

CD69

CD40L (CD154)
Risk Factor: Foreign Sequence

- Activated T helper cell
- Antigen
- CD40L
- HLA-binding (in silico, in-vitro), PBL/DC-T cell assays
- Immune system
Risk Factor: Pre-existing ADA

- Resting B cell
- Activated B cell
- Secreted ADA
- Plasma cell, high affinity, polyclonal secreted ADA
- Memory responses
- Activated T helper cell
- Activated CD4+ T helper cell
- Activated CD40L

Immune system
Pre-Existing Abs to Biotherapeutics are relatively common

Survey of historical clinical immunogenicity data analysis:
13 biotherapeutics evaluated in ~ 40 clinical studies.

Products with Pre-Existing Abs

- Pre-existing Abs: 46.2%
- No Pre-existing Abs: 53.8%
Unclear Association of Pre-Existing Abs to Immunogenicity Risk

Comparison of pre-existing antibodies with post treatment ADA induction

Products with Pre-Existing Abs
- 66.7% Associated with ADA induction
- 33.3% No association with ADA induction

Subjects Positive for Pre-Existing Abs
- 67.4%
- 16.8%
  - Elevated Ab titer post dose
  - Decreased Ab titer post dose
  - Flat Ab titer post dose

Subjects from Studies Showing Pre-Existing Abs
- 86.8%
  - ADA elevation from positive baseline
  - ADA elevation from negative baseline

13.2%
Risk Factor: Pre-existing ADA

- Resting B cell
- Activated B cell
- Plasma cell
- Memory responses
- Secreted ADA
- High affinity, polyclonal secreted ADA
- CD40
- CD40L
- T helper cell
- Activated T helper cell
- Treg anergized
- Antigen-presenting Cell
- CD4
- TCR

Immune system

Pfizer Internal Use Only
Risk Factor: Foreign Sequence

Immune system

ADA response

Precursor cells?

CD4

CD40L

Activated B cell

Activated T helper cell

Resting B cell

Risk Factor: Foreign Sequence
Will immunogenicity profile change if $x$ changes? $X =$

- Study patient population
- Route of administration
- Product formulation
- Manufacturing process

Immune system → ADA response?
"Predictive tools" = Markers for Risk Factors?

Protein

Innate immune signals

Antigen presenting Cell

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Summary

Immunogenicity risk assessment is an expected aspect of biopharmaceutical development planning.

Risk factors have been identified, but the degree to which any risk factor increases probability of immune response and how different risk factors “interact” are poorly understood.

Use risk assessment to guide nonclinical/clinical testing strategies.

Need for tools to better understand key risk factors, increase confidence in decision making.
Acknowledgements

Pfizer PDM Colleagues, including

Li Xue

Tim Hickling

Boris Gorovits