Considerations for Immunogenicity Assessment at Various Clinical Phases

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Immunogenicity Assessment Is An Integral Part of Biotherapeutic Development

Antibody-dependent mechanisms of action (ADAs) are defined as presence of host antibodies directed towards the biotherapeutic in the circulation.
Outline

• Immunogenicity assessment at various clinical stages
  • FIH study: risk-based strategies for immunogenicity assessment
  • Bioanalytical strategy: a tiered approach
  • Phase II study and beyond: refine immunogenicity assessment strategy based on evolved clinical data

• Case studies of immunogenicity monitoring plan in various clinical phases
  • Case study#1: Immunogenicity monitoring of a bispecific mAb in a Phase I study
  • Case Study#2: Updated immunogenicity assessment plan to align with the modified Phase III development plan

• Summary
• Acknowledgements
Immunogenicity Risk Assessment

How Likely Is an Antibody Response?

**How Human is the Drug?**
- Human
- Humanized
- Chimeric
- Mouse

**Homology of Drug to Endogenous Counterpart**
- High
- Partial
- Low

**Dosing/Dose Regimen Plan**
- Frequency: Single-Acute–Chronic–Intermittent
- How much Drug: Very High/High/Average/Low

**Patient Immune Status (disease + concomitant medication)**
- Suppressed
- Normal
- Activated

**Impact of Drug on Immune System**
- Immunosuppressant
- Immune Stimulator

**Route of Administration of Drug**
- Oral
- i.v.
- i.p.
- s.c.
- Inhaled

**Clearance of Drug**
- Fast
- Slow

Adapted from Koren et al 2008
**Immunogenicity Risk Assessment**

*How Serious Could ADA Response Be?*

<table>
<thead>
<tr>
<th>Less serious</th>
<th>More serious</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Is there an Endogenous Version of the Drug?</strong></td>
<td></td>
</tr>
<tr>
<td>No - Yes</td>
<td></td>
</tr>
<tr>
<td><strong>Endogenous Counterpart of Drug</strong></td>
<td></td>
</tr>
<tr>
<td>Redundant – Unique</td>
<td></td>
</tr>
<tr>
<td><strong>Homology of Drug to Endogenous Counterpart</strong></td>
<td></td>
</tr>
<tr>
<td>Low – Partial - High</td>
<td></td>
</tr>
<tr>
<td><strong>Consequence of Cross blocking ADA Would Be?</strong></td>
<td></td>
</tr>
<tr>
<td>Tolerizeable – Manageable – Fatal</td>
<td></td>
</tr>
<tr>
<td><strong>Can you dose over ADA?</strong></td>
<td></td>
</tr>
<tr>
<td>No MTD – Low MTD</td>
<td></td>
</tr>
<tr>
<td><strong>Disease Treated</strong></td>
<td></td>
</tr>
<tr>
<td>Life Threatening – Non Life Threatening</td>
<td></td>
</tr>
<tr>
<td><strong>Other Options</strong></td>
<td></td>
</tr>
<tr>
<td>Alternate treatment available – Only Therapy</td>
<td></td>
</tr>
<tr>
<td><strong>Can Crosslinking ADA Alter the Impact of Drug?</strong></td>
<td></td>
</tr>
<tr>
<td>No – Yes (Reverses Antagonist/Blocking to Activating)</td>
<td></td>
</tr>
</tbody>
</table>

Adapted from Koren et al 2008
Immunogenicity: Consequences

Clinical Sequelae

- Binding ADA
- PK-altering ADA
- Neutralizing ADA
- Allergic ADA
- Cross-reactive neutralizing ADA
## Interpreting Immunogenicity Data in Context

<table>
<thead>
<tr>
<th>Status</th>
<th>ADA</th>
<th>PK/PD</th>
<th>Safety</th>
<th>Efficacy</th>
<th>Interpretation</th>
</tr>
</thead>
<tbody>
<tr>
<td>Optimal</td>
<td>Yes /No*</td>
<td>No</td>
<td>No</td>
<td>No</td>
<td>ADA not detected*, no apparent safety &amp; efficacy concerns with respect to immunogenicity</td>
</tr>
<tr>
<td>Acceptable</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>No</td>
<td>ADA present but minimal effect on PK/PD No clinically significant S or E concerns regarding immunogenicity</td>
</tr>
<tr>
<td>Tolerable [Benefit &gt; Risk]</td>
<td>Yes</td>
<td>Yes</td>
<td>No</td>
<td>Yes</td>
<td>ADA present and has effect on PK/PD No efficacy impact or impact can be managed with dose adjustments or changes in frequency Safety concerns regarding immunogenicity are none or minimal &amp; can be managed with premedication or symptomatic treatment</td>
</tr>
<tr>
<td>No Go [Risk &gt; Benefit ]</td>
<td>Yes</td>
<td>Yes/No</td>
<td>Yes/No</td>
<td>Yes/No</td>
<td>ADA present and confers limits on efficacy ADA present and confers limits on safety</td>
</tr>
</tbody>
</table>

* Assay method could be questioned if no ADA responses detected
Using A Tiered Approach for Immunogenicity Assessment

Clinical serum samples

Screening Assay

- +

Confirmatory Assay

- +

Characterization of immunoreactivity
  • Titering
  • Neutralizing antibody
  • Other

Data report

For a typical antibody program in Phase I, II, III

For a typical antibody program in Phase III and beyond
Key References

• Healthy Authority Guidance
  • FDA Guidance for Industry: Immunogenicity Assessment for Therapeutic Protein Products (2014)
  • FDA Draft Guidance for Industry: Assay Development and Validation for Immunogenicity Testing of Therapeutic Protein Product (2016)
  • EMA Guidance on Immunogenicity Assessment of Therapeutic Proteins (2017)

• Industrial whitepapers and papers
Case Study#1

Monitoring immunogenicity of a bispecific monoclonal antibody anti-A/B in a Phase I study
More Rigorous Immunogenicity Monitoring Plan In The Phase I Study

Risk Based Assessment: medium
- Risk Factors: new modality; chronic treatments; SC dosing; targeting autoimmune diseases

Analytical strategy
- Assay format: bridging ELISA
- Screen, titer, confirm, characterization (domain mapping)

High immunogenicity observed in the repeated-dose cynomolgus monkey toxicology study
- ADAs detected in 97% (31 of 32) anti-A/B treated cynos
- ADA responses were predominantly towards the anti-B Fab
- High ADA signals correlate with loss of PK and PD
- Safety findings observed in some cynos with high ADA signals
  - consistent with ADA-related effects and not direct toxicological effects of anti-A/B

Include multiple interim analysis for closely monitoring immunogenicity in the Phase I study
- Immunogenicity in cyno monkeys generally not considered predictive of clinical incidence
- Combination of high incidence (97%) and high responses (1.54-6.96) was unexpected
- Limited clinical experience with bispecific mAbs
Case Study#2

Updated immunogenicity assessment strategy to align with the modified Phase III development plan
Modified Immunogenicity Assessment Strategy To Align with The Updated Phase III Development Plan

Drug: anti-X, a humanized mAb

Overall low ADA incidences (<6.3%) observed in the complete Phase I & II studies
• No obvious evidence of ADA impact on drug exposure, efficacy and safety

Original analytical strategy to support Phase III study
• Assay format - bridging ELISA
• Tiered approach - screen, titer, confirm
• Characterization - neutralizing antibody (NAb) analysis

Additional analytical work implemented to support the modified Phase III development plan
• Identification of a host cell protein (HCP) in drug materials triggered a modification of Phase III study
  • Tiered approach to monitor antibodies to HCP besides ADAs
• Applied in-study CPF instead of validation CPF for data analysis
Monitoring Both Antibodies to HCP and Drug in The Modified Phase III Studies

• Anti-X is produced in Chinese Hamster Ovary (CHO) cells. A process-related CHO derived protein impurity has been identified as CHO phospholipase B-like 2 (PLBL2) protein.

• High levels of PLBL2 (34-328ng/mL) detected in clinical materials used in the completed phase II studies.

• Anti-PLBL2 antibody was measured in the Phase II studies and high incidences (up to 98%) were observed, with no clinical sequelae.

• Process improvement was made to reduce PLBL2 levels in the Phase III materials (0.2-0.4ng/mL)

• Immunogenicity assessment strategy in Phase III studies was modified
  • Antibodies to anti-X and PLBL2 protein were monitored
## Immunogenicity Results in Phase II & III Studies

<table>
<thead>
<tr>
<th>Study Phase</th>
<th>PLBL2 levels in drug materials (ng/mg)</th>
<th>Anti-X Dose (mg/dose, Q4W)</th>
<th>Total PLBL2 exposure (ug/dose)</th>
<th>Anti-PLBL2 antibody incidence</th>
<th>ADA incidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>IIa</td>
<td>34-137</td>
<td>250</td>
<td>8.5-34.3</td>
<td>98%</td>
<td>2%</td>
</tr>
<tr>
<td>IIa</td>
<td>34-137</td>
<td>125 250 500</td>
<td>4.3-17.1 8.5-34.3 17.0-68.5</td>
<td>90%</td>
<td>1%</td>
</tr>
<tr>
<td>IIb</td>
<td>242-328</td>
<td>37.5 125 250</td>
<td>9.1-12.3 30.3-41.0 60.5-82.0</td>
<td>74%</td>
<td>6%</td>
</tr>
<tr>
<td>III</td>
<td>0.2-0.4</td>
<td>37.5 125</td>
<td>0.0075-0.015 0.025-0.05</td>
<td>18%</td>
<td>14%</td>
</tr>
</tbody>
</table>

- Lack of correlation between ADA and anti-PLBL2 antibody responses
- Decreased PLBL2 exposure led to significantly decreased anti-PLBL2 Ab positive incidence in the Phase III study
Guidance for NAb Assay Format Selection

- USP 1106.1
- White paper by AAPS
NAb Results Of Phase III Studies

• **Assay format**
  - Competitive ligand binding ELISA, using drug for capture and target conjugate for detection
  - Used study baseline samples for cutpoint determination

• **Phase III NAb results**
  - NAbs detected in 13 of 2052 anti-X treated subjects
    - all treatment-induced NAbs
    - NAb positive patients also had higher ADA responses

• Presence of NAbs had no apparent impact on safety

• Patients with higher NAb signals appeared to have lower drug exposure as well as lower than expected efficacy
Clinical impact of ADAs and anti-PLBL2 Antibodies

- No apparent safety signals attributed to presence of ADAs (NAbS) and higher levels of anti-PLBL2 antibodies.
- No apparent impact on the average or distribution of drug exposure and pharmacodynamics responses
  - Except for patients with higher NAb responses
- No consistent trends to suggest impact of positive ADAs and anti-PLBL2 antibodies on overall trial efficacy
  - Except impact on efficacy in patients with higher NAb responses
Summary

- Immunogenicity assessment is an integral part of drug development, and it is a key element of product safety and quality.

- Prediction of immunogenicity of biotherapeutics is challenging and must be assessed in the representative population for every indication being considered.

- Fit for purpose methods and “tiered” strategies are used to assess immunogenicity. These strategies are often modified or evolved based on various considerations including:
  - new modalities, changed CDP
  - evolved strategy by incorporating clinical data

- Immunogenicity data must be assessed in the context of other clinical readouts PK, PD, safety, & efficacy.
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