Integration of PK-PD-ADA data for assessment of immunogenicity impact

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Presentation outline

- Strategy for assessment and reporting of immunogenicity
- Integration of PK-PD into immunogenicity assessment
- Case study
Strategy for immunogenicity evaluation

EMA Guideline on Immunogenicity assessment of therapeutic proteins
Annex 1: An example of a strategy for immunogenicity assessment
Strategy for immunogenicity evaluation

EMA Guideline on Immunogenicity assessment of therapeutic proteins
Annex 1: An example of a strategy for immunogenicity assessment

Robert Nelson, EBF Focus Workshop
Lisbon, September 2018
Assessing and reporting immunogenicity

Assessment and Reporting of the Clinical Immunogenicity of Therapeutic Proteins and Peptides—Harmonized Terminology and Tactical Recommendations

Assessing and reporting immunogenicity

- Determining the characteristics of the ADA response
  - ADA-positive
  - ADA-negative
  - ADA-inconclusive: drug is present at a level that can interfere with ADA detection
  - Unevaluable: no reportable result after drug administration
Assessing and reporting immunogenicity

- Pre-existing ADA
  - Baseline ADA-positive subjects
  - Titer range

- ADA incidence and titer
  - Overall ADA incidence
  - Treatment-induced ADA incidence
  - Treatment-boosted ADA
Assessing and reporting immunogenicity

- **Kinetics of ADA**
  - Onset
  - Duration
    - Transient response
    - Persistent response

- **Neutralizing ADA**
  - Neutralizing or non-neutralizing
  - Incidence and kinetics

- **Cross-reactivity**
  - When a biologic is identical or nearly identical to an endogenous protein
Determining the relationship of ADA with clinical efficacy and safety

- **Efficacy**
  - Primary non-response
  - Loss of response

- **Safety**
  - Acute Adverse Events (AEs)
    - e.g. anaphylaxis
    - investigation of drug-specific IgE
  - Non-acute AEs
    - Delayed hypersensitivity
    - Responses secondary to immune complex and complement-mediated reactions
Determining the impact of ADA on PK & PD

- ADA formation may impact the **pharmacokinetics (PK)** of the therapeutic, i.e., the relationship between dose and the obtained concentrations in e.g. serum
- Can impact the PK of therapeutic in diverse ways
  - Clearing ADA response
  - Drug sustaining ADA response
Determining the impact of ADA on PK & PD

- Clearing ADA response

Red: ADA-positive
Black: ADA-negative
Determining the impact of ADA on PK & PD

- Drug sustaining ADA response

Declined clearance / higher exposure to active drug

Daniela Stoellner, on behalf of EBF TT-63: Handling of PK data from ADA positive animals
EBF Open Symposium 2016
Determining the impact of ADA on PK & PD

- ADA formation may impact the **pharmacokinetics** (PK) of the therapeutic, i.e., the relationship between dose and the obtained concentrations in e.g. serum
- Can impact the PK of therapeutic in diverse ways
  - Clearing ADA response
  - Drug-sustaining ADA response
- Both neutralizing and non-neutralizing ADA can impact the clearance
- Often the first bioanalytical data which gives an indication of immunogenicity
Determining the impact of ADA on PK & PD

- ADA formation may impact the **pharmacodynamics** (PD) of the therapeutic, which describes the relationship between systemic concentrations (exposure) and therapeutic effects
  - May ultimately affect the efficacy and/or toxicity profile
Case study

- Monoclonal antibody (mAb) therapeutic
  - Soluble target in inflammatory disease
  - Binds to and neutralizes target
The assays

- ‘Free’ PK
  - Anti-idiotypic sandwich immunoassay
  - Range 100 – 8000 ng/mL
  - Interference of target (and ADA)
### The assays

- **Total target**
  - Sandwich immunoassay
  - mAb non-competitive with therapeutic (free + bound)
    - Excess therapeutic added to favour bound
  - Range 50–50000 pg/mL
The assays

- Total target
The assays

- **ADA**
  - Solution bridging immunoassay
  - SPE of target & acid dissociation
  - Sensitivity: 6.1 ng/mL (LPC at 10 ng/mL)
  - Drug tolerance: 50 µg/mL at 100 ng/mL PC level
  - Target tolerance: 1000 ng/mL
The assays

- **Neutralizing ADA**
  - Adapted from potency bioassay
  - Acid dissociation and SPE of drug
Integration of PK-PD-ADA
Simulated data based on real case

- **Case 1**

- Rapid elimination of drug – driver?
Integration of PK-PD-ADA
Simulated data based on real case

- **Case 1**

  - Elimination of drug driven by increase in target levels
  - After this period, drug returned to normal elimination profile
Integration of PK-PD-ADA
Simulated data based on real case

- Case 1

- ADA was observed
  - Low titer, neutralizing
Integration of PK-PD-ADA

- **Case 1 summary**
  - Changes in concentration-time profile of therapeutic
    - Driven by production of target
  
  - ADA response was observed
    - Characterized as low titer, neutralizing, sustained
    - Did not impact the binding to the target or the drug elimination
Integration of PK-PD-ADA
Simulated data based on real case

- Case 2

- Rapid elimination of drug – driver?
Integration of PK-PD-ADA
Simulated data based on real case

- Case 2

- Concurrent alteration in target engagement
Integration of PK-PD-ADA
Simulated data based on real case

- **Case 2**

- ADA observed
  - moderate titer, transient, non-neutralizing
Integration of PK-PD-ADA

- **Case 2 summary**
  - Changes in concentration-time profile of therapeutic
    - Could not be explained by target levels
  - ADA response was observed
    - Characterized as non-neutralizing, transient
    - Impacted the drug elimination and its ability to sequester target
Conclusions

- Interpretation of immunogenicity requires more than just ADA and NAb assessment
  - Integration of PK and PD data helps build the picture of impact and relevance of ADA

- Understand your bioanalytical assays
  - What they measure
  - Inter-dependencies
  - What the data mean
Acknowledgments

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Thank you for your attention!