Progress in Clinical Neutralising Antibody assays

Presenter: James Munday
on behalf of the EBF

Today's challenges and solutions in assessing immunogenicity in patients

19 -20th Sept 2018

Lisbon

Content for session

15:00 – 15:40	**Tea break & Networking**
15:40 – 17:30	**Progress in Clinical nAb assays**
15:40 – 16:00	Introduction to the session, including case study *James Munday, on behalf of the EBF (case study on behalf of Covance)*
16:00 – 16:20	Integration of PK-PD-ADA data for assessment of immunogenicity impact *Robert Nelson, Novimmune*
16:20 – 16:45	Inferring Neutralising Antibodies – When is data integration appropriate? *Shobha Purushothama, Biogen*
16:45 – 17:30	Free podium and Q&A 16:45 – 17:00: Case study by Floris Loeff (Sanquin), incl. 5 min Q&A 17:00 – 17:30: Q&A, incl. pre-submitted questions
17:30	End of day 1

Assessing Immunogenicity in the clinic

Protein

Non-immunogenic

No adverse effect

Immunogenic

Anaphylactic reaction

(Hyper sensitivity)

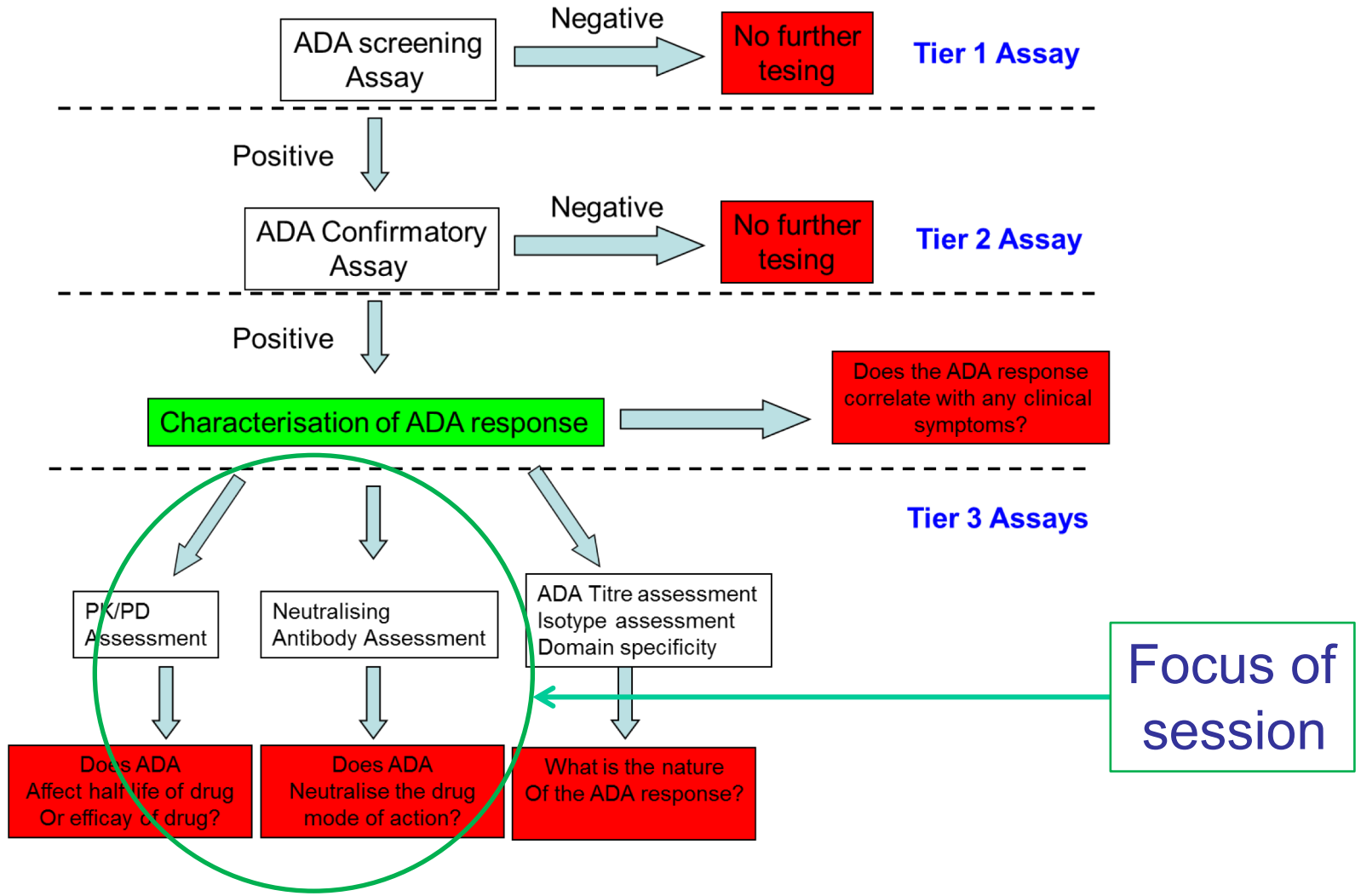
Altered PK/PD

Neutralise compound

Mode of action

Induce antibody response to native protein (ADA)

Tiered assay approach for immunogenicity in a GCP study



Immunogenicity = ADA + PK + PD/NAb + Clinical symptoms

White Paper Guidance

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White Paper

Strategies to Determine Assay Format for the Assessment of Neutralizing Antibody Responses to Biotherapeutics

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Abstract Most biotherapeutics can elicit immune responses in dosed recipients generating anti-drug antibodies (ADAs). Neutralizing antibodies (NAbs) are a subpopulation of ADAs that can potentially impact patient safety and directly mediate loss of drug efficacy by blocking the biological activity of a therapeutic product. Therefore, NAb detection is an important aspect of immunogenicity assessment, requiring sensitive and reliable methods reflective of the therapeutic mechanism of action (MoA). Both cell-based and non cell-based assays are viable options for NAb assessment. However, the scientific approach for the selection of a suitable assay format (cell-based or non cell-based) for NAb assessment is not currently well defined. In this manuscript, the authors summarize the design and utility of cell-based and non cell-based NAb assays and recommend a NAb assay format selection approach that relies on a combination of three factors. These include (i) the therapeutic MoA, (ii) the evidence of desirable assay performance characteristics, and (iii) risk of immunogenicity. The utility of correlating NAb response with pharmacodynamic data is also discussed. The aim of this paper is to provide a consistent strategy that will guide the selection of scientifically justified assay formats capable of detecting clinically relevant NAbs for biotherapeutics with varying MoAs and diverse complexity.

KEYWORDS: assay format; biotherapeutic; mechanism of action; neutralizing antibody.

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Shalini Gupta - Amgen

Presented at EBF Immunogenicity meeting in 2016

Considerations for defining approaches for NAb assays

MoA	Drug Modality	Drug Target	Drug-target Interaction	Examples	Recommended Assay Format
Agonist	Recombinant protein or antibody	Cellular receptor	Drug binds and activates receptor	Cytokines, growth factors, EPO agonists with no homology to endogenous protein	Cell-based assay Cell-based assay as primary choice, non cell-based assay as an alternative
Antagonist	Monoclonal antibody	Humoral target	Drug binds and inhibits the target	Golimumab, Ustekinumab, Adalimumab	Non cell-based CLB assay
	Monoclonal antibody	Cellular receptor	Drug binds cellular receptor and competitively inhibits receptor-ligand interaction	Natalizumab, Trastuzumab, Tocilizumab	Cell-based assay or non cell-based assay
	Soluble receptor	Ligand	Soluble receptor binds ligand and blocks receptor-ligand interaction	Etanercept, Abatacept	Non cell-based CLB assay recommended; cell-based assay possible with a suitable cell line
Targeted intra-cellular delivery of a potent cytotoxin mediated by antibody	ADC	Cellular receptor	ADC binds the cellular receptor and mediates the internalization of payload	Brentuximab vedotin, Adotrastuzumab emtansine	Cell-based assay(s)
Target cell lysis through antibody effector function	Monoclonal antibody	Target cell receptor, FcγR or complement	Antibody binds to target cell receptor through variable region and FcγR or complement through Fc domain	Rituximab, Cetuximab, Alemtuzumab	Cell-based effector assay recommended, cell-based binding assay or non cell-based CLB assay acceptable with justification
Enzyme replacement	Enzyme	Replace deficient protein in circulation or in target cells; may need cellular receptor for enzyme uptake	Enzyme functions in circulation or through cellular uptake	Human factor IX, Imiglucerase, Idursulfase, Galsulfase	Enzyme bioactivity assay and/or cell-based assay; two assay may be needed

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Implementing Nab assays that have an appropriate scientific rationale

3 Area's that define an appropriate scientific rationale:

- Risk Based Assessment
  - What is the likely need of assay for characterization of unwanted immunogenicity
  - Safety impact of non redundant endogenous counterparts
- Mechanism of Action
  - Does assay reflect biological mechanism for therapeutic
- Assay Performance
  - Sensitivity
  - Precision
  - Matrix interference
  - Drug Tolerance

Session today will cover case studies of how these areas can be addressed