" Immunogenicity in Biotherapeutic Development"

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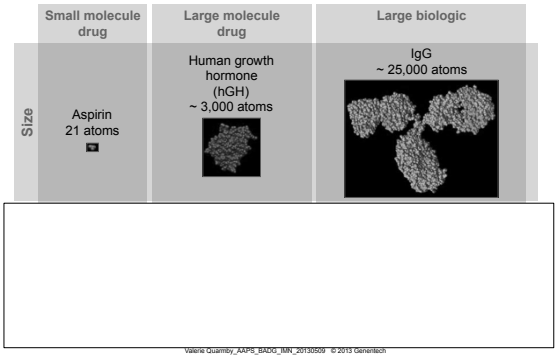
The image

Outline

- What is immunogenicity?
- Why does immunogenicity occur?
- Potential consequences of immunogenicity
- Case studies
- Immunogenicity assessment methods and strategies.
- Immunogenicity and product quality
- Regulatory environment and guidances
- Take Home Messages

Size and Structural Complexity



What is Immunogenicity?

- In the context of biotherapeutics, immunogenicity refers to the production of an unwanted immune response.
- One hallmark of immunogenicity is the presence of host antibodies directed at the biotherapeutic in the circulation. These are typically called anti-therapeutic antibodies (ATA) or anti-drug antibodies (ADA)
- Clinical consequences vary.

Immunogenicity in Biotherapeutic Development

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- Immunogenicity of biotherapeutics is a high profile concern for industry and for regulatory authorities
  - Immunogenicity may impact safety and/or efficacy
  - FDA & EMA require that immunogenicity of biotherapeutics be evaluated
  - Development of biotherapeutics for chronic use is increasing the need to understand potential implications of immunogenicity
  - Immunogenicity strategies and data are essential components of Target Product Profiles, INDs, BLAs, CTDs & USPIs

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Genesis of an ATA response

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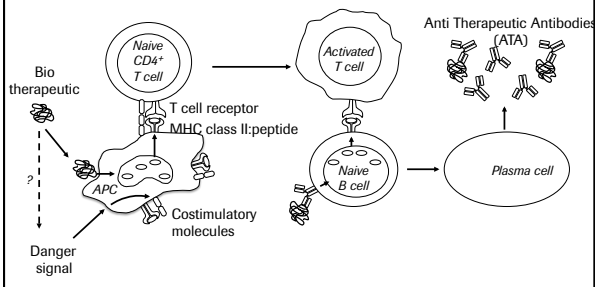

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Immunogenicity & Clinical Sequelae

Clinical Impact	Clinical Outcome
Safety	➢ Hypersensitivity or anaphylactic reactions ➢ Neutralize activity of endogenous counterpart with unique function causing deficiency syndrome ➢ Immune complex formation
Efficacy	➢ Neutralize activity of therapeutic protein ➢ Increase or decrease efficacy by extending or curtailing half life ➢ Increase or decrease efficacy by changing bio-distribution
Pharmacokinetics	➢ Extend, or curtail half life life ➢ Alter biodistribution ➢ PK changes may dictate changes in dosing
None	➢ No discernible impact

Adapted from Susan Kirshner, FDA, AAPS NBC, 2010

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Example 1: PEG-rhuMGDF

Impact of ATA on platelet counts

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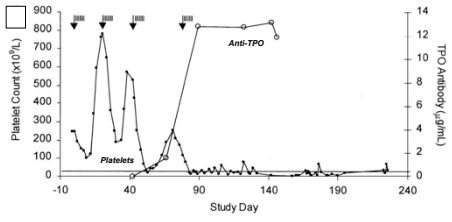
In Normal Human and Cancer Patients



Li J et al. 2001

Example 2 - Epoetin Alfa

Impact of ATA on erythrocyte counts

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VOLUME 346 FEBRUARY 14, 2002 NUMBER 7

PURE RED-CELL APLASIA AND ANTIERYTHROPOIETIN ANTIBODIES IN PATIENTS TREATED WITH RECOMBINANT ERYTHROPOIETIN

NICOLE CASADEVALL, M.D., JOELLE NATAF, M.D., BEATRICE VIRON, M.D., AMIR KOLTA, M.D., JEAN-JACQUES KILADJIAN, M.D., PHILIPPE MARTIN-DUPONT, M.D., PATRICK MICHAUD, M.D., THOMAS PAPO, M.D., VALERIE UGO, M.D., IRENE TEYSSANDIER, B.S., BRUNO VARET, M.D., AND PATRICK MAYEUX, PH.D.

Example 3 - Natalizumab

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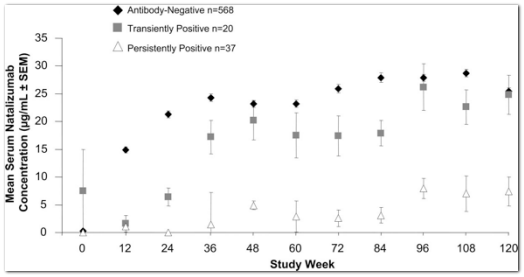

The value observed in transiently positive patients at baseline (week 0) was due to one patient who had natalizumab concentrations above the limit of quantification.

Calabresi et al (2007)

Example 3 - Natalizumab

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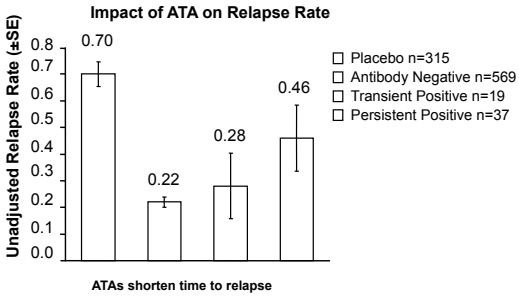

Calabresi et al (2007)

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Immunogenicity Assessments in Biotherapeutic Development

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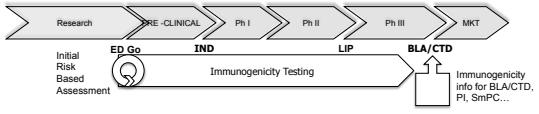

Immunogenicity Risk Assessment

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Higher Risk	Lower Risk
Existence of endogenous counterpart	No endogenous counterpart
Unique activity	Redundant activity
Sole therapy	Other therapies
Non Life threatening disease	Life threatening disease
Chronic treatment	Single dose treatment
Replacement therapy	Non replacement therapy
Non - immunosuppressed subjects	Immunosuppressed subjects
Immunogenicity of the administration route: intradermal > inhalation > subcutaneous > intraperitoneal > intramuscular > intravenous	

Recommendations on Risk-Based Strategies for Detection and Characterization of Antibodies against Biotechnology Products
Koren et al (2008) JIM
Risk Based Approach to Immunogenicity Concerns of Therapeutic Protein Products
Rosenberg & Worobec (2004 & 2005) BioPharm International

Perceived Risk Level drives Immunogenicity Strategy[18]

Type of Biotherapeutic	Perceived Risk	Sample Collection Frequency	Sample Testing Frequency
"Replacement Tx" w/ Non-Redundant Critical Endogenous Homolog	High	More frequent during all phases of clinical development	Consider whether real-time sample analysis would impact patient treatment
"Replacement Tx" w/ Redundant Homologue, Protein with unique structure, some mAbs	Medium	More frequent during Phase I,II, less frequent during Ph III	Typically Batch analysis.
Some mAbs	Low	Same as for Medium Risk	Batch analysis

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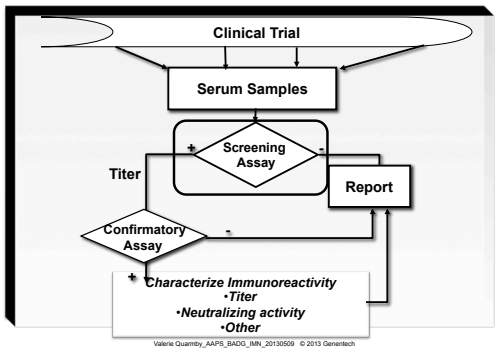

ATA Screening Assay

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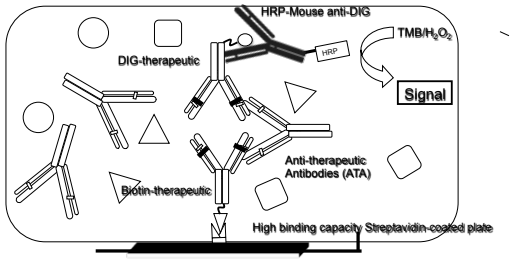

Interpreting Immunogenicity Data in Context

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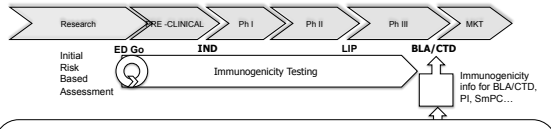

Product Insert - " Immunogenicity" Section for Lucentis

As with all therapeutic proteins, there is the potential for an immune response in patients treated with LUCENTIS.

The pre-treatment incidence of immunoreactivity to LUCENTIS was 0%-5% across treatment groups.

After monthly dosing with LUCENTIS for 6 to 24 months, antibodies to LUCENTIS were detected in approximately 1%-8% of patients.

The clinical significance of immunoreactivity to LUCENTIS is unclear at this time.

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(Some) Factors involved in immunogenicity

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Product Factors

Process
- Product related variants
- Process related impurities
- Host Cell Proteins
- Aggregates

Stability
- Formulation

Storage
- Degradation
- Conformational changes
- Aggregation

Clinical Factors

Dose
- Dose level
- Dose Frequency
- Intermittent dosing

Route
- SC or ID>IM>IV

Patient Status
- Disease status
- Immune status
- Genetic background
- Pre & co-medications

Immunogenicity Risk & Product Quality

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Immunogenicity is a key metric of product safety & product quality.

–Most product related variants assumed to have low immunogenic potential

–Some product related variants & process related impurities could lead to an increased risk of immunogenicity

Product related variants & process related impurities that may lead to an increased risk of immunogenicity are "high criticality" product quality attributes

These are tracked as CQAs in QBD product control systems.

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The External Environment is evolving….

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- Industry Immunogenicity Method Best Practices captured in "White Papers":
  - Sponsored by AAPS, Biosafe & CLSI.
  - Co-authored by SMEs from many companies w/ FDA input
  - USP monograph on Immunogenicity Assays also in preparation
- FDA Perspectives & Recommendations captured in:
  - Industry White Papers
  - FDA talks & co-authored papers
  - DRAFT FDA Guidances
- EMA Perspectives & Recommendations captured in:
  - General Guidelines on Immunogenicity Assessment of Biotechnology-Derived Therapeutic Proteins
  - Product specific annexes

A "Biosimilar" Regulatory Environment is emerging

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- FDA: Developing Biosimilar guidelines
  - 2010 - Public hearing & input
- EMA: Extensive Biosimilar guidelines, recently expanded to mAbs.
  - 2011 - Workshop on Draft guidelines on mAb biosimilars & on mAb Immunogenicity
  - 2012 – New Guidelines on mAb biosimilars and mAb immunogenicity
- Roche Biosimilar Task Force Position on Immunogenicity:
  - Immunogenicity can't be predicted;
  - Immunogenicity must be assessed in clinic, prior to approval, in the specific target population.
  - Immunogenicity can't be extrapolated from one indication to others.
  - Immunogenicity can't be extrapolated from one product to others.

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Key Take-Aways

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- Immunogenicity is a key metric of product safety & product quality.
- Drivers of unwanted immune responses to therapeutic proteins are complex & nuanced
- Immunogenicity cannot be predicted and must be assessed in each indication for a therapeutic protein.
- Fit for purpose methods and "tiered" strategies are used to assess immunogenicity
- Immunogenicity data must be assessed in context of PK, PD, safety, & efficacy.
- Immunogenicity clinical consequences vary but can be severe.

AAPS & Immunogenicity

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- AAPS TPIFG
  - Chair: Valerie Quarmby
  - Members mtg: May 21, 2013 from 12:15 pm.
  - Newsletter:
- AAPS NBC Sessions on Immunogenicity:
  - Advanced Immunogenicity Workshop, May 18 & 19,
  - Roundtable: New FDA guidance, May 20 8:00 am
  - Symposium: Quantitative Evaluation of the Impact of Immunogenicity on PK/PD & Efficacy of Therapeutic Proteins", May 21 8:15 am

Credits

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- Tom Gelzleichter
- Amita Joshi
- Ariela Kellman
- Scott Chandler
- Greg Spaniolo
- Dan Coleman
- An Song
- Rob Hendricks
- Cheryl Schofield
- Chris Morrow
- Cecilia Leddy
- Linda Lin
- Alyssa Morimoto
- Eric Wakshull
- Sue Brignoli
- Patty Siguenza
- Tom Patapoff
- Jamie Moore
- Mary Cromwell
- Reed Harris
- Paul Motchnik