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Immunogenicity and Pharmacovigilance in Similar Biotherapeutic Products (SBPs)

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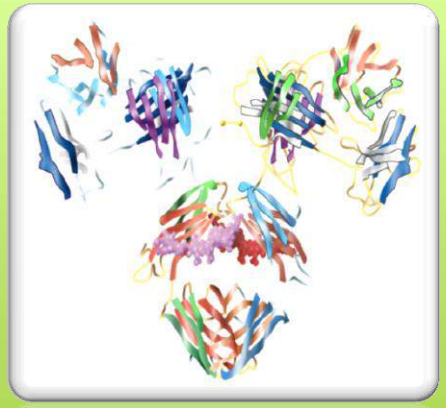
Agenda

1. **Immunogenicity: Why Biotherapeutics are Different**

2. **Pharmacovigilance: Looking to the Future**

Immunogenicity: Why Biotherapeutics are Different



Immunogenicity and SBPs Overview

- Biotherapeutics, even fully human products, are immunogenic to varying extents.[1]
- Immunogenicity for biotherapeutics can cause unintended clinical consequences.[2, 3]
- Immunogenicity results from the product, dose, regimen, duration, concomitant meds, and patient – not just the active substance. [2, 3]
- In vitro and animal studies for comparison of immunogenicity are important, but not alone sufficient to predict immune response in humans.[4]
- Head-to-head clinical trials in a setting sensitive to immunogenicity should be conducted to allow determination of immunogenic similarity between a reference and a SBP (also called biosimilar).[4]

1. Singh, S. K., J. Pharm. Sci., 100: 354–387 (2011) doi: 10.1002/jps.22276
2. Buttel et al, Biol. 39:2, 100-109 (2011).
3. A.S. Rosenberg, Dev. Biol., 112, 15–21 (2003).
4. WHO Guidelines on Evaluation of Similar Biotherapeutic Products (SBPs) (2009), http://www.who.int/biologicals/areas/biological_therapeutics/BIOTHERAPEUTICS_FOR_WEB_22APRIL2010.pdf.

Most Biotherapeutics Are Immunogenic

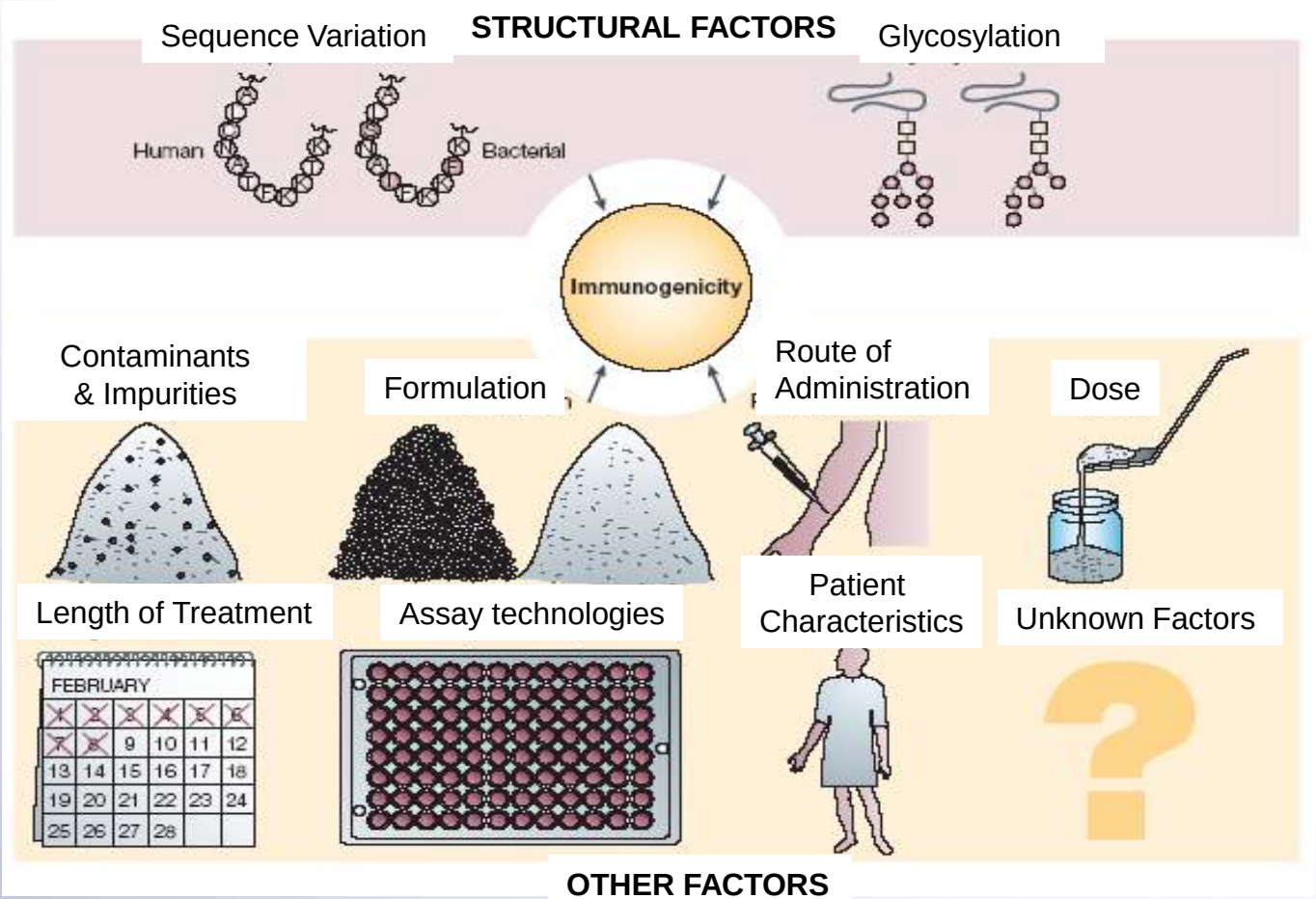
Class	Substance	Indication	Reactivity (%)
Antibodies	Anti-CD3 (OKT3)	Immunosuppressant	<1%
	Anti-Her2	Mamma-tumor	<1%
	Anti-IgE	Allergic asthma	<1%
	Anti-Il-2R	Immunosuppressant	18%
	Anti-TNF-α	RA, M. Crohn	10%
Receptors	CD4	HIV	<1–12%
	TNF receptor	Multiple sclerosis	16%
	Il-1 receptor	Leukemia	<1%
Cytokines	Il-2	Tumor	52%
	Il-3	Tumor	>80%
	Il-12	HCV	<1%
Interferons	IFN-α2a	HCV	27–60%
	IFN-β	Multiple sclerosis	45%
Enzymes	Factor VIII	Hemophilia	10–30%
	DNase	Cystic fibrosis	9%
	Plasm.-activator	Ischemia	<1%
Hormones	Insulin	Diabetes	44–60%
	HGH	Growth	16%
	G-CSF	Neutropenia	4%
	GM-CSF	Tumor	25–80%
	EPO	Anemia	<1%

Type	Drug Name	Mab – Target	Immunogenicity
Murine	*Orthoclone OKT3*	*Muromanamab (IgG_{2a}) CD3*	*86% IgG / 21% IgM / 29% IgE*
Murine-human Chimeric	*REMICADE*	*Infliximab (IgG1) – TNF*	***10-15% in RA,GI***
	Rituxan	*Rituximab (IgG1) – CD20*	*1%*
	Simulect	*Basiliximab (IgG1) – CD25*	*< 2%*
	Erbitux	*Cetuximab (IgG1) – EGF Rc*	*5%*
Humanized	*Zenapax*	*Daclizumab (IgG1) – CD25*	*14%*
	Synagis	*Palivizumab – (IgG1) – RSV gpF*	*0.7%*
	Raptiva	*Efalizumab (IgG1) – CD11a*	*1-4%*
	Tysabri	*Natalizumab (IgG4) - $\alpha_4\beta_1$*	*9%*
	Herceptin	*Trastuzumab (IgG1) - Her-2*	*.1%*
"Fully Human"	*Humira*	*Adalimumab (IgG1) - TNF*	*5% (1-12%)*
	Vectibix	*Panitumumab (IgG2) – EGFR*	*4%*
	CNTO 148	*Golimumab (IgG1) – TNF*	***5%***
	CNTO 1275	*Ustekinumab (IgG1) – IL12/23*	***5%***

See, e.g., Baker et al., Self/Nonself, 1:4, 314-322, 2010

- All classes of biotherapeutics can show immunogenicity under certain circumstances.
- Even when fully human
  - Neo-antigens due to variants, impurities, handling, idiotypes (for mAbs)
  - Tolerance can be broken due to unusual dose, route, possible adjuvants, etc.

Many Factors Affect Immunogenicity



Denaturation
Aggregation

Container

Concomitant Medications

Schellekens 2003, *Neurology* 61 (Suppl 5), S11-12

Clinical Impact of Immunogenicity

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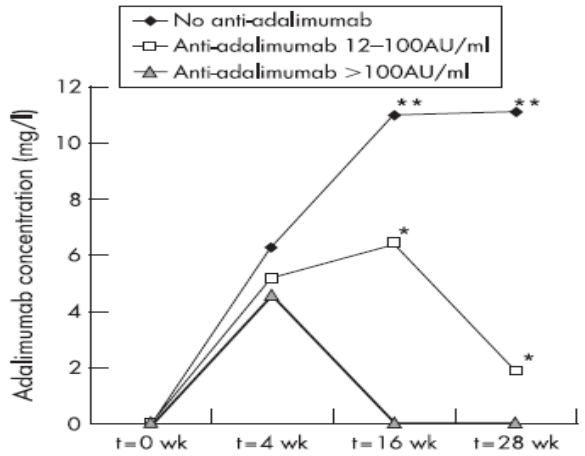
IMPACT	BIOPHARMACEUTICAL
Loss of efficacy (may reflect neutralization or decreased half-life)	Insulin, Streptokinase, Factor VIII, IFN-alpha 2, IFN-beta, IL-2, GM-CSF
Enhancement of activity	Growth hormone
Neutralization of native protein	MDGF (TPO), EPO
Hypersensitivity Rxns	Several
Infusion/Injection reactions	Many
No clinical consequence	Many

IFN = Interferon; GM-CSF = Granulocyte macrophage colony-stimulating factor; MDGF (TPO) = monocyte-derived growth factor; EPO = epoetin

Malucchi, Bertolotto, Immunogenicity of Biopharmceuticals, ch. 2, p. 27-51 (2008)
Casadevall et al., NEJM 346:469 (Feb. 2002).
Grossberg et al., 31 J. Interferon & Cytokine Research 337 (2011)
Creeke & Farrell, Ther. Adv. Neurological Disorders 6:3 (Jan. 2013)
FDA, Guidance for Industry, Immunogenicity Assessment for Therapeutic Protein Products (2014)

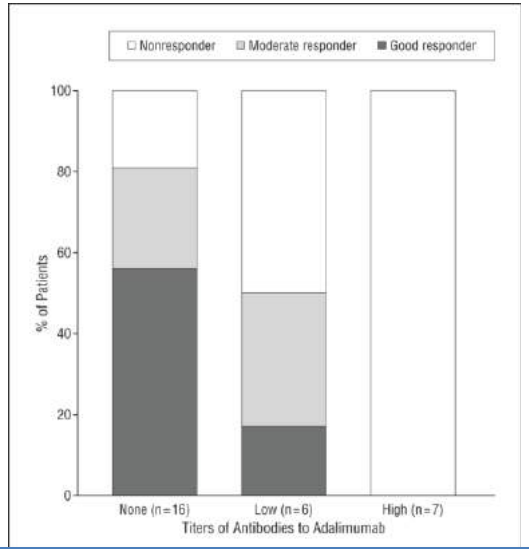
Clinical Impact of Anti-drug Antibodies (ADA) - Ex. Adalimumab

PK



Adalimumab concentrations were significantly lower in patients with high anti-adalimumab antibody concentrations than in those with low (*p<0.001) or absent (**p<0.001) antibodies at week 16.

Efficacy



The percentages of nonresponders, moderate responders, and good responders on the Psoriasis Area and Severity Index are shown for patients with low, high, and no titers of antibodies to adalimumab at week 24. The difference among the 3 groups was statistically significant (P < .001).

L Lecluse et al., Arch Dermatol. 2010;146(2):127-132

Even Identical Active Substance Does Not Ensure Similar Immunogenicity

- Examples of some factors thought to have caused increased denaturation, aggregation, and/or immunogenicity:
  - Formulation changes
  - Silicone used to coat pre-filled syringes
  - Tungsten used to make pre-filled syringes
  - Metal leachates from needles
  - Leachates from rubber stoppers
  - Agitation
  - Temperature elevation

Haag-Weber M et al.. Clin Nephrol. 2012, 77:1, 8-17
Seidl A et al.. Pharm Res. 2011; DOI: 10.1007/S11095-011-0621-4
Schmidt CA, et al. Arq Bras Endocrinol Metab 2003;47:183-9
Schellekens H. Eur J Hosp Pharm 2004;3:43-7
Combe, et al. Pharmacotherapy 2005;25:954-62
Singh AK, World Congress of Nephrology 21-25 April 2007; Rio de Janeiro Brazil
Park S, et al. J Pharm Sciences, Sept 2008; DOI 10.1002:1688-1699

Establishing Similar Immunogenicity

- Analytics do not predict immunogenicity well.
- Immunogenicity in animals is not predictive of immunogenicity in humans.
- Head-to-head clinical studies are needed*:
  - Should be in a highly sensitive setting, i.e., one where immunogenicity rates for the originator are highest; e.g.
    - Avoid immunosuppressed patients (disease or meds)
    - Sufficient duration of therapy; appropriate dose, route, and regimen
  - Should use appropriate assays for anti-drug Abs (ADA)
    - Sensitive, even in the presence of drug
    - Able to detect all Abs to either molecule (originator and/or SBP)
    - Observed antigenicity should be further studied:
      - Titre, neutralization, cross-reactivity
      - Correlations with safety, efficacy, and PK

* See WHO Guidelines on Evaluation of SBPs

Pharmacovigilance: Looking to the Future

Best practices of robust pharmacovigilance systems

- **Clear governance –** laws establish national authorities to oversee pharmacovigilance and enforce reporting and monitoring.
- **Central database** – safety analysis depends on robust, comprehensive data.
- **Centralized or closely coordinated analysis –** within and across countries, a dedicated unit exists to collect and evaluate adverse events, with appropriate medical information for analysis.

Pharmacovigilance today

- Systems developing at different rates, with different requirements
  - Many countries still without strong pharmacovigilance systems
  - INN system weakening, different approaches to naming at national levels
- Focus on the development of comprehensive pharmacovigilance systems including**:**
  - Need to establish basic pharmacovigilance guidance to ensure patient safety
  - Improving identification, naming of products, record keeping
  - Increased emphasis on robust adverse event collection/reporting, surveillance, signal detection and evaluation
  - Focus on risk in context of benefit
    - Important to take the entire prescription/dispensing/using/ADR reporting chain into consideration for traceability

Post approval Surveillance –
Justifying the risk management approach

- **Routine Pharmacovigilance activities**
  - Reporting of adverse drug reactions
    - Spontaneous
    - Literature reports
    - Queries in external databases (e.g. FDA)
    - Structured (e.g. questionnaires)
- **Additional Pharmacovigilance activities**
  - Post-approval efficacy study
  - Post-approval safety study
  - Non-clinical study
  - Pharmacoepidemiology study
  - Registries
  - Effectiveness of risk minimization measures

Post approval Surveillance –

Importance of product identification

- **Both routine and active surveillance depend on accurate product identification**

- **Accurate identification may be challenging for multisource biotherapeutics**
  - Reduced brand identity
  - Shared non-proprietary names
  - Shared codes for reimbursement claims
- **Policymakers should ensure that unique identifiers are available and accessable by stakeholders**

End Goal: Access to novel biotherapeutics & SBPs supported by continuous **monitoring and assessment of benefit/risk**

Traceability for biotherapeutic products:

The need to ensure no disconnects between prescribing, dispensing and adverse event (AE) reporting

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AE Report

In the event patient experiences an AE, reporter knows exactly which brand the patient was dispensed

Prescription by brand

Prescription by INN*

Pharmacist dispenses per physician stated brand or contacts physician to agree change

Pharmacist dispenses an available or cheapest biotherapeutic with same INN

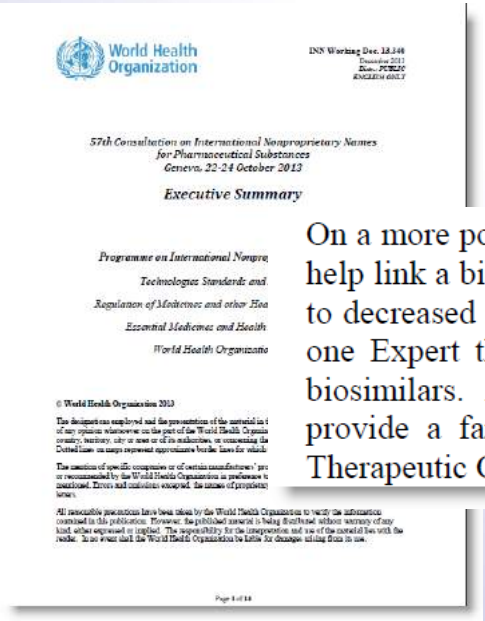
AE Report

In the event patient experiences an AE, reporter does not have immediate access to the precise brand dispensed to the patient

*International Nonproprietary Name

Biological Qualifier is important step

- ***Currently under discussion at WHO. Should be accompanied by:***
  - Reinforcing WHO expectations for application of the INN system by the national regulatory authorities (NRAs)
  - Clarification of the recommended procedures for assigning a WHO-issued distinguishable INN, including Biological Qualifier
  - Emphasizing expectation that any Biological Qualifier is within the labeling requirements of the INN


World Health Organization

INN Working Doc. 13.346

57th Consultation on International Nonproprietary Names for Pharmaceutical Substances Geneva, 22-24 October 2013

Executive Summary

Programme on International Nonpro

Technologies Standards and

Regulation of Medicines and other Hea

Essential Medicines and Health

World Health Organizatio

© World Health Organization 2013

World Health Organization. ***57th Consultation on International Nonproprietary Names for Pharmaceutical Substances Geneva, 22-24 October 2013, Executive Summary***

On a more positive note, the basic idea of a BQ appeared acceptable to the INN Expert Group, would help link a biosimilar to its reference product and to other biosimilars, which in turn would contribute to decreased mis-prescribing and improved pharmacovigilance. Indeed, it was mooted by more than one Expert that such a scheme should apply to all biological medicinal products and not just to biosimilars. A three letter code was considered to be somewhat limited and a four letter code would provide a far greater number of combinations, or a coding system based upon the Anatomical Therapeutic Chemical (ATC) classification system may be useful.

Global Pharmacovigilance – beyond INNs

- Further work is needed to advance guidance on the processes and systems for pharmacovigilance
  - For global consistency
- Building on the WHO Pharmacovigilance Toolkit
  - Specific advice on the treatment of biotherapeutics (including SBPs, “non-comparable” biotherapeutics[1])
- Providing a blueprint for a robust pharmacovigilance system
  - Recognising the need for simple, effective systems that are achievable in all country contexts
  - While allowing global detection and analysis of signals on the level of individual products and product class

[1] http://www.ifpma.org/uploads/media/Non-comparable_Biotherapeutic_Products__English__02.pdf

Immunogenicity and SBPs: Summary

- Biotherapeutics, even fully human products, are often immunogenic.
- Immunogenicity is often clinically relevant.
- Immunogenicity is a property of the product, dose, regimen, duration, concomitant meds, patient - not just active substance.
- Comparability of immunogenicity should include both evaluations in vitro, animal studies, and clinical testing.
- Even a product that is highly similar analytically can be different in immunogenicity.
- Head-to-head clinical trials in a setting highly sensitive to immunogenicity can allow assessment of immunogenic similarity.
- Care must be taken to ensure assays are sensitive and appropriate.

Pharmacovigilance and SBPs: Summary

- Pharmacovigilance is an essential part of understanding and managing the risk and benefit of any medicinal product – particular importance for biotherapeutics
- Pharmacovigilance is also a key pillar in the concept of biosimilarity
- Corner stones of effective safety management:
  - A robust and transparent national pharmacovigilance system
  - Active participation and communication by all stakeholders
- Product-level traceability is a prerequisite for effective pharmacovigilance
  - Globally accepted Biological Qualifier could provide an effective means to deliver for all biologic medicines
- WHO is key player in helping individual countries establish the necessary conditions for good pharmacovigilance
- Clinicians have a critical role to play in ensuring effective recording and reporting of adverse events