First Latin American Educational Workshop on
Similar Biotherapeutic Products

20 January 2015, Sheraton Maria Isabel Hotel & Towers, Mexico City, Mexico

Thijs J Giezen, PharmD, PhD, MSc, The Netherlands

- Hospital Pharmacist, Foundation Pharmacy for Hospitals in Haarlem, The Netherlands

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Safety assessment and risk management of biosimilars: a regulatory perspective

Thijs J Giezen, PharmD, PhD, MSc

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Safety of biologicals

Safety of biologicals: a classification

1. Exaggerated pharmacology
   - e.g. TB with TNF-alpha inhibitors

2. Immunological reactions
   - e.g. anaphylactic reactions, neutralizing antibodies

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Clinical safety during biosimilar development

Collection of clinical safety data

- During the complete clinical development programme
- All data should be submitted to regulatory authorities

http://www.ema.europa.eu/docs/en_GB/document_library/Scientific_guideline/2009/09/WC500003920.pdf

Exaggerated pharmacology

- Safety profile expected to be comparable
- Differences might preclude approval as a biosimilar
- Adverse events (AEs) known for reference product is the basis
- Compare AEs in terms of type, severity and frequency

Exaggerated pharmacology: example

- Higher incidence of serious infections in pivotal clinical trial biosimilar infliximab
- Difference assessed as chance finding:
  - No adequate diagnosis and/or had pre-existing lesions in 4 cases
  - Total rate of infections was similar
  - No mechanistic explanation

Immunogenicity assessment (I)

- Starts already during quality assessment
- Important during clinical development
- Studied in a comparable manner in sensitive population

Immunogenicity assessment (II)

- Number of data based on experience with reference product and/or product class
- Generally one year for chronically administered products
- Assessed in relation to clinical efficacy and safety

Immunogenicity assessment: example

- Infliximab:
  - Antibodies is related to hypersensitivity/ infusion related reactions

- Found in both treatment arms

Immunogenicity: an exemption

- Lower immunogenicity for biosimilar might be acceptable
  - Could erroneously suggest more efficacy for biosimilar
  - Subgroup analysis is advised to preclude higher efficacy

Extrapolation of indication

- Safety should also be considered
- AEs related to exaggerated pharmacology will apparently be similar
- Immunogenicity might differ between indications: justification is needed

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Pharmacovigilance and risk management

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Pharmacovigilance

- Same rules and obligations apply to biosimilars
- Risk Management Plan (RMP) should be submitted

Giezen TJ, Schneider CK. Safety assessment of biosimilars in Europe: a regulatory perspective. Generics and Biosimilars Initiative Journal (GaBI Journal). 2014;3(4):180-3. doi: 10.5639/gabij.2014.0304.041

Risk Management Plan

- Should be based on RMP of reference product
- Immunogenicity and infusion-related reactions should specifically be addressed
- Post-marketing studies if needed
- Risk minimization measures

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Biosimilars in clinical practice

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Biosimilars in clinical practice

- Traceability:
  - Product responsible for AE
  - (Hospital) pharmacists may play important role
- Switching
  - Emotions are involved
  - What is the evidence

Switching induces immunogenicity…

interchangeable. Switching between two similar biologic drugs increases the risk of anti-drug antibodies, which can lead to adverse immunologic reactions and decreased drug efficacy. Because the patient has received multiple drugs, the

nal prescription. However, unlike small-molecule drugs, a biologic therapy that is repeatedly interchanged with a biosimilar agent might promote increased immunogenicity that could compromise the efficacy and safety of both medications.[29]

rules to prohibit the automatic substitution of biopharmaceuticals. Also, medical societies such as the French [33] and the Portuguese [34] Society of Nephrology have stated that there is no safe interchangeability of biopharmaceuticals. The main concern about switching from one biological medicine to another is the issue of immunogenicity.

qualified healthcare professional (8). As a consequence of their complexity, automatic substitution of biologics could give rise to different clinical consequences and should be ruled out for reasons of patient safety (9, 58).

Some definitions

- **Switching**: Decision by the treating physician to exchange one medicine for another medicine with the same therapeutic intent in patients who are undergoing treatment
- **Substitution**: Practice of dispensing one medicine instead of another equivalent and interchangeable medicine at the pharmacy level without consulting the prescriber

Ebbers HC, Chamberlain P. Interchangeability. An insurmountable fifth hurdle? Generics and Biosimilars Initiative Journal (GaBI Journal). 2014;3(2):88-93. doi: 10.5639/gabij.2014.0302.022

Switching the evidence (I)

Drug	Number of studies	Number of patients
hGH	*12*	*401*
ESA	35	11.249
GCSF	*10*	*374*
Total	57	12.024

Expert Opin Biol Ther (2012) 12 (11):1473-1485

Switching the evidence (II)

- 98 patients switched from originator rhGH to Omnitrope
- No negative impact on clinical efficacy based on prediction models
- No reports of serious or unexpected adverse drug reactions
- 18 patients experience pain at injection site, 6 patients switched back to originator

Biol Ther (2013) 3:35–43

Switching the evidence (III)

- After 1 year RA and ankylosing spondylitis studies
  - 246 patients continuously treated with Inflectra
  - 230 patients switched from Remicade to Inflectra
  - Similar clinical efficacy at weeks 78 and 102
  - Comparable safety profile

Open-label extension study of the PLANETRA study
www.prnewswire.com

Switching the evidence (IV)

- Phase III trial of Abasria (insulin glargin)
- Limited number of patients switched from Lantus to Abasria
- Significant higher level of antibodies in the switch group compared to the continuous Lantus users
- However, antibody levels were low and no negative impact on efficacy and safety

http://www.ema.europa.eu/docs/en_GB/document_library/EPAR_-_Public_assessment_report/human/002835/WC500175383.pdf

Switching: the evidence

- Studies do not show safety problems

- In clinical practice switching occurs:
  - Reference product <——> reference product
  - Intravenous <——> subcutaneous

Concluding remarks

Concluding remarks

- Safety assessment is important and should be comparable
- Immunogenicity is of special importance
- Differences might question biosimilarity
- Extrapolation should be justified
- Switching at population level is safe

Concluding remarks

Biosimilars can be safely used in clinical practice