Biosimilar mAbs
Clinical issues
Regulatory perspective

EMEA Workshop
on Biosimilar Monoclonal Antibodies
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Mechanisms of action can be complex!

- **Example: TNFα antagonism**

  - **TNF-R1 (CD120a; p55/60)**
    - (most tissues; mTNFα and sTNFα)
  - **TNF-R2 (CD120b; p75/80)**
    - (only immune cells; only mTNFα)

  ![Diagram](www.wikipedia.org)

  - **Cellular proliferation**
  - **Apoptosis**
  - **Inflammation**
  - **Differentiation**
  - **Tumourigenesis**
  - **Viral replication**

  (TNF-R1 signalling)
Can the mechanism of action be understood as a sole ligand-receptor interaction? (or its inhibition by a mAb?)

Is it important what comes „after“?

Does the mechanism of action have to be known?
Licensed mAbs: Efficacy and safety

Example anti-TNF$\alpha$ antibodies*): How to design a biosimilar development programme?

Licensed indications:
- Rheumatoid arthritis
- Adult Crohn’s disease
- Paediatric Crohn’s disease
- Ulcerative colitis
- Ankylosing spondylitis
- Psoriatic arthritis
- Psoriasis

Therapeutic equivalence?
Non-inferiority?

All indications?
Extrapolation of efficacy?
Extrapolation of safety??

What endpoints?
(Activity or Benefit?)
(Phase II or Phase III endpoints?)

*) example chosen since well suitable to explain regulatory issues
Extrapolation of indications

Guideline on Similar Biological Medicinal Products containing Biotechnology-Derived Proteins as Active Substance: Non-Clinical and Clinical Issues:

» „In case the originally authorised medicinal product has more than one indication, the efficacy and safety of the medicinal product claimed to be similar has to be justified or, if necessary, demonstrated separately for each of the claimed indications.“

» „In certain cases it may be possible to extrapolate therapeutic similarity shown in one indication to other indications of the reference medicinal product.“

» „Justification will depend on e.g., clinical experience, available literature data, whether or not the same mechanisms of action or the same receptor(s) are involved in all indications.“

» Distribution, density, avidity and other characteristics of these receptors per indication?

» „Possible safety issues in different subpopulations should also be addressed.“
Mechanisms of action can be complex!

- **Example:** TNFα antagonism

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- Cellular proliferation
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TNF-α (Tumor Necrosis Factor-α) is a protein that plays a crucial role in various biological processes. It is involved in the regulation of inflammation, cellular proliferation, differentiation, and cell death. TNF-α binds to specific receptors on target cells, activating signaling pathways that can lead to various biological outcomes. Different isoforms of TNF-α, such as membrane-bound (mTNFα) and soluble (sTNFα), can interact with different receptor complexes, influencing their functional outcomes. Understanding the mechanisms of TNF-α action is essential for the development of targeted therapies for diseases such as cancer, inflammation, and autoimmune disorders.
Spectrum of Uncertainty

Can these ever be biosimilar?

How similar is biosimilar?

Can these be bioidentical?

Peptides Protein Glycosylated mAbs Blood products ATMP

Source: Cecil Nick, Parexel
Spectrum of Uncertainty

Can these ever be biosimilar?

Can these be bioidentical?

Acceptable Endpoints

PD

Low variability e.p.

High variability e.p.

Surrogate e.p.

Complexity of Product

Primary Structure

Higher structure

Glycosylation

Related Impurities

Process Impurities

Peptides Protein Glycosylated mAbs Blood products ATMPs

Source: Cecil Nick, Parexel
Extrapolation

- **Extrapolation of indications:**
  - What if mechanism of action is poorly understood? (e.g. interferons)
  - What if clinical endpoints for other indication(s) are not sensitive enough?

- **Recent „milestones“:**
  - Guideline on biosimilar LMWH (**extrapolation**)
  - Reflection paper on biosimilar alpha-interferons („**PD fingerprinting“**
Case-by-case puzzle?

**mAb 1**

- Comparative physico-chemical and biological characterization
  - Combined Method 1+2
  - Potency assay
  - Comparative PK
  - Non-clinical Comparative toxicity
  - Clinical endpoint INDICATION #1
  - Comparative safety INDICATION #1
  - Known Class effects
  - Surrogate Marker INDICATION #2
  - Surrogate Marker INDICATION #3

**mAb 2**

- Comparative physico-chemical and biological characterization
  - Combined Method 1+2
  - Bio-assay #1
  - Bio-assay #2
  - Bio-assay #3
  - Comparative PK
  - PD marker #1
  - Non-clinical Comparative toxicity
  - PD marker #2
  - PD marker #3
  - Surrogate Endpoint
  - Comparative safety
  - PD marker #4
  - Surrogate Marker INDICATION #1
  - Surrogate Marker INDICATION #2
  - Surrogate Marker INDICATION #3
  - PD marker #5
  - PD marker #6
  - PD marker #7
  - PD marker #8
  - PD marker #9
Immunogenicity

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

Nicole Casadevall, M.D., Joelle Nataf, M.D., Béatrice 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., Valérie Ugo, M.D., Irene Teyssandier, B.S., Bruno Varet, M.D., and Patrick Mayeux, Ph.D.
Immunogenicity

- mAbs are not for substitution of endogeneous proteins like recent biosimilars (EPO, G-CSF,…)
- Is the perception of risk different?
  » Antibodies against mAbs are mostly anti-idiotype (not anti-isotype)
  » Endogeneous IgG abundant!

- Is Immunogenicity the „highest“ safety concern?
- …but immunogenicity nevertheless important!
Practical issues

- Acceptability of biosimilar mAbs, e.g. in the oncological setting?
  (or: To what extent is the „biosimilar“ philosophy known to patients and physicians?)

- How to practically deal with phase I PK/PD studies in patients:
  » Are usually single dose studies
  » Cross-over?
  » How to continue treatment? Switch to reference?
The floor is yours!