Biosimilars: their place in clinical practice

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What is a biologic therapy for RA?

A protein-based drug designed to target specific aspects of the inflammatory process.
Evolution of monoclonal antibody R&D

Chimeric recombinant antibodies

Phage display synthetic antibodies

Transgenic human antibodies

INFLIXIMAB

adalimumab

GOLIMUMAB

Lonberg et al. Nature Biotech 2005; 23(9): 1117
All monoclonal antibodies begin with the mouse....

Normal Mouse

Immunize with human TNFα

Mouse Antibody

IFX, RTX

chimeric

ADA

human
Golimumab was generated from a *humanized* mouse.

Normal Mouse → Mouse Antibody Genes Suppressed → Human Antibody Genes Inserted → Human Antibody Transgenic Mouse

- **Immunize with human TNFα**
  - Mouse Antibody
  - RTX, IFX chimeric
  - ADA human

Golimumab human antibody

Contemporary RA management: approved biologic pharmacotherapeutic options

- **Etanercept**
  - TNFα
  - 1998

- **Infliximab**
  - TNFα
  - 1999

- **Anakinra**
  - IL-1
  - 2001

- **Adalimumab**
  - TNFα
  - 2002

- **Rituximab**
  - B cells
  - 2006

- **Abatacept**
  - T cells
  - 2005

- **Golimumab**
  - TNFα
  - 2009

- **Certolizumab pegol**
  - TNFα
  - 2009

- **Tocilizumab**
  - IL-6 receptor
  - 2010

Myth: UK rheumatologists have not yet had experience with biosimilars

Batch to batch variation with current biologic manufacture is such that we have all been using them for >10 years….

But

There are varying degrees of bio“similarity”……….
There are varying degrees of bio"similarity"

The “parent” compound….

Similar, yet very different….
# Biological Products: Complexity

## Inherent complexity
- Size
- Structure
- Physiochemistry
- Heterogeneity

## Added complexity
- Manufacturing process
- Formulation
- Handling
- Route of administration

The complexity of Biological Products makes identical copies **impossible**
Biosimilars are **Not** Generics

- Follow-on products of traditional chemical pharmaceuticals are exact chemical copies
  - These are true generics

- Follow-on products of innovator biological pharmaceuticals are only similar ‘copies’
  - There are no ‘biogenerics’
  - There are only similar products, i.e. ‘biosimilars’
Biological Product Complexity

Adapted from: Steven Kozlowski; FDA

\[ (9,600)^2 \approx 10^8 \]

potential variants

- Pyro-Glu (2)
- Deamidation (3 x 2)
- Methionine oxidation (2 x 2)
- Glycation (2 x 2)
- High mannose, G0, G1, G1, G2 (5)
- Sialylation (5)
- C-term Lys (2)
- \[ 2 \times 6 \times 4 \times 4 \times 5 \times 5 \times 2 = 9,600 \]
A small change can make a big difference

Example: Immune effector function of an antibody molecule

Presence or absence of one sugar residue (fucose) can affect the biological activity (killing of target cells)

Changes in immune effector function may influence potency, but also affect the safety of the drug

Adapted from: M. Clark

http://www-immuno.path.cam.ac.uk/~mrc7/ (accessed July 2010)
What do physicians and patients want from a “biosimilar” therapeutic for RA?

- Same pharmacological action and antigen binding
- Equivalent effectiveness to parent molecule
- Equivalent safety and tolerability to parent molecule
- Durability of response (ie no higher immunogenicity with loss of response)
The patent for Remicade, expires in the E.U. in 2014……
The South Korean company Celltrion’s CT-P13 (Remsima).

Week 14

Week 30

Per patient population

CT-P13 demonstrated **therapeutic equivalence** to Remicade

- Week 30, ACR20 responses were 60.9% for CT-P13 and 58.6% for INX (95% CI −6% to 10%) in the intention-to-treat population.

- The proportions in CT-P13 and INX groups achieving good or moderate EULAR responses (C reactive protein (CRP)) at week 30 were 85.8% and 87.1%, respectively.

- Low disease activity or remission according to DAS28–CRP, ACR–EULAR remission rates, ACR50/ACR70 responses and all other PK and PD endpoints were highly similar at week 30.

**Incidence of drug-related adverse events** (35.2% vs 35.9%) and **detection of anti-drug antibodies** (48.4% vs 48.2%) were highly similar for CT-P13 and INX, respectively.

CT-P13 demonstrated **comparable PK profile and immunogenicity** to Remicade.

CT-P13 was **well tolerated**, with a **comparable safety profile** to that of Remicade.

Patients with latent TB were recommended for prophylactic TB medication.

Latent TB in patients receiving prophylactic TB medication did not convert to active TB.

HOWEVER: There were three cases of active TB in the CT-P13 group and none in the Remicade group.

- The incidence of active TB in patients receiving Remicade was 0% and for CT-P13 in 1.0%.
- 42% of patients in PLANETRA were from countries listed in WHO Global tuberculosis report as having higher TB incidence. 3 TB cases were from Philippines, Poland, Mexico.
- Claimed to be similar to that described in ATTRACT (0.3%) and ASPIRE (0.5%). and was not considered significant, as whereas ATTRACT and ASPIRE included only centres in North America and Western Europe.
The challenge for comparing safety

- Relatively small numbers tested prior to licence in conventional trials.
- But even smaller numbers tested prior to approval for biosimilars.
- Safe comparison of rare events cannot be made with certainty prior to approval.

Preclinical and safety in healthy volunteers  Phase II trials  Phase III trials  License
The challenge for comparing safety

Phase II trials
Phase III trials
Preclinical and safety in healthy volunteers

Safety evaluation becomes more reliable

Post marketing Experience
Celltrion received approval in Korea on July 23rd 2012 for the product for treatment of rheumatoid arthritis, ulcerative colitis, Crohn’s disease, ankylosing spondylitis, and psoriasis.

Remsima™ (infliximab) receive positive opinion from EMA CHMP in June 2013 for ankylosing spondylitis, rheumatoid arthritis, Crohn’s Disease, ulcerative colitis, psoriasis and psoriatic arthritis.

Remsima™ is the world’s first biosimilar mAb to receive positive opinion from an advanced and developed nations’ regulatory body.

Celltrion elected for the path of centralized approval procedure instead of obtaining approval from each country’s regulatory authority, with the sales of Remsima™ in Europe as its goal.
Roche, the Swiss company that developed the brand-name Rituxan, secured global patent protection until the end of 2013, with the exception of the U.S., where the drug is protected from competition until 2018.

Rituxan is Roche's best-selling drug: sales reached 3.3 billion Swiss francs in the first half of 2012, an increase of 8.4% from the same period of the year before. That works out to about $7.1 billion a year in sales.

Thus several companies began scrambling to produce their own versions of this biologic.
Teva halts tests of cancer drug biosimilar

The pharmaceutical giant Teva has suspended third-phase testing of its rituximab biosimilar used in the treatment of cancer and rheumatoid arthritis.
What are the hurdles?

- **Regulatory uncertainty** may be underlying Teva’s and Lonza’s October 2012 discontinuation of their planned 544-patient, Phase III clinical trial of a Rituxan biosimilar while considering the best path to a regulatory approval in Europe, where patent protection lapsed in 2013 and in the U.S. in 2018.

- Teva reported that given the changes in the regulatory environment, *they wanted to get input from regulators on how to design the trial program* but remained *firmly committed to the development of biosimilars*.

- Teva also reported that because of *changes in the competitive environment*, they are evaluating the path forward for biosimilar rituximab.
Until very recently, biosimilars were expected to become an increasingly large part of the world market for global pharmaceuticals, potentially reaching up to a 50% market share.

By 2020 twelve of the top-selling biologicals will have lost patent protection, opening up an estimated $24 billion in E.U. sales and $30 billion in U.S. sales.

However, there appears to be reduced “momentum” on the part of some key players on track to produce biosimilars.
Potential barriers to biosimilar development include:

- **significant technical difficulties**
  - biosimilars are produced in living systems and inherently far more complex than generic small molecule drugs

- **potential regulatory issues**
  - concomitantly rigorous steps, product testing, and approval.

- **surfacing submarine patents**
- **halted clinical trials**
- **and especially potential product pricing**

There has been recent volatility in the field with clear commercialization successes yet to emerge.
Samsung halted its SAIT101 biosimilar Rituxan program in October 2012, telling a Korean newspaper that clinical development stopped for "some internal reasons," with speculation that recent regulatory guidelines from U.S. regulators could be partly to blame for the delay.

Companies still in the Rituxan race include:

- Sandoz (Novartis’ generic unit), which is currently conducting a Phase I/II trial testing its biosimilar GP2013 in rheumatoid arthritis and a Phase III trial in patients with advanced folicular lymphoma.
- Pfizer with its PF-o5280586 for rheumatoid arthritis and NHL,
- Merck with MK8808 in RA patients,
- Celltrion in a joint venture with Hospira, testing CT-P10 in a Phase I trial for RA and another Phase I for lymphoma.
Avoid allowing drugs that are not adequately tested coming to market or being mandated for use just because they are cheaper.

Avoid regulatory hurdles that are so draconian as to deny access of potentially beneficial drugs to a wider population.

If biosimilars ultimately prove to be equivalent in every way, then do we have a moral responsibility to prescribe the cheapest agents in future?
The issues: we will need to re-think the way we prescribe

- We were trained as doctors to prescribe the generic, not the brand name, for synthetic chemical drugs.

- In the future for biologic therapies we will need to prescribe by brand name.

If biosimilars ultimately prove to be equivalent in every way, then do we have a moral responsibility to prescribe the cheapest agents in future?
The treatment target is clinical remission or, if remission is unlikely to be achievable, at least LDA.

Methotrexate inadequate responders

TNF-inhibitor, ADT, TCZ (no preference); biosimilars once approved

Special cases RTX

*The treatment target is clinical remission or, if remission is unlikely to be achievable, at least LDA

Stricter criteria: Boolean, SDAI, CDAI remission (LDA)

If sustained remission and after tapering GC, biologics might be tapered

Green boxes indicate new EULAR 2013 recommendations

EULAR Recommendations: Phase II

*The treatment target is clinical remission or, if remission is unlikely to be achievable, at least LDA*

Any other biologic, except biosimilar of IFX after IFX

Tofacitinib can be used after 1 or preferably 2 biologics (safety/price)

If sustained remission and after tapering GC, biologics might be tapered

EULAR Recommendations: Phase III

Green boxes indicate new EULAR 2013 recommendations

Patients failing first biologic

Stricter criteria: Boolean, SDAI, CDAI remission (LDA)
Summary: mAb biosimilars raise many issues

- ...it is clear why the 'generic' approach is not applicable to biotechnological products – a fact that is all the more relevant for mAbs, which are considerably more complex than currently developed biosimilars, such as human growth hormone, insulin or erythropoietin.

- ...glycosylation patterns are likely to be among the most crucial issues for biosimilar mAb development because these modifications can influence binding, immunogenicity and effector activity of a mAb molecule.

- Extrapolating from efficacy in one indication (e.g. psoriasis), efficacy in another indication (e.g. rheumatoid arthritis) can thus be particularly challenging for a biosimilar mAb.

- Another important consideration is the design of the clinical comparative trial. An equivalence study to demonstrate biosimilarity against a reference mAb might be expected to require a large number of patients, and might thus be by far more extensive than the pivotal trial for a stand-alone development.

- As comparative trials to establish similarity of efficacy and safety can require a large number of patients, it might well be that for certain mAbs the biosimilar approach is simply not feasible.

Schneider CK, & Kalinke U. Nature Biotechnology 2008; 26: 985–990