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# Biosimilars in rheumatology: pharmacological and pharmacoeconomic issues

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## ABSTRACT

*Rheumatoid arthritis (RA) societal costs are high because the disease may cause not only restricted joint mobility, chronic pain, fatigue, and functional disability, but also psychological distress. Direct health care costs represent about one-fourth of all costs and are prevalently represented by in-patient care expenditures. The introduction of biologics disease-modifying anti-rheumatic drugs (B-DMARDs), has really changed the perspectives of the patients not fully responding to conventional DMARDs, but the direct costs for drugs has really modified the expenditure for this disease and many other diseases, i.e. psoriatic arthritis, spondyloarthropathies. Increasing pressure for lower cost versions of biological medicines, the scientific technology (particularly analytical technology) that continues to improve will lead to the introduction through reverse engineering of biosimilar drugs in rheumatology. The hope is to provide cost savings, which may broaden access to biopharmaceuticals and stimulate further research. The need for patients to have a biosimilar product, with comparable efficacy and safety, will be discussed in this paper along with all the possible issues that will govern the assessment of the bioequivalence and of the interchangeability.*

## Introduction.

The efficacy of disease-modifying anti-rheumatic biological drugs (B-DMARDs) has been shown over the last fifteen years in several trials either in rheumatoid arthritis (RA) as well as in psoriatic arthritis (PsA) or in spondyloarthropathies (SpAs) (1). For many of the biologics, Registries have confirmed efficacy and in general safety, thus stressing their real value in clinical practice.

There is no doubt that all the B-DMARDs have shown efficacy and

good safety. This applies to TNF (tumour necrosis factor) inhibitors, to IL6 (interleukin 6-receptor) inhibitors, to cell targeting biologics either B-cell (anti-CD20) or T-cell targeting (CTLA4-Ig). The key point is that all these biologics are really expensive and, because of the price, not all the patients can be given these drugs and in general only those with more severe and aggressive disease will receive such therapies.

The advent of technologies allowing to re-produce these drugs have open new avenues and new perspectives in terms of chances to care for these patients, and this is the reason why many stakeholders have expressed their interest in biologically derived molecules, reproducing the original biologics. The reproduced drugs are called biosimilars and in this term the concept of similarity appears crucial for the patient and the health authorities.

## The cost issue – rheumatoid arthritis (RA) as the paradigm

A pivotal question when evaluating the long term outcome of patients with rheumatoid arthritis (RA) is how the disease itself evolves over time and to what extent new treatments contribute to such changes.

Among the RA population of working age, high sick leave and work disability rates have been found. The work disability rates across studies vary importantly and are influenced by a large number of socio-demographic and disease-related factors.

Most studies have used the human capital (HC) method to estimate productivity costs. With this method the overall productivity loss is considered as a consequence of a disease, comprising loss of income due to work disability. In real world, indeed, the paid production loss is likely lower. In case of long-term absence, the work can be done by someone drawn from the ranks of the unemployed or by reallocating

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employees in the workplace. These considerations have led to the development of the friction cost (FC) method. The FC-method is based on the idea that the production loss, due to a disease, depends on the time that working organizations need to restore the initial level of production.

Furthermore, the assessment of a unit of productivity loss (such as one hour of work, one working day) may be based on different sources, such as personal wages, average national income, or the national product (the so-called "added value").

Another aspect of the problem that has to be considered is the influence of disease on loss of household productivity that is expected to be high, since a general RA population predominantly includes females and persons of older age. This means that global productivity costs due to RA should be estimated from a societal point of view including costs of loss of productivity valued by the FC-method together with costs due to loss of household productivity. Finally the influences of different sources to assess productivity (using the gross national wage or the "added value") should also be evaluated (2, 3).

From a pharmacoeconomic point of view the elevated acquisition costs of TNF antagonists may be a barrier preventing patients with rheumatoid arthritis to benefit from these agents (4). The prevalence of rheumatoid arthritis (RA) is relatively low. It is estimated at 0.5–1% worldwide, but the chronic course of the disease and its onset relatively early in life lead to a remarkable social (and economic) impact.

The RA societal costs are high because the disease may cause not only restricted joint mobility, chronic pain, fatigue, and functional disability, but also psychological distress. More than one third of patients will be work-disabled within 10 years after disease onset, making productivity losses the predominant economic burden of the disease (5).

Direct health care costs represent about one-fourth of all costs and are prevalently represented by in-patient care expenditures.

For example, in Sweden and the UK, drugs represent a minor cost: 3–4% of

total costs and 13–15% of direct costs. However, the introduction of "biologics" in the treatment of RA has modified the distribution of costs associated with this disease (6) and (in Finland) the frequency of continuous work disability (7).

As drug budgets have been increasing, the interesting economic question is whether savings in other resources will counterbalance the increased cost of drugs, or whether overall costs in RA will increase. If global costs increase, it is important to discern if, together the growth of the expenses, an associated gain in health can be demonstrated. In fact, from a societal perspective, this gain justifies additional expenditures (4, 8).

This question raises the problem of how to make predictions of both costs and outcome when no or only limited data on the use of such treatments in clinical practice are available, and any assessment must be based on short-term clinical trials carried out in selected patient groups, as it happens in the case of rheumatoid arthritis. The key issue when performing cost-effectiveness analyses of new treatments in chronic diseases is that clinical trials are generally short compared with the duration of the disease, and limited data on the use of this new treatments in clinical practice are available. The health and the potential economic benefits ascribable to new treatments will be evident only in long trial period, because the delay of the development of functional disability will lead to lower levels of resource consumption and maintain the patient's ability to work longer. Several studies have also shown that patients' quality of life decreases as RA progresses. As a consequence, slowing disease progression can be expected to maintain quality of life at a higher level for a longer period of time (9; 10). Thus a baseline algorithm representing disease progression, resource consumption, and the quality of life in patients using current treatments is required. The new treatments can be evaluated against this baseline within a period of time exceeding that of the clinical trials. Clinical, epidemiologic and economic data must be combined in economic models.

In fact, economic evaluation implies the use of some types of model that often represent the only way to illustrate disease processes and their economic impact and to estimate the impact of changes in treatment strategies.

Economic evaluations compare treatment strategies in terms of their costs and their effectiveness. Results are expressed as the extra cost for each additional "unit of health" gained with one treatment strategy compared with another.

A disease model that serves as a baseline for analysis of the cost-effectiveness of new treatments of RA must comprehend epidemiologic data, information about resource consumption at any disease severity level and an efficacy measure coming from clinical trials.

Both direct and indirect costs should be included in analysis. In the pre-biologic era direct costs were very low, as treatment was limited and drugs, both conventional DMARDs and NSAIDs, are generally inexpensive. Fortunately 65–70% of the patients still respond pretty well to conventional DMARDs. The cost effective analysis therefore applies to the most severe 30–35% of the whole rheumatoid population.

The cost-effectiveness of anti-TNF drugs was investigated by Chen *et al.* by using The Birmingham Rheumatoid Arthritis Model (BRAM), a simulation model which was designed to produce incremental cost-effectiveness comparisons, and to test them through robust sensitivity analyses. The BRAM model, which incorporates improvements in quality of life and mortality, was applied to twenty-nine randomised controlled trials with etanercept, infliximab, and adalimumab. Incremental cost-effectiveness ratios (ICERs) for first-line use of TNF antagonists as monotherapy are of about 50,000 GB pounds per quality-adjusted life-year (QALY) for etanercept and adalimumab (infliximab therapy looked always more costly) (11).

Combining methotrexate and a TNF inhibitor as first-line treatment generates much higher ICERs as it precludes subsequent use of cheap methotrexate. ICERs for sequential use of methotrexate and TNF antagonists do not offer any

costs advantage compared with using the TNF inhibitor alone (11, 12).

Results were similar in another pharmacoeconomic review of two cost-effectiveness and six cost-utility studies with etanercept, adalimumab, and infliximab, although the studies were not focused on patients with clinically moderate rheumatoid arthritis (13).

Overall costs of TNF antagonists look higher than those of traditional DMARDs, but TNF antagonists produced more QALYs. Despite differences in study design and assumptions, modelling comparison of TNF antagonists with traditional DMARDs consistently resulted in ICERs of less than 50,000 dollars per QALY gained. Through no formal cost-effectiveness threshold has been established in the U.S. and Europe, historically any drug is considered cost-effective if the ICER is less than 50,000 dollars per QALY gained. However, values as high as 100,000 U.S. dollars per QALY gained, as it may sometimes happen in sensitivity analyses under certain assumptions, have also been used to justify additional drug spending (13).

The most difficult issue when results from short-term trials are extrapolated to the longer term is the assumptions made for treatment continuation, as no data are available. The only possibility (coming exclusively from the economic models) is to use the results for the period during which trial data are available and estimate the effect of the benefit achieved within the trial carried over to a longer period, including, however, a potential loss of effect at treatment discontinuation.

A complete econometric model was constructed on anti-TNF drugs by Brennan and co. in 2007; in this paper the cost-utility of TNF-antagonists (infliximab, etanercept and adalimumab) as a class compared with conventional DMARD therapy (*e.g.* hydroxychloroquine, methotrexate, intramuscular gold, sulphasalazine and leflunomide) using a decision analytic model populated by BSRBR (British Society for Rheumatology Biologics Registry) data, with a time horizon over the full patient lifetime was evaluated (14).

The aim of this study was to answer two main questions:

- i. If the current pattern of TNF-antagonist use should be considered cost-effective when compared with conventional DMARDs
- ii. If the strict adherence to the guidance from NICE (National Institute for Health and Clinical Excellence) and the BSR are consistent with the cost effectiveness of TNF-antagonist therapy.

Evidence on subsidiary questions concerning cost-effectiveness in subgroups and for sequential anti-TNF-therapy was also examined. The results for analysing current UK practice with TNF-antagonist therapies showed an estimated discounted mean lifetime cost of nearly £58 000 on TNF-antagonist therapy *vs.* around £21 000 on conventional DMARDs. The mean incremental cost of around £37 000 achieved an estimated mean discounted QALY gain of 1.5583 over a lifetime. The incremental cost per QALY gained was estimated at £23.882. This is around the range that has previously been considered acceptable by NICE. The Probabilistic Sensitivity Analysis (PSA) for examining uncertainty confirmed this, showing an 84% probability of being cost-effective at a £30 000 threshold.

If the 2001 NICE guidelines were strictly adhered to, and EULAR non-responders were withdrawn from therapy at 3 months, practice would be marginally more cost-effective (£22 000 per QALY gained), but with a reduction in mean lifetime costs in the TNF-strategy of 7% (around £4000).

Finally, sequential therapy with two TNF-antagonists appears to have the same order of cost-effectiveness as single therapy.

Summarising the evidence so far available, the efficacy, safety, and quality of life advantages of TNF antagonists, compared with traditional therapies of rheumatoid arthritis, support using TNF antagonists (and other biodrugs) more often than today, including possibly in patients with clinically moderate disease.

To this end, biosimilar drugs that through a reverse engineering process should cost less than the originators, are currently under strict pharmacological and clinical scrutiny.

### **What is the biosimilar and at what level of evidence is it interchangeable with the originator?**

The European Medicines Agency (EMA) wording is “Similar Biological Medicinal Products Containing Biotechnology-Derived Proteins“. A biosimilar is a biological product that is highly similar to the reference product, with possible minor differences in clinically inactive components but with no clinically meaningful differences between the biological product and the reference product (originator) in terms of safety, purity, and potency of the product. When this occurs there should be bioequivalence and interchangeability. Therefore structural and functional characterisation, animal studies, pharmacokinetic (PK) and pharmacodynamic (PD) studies in humans, clinical immunogenicity and clinical knowledge are all necessary to accept the concept that a “highly similar” product is really “biosimilar”.

Biological originator medicines (biologics) are generally complex molecules, in general large proteins, and on this ground they can really be difficult to fully characterise. This is the reason why it may be a real challenge in terms of starting material, manufacturing process, and methods of control to reproduce a biologic drug thus creating a structurally identical molecule.

The FDA requires that the application for a biosimilar should be based upon analytical studies demonstrating that the biological product is “highly similar” to the reference product, on animal studies (including the assessment of toxicities) and on a clinical study (or clinical studies) including the assessment of immunogenicity and pharmacokinetics (PK) or pharmacodynamics (PD)) that are sufficient to demonstrate safety, purity, and potency in one or more appropriate conditions of use for which the reference product is licensed.

EMA requires comparative efficacy clinical trial, to show clinical comparability and immunogenicity assessments and risks in different indications.

Certainly the concept of the “biosimilar” is completely different from the “originator” product. The originator had to show the different mode of ac-

tion, the clinical efficacy, the immediate and long-term safety profile. The “biosimilar” has to demonstrate that it is biosimilar. The concept that even an aminoacid substitution or difference renders the molecule “not-biosimilar” is of absolute importance, yet many biologics are antibodies, therefore proteins that underwent post-transcriptional modification. They are produced by mammalian cell lines and depending on the clone and production process, micro-variation like asparagine de-amidation or iso-aspartic acid isomerisation may occur, and can impact both the 3D-structure and the antigen binding properties (15). As such they will unlikely to be structurally totally identical in terms of tolerability, immunogenicity and safety that have to be fully proven in formal studies. Therefore even trials have to be designed in a totally different manner. With this in mind, non-clinical and clinical studies should aim, through sensitive end-points, to show the clinical bioequivalence.

Once the biosimilarity is demonstrated the product should produce the same clinical results as the originator, and along this line even safety and reduced efficacy risks of alternating or switching should not be greater than with repeated use of the originator drug. This can be summarised as biosimilarity and bioequivalence.

If this is true then interchangeability will be possible. If the product is interchangeable then the biosimilar can substitute for the originator without the authorisation of the health care provider. At this point the biosimilar is interchangeable. Substitution of an originator with a biosimilar should be defined at a state level and following the opinion of a qualified health professional.

Several other issues ensue when the interchangeability is in place, and this includes (for recombinant proteins) that the tolerability of the combination with conventional drugs (methotrexate, leflunomide, antimalarials, etc.) is the same, that it may be possible to extrapolate therapeutic similarity to other indications, that it will be possible to apply the indications in pediatric illnesses, etc.

Up to now at least three biosimilars are in progress in some countries and in

the process to be tested in the western world, *i.e.* etanercept, infliximab and rituximab.

### Cost saving is real with biosimilars

The real advantage of biosimilars when compared to the originators is the cost saving. This has been shown to be real in the erythropoietin (EPO) market. It has been estimated that the projected saving in Germany by 2020, will be around 8 Billion Euros (Schneider KK, EMA – CHMP Biosimilar Working Party, personal communication 2012). This means a real chance of increasing the access to the patients.

### Warnings

If the biosimilar is truly interchangeable with the originator (interchangeability means that a pharmacist can substitute the “originator” with the “biosimilar” without intervention of the caring physician), no adverse reactions should occur when switching from the “originator” to the “biosimilar”. It has recently been reported that a “rituximab” biosimilar has produced anaphylactic reactions after the patients were switched to the biosimilar in Mexico and this raises the real issue of what should be the real definition of the biosimilarity and of the bioequivalence in terms of safety (16).

### Conclusion

To summarise for any biosimilar, the bioequivalence should be demonstrated in clinical trial (s), the immunogenicity has to be tested, the PK in humans is a necessary analysis, and safety must be assessed thoroughly to definitely accept the “bio-identity” and as such “the biosimilar interchangeability” of any molecule (17-20).

### References

1. FLEISCHMANN R, WELLS AF, KAVANAUGH A: New biologic agents in patients with rheumatoid arthritis. *Update to Rheum Dis Clin NA* 2011; 4: 3-20.
2. VAN DEN HOUT WB: The value of productivity: human-capital versus friction-cost method. *Ann Rheum Dis* 2010; 69 (Suppl. 1): i89-i91.
3. FILIPOVIC I, WALKER D, FORSTER F, CURRY AS: Quantifying the economic burden of productivity loss in rheumatoid arthritis. *Rheumatology* (Oxford) 2011; 50: 1083-90.

4. KIRCHHOFF T, RUOF J, MITTENDORF T *et al.*: Cost of illness in rheumatoid arthritis in Germany in 1997-98 and 2002: cost drivers and cost savings. *Rheumatology* (Oxford) 2011; 50: 756-61.
5. BARRETT EM, SCOTT DG, WILES NJ, SYMONS DP: The impact of rheumatoid arthritis on employment status in the early years of disease: a UK community-based study. *Rheumatology* (Oxford) 2000; 39: 1403-9.
6. KOBELT G, JONSSON L, YOUNG A, EBERHARDT K: The cost-effectiveness of infliximab (Remicade) in the treatment of rheumatoid arthritis in Sweden and the United Kingdom based on the ATTRACT study. *Rheumatology* (Oxford) 2003; 42: 326-35.
7. RANTALAIHO VM, KAUTIAINEN H, JARVENPAA S *et al.*: Decline in work disability caused by early rheumatoid arthritis: results from a nationwide Finnish register, 2000-8. *Ann Rheum Dis* 2012 Jun 7. [Epub ahead of print]
8. SCHOELS M, WONG J, SCOTT DL *et al.*: Economic aspects of treatment options in rheumatoid arthritis: a systematic literature review informing the EULAR recommendations for the management of rheumatoid arthritis. *Ann Rheum Dis* 2010; 69: 995-1003.
9. BOONEN A, PATEL V, TRAINA S, CHIOU CF, MAETZEL A, TSUJI W: Rapid and sustained improvement in health-related quality of life and utility for 72 weeks in patients with ankylosing spondylitis receiving etanercept. *J Rheumatol* 2008; 35: 662-7.
10. HARRISON MJ: Challenges in assessing costs of rheumatoid arthritis. *Case Manager* 2003; 14: 65-72.
11. CHEN YF, JOBANPUTRA P, BARTON P *et al.*: A systematic review of the effectiveness of adalimumab, etanercept and infliximab for the treatment of rheumatoid arthritis in adults and an economic evaluation of their cost-effectiveness. *Health Technol Assess* 2006; 10: iii-xiii, 1.
12. TANNO M, NAKAMURA I, ITO K *et al.*: Modeling and cost-effectiveness analysis of etanercept in adults with rheumatoid arthritis in Japan: a preliminary analysis. *Mod Rheumatol* 2006; 16: 77-84.
13. DOAN QV, CHIOU CF, DUBOIS RW: Review of eight pharmacoeconomic studies of the value of biologic DMARDs (adalimumab, etanercept, and infliximab) in the management of rheumatoid arthritis. *J Manag Care Pharm* 2006; 12: 555-69.
14. BRENNAN A, BANSBACK N, NIXON R *et al.*: Modelling the cost effectiveness of TNF-alpha antagonists in the management of rheumatoid arthritis: results from the British Society for Rheumatology Biologics Registry. *Rheumatology* (Oxford) 2007; 46: 1345-54.
15. REICHERT JM, BECK A: Biosimilar monoclonal antibodies. *mAbs* 1:5, 394-416; September/October 2009; © 2009 Landes Bioscience.
16. COFEPRIS: <http://www.cofepris.gob.mx/AZ/Paginas/Farmacovigilancia/Comunicados.aspx-04/04/2012>
17. REICHERT J: Next generation and biosimilar monoclonal antibodies. *mAbs* 3:3, 223-240; May/June 2011; © 2011 Landes Bioscience.

18. FOOD AND DRUG ADMINISTRATION: Scientific considerations in demonstrating biosimilarity to a reference product: draft guidance February 2012. Available from URL: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291128.pdf>. Accessed April 4. 2012.
19. FOOD AND DRUG ADMINISTRATION: Quality considerations in demonstrating biosimilarity to a reference product: draft guidance February 2012. Available from URL: <http://www.fda.gov/downloads/Drugs/GuidanceComplianceRegulatoryInformation/Guidances/UCM291134.pdf>. Accessed April 4. 2012.
20. AHMED I, KASPAR B, SHARMA U: Biosimilars: impact of biologic product life cycle and European experience on the regulatory trajectory in the United States. *Clin Ther* 2012; 34: 400-19.