

UNRAVELLING THE MYSTERY BETWEEN STRUCTURE AND SUSTAINED CLINICAL OUTCOMES

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Chairperson

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Speakers

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MEETING SUMMARY

Targeted biologics have revolutionised the treatment and outlook of patients with inflammatory joint diseases. The combination of high-cost long-term therapy straining healthcare systems with impending expiry of key biologics patents has led to heightened interest in the development of biosimilars. The expanding landscape of biosimilars has triggered, in healthcare providers, the need to explore the option to non-medically switch stable patients from costly reference products to less expensive alternatives. Currently, there are many unknowns surrounding the effects of non-medical switching on patient outcomes and cost-effectiveness. Prof Edward Keystone opened the symposium by discussing the constantly evolving landscape of biologics, highlighting that their high cost is becoming an increasing challenge and has created the issue of non-medical switching. Dr Leigh Revers provided a background to the structural and functional relationships of biologic therapies, stressing the need for careful control of the manufacturing processes of these large and complex molecules. Prof Keystone presented the long-term data currently available for anti-tumour necrosis factor (anti-TNF) agents and examined how sustainability of response can be influenced by multiple factors. Prof Thomas Dörner concluded the symposium by stressing the importance of the prescribing doctor being in control of which biologics their patients receive to ensure effective pharmacovigilance. The challenge of non-medical switching was discussed along with the potential trial designs that could help to determine if biologics and biosimilars could be interchangeable.

How Biologics Work: What We Know and What We Do Not Know

Professor Edward Keystone

Biologics have changed the landscape of modern therapy for inflammatory diseases. For patients that fail conventional disease-modifying anti-rheumatic drugs, biologics can provide a substantial reduction of disease signs and symptoms, a significant inhibition of radiographic progression and joint damage, and improvements in quality of life.

There are currently three classes of TNF inhibitors: recombinant receptor/Fc fusion proteins (etanercept), monoclonal antibodies (infliximab, adalimumab, golimumab), and PEGylated Fab' fragment (certolizumab pegol).¹ Some of the newer biologics include: rituximab, an anti-B cell chimeric monoclonal antibody; abatacept, a co-stimulation blocker recombinant fusion protein; and tocilizumab, an anti-interleukin-6 recombinant humanised monoclonal antibody.²

Despite biologics being available to treat rheumatic diseases for some time, there are still many unknowns. Biomarkers or reliable predictors of response are needed, as well as a sustained response leading to cure and reversal of pre-existing joint damage. A key challenge surrounding the use of biologics is payer restriction. The issue of increasing healthcare costs in the UK highlights the need for more affordable therapies. In 1997, the total healthcare expenditure was £54.9 billion, a value that has risen every year until 2013.³

The introduction of lower cost biologics has raised the issue of non-medical switching between therapies. Medically-driven switching occurs when patients have had an inadequate response or experienced an intolerable adverse event to a biologic.^{4,5} Non-medical switching occurs when a patient has an adequate response and has tolerated treatment well, but a desire for cost saving or patient preference drives the decision.⁶⁻⁸

The potential cost-saving benefits of non-medical switching have not been established. A study by Liu et al.⁶ comparing total medical costs for patients that were maintained on treatment and those that switched from adalimumab to another injectable biologic, reported that non-medical switching increased healthcare costs.⁶ These initial

data suggest that the issues of costly biologics are not necessarily addressed with a switch to cheaper treatments. Currently there is insufficient robust evidence to provide a definitive answer regarding the effects of non-medical switching.

Structural to Function Relationship of Monoclonal Antibody Therapies

Doctor Leigh Revers

A wealth of experience of using biologics to effectively treat rheumatoid arthritis (RA) patients is available;⁹ however, with the changing treatment landscape there is a need for physicians to be better informed about the development of biologics and how they differ from the more conventional small molecule drugs that are prevalent in pharmacopoeias.

Biologics are best described as pharmaceutical ingredients derived from living organisms that cannot reasonably be synthesised by chemical means. However, the synthesis of such complex biologic molecules could one day be a reality: a study published by Wang et al.¹⁰ in 2013 reported the first total chemical synthesis of erythropoietin, a less complex biologic than a monoclonal antibody.

The history of biologics began in 1921 with the discovery of insulin by Banting and Best in Toronto, Canada, which led to approval of the first biotech drug, insulin isophane, by the US Food and Drug Administration (FDA) in 1982. The first glycoprotein biologic, epoetin alfa was developed in 1989, followed by the humanised monoclonal antibody, daclizumab, from Roche in 1996, and the human monoclonal antibody, adalimumab, from AbbVie in 2002. Over the past decade, numerous more biologics have become available, creating a complex market.¹¹

Small molecule drugs are synthetic and uniform, making them predictable and easy to characterise. Biologics however, are biosynthetic molecules that are large and heterogeneous, with a 3-dimensional structure, making them more complex, sensitive, and difficult to fully characterise. The high cost of biologics has led to the development of biosimilar molecules. A biosimilar is an approved, new version of an innovator biologic, following patent expiry that has undergone rigorous comparability tests and shows no clinical differences. The term

'biosimilar' used by the European Medicines Agency (EMA) reflects that they recognise possible non-equivalence and structural differences between reference products and biosimilar agents.

The manufacture of biologics and biosimilars follows the same broad steps: development of a host cell, establishment of a master cell

bank, production of protein, purification, analysis, and formulation prior to storage and handling.¹² Manufacturing of both biologics and biosimilars requires high levels of control over the organism used to prepare the molecules. The process of transcription and translation from DNA is a reliable process to create the proteins needed.

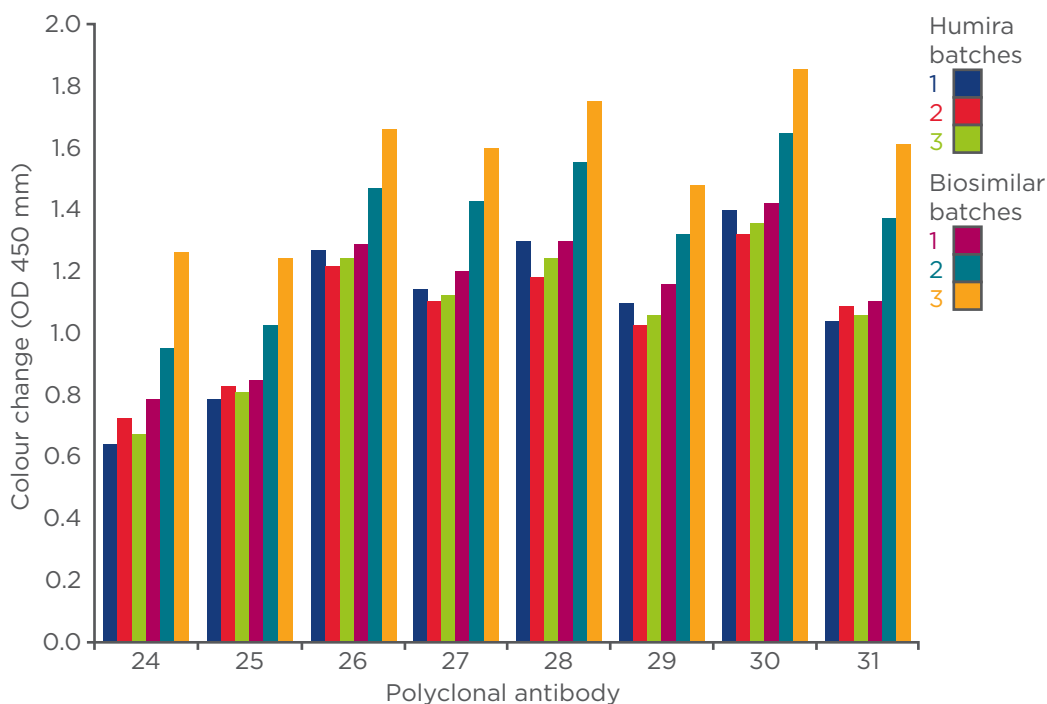


Figure 1: Inconsistencies between adalimumab and non-approved biosimilar monoclonal antibodies in the constant region-2.¹⁶

OD: optical density.

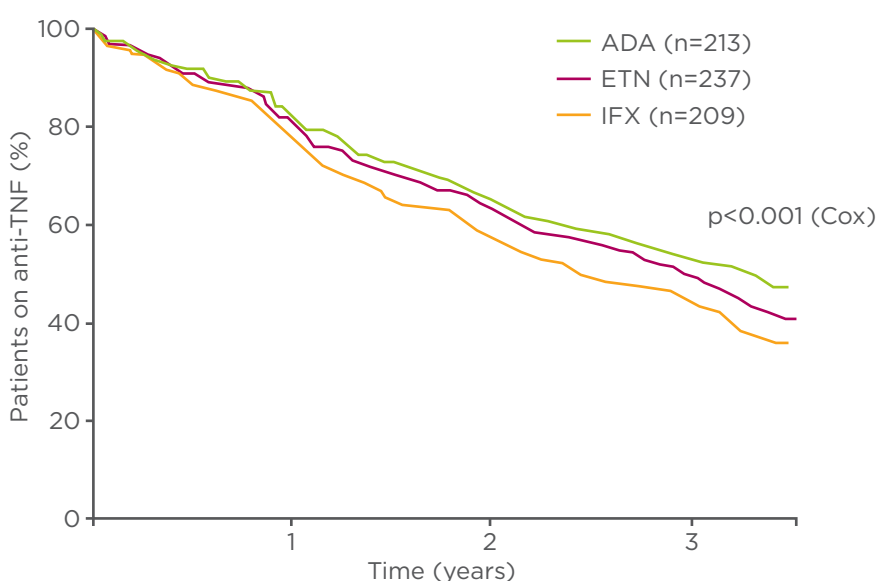


Figure 2: Comparison of drug retention rates between anti-tumour necrosis factor therapies in rheumatoid arthritis patients from the Swedish Clinical Quality Management - Rheumatoid Arthritis registry.²⁹

ADA: adalimumab; ETN: etanercept; IFX: infliximab; anti-TNF: anti-tumour necrosis factor.

Post-translational modification of proteins, however, is difficult to replicate and the sponsor of a biosimilar will never have access to the innovator's host cell. The addition of branched sugar molecules to proteins involves many different enzymes and follows no template.¹³ Glycoforms are glycoprotein molecules with the same protein component but different assemblies of sugar chains, hence why all antibodies produced are a complex mixture of products.¹⁴

The challenge for the manufacture of biosimilars is the lack of detailed, publicly available information regarding the manufacturing process of biologics. The synthesis of biologics often undergoes manufacturing changes over time for a variety of reasons, e.g. to upscale production; these manufacturing changes significantly differ from the biosimilarity exercise as for such small process changes, only quality and analytical studies are required to evaluate the product. The manufacture of biosimilars will have fundamental differences to biologics, such as a different cell-line and a knowledge gap in the synthesis process of the innovator. Regulators require comparative clinical studies to ensure that differences between biosimilars and the reference biologic do not translate into differences in efficacy and safety.¹⁵

The rapidly increasing numbers of manufacturers of biologics could affect product consistency. Many quality attributes are measured for biologics; an inherent drift in manufacturing is expected to either cause a divergence or convergence of these attributes. There are reports of inconsistencies between originator and non-approved versions of biosimilars in the literature. Wang et al.¹⁶ found differences in higher order structure comparability of adalimumab and biosimilar monoclonal antibodies in the constant region-2 using an antibody array enzyme-linked immunosorbent assay (ELISA) (Figure 1), with similar results on trastuzumab. These results raise concerns over variability in the antigenicity and therefore the potential immunogenicity of biosimilars.¹⁶ Independent research in the USA examined glycoforms of infliximab and biosimilar CT-P13 and reported differences between the two molecules related to the addition of fucose.¹⁷

In conclusion, biologics are larger and more complex than conventional chemical drugs, and can only be synthesised organically. Biosimilars cannot be described as generics, but as substances similar in structure to originator

biologics. The complex post-translational modifications of monoclonal antibody biologics create a key challenge for biosimilar manufacturers. Slight alterations in the manufacturing process can lead to clinically relevant changes, particularly related to potency. The imminent expiration of some key biologic patents is driving the increased development of less costly biosimilars. All biosimilars that come to the market, however, should be closely monitored and evaluated before and upon approval.

What We Know: Evidence on Long-term Data and Immunogenicity

Professor Edward Keystone

Numerous clinical trials have documented the long-term response of patients to anti-TNFs. The sustainability of biologics can be affected by a variety of factors including: the development of drug-drug antibodies, the combination of biologics with methotrexate, the number of biologics a patient has been treated with previously, baseline disease activity, and the nature of biologics in TNF inadequate responders. Early use of biologics can also have an impact on sustainability of response, with patients treated early tending to do better than those in whom treatment was delayed.¹⁸⁻²⁴

Vincent et al.²⁵ performed a systematic analysis of studies measuring the development of anti-drug antibodies to a range of anti-TNF biologics. For infliximab, the 26 studies analysed covered a range of rheumatic diseases and had a large variation in duration, ranging from 2 to >360 weeks. Anti-infliximab antibodies developed in 6-61% of all patients, and in 10-50% of RA patients, specifically. These numbers reflect those seen in the clinic with infliximab monotherapy. The other biologics analysed in the study, adalimumab, etanercept, certolizumab, and golimumab, also demonstrated a wide range in the rate of anti-drug antibodies developed.²⁵

Collectively, the data regarding anti-drug antibodies shows that all anti-TNF therapies may be associated with the appearance of such antibodies. However, the large variability in the number, design, and duration of studies assessing anti-drug antibodies, as well as the techniques used for detection, should be taken into account. Currently, there are a number of

methods available to detect anti-drug antibodies, ranging from standard direct/indirect enzyme-linked immunosorbent assays to homogenous mobility shift.²⁵⁻²⁷ The development of more sensitive methodologies has translated into an increase in the number of anti-drug antibodies detected. The study by Bartelds et al.²⁸ in 2011 assessed the effect of anti-adalimumab antibodies on sustained disease activity and remission in 200 patients. The results showed a significant correlation between anti-drug antibodies, clinical response, and sustainability of this response.²⁸

The durability of response to biologic treatment in rheumatologic diseases has been characterised; registration studies and surveillance databases provide ≥ 5 years of data*.²⁹⁻³¹ The ARTIS study reported higher discontinuation rates in infliximab-treated patients compared with adalimumab and etanercept. Etanercept showed the greatest sustainability with 55% of patients remaining on treatment at the end of 5 years.³¹ The DANBIO study of biologic monotherapy-treated patients also found that etanercept had the greatest adherence rate (56%) and infliximab the least (41%), at 4 years.³⁰ The Swedish Clinical Quality Management (SCQM)-RA registry reported significant differences in rates of discontinuation between anti-TNF therapies. However, in this study, adalimumab-treated patients showed the greatest attrition to therapy (Figure 2).²⁹

Long-term treatment with the biosimilar CT-P13 (biosimilar of the infliximab reference product) has been analysed in the PLANETRA study. The study reported clinical responses and immunogenicity in comparison with infliximab. At 54 weeks, the response was similar between both therapies, while 52.3% and 49.5% of CT-P13 and infliximab-treated patients were positive for anti-drug antibodies, respectively. Interestingly, both therapies displayed an approximate 20% decrease in American College of Rheumatology (ACR) criteria for 20% improvement (ACR20) response if either positive or negative for anti-drug antibodies.³² In the extension phase of the PLANETRA study, infliximab-treated patients were switched to CT-P13 for a further 48 weeks. At the end of study (102 weeks), the number of patients achieving ACR20 was similar between the CT-P13 maintenance group and the infliximab to CT-P13 switch group (71.7% and 71.8%, respectively). In the maintenance group, 40.3% of patients were positive for anti-drug antibodies,

compared with 44.8% in the infliximab to CT-P13 switched group.³³

In conclusion, rheumatic patients can achieve a sustained response with biologic therapies, and long-term data for anti-TNF biologics continue to emerge. The sustainability of anti-TNF biologics can be influenced by several factors, including immunogenicity. Due to the complex and evolving biologic treatment landscape, the challenge of how to clinically inform and follow up non-medical switching between therapies needs to be addressed, and more rigorous data are needed to inform patients with sustained clinical responses about non-medical switching.

What We Do Not Know: Data Generation Needs to Support Switching of Stable Patients

Professor Thomas Dörner

The definitions used to describe treatment of patients with biosimilars can vary between regulatory bodies, physicians, and pharmacists. 'Interchangeability' is a status given to a product and decided by regulatory agencies. The FDA define it as "an interchangeable biologic product, in addition to meeting the biosimilarity standard, is one that is expected to produce the same clinical result as the reference product in any given patient."³⁴ The European Commission however, explain it slightly differently as: "the medical practice of changing one medicine for another that is expected to achieve the same clinical effect in a given clinical setting and in any patient."³⁵

'Transitioning' and 'switching' are actions performed by physicians and describe a single transition of patients from a reference product to a biosimilar. The term 'substitution' refers to an action performed by pharmacists and is very different: "dispensing one medicine for another equivalent and interchangeable medicine at the pharmacy level without consulting the prescribing physician."³⁵

The need to medically-switch patients is common practice and has a strong evidence base.^{4,5,36} Non-medical switching involves changing stable patients either to different agents from the same class, or from a reference product to its biosimilar, or vice versa.⁶ The motivation behind such switches can range from the potential for cost savings and procurement policies to patient preference.⁷

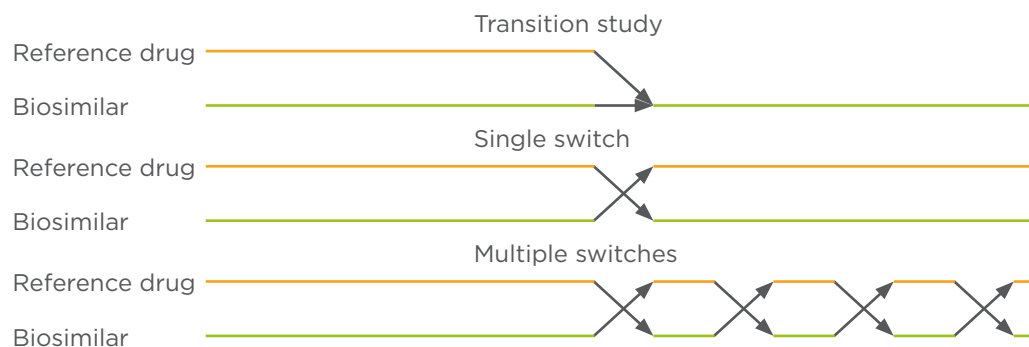


Figure 3: Study designs: transition, substitution, and interchangeability.³⁹

Reference products currently available have been uniquely identified and differ in mechanism of action; all have undergone the same full clinical development pathways required for regulatory approval.^{37,38} The number of biologics for the treatment of inflammatory and rheumatic diseases is expected to increase substantially in the near future, creating the clinical challenge of identifying the right drugs for patients at each stage of treatment.³⁹

A review by Ebbers et al.⁴⁰ analysed data from 12,039 patients, switched between either reference products or biosimilars of human recombinant growth hormones, erythropoietins, and granulocyte colony-stimulating agents. The study concluded that there are limited clinical data investigating the effects of switching and transitioning to biologics, and many of the identified studies were not designed to identify switching-related adverse events.⁴⁰ There is a need for substantive data and adequate post-marketing surveillance regarding non-medical switching. Currently, according to these results, there is no indication that switching impacts therapy safety and efficacy.

A study of non-medical switching from infliximab to adalimumab in 36 inflammatory bowel disease patients with Crohn's disease reported that 47% of switched patients required dose optimisation and 28% required treatment interruption, compared with 16% and 2%, respectively, in the 'continue on infliximab' group. The results suggest that adherence to the first anti-TNF is recommended if patients are stable.⁴¹

The British Society for Rheumatology (BSR) advises against summarily switching all patients to biosimilars, recommending that switching should only be undertaken on a case-by-case basis until further data are available to support the

approach.⁴² The ACR concurs, believing that there are too many unknowns about biosimilars to ensure that switching will be a safe practice.⁴³ However, guidance from the British Society of Gastroenterology (BSG) states that there is sufficient evidence to recommend switching for stable patients or those in remission on Remicade® therapy to Remsira® or Inflectra® at the same dose and dose interval.⁴⁴

There is increasing evidence regarding switching among reference products and biosimilars for several indications, including rheumatic diseases. However, the study designs between trials can vary widely, creating the need for robust data regarding switches and interchangeability to be generated.^{45,46}

Repeated switching between biosimilar and reference product may increase immunogenicity.⁴⁷ The interchangeability of reference products and biosimilars needs to be demonstrated by repeated switches between the two. This would require randomised controlled trials that include at least two switches and appropriate control groups (Figure 3).³⁹ However, such scenarios do not reflect common practice, and rigorous clinical studies to address aspects of non-medical switching cannot be expected.⁴⁸

Global post-marketing surveillance is needed to gain a better understanding of long-term efficacy and safety, as there could be limitations in pre-approval studies. Sufficient pharmacovigilance is needed to continually assess the risk-benefit profile of every drug and minimise the risks associated with their use.⁴⁹ Effective pharmacovigilance requires tracking, tracing, and analysis of specific products. However, the traceability of biologics and biosimilars poses novel challenges in pharmacovigilance. A clear naming system is needed, as well as robust systems to ensure

traceability through the pharmaceutical supply chain and efficient transfer of exposure information to pharmacovigilance data sources.^{50,51}

In conclusion, both reference products and their biosimilars are important expansions of treatment options for rheumatic diseases. Switching between different biologics, and even between versions thereof, is an emerging field, which may impact on pharmacovigilance requirements, and highlights the need for further study and awareness. Pharmacovigilance overall is critical, and requires exact identifiers; it may enable adverse effects or any other possible drug-related problems in clinical practice to be detected, assessed, understood, and prevented.

Question and Answer Session

If biologics are a mixture, why is there a fear of biosimilars working differently?

Dr Revers responded that contamination can be removed from biologic molecules, while it is a case of maintaining consistency in a product. He stated that the issue largely resides with the fact that comparisons were initially made between biosimilars and biologics, and the consistency needs to be maintained between them. This is particularly difficult for manufacturers when there are more than 30 entrants to the market. Dr Revers added that he is very open to biosimilars if they are tracked appropriately.

What is the difference between non-medical switching and interchangeability?

Prof Keystone clarified that the FDA definition of 'interchangeability' means patients can be switched from a reference product to a biosimilar and then

switched again, back to the reference product, and it is the pharmacist that makes the decision. Prof Keystone noted that it is a very difficult definition to achieve, and studies of switching both ways are needed, adding that currently the FDA has not given any of the products interchangeability status.

How do you explain the difference in terms of anti-drug antibodies? There were definitely more anti-drug antibodies with etanercept, 13% versus the biosimilar.

Prof Keystone felt that this is not currently clear. He stated that there are a lot of suggestions that maybe it is bad to switch etanercept due to anti-drug antibodies and that others say it is a detectability issue. He concluded that the answer is not known.

Are the data presented on availability of Humira and its biosimilar from products approved in the European Union, USA, or other countries?

Dr Revers stated that he was not sure how to answer. One of the interesting stories about biosimilars that emerged in the symposium is that manufacturers of originators are asked: 'How consistent are your products?', because if there are new companies making biosimilars, surely the manufacturers of the originators have been making changes to their product and therefore the product today is not the same as when it first launched. Examples have been seen that demonstrate the variability in products. Differences in etanercept have been noted between the USA and European Union, indicating changes from the originator product. Dr Revers commented on the imminent entrance of many biologics, and the need for each to be sufficiently tracked.

Footnotes

(*) 10-year data has also been published.²²

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