BIOLOGIC THERAPIES: CLINICAL PRACTICE IN A CHANGING ENVIRONMENT

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MEETING SUMMARY

Biological therapies have been in use for treating psoriasis for a decade now, and they have greatly improved disease outcomes and quality of life for patients. The success of biologic therapies has been assisted by the development of evidence-based guidelines for their use, and the achievement of consensus on treatment goals. The future of biologic therapies for psoriasis will be different from the past decade, with new anti-inflammatory targets for antibodies being developed and the increasing availability of biosimilar versions of existing antibodies as patents expire. While reduced costs may exert a pressure to switch to biosimilars, it is important to appreciate that they may not be identical in efficacy. Biologics are large, complex molecules, produced by biosynthetic means, which inherently lead to variations in structure. These slight variations in the manufacture of biologics can lead to clinically relevant changes in efficacy. As more biosimilars become available, their interchangeability becomes an important challenge for use in clinical practice, both between a biosimilar and the originator, and between two different biosimilars. Thus, robust trials of interchangeability are urgently needed. Caution in the use of an increased range of biosimilars will also be needed as switching between drugs can potentially increase immunogenicity and neutralise the drug's efficacy.

The introduction of biologic therapies has been a great achievement in the treatment of psoriasis. The new biologics and biosimilars coming into practice will need to be used with care, for which robust data on safety, efficacy, and interchangeability will be needed, as well as continuing pharmacovigilance.

The Biologics' Journey

Professor Matthias Augustin

Psoriasis treatment has changed greatly in the past decade. Before the introduction of biologic therapies, the majority of available treatments were topical, patients spent a long time (over a month) in hospital, and there were no evidence-based guidelines to provide a standardised approach to treatment. Today, psoriasis is a key disease in dermatology, and healthcare has improved markedly. Systemic treatment is standard, inpatient treatment

is rare, guidelines ensure optimisation of both topical and systemic treatment, and patient quality of life is much improved. Patient needs are now the driver for treatment goals,[1,2] and are used in the development of outcomes, instruments, and treatment pathways.[3-7] In Germany, improvements in psoriasis treatment and a reduction in patients with severe disease have been demonstrated over the last 10 years (PsoHealth 1, PsoHealth 2, PsoHealth 3; www.psonet.eu), a result of the implementation and regular review of goals and indicators for quality of care. The introduction of biologic therapies has played a key role in these improvements.

From 2005, with the first approvals of antibody therapies for psoriasis (efalizumab, etanercept, infliximab), to 2015, many more biologics have become available. Concurrently, guidelines to regulate their use, consensus on treatment goals, and registries (www.psonet.eu) to track long-term safety and efficacy have been implemented by the dermatology community to ensure that the best use is made of biologics as they are developed.[4,5] In the next decade, new developments in biologics and biosimilars will need to be incorporated into the goals and guidelines so that we continue to improve outcomes for our patients.

The past decade has also demonstrated the safety of tumour necrosis factor (TNF)-alpha antagonists in psoriasis. Long-term safety data for adalimumab from global clinical trials, including over 20,000 patients with a variety of immune-mediated inflammatory diseases, show a markedly positive safety profile for patients with psoriasis and psoriatic arthritis.[8] Rates of serious adverse events and serious infections were low, and mortality was similar to or lower than expected for the general population. A slightly higher incidence of malignancies in patients with psoriasis was confirmed by a Finnish study, which showed that risk for malignancy and comorbidity in psoriasis patients was altered compared with the general population.[9] European psoriasis registries, coordinated under the PsoNet organisation (www.psonet.eu), show no negative safety signals for adalimumab, or for TNF antagonists as a class, compared with systemic treatments.

The development of biosimilars is an area of growth for many pharmaceutical companies, due to the reduced cost of development compared with new drugs. How will the influx of biosimilars change healthcare for psoriasis? Further uptake of biosimilars will mostly depend on regulation and reimbursement. Treatment of biosimilars by regulatory agencies varies globally; while the EU has nearly 10 years of experience in licensing biosimilars, the US lags behind. Regulatory agencies require biosimilars to demonstrate similarity in quality, safety, and efficacy to a licensed reference biotherapeutic product in a clinical trial and in post-marketing surveillance, as the complex manufacturing process means that the biosimilar will not be identical to the reference product and it cannot be assumed to behave identically. The interchangeability of the biosimilar and reference product should also be addressed. The majority of payors have little knowledge of biosimilars, but according to a survey of German healthcare stakeholders,[10] the potential for less costly biosimilars to generate savings in healthcare systems is being explored.[11] There may be pressure from payors to make greater use of biosimilars through prescribers' budgets, and dermatologists will need to balance this pressure against patient needs. Treatment guidelines are now being rewritten to address the issues and opportunities in adopting biosimilars.

Structure to Function: The Importance of Consistency

Professor Leigh Revers

Biologics are important and highly effective in the treatment of psoriasis and other immune-mediated inflammatory diseases.[12] Biologic drugs are active pharmaceuticals synthesised by living organisms, consisting of large whole proteins and complex assemblies, and cannot be synthesised chemically. This has important implications for their use, and for producing copies of them, i.e. biosimilars. With the upcoming expiry of a number of patents for successful biologics, many competitors will look to profit from making their own versions.

Biologics are largely therapeutic monoclonal antibodies, and the precise way in which these most complex of drugs exert their clinical effects is not fully understood. Infliximab and adalimumab bind soluble TNF-alpha, preventing downstream signalling responses such as cytokine release, apoptosis, T cell activation, or inflammation. However, they can also act on membrane-bound TNF-alpha, triggering effects such as antibody-dependent cell-mediated cytotoxicity.[13] These differing mechanisms of TNF-alpha inhibition all contribute to the efficacy of the biologic in a

patient, and patients will vary in their response, depending to some extent upon their particular genetic polymorphisms. This degree of unpredictability in the efficacy of the reference biologic creates an additional challenge when attempting to demonstrate that a different manufacturer's version, which is known to contain minor but detectable compositional differences, has the same therapeutic value.

There are crucial differences between small-molecule drugs and biologics, which are important when considering biosimilars in comparison with generic drugs. Small-molecule drugs are simple, uniform, chemically synthesised structures, whose molecular structures are predictable and straightforward to characterise. Biologics are large, complex, heterogeneous molecules produced by living organisms (i.e. they are mixtures), whose three-dimensional structure is more easily perturbed; their chemical structures are variable and far more difficult to characterise completely. Monoclonal antibodies, in particular, are especially large molecules; all of these proteins undergo post-translational modification when produced by cells, resulting in a range of versions with different sugar chains attached (known as glycoforms).[14] Such post-translational glycosylation has been found to affect the potency of monoclonal antibodies (Figure 1).[15] This has raised concerns that differences in the relative proportions of glycoforms among biosimilars and the reference biologic may lead to differences in efficacy in individual disease settings, as exemplified by Health Canada's ruling that restricts the indications for a biosimilar of infliximab.[16] In some cases, engineered glycosylation may improve the clinical activity of a biologic, as in the case of lenograstim, a glycosylated version of filgrastim. These biologics that have been altered for improved clinical performance are sometimes referred to as 'biobetters'.[17]

Importantly, post-translational modifications are known to be highly sensitive to changes in the manufacturing process, and process variations between one manufacturer and another are inevitable. Thus, even slight alterations in manufacturing processes can lead to clinically relevant changes in potency or efficacy, the effects of which can range from benign to severe.[18,19] Manufacturers of reference products, such as adalimumab, have recently begun publishing manufacturing consistency data over the product's lifecycle. It has yet to be seen whether biosimilar manufacturers can achieve a similar level of consistency. With the emergence of multiple manufacturers of biosimilars, there is the inherent potential for divergence among these drugs as manufacturing drift occurs over time, which could be a future problem for clinicians (Figure 2).

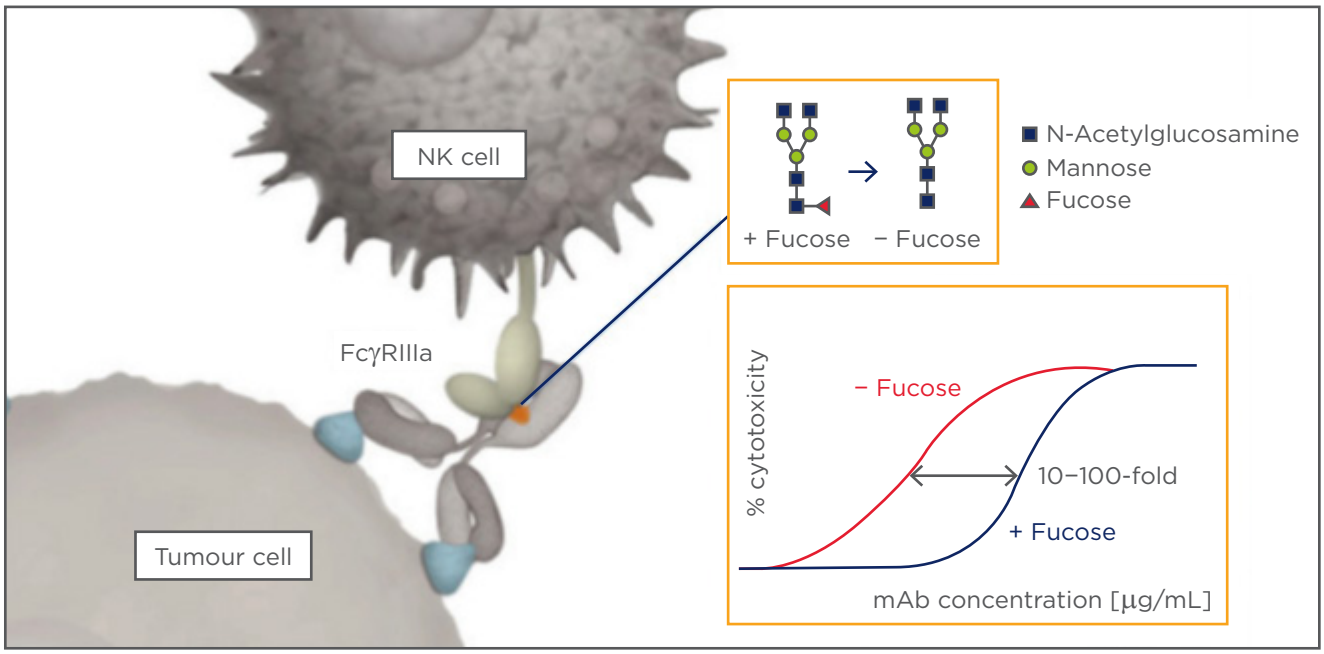

Figure 1: Differences in glycoforms can affect the potency of antibody-dependent cell-mediated cytotoxicity, as shown here in the recruitment of natural killer (NK) cells to the site of a tumour.[15]
mAb: monoclonal antibody.

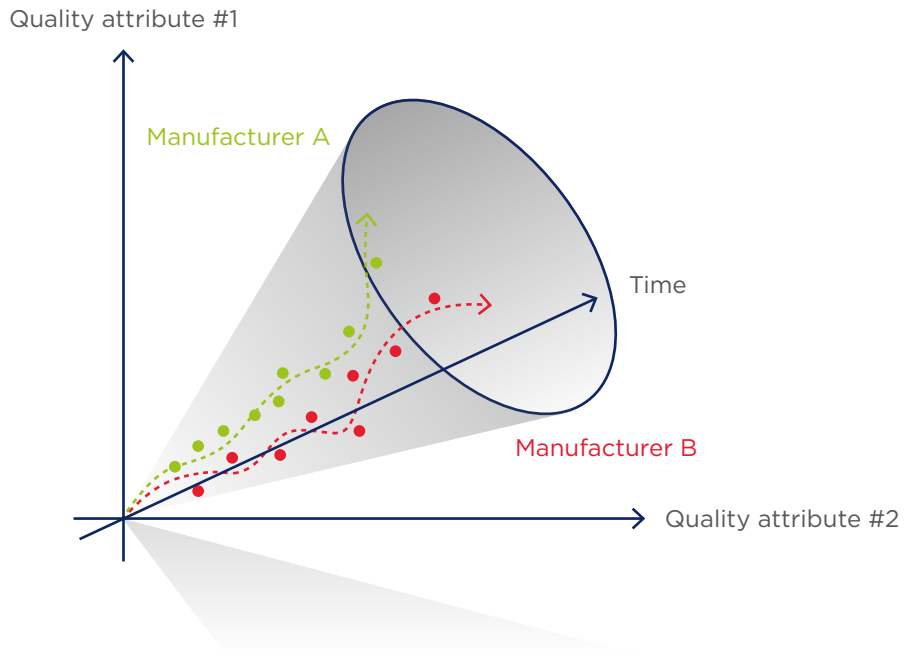

Figure 2: Multiple manufacturers' inherent drift will cause divergence in product structure.

With large numbers of biosimilars anticipated in the near future, there will be an increased need for regulatory vigilance to ensure the continued consistency of these products over the long term.

In summary, biosimilars are not generics: they are far larger and more complex. The challenge for the manufacturers is to ensure continued, parallel product consistency into the future, and, as more biologic therapy patents expire over the next 5 years, this will become an extremely important issue.

The Changing Environment – What Does This Mean for Clinical Practice?

Professor Luis Puig

The increasing availability of biosimilars to established biological therapies for psoriasis expands clinicians' choice, but how can we make the right treatment choices? There is a need to understand the comparability of biosimilars and for evidence to support switching from one to another. The European Medicines Agency (EMA) requires a full clinical trial to demonstrate safety and efficacy for each indication of a new biologic therapy, whereas for biosimilars the key regulatory requirement is availability of clinical data to prove comparable safety and efficacy to the reference biologic.[20] While interchangeability with the originator product is inherent in generic drugs due to the reproducibility of their manufacture, granting of biosimilar status by a regulatory body does not necessarily imply interchangeability.[21-23] There is a large number of biosimilars in development and approaching registration; therefore we need to be able to assess how to use them in practice.

For clinicians, an important issue in clinical practice is that of switching from a reference biologic to a biosimilar (or vice versa), or from one biosimilar to another (although from regulatory requirements a biosimilar can only be considered similar to the reference product and not to any other biosimilar). Patients may be switched due to failure of a biologic, i.e. inadequate response or intolerable adverse events, to a different biological agent, either within the same class (e.g. anti-TNF monoclonal antibody) or to a different class, which can be safe and effective.[24-27] However, switching from a reference biologic to its biosimilar (or vice versa) when there is a lack of efficacy is not sensible because the antidrug antibodies (ADA) underlying the loss of efficacy will cross-react with the biosimilar.[28,29] Non-medical switching, when a patient is switched to a different biologic or biosimilar although their current therapy is effective and well tolerated, is usually a result of intended cost savings or patient preference.[30] There are very few clinical data for this situation, making it difficult to assess the clinical and health economic consequences of this practice.[31] While the available data

(mainly for epoetin) suggest that switching seems to be relatively safe, it is difficult to design large trials to prove the absence of adverse effects due to non-medical switching of biosimilars. However, some trials suggest that non-medical switching may be associated with loss of response and increased healthcare utilisation.[32,33]

Assessing the interchangeability and automatic substitution of biosimilars is an important issue. The FDA requires biosimilar manufacturers to demonstrate that switching between a biosimilar and its reference product during the course of treatment does not cause loss of efficacy or safety issues. An interchangeable biologic can be substituted by a pharmacist for its reference without prior permission from the original prescriber. The EMA, however, does not evaluate interchangeability. A review of switching in clinical trials within the classes of erythropoetin, growth hormone, or granulocyte colony-stimulating factor concluded that patients could be safely switched from one product to another, but the data in this study were limited. Studies were generally too short to identify any long-term side effects, and the trials were not designed to identify switching-related adverse events.[34] More data are needed from appropriately-designed trials.

Study designs to compare the efficacy of reference drugs and biosimilars include transition studies, from the reference to the biosimilar; substitution studies, with a single crossover between biosimilar and reference; and interchangeability studies, with multiple switches between biosimilar and reference.[35] Studies evaluating a single-sided switch from the reference product to the biosimilar cannot be regarded as demonstrating interchangeability or switching. The ongoing NOR-SWITCH study is one such example, which aims to investigate potential differences in the rate of loss of response between patients continuing to receive infliximab and those switched to a biosimilar (NCT02148640, www.clinicaltrials.gov). The use of transition study design and the total of 250 patients in each arm means that the rate of loss of response in the two arms could be as different as 11% and 30% and still be considered statistically comparable. The PLANETAS open-label study extension, also a transition study, concluded that there was no significant difference between infliximab and a biosimilar in the development of ADA and loss of efficacy, although the data do suggest a trend towards a difference between the reference and the biosimilar.[36] The question of the level of difference we would consider adequate to demonstrate no change in safety and efficacy is yet to be resolved. Furthermore, while biosimilars are each compared with their reference product, studies comparing one biosimilar to another are not performed, making it difficult to know whether switching between biosimilars is safe.[37]

Repeated switches between biosimilars and originators may increase immunogenicity with potentially negative effects.[29] Immune responses to a biologic can influence its safety and efficacy,[38] and cannot be predicted from the chemical characterisation of the product.[28] Switching and intermittent exposure to a biologic is prone to increase immunogenicity,[28] and psoriasis (or its treatment with biologics in monotherapy) may be associated with a higher risk of immunogenicity than other immune-mediated inflammatory diseases.[39] Data from a comparison of infliximab and a biosimilar in patients with inflammatory bowel disease suggest that there is likely to be cross-reactivity.[40] Immunogenicity should always be assessed in switching studies, as it can cause serious adverse events, as well as drug neutralisation and loss of efficacy. Differences in immunogenicity are best determined by immunogenicity analysis in the most immunocompetent patient population.[41,42]

Traceability will be important for pharmacovigilance in order for adverse events developing after several months of treatment to be correctly attributed. This will be possible only through large pharmacovigilance databases and through specific studies and registries, as well as the use of individually identifiable product names and batch numbers.[43] However, centralised databases may not be available in many countries, and problems with reliable labelling do occur, such as with a recent withdrawal of an incorrectly labelled infliximab biosimilar in Spain. Given the limitations of post-authorisation data, it is currently not possible to conclude an absence of risk for switching between biologics and originators.[29,34] Therefore, more trial data are needed for us to use the upcoming range of biosimilars confidently in clinical practice.

Q&A session

How do you foresee potential divergence in structure in a world with several biosimilar manufacturers?

Prof Revers replied that it will be a challenge to the regulatory agencies. Healthcare professionals would have a role to play in ensuring that the use of individual biosimilars is tracked when products

are substituted; lot numbers will be important in tracking any problems that may arise due to subtle structural differences in the biosimilars. Manufacturers with a great deal of experience in producing biologics are likely to be able to meet regulatory requirements, and one might have greater confidence in their biosimilars.

My hospital has mandated a switch for all patients on a biologic to a biosimilar – is this a good idea, and what should I watch out for?

Prof Puig replied that it depended on the balance of cost savings versus the risk of losing drug response or immunogenicity of adverse events.

How are different batches and biosimilars captured in registries?

Prof Puig replied that, in Spain, the trade names are used. Prof Augustin agreed that this was also the case in Germany but that unfortunately they did not have the means to record batch numbers.

Doesn't the monitoring of critical quality attributes by manufacturers maintain consistency between lots and prevent the divergence referred to by Prof Revers?

Prof Revers responded by questioning what should be considered to be a critical quality attribute for the biosimilars. A quality attribute is something that is measured physically or chemically for a molecule, and the problem with monoclonal antibodies is that we are not completely sure how they work so it is difficult to determine a set of critical quality attributes. He suggested that some divergence is essentially unavoidable over time, which is why tracking batches of different manufacturers' biosimilars is important.

Will biologics be chemically synthesised in the future?

Prof Revers replied that, while synthesising single chain proteins was possible, it is expensive, and the synthesis of complex structures including antibodies was still at least 15 years away.

Do you think that the guidelines will need to be rewritten now that we have biosimilars?

Prof Puig replied that they would have to be adapted, since, if the regulatory agencies have approved a biosimilar, it can be used.

Should we preserve what we have achieved in the last decade and move forward only when we have solid clinical evidence, in particular for patients with good disease control?

Prof Puig replied that it depended on the healthcare system, and the problem of gaining evidence was that in some cases the population size that would be required would be too great. Prof Revers added that he thought in the future there may be less reliance on complex monoclonal antibodies, and that smaller chemical drugs would be developed that targeted the same mechanisms and have the same clinical effect while reducing some of the problems such as cross-reactivity and variation in production.

In Europe, why haven't authorities like the EMA considered the issues of interchangeability?

Prof Revers replied that the risks with switching biologics and issues with interchangeability were always a concern with such complicated biological molecules, and that this might be part of the reason why the FDA has taken so long to develop guidelines.

REFERENCES

1. Augustin M et al. The patient benefit index: a novel approach in patient-defined outcomes measurement for skin diseases. Arch Dermatol Res. 2009;301:561-71.

2. Blome C et al. Dimensions of patient needs in dermatology: subscales of the patient benefit index. Arch Dermatol Res. 2011;303:11-7.

3. Augustin M et al. Routine skin cancer screening in Germany: First data on the impact on health care in dermatology. J Dtsch Dermatol Ges. 2010;8:674-80.

4. Mrowietz U et al. Definition of treatment goals for moderate to severe psoriasis: a European consensus. Arch Dermatol Res. 2011;303:1-10.

5. Nast A et al. [S3-Guidelines for the therapy of psoriasis vulgaris]. J Dtsch Dermatol Ges. 2006;4 Suppl 2:S1-126.

6. Radtke MA et al. Evaluation of quality of care and guideline-compliant treatment in psoriasis. Development of a new system of quality indicators. Dermatology. 2009;219:54-8.

7. von Kiedrowski R et al. Psoriasis mit Gelenkbeteiligung – Ein interdisziplinärer Leitfaden für die Diagnosestellung und Therapie. Der Dtsch Dermatol. 2013;3:Supplement.

8. Burmester GR et al. Adalimumab: long-term safety in 23 458 patients from global clinical trials in rheumatoid arthritis, juvenile idiopathic arthritis, ankylosing spondylitis, psoriatic arthritis, psoriasis and Crohn's disease. Ann Rheum Dis. 2013;72:517-24.

9. Hannuksela-Svahn A et al. Psoriasis, its treatment, and cancer in a cohort of Finnish patients. J Invest Dermatol. 2000;114:587-90.

10. HEXAL. [HEXAL launches information campaign "Biosimilars create space"

Current poll: healthcare players misjudge savings.] Available at: http://www.hexal.de/presse/pressemeldungen/show_pressemeldung.php?start=1&selected_kat=14&which=723. Last accessed: 16 November 2015.

11. Haustein R et al. Saving money in the European healthcare systems with biosimilars. GaBI J. 2012;1:120-6.

12. Taheri A, Feldman SR. Biologics in Practice: How Effective Are Biologics? The Dermatologist. 2012;20(11).

13. Tracey D et al. Tumor necrosis factor antagonist mechanisms of action: a comprehensive review. Pharmacol Ther. 2008;117:244-79.

14. Rudd PM et al. The glycosylation of the complement regulatory protein, human erythrocyte CD59. J Biol Chem. 1997;272:7229-44.

15. ProBioGen. GlymaxX®: Elegant Glyco-Engineering to Boost the ADCC Activity of Antibodies. Available at: http://www.probiogen.de/innovative-technologies/adcc-enhancement.html. Last accessed: 16 November 2015.

16. Health Canada. Summary Basis of Decision (SBD) for Remsima. Available at: http://www.hc-sc.gc.ca/dhp-mps/prodpharma/sbd-smd/drug-med/sbd_smd_2014_remsima_160195-eng.php. Last accessed: 16 November 2015.

17. Weise M et al. Biosimilars-why terminology matters. Nat Biotechnol. 2011;29:690-3.

18. Chirino AJ, Mire-Sluis A. Characterizing biological products and assessing comparability following manufacturing changes. Nat Biotechnol. 2004;22:1383-91.

19. Revers L, Furczon E. An introduction to biologics and biosimilars. Can Pharm J. 2010;143:184.

20. Krishnan A et al. Global regulatory landscape of biosimilars: emerging and established market perspectives. Biosimilars. 2015;5:19-32.

21. European Medicines Agency. Questions and answers on biosimilar medicines (similar biological medicinal products). Available at: http://www.ema.europa.eu/docs/en_GB/document_library/Medicine_QA/2009/12/WC500020062.pdf. Last accessed: 16 November 2015.

22. Health Canada. Guidance for sponsors: information and submission requirements for subsequent entry biologics (SEBs). Available at: http://www.hc-sc.gc.ca/dhp-mps/brgtherap/applic-demande/guides/seb-pbu/seb-pbu_2010-eng.php. Last accessed: 16 November 2015.

23. Ministry of Health, Labour and Welfare. Guidelines for the Quality, Safety and Efficacy Assurance of Follow-On Biologics. Available at: http://www.pmda.go.jp/files/000153851.pdf. Last accessed: 16 November 2015.

24. D'Haens GR et al. The London Position Statement of the World Congress of Gastroenterology on Biological Therapy for IBD with the European Crohn's and Colitis Organization: when to start, when to stop, which drug to choose, and how to predict response? Am J Gastroenterol. 2011;106:199-212.

25. Ormerod AD. Switching biologics for psoriasis. Br J Dermatol. 2010;163:667-9.

26. Singh JA et al. 2012 update of the 2008 American College of Rheumatology recommendations for the use of disease-modifying antirheumatic drugs and biologic agents in the treatment of rheumatoid arthritis. Arthritis Care Res (Hoboken). 2012;64:625-39.

27. Smolen JS et al. EULAR recommendations for the management of rheumatoid arthritis with synthetic and biological disease-modifying antirheumatic drugs: 2013 update. Ann Rheum Dis. 2014;73:492-509.

28. Schellekens H. Bioequivalence and the immunogenicity of biopharmaceuticals. Nat Rev Drug Discov. 2002;1:457-62.

29. Scott BJ et al. Biosimilar monoclonal antibodies: A Canadian regulatory perspective on the assessment of clinically relevant differences and indication extrapolation. J Clin Pharmacol. 2015;55 Suppl 3:S123-32.

30. European Commission. Market Access and Uptake of Biosimilars. Consensus Information Paper 2013. What you need to know about Biosimilar Medicinal Products. Available at: http://ec.europa.eu/DocsRoom/documents/8242/attachments/1/translations/en/renditions/native. Last accessed: 16 November 2015.

31. Reynolds A et al. When is switching warranted among biologic therapies in rheumatoid arthritis? Expert Rev Pharmacoecon Outcomes Res. 2012;12:319-33.

32. Rubin DT et al. Analysis of outcomes after non-medical switching of anti-tumor necrosis factor agents. Abstract SAT0139. EULAR 2015, 10–13 June 2015.

33. Van Assche G et al. Switch to adalimumab in patients with Crohn's disease controlled by maintenance infliximab: prospective randomised SWITCH trial. Gut. 2012;61:229-34.

34. Ebbers HC et al. The safety of switching between therapeutic proteins. Expert Opin Biol Ther. 2012;12:1473-85.

35. Dorner T, Kay J. Biosimilars in rheumatology: current perspectives and lessons learnt. Nat Rev Rheumatol. 2015;doi:10.1038/nrrheum.2015.110. [Epub ahead of print.]

36. Park W et al. Efficacy and Safety of CT-P13 (Infliximab Biosimilar) over Two Years in Patients with Ankylosing Spondylitis: Comparison Between Continuing with CT-P13 and Switching from Infliximab to CT-P13. Arthritis Rheum. 2013;65:L15-1331.

37. World Health Organization. Programme on International Nonproprietary Names. 56th Consultation on International Nonproprietary Names for Pharmaceutical Substances. INN Working Doc. Available at: http://www.who.int/medicines/services/inn/56th_Executive_Summary.pdf?ua=1. Last accessed: 16 November 2015.

38. Reinisch W, Smolen J. Biosimilar safety factors in clinical practice. Semin Arthritis Rheum. 2015;44:S9-15.

39. Garces S et al. The immunogenicity of anti-TNF therapy in immune-mediated inflammatory diseases: a systematic review of the literature with a meta-analysis. Ann Rheum Dis. 2013;72:1947-55.

40. Ben-Horin S et al. Cross-immunogenicity: antibodies to infliximab in Remicade-treated patients with IBD similarly recognise the biosimilar Remsima. Gut. 2015. [Epub ahead of print].

41. Choy E, Jacobs IA. Biosimilar safety considerations in clinical practice. Semin Oncol. 2014;41 Suppl 1:S3-14.

42. Mould DR, Green B. Pharmacokinetics and pharmacodynamics of monoclonal antibodies: concepts and lessons for drug development. BioDrugs. 2010;24:23-39.

43. Puig L et al. Biosimilars in Dermatology: Current Situation (Part II). Actas Dermosifiliogr. 2015;106:550-4.