Australian Government

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Literature Review of International Biosimilar Medicines: Update March – May 2017

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Sponsor:	National Medicines Policy Section
	Department of Health
	Australian Government

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Version: FINAL

Release Date: 19 September 2017

Introduction

This report provides an update to the comprehensive literature search previously conducted that examined all international and Australian clinical, academic and policy journals and media articles or sources in relation to biosimilar medicines for the purpose of providing evidence which may inform policy development and the communication activities of the Australian Government's Biosimilar Awareness Initiative (the Initiative).

The broad objectives are to provide a review of the literature pertaining to:

- current international polices on biosimilar medicines;
- status of biosimilar use and substitution internationally;
- any current programmes aimed at increasing the uptake or confidence in biosimilars (and an evaluation of their success);
- biosimilar uptake and substitution; and
- impact of biosimilars (if any) on adverse events and health outcomes.

The five stated broad objectives for the review relate to four stages that influence biosimilar use; that is, the national and international regulatory environment that is the foundational determinant of biosimilar availability and associated switching and substitution (Policy); the subsequent uptake of biosimilars by prescribers, pharmacists and patients (Uptake); outcomes resulting from the use of biosimilars outside of the clinical development pathway (Outcomes); and finally the stakeholder perceptions that influence uptake, including the factors that modify these perceptions such as advocacy and associated programmes (Perceptions).

Figure 1: Stages influencing biosimilar uptake and use
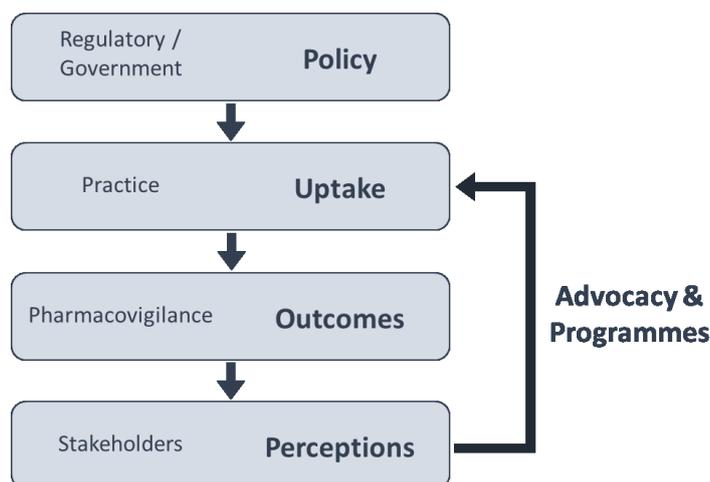
In the context of this review it is critical to appreciate that the fundamental central factor to each of these areas is the potential uncertainty that exists in evidence regarding substitution, switching and extrapolation of indication, which is unique to the consideration of biosimilar medicines. This potential uncertainty originates from the highly complex nature of these medicines and the clinical development pathway of biosimilar medicines that extends from initial laboratory-based characterisation (protein structure, pharmacokinetics, etc.) through to the design and conduct of phase III clinical trials to provide evidence of similarity in clinical safety and efficacy in specific patient populations. The considerations involved in each

of these steps are significantly different to those associated with traditional small molecule drugs with which governments, regulators, prescribers, pharmacists and patients are well accustomed. In reflection of this, the following central themes have been identified:

1. Determining Access and Subsidisation: Regulatory, Government and Healthcare Provider Considerations of Biosimilar Medicines

2. Biosimilar Medicine Uptake: Current Practice of Prescribers, Pharmacists and Patients

3. Adverse Events and Health Outcomes of Biosimilar Medicines (Pharmacovigilance): Impact of Substitution, Switching and Extrapolation of Indication

4. Evaluating and Improving Stakeholder Biosimilar Awareness, Confidence, Attitudes and Acceptance of Biosimilar Medicine

Overview of the Published Biosimilar Literature

This report includes literature published between 27 March 2017 and 31 May 2017.

Given the nature of the publications on biosimilars, it is not possible to differentiate articles of an educational nature or those pertaining specifically to biosimilar development from those that specifically seek to contribute new knowledge to the topic, and as such are pertinent to this review, through the use of specific search terms or exclusion criteria. Therefore, filtering of publications relevant to this review through hand-searching was necessary.

Analysis of these manuscripts identifies the following broad types of contributions:
- Education pieces and literature reviews
- Commentaries and individual opinion pieces
- Preclinical characterisation of potential biosimilar medicines
- Technical/methodological development
- Clinical trials of potential biosimilar medicines
- Investigator-initiated studies and case series

Consistent with the observations of the prior review, within the time period encompassed by this update there has continued to be a significant number of papers published that were of an educational or review nature. As discussed previously, these manuscripts have not specifically sought to extend or expand the knowledge base in this area but instead restate what is already known or identified as uncertainties in order to inform the reader of these issues. Some manuscripts provide a broad, relatively superficial, overview of biosimilar medicines. Other manuscripts provide an in-depth review of specific biosimilar medicines reporting only on previously published data but not contributing new information. In the context of this review, these papers do not contribute meaningfully to the specific aims of the Initiative; however, they play an important role in propagating the general understanding within the broader scientific and medical communities. A list of manuscripts of this nature published during the period encompassed by this update is provided in Appendix 1.

Within this quarter there has again been a significant number of manuscripts published that focus upon fundamental and technological issues relating to the production and characterisation of biological agents, including the statistical approaches to these assessments. The regulatory pathway for biosimilar

medicines is built upon the rigorous and extensive characterisation of the physicochemical (e.g. amino acid sequence, glycosylation pattern) and pharmacological properties (e.g. target binding) of the potential biosimilar medicine in comparison with the reference product. Due to the highly detailed and technical nature, the specific content of which is outside of the scope of the communication aims of the Initiative, these manuscripts will not be discussed in greater detail in this review. A list of manuscripts of this nature published during the period encompassed by this update is provided in Appendix 2. However, the results of this extensive characterisation and comparison process provides the critical foundation upon which potential biosimilar medicines can then be subjected to further clinical evaluation in the phase I and phase III trials that are reported upon in Theme 1 of these reviews.

This update period has seen the publication of the much awaited NOR-SWITCH study [1]. NOR-SWITCH was a phase 4 randomised, non-inferiority, double-blind trial with 52 weeks of follow-up that aimed to specifically assess the efficacy, safety, and immunogenicity of switching from originator infliximab to biosimilar infliximab (CT-P13). NOR-SWITCH provides high quality evidence of the outcomes associated with switching from originator infliximab to biosimilar infliximab (CT-P13). The study is described in detail in Theme 3 of this update. Also published within this update period and presented within Theme 3, are four large, nation-wide or multicentre, observational studies reporting on the outcomes of switching patients from originator infliximab to biosimilar infliximab [2-5]. The results of these observational studies complement the findings of NOR-SWITCH and add to the growing body of evidence related to switching between originator infliximab and CT-P13.

THEME 1: Determining Access and Subsidisation: Regulatory, Government and Healthcare Provider Considerations of Biosimilar Medicines

In the development and regulatory evaluation process of potential biosimilar medicines, compounds that demonstrate appropriate results in the extensive physicochemical and pharmacological characterisation are then subjected to clinical evaluation in phase I studies to compare their pharmacokinetic (PK) characteristics with those of the reference product. As these studies are specifically designed to assess pharmacokinetic endpoints these studies are typically conducted in healthy volunteers but may be conducted in patients depending upon a range of factors such as the potential risks associated with the use of the agent.

During the current update period three phase I pharmacokinetic studies comparing a potential biosimilar medicine with a reference product were reported. In each of the trials reported, the potential biosimilar met the pre-specified acceptance criteria for the relevant pharmacokinetic/pharmacodynamic parameter endpoints. A summary of the results of these studies are presented in the table below (Table 1).

Table 1: *Summary of phase I pharmacokinetic studies of potential biosimilar medicines*

Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
Etanercept						
LBEC0101 (LG Chem Ltd)	Enbrel 25mg	Randomised, double-blind, single dose, two-treatment, crossover study	Healthy volunteers (Korean males, n=43 completed PK analysis)	90% CI for the ratio of treatment means for area under the concentration-time curve from time zero to the last quantifiable concentration (AUC_{last}), area-under-the-curve from time zero extrapolated to infinite time (AUC_{inf}) and maximal plasma concentration (C_{max}) were within the pre-specified limits of 80-125% for the comparison between LBEC0101 and Enbrel	All subjects were anti-drug antibody (ADA) negative before the first dose. Five subjects showed a positive ADA result after conduct of Period 1, of which 1 received LBEC0101 and 4 received Enbrel. An additional 2 subjects showed a positive ADA results after conduct of Period 2, both of which received Enbrel. The incidence of ADA development was not significantly different between the treatments.	[6]
Trastuzumab						
ABP 980 (Amgen Inc)	US and EU Herceptin (trastuzumab)	Randomised, single-blind, single dose, three-arm, parallel group study (1:1:1)	Healthy volunteers (n=148)	90% CI for the ratio of treatment means for area under the concentration-time curve from time zero to the last quantifiable concentration (AUC_{last}), area-under-the-curve from time zero extrapolated to infinite time (AUC_{inf}) and maximal plasma concentration (C_{max}) were within the pre-specified limits of 80-125% for the comparisons of ABP 980 with US Herceptin and ABP 980 with EU Herceptin, as well as for US and EU Herceptin.	There were no pre-existing binding ADAs detected at baseline and no subjects developed binding or neutralising ADAs at the end of the study.	[7]

Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
Bevacizumab						
BS-503a (Daiichi Sankyo Co Ltd)	Avastin	Randomised, double-blind, single dose, two-arm, parallel group study (1:1)	Healthy volunteers (n=113)	90% CI for the ratio of treatment means for area under the concentration-time curve from time zero to the last quantifiable concentration (AUC_{last}), area-under-the-curve from time zero extrapolated to infinite time (AUC_{inf}) and maximal plasma concentration (C_{max}) were within the pre-specified limits of 80-125%.	All subjects were ADA negative at baseline. ADAs were detected in all samples on Day 14, except for one subject in the Avastin group. On Day 78, 7 subjects from the BS-503a group and 6 subjects from the Avastin group remained ADA positive.	[8]

Potential biosimilar medicines that demonstrate appropriate pharmacokinetic parameters in phase I studies are then subject to phase III clinical trials to evaluate efficacy and safety outcomes in comparison with the reference product. Within the update period there was a single report describing the clinical outcomes obtained in phase III clinical trials of a potential biosimilar pegfilgrastim.

❖ Harbeck et al, 2017: Proposed biosimilar pegfilgrastim (LA-EP2006) compared with reference pegfilgrastim in Asian patients with breast cancer: an exploratory comparison from two Phase III trials [9]

Previously, two prospective, double-blind, randomised phase III trials (PROTECT-1 and -2) demonstrated similar efficacy and safety of the proposed biosimilar pegfilgrastim (LA-EP2006) compared with reference pegfilgrastim (Neulasta®) in patients with breast cancer receiving neoadjuvant or adjuvant chemotherapy treatment with TAC (docetaxel, doxorubicin and cyclophosphamide). This study presents a pooled subgroup analysis of patients of Asian ethnicity enrolled in these two studies based on classification according to the US FDA Guidance for Industry Collection of Race and Ethnicity Data in clinical trials. Eligible patients were randomised 1:1 to be administered either LA-EP2006 or reference pegfilgrastim as a 6mg subcutaneous injection on Day 2 of each chemotherapy cycle. The primary efficacy endpoint was the duration of severe neutropenia (DSN) defined as number of consecutive days with grade 4 neutropenia (ANC <0.5 x 10^9/L) during the first chemotherapy cycle. A total of 174 Asian patients were identified from the PROTECT-1 and PROTECT-2 studies and included in the subgroup analysis data set (LA-EP2006 n=90; reference pegfilgrastim n=84). During Cycle 1, the mean DSN were 1.36 ± 0.98 days for LA-EP2006 treated patients and 1.35 ± 1.06 days for reference pegfilgrastim treated patients; the difference in DSN between the groups was 0.01 days (95%CI -0.30 – 0.32), indicating statistical equivalence. Treatment emergent adverse events (TEAE) were similar across the groups, with 96.7% of the LA-EP2006 group and 97.6% of the reference pegfilgrastim group reporting a TEAE. TEAEs considered related to the study treatment were reported in 27.8% of LA-EP2006 treated patients and 21.4% of reference pegfilgrastim treated patients. Immunogenicity results were similar with no post-dose binding or neutralizing anti-drug antibodies (ADAs) detected in any patients at any time. The authors concluded that "*in Asian patients with breast cancer receiving cytotoxic chemotherapy, LA-EP2006 showed similar clinical efficacy and safety compared with reference pegfilgrastim*" and that "*These data were similar to those observed in the overall study population, and with those observed with other studies in Asian populations*".

Once biosimilarity of the new product against the reference has been established through phase I and III trials, it is the national and international regulatory environment that is the foundational determinant of use. Within this quarterly update period, three publications were identified that related to this topic which examined the economic impact of the introduction of a biosimilar within a local region; while these papers do not specifically relate to policy, the cost of treatment is a strong determinate informing policy relating to biosimilar access and use.

❖ Gulacsi et al, 2017: The Rituximab Biosimilar CT-P10 in Rheumatology and Cancer: A Budget Impact Analysis in 28 European Countries [10]

This study, funded by Celltrion Healthcare Co. Ltd., examined the budgetary impact of the introduction of the rituximab biosimilar (CT-P10) into 28 European countries based on IMS sales data, thereby reflecting real-life utilisation. The model examined a 1-year time horizon and considered use in all indications, including off-label use, in the 28 EU member states. The uptake of the rituximab biosimilar was estimated at 30% in all diagnoses, rituximab-naïve and patients switching from originator rituximab were not distinguished. Official price lists of originator rituximab were used in the model, and the biosimilar was assumed to be 70% of the originator cost. Secondary analyses also examined the budgetary impact of (1) a 50% market share uptake and (2) a 3-year time horizon with uptake of 30% in the first year, 40% in the second year and 50% in the third year.

The total projected budget saving in Europe was €90.04 million, of which 26.9% was saving in the treatment of rheumatoid arthritis (RA), 43.3% in the treatment of non-Hodgkin's lymphoma (NHL), 19.8% in the treatment of chronic lymphocytic leukaemia (CLL) and 10.0% in the treatment of other diagnoses. Seventy percent of the total cost savings were realised in five countries (Germany 22.8%, Italy 17.7%, France 13.5%, Spain 8.4% and UK 7.5%). Projected budget savings would permit access to rituximab for 7531 additional patients (2857 RA, 2263 NHL, 1624 CLL, 787 other diagnoses), equivalent to a 6.4% increase in the number of rituximab-treated patients. In a second scenario, uptake of 50% over a 1-year horizon resulted in a projected total budget saving of €150.10 million, allowing access to rituximab treatment for an additional 12,551 patients. In the three-year horizon scenario, projected savings across the EU member states over the 3-year period were projected to be approximately €570 million, equating to 47,695 additional patients accessing rituximab.

❖ Severs et al, 2017: The Economic Impact of the Introduction of Biosimilars in Inflammatory Bowel Disease [11]

In this paper, the authors examined the predicted impact of the introduction of anti-TNF biosimilars on annual inflammatory bowel disease (IBD)-specific health care costs in The Netherlands, compared with no biosimilar introduction (reference scenario). Health care costs and prescription rates of anti-TNF therapy were extracted from the previously conducted COIN study, and the number of Dutch adult IBD patients were estimated from the Vektis database (centre for information and standardisation for insurance companies). The model assumed that the cost of anti-TNF compounds would increase annually by 1%, the costs of the biosimilar would exponentially decline, with a minimum of 30% and maximum of 60%, plateauing to 40% of the originator cost after 5 years, and the manufacturer response to the introduction of

biosimilars would gradually result in a reduction of 50% of the original price for the originator product. In treatment-naïve patients, the model assumed 80% of patients would initiate therapy with infliximab, of which 20% would receive Remicade® and 80% biosimilar infliximab; the remaining 20% of patients would initiate therapy on subcutaneous Humira®. The model also assumed a relatively high price reduction of 50% would be necessary to induce a switch to biosimilars in existing anti-TNF users; when this threshold price reduction would be reached, 80-85% of anti-TNF users would be expected to gradually switch towards biosimilar therapy.

Based on the evaluated scenario, a total cost saving of €9,850 per Crohn's disease patient and €2,250 per ulcerative colitis patient was projected over the simulated 5-year period. The introduction of biosimilars is therefore predicted to yield total healthcare savings of €493 million in The Netherlands over the total 5 simulated years, equalling a 28% reduction in total costs. The authors note "*the economic impact of biosimilars is most sensitive to the factual price reductions of anti-TNF therapy, but also depends highly on the threshold price reduction from which physicians switch patients towards biosimilars, and on the extent to which switching takes place once threshold prices are reached*".

❖ Rencz et al, 2017: Cost-utility of biological treatment sequences for luminal Crohn's disease in Europe [12]

This study examined optimal sequence of initiation of biological treatments for Crohn's disease from a cost-effectiveness perspective. Whilst not the specific aim of the study to examine the budgetary impact of biosimilar treatments, the model did examine biosimilar infliximab as a biologic option, along with originator infliximab, adalimumab and vedolizumab. The model assumed a cost reduction from the list price of 30% for both biosimilar and originator infliximab, and 20% for adalimumab; efficacy data was taken from meta-analysis of RCT data. Noting that the same treatment could not be used twice in the sequence, including switching of biosimilar to/from originator infliximab, the most cost-effective sequence was biosimilar infliximab – adalimumab – vedolizumab, which was primarily driven by biologic cost.

Commentary

The authors provide no justification for the selected price reductions of 30% for infliximab and 20% for adalimumab; ultimately as cost was the driver for the most cost-effective sequence of available biologics, it is likely to have significantly influenced the conclusions of the study.

THEME 2: Biosimilar Medicine Uptake: Current Practice of Prescribers, Pharmacists and Patients

During the current review update period two manuscripts were published that address the theme of biosimilar uptake; one investigating a range of biosimilars across Europe, the other focusing specifically on G-CSF within a selected region of Italy.

❖ Remuzat et al, 2017: Key drivers for market penetration of biosimilars in Europe [13]

This manuscript aimed to identifying the key drivers of biosimilar uptake and to evaluate the impact of incentivisation policies within the ten largest EU pharmaceutical markets. All biosimilars approved by the EMA between 2006 and January 2016 were considered in this analysis of uptake in Belgium, France, Germany, Greece, Hungary, Italy, Poland, Spain, the UK and Sweden. Twenty biosimilar products were available during the study across six therapeutic classes including G-CSF; EPO; insulin; anti-TNF; gonadotropins; and HGH. A three step process was utilised to identify the key drivers for the uptake of biosimilars including; a literature review to identify incentive policies in the selected countries, data extraction (2006 – 2015) from the IMS MIDAS (Multinational Integrated Data Analysis System) and Price Insights databases (including market launch dates, official listed prices and sales) and regression model analysis of the relationship between biosimilar uptake and several covariates including; biosimilar price discounts, incentive policies, market competition, distribution channel (hospital, retail or mixed) and pharmaceutical expenditure (per capita).

The regression model that best fitted the data was a generalised linear model with a normal distribution, an identity link function, with therapeutic class as a random effect. The model performance measures of Akaike Information Criterion and root-mean-square-error were 49.73 and 0.1852 respectively.

The number of incentive policies in place and the date of first biosimilar market entry were correlated with biosimilar uptake. The pharmaceutical expenditure per capita and the highest generic uptake were inversely correlated with the biosimilar uptake, whereby the highest pharmaceutical expenditure per capita and the highest generic uptake was associated with lower rates of biosimilar uptake. Generic price discount over originator and the market competition (number of biosimilar products available per therapeutic class) displayed a correlation with biosimilar uptake, but did not achieve statistical significance ($p > 0.05$). The biosimilar price discount over originator price did not correlate with biosimilar uptake ($p = 0.78$). The authors propose that this observation may be accounted for by the fact that "*originators tend in some cases to adjust their prices in order to maintain competitiveness*" and that this not unexpected as "*applying to the biosimilar market the same concepts as to generic products, which are unlikely to work, as the market is totally different, especially with a different competition framework mainly characterised by the need to promote biosimilars and the lack of automatic substitution by the pharmacists*".

The authors identify a number of weaknesses with their findings including the confidentiality of market prices, which affected their price discount calculations. The small number of biosimilars available posed limitations upon the modelling accuracy and also that the summation of incentive policies assumed equal weighting of importance between these policies within each country. The authors concluded that this analysis indicates that "*incentive policies to enhance uptake remain an important driver of biosimilar penetration*" and that "*policy decision-makers, need to get themselves more involved in physician and patient education to ensure better understanding and adoption of biosimilars, and to implement financial incentives for cost-effective prescribing.*"

❖ Trotta et al, 2017: Impact of Guidance on the Prescription Patterns of G-CSFs for the Prevention of Febrile Neutropenia Following Anticancer Chemotherapy: A Population-Based Utilization Study in the Lazio Region [14]

In November 2015, a specific guidance was issued to specialist providers of G-CSF prescriptions in Lazio, a region in Italy with an approximate population of 6 million people, stating that all G-CSF products (biosimilar or originator) are therapeutically equivalent for the prevention of chemotherapy induced febrile neutropenia. As part of this pharmaceutical policy intervention an Electronic Registry of Therapeutic Plans was established in July 2015 to monitor G-CSF usage. This observational record linkage investigation reports all the therapeutic plans recorded for G-CSF use in chemotherapy induced febrile neutropenia from July 2015 until June 2016 in order to assess the impact of the interventional guidance on G-CSF biosimilar utilization in this group of patients by evaluating temporal trends in the pre- and post-intervention periods. The authors stated that with respect to biosimilars "*no studies have evaluated the ability of guidance to change prescribing attitudes in real-world practice*". A total of 7082 therapeutic plans were eligible for analysis during the study period corresponding to 6592 patients, which comprised of 5261 G-CSF naïve patients and 1331 experienced patients. All G-CSF products available in the region were included in the study; (1) filgrastim originator (Granulokine®, Neupogen®), (2) filgrastim biosimilar (Nivestim®, Tevagrastim®, Zarzio®), (3) pegfilgrastim (Neulasta®), (4) lenograstim (Granocyte®, Myelostim®) and (5) lipefilgrastim (Lonquex®). The mean age of patients (60 years) was similar across all the treatment groups, with the most frequently identified tumour types being breast (n=2001), haematological malignancy (n=1387) and lung cancer (933), with the majority of patients (66.9%) presenting with advanced-stage tumours. The total number of therapeutic plans using biosimilar filgrastim increased significantly from 828 (33.8%) in the pre-intervention period to 1808 (48.2%) in the post-intervention period (% difference 14.4%, p < 0.001). The total number of therapeutic plans using lenograstim and pegfilgrastim decreased significantly after the intervention (% difference -6.0 and -7.8% respectively, p < 0.001). Filgrastim originator and lipegfilgrastim utilization was not significantly different in the pre- and post-intervention groups. Similar patterns of uptake were observed in both the naïve and experienced sub-populations. The authors claimed the study confirmed that "*sharing evidence with prescribers and clinicians with the aim to deliver specific guidance on the appropriate use of drugs can induce significant changes in prescribing behaviours*" and concluded that "*switching patterns can be influenced or managed by specific guidance*".

THEME 3: Adverse Events and Health Outcomes of Biosimilar Medicines (Pharmacovigilance): Impact of Substitution, Switching and Extrapolation of Indication

Within the period encompassed by this update, there have been ten publications that specifically examine this theme, all relating to infliximab, with a specific emphasis upon the outcomes associated with switching from originator product to the biosimilar (CT-P13) across the spectrum of indications for which infliximab is approved. With the exception of the double-blind randomised NOR-SWITCH study [1], these have primarily been observational in nature with relatively small patient populations. However, in this update period these observational studies include a number of large nation-wide or multicentre studies [2-5].

❖ Jorgensen et al, 2017: Switching from originator infliximab to biosimilar CT-P13 compared with maintained treatment with originator infliximab (NOR-SWITCH): a 52-week, randomised, double-blind, non-inferiority trial [1]

The aim of the NOR-SWITCH study, a randomised, non-inferiority, double-blind, phase 4 trial with 52 weeks of follow-up, was to examine the efficacy, safety, and immunogenicity of switching from originator to biosimilar infliximab (CT-P13). A total of 482 patients were enrolled and randomised 1:1 to originator or biosimilar infliximab. One patient was excluded from the CT-P13 group within the full analysis and safety set. Within the full analysis set 32% (n=155) had Crohn's disease (CD), 19% (n=93) had ulcerative colitis (UC), 19% (n=91) had spondyloarthritis, 16% (n=77) had rheumatoid arthritis (RA), 6% (n=30) had psoriatic arthritis (PsA), and 7% (n=35) had chronic plaque psoriasis.

A total of 408 patients were included in the per-protocol set (infliximab originator=202, CT-P13=206). The primary endpoint of the study was disease worsening, as assessed by predefined changes in disease specific activity measures (eg. Harvey-Bradshaw [CD], Partial Mayo score [UC], Disease Activity Score in 28 joints [RA]) or *"a consensus about disease worsening between investigator and patient leading to major change in treatment"*. The secondary endpoints included time to disease worsening, study drug discontinuation, overall remission status based on the main composite measures, changes (follow-up minus baseline) in investigator and patient global assessments, and changes in inflammatory markers (erythrocyte sedimentation rate and C-reactive protein). Disease activity was low at baseline as indicated by disease specific and general measures.

By week 52, disease worsening occurred in 26% (n=53) of patients in the originator infliximab group as compared with 30% (n=61) of patients in the CT-P13 group (per-protocol set). The 95% CI of the adjusted risk difference was within the prespecified noninferiority margin of 15% (risk difference = −4.4%; 95%CI: −12.7% to 3.9%) and as such CT-P13 was non-inferior to originator infliximab. With regards to disease worsening, the adjusted relative risk in the CT-P13 group compared with the originator infliximab group was 1.17 (95%CI: 0.82–1.52). Remission occurred in 61% (n=123) of patients in the originator infliximab group as compared with 61% (n=126) of patients in the CT-P13 group corresponding to an adjusted rate difference of 0·6% (95%CI: −7·5% to 8·8%, per-protocol set). There were no statistically significant differences in patient reported measures with the exception of the Modified Health Assessment Questionnaire (MHAQ; mean = 0.08; 95%CI: 0.01 to 0.15) and Short Form Health Survey t-scores using Norwegian norms physical component summary score (SF-36; mean = −1·60; 95%CI: −2·74 to −0·46), both of which were in the favour of CT-P13. Over the course of the study trough drug concentrations were similar in the two groups. Neutralising anti-drug antibodies were observed at any timepoint (including at

baseline) in 11% (n=26) of patients in the originator infliximab group as compared with 13% (n=30) of patients in the CT-P13 group (full analysis set). The incidence of neutralising anti-drug antibodies first detected during the treatment phase of the study was 7% (n=17) in the originator infliximab group as compared with 8% (n=19) of patients switched to CT-P13 (full analysis set). The authors conclude that the "*findings from the NOR-SWITCH trial showed that switching from infliximab originator to CT-P13 was not inferior to continued treatment with infliximab originator according to our prespecified non-inferiority margin*" and that "*there was no suggestion of differences in safety or immunogenicity between the two treatment groups*".

❖ Glintborg et al, 2017: A nationwide non-medical switch from originator infliximab to biosimilar CT-P13 in 802 patients with inflammatory arthritis: 1-year clinical outcomes from the DANBIO registry [2]

The aims of this observational study were to assess the impact of a nationwide switch in Denmark from originator to biosimilar infliximab (CT-P13) on disease activity post-switch and to determine the 1-year retention rates. This study utilised the nationwide Danish quality registry, DANBIO, which covers >95% of adults with rheumatic diseases receiving bDMARDs and requires disease activity and outcomes to be monitored at least biannually.

The impact of switching from originator infliximab to biosimilar infliximab on disease activity was assessed within a group of 802 patients with inflammatory arthritis (rheumatoid arthritis=403, psoriatic arthritis=120, axial spondyloarthritis=279) who switched from originator to biosimilar infliximab prior to 1 January 2016. Disease activity, as assessed through a variety of disease relevant activity measures (eg. DAS28, ASDAS, HAQ, BASDAI, CRP), were compared at three time points; 3 months prior to switching, at the time of switching and 3 months post switching. The median treatment duration with originator infliximab prior to switching was 6.8 years (interquartile range: 4.3–9.5). Within this group there were no clinically meaningful differences in disease activity measures at 3 months post switching.

One-year retention rates for the group of patients who switched from reference infliximab to biosimilar infliximab were compared against a historical group consisting of all patients within the DANBIO registry that received treatment with originator infliximab prior to January 2014. A total of 1121 patients were included in the historical control cohort. The median treatment duration of originator infliximab treatment in this group was 5.3 years (interquartile range: 3.0-8.0). The adjusted one-year retention rates were slightly lower in the switched cohort as compared with the historical cohort, with an adjusted absolute risk difference of 3.4% (83.4% [95%CI: 80.8 to 86.2] versus 86.8% [95%CI: 84.8 to 88.8]; p=0.03) and the switched group had a higher relative risk of treatment withdrawal as compared with the historical group (HR=1.31; 95%CI: 1.02–1.68; p=0.03). In the context of an open label study utilising a historic control group the authors note that "*This difference is not necessarily attributable to CT-P13* [biosimilar infliximab]*, but could also represent a 'nocebo-effect', that is, negative expectations towards the drug or residual confounding*".

The authors conclude that that their results indicate that "*a nationwide non-medical switch from INX* [originator infliximab] *to CT-P13* [biosimilar infliximab] *in 802 patients with inflammatory arthritis, who had previously been treated with INX* (originator infliximab) *for >6 years, had no apparent negative impact on disease activity*".

❖ Fiorino et al, 2017: The PROSIT-BIO Cohort: A Prospective Observational Study of Patients with Inflammatory Bowel Disease Treated with Infliximab Biosimilar [5]

This manuscript reports on the outcomes from a prospective, multi-centre, cohort study of 547 patients with moderate to severe and chronically active ulcerative colitis (UC) and Crohn's disease (CD) treated with biosimilar infliximab (CT-P13) in Italy between April 2015 and March 2016. This study aimed to evaluate the efficacy, safety and immunogenicity of CT-P13 in patients with inflammatory bowel disease. Patients were stratified into 3 groups;

    A. anti-TNF naïve (n=311, including 12 paediatric patients)

    B. previously treated with, but not currently receiving an antiTNF agent (n=139; infliximab=34, adalimumab = 105, golimumab = 3). The median duration since last treatment with an anti-TNF agent was 9 months for infliximab and 10 months for the other agents (range: 6-23 months). The predominant reasons for stopping the previous treatment were loss of response (63%) and adverse events (23%).

    C. switched from originator infliximab to biosimilar infliximab (CT-P13) (n=97, including 13 paediatric patients). The mean number of infliximab infusions prior to switching was 18±14 infusions (range 1–72).

The primary endpoint was the rate of serious adverse events which were defined as "*the occurrence of death, a life threatening adverse event, inpatient hospitalization or prolongation of existing hospitalization, a persistent or significant incapacity or substantial disruption of the ability to conduct normal life functions, and any condition that on appropriate medical judgment, might jeopardize the patient and might require medical or surgical intervention, including withdrawal of the ongoing therapy with CT-P13*". Secondary endpoints were efficacy, indicated by clinical remission/response and treatment persistency, and immunogenicity, indicated by the occurrence of infusion reactions and loss of response.

A total of 434 patients completed the minimum treatment and follow-up time of 8 weeks or had failed treatment prior to that point. The incidence of serious adverse events did not differ significantly between the three groups. Serious adverse events occurred in 4.2% of the treatment naïve group (group A, 13/311) as compared with 5.2% in those directly switching from originator to biosimilar infliximab (group C, 5/97) and 7.2% in those with a more distant history of treatment with assorted anti-TNF agents (group B, 10/139). The treatment failure rate was 10.0% in the treatment naïve group (group A; 95%CI: 6.5% to 14.5%) whilst there were no treatment failures in those that directly switched from originator infliximab to biosimilar infliximab (group C; 95%CI: 0.0% to 3.8%; p=0.005). In the group with a more distant history of treatment with assorted anti-TNF agents (group B) the failure rate was 11.1% (95%CI: 5.7% to 19.0%). Infusion reactions occurred in 3.2% of anti-TNF naïve patients (group A, 10/311) as compared with 7.2% in the directly switching group (group C, 7/97) and 15.1% of patients with a more distant history of treatment with assorted anti-TNF agents (group B, 21/139). Of the 21 patients from group B that experienced an infusion reaction, nine occurred amongst the 34 patients from this group that had previously been treated with originator infliximab. The remaining 12 infusion reactions in group B occurred amongst the 105 patients that had previously been treated with anti-TNF agents other than infliximab. The authors acknowledged that "*no direct comparison was performed*" but concluded that that "*no alarming signals of immunization have been detected in patients switched from the infliximab*" and that "*we have*

demonstrated in the evaluated time frame that the safety profile and efficacy of CT-P13 biosimilar is in line with the existing literature of infliximab".

❖ Balint et al, 2017: Frequency and characteristics of infusion reactions during biosimilar infliximab treatment in inflammatory bowel diseases: results from Central European nationwide cohort [4]

This prospective, observational study aimed to assess the frequency and characteristics of infusion reactions to biosimilar infliximab (CT-P13) in 384 patients with inflammatory bowel disease (Crohn's disease [CD] and ulcerative colitis [UC]) treated at 13 Hungarian and 1 Czech centres between June 2014 and September 2015. A total of 28 patients (9.6%; 18 CD, 10 UC) developed an infusion reaction, most frequently during the 2nd or 3rd infusions. All infusion reactions were considered to be mild to moderate and were managed with a decreased infusion rate or administration of antihistamines or corticosteroids. Antidrug antibodies (ADA) were detected in 14/28 patients that experienced an infusion reaction. Biosimilar infliximab was ceased in 17/28 patients that experienced an infusion reaction. Previous treatment with originator infliximab (30% vs. 3.1%; p<0.001; OR=6.3 [2.7–14.6]) and ADA positivity (32.6% vs. 4.1%; p<0.001; OR=19 [5–73]) during induction were associated with an increased risk of experiencing an infusion reaction. The authors concluded that "*patients with previous exposure to anti-TNF-alpha and ADA positivity during the induction therapy were more likely to develop infusion reactions*" and that "*our results suppose a lower immunogenicity of the biosimilar in CD and similar rates and characteristics of infusion reaction with the originator*".

Commentary

Whilst the authors indicated that the results of the observational study indicates "*lower immunogenicity*" the authors acknowledge that "*this study has no power to assess differences regarding to immunogenicity between Inflectra and Remsima*" but conclude that their "*results suppose a lower immunogenicity of the biosimilar in CD and similar rates and characteristics of infusion reaction with the originator*" on the basis that 9.8% of CD patients in this study developed an infusion reaction which is lower than the range of 16-21% reported in the originator infliximab (Remicade) studies (ACCENT I and II). However, the authors also note that the observed frequency in this study in UC patients is similar to the 9.9-11.6% range reported in the originator infliximab (Remicade) studies (ACT 1 and 2).

❖ Gisondi et al, 2017: Infliximab biosimilar CT-P13 in the treatment of chronic plaque psoriasis. Data from the Psobiosimilars registry [3]

The objective of this study was to investigate the effectiveness and safety of infliximab biosimilar CT-P13 in patients with psoriasis (n=204) registered in the Psobiosimilars registry, a web-based (http://www.psobiosimilars.it), observational registry designed to assess the long-term effectiveness and safety of biosimilars for psoriasis in Italy, from July 2015 to December 2016. Patients were stratified in two groups;

A. Patients who switched from the infliximab originator to the biosimilar (CT-P13) (n=122); details regarding infliximab treatment history were not provided

B.   Patients naïve to the originator who commenced CT-P13 (n=82).

Within the switching group, Psoriasis Area and Severity Index (PASI) score remained unchanged at 6 months post-switch (2.05 ± 2.8 vs 2.2 ± 3.2 [mean ± SD]; p=0.3). Within the treatment naïve group, there was a significant reduction in PASI at 6 months as compared with baseline (7.2 ± 7.1 vs 20.8 ± 12.1; p=0.001). Sixteen adverse events were recorded, including infusion reactions and viral infections, and there were no significant differences in adverse events between the two groups. The authors conclude that the "*principal finding of this study is that patients with chronic plaque psoriasis who respond to the infliximab originator can be switched to the biosimilar CT-P13 without experiencing a significant change in clinical response or additional adverse events including infusion reactions*".

❖ Buer et al, 2017: Switching from Remicade to Remsima is Well Tolerated and Feasible: A Prospective, Open-Label Study [15]

This prospective observational study reports on the outcome associated with switching 143 patients with inflammatory bowel disease (CD=99, UC=44) treated at the Oslo University Hospital Department of Gastroenterology. All patients had received originator infliximab for a period of at least 10 months prior to switching (CD median= 87 months, IQR=54 months; UC median= 57 months, IQR=47 months). Patients were switched from originator infliximab to biosimilar infliximab regardless of disease activity or concomitant therapy. Patients were followed prospectively for 6 months after switching and no significant changes in disease activity, as defined by Harvey-Bradshaw Index (for CD) and Partial Mayo Score (for UC), were detected. There were no statistically significant differences in biological markers of inflammation (C-reactive protein, fecal calprotectin or haemoglobin) at any time point before or after switching. At the time of the switch, 87% of CD and 88% for UC patients were in remission. At 6 months post-switch, 81% of CD and 95% of UC patients were in remission. Of those in remission at the time of switching, 71% [n=69] of CD patients and 73% [n=32] of UC patients remained in remission. At the time of switching infliximab doses and treatment intervals varied considerably between patients, with only 49% receiving treatment 8-weekly and 66% receiving a dose of 4-6mg/kg. In this context, no change in the mg/kg/week (p=0.62) or in the infliximab concentrations (p=0.07) was detected following the switch to biosimilar infliximab. On this basis the authors conclude that "*switching from Remicade to Remsima in a real-life IBD population is feasible and well tolerated with few adverse events, including very limited ADA formation and loss of response*".

❖ Benucci et al, 2017: Safety, efficacy and immunogenicity of switching from innovator to biosimilar infliximab in patients with spondyloarthritis: a 6-month real-life observational study [16]

This observational study reports on the outcomes associated with switching 41 patients with spondyloarthritis (SpA) from originator to biosimilar infliximab at three Italian rheumatology centres. Prior to switching, patients had clinically inactive or moderate disease activity and had been treated for at least 6 months with originator infliximab (median = 73.7 months; range 6 to 144). Following six months of treatment with biosimilar infliximab there were no statistically significant changes in a variety of disease activity indices (eg. BASDAI: 2.73 ± 1.5 vs. 2.6 ± 1.3, p=0.27; BASFI: 2.34 ± 1.3 vs. 2.17 ± 1.2, p=0.051; DAS28-CRP: 2.66 ± 0.67 vs. 2.67 ± 0.35, p=0.92), whilst there was an improvement in the duration of morning stiffness (7.2 ± 6.9 vs. 5.8 ± 6, p = 0.02). Following switching there was no change in infliximab concentrations (4.22 ± 2.89 vs. 4.84 ± 2.86 µg/mL, p = 0.80) or anti-drug antibody concentrations (27.76 ± 17.13 vs. 27.27 ± 17.28 ng/mL, p = 0.98). The authors concluded that their *real-life experience shows that*

the switch from iINX (originator infliximab) *to CT-P13* (biosimilar infliximab) *is feasible, safe and efficacious*" and that "*it could also lead to savings useful for the sustainability of national healthcare systems*" whilst suggesting that "*careful assessment of the adverse events and immunogenicity of the switch is still necessary*".

❖ Sieczkowska-Golub et al, 2017: Induction Therapy with Biosimilar Infliximab in Children with Crohn's Disease [17]

This manuscript reports on the outcomes of 36 children who received biosimilar infliximab (CT-P13) induction therapy between March 2014 and July 2015 at three Polish centres for Crohn's Disease with severe luminal disease and/or perianal involvement that was resistant to standard treatment. Patients were assessed prior to commencing induction and at week 14. Of the 36 patients, 27 (75%) were naive to anti-TNFα agents. Two patients did not complete induction due to either joint pain or an infusion reaction. At week 14, there was a clinically and statistically significant decrease in the Paediatric Crohn's Disease Activity Index with remission achieved in 67% of patients (24/36) and a clinical response achieved in a further 7 patients. The authors concluded that "*Our assessment showed that biosimilars have similar efficacy as reference molecule in inducing the remission in CD paediatric patients*" whilst noting the limitations of a study of this nature.

❖ Abdalla et al, 2017: Long-term safety and efficacy of biosimilar infliximab among patients with inflammatory arthritis switched from reference product [18]

This prospective observational study of a cohort of 34 patients with inflammatory arthritis (rheumatoid arthritis n=17; ankylosing spondylitis n=9; psoriatic arthritis n=4; inflammatory bowel disease-related spondyloarthropathy n=3) aimed to evaluate the efficacy and safety of switching from originator infliximab to biosimilar infliximab (CT-P13). Of these patients, 32.4% were receiving monotherapy and 35.3% combination with methotrexate. The remaining patients were receiving other disease modifying antirheumatic drugs (sulfasalazine n=4; leflunomide n=2; cyclosporin n=2; methotrexate + other DMARD combination n=3). The median duration of infliximab treatment prior to switching was 57 (range: 1 to 181) months. Following switching the mean duration of follow-up was 15.8 months (SD=6.3). Following switching, there were no statistically significant differences in the Patient Global Assessment and Health Assessment Questionnaire (p=0.111 for both outcomes). There was a statistically significant increase in the median CRP (from 1.95 to 4.0, p=0.001) but this was considered to have remained within the reference range. Mean patient pain scores displayed a small but statistically significant increase following switching to biosimilar infliximab (visual analogue scale = 6.85mm; 95%CI: 0.24–13.45; p=0.043). Five patients discontinued biosimilar infliximab (pregnancy n=1; secondary failure n=2; dizziness n=1; consent withdrawn to switch back to reference product due to subjectively feeling worse without objective deterioration n=1). The authors concluded that patients "*switched from the reference to the biosimilar infliximab experienced comparable efficacy and safety profile over the follow-up period (15.8 months) without major safety issues*".

❖ Harkin et al, 2017: The Effect of Biosimilars (Inflectra,) in the management of Acute Severe Ulcerative Colitis [19]

The authors report a small retrospective case series of 13 patients that received biosimilar infliximab (Inflectra®) as "*rescue*" therapy for acute severe ulcerative colitis (median Mayo score = 11). The median follow-up was 12 months (range: 0 to 24 months). The authors report that of these 13 patients, 11 (84.6%) have been successfully managed with ongoing biosimilar, 7 of whom received combination therapy with either azathioprine (n=6) or 6-mercaptopurine (n=1), one proceeded to colectomy and one lost response with disease control which was subsequently restored following a change to adalimumab. No serious adverse events were reported.

THEME 4: Evaluating and Improving Stakeholder Biosimilar Awareness, Confidence, Attitudes and Acceptance of Biosimilar Medicines

Four original research articles were published during the review update period addressing the topic of biosimilar perception amongst healthcare professionals. As with the previous update period, this includes a manuscript that focusses upon perception toward the administration device rather than the drug molecule itself.

❖ Egeth et al, 2017: Patient and Healthcare Professionals Preference for Brenzys vs. Enbrel Autoinjector for Rheumatoid Arthritis: A Randomized Crossover Simulated-Use Study [20]

This randomised, crossover, simulated-use study, conducted in Australia and Canada, aimed to assess patient and healthcare practitioner preferences and perspectives on ease of use of biosimilar etanercept (Brenzys) autoinjector compared with originator etanercept (Enbrel) autoinjectors. A total of 191 patients with rheumatoid arthritis who were either autoinjector-naïve (82%) or autoinjector-experienced (18%) and 90 health care practitioners (rheumatologists n=31, nurses n=59) experienced in managing patients with rheumatoid arthritis were enrolled. Participants in the study were blinded to the study sponsor (Merck & Co). Participants received training in how to use each device followed by a single administration into an injection pad. The sequence order was balanced with 50% of participants first receiving Brenzys autoinjector first followed by the Enbrel device and vice versa. After receiving training and using both devices participants completed a questionnaire that asked participants to compare the two devices with regards to overall preference, ease of use, ease of cap removal, ease of dose administration and visual indication that the full dose had been administered. Patients were asked which device they would recommend to other patients whilst healthcare practitioners were asked which device they would recommend to patients. Patients that were experienced with the Enbrel autoinjector were also asked which device they would prefer to choose to manage their condition. For all items, patients were significantly more likely to prefer the Brenzys autoinjector (p<0.001 for all items except cap removal for which p<0.05). Healthcare practitioners were significantly more likely to prefer Brenzys for all items (p<0.001) with the exception of ease of cap removal (p=0.053). Overall, 74.3% of patients (142/191) indicated that they would prefer the Brenzys autoinjector (95%CI: 67.5%–80.3%; p<0.001) and 83.1% (74/89) of healthcare practitioners indicated that they would recommend the Brenzys autoinjector to patients (95%CI: 73.7%–90.2%; p<0.001).

Commentary

This study highlights the importance of the administration device to many biologic medicines. As devices are proprietary and there may be differences in how they function it is vital that patients receive appropriate education on the device, particularly in the context of switching between an originator product and the biosimilar or vice versa.

❖ Waller et al, 2017: Assessing physician and patient acceptance of infliximab biosimilars in rheumatoid arthritis, ankylosing spondyloarthritis and psoriatic arthritis across Germany [21]

This study, sponsored by Merck & Co, investigated the treatment preferences and motivation of rheumatologists with respect to biosimilars and explored the attitudes of their patients to biosimilars. In order to be eligible for participation, the rheumatologists must have already prescribed biosimilars. Data was collected from rheumatologists using an online survey between December 2015 and March 2016. A total of 50 rheumatologists participated in the study. Based upon the responses provided rheumatologists were classified into one of three categories based upon the factors that they selected as having an influence upon their attitudes and behaviours;

1. primarily concerned with symptom improvement and disease modification (referred to as 'investigative')
2. primarily concerned with safety (referred to as 'conservative')
3. primarily concerned with 'other' factors, e.g. budgetary impact (referred to as 'other')

Of the 50 rheumatologists that participated, 23 were classified as 'investigative', 17 as 'conservative' and 10 as 'other'. When asked to assume that there were no prescribing guidelines or other restrictions with respect to biosimilar medicines, greater than 95% of respondents indicated that they would prefer to prescribe the originator product rather than the biosimilar, particularly in the context of first-line or second-line therapy. Respondents were asked to choose from a list of eight potential options regarding their reasons for prescribing a biosimilar in preference to the originator. The selection of multiple options was permitted. The option "*I wanted to get experience with the new product(s)*" was selected by 86% of those classified as 'investigative' selected as compared with 65% and 50% of those classified as 'conservative' and as 'other' respectively. The option "*Due to the lower cost*" was selected as a reason for prescribing a biosimilar more frequently in those classified as being either 'conservative' (71%) or 'other' (88%) as compared to those classified as 'investigative' (64%).

Participating rheumatologists subsequently recruited eight patients aged ≥18 years, with a diagnosis of rheumatoid arthritis (RA), axial spondyloarthritis (AxSpA) or psoriatic arthritis (PsA) and who were being treated with either originator or biosimilar infliximab (1:2 ratio). A total of 261 patients (133 RA, 65 PsA and 63 AxSpA) completed an online survey and were stratified into four groups based upon their treatment history;

1. patient receiving biosimilar infliximab who was previously biologic naïve
2. patient receiving biosimilar infliximab who was previously treated with the originator
3. patient receiving originator infliximab initiated after February 2015
4. patient receiving originator infliximab initiated before January 2015

The majority of patients in each of the four groups were either satisfied or very satisfied with their current treatment (assessed with a seven point Likert scale); less than ~5% in any group were dissatisfied. When patients were asked to select from a range of potential concerns, 14% of patients receiving biosimilar infliximab who were previously biologic naïve (group 1) selected the option "*I think this version is a cheaper and less-effective version*" as compared with 0–6% of patients in the other groups.

When rheumatologists were asked to reflect upon their experiences when prescribing biosimilars to patients, respondents indicated that 70% of patients who were previously biologic naïve would "*accept the*

biosimilar without reluctance" but that acceptance was reduced to 56% in "*patients currently receiving a biooriginator and with no clinical reason for a change in therapy*". Similarly, 7.3% of biologic naïve patients and 18.5% of those currently treated with originator indicated that they would not accept treatment with the biosimilar.

Commentary

This study provided respondents with only a limited number of options from which to select, significantly limiting the interpretation of these results. For some items, respondents were also able to select multiple options but there was no mechanism for respondents to indicate which of these factors they considered to be most important. The authors acknowledge that this study did not explore the reasons for the responses that were provided.

❖ Sullivan et al, 2017: Assessing gastroenterologist and patient acceptance of biosimilars in ulcerative colitis and Crohn's disease across Germany [22]

In a second study by the authors investigated, again sponsored by Merck & Co, using the same methods as for their above manuscript [21], the treatment preferences and motivation of gastroenterologists with respect to biosimilars and the attitudes of their patients to biosimilars. Data was collected from gastroenterologists and their patients using an online survey undertaken between December 2015 and March 2016.

A total of 25 gastroenterologists participated in this study, with 11 classified as 'investigative', 7 as 'conservative' and 7 as 'other'. When asked to assume that there were no prescribing guidelines or other restrictions with respect to biosimilar medicines, 88% of respondents indicated they would prefer to prescribe the originator product rather than the biosimilar. As with the above study [21], when asked to choose from a list of eight potential options regarding their reasons for prescribing a biosimilar in preference to the originator 89% of 'investigative' and 100% of 'conservative' gastroenterologists selected the option "*I wanted to get experience with the new product(s)*".

A total of 136 patients (69 CD, 67 UC) completed the survey. The majority of patients in each of the four groups were either satisfied or very satisfied with their current treatment (assessed with a seven point Likert scale).

Commentary

This study is subject to the same limitations as the manuscript by Waller et al [21]. Further, the results section describing the patient responses in this paper is very brief and several of the figures within the publication are mislabelled. As such it is difficult to interpret the responses that were provided by patients.

❖ Manalo et al, 2017: The Current State of Dermatologists' Familiarity and Perspectives of Biosimilars for the Treatment of Psoriasis: A Global Cross-Sectional Survey [23]

This survey, conducted in early 2015, aimed to assess dermatologists' familiarity with, and attitudes towards, biosimilars including interchangeability, indication extrapolation, and immunogenicity. The study did not explore the reasons for the ratings that were provided by respondents. A total of 116 responses were received, predominantly from clinicians based in the US (79.3%). With regards to familiarity with biosimilars, assessed using a Likert scale from 1 (very unfamiliar) to 5 (very familiar), 37.0% of respondents were fairly to very familiar with biosimilars, 33.6% were moderately to slightly unfamiliar and 29.3% were very unfamiliar. When respondents were asked to rate their comfort level in potentially prescribing biosimilars, using a Likert scale from 1 (very uncomfortable) to 5 (very comfortable), the mean value fell below the middle of the scale (2.8±1.2). However, this comfort level increased to 3.3 (±1.0) in the scenario where the FDA had approved the product for indications including psoriasis on the basis of non-psoriasis studies (extrapolation of indication). With regards to immunogenicity, the majority of respondents (62.3%) were undecided as to whether there is a greater risk of immunogenicity associated with a biosimilar as compared to originator product. When asked if they were "*concerned for safety issues if patient is switched around from originator biologic to multiple other biosimilars*" respondents were on average somewhat to very concerned (3.4±1.0). Overall, the 43 respondents rated themselves as fairly to very familiar with biosimilars also rated themselves as being the most comfortable in prescribing a biosimilar for psoriasis.

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APPENDIX 1

The following list contains manuscripts that were published during the review period that are of an educational or review nature. These manuscripts did not contribute new information to literature on biosimilar medicines. Some manuscripts provide a broad, relatively superficial, overview of biosimilar medicines. Other manuscripts provide an in-depth review of specific biosimilar medicines, reporting only on previously published data, but not contributing new information.

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APPENDIX 2

The following list contains manuscripts that were published during the review period that are of a technical nature and relate to topics such as the physicochemical and pharmacological characterisation of potential biosimilar medicines.

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