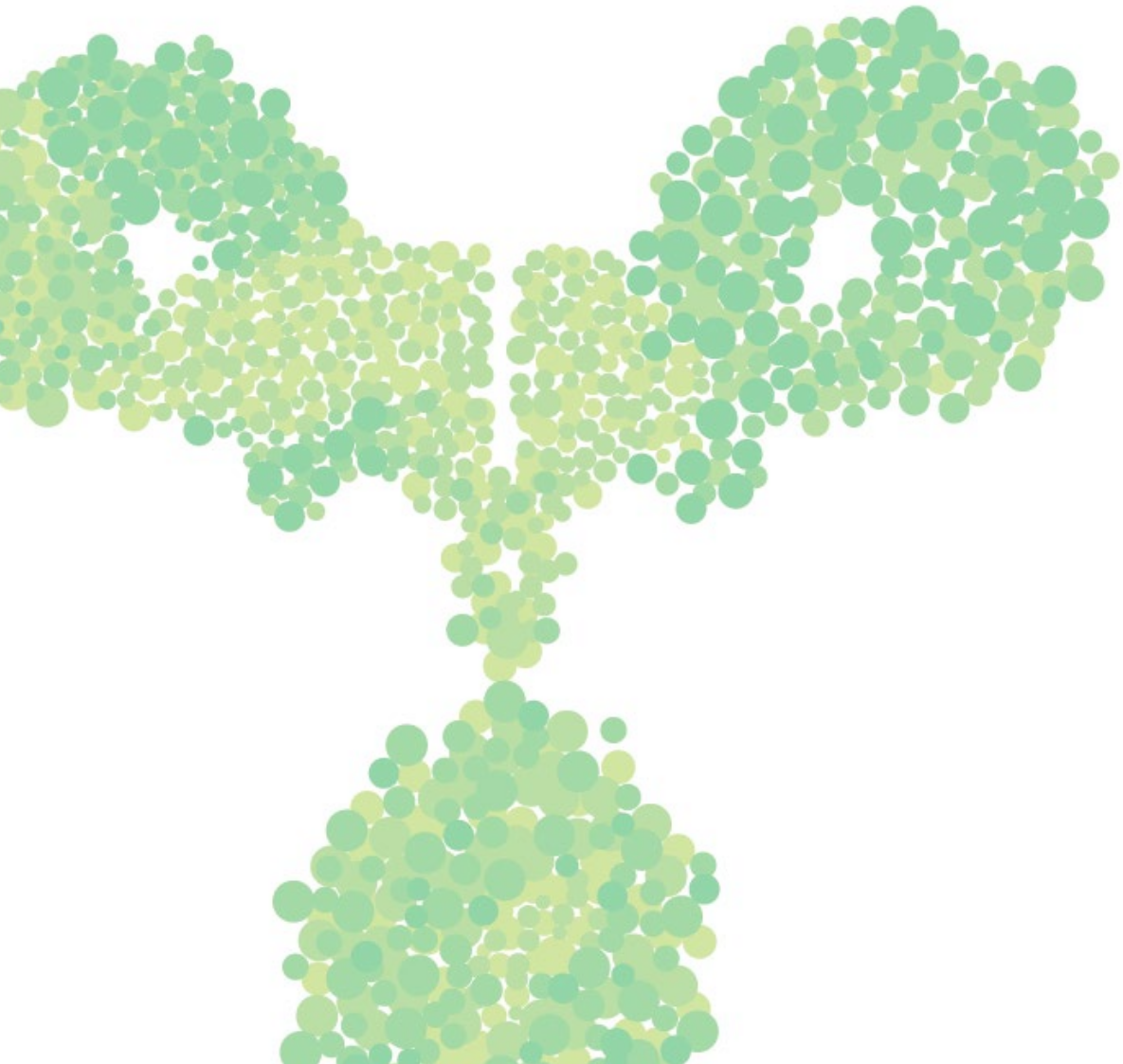
GBMA EDUCATION

University of South Australia | School of Pharmacy and Medical Sciences

International Biosimilar Medicines

Review of the Literature: Quarterly Update

January 2019 – March 2019



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INTRODUCTION

This report provides an update to the comprehensive literature search previously conducted on behalf of the Department of Health. To inform activities related to GBMA Education's Biosimilar Education Grant, these reviews examine all international and Australian clinical, academic and policy journals in relation to biosimilar medicines.

The reviews are conducted with an emphasis on ensuring that the evidence is up-to-date in the following key topic areas:

- Comparability of biosimilar medicines to reference biological medicine, specifically in reference to substitution (including single switch and multiple switch scenarios), and extrapolation of indication
- Biosimilar medicine uptake related to prescribing and dispensing trends, particularly evidence relating to policies on biosimilar medicine use
- Health outcomes and adverse events of biological and biosimilar medicines from a pharmacovigilance perspective, and
- Current perceptions of biosimilar medicines (qualitative and quantitative evidence) relating to awareness, confidence, attitudes and acceptance.

The 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; the subsequent uptake of biosimilar medicines by prescribers, pharmacists and participants; outcomes resulting from the use of biosimilar medicines outside of the clinical development pathway; and finally the stakeholder perceptions that influence uptake, including the factors that modify these perceptions such as advocacy and associated programmes. In reflection of this, the following central themes have been identified.

Determining Access and Subsidisation

This theme is based on the clinical development pathway of biosimilar medicines, including phase I studies 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.

As a strong determinant informing policy relating to biosimilar access and use, this theme also examines the economic impact of the introduction of biosimilar medicines.

Biosimilar Medicine Uptake

This theme examines uptake, switching and substitution of biosimilar medicines, including the international status and a specific focus on policy changes involving prescribers, pharmacists and patients.

Health Outcomes and Adverse Events

This theme captures evidence related to pharmacovigilance activities required to detect adverse events and health outcomes with biosimilar medicines, specifically to determine the impact of substitution, switching and extrapolation of indication.

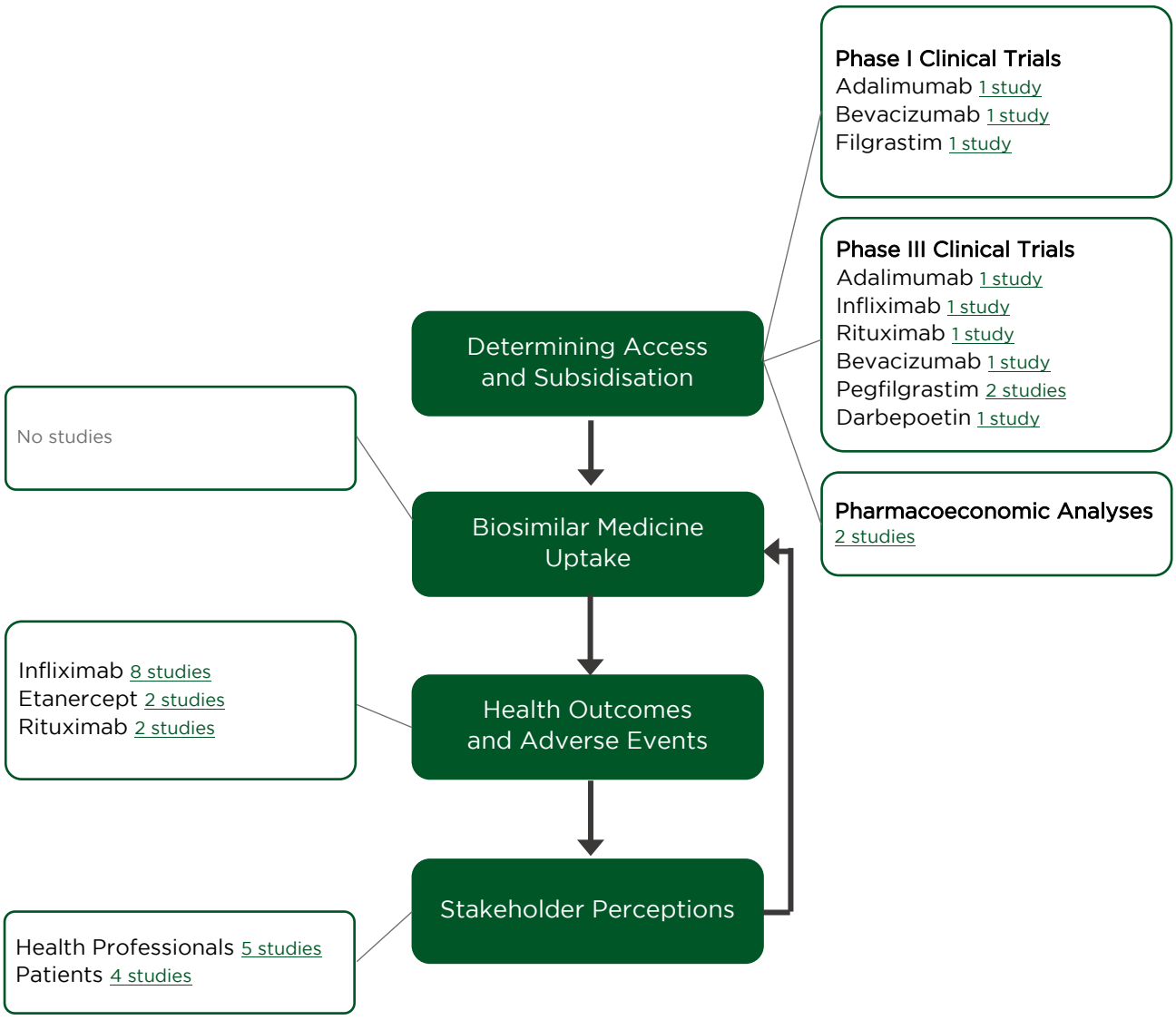
Stakeholder Perceptions

This theme encompasses the literature pertaining to evaluating and improving the awareness, confidence, attitudes and acceptance of biosimilar medicines by stakeholders, including literature that describes or evaluates any existing programs that aim to increase stakeholder understanding and confidence in biosimilar medicines.

OVERVIEW OF THE LITERATURE

This report includes literature published between 1 January 2019 and 31 March 2019.

The following figure summarises the literature reviewed in this update period (follow hyperlinks within diagram to corresponding study summaries).



Appendix 1: Educational/Review Articles
49 manuscripts

Appendix 2: Technical
16 manuscripts

DETERMINING ACCESS AND SUBSIDISATION

Phase I Clinical Trials

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 participants depending upon a range of factors such as the potential risks associated with the use of the agent.

During the current update period, there were three papers that reported phase I pharmacokinetic studies comparing a potential biosimilar medicine with a reference product. 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 Table 1.

Return to OVERVIEW

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
ADALIMUMAB						
GP2017	EU Humira® and US Humira®	Randomised, double-blind, three-arm, parallel, single-dose study	Healthy adult males (n=318; randomised 1:1:1)	90% CI of the ratio of geometric least square means for $AUC_{0\text{-}inf}$ and C_{max} were within the pre-defined equivalence interval of 80-125% for the comparisons of GP2017 with either EU Humira® or US Humira®, and between EU Humira® and US Humira®.	62, 74 and 73 subjects were positive for ADAs in the GP2017, EU Humira® and US Humira® groups respectively. The kinetics of ADA development over the 72 days following single dose administration were similar across the three treatment groups.	von Richter et al[1]
GP2017 Autoinjector versus GP2017 Pre-Filled Syringe	None	Randomised, open-label, two-arm, parallel, single-dose study	Healthy adult males (n=108; randomised 1:1)	90% CI of the ratio of geometric least square means for $AUC_{0\text{-}inf}$ and C_{max} were within the pre-defined equivalence interval of 80-125% for the comparisons of GP2017 administered via the auto-injector or pre-filled syringe.	37 subjects in the auto-injector and 39 subjects in the pre-filled syringe group had at least one positive ADA result; no differences were noted between the groups.	

Return to OVERVIEW

Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
BEVACIZUMAB						
CT-P16	EU Avastin® or US Avastin®	Randomised, double-blind, three-arm, parallel, single-dose study	Healthy adult males (n=144; randomised 1:1:1)	90% CI of the ratio of geometric least square means for AUC_{last}, $AUC_{0\text{-}inf}$ and C_{max} were within the pre-defined equivalence interval of 80-125% for the comparisons of CT-P16 with either EU Avastin® or US Avastin®, and between EU Avastin® and US Avastin®.	Seven subjects tested positive for ADAs on at least one occasion after administration of study drug (2 subjects each in the CT-P16 and EU Avastin® groups, and 3 subjects in the US Avastin® group).	Cho et al[2]

Return to OVERVIEW

Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
FILGRASTIM						
PF-06881893 (Nivestym®)	US Neupogen®	Randomised, open-label, two-arm, crossover, single-dose study	Healthy adults (n=24; randomised 1:1)	90% CI of the ratio of geometric least square means for PK ($AUC_{0\text{-}inf}$ and C_{max}) and PD ($AUEC_{ANC}$ and ANC_{max}) parameters were within the pre-defined equivalence interval of 80-125% for the comparison of Nivestym® with Neupogen®.	3/12 subjects in the Neupogen®-Nivestym® group had positive ADAs during the study, of which 2 were positive prior to dose administration on Day 1. No subjects in the Nivestym-Neupogen® group had positive ADAs at any visit.	Yao et al[3]
PF-06881893 (Nivestym®)	US Neupogen®	Randomised, open-label, two-arm, crossover, multiple-dose study	Healthy adults (n=60; randomised 1:1)	90% CI of the ratio of geometric least square means for PK (Day 5 $AUC_{0\text{-}24}$ and C_{max}) and PD ($AUEC_{CD34+}$ and $CD34+_{max}$) parameters were within the pre-defined equivalence interval of 80-125% for the comparison of Nivestym® with Neupogen®.	1/30 subjects in the Nivestym®-Neupogen® group had positive ADAs during the study, compared to 0/30 subjects in the Neupogen®-Nivestym® group.	
PF-06881893 (Nivestym®)	US Neupogen®	Randomised, open-label, two-arm, parallel, multiple-dose study (comparative immunogenicity)	Healthy adults (n=256; randomised 1:1)	Not assessed.	Non-inferiority for immunogenicity of Nivestym® versus Neupogen® was demonstrated, with 7.4% subjects exhibiting positive post-dose ADAs in the Nivestym® group, compared to 4.9% in the Neupogen® group.	

Phase III Clinical Trials

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 were 7 reports of phase III trials of potential biosimilars.

ADALIMUMAB

Cohen et al: An open-label extension study to demonstrate long-term safety and efficacy of ABP 501 in patients with rheumatoid arthritis[4]

SPONSOR: Amgen Inc

REFERENCE PRODUCT: none

OBJECTIVE(S): To assess the safety of biosimilar adalimumab (ABP 501) over 72 weeks in participants who had previously received treatment with biosimilar adalimumab (ABP 501) or reference product adalimumab (Humira®)

DESIGN: Open label single arm extension to a 26-week phase 3 randomized, double-blind, controlled equivalence study

SAMPLE SIZE: Continued ABP501 = 230, switched from reference product to biosimilar = 237

PATIENT CHARACTERISTICS: Proportion of participants with at least a 20% improvement in American College of Rheumatology core set measurements from baseline (ACR20) at baseline of open label extension study = 73.3% (340/464); mean DAS28-CRP change from the parent study baseline to baseline of open label extension study = −2.25 (n = 440); proportion of participants positive for anti-drug antibodies at baseline of open label extension study: switching from reference product to ABP501 = 34.2% (n = 81) vs continued ABP 501 = 32.3% (n = 74), neutralising anti-drug antibody positive at baseline of open label extension: switching from reference product to ABP501 = 21 (8.9%) vs continued ABP 501 = 13 (5.7%)

RESULTS: Adverse events were reported in 62.4% of participants that continued treatment with ABP 501 as compared with 65.0% in those who switched from reference product to ABP 501. The most common adverse event was infection which occurred in 38.9% of those who continued ABP 501 and 42.6% of those who switched from the reference product. A total of 25 serious adverse events occurred in 10.9% of participants in the group that continued ABP 501 as compared with 21 events that occurred in 8.9% of participants in the switching group. Relative to the baseline of the open label extension study, 116 (48.9%) participants who switched from reference adalimumab to ABP 501 tested positive for anti-drug antibodies at any time during the study as compared with 124 (54.1%) participants in the group that continued treatment with ABP 501. Neutralising anti-drug antibodies were detected in 33 (13.9%) participants who switched from reference adalimumab to ABP 501 as compared with 33 (14.4%) participants in the group that continued treatment with ABP 501.

With regards to efficacy, the ACR20 response rate at week 70 was 78.8% (327/415 subjects). The percentage of ACR20 responders were considered "… comparable in the group that transitioned from adalimumab to ABP 501 and the group that continued on ABP 501". The overall mean DAS28-CRP change from the parent study baseline at week 70 was − 2.60 (n = 412).

Return to OVERVIEW

INFLIXIMAB

Ye et al: Efficacy and safety of biosimilar CT-P13 compared with originator infliximab in patients with active Crohn's disease: an international, randomised, double-blind, phase 3 non-inferiority study[5]

SPONSOR: Celltrion, Pfizer

REFERENCE PRODUCT: infliximab (not specified)

OBJECTIVE(S): To demonstrate non-inferior efficacy of biosimilar infliximab (CT-P13) compared with reference product infliximab in patients with active Crohn's disease who were naïve to biological therapy and to assess the safety and efficacy of switching at week 30

DESIGN: Randomised, multicentre, double-blind, phase III non-inferiority study

SAMPLE SIZE: 220 participants were randomised 1:1:1:1. A total of 111 participants were randomised to CT-P13 for the first 30 weeks and 109 to reference product infliximab. Of these 56 participants were randomised to receive CT-P13 initially and continue CT-P13 at week 30, 55 to receive CT-P13 initially and then switch to reference product infliximab, 54 to initially receive reference product infliximab and continue reference product infliximab and 55 to initially receive reference product infliximab and then switch to CT-P13.

PATIENT CHARACTERISTICS: Participants were aged 18–75 years; mean disease duration (years) = 4·2 years (biosimilar) vs 5·3 (originator); mean Crohn's Disease Activity Index at baseline = 296·3 (biosimilar) vs 295·7 (originator), median calprotectin at baseline (μg/g) = 516·5 (biosimilar) vs 459·0 (originator).

EQUIVALENCE CRITERIA: Noninferiority was defined as a lower limit of the two-sided 95% confidence interval (CI) for the difference in response rate at week 6, defined as a ≥70-point decrease in the Crohn's Disease Activity Index (CDAI-70), between CT-P13 and infliximab of greater than −20%.

RESULTS: A CDAI-70 response at week 6 was achieved by 77/111 (69.4%, 95%CI: 59.9 to 77.8) participants assigned to receive CT-P13 as compared with 81/109 (74.3%, 65.1 to 82.2) participants assigned to receive reference product infliximab, equating to a difference of −4·9% with 95% confidence interval of −16.9 to 7.3 which was within the prespecified non-inferiority criteria. At week 30, CDAI-70 response rates were 76.6% (95%CI: 67.6 to 84.1) in the biosimilar group and 75.2% (95%CI: 66.0 to 83.0) in the reference product group equating to a difference of 1.3% (95%CI: −10.3 to 12.9). At week 54, CDAI-70 response rates were 78.6% in those that had continued treatment biosimilar infliximab, 70.4% in those who continued treatment with reference product infliximab, 70.9% in those who switched from biosimilar to reference product and 76.4% in those that switched from reference product to biosimilar. Infusion related reactions occurred in 8 (7.2%) participants in the biosimilar group prior to week 30 as compared with 9 (8.3%) participants in the reference product group. At week 30, infusion reactions occurred in one participant from the group that continued reference product and one participant that switched from biosimilar to reference product. A single participant in the group that continued biosimilar infliximab experienced an infusion reaction after week 30. Anti-drug antibodies were detected in 15 (14%) participants in the biosimilar group as compared with 19 (17%) in the reference product group at week 14 and in 43 (39%) in the biosimilar group as compared with 49 (45%) in the reference product group at week 30. At week 54, antidrug antibodies were detected in 22 (39%) participants in the group that continued the biosimilar, in 21 (39%) participants that continued reference product, in 18 (33%) participants that switched from biosimilar to reference product and in 30 (55%) participants that switched from reference product to biosimilar. Antidrug antibody positivity at week 54 but not at weeks 14 or 30 occurred in two participants in the group that continued the biosimilar, three participants that switched from biosimilar to reference product and seven that switched from reference product to biosimilar. Neutralising anti-drug antibodies were first detected at week 54 in one participant from the group that continued the biosimilar and one participant that switched from biosimilar to reference product.

Return to OVERVIEW

RITUXIMAB

Suh et al: Long-Term Efficacy and Safety of Biosimilar CT-P10 Versus Innovator Rituximab in Rheumatoid Arthritis: 48-Week Results from a Randomized Phase III Trial[6]

SPONSOR: Celltrion

REFERENCE PRODUCT: Mabthera® (EU), Roche and Rituxan® (US), Genentech

OBJECTIVE(S): To investigate long-term clinical outcomes of extended treatment for up to 48 weeks with biosimilar rituximab (CT-P10) as compared with reference product in participants with rheumatoid arthritis (RA).

DESIGN: Randomized, double-blind, active-controlled, parallel-group phase III study

SAMPLE SIZE: As described previously[a], 161 participants were randomised to CT-P10, 151 to US-reference product and 60 to EU-reference product. A second treatment course was administered to 140/161 (87.0%) participants in the CTP-10 arm, 134/151 (88.7%) in the US-reference product arm and 56/60 (93.3%) in the EU-reference product arm

PATIENT CHARACTERISTICS: Participants aged 18–75 years with active rheumatoid arthritis (1987 American College of Rheumatology criteria) at least 6 months prior to randomisation with ≥6 swollen joints and ≥6 tender joints, and serum CRP ≥1.5 mg/dL or an ESR ≥28 mm/hour. Participants had received methotrexate (at least 7.5mg) for at least 12 weeks and had experienced an inadequate response or were intolerant to anti-TNF agents and had not received rituximab. At baseline anti-drug antibodies were detected in 19 participants randomised to the CT-P10 group and 20 participants in the reference product group.

EQUIVALENCE CRITERIA: Equivalence criteria was based on DAS-28-CRP response at 24 weeks and was previously reported. This manuscript reports on the outcomes at week 48.

RESULTS: At week 48 the mean decrease (±SD) in DAS28-CRP from baseline was −2.7 ± 1.2 for the CT-P10 group as compared with −2.6 ± 1.3 in the combined reference product groups which was similar to the week 24 values of − 2.3 ± 1.1 in the CT-P10 and −2.3 ± 1.2 in the combined reference product group. At week 48, low disease activity was achieved by 17.3% of participants in the CT-P10 group as compared with 11.4% in the combined reference product group whilst remission was achieved in 17.3% and 22.8% CT-P10 and combined rituximab groups, respectively. Anti-drug antibodies were detected at week 48 in seven participants in the CTP-10 group as compared with 18 in the combined reference product group with one participant from each group testing positive to neutralising anti-drug antibodies.

[a] Park W, Bozic-Majstorovic L, Milakovic D et al. Comparison of biosimilar CT-P10 and innovator rituximab in patients with rheumatoid arthritis: a randomized controlled Phase 3 trial. mAbs 2018; 10: 934-43

Return to OVERVIEW

BEVACIZUMAB

Thatcher et al: Efficacy and Safety of the Biosimilar ABP 215 Compared with Bevacizumab in Patients with Advanced Nonsquamous Non–small Cell Lung Cancer (MAPLE): A Randomized, Double-blind, Phase III Study[7]

SPONSOR: Amgen Inc

REFERENCE PRODUCT: Avastin®, Roche

OBJECTIVE(S): To compare clinical efficacy and safety of a proposed bevacizumab biosimilar (ABP 215) with bevacizumab reference product (Avastin®) in patients with advanced non-squamous non–small cell lung cancer (NSCLC) receiving first-line chemotherapy with carboplatin and paclitaxel

DESIGN: Randomized, double-blind, active-controlled

SAMPLE SIZE: A total of 642 patients were randomized to ABP 215 (n = 328) and reference product bevacizumab (n = 314), 324 (98.8%) and 309 (98.4%) patients in the ABP 215 and bevacizumab group, respectively, received at least 1 dose.

PATIENT CHARACTERISTICS: Participants with histologically or cytologically confirmed, stage IV or recurrent metastatic non-squamous NSCLC with measurable disease according to the modified RECIST v1.1

EQUIVALENCE CRITERIA: Containment of the 90% confidence interval for the risk ratio in the objective response rate (ORR), defined as the rate of the best overall response of either complete response (CR) or partial response (PR) according to RECIST v1.1, between ABP 215 and reference product within the prespecified equivalence margin of 0.67 to 1.5.

RESULTS: A total of 128 (39.0%) participants in the ABP 215 arm achieved an objective response as compared with 131 (41.7%) in the reference product arm, equating to a risk ratio for the ORR of 0.93 with a 90% confidence interval of 0.80 to 1.09 which was within the predefined equivalence criteria. Two complete responses were observed in each arm. Serious adverse events occurred in 26.2% of participants in the ABP 215 arm as compared with 23.0% in the reference product arm. Hypertension occurred in 6.8% of participants in the ABP 215 arm as compared with 5.5% in the reference arm whilst gastrointestinal perforation occurred in 3 participants in the biosimilar arm and 4 participants in the reference product arm. Anti-drug antibodies were detected in 4 participants in the biosimilar arm and 7 participants in the reference product arm and were transient in 3 participants from each arm. No neutralising antibodies were detected.

Return to OVERVIEW

PEGFILGRASTIM

Kahan et al: Efficacy and safety of RGB-02, a pegfilgrastim biosimilar to prevent chemotherapy-induced neutropenia: results of a randomized, double-blind phase III clinical study vs. reference pegfilgrastim in patients with breast cancer receiving chemotherapy[8]

SPONSOR: Gedeon Richter

REFERENCE PRODUCT: Neulasta®, Amgen

OBJECTIVE(S): To evaluate efficacy and safety of a proposed pegfilgrastim biosimilar (RGB-02) in breast cancer patients receiving up to 6 cycles of chemotherapy with doxorubicin and docetaxel

DESIGN: Prospective, randomized, double-blind, parallel-group, multinational, multicentric trial

SAMPLE SIZE: 239 participants randomized 1:1 to RGB-02 (n = 121) and the reference product (n = 118). Participants in the reference group switched to RGB-02 for the third and subsequent chemotherapy cycles.

PATIENT CHARACTERISTICS: Chemotherapy-naïve women ≥18 and ≤ 65 years of age with invasive breast cancer (Stage IIB and III)

EQUIVALENCE CRITERIA: Containment of the 95% confidence interval of the difference in the mean duration of severe neutropenia, defined as an absolute neutrophil count < 0.5 $x10^9$/L, between -1 and +1 days following the first cycle of chemotherapy.

RESULTS: The mean duration of severe neutropenia following chemotherapy cycle 1 was 1.7 (± 1.14) days in the RGB-02 group as compared with 1.6 (± 1.31) days in the reference product group, equating to a least squares mean difference of 0.1 days (95% CI: -0.2 to 0.4) which was within the defined equivalence criteria. Bone pain was the most frequently reported pegfilgrastim related adverse event which occurred in 14 participants (11.6%) in the RGB-02 group as compared with 20 participants (17.1%) in the reference product group. No samples were confirmed as positive for anti-drug antibodies during either the double-blind phase (chemotherapy cycles 1 and 2) or subsequent chemotherapy cycles.

Return to OVERVIEW

Waller et al: Randomized phase 3 efficacy and safety trial of proposed pegfilgrastim biosimilar MYL-1401H in the prophylactic treatment of chemotherapy-induced neutropenia

SPONSOR: Mylan Inc and Biocon Ltd

REFERENCE PRODUCT: Neulasta® (EU), Amgen

OBJECTIVE(S): To demonstrate equivalence in the safety and efficacy of a proposed pegfilgrastim biosimilar (MYL-1401H) with reference product pegfilgrastim in the prophylaxis of chemotherapy induced neutropenia in participants with breast cancer receiving neoadjuvant or adjuvant TAC (docetaxel 75 mg/m^2, doxorubicin 50 mg/m^2, cyclophosphamide 500 mg/m^2) chemotherapy

DESIGN: Randomized, double-blind, parallel-group trial

SAMPLE SIZE: 194 participants randomized 2:1, MYL-1401H = 127, reference pegfilgrastim = 67

PATIENT CHARACTERISTICS: Aged ≥ 18 years with newly diagnosed stage II/III breast cancer and adequate staging workup and surgery if receiving adjuvant therapy, chemotherapy and radiotherapy naïve, Eastern Cooperative Oncology Group performance status ≤ 1, baseline absolute neutrophil count ≥ 1.5 × 10^9/L; anti-drug antibody positive at baseline: MYL- 1401H = 15% (19/126) vs reference product = 18% (12/67); no participants had neutralising anti-drug antibodies.

EQUIVALENCE CRITERIA: Containment of the 2-sided 95% confidence interval for the difference in the least square mean duration of severe neutropenia, defined as days with absolute neutrophil count less than 0.5 × 10^9/L in chemotherapy cycle 1 within the range of ± 1 day.

RESULTS: The mean duration of severe neutropenia in the MYL-1401H group was 1.2 days (± 0.93) as compared to 1.2 days (± 1.10) in the reference product group. The 95% confidence interval for the difference in least squares mean duration of severe neutropenia was -0.285 to 0.298 days which was within the prespecified equivalence range of ± 1 day. Treatment emergent adverse events occurred in 90% (n=114) of participants in the MYL-1401H as compared with 87% (n=58) of participants in the reference product group. Of those negative for anti-drug antibodies at baseline, a single participant in the reference product group and no participants in the MYL-1401H group subsequently tested positive.

Return to OVERVIEW

DARBEPOETIN

Lee et al: Efficacy and safety of CKD-11101 (darbepoetin alfa proposed biosimilar) compared with NESP in anaemic chronic kidney disease patients not on dialysis

SPONSOR: Chong Kun Dang pharm

REFERENCE PRODUCT: NESP®, Kyowa Hakko Kirin

OBJECTIVE(S): To evaluate the efficacy and safety of a proposed darbepoetin biosimilar (CKD-11101) as compared with reference product darbepoetin in the management of anaemia in participants with chronic kidney disease who are not on dialysis and to assess the long-term safety of CKD-11101, including switching from reference product to CKD-11101.

DESIGN: Randomized, double-blind, multi-centre phase III

SAMPLE SIZE: 248 participants were randomized, CKD-11101 = 118, reference product = 130

PATIENT CHARACTERISTICS: participants aged ≥19 years of age with chronic kidney disease stage three or higher (estimated glomerular filtration rate of <60 mL/min/ 1.73 m2 by the Modification of Diet in Renal Disease study (MDRD) equation) and not on dialysis; haemoglobin levels ≥ 8 g/dL and ≤ 10 g/dL, ferritin levels ≥ 100 ng/mL and transferrin saturation ≥ 20%, no history of antibodies or hypersensitivity to erythropoietin

EQUIVALENCE CRITERIA: Containment of the 95% confidence interval for the difference in the change in mean haemoglobin level within a range of ± 0.5 g/dL and containment of 95% confidence interval for the difference in the mean darbepoetin dose within a range of ±36 mcg at the end of a 4-week evaluation period following a 20-week stabilisation period.

RESULTS: The difference in mean haemoglobin level change between the proposed biosimilar and reference product groups was 0.01 g/dL with a 95% confidence interval of 0.213 to 0.242 which was within the predefined equivalence criteria. The difference in mean dose between the proposed biosimilar and reference product groups 1.40 mcg with a 95% confidence interval of -6.859 to 4.059 which was within the predefined equivalence criteria. In the first 24-weeks there were no significant differences between the proposed biosimilar and reference product groups in the incidence of adverse events ($p > 0.05$). At 52 weeks there were no adverse drug reactions in the group that continued treatment with CKD-11101 as compared with four (details not provided) in the group that switched from reference product to CKD-11101 ($p = 0.128$).

Pharmacoeconomic Analyses

Once biosimilarity of potential biosimilars against the reference product 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, 2 publications were identified that examined the economic impact of the introduction of biosimilars.

Hornyák et al: Price competition and reimbursement of biosimilar granulocyte-colony stimulating factor in Hungary [9]

SPONSOR: Hungarian Government and the European Union

LOCATION(S): Hungary

DATES: Between 1 July 2011 and 30 June 2014

DESIGN: Data derived from the financing database of the single health-care financing agency, the Hungarian National Health Insurance Fund Administration (NHIFA), was used to retrospectively analyse change in the number of patients and change in expenditure, from public drug turnover data published by the NHIFA.

OBJECTIVE(S): To examine the impact of two consecutive drug financing bids on changes in use of originator and biosimilar filgrastim over two 12-month periods (1 July 2012 to 30 June 2013 and 1 July 2013 to 30 June 2014), compared to the preceding 12 months (1 July 2011 – 30 June 2012).

RESULTS: A 44% reduction in expenditure was observed in the first year of the financing bids, due to a 74% reduction in originator use and 143% increase in biosimilar use. Similar results were seen in the second year of the bid process (overall -52% expenditure; originator -81% and biosimilar +133%). During the first year a 4.5% reduction in the number of patients treated (13,352 patients) was observed, compared to the 12 months prior to the bid process (13,972 patients), with a further 1.3% reduction during the second year.

REVIEWER COMMENTARY: The authors stated that a limitation of the study was "*the reason behind the drop in patient numbers has not been studied*" and noted that "*regulations for the use of the drugs have not changed during the study period*".

Return to OVERVIEW

Grynberg et al: A cost-effectiveness analysis comparing the originator follitropin alfa to its biosimilars in patients undergoing a medically assisted reproduction program from a French perspective [10]

SPONSOR: Merck Santé S.A.S.

LOCATION(S): France

DATES: Costs pertaining to drugs, hospitalizations, specialist visits, and examinations were based on 2017 tariffs

DESIGN: Costs were retrieved from the French Programme de Medicalisation des Systemes d'Information (PMSI) hospital database, literature review, and French clinical experts. Live birth rates were obtained from phase III clinical trials demonstrating biosimilarity between originator follitropin alfa (Gonal-F®) and biosimilar (Ovaleap® and Bemfola®).

OBJECTIVE(S): To assess the cost-effectiveness of the originator follitropin alfa (Gonal-F®) in patients undergoing a medically assisted reproduction program in comparison to biosimilar follitropin alfa (Bemfola® and Ovaleap®) in France.

RESULTS: Based on the treatment costs of €3826 and €3567, and live birth rates of 32% and 27% for the comparison of Gonal-F® and Ovaleap® (taking into account Ovarian Hyperstimulation Syndrome), the originator was the cost-effective strategy with an ICER of €4804. Similar results were seen in the comparison of Gonal-F® and Bemfola® with an ICER of €3275, based on treatment costs of €4122 and €3843 and live birth rates of 40% and 32% for the originator and biosimilar respectively.

REVIEWER COMMENTARY: This cost-effectiveness analysis is based upon the assumption of a difference in live birth rates, however it should be noted that the live birth rates used in this study were obtained from the phase III clinical trials which were not statistically significantly different and these phase III trials were not powered for this endpoint.

Return to OVERVIEW

BIOSIMILAR MEDICINE UPTAKE

This theme encompasses papers examining the current practice of prescribers, pharmacists and patients, and the policy informing such,

During the update period, no papers were published examining this theme.

HEALTH OUTCOMES AND ADVERSE EVENTS

Within the period encompassed by this update, there have been 11 papers that have examined pharmacovigilance of biosimilar medicines, specifically the impact of substitution, switching and extrapolation of indication.

INFLIXIMAB

Goll et al: Long-term efficacy and safety of biosimilar infliximab (CT-P13) after switching from originator infliximab: Open-label extension of the NOR-SWITCH trial[11]

SPONSOR: Non-commercial

LOCATION(S): Norway

DESIGN: 26-week open label extension study to the previously reported 52-week randomised, double blind, parallel-group study[b]

DATES: Participants were unblinded on October 17th 2016 at which time all but 68 participants had completed the extension study.

OBJECTIVE(S): To compare the efficacy and safety outcomes switching to biosimilar infliximab (CT-P13) after 52 weeks of treatment with originator infliximab with those associated with continuous treatment with biosimilar infliximab.

PATIENT CHARACTERISTICS: A total of 380 participants out of the original 482 participants in the NOR-SWITCH study participated in the extension study; 187 participants continued treatment with biosimilar infliximab and 183 switched from originator to biosimilar infliximab. The extension study cohort consisted of 127 (33%) participants with Crohn's disease, 80 (21%) with ulcerative colitis, 67 (18%) ankylosing spondylitis, 55 (15%) with rheumatoid arthritis, 20 (5%) with psoriatic arthritis and 31 (8%) with psoriasis.

OUTCOME(S): The primary end-point was disease worsening, defined as worsening in disease-specific composite measures and/or a consensus on disease worsening between investigator and patient leading to major change in treatment, during the 26-week extension period follow-up.

RESULTS: At the end of the 26-week extension period 116 (61.1%) participants in the group that continued biosimilar infliximab and 117 (67.6%) participants in the group that switched from originator to biosimilar were in clinical remission. This corresponds to an adjusted rate difference of -4.9% (95%CI: -13.4 to 3.7). Disease worsening occurred in 32 (16.8%) participants in the group that continued biosimilar infliximab as compared with 20 (11.6 %) participants in the group that switched from originator to biosimilar, corresponding to an adjusted risk difference of 5.9% (95%CI: -1.1 to 12.9). Adverse events were reported in 87 (44%) and 74 (40%) of participants in the groups that continued biosimilar infliximab and switched from originator to biosimilar, respectively. Anti-drug antibodies were detected during the extension period in 5 participants in the group that continued biosimilar infliximab and in 4 participants in those who switched from originator to biosimilar.

[b] Jørgensen KK, Olsen IC, Goll GL et al. 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. Lancet 2017; 389(10086): P2304-2316.

Return to OVERVIEW

Ilias et al: Outcomes of Patients with Inflammatory Bowel Diseases Switched from Maintenance Therapy with a Biosimilar to Remicade[12]

SPONSOR: Non-commercial

LOCATION(S): Hungary

DESIGN: Prospective, observational

DATES: Post-September 2017

OBJECTIVE(S): To evaluate the outcomes associated with switching from biosimilar infliximab (CT-P13) to originator infliximab in patients with inflammatory bowel disease.

PATIENT CHARACTERISTICS: 174 patients, Crohn's disease = 136, ulcerative colitis =38; prior exposure to originator infliximab = 11% (Crohn's disease), 7.9% (ulcerative colitis); proportion receiving concomitant azathioprine = 50.7% (Crohn's disease), 35.1% (ulcerative colitis); median Crohn's disease activity index (CDAI) at switch = 57 (IQR: 32-112), median partial Mayo (pMayo) score at switch = 1 (IQR: 0–2)

OUTCOME(S): Change in disease activity measures, proportion of patients in remission, anti-drug antibody positivity, infliximab trough concentrations

RESULTS: There were no statistically significant differences in the mean CDAI and pMayo scores at week -8 prior to switch, baseline (at time of switch), 16 weeks post switch and 24 weeks post switch (Crohn's disease, p=0.53, ulcerative colitis, p=0.57). There were no significant differences in the proportion of patients in clinical remission across those time points (p=0.98) and there were no differences in anti-drug antibody positivity (p=0.87) or mean infliximab trough concentrations (p=0.071). A single patient with Crohn's disease who was anti-drug antibody negative at the time of switching developed high anti-drug antibody positivity. Four infusion reactions occurred through to week 24, all of which occurred in patients with detectable anti-drug antibodies prior to switching.

Return to OVERVIEW

Layegh et al: Efficacious transition from reference infliximab to biosimilar infliximab in clinical practice[13]

SPONSOR: None

LOCATION(S): Reade, Netherlands

DESIGN: Single centre retrospective cohort study

DATES: Analysis conducted in January 2018, switching in September 2015 – June 2016

OBJECTIVE(S): To describe the outcomes associated with switching from originator infliximab to biosimilar infliximab in patients with rheumatoid arthritis and psoriatic arthritis.

PATIENT CHARACTERISTICS: 47 patients offered switch to biosimilar infliximab, 45 patients agreed to switch, 41 patients with rheumatoid arthritis, 4 patients with psoriatic arthritis; median disease duration = 17 years, median duration of treatment with originator infliximab = 11 years, concomitant methotrexate = 31 (69%)

OUTCOME(S): Treatment retention rate

RESULTS: At 2 years post-switching, 39 (87%) patients were still receiving biosimilar infliximab. Two patients had switched to an alternative treatment due to inefficacy. Three patients switched back to originator infliximab "*due to inefficacy according to the patients; however, this could not be objectified by the rheumatologist*" within 2-5 months of switching to the biosimilar. At 2 years, one of these patients remained on originator infliximab and two had ceased infliximab treatment.

Return to OVERVIEW

van Hoeve et al: Efficacy, pharmacokinetics and immunogenicity is not affected by switching from infliximab originator to a biosimilar in pediatric patients with inflammatory bowel disease[14]

SPONSOR: None

LOCATION(S): University Hospitals Leuven, Belgium

DESIGN: Prospective, observational

DATES: Maintenance therapy between July 2017 and January 2018

OBJECTIVE(S): To evaluate the long-term changes in infliximab trough concentrations, immunogenicity and remission rates during maintenance in paediatric patients with inflammatory bowel disease who were switched from originator infliximab to biosimilar infliximab (CT-P13).

PATIENT CHARACTERISTICS: 42 patients were eligible for the study, Crohn's disease = 26, ulcerative colitis = 16; median age at initiation of infliximab = 12.6 years (9.4-14.3); median disease duration prior to starting infliximab = 3.5months (2.0-9.0); median duration of originator infliximab treatment = 13.5 months (6.8-35.5); proportion of patients in remission at last infusion prior to switching = 76.2% (32/42), 6 patients did not have maintenance trough infliximab concentration data.

OUTCOME(S): The primary aim was to evaluate whether there was a significant difference between infliximab trough concentrations and/or anti-drug antibodies after switching to the biosimilar infliximab over a one year period.

RESULTS: There was no difference (p=0.900) in the median infliximab trough concentration six months prior to switching (5.7 μg/mL) as compared with six months post-switching (6.5 μg/mL). There was no difference (p= 0.171) in the median infliximab dose at the last dose prior to switching (8.0 mg/kg range: 6.7-10.8) as compared with six months post switching (8.0 mg/kg, range: 6.7-13.3). A single patient developed low level anti-drug antibodies in the six months after switching which coincided with the cessation of concomitant azathioprine in the context of disease remission.

Return to OVERVIEW

Riller et al: Infliximab biosimilar for treating neurosarcoidosis: tolerance and efficacy in a retrospective study including switch from the originator and initiation of treatment[15]

SPONSOR: None

LOCATION(S): Pitié-Salpêtrière Hospital, Assistance Publique Hôpitaux de Paris, France

DESIGN: Retrospective single-centre

DATES: Patients treated with biosimilar infliximab between February 2016 and August 2018

OBJECTIVE(S): To describe the efficacy and tolerability of biosimilar infliximab in neurosarcoidosis including switching from originator infliximab to biosimilar.

PATIENT CHARACTERISTICS: 20 patients with neurosarcoidosis, meningeal involvement (n = 15), cerebral involvement (n = 10), myelitis (n = 9), and/or cranial nerve involvement (n = 5); 12 patients received biosimilar infliximab only, 8 patients received the originator infliximab and were considered to be in partial or complete remission when switched to biosimilar, median duration of originator infliximab = 22.5 months (range 5–60)

OUTCOME(S): Disease activity as assessed using the extra-pulmonary physician organ severity tool (ePOST)

RESULTS: The median duration of follow-up was 25 months (19–28). A total of six patients relapsed following introduction of biosimilar infliximab. There was no statistical difference in the relapse rates (p = 0.40) and time-to-relapse (p = 0.51) between the group that had previously received originator infliximab and switched to biosimilar compared with those only receiving the biosimilar treatment groups. Of the six patients that relapsed, five patients switched to the originator of whom four did not improve and were subsequently switched back to the biosimilar. Of the 20 patients included in the study, 16 were tested for the presence of anti-drug antibodies and no patients tested positive.

REVIEWER COMMENTARY: Details regarding clinical response of the patients who were switched to originator infliximab and then switched back to biosimilar infliximab are not provided. The basis for the selection of the 16/20 patients who underwent anti-drug antibody testing was not provided.

Return to OVERVIEW

Kim et al: Long-term efficacy and safety of CT-P13, a biosimilar of infliximab, in patients with inflammatory bowel disease: A retrospective multicenter study[16]

SPONSOR: None

LOCATION(S): Korea

DESIGN: Retrospective, 16 centres

DATES: Patients treated between July 2012 and December 2017

OBJECTIVE(S): To evaluate the long-term efficacy and safety of biosimilar infliximab (CT-P13) in adults with Crohn's disease and ulcerative colitis

PATIENT CHARACTERISTICS: 368 patients, 227 with Crohn's disease and 141 with ulcerative colitis; anti-TNF therapy naïve = 149 (Crohn's disease), 118 (ulcerative colitis); switched from originator to biosimilar = 78 (Crohn's disease), 23 (UC); duration of treatment with originator infliximab = not stated, mean number of CT-P13 infusions = 17.9 (Crohn's disease), 13.6 (ulcerative colitis)

OUTCOME(S): Retention rates at 1, 3 and 5 years, Disease activity as assessed using the Crohn's Disease Activity Index (CDAI) and Mayo scores or partial Mayo scores (Mayo score without endoscopy) for ulcerative colitis

RESULTS: Amongst the anti-TNF therapy naïve group the retention rates at 1, 3, and 5 years was 86.1%, 68.5%, and 58.7% in Crohn's disease patients, respectively, and 69.7%, 46.0%, and 26.7% in ulcerative colitis patients, respectively. Whilst amongst the patients that switched from originator to biosimilar infliximab the retention rates at 1, 3, and 5 years was 88.5%, 66.1%, and 44.8% in Crohn's disease patients, respectively, and 73.9%, 42.5%, and 42.5% in ulcerative colitis patients, respectively. These retention rates were not statistically significantly different from the values observed in the anti-TNF naïve patients at the same timepoints (Crohn's disease: P=0.623, ulcerative colitis: P=0.973).

A total of 51 patients (13.9%) experienced an adverse event during treatment with biosimilar infliximab, of whom 16 (4.3%) discontinued CT-P13 therapy due to the adverse event after a median of 6 infusions (IQR 4.3-7.8).

Return to OVERVIEW

Macaluso et al: POSIB SB2—a Sicilian prospective observational study of IBD patients treated with infliximab biosimilar SB2[17]

SPONSOR: None

LOCATION(S): Sicily, Italy

DESIGN: Multicentre, observational, prospective study

DATES: Consecutive patients starting treatment with SB2 after March 2018 – September 2018 Results are presented for the first 6 months.

OBJECTIVE(S): To describe the safety and efficacy of biosimilar infliximab (SB2) in patients with inflammatory bowel disease.

PATIENT CHARACTERISTICS: 77 patients, infliximab naïve = 66 (85.7%), Switched from originator infliximab to SB2 = 8 (10.4%), switched from biosimilar infliximab (CT-P13) to biosimilar infliximab (SB2) = 3 (3.9%); concurrent azathioprine 2 (2.6%), concurrent methotrexate = 3 (3.9%), steroid dependent = 46 (59.7%), steroid refractory = 7 (9.1%)

OUTCOME(S): The primary end-point is the rate of serious adverse events. The secondary end points include the of proportion of patients achieving steroid-free clinical remission (defined by a Harvey-Bradshaw Index <5 for Crohn's disease and Partial Mayo Score <2 for ulcerative colitis) and treatment response (reduction in Harvey–Bradshaw Index ≥3 for Crohn's disease and Partial Mayo Score ≥2 for ulcerative colitis compared with baseline) at 8 weeks.

RESULTS: The mean follow-up reported in this ongoing study was 2.2 (± 1.7) months, equating to a cumulative number of infusions of SB2 of 215. Serious adverse events were reported in seven patients (9.1%) including three infusion reactions, three arthritic flares and a single case of flu-like symptoms. Of 35 patients that had completed follow-up at 8 weeks, 17 patients (48.6%) were in steroid-free remission, eight patients (22.8%) had achieved a partial response and 10 had no response (28.6%).

REVIEWER COMMENTARY: The details of the baseline characteristics specifically for the 35 patients with follow-up at 8 weeks were not provided.

Return to OVERVIEW

ETANERCEPT and INFLIXIMAB

Lund et al: Effectiveness and safety of switching to biosimilar infliximab and etanercept in patients with psoriasis[18]

SPONSOR: None

LOCATION(S): Department of Dermatology, Bispebjerg Hospital, Copenhagen, Denmark

DESIGN: Retrospective analysis of the DERMBIO registry

DATES: Patients switched between March 1st 2015 and October 1st 2017

OBJECTIVE(S): To describe the treatment effect and adverse events after switching from the originator etanercept and infliximab to the biosimilar.

PATIENT CHARACTERISTICS: 69 patients with moderate to severe psoriasis, 45 switched from originator infliximab to biosimilar infliximab, 24 switched from originator etanercept to biosimilar etanercept

ENDPOINT(S): Patient reported outcomes, Psoriasis Area and Severity Index (PASI), Dermatology Life Quality Index (DLQI)

RESULTS: Following switching to the biosimilar product, 33 (73.3%) patients receiving infliximab and 14 (58.3%) of patients receiving etanercept reported the "*same or better*" effect whilst 12 (26.7%) patients receiving infliximab and 10 (41.7%) patients receiving etanercept reported feeling "worse". The authors note that "*…these patients were generally well-treated with close-to-zero in PASI score before switching, the absolute mean change in PASI was small in each group and not different among patients who reported the same or a better effect compared to patients reporting a worse effect after switching.*" Following switching to the biosimilar the DLQI remained the same or improved in 69% of patients receiving either drug. Following switching the proportion of patients reporting an adverse event increased from 6.7% (n=3) to 22.2% (n=10) in the infliximab group and from 0% to 16.7% (n=4) in the etanercept group with newly reported adverse events of fatigue, gastrointestinal complaints and pruritus.

REVIEWER COMMENTARY: Statistical analysis of the PASI and DLQI results was not performed. The authors noted that patients "*were given the opportunity to specifically report adverse events and change in effectiveness after the switch from the original drug to the biosimilar*" and that "*A limitation of real-life studies is the unblinded nature of the comparisons, which tends to inflate the role of patient subjectivity*".

Return to OVERVIEW

ETANERCEPT

Pescitelli et al: Clinical experience with the etanercept biosimilar SB4 in psoriatic patients[19]

SPONSOR: None

LOCATION(S): Florence University Dermatological Unit, Tuscany, Italy

DESIGN: Observational, not further specified

DATES: Not specified

OBJECTIVE(S): To describe the safety and efficacy of biosimilar etanercept (SB4) in patient with moderate to severe psoriasis and or psoriatic arthritis who were switched from originator etanercept or were etanercept naïve.

PATIENT CHARACTERISTICS: 44 patients, mean age = 54.7 years; mean duration of disease = 24.7 years; prior biologic treatment = 7; etanercept naïve = 12, mean PASI score prior to commencing SB4 = 13.09+ 2.25; switching from originator to SB4 = 32, duration of originator etanercept = 67.15+26.41 months, mean PASI score prior to switch to SB4 = 2.15+1.88

ENDPOINT(S): Disease activity as assessed according the PASI and DAS28 at 12 and 24 weeks after switching to or initiating etanercept treatment with SB4

RESULTS: Amongst those that switched from originator etanercept to SB4, when comparing baseline values with week 12 and 24 there were no statistically significant differences in the DAS28 whilst the PASI decreased from 2.15+1.88 at baseline to 1.51+1.35 at week 12 and 1.20+1.15 at week 24 ($P < 0.001$). Injection site reaction occurred in 4 patients.

Amongst those who were naïve to etanercept, a greater than 50% improvement in PASI score was observed in 8 out of 12 patients as soon as week 12, with a 75% improvement observed in 9 out of 10 at week 24. Two patients discontinued at week 16 as a result of disease worsening.

Return to OVERVIEW

RITUXIMAB

Tony et al: Safety and Immunogenicity of Rituximab Biosimilar GP2013 After Switch From Reference Rituximab in Patients With Active Rheumatoid Arthritis[20]

SPONSOR: Sandoz, Hexal AG

LOCATION(S): 54 centres across US, Germany, Poland, and Hungary

DATES: Not specified

DESIGN: Randomized, double-blind, controlled study

OBJECTIVE(S): To evaluate the safety of switching from reference rituximab to biosimilar rituximab (GP2013) compared with treatment continuation with reference rituximab in patients with rheumatoid arthritis who had received at least one full treatment course of reference rituximab 6 to 18 months prior to randomization and received a stable dose methotrexate and folic acid for at least 4 weeks prior to randomization.

PATIENT CHARACTERISTICS: 107 patients, switching to GP2013 = 53, continuing reference rituximab = 54; mean number of previous rituximab courses = 4.1 ± 3.3 (switching) vs 5.0 ± 3.8 (continue reference); mean time since last rituximab course (weeks) = 35.8 ± 13.2 (switching) vs 39.85 ± 15.0 (continue reference); mean methotrexate dose (mg/week) = 14.5 ± 6.2 (switching) vs 15.5 ± 5.1 (continue reference), percent receiving corticosteroids = 43.4% (switching) vs 48.1% (continue reference), mean prednisolone equivalent dose (mg) = 5.4 ± 1.8 (switching) vs 4.6 ± 2.4 (continue reference); number of participants positive for anti-drug antibodies at screening = 1 (switching) vs 1 (continue reference)

OUTCOMES: The incidence of infusion-related reactions, anaphylactic reactions, hypersensitivity and anti-drug antibodies at weeks 2, 12 and 24.

RESULTS: Infusion related reactions occurred in 6/53 (11.3%) participants in the switching group as compared with 10/54 (18.5%) in the group that continued reference rituximab, equating to a difference of −7.2% (95%CI: −26.0 to 11.4). The infusion reaction was considered severe in one participant in the switching group. Hypersensitivity reactions occurred in 5/53 (9.4%) participants in the switching group as compared with 6/54 (11.1%) in the group that continued reference rituximab, equating to a difference of −1.7% (95%CI: −20.6 to 16.9). Hypersensitivity was considered severe in one participant in the switching group. One participant who was negative for anti-drug antibodies at screening and in the group that continued reference rituximab developed anti-drug antibodies during follow-up. No adverse events were reported in this participant. The two participants who were anti-drug antibody positive at screening were negative at all other time points.

Return to OVERVIEW

Stubbs et al: Comparison of Rituximab originator (MabThera) to biosimilar (Truxima) in patients with immune-mediated thrombotic thrombocytopenic purpura[21]

SPONSOR: None

LOCATION(S): UCLH, London, United Kingdom

DATES: May 2016 to May 2018, institutional switch to biosimilar rituximab in May 2017

DESIGN: Observational

OBJECTIVE(S): To compare the outcomes associated with the use of originator and biosimilar rituximab (Truxima®) for acute immune-mediated thrombotic thrombocytopenic purpura (iTTP) episodes or preventatively in patients in which the ADAMTS13 (a target of auto-antibodies in iTTP) levels had decreased from normal range to less than 20 iu/dL.

PATIENT CHARACTERISTICS: Forty-five patients were treated with originator rituximab (MabThera®) and 39 with the rituximab biosimilar (Truxima®); acute treatment median platelet counts at day 1 = 18x10^9/L (95% CI: 9–34) (originator) vs 14x10^9/L (95% CI: 6–18) (biosimilar)

OUTCOMES: Treatment response as assessed by platelet counts, ADAMTS13 activity, and CD19 levels at day 1 (D1), day 28 (D28) and 3 months.

RESULTS: Both groups received a median number of infusions of 4 (range 1–8). In patients receiving treatment for an acute episode the median dose was 375 mg/m^2. However, for patients receiving preventative therapy, the median dose of originator rituximab was 500 mg whilst in the biosimilar group 10 patients (52%) received 375 mg/m^2 whilst 9 (47%) received a flat dose of 500 mg.

Amongst patients treated acutely, the median platelet counts at day 28 were 246 x10^9/L (95%CI: 174–326) in patients treated with originator rituximab as compared with 226 x10^9/L (95%CI: 194–283) in those receiving biosimilar rituximab and at 3 months, median platelet counts were 265 x10^9/L (95%CI: 217–318) and 245 x10^9/L (95%CI: 223–321), respectively. There were no statistically significant differences between the group receiving originator or biosimilar at any time point for platelet counts (D28 P = 0.77, 3 months P = 0.71), ADAMSTS13 (D28 P = 0.27, 3 months P = 0.26) or CD19 levels (D28 P = 0.14, 3 months P = 0.56).

Amongst patients receiving preventative therapy, the median platelet counts at D28 were 272 x10^9/L (95%CI: 258–297) in those receiving originator rituximab as compared with 267 x10^9/L (95%CI: 253–314) for those receiving biosimilar rituximab and at 3 months median platelet counts were 273 x10^9/L (95%CI: 246–317) and 273 x10^9/L (95%CI: 234–328) respectively. There were no statistically significant differences between the group receiving originator or biosimilar at any time point for platelet counts (D28 P = 0.68, 3 months P = 0.99) or ADAMSTS13 (D28 P = 0.61, 3 months P = 0.34). The median CD19 percentage at day 1 did not differ between the groups (originator = 13.0%, 95%CI: 10.2–19.4 vs biosimilar = 12.2%, 95%CI: 8.59–13.3, P = 0.22) but at day 28 it was statistically significantly lower (P = 0.0042) in the biosimilar group at 0.02% (95%CI: 0.01–0.05) as compared with 0.09% (95%CI: 0.05–0.14) in the originator group. However, at 3 months there was again no difference between the groups (biosimilar = 0.03%, 95%CI: 0.01–0.22 vs originator = 0.08, 95%CI: 0.05–0.13, P = 0.19).

The authors estimated that switching from originator rituximab to biosimilar, assuming an average patient weight and a 4-dose course of 375 mg/m^2, resulted in a saving of approximately £4000 per patient, equating to £160 000 per year in this institution.

REVIEWER COMMENTARY: Whilst a statistically significant difference in the median depletion of CD19 cells was observed at day 28 in the preventative setting, with greater depletion observed in the biosimilar group, this was not reflected in platelet counts or ADAMTS13 levels. This statistical result should also be viewed in the context that approximately half of the patients receiving preventative therapy with biosimilar rituximab were administered a dose of 375 mg/m^2 whilst all patients receiving originator were administered a fixed dose of 500 mg. The basis for the apparent difference in clinical practice with the biosimilar as opposed to the originator is not discussed. The cost savings in the context of preventative therapy and fixed dosing of 500mg were not provided.

STAKEHOLDER PERCEPTIONS

During the quarterly update period, 8 papers have explored the topic of evaluating and improving stakeholder awareness, confidence, attitudes and acceptance of biosimilar medicines.

HEALTH PROFESSIONALS

Giuliani et al: Knowledge and use of biosimilars in oncology: A survey by the European Society for Medical Oncology[22]

SPONSOR: None, investigator initiated. Authors declare multiple competing interests and consultancy roles

LOCATION(S): Survey completed during European Society for Medical Oncology (ESMO) 2017 Congress

DESIGN: 19 question survey completed on paper or online containing checkbox and open response questions

DATES: September – October 2017

OBJECTIVE(S): Assess current levels of knowledge, understanding and comfort of use of biosimilars among prescribers specialised in oncology

PARTICIPANTS: ESMO congress attendees identified as prescribing physicians from Europe and Asia-Pacific regions

RESULTS: Survey responders (n=480) identified as being prescribing physicians from Europe (n=321), Asia (n=84), America (n=55), Africa (n=13) or Australia (n=7). 74.6% of the participants correctly identified a biosimilar medicine as '*highly similar to an approved biological medicine, with no clinically meaningful differences in safety and efficacy profile*'. Sub-analysis showed that 77.9% of European prescribers were able to identify this definition, whereas this proportion was 64.6% for Asia-Pacific prescribers. The authors reported that overall 49.0% of the responding prescribers used biosimilars in routine clinical; the proportion of physicians using biosimilars was higher in Asia-Pacific compared with Europe (56.3% and 46.5% respectively). 24.1% of prescribers stated that they did not prescribe biosimilars due to lack of approval or reimbursement in their country. 61.7% of prescribers were able to identify extrapolation of indications as '*authorisation of a biosimilar in indications of the reference biologic in the absence of specific clinical trial/data for the biosimilar in those indications'*. A smaller proportion of Asia-Pacific prescribers selected this definition in comparison to European prescribers (53.2% vs 65.4%). Overall, 86.7% of prescribers identified that they would like more educational activities concerning biosimilars. A higher proportion of Asia-Pacific prescribers expressed this view (97.9%) compared with European prescribers (82.9%). Responses from European prescribers indicated further training was required on the efficacy and safety of biosimilars whereas Asia-Pacific prescribers were found to require training tailored for the use of biosimilars in developing countries. The authors concluded that "*differences in responses between European and Asia-Pacific prescribers may be attributed to differences in guidance available in the two regions. Efforts should be made worldwide to align definitions and regulatory standards for the development and approval of biosimilars*".

Return to OVERVIEW

Karateev and Belokenova: Evaluation of Physicians' Knowledge and Attitudes Towards Biosimilars in Russia and Issues Associated with Their Prescribing[23]

SPONSOR: Pfizer

LOCATION(S): Russia

DESIGN: Online questionnaire containing 19 questions adapted to include questions relevant to Russian context. Previous ECCO survey translated into native (Russian) language

DATES: June – July 2016

OBJECTIVE(S): To investigate knowledge and attitudes of physicians towards biosimilars in Russia

PARTICIPANTS: Clinicians from a range of specialties (rheumatology, gastroenterology, hematology and oncology) across Russia were recruited using snowball-sampling. Respondents received remuneration.

RESULTS: The authors claim this manuscript to be the first to investigate physicians' knowledge and attitudes towards biosimilars in Russia. The authors provided context for the prescribing of biologic medicines in the Russian healthcare setting. State procurement of biologic medicines is via 'winner-takes-all' tenders with Russian manufacturers offered preference such as a 15% price buffer. This results in a single brand (reference or biosimilar) of a biologic being available. Biologic medicines, including biosimilars, are prescribed using the international non-proprietary name (INN). The authors explained that physicians can often only prescribe one locally produced biosimilar, and no reference product which may result in unintended switching and difficulty with pharmacovigilance. Of the 206 physicians who participated in the survey, 43% had prescribed biologic therapies in the past 12 months and self-identified as being familiar with biosimilars, whereas approximately one in five had not prescribed biologics. The authors rated the general level of understanding as low based upon responses to two questions that investigated the level of biosimilar understanding, only 20% of participants could correctly identify that biosimilars were different from generic drugs and that they were not identical copies of reference products. 66% of physicians responded positively regarding the introduction of biosimilars in Russia, with 91% confirming that they would be comfortable treating patients with a biosimilar provided equivalent safety and efficacy had been demonstrated. Potential benefits of biosimilars identified by the physicians included improved affordability, increased patient access and treatment options. Reasons for a neutral or negative attitude towards biosimilars included not understanding the rationale for extrapolation, lack of experience, and a belief that "*locally produced biosimilars to be of lower clinical efficacy, safety and quality than internationally produced biosimilars*". 53% of physicians sampled reported a negative attitude towards automatic pharmacist without prescriber approval, respondents stated that "*the right of the physician to choose the most appropriate medicine for their patient should be preserved*". The majority of respondents (64%) expressed a preference for prescribing biologics (including biosimilars) by brand rather than INN to allow pharmacovigilance.

REVIEWER COMMENTARY: The generalizability of these findings is questionable due to the unique Russian healthcare procurement processes and differences in local regulatory procedures.

Return to OVERVIEW

Teeple et al: Physician attitudes about non-medical switching to biosimilars: results from an online physician survey in the United States[24]

SPONSOR: Jansson Scientific

LOCATION(S): United States

DESIGN: Preliminary 60 minute quantitative phone interview followed by 15 minute online survey

DATES: June 2016 – January 2017

OBJECTIVE(S): To investigate attitudes of US physicians towards switching patients from originator to biosimilar biologic medicines.

PARTICIPANTS: Physicians specializing in rheumatology, dermatology and gastroenterologists recruited from a standing research panel, currently practising in the US and prescribing biologics

RESULTS: This manuscript reports a survey of 297 physicians in the US. The specialties of physicians who responded included gastroenterology (35%), dermatology (35%) and rheumatology (30%). 60% of the respondents reported to see more than 250 patients on average per month and 55% of respondents reported prescribing biologic medicines for more than half of their patients with rheumatoid arthritis, Crohn's disease, ulcerative colitis, psoriasis and psoriatic arthritis. Physicians' level of familiarity with biosimilars was described by the authors as variable, 84% of respondents self-reported some level of familiarity with biosimilars. The majority of respondents (88%) correctly identified the definition of a biosimilar from multiple options and 56% knew that the US FDA's approval processes were different for biologics and biosimilars. However, fewer respondents (44%) correctly referred to statements describing biologic interchangeability. The physicians surveyed expressed concerns regarding the use of biosimilars in their patients. 63% of physicians indicated more long-term data was required to provide confidence when prescribing biosimilars. Overall, 44% of physicians expressed confidence that biosimilar medications are safe, whereas 42% thought taking a biosimilar is riskier than using the reference biologic. Positive attitudes were expressed by 60% of respondents regarding the impact of non-medical switching (i.e. when switching occurs for no medical reason) on costs to the healthcare system, and 53% believed non-medical switching from an originator biologic to a biosimilar would reduce patient out-of-pocket costs.

REVIEWER COMMENTARY: The results of this survey must be viewed in the context of the time at which it was conducted (June 2016) which coincided with the first FDA approvals of biosimilar medicines in the US.

Return to OVERVIEW

Cook et al: Academic oncology clinicians' understanding of biosimilars and information needed before prescribing[25]

SPONSOR: None, investigator initiated. Author declared Genentech consultancy

LOCATION(S): United States

DESIGN: 12 question online questionnaire followed by in-depth interview. Interviewees purposively selected based upon questionnaire responses

DATES: January – May 2018

OBJECTIVE(S): To investigate oncology clinicians' understanding of biosimilars and the information they consider important to assess before prescribing them

PARTICIPANTS: Oncology clinicians practicing at a single academic healthcare system in the US

RESULTS: A total of 98 oncology clinicians were contacted for the survey and a response rate of 78.6% (77/98) was reported. The respondents understanding of biosimilar medicines was assessed by analysis of open-ended definitions related to biosimilars. 57 (74%) of the clinicians identified one or none of the four required components of the definition and only one participant (1/98) included all four required components in their open-ended biosimilar definition. To further test knowledge regarding biosimilar medicines participants were provided with a true/false statement describing a non-biologic generic medicine, 31 (40.3%) respondents incorrectly identified this statement as a true description of a biosimilar. Overall, 21 (28.4%) participants correctly selected one or more of the current biosimilar indications in oncology (lung, renal, and colorectal) and 48 (62.3%) correctly identified safety and efficacy as the single requirement that a biosimilar must meet to become interchangeable. 41 (53.2%) clinicians stated that they would be likely or highly likely to use biosimilars in the clinic, and 73 (94.8%) indicated that they are willing to prescribe an interchangeable biosimilar. The respondents identified that the most important consideration before initiating a biosimilar was safety and efficacy (4.51 out of 5 on a Likert scale where 5 is the most important). The second most important factor was identified as cost differences (4.34 out of 5).

Return to OVERVIEW

PATIENTS/HEALTH PROFESSIONALS

Fenwick et al: Nurse and Patient Perceptions and Preferences for Subcutaneous Autoinjectors for Inflammatory Joint or Bowel Disease: Findings from a European Survey[26]

SPONSOR: Biogen International GmbH

LOCATION(S): UK and Germany

DESIGN: Head-to-head comparative studies. 2 surveys were administered as face-to-face interviews. The first survey compared user preference of Imraldi® (Biogen) and Humira® autoinjector devices. The second study compared user preference of Imraldi® and Enbrel MyClic® autoinjector devices.

OBJECTIVE(S): Market research to determine whether the adalimumab biosimilar Imraldi® auto-injector device's attributes improve patient and nurse satisfaction compared with Humira® and Enbrel MyClic® auto-injector devices.

PARTICIPANTS: Practice nurse / nurse practitioners with experience in biologic therapy and Humira® auto-injection patient education. Patients with a history of Humira self-injection greater than 3 months.

RESULTS: 101 specialist nurses from the UK and Germany (n=50 and 51 respectively) with experience of supporting patients using adalimumab autoinjectors (Humira® [100% of nurse participants] and/or Enbrel MyClic® [65% of nurse participants]) were surveyed to determine their preferences regarding a new biosimilar adalimiumab Imraldi® autoinjector device (SB5, Biogen Inc.). 151 patients from the UK and Germany (n=90 and 61 respectively) with a variety of inflammatory conditions, including rheumatoid arthritis (37%), ulcerative colitis (23%), Crohn's disease (30%), psoriatic arthritis (15%) were also surveyed. 92% of participants were using the Humira® autoinjector and 3% using the Enbrel MyClic® autoinjector at the time of the study. Participating nurses rated the importance of the device design in the treatment of inflammatory joint or bowel disease with a mean score of 6.27 on a 7-point scale (where 1 = not at all important; 7 = extremely important).

Participants stated a preference for the Imraldi® autoinjector to both the Humira® autoinjector (85% of nurses and 78% of patients) and the Enbrel MyClic® autoinjector (86% of nurses and 79% of patients). Perceived advantages included ease of use, fits well in hand, initiation mechanism not requiring thumb trigger, large visual control suitable for hearing impaired, double click suitable for visually impaired and only requires removal of one cap.

REVIEWER COMMENTARY: As acknowledged by the authors, study design was limited by potential sources of bias including participants' prior experience with the marketed devices, the same nurses and patients participated in both studies resulting in prior Imraldi® device training. Additionally, due to their participation in both studies participants are likely to have realized that the Imraldi® autoinjector was the focus of this study. The authors concluded that "*The study order may therefore have biased the Imraldi versus Enbrel MyClic autoinjector study results*."

Return to OVERVIEW

PATIENTS

Teeple et al: Patient attitudes about non-medical switching to biosimilars: results from an online patient survey in the United States[27]

SPONSOR: Jansson Scientific

LOCATION(S): United States

DESIGN: Preliminary 60 minute quantitative phone interview followed by 20 minute self-administered online survey

DATES: December 2016 – January 2017

OBJECTIVE(S): To investigate attitudes of US patients towards switching from originator to biosimilar biologic medicines.

PARTICIPANTS: Patients currently taking a biologic medicine recruited from 2 patient advocacy groups

RESULTS: A total of 1696 patients with rheumatoid arthritis (37%), psoriasis (19%), psoriatic arthritis (23%), Crohn's disease (15%), or ulcerative (6%) currently taking a biologic medicine responded. Of the participants who completed the survey, 993 were patients associated with advocacy groups, and 703 were from a research panel. 86% of participants reported a minimum one-year history of any biologic medication use, however 33% had been receiving their current biologic for less than 1 year. 64% of patients who responded reportedly had not heard of biosimilars. Of the 36% of patients who had heard of biosimilars, 90% were aware that biosimilars were not identical to the originator biologic, however only 16% understood that biologics and biosimilars have a different FDA approval process. Overall, 45% indicated willingness to switch to a biosimilar medication, however nearly all respondents (94%) stated that the "*decision to switch should be between a doctor and patient, rather than payer-driven*". Participants identified concerns with biosimilars included safety (62%) and loss of copay support or services from the manufacturer of their current biologic (71%).

REVIEWER COMMENTARY: The results of this survey must be viewed in the context of the time at which it was conducted (December 2016) which coincided with the first FDA approvals of biosimilar medicines in the US. The authors identified weaknesses in this Jansson sponsored study including that "*Some patients were recruited from advocacy organizations; thus, the survey responses from these patients may not reflect the views of patients not associated with such groups*".

Return to OVERVIEW

Frantzen et al: Patients' information and perspectives on biosimilars in rheumatology: A French nation-wide survey[28]

SPONSOR: None

LOCATION(S): France

DESIGN: Nationwide survey available to patients through rheumatology departments and national patient associations

DATES: March - July 2017

OBJECTIVE(S): To investigate rheumatology patients' knowledge and perspectives of biosimilars

PARTICIPANTS: Rheumatology patients

RESULTS: Out of the 629 patients from across France who responded to this survey, 65% were rheumatoid arthritis patients and 35% were patients with spondyloarthritis. 68% of respondents stated prior or current biologic treatment, 7% (n=44) identified as having being treated with a biosimilar. 28% of respondents (n=176) had never heard of biosimilars, 29% (n=180) were aware of their existence but did not know what they were, 34% (n=211) knew what the term biosimilar referred to, 9% (n=62) stated that they were familiar with biosimilars. The authors stated that "*Most of the 229 biosimilar naive patients knowing what the term "biosimilar" refers to (187/229) were members of a patient association*."

Return to OVERVIEW

Pinero-Lopez et al: Readability assessment of package leaflets of biosimilars[29]

SPONSOR: None, investigator initiated

LOCATION(S): Europe

DESIGN: Cross-sectional analytical study of three indices of readability of consumer medicines information leaflets for all biosimilar medicines authorised by the EMA.

DATES: Package leaflets accessed 31st August 2017

OBJECTIVE(S): Assess the degree of readability of package leaflets for biosimilar medicines

PARTICIPANTS: None

RESULTS: The readability of the text contained in the package insert patient information leaflets for all EMA authorised biosimilars (n=35) was investigated using quantitative measurements previously used to assess health related written materials including The Flesch-Kincaid Grade Level (FKGL) and the Flesch Reading Ease (FRE) Index. Both measures apply a formula incorporating variables including word count, sentence count and syllable count. Total length of the text was also measured, with the authors assuming that the longer the text the more difficult it is to read. As measured by the FRE Index, no biosimilar package inserts were determined to be easy to understand. FKGL analysis suggested that all the biosimilar package inserts were more difficult to read than is recommended by the EMA, requiring a minimum of a college level education. However, when the authors compared the biosimilar inserts with their reference medicine inserts, no significant differences in difficulty were observed.

REVIEWER COMMENTARY: The authors identified limitations including the fact that patient understanding was not directly measured and that in the clinical setting the package insert is not intended to be the only source of information regarding a medicine. The authors noted that previous work analysing the readability of non-biologic and reference biologic package inserts found that those leaflets did not meet EMA standards of readability, suggesting that the issue of package insert readability is not unique to biosimilar medicines.

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29. Pinero-Lopez MA, Figueiredo-Escriba C, Modamio P et al. Readability assessment of package leaflets of biosimilars. BMJ Open; 9: e024837.

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. This list includes several network meta-analyses, the results of which are consistent with the individual studies previously reported.

1. Argollo M, Fiorino G, Gilardi D et al. Biosimilars of adalimumab in IBD: are we ready for that? Current Pharmaceutical Design 2019; 11: 11.
2. Azevedo VF, Babini A, Caballero-Uribe CV et al. Practical Guidance on Biosimilars, with a Focus on Latin America: What Do Rheumatologists Need to Know? Journal of Clinical Rheumatology 2019; 25: 91-100.
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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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