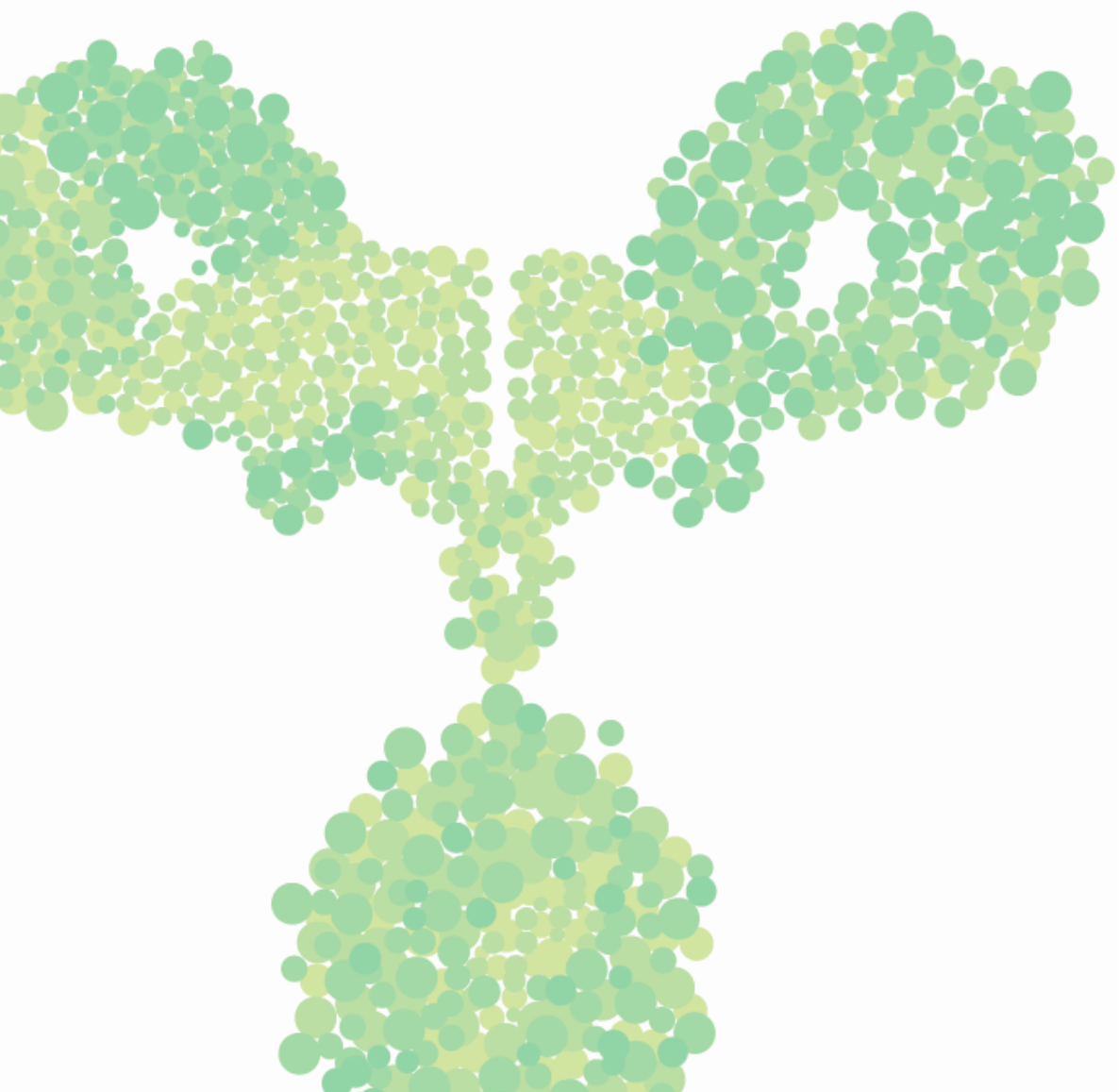
GBMA EDUCATION

University of South Australia | School of Pharmacy and Medical Sciences

International Biosimilar Medicines

Review of the Literature: Quarterly Update

June 2018 – September 2018



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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 the 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.

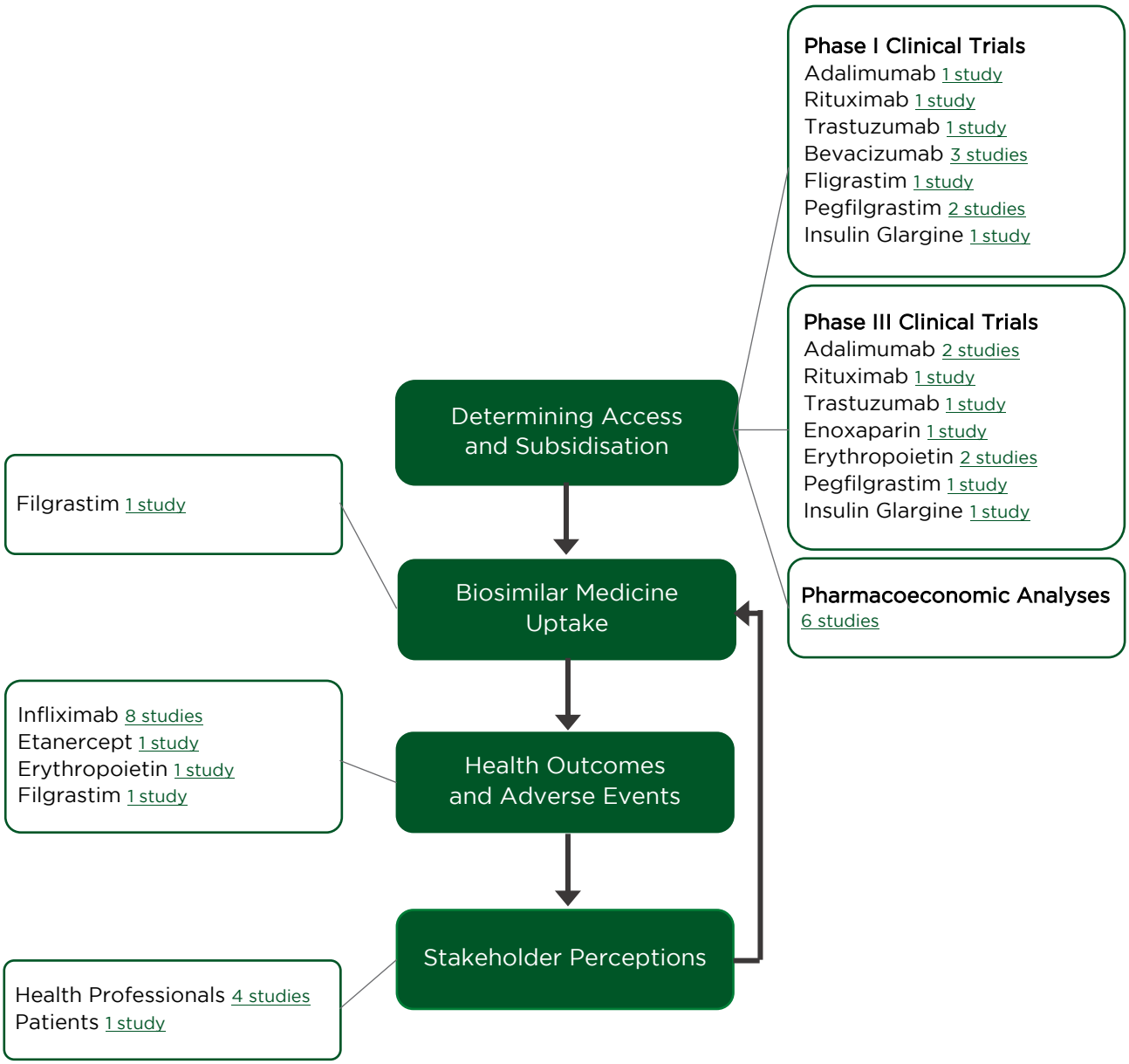
Stakeholder Perceptions

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 June 2018 and 30 September 2018

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



Appendix 1: Educational/Review Articles
73 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 10 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.

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						
M923	US Humira and EU Humira	Randomised, double-blind, three-arm, parallel, single-dose study	Healthy adults (n = 324; randomised 1:1:1)	90% CI of the ratio of geometric least square means for AUC_{0-336}, AUC_{0-inf} and C_{max} were within the pre-defined equivalence interval of 80-125% for the comparisons of M923 with either US Humira or EU Humira, and between US Humira and EU Humira.	The rates of ADA formation were similar across all study arms. The proportion of ADA responses increased to 78.0%, 73.1% and 75.7% at Day 71 in the M923, US Humira and EU Humira arms, respectively.	Hillson et al [1]

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Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
RITUXIMAB						
CT-P10	US-RTX (Rituxan) and EU-RTX (MabThera)	Randomised, double-blind, three-arm, parallel, multiple-dose study	Patients with active RA (n = 189; randomised 1:1:1)	90% CI of the ratio of geometric least square means for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max} were within the pre-defined equivalence interval of 80-125% for the comparisons of CT-P10 with either US-RTX or EU-RTX, and between US-RTX and EU-RTX.	Refer description of phase III component below.	Park et al [2]

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Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
TRASTUZUMAB						
MYL-1401O	US Herceptin and EU Herceptin	Randomised, double-blind, three-arm, parallel, single-dose study	Healthy adult males (n = 132; randomised 1:1:1)	90% CI of the ratio of geometric least square means for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max} were within the pre-defined equivalence interval of 80-125% for the comparisons of MYL-1401O with either US Herceptin or EU Herceptin.	No treatment-induced or treatment-boosted ADA-positive subjects in the study.	Waller et al [3]

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Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
BEVACIZUMAB						
ABP 215	EU Avastin	Randomised, single-blind, two-arm, parallel, single-dose study	Healthy adult males (n = 48; randomised 1:1)	90% CI of the ratio of geometric least square means for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max} were within the pre-defined equivalence interval of 80-125% for the comparison of ABP 215 with EU Avastin.	No positive binding ADAs were detected during the study.	Hanes et al [4]
DRL_BZ	US Avastin and EU Avastin	Randomised, double-blind, three-arm, parallel, single-dose study	Healthy adult males (n = 149; randomised 1:1:1)	90% CI of the ratio of geometric least square means for $AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max} were within the pre-defined equivalence interval of 80-125% for the comparisons of DRL_BZ with either US Avastin or EU Avastin, and between US Avastin and EU Avastin.	One subject (DRL_BZ n=1) had positive ADAs at Day 85; no ADAs were detected in any other subjects.	Wynne et al [5]

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Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
MIL60	EU Avastin	Randomised, double-blind, two-arm, parallel, single-dose study	Healthy adult males (n =78; randomised 1:1)	90% CI of the ratio of geometric least square means for $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$ and C_{max} were within the pre-defined equivalence interval of 80-125% for the comparison of MIL60 with US Avastin.	Two subjects (MIL60 n=1, EU Avastin n=1) had positive ADAs during the study.	Zhang et al [6]
BAT1706	EU Avastin	Randomised, double-blind, two-arm, parallel, single-dose study	Healthy adult males (n =82; randomised 1:1)	90% CI of the ratio of geometric least square means for $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$ and C_{max} were within the pre-defined equivalence interval of 80-125% for the comparison of BAT1706 with US Avastin.	No positive ADAs were detected during the study.	
IBI305	EU Avastin	Randomised, double-blind, two-arm, parallel, single-dose study	Healthy adult males (n =100; randomised 1:1)	90% CI of the ratio of geometric least square means for $AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$ and C_{max} were within the pre-defined equivalence interval of 80-125% for the comparison of IBI305 with US Avastin.	Two subjects (IBI305 n=2) had positive ADAs prior to dosing and during the study.	

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Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
FILGRASTIM						
Leucostim	Neupogen	Randomised, open-label, two-arm, crossover, single-dose study	Healthy adults (n = 56)	90% CI of the ratio of geometric least square means for PK ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max}) and PD (ANC $AUEC_{0\text{-last}}$ and E_{max}) parameters were within the pre-defined equivalence interval of 80-125% for the comparison of Leucostim with Neupogen.	Not reported	Choi et al [7]

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Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
PEGFILGRASTIM						
LA-EP2006	Neulasta	Randomised, double-blind, two-arm, crossover, single-dose study	Healthy adults (n = 185)	90% CI of the ratio of geometric least square means for PK ($AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$ and C_{max}) and PD (ANC $AUEC_{0\text{-}last}$ and E_{max}) parameters were within the pre-defined equivalence interval of 80-125% for the comparison of LA-EP2006 with Neulasta.	Five subjects (Period 1: LA-EP2006 n=1, Neulasta n=3; Period 2: Neulasta n=1) had positive ADAs during the study. None of the detected antibodies were neutralising.	Nakov et al [8]
INTP5	Neulasta	Randomised, assessor-blind, four-arm, crossover, single-dose study	Healthy adults (n = 344)	90% CI of the ratio of geometric least square means for PK ($AUC_{0\text{-}last}$, $AUC_{0\text{-}inf}$ and C_{max}) and PD (ANC and CD34+ $AUEC_{0\text{-}last}$ and E_{max}) parameters were within the pre-defined equivalence interval of 80-125% for the comparison of INTP5 with Neulasta at each of the dose levels (3 mg and 6 mg).	No positive neutralising ADAs were detected during the study.	Singh et al [9]

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Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
INSULIN GLARGINE						
MK-1293	EU Lantus	Randomised, double-blind, two-arm, replicate, crossover, single-dose study	Patients with T1DM (n = 76)	90% CI of the ratio of geometric least square means for PK (AUC_{0-24} and C_{max}) and 95% CI of the ratio of arithmetic means for PD (GIR AUC_{0-24}, AUC_{0-12}, AUC_{12-24} and GIR_{max}) parameters were within the pre-defined equivalence interval of 80-125% for the comparison of MK-1293 with EU Lantus.	Not reported	Crutchlow et al [10]
MK-1293	EU Lantus and US Lantus	Randomised, double-blind, three-arm, crossover, single-dose study	Healthy adult males (n = 109)	90% CI of the ratio of geometric least square means for PK (AUC_{0-24} and C_{max}) and 95% CI of the ratio of arithmetic means for PD (GIR AUC_{0-24}, AUC_{0-12}, AUC_{12-24} and GIR_{max}) parameters were within the pre-defined equivalence interval of 80-125% for the comparison of MK-1293 with either EU Lantus or US Lantus, and between US Lantus and EU Lantus.	Not reported	

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 9 reports of phase III trials of potential biosimilars.

ADALIMUMAB

Blauvelt et al: Phase III randomized study of the proposed adalimumab biosimilar GP2017 in psoriasis: Impact of multiple switches [11]

SPONSOR: Hexal AG

REFERENCE PRODUCT: Humira (AbbVie) sourced from EU or US

OBJECTIVE(S): To demonstrate equivalent efficacy, safety and immunogenicity between GP2017 and reference adalimumab and to assess the impact of multiple switches between GP2017 in adult patients with active, clinically stable, moderate-to-severe plaque psoriasis

DESIGN: Randomized, double blind, multicentre phase III confirmatory study. Eligible patients were randomised 1:1 for 16 weeks (treatment period 1) and rerandomized at week 17 in a 2:1 ratio to continue their originally assigned treatment until week 35 or to receive either GP2017 or reference adalimumab during three alternating 6-week periods (treatment period 2). At week 35 participants then continued a further 16 weeks of the treatment they received in treatment period 1.

SAMPLE SIZE: A total of 231 and 234 patients were randomized to GP2017 and reference adalimumab, respectively. At week 17, 379 patients were rerandomized: 126 patients to undergo treatment switching (63 patients from treatment), 126 continued GP2017 and 127 continued reference adalimumab.

PATIENT CHARACTERISTICS: Clinically stable, moderate-to-severe chronic plaque psoriasis for ≥ 6 months, defined as PASI ≥ 12, Investigator's Global Assessment (IGA) score ≥ 3 and ≥ 10% body surface area affected by plaque psoriasis. Most patients (87.5%) had received prior psoriasis therapy, most commonly topical treatment (76.3%), with 21.1% of patients having received prior biologic systemic therapy. Mean duration of plaque psoriasis = 16.1 years.

EQUIVALENCE CRITERIA: Containment of the 95% confidence interval (95% CI) for the difference in PASI 75 response rates between treatments at week 16 within a margin of 318%.

RESULTS: At week 16 the PASI 75 response rates were 66.8% in the GP2017 and 65.0% in the reference adalimumab groups equating to a difference of 1.8% with a 95% CI -7.46 to 11.15 which was within the predefined equivalence margin and therefore GP2017 is considered equivalent to reference adalimumab. During treatment period 1 there were no relevant differences in adverse events between the groups. One or more adverse events occurred in 52.5% of participants in the reference group and 50.2% in the GP2017 group. Antidrug antibodies were detected in 36.8% and 34.1% of participants in the GP2017 and reference groups respectively during this period. In treatment period 2 the rates of anti-drug antibodies in those who continued reference adalimumab were similar to those who switched to reference from GP017 (45.1% vs 47%, respectively) and amongst those who continued GP2017 as compared with those that switched to GP2017 from reference (35.8% vs 39%, respectively). For patients that were rerandomized after treatment period 1, the mean absolute PASI and mean percentage changes from baseline remained similar through to week 51 between the groups that continued treatment and those in the switching group.

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Fleischmann et al: A comparative clinical study of PF-06410293, a candidate adalimumab biosimilar, and adalimumab reference product (Humira) in the treatment of active rheumatoid arthritis [12]

SPONSOR: Pfizer Inc

REFERENCE PRODUCT: Humira (AbbVie) sourced from EU

OBJECTIVE(S): To compare the efficacy, safety, immunogenicity, pharmacokinetics, and pharmacodynamics of a proposed adalimumab biosimilar (PF-06410293) with reference adalimumab in biologic-naïve patients with active rheumatoid arthritis (RA) despite treatment with methotrexate (MTX) and to assess the impact of switching from reference product to PF-06410293 after 26 weeks of treatment with the reference product through to 72 weeks. This manuscript reports only on the first 26 weeks of treatment.

DESIGN: Double-blind, randomized, comparative clinical study

SAMPLE SIZE: A total of 297 participants were randomised to PF-06410293 and 300 to reference product.

PATIENT CHARACTERISTICS: Patients aged >18 years with a diagnosis of active RA for at least 4 months (2010 American College of Rheumatology/European League Against Rheumatism criteria) and a high-sensitivity C-reactive protein (hs-CRP) of at least 8 mg/L at screening who had not received adalimumab, lymphocyte depleting therapy or more than two doses of a biologic.

EQUIVALENCE CRITERIA: Containment of the 95% confidence interval (CI) for the difference in the proportion of participants achieving and American College of Rheumatology 20% improvement (ACR20) response at week 12 within the range of -14% to 14% and, as requested by the FDA, containment of the 90% CI for this difference within the asymmetric margin of –12% to 15%.

RESULTS: ACR 20 response was observed in 204/297 (68.7%) in the PF-06410293 group as compared with and 218/300 (72.7%) in the reference product group equating to a difference of –3.98%. Response data was imputed for 19 participants which resulted in ACR20 responses in 203/297 (68.4%) participants in the PF-06410293 group and 214/300 (71.3%) reference product group equating to a difference of -2.98% with 95% CI of -10.38% to 4.44%, which is contained within the prespecified equivalence range of -14% to +14%, and an FDA requested 90% CI of -9.25% to 3.28%, which is contained within the predefined asymmetric margin of –12% to 15%. Overall infection rates were similar between the PF-06410293 and reference groups at 24.9% and 25.1% respectively. Injection site reactions were reported by five (1.7%) participants in the PF-06410293 group and six (2.0%) in the reference product group. Anti-drug antibodies were detected in at least one post-dose sample in 44.4% participants in the PF-06410293 group and 50.5% in the reference product group. Of those who tested positive for anti-drug antibodies, 31.1% were neutralising antibodies in the PF-06410293 group and 27.8% in the reference product group.

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RITUXIMAB

Park et al: Comparison of biosimilar CT-P10 and innovator rituximab in patients with rheumatoid arthritis: a randomized controlled Phase 3 trial [2]

SPONSOR: Celltrion Inc

REFERENCE PRODUCT: Rituxan (Genentech Inc) sourced from EU and US

OBJECTIVE(S): To demonstrate PK equivalence of a rituximab biosimilar (CT-P10) with EU and US reference product over 24 weeks (reported in Phase I Clinical Trials section) and to demonstrate efficacy and safety equivalence of CT-P10 with EU and US reference product through to week 24 in patient with rheumatoid arthritis.

DESIGN: Randomized, double-blind

SAMPLE SIZE: A total of 161 participants were randomised to CT-P10, 151 to US-reference product and 60 to EU-reference product. Of these participants 189 (CTP-10=52, US-reference=65, EU-reference=60) participated in both the intensive pharmacokinetic component of the study and the efficacy, pharmacodynamic and safety evaluation.

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 antidrug antibodies were detected in 19 participants randomised to the CT-P10 group and 20 in the reference product group.

EQUIVALENCE CRITERIA: Containment of the 95% confidence interval (CI) of the difference in mean change in Disease Activity Score using 28 joints-C-reactive protein (DAS28-CRP) score from baseline to week 24 between CT-P10 and the combined EU and US reference product group.

RESULTS: The adjusted least squares mean change from baseline in DAS28-CRP at week 24 in the CT-P10 group was −2.13 as compared with −2.09 in the reference group equating to a difference of -0.04 with 95% confidence intervals of −0.29 to 0.21 which is within the predefined equivalence criteria of -0.5 to 0.5. At week 24 anti-drug antibodies were detected in 24 participants in the CT-P10 group and 49 in the reference product group of whom seven participants from each group were positive at baseline. Two participants in each group tested positive for neutralising antibodies, one at baseline in the CT-P10 group and one at week 24 in the reference product group. Infusion related reactions were reported in 14.3% of participants in the CT-P10 group as compared with 4.6% in the US reference product group and 20.0% in the EU reference group after the first infusion which decreased after the second infusion to 2.6%, 0.7% and 1.7%, respectively.

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TRASTUZUMAB

von Minckwitz et al: Efficacy and safety of ABP 980 compared with reference trastuzumab in women with HER2-positive early breast cancer (LILAC study): A randomised, double-blind, phase 3 trial [13]

SPONSOR: Amgen Inc

REFERENCE PRODUCT: Herceptin, source not specified

OBJECTIVE(S): To compare the safety, tolerability, and immunogenicity of a proposed trastuzumab biosimilar (ABP 980) with reference trastuzumab in women with HER2 positive early breast cancer when given in combination with standard-of-care neoadjuvant and adjuvant cancer treatment, including switching during adjuvant treatment.

DESIGN: Randomised, multicentre, double-blind, active-controlled, phase 3 equivalence trial

SAMPLE SIZE: A total of 364 participants were randomised to the ABP 980 group and 361 to the reference trastuzumab group of whom 358 participants in the ABP 980 group and 338 participants in the reference group were included in the neo-adjuvant analysis. Of these 323 participants from the ABP 980 completed adjuvant treatment with ABP980 whilst for the reference group 164 participants completed adjuvant treatment with reference trastuzumab and 157 participants completed adjuvant treatment by switching to ABP 980.

PATIENT CHARACTERISTICS: Women aged 18 years or older with histologically confirmed invasive breast cancer who were planning to have surgical resection of their breast tumour with sentinel or axillary lymph node dissection.

EQUIVALENCE CRITERIA: Containment of the 90% confidence interval (CI) for risk difference for pathological complete response, in breast tissue and axillary nodes assessed by the local laboratory, between the ABP 980 and trastuzumab groups within the limits of –13% and 13% and if successful containment of the 90%CI for the risk ratio between ABP 980 and reference product within the limits of 0.759 to 1.318.

RESULTS: All participants that underwent surgery (n=696) were assessable for the primary endpoint of pathological complete response, of whom 358 received ABP 980 and 338 who received reference trastuzumab. Based on local laboratory assessments, 172/358 (48%) who received neoadjuvant ABP 980 and 137/338 (41%) of 338 patients who received neoadjuvant trastuzumab achieved a pathological complete response equating to a risk difference of 7.3% with a 90%CI of 1.2-13.4, the upper limit of which is outside the predefined limit of 13%. The risk ratio for pathological complete response was 1.188 with a 90% confidence interval of 1.033 to 1.366, the upper limit of which was above the predefined limit of 1.318. In a sensitivity analysis conducted based upon a review of "*representative tumour samples*" by the central pathology laboratory, complete pathological response was observed in 162/339 (48%) participants in the ABP 980 group and 138/330 (42%) in the reference group. Within these samples the risk difference was 5.8% with 90%CI of -0.5 to 12.0 and the ratio was 1.142 with 90% of 0.993 to 1.312, both of which were within the predefined equivalence criteria. During the neoadjuvant phase grade 3 or worse adverse events occurred in 54/364 (15%) participants in the ABP 980 group as compared with 51/361 (14%) participants in the reference group the most common of which was neutropenia which occurred in 21 participants in both groups. Cardiac failure events occurred during the neo-adjuvant phase in 6 participants in the ABP 980 group and in a single participant in the reference group. Anti-drug antibodies were detected in two participants from each group during the neoadjuvant phase. During the adjuvant phase, four participants in the group that switched from reference product to ABP 980 developed anti-drug antibodies.

REVIEWER COMMENTARY: The results of this study may have been impacted by variability in pathology laboratory assessment of tumour response. This study utilised assessment of pathological complete response by local laboratories for logistical reasons but this may have introduced greater variability. "*Representative tumour samples*" were subject to analysis by a central laboratory which resulted a different conclusion with regards to the equivalence criteria. Further details comparing the local versus central analysis are not provided.

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ENOXAPARIN

Ramacciotti et al: Efficacy and safety of a biosimilar versus branded enoxaparin in the prevention of venous thromboembolism following major abdominal surgery: A randomized, prospective, single-blinded, multicenter clinical trial [14]

SPONSOR: Cristália Produtos Químicos Farmacêuticos LTDA, Brazil

REFERENCE PRODUCT: Enoxaparin (Sanofi)

OBJECTIVE(S): To compare the efficacy and safety of enoxaparin Cristália with enoxaparin Sanofi for the prophylaxis of venous thromboembolism (VTE) in participants undergoing general abdominal surgeries at high risk.

DESIGN: Randomized, prospective, single-blinded

SAMPLE SIZE: A total of 243 participants were randomised of which 111 received enoxaparin Cristália and 110 received enoxaparin Sanofi.

PATIENT CHARACTERISTICS: Patients undergoing major abdominal surgery with formal indication of chemoprophylaxis for VTE according to the eighth American College of Chest Physicians guidelines.

EQUIVALENCE CRITERIA: An upper limit of the 95% confidence interval (CI) for the absolute risk difference in the incidence of VTE up to 4 days after the end of treatment administration between enoxaparin Cristália and enoxaparin Sanofi of 20%.

RESULTS: A total 81 participants in the enoxaparin Cristália group and 88 participants in the enoxaparin Sanofi group were included in the analysis. The incidence of VTE was 4.9% in the Cristália group and 1.1% in the Sanofi group equating to an absolute risk difference of 3.80% with 95% CI of -1.4% to 9.0% the upper limit of which is below the specified equivalence criteria of 20%. The incidence of bleeding in the enoxaparin Cristália group was 9.9% as compared with 6.4% in the enoxaparin Sanofi group (p=0.21).

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ERYTHROPOIETIN

Fishbane et al: Intravenous epoetin alfa-epbx versus epoetin alfa for treatment of anemia in end-stage kidney disease [15]

SPONSOR: Hospira Inc, Pfizer

REFERENCE PRODUCT: Epoetin alpha (Amgen)

OBJECTIVE(S): To compare the safety and efficacy of the proposed erythropoietin alpha biosimilar (epoetin alfa-epbx) to reference epoetin alfa in patients on haemodialysis with end stage kidney disease and anaemia.

DESIGN: Randomized, active-controlled, parallel-group, double-blind

SAMPLE SIZE: A total of 306 patients were randomised to each of the epoetin alfa-epbx and reference product groups.

PATIENT CHARACTERISTICS: Patients aged 18-80 years on haemodialysis with end stage kidney disease who were receiving stable IV erythropoietin alfa treatment one to three times per week (<600 U/kg/week) for at least 4 weeks before randomization and adequate iron stores (ferritin >100 Qg/L and transferrin saturation >20%). At baseline seven patients were positive for anti-drug antibodies (three randomised to epoetin alfa-epbx and four to the reference product group).

EQUIVALENCE CRITERIA: Containment of the 95% confidence interval for the least squares mean difference in mean weekly haemoglobin level between weeks 20 and 24 within -0.5 to 0.5 g/dl and containment of the 95% confidence interval for the least squares mean difference in mean erythropoietin dose between weeks 20 and 24 within -45 to 45 units/kg/week between the proposed biosimilar and the reference product.

RESULTS: The least squares mean difference between epoetin alfa-epbx and reference product in mean weekly haemoglobin levels between weeks 20 and 24 was -0.12 g/dl, with a 95% CI of -0.25 to 0.01 g/dl, which was within the prespecified equivalence criteria of 30.5 g/dl. Over the 24-week treatment period, there was no statistically significant difference in mean weekly haemoglobin levels between epoetin alfa-epbx and the reference group (P=0.76). With respect to the mean weekly erythropoietin dose, the least squares mean difference between epoetin alfa-epbx and reference product was 0.37 U/kg/week, with a 95% CI of -10.40 to 11.13 units/kg/week per week, which was also within the prespecified equivalence margin of 345 U/kg per week. Over the 24-week treatment period, there was no statistically significant difference in mean weekly erythropoietin dose, by body weight, between epoetin alfa-epbx and the reference group (p=0.11). Two participants developed anti-drug antibodies during the study, one in each group and no cases of pure-red cell aplasia developed.

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Thadhani et al: Switching from Epoetin Alfa (Epogen) to Epoetin Alfa-Epbx (Retacrit) Using a Specified Dosing Algorithm: A Randomized, Non-Inferiority Study in Adults on Hemodialysis[16]

SPONSOR: Hospira Inc, Pfizer

REFERENCE PRODUCT: Epogen (Amgen)

OBJECTIVE(S): To investigate how switching from erythropoietin alpha reference product (Epogen) to biosimilar erythropoietin alpha (Retacrit) affects the maintenance of haemoglobin levels in patients on haemodialysis when using a specified dosing algorithm over 24 weeks.

DESIGN: Multicentre, prospective, randomized, parallel group, open-label, non-inferiority study

SAMPLE SIZE: 432 participants were randomized with 221 group switching to Retacrit and 211 in the group to continue reference product.

PATIENT CHARACTERISTICS: Adults (≥18 years old) with anaemia and CKD who had been receiving in-centre haemodialysis for at least 120 days and have received IV Epogen® treatment for anaemia in accordance with the Fresenius Medical Care North America dosing algorithm for at least 16 weeks.

EQUIVALENCE CRITERIA: A lower limit of the 95% confidence intervals (CI) for the difference in the estimated proportion of time that patients had haemoglobin levels in the target range no less than –12.5%

RESULTS: During the final 8 weeks of the study, the estimated proportion of time that participants had haemoglobin levels in the target range was 61.9% (95% CI 57.5–66.2) for the group that switched to Retacrit as compared with 63.3% (95% CI 58.7–67.7) in the group that continued reference product. This equates to a different in proportions between the treatment arms of -1.4% with a 95% CI ranging from -7.6% to 4.9%, the lower limit of which is above the prespecified limit of -12.5%. During the final 8 weeks of treatment, the 101/178 (56.7%) in the Retacrit group had haemoglobin levels in the range 10–11 g/dL as compared with 92/173 (53.2%) in the reference product group. With regards to the dose requirement, the least-squares mean (SE) change from baseline was –1,861.8 (563.5) units/week for the Retacrit group as compared with –799.8 (573.1) units/week for the reference product group.

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PEGFILGRASTIM

Desai et al: Clinical confirmation to demonstrate similarity for a biosimilar pegfilgrastim: A 3-way randomized equivalence study for a proposed biosimilar pegfilgrastim versus US-licensed and EU-approved reference products in breast cancer patients receiving myelosuppressive chemotherapy [17]

SPONSOR: Apobiologix

REFERENCE PRODUCT: Neulasta (Amgen), sourced from US and EU

OBJECTIVE(S): To compare the efficacy and safety of the proposed pegfilgrastim (APO-Peg) biosimilar to the US and EU-licensed pegfilgrastim reference product in patients with early breast cancer receiving chemotherapy.

DESIGN: Randomized, controlled, assessor-blinded

SAMPLE SIZE: A total of 294 patients were randomised to APO-Peg with 148 and 147 randomised to US and EU reference product. However, 298 patients were treated with APO-Peg, 147 with US reference and 144 with EU reference.

PATIENT CHARACTERISTICS: Female patients≥18 years of age with Stage IIA, IIB or IIIA breast cancer within 60 days of complete surgical resection of the primary breast tumour, who were suitable and intended to undergo adjuvant treatment with TAC (docetaxel, doxorubicin, cyclophosphamide) chemotherapy

EQUIVALENCE CRITERIA: Containment of the 95% confidence interval for the difference in mean duration of severe neutropenia, defined as the number of days with an absolute neutrophil count below 0.5 x 10^9/L, during chemotherapy cycle 1 between the proposed pegfilgrastim biosimilar reference product within a range of −0.5 days to +0.5 days.

RESULTS: When analysed as treated, rather than as randomised, the least squares mean duration of severe neutropenia in cycle 1, in the APO-Peg group was 1.6 days (95% CI: 1.46 to 1.77) as compared with 1.0 (95% CI: 1.17 to 1.61) and 2.0 (95% CI: 1.41 to 1.86) in the US and EU reference product groups respectively. This equated to a difference between APO-Peg and US reference product of 0.2 days (95% CI: -0.04 to 0.50) and 0.02 days (95% CI: -0.03 to 0.51) for EU reference product which were within the equivalence criteria of −0.5 days to +0.5 days. If analysed on an as randomised basis, rather than as treated, the 95%CI for the difference between APO-Peg and US reference was -0.03 to 0.51 which exceeds to the upper limit of the predefined equivalence criteria. Bone pain was the most common adverse event directly related to pegfilgrastim treatment which occurred in 45.2% of patients in the APO-Peg group as compared with 52.6% and 56.0% in the US and EF reference groups respectively. The incidence of antidrug antibodies is stated as "…*low and similar across treatment arms*…" but data is not provided.

REVIEWER COMMENTARY: When analysed on the as randomised basis, rather than as treated, when compared with US reference product the 95%CI for the difference in mean duration in severe neutropenia exceeded the upper limit by 0.01 days which equates to 14.4 minutes and is not clinically significant in the context of absolute neutrophil counts being collected daily.

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INSULIN GLARGINE

Blevins et al: Efficacy and safety of MYL-1501D versus insulin glargine in patients with type 2 diabetes after 24 weeks: Results of the phase III INSTRIDE 2 study [18]

SPONSOR: Mylan Inc and Biocon Limited

REFERENCE PRODUCT: Lantus (Sanofi)

OBJECTIVE(S): To determine whether once-daily MYL-1501D is non-inferior to once-daily reference insulin glargine with regards to efficacy, safety and immunogenicity when administered in combination with oral antidiabetic drugs in patients with type 2 diabetes (T2DM).

DESIGN: Multicentre, open-label, randomized, parallel-group

SAMPLE SIZE: A total of 277 and 283 patients were randomised to the MYL-1501D and reference product groups respectively.

PATIENT CHARACTERISTICS: Patients aged 18-65 with an established diagnosis of T2DM, had stable weight in the 3 months before screening and who were either insulin naïve or currently receiving once daily insulin glargine at a stable dose for at least 3 months before screening. Insulin naïve patients had an HbA1c concentration of >58 to ≤91 mmol/mol. Patients currently receiving insulin glargine had a diagnosis of T2DM ≥1 year before screening, were on a stable dose of an oral antidiabetic drugs for ≥3 months before screening and had a glycated haemoglobin (HbA1c) concentration of <91 mmol/mol.

EQUIVALENCE CRITERIA: An upper limit of the two-sided 95% CI for the difference in the mean change in HbA1c from baseline to week 24 between MYL-1501D and reference insulin glargine of no greater than 0.4%.

RESULTS: The mean change in HbA1c from baseline to week 24 was −0.60% (95% CI −0.78, −0.41) and − 0.66% (95% CI −0.84, −0.48) for the MYL-1501D and reference insulin glargine groups, respectively equating to a least squares mean difference of 0.06% (95% CI −0.10, 0.22); the upper limit of 0.22 is below the predefined non-inferiority limit of 0.4% MYL-1501D is considered non-inferior to reference insulin glargine.

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, 5 publications were identified that examined the economic impact of the introduction of biosimilars, a strong determinant informing policy relating to biosimilar access and use.

Trautman et al: Patient-administered biologic and biosimilar filgrastim may offer more affordable options for patients with nonmyeloid malignancies receiving chemotherapy in the United States: A budget impact analysis from the payer perspective [19]

SPONSOR: Teva Branded Pharmaceutical Products R & D

LOCATION(S): USA

DATES: Market share distributions of tbo-filgrastim, originator filgrastim, and biosimilar filgrastim (filgrastim-sndz) were based on IMS Health NDC-level sales data from October 2015 to March 2016

DESIGN: An interactive budget impact model was developed to estimate the changes in drug cost associated with projected increases in the market share of filgrastim-sndz from 10% to 12% and tbo-filgrastim from 5% to 10% with a corresponding decrease in filgrastim market share from 85% to 78%. It was assumed that 20% of patients would self- administer at home and that there was a patient co-payment of US$54 per prescription. The total budget impact was calculated using a 1-year time horizon for a 1 million-member health plan.

OBJECTIVE(S): To estimate the annual economic cost of increasing utilization of tbo-filgrastim and biosimilar filgrastim (filgrastim-sndz) as a patient- (home-) administered treatment option for patients with nonmyeloid malignancies undergoing myelosuppressive chemotherapy from a US payer perspective.

RESULTS: Increasing the market share for tbo-filgrastim to 5% and filgrastim-sndz to 2% would decrease total annual plan cost from US$53,298,217 to US$52,828,832, a saving of US$469,385.

Gibofsky et al: Short-term costs associated with non-medical switching in autoimmune conditions [20]

SPONSOR: AbbVie

LOCATION(S): USA

DATES: June 2017 onward

DESIGN: A survey of clinicians regarding their expectations of the impact on consultation times and laboratory testing associated with non-medical switching from originator to biosimilar was conducted. An economic model of the impact of non-medical switching was then constructed using US prevalence rates of the conditions of interest obtained from the literature, treatment related costs from 2016 Medicare physician fee schedule published by the Centers for Medicare and Medicaid Services (CMS).

OBJECTIVE(S): To estimate the costs associated with non-medical switching from originator to biosimilar over a three-month period in stable rheumatology, gastroenterology and dermatology patients including the extra time physicians expect to spend in consultations in the setting of non-medical switching and any anticipated additional laboratory tests and procedures.

RESULTS: A total of 31 rheumatologists, 31 gastroenterologists, and 32 dermatologists participated in the survey. The majority of responding clinicians (85%) expect that a consultation associated with non-medical switching to be of longer duration than a routine clinic visit. Across the three therapeutic areas clinicians anticipate that a visit associated with non-medical switching will take 6 minutes longer than a routine visit, equating to an increased cost ranging from US$20 to US$27, and that there will be an average of 3.8 additional laboratory tests conducted (rheumatology =4.3, gastroenterology =3.9, dermatology: 3.1), equating to a cost ranging from $58 to US$135. Over a three-month period, this equates to an average cost of $336 per patient (rheumatology= $313; gastroenterology= $469; dermatology= $233).

REVIEWER COMMENTARY: Details regarding how potential survey participants were identified are not provided and details of the survey questions are not provided. The basis on which clinicians predicted the impact of non-medical switching might have on consult duration and ordering of laboratory tests are not described beyond "*physicians were asked to answer the survey questions based on their expectations*". The authors note that "*To date, the switching cost burden of originator-to-biosimilar NMS* [non-medical switching] *has not been well characterised*".

Yazdany et al: Out-of-pocket costs for infliximab and its biosimilar for rheumatoid arthritis under Medicare Part D [21]

SPONSOR: Non-commercial

LOCATION(S): USA

DATES: June 2017 onward

DESIGN: Analysis of nationwide benefit design data for all Part D plans from the June 2017 Medicare Prescription Drug Plan Formulary, Pharmacy Network, and Pricing Information Files to calculate mean total cost and out-of-pocket cost requirements for infliximab-dyyb and infliximab assuming a standard 8-week dosing regimen

OBJECTIVE(S): To compare the coverage and cost-sharing for biosimilar infliximab (infliximab-dyyb) with originator infliximab.

RESULTS: A total of 2547 plans were analysed. Biosimilar infliximab was covered by 10% of plans as compared with 96% of plans for originator infliximab. Biosimilar infliximab was associated with a lower mean total cost per 8-week prescription of US$2185 as compared with US$2667 for originator; equivalent to US$14 202 and US$17 335 annually, respectively. Coinsurance cost-sharing rates were similar between biosimilar and originator (26.6% vs 28.4%, respectively). The projected annual out-of-pocket costs were higher for infliximab-dyyb at US$5118 as compared with US$3432 for originator infliximab.

Gizzo et al: A cost-effectiveness modeling evaluation comparing a biosimilar follitropin alfa preparation with its reference product for live birth outcome in Germany, Italy and Spain [22]

SPONSOR: Merck KGaA

LOCATION(S): Spain, Italy and Germany

DATES: Drug prices as at June 2017

DESIGN: The costs for assisted reproductive therapy were extracted from the relevant national data source. Live birth rates were obtained from a phase III clinical trial demonstrating biosimilarity between Ovaleap and originator GONAL-f.

OBJECTIVE(S): To compare the overall costs to achieve live birth using originator follitropin alfa (GONAL-f) with biosimilar follitropin alfa (Ovaleap) in Spain, Italy and Germany.

RESULTS: Drug costs per patient were higher for originator follitropin alfa than biosimilar in all three countries, with larger cost differences in Germany (€157.38) and Italy (€141.50) than in Spain (€22.41). Assuming live-birth rates of 32.2% for originator follitropin alfa and 26.8% for biosimilar follitropin alfa the estimated overall costs per live birth per patient per cycle were lower for patients treated with reference follitropin alfa than those treated with biosimilar in all three countries (difference in Germany €1050.30; difference in Italy €1192.15; difference in Spain €2907.66).

REVIEWER COMMENTARY: The cost per live birth analysis assumes a difference in live birth rates between originator (32.3%) and biosimilar follitropin (26.8%). These values were obtained from a phase III clinical trial [#]. However, in the phase III study the difference in live births between biosimilar and originator was not statistically significant with an odds ratio of 0.78 (95% CI: 0.47–1.29, p=0.335) and, as Gizzo et al note, the phase III study "*not powered to analyze differences in live birth rate*".

[#] Strowitzki T, Kuczynski W, Mueller A, et al. Randomized, active controlled, comparative phase 3 efficacy and safety equivalence trial of Ovaleap (recombinant human follicle-stimulating hormone) in infertile women using assisted reproduction technology (ART). *Reprod Biol Endocrinol* 2016; 14: 1

Gonzalez-Fernandez et al: Cost evolution of biological agents for the treatment of spondyloarthritis in a tertiary hospital: Influential factors in price [23]

SPONSOR: None

LOCATION(S): La Paz University Hospital, Spain

DATES: 2009-2016

DESIGN: Retrospective, observational

OBJECTIVE(S): To calculate the annual cost per patient and the cost of each biological drug for treating patients with spondyloarthritis in a Spanish tertiary hospital according to clinical practice and to identify the factors that affect treatment cost, such as the use of biosimilars.

RESULTS: With regards to the impact of biosimilars, the authors note that "*…the release of a biosimilar infliximab increased the rebates to 31.9% in 2016, with a gradual increase in bonus units over time, while the original Ifx* [infliximab] *rebate was 5.8%*".

Manova et al: Comparative price analysis of biological products for treatment of rheumatoid arthritis [24]

SPONSOR: Non-commercial

LOCATION(S): Bulgaria, Romania, Greece, France, Latvia, Slovakia, Lithuania, Portugal, Italy, Slovenia, Spain, Belgium, the Czechia, Poland, Hungary, Denmark, Finland and Estonia

DATES: As at December 2017

DESIGN: Drug price data was obtained from the official web pages of the responsible pricing institutions in the relevant countries

OBJECTIVE(S): To conduct a comparative analysis of the officially published manufacturer price, and where were available the retail prices of biological products for rheumatoid arthritis among seventeen EU countries.

RESULTS: Manufacturers' and retail prices of biosimilar products were established only for etanercept, rituximab, and infliximab. Comparison of the differences between manufacturer prices of originator and biosimilars indicates a difference of 36% for etanercept, 39% for rituximab, and 31% for infliximab. Differences in retail price between originator and biosimilar were 11% for etanercept, 86% for rituximab and 143% for infliximab.

REVIEWER COMMENTARY: The data presented lacks clarity and in some instances details, such as axis labels, are missing making the methods and results difficult to interpret.

BIOSIMILAR MEDICINE UPTAKE

This theme encompasses papers examining the current practice of prescribers, pharmacists and patients, and the policy informing such. During the period, there was one paper published examining this theme.

FILGRASTIM

Kozlowski et al: Uptake of the biologic filgrastim and its biosimilar product among the Medicare population [25]

SPONSOR: None

LOCATION(S): USA

DATES: January 1, 2014, and December 31, 2016

DESIGN: Analysis of Medicare Part B claims using Healthcare Common Procedure Coding System billing codes

OBJECTIVE(S): To evaluate the uptake of biosimilar filgrastim-sndz (Zarxio) and tbo-filgrastim with originator filgrastim product (Neupogen)

RESULTS: Monthly administrations of filgrastim-sndz increased to 32% of all filgrastim use and tbo-filgrastim increased to 16% whilst there was a corresponding decrease in the originator filgrastim product from 97% to 52%. Amongst those that had received filgrastim-sndz, 22% had previously received the originator filgrastim.

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

Armuzzi et al: The PROSIT cohort of infliximab biosimilar in IBD: A prolonged follow-up on the effectiveness and safety across Italy [26]

SPONSOR: None

LOCATION(S): Italy, nationwide

DESIGN: Prospective, observational

DATES: April 2015 to August 2017 (extending a previous report)

OBJECTIVE(S): To evaluate the effectiveness, safety, and immunogenicity of CT-P13 in patients with inflammatory bowel disease, in induction and maintenance of remission.

PATIENT CHARACTERISTICS: 810 patients (452 CD, 358 UC; increased from 547 patients previously reported) including;

- naïve to any antiTNFα biologic (n=459)
- previously exposed to anti-TNFα biologic, (n=196 including 45 previously exposed to infliximab)
- switched from originator infliximab to CT-P13 (n=155)

Mean duration of follow-up reported is 344.7 3 215.6 days (increased from 4.3 months in previous report). Exposure to CT-P13 equates to a total of 6501 infusions and 674 patient-years.

OUTCOME(S): Primary endpoint was the evaluation of safety in terms of rate of serious adverse events. Secondary endpoints were clinical remission/response, treatment persistency, change in disease activity measures (Mayo score, Harvey-Bradshaw Index), immunogenicity and predictive factors of safety and efficacy.

RESULTS: Serious adverse events occurred in 79/459 (17%) patients naïve to any antiTNFα biologic, 57/196 (29%) of those previously exposed to anti-TNFα biologic and 18/155 (11%) switched from originator infliximab to CT-P13 of which infusion reactions accounted for 34/459 (7.4%), 26/196 (13.2%) and 11/155 (7.1%) respectively. A total of 754 patients completed the minimum treatment and follow-up time of 8 weeks or had failed earlier. The failure rates were 7.4% in patients naïve to any antiTNFα biologic, 7.6% in those previously exposed to anti-TNFα biologic and 2% switched from originator infliximab to CT-P13. Mayo score and Harvey-Bradshaw Index in the full cohort decreased significantly at month 6 ($P < 0.0001$) and remained stable at month 12, which was significant not only those patients naïve to any antiTNFα biologic and those previously exposed to anti-TNFα biologic ($P < 0.0001$) but also those who switched from originator infliximab to CT-P13 A and B ($P < 0.0001$) but also in group C ($P = 0.01$, $P < 0.001$). Assuming a mean dose of 350mg per infusion and a mean price reduction of 35% compared to originator the estimated cost saving associated with the use of the biosimilar was €3.8 million per year.

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Balint et al: Infliximab biosimilar CT-P13 therapy is effective in maintaining endoscopic remission in ulcerative colitis - Results from multicenter observational cohort [27]

SPONSOR: Non-commercial

LOCATION(S): Hungarian (n=4) and Czech (n=1) inflammatory bowel disease centres

DESIGN: Prospective, observational

DATES: Between June 2014 and June 2017

OBJECTIVE(S): To evaluate the efficacy of CT-P13 therapy in maintaining mucosal healing in ulcerative colitis

PATIENT CHARACTERISTICS: 75 patients with either moderate or severe acute relapse (inpatients, n=22) or chronic, steroid-dependent, and/or immunomodulatory-refractory disease (outpatients, n=39). Concomitant use of azathioprine or 6-mercaptopurine increased from 40.9% at baseline to 45.9% at week 54.

OUTCOME(S): The primary end-point of this study was mucosal healing (Mayo endoscopic sub-score 0 or 1) and complete mucosal healing (Mayo endoscopic sub-score 0) assessed at weeks 14 and 54. Secondary aim was to assess remission rates and influencing factors of successful therapy.

RESULTS: A total of 61 patients completed 54 weeks of treatment, with 13 patients ceasing CT-P13 due to allergy or loss of response. Of the 61 patients that completed 54 weeks of treatment, mucosal healing occurred in 65.5 % at week 14 and 62.1 % at week 54 ($p = 0.3$) and complete healing occurred in 31% and 38% at weeks 14 and 54. Corticosteroid free mucosal healing was achieved in 55.2% of these patients. The rates of remission, partial response, and nonresponse at week 54 were 51.7%, 36.7%, and 11.6%, respectively.

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Gervais et al: Switching from originator to biosimilar infliximab in paediatric inflammatory bowel disease is feasible and uneventful [28]

SPONSOR: None

LOCATION(S): Scotland, nationwide

DESIGN: Prospective, observational

DATES: September 2016 and January 2018

OBJECTIVE(S): To describe the safety and efficacy of switching from originator infliximab to biosimilar infliximab in paediatric patients with inflammatory bowel disease. Education about biosimilars was provided to patients

PATIENT CHARACTERISTICS: 33 paediatric patients with inflammatory bowel disease (Crohn's disease =26, ulcerative colitis = 4, unclassified = 3). Median age at diagnosis = 11.8 years. Median age at infliximab commencement = 13.7years. Concomitant azathioprine or methotrexate = 25 (76%). Concomitant corticosteroids = none. Median duration of infliximab treatment prior to switching = 1.6 years.

OUTCOME(S): Disease activity and treatment persistence at 6- and 12-months post-switch

RESULTS: A total of 39 patients receiving originator infliximab in 2016/17 were identified, of whom 33 were switched to biosimilar infliximab. At the time of switching 25 patients were in remission and eight had active disease. Two patients considered clinically eligible to switch declined, equating to a 94% acceptance rate for those considered clinically eligible to switch. Of the remaining four patients that did not switch one patient was considered ineligible on medical grounds, one transitioned and two had planned discontinuation of infliximab.

Two patients did not complete follow-up at 6 months; one changed therapy to adalimumab due to pharmacodynamic loss of response and one patient transferred to an adult service. At 6 months post-switch 25 of 31 patients (87%) were in remission. Two additional patients did not complete 12 months follow-up as they were in complete remission and treatment was ceased. At 12 months post-switch 24 of 29 were in remission. No significant changes in biochemical markers (ESR, CRP and albumin) were detected at 6- or 12-months post-switching (P>0.1). The median infliximab trough level at baseline was 2.9mg/l (1.8,5.4) as compared with 4.4 mg/l (2.9, 7.5) at 12 months but 16 patients underwent dose escalation over this period. No infusion reactions after a total of 264 infusions.

The authors estimate a cost saving of £66000 (€75,900), equivalent to £1500 per patient per year, by switching to biosimilar infliximab over the study period.

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Glintborg et al: Does a mandatory non-medical switch from originator to biosimilar infliximab lead to increased use of outpatient healthcare resources? A register-based study in patients with inflammatory arthritis [29]

SPONSOR: Partly funded by AbbVie

LOCATION(S): Denmark, nationwide

DESIGN: Registry (DANBIO)

DATES: Switched from INX to CT-P13 between 20 March and 1 January 2016

OBJECTIVE(S): To investigate if switching from originator infliximab to biosimilar infliximab (CT-P13) in patients with inflammatory arthritis affected outpatient consultation rates and services provided within departments of rheumatology 6 months after switching as compared with the 6 months prior to switching.

PATIENT CHARACTERISTICS: 769 patients with rheumatoid arthritis, psoriatic arthritis or axial spondyloarthritis identified in the DANBIO registry who switched from originator infliximab to CT-P13. Patients were included if they had ≥1 outpatient contact related to inflammatory joint disease at departments that registered patients in DANBIO.

OUTCOME(S): Difference outpatient consultation rates with physicians and nurses before and after switching.

RESULTS: A total of 6718 out-patient visits occurred of which 2995 (45%) occurred in the 6 months prior to switching, 689 (10%) occurred on the switch date and 3034 (45%) occurred in the 6 months after the switch date. There was no significant difference in the mean visit rate before and after switching (3.89 vs 3.95 respectively, p=0.35). After switching, 239 patients (31%) had fewer visits (mean −1.6, SD 1.0), 271 patients (35%) maintained consistent visits and 259 patients (34%) had increased visits (mean 1.6, SD 1.0) when compared to pre-switching. Results suggest that there was "…*no clinically relevant increase in use of outpatient health care resources 6 months after compared with 6 months before mandatory switch from originator to biosimilar infliximab*."

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Guerra Veloz et al: Switching from reference infliximab to CT-P13 in patients with inflammatory bowel disease: Results of a multicenter study after 12 months [30]

SPONSOR: Kern Pharma Biologics

LOCATION(S): Hospital Virgen Macarena and Hospital Juan Ramon Jiménez, Spain

DESIGN: Observational

DATES: 2016 to 2017

OBJECTIVE(S): To assess the effectiveness and safety of switching from originator infliximab to CT-P13 in patients with inflammatory bowel disease for up to 12 months

PATIENT CHARACTERISTICS: 167 patients (Crohn's disease = 116, ulcerative colitis = 51) previously treated with originator infliximab of whom 146 were in remission. Concomitant thiopurine treatment = 50% (CD) and 51% (UC). Median age of patients (range) = 40.5 (28-54) years (CD) and 46 (34-58) (CD).

OUTCOME(S): The change in clinical remission at 12 months where remission was defined as either Harvey-Bradshaw score ≤ 4 in patients with CD or a partial Mayo score ≤ 2 in patients with UC without the need for steroids, surgery or an increased dose at the established follow-up time.

RESULTS: Overall, remission at 12 months was 71.7% (109/152) after 12-months as compared to 87.4% (146/167) prior to switching, equating to a loss of efficacy of 15.7% which the authors consider was "…*similarly to that reported for the reference product*". A total of 15 patients discontinued CTP-13 during follow-up of whom 7 (CD=2, UC=5) stopped treatment due to remission with mucosal healing, 7 due to adverse events (CD=4, UC=3). Of those in remission prior to switching, 71/103 patients with CD and 31/43 patients with UC remained in remission at 12 months.

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Nikiphorou et al: Survival and safety of infliximab bio-original and infliximab biosimilar (CT-P13) in usual rheumatology care [31]

SPONSOR: Pfizer

LOCATION(S): Jyväskylä Central Hospital, Finland

DESIGN: Retrospective analysis of electronic clinical database

DATES: Patients commencing treatment from 2008 onward

OBJECTIVE(S): To compare the survival of biosimilar infliximab (CT-P13) and originator infliximab over a two-year period and to explore the reasons for drug discontinuation in patients who started on either of the two drugs from the beginning or those who switched from originator to biosimilar.

PATIENT CHARACTERISTICS: 395 patients were analysed, rheumatoid arthritis = 31%, ankylosing spondylitis (AS)/ spondyloarthritis (SpA) = 28%, concomitant methotrexate = 80%, originator infliximab as first infliximab product = 296, Biosimilar infliximab as first infliximab product = 99,

OUTCOME(S): Rate of drug discontinuation

RESULTS: Amongst patients who were infliximab naïve, 62% of those who commenced originator infliximab as their first product discontinued over the first 2 years as compared 30% of those commenced biosimilar infliximab as their first product. The most common reason for discontinuing originator infliximab and biosimilar infliximab is stated as "*Switch^/other*" where "^*Switch to biosimilar due to local hospital policy"* followed by inefficacy (53% originator group vs 5% biosimilar group) and side effects (9.1% originator group vs 5% biosimilar group). Amongst those that switched from originator to biosimilar the most common reasons to discontinue were ""*Switch^/other*" followed by side effects (5.4%), not known (4.3%) and inefficacy (3.2%).

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Park et al: Infliximab biosimilar CT-P13 therapy in patients with Takayasu arteritis with low dose of glucocorticoids: A prospective single-arm study [32]

SPONSOR: Study medication provided by Celltrion

LOCATION(S): Seoul, Korea

DESIGN: Prospective, open label

DATES: Patients enrolled March 2013 to September 2017

OBJECTIVE(S): To evaluate the efficacy and safety of infliximab biosimilar CT-P13 in patients with active Takayasu arteritis (TAK)

PATIENT CHARACTERISTICS: 11 relapsing active patients and 1 newly diagnosed patient with Takayasu arteritis. Concomitant immunosuppressive agents at stable dose were permitted. Mean age at onset = 42.5 years (3 SD 14.8 years). Mean disease duration prior to CT-P13 = 4.4 years (3 SD 5.2 years).

OUTCOME(S): The primary efficacy endpoint was the achievement of partial or complete remission at week 30. Secondary endpoints were changes in modified Indian Takayasu Clinical Activity Score (ITAS2010) and changes in concentrations of EST, CRP, TNFα and IL-6.

RESULTS: At week 30, three of 11 patients achieved complete remission. Six patients achieved a partial remission. ITAS2010 decreased from a median of 11.0 (IQR 10.0–11.8) at baseline to 6.0 (IQR 5.0–9.0) at week 30 ($p = 0.004$). Levels of ESR and CRP were also significantly reduced at week 30 compared to baseline; ESR [56.0 (44.0–82.5) vs. 26.0 (20.0–56.5), $p = 0.031$] and CRP [1.3 (0.7–2.6) vs. 0.2 (0.1–2.1), $p = 0.019$].

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Smits et al: Drug survival and immunogenicity after switching from Remicade to biosimilar CT-P13 in inflammatory bowel disease patients: Two-year follow-up of a prospective observational cohort study [33]

SPONSOR: None

LOCATION(S): Radboud University Medical Center, Netherlands

DESIGN: Prospective, observational

DATES: Extending previous 12-month follow-up report

OBJECTIVE(S): To describe the 2-year pharmacokinetic, immunogenicity, effectiveness and drug survival outcomes in a prospective cohort of patients who switched from originator infliximab to biosimilar infliximab (CT-P13).

PATIENT CHARACTERISTICS: 83 patients; Crohn's disease =57, Ulcerative colitis = 24, unclassified = 2. Median duration of originator infliximab prior to switching = 25 months (IQR 9–36). Concomitant thiopurines = 48 (58%). Concomitant methotrexate = 7 (8%). Clinical remission greater than 4 months prior to switching = 43 (52%). Clinical remission at time of switch = 53(64%). Five patients were positive for anti-drug antibodies prior to switching.

OUTCOME(S): Main endpoints for this report were trough infliximab concentrations levels (TLs) and the development of anti-drug antibodies at weeks 0, 16, 52, and 104 after switching from originator infliximab to CT-P13. Additional endpoints included the discontinuation rate, drug survival and change in disease activity as measured by the Harvey Bradshaw Index (HBI) for Crohn's disease and the Simple Clinical Colitis Activity Index (SCCAI) for ulcerative colitis (UC).

RESULTS: There were no significant differences in median trough infliximab concentrations across time between baseline, week 16, week 52, and week (3.6 Qg/mL (IQR 1.7–5.5) vs 4.2 Qg/mL (IQR 2.1– 5.9) vs 3.8 Qg/mL (IQR 2.1–6.1) vs 4.1 Qg/mL (IQR 2.4–6.1) respectively, P = 0.079). However, dosing was increased in 14 (25%) patients due to low infliximab trough concentrations (n = 5), disease activity (n = 2), or both (n = 7) and decreased in 6 (11%) patients due to supratherapeutic concentrations (n = 3), remission (n = 2), or both (n = 1). Two patients developed anti-drug antibodies prior to week 52 and no additional patients became anti-drug antibody positive between weeks 52 and 102. The authors note that "*Our immunogenicity data at year 2 of follow-up are reassuring and are similar to historic cohorts of Remicade-treated IBD patients*". At week 104, 55 (66%) patients remained on CT-P13; 7 patients discontinued due to remission, 10 patients discontinued due to loss of response and 8 due to adverse events which the authors consider "*…is in line with described Remicade cohorts*". There were no significant changes in the median HBI and SCCAI during follow-up (*P* = 0.491 and 0.343 respectively). Overall the authors suggest that "*These results are reassuring and suggest that switching to CT-P13 does not impact long-term clinical outcomes*".

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ETANERCEPT

Gisondi et al: Etanercept biosimilar SB4 in the treatment of chronic plaque psoriasis. Data from the Psobiosimilars registry [34]

SPONSOR: Psobiosimilars registry is supported by Biogen, Mundipharma and Pfizer

LOCATION(S): Italian dermatological public hospitals

DESIGN: A web-based registry

DATES: July 2015 and June 2018

OBJECTIVE(S): To investigate the effectiveness and safety of etanercept biosimilar SB4 in patients with psoriasis registered in the Psobiosimilars registry.

PATIENT CHARACTERISTICS: 197 patients were identified in the registry, of whom 158 switched from originator etanercept to SB4 and 39 who were naïve to the originator.

OUTCOME(S): Change in PASI score between baseline and month 6 post switch or commencement.

RESULTS: In the switching group PASI was unchanged (3.1 3 3.3 at baseline, 2.0 3 2.1 at month 3, 1.8 3 1.9 at month 6, p=not significant) indicating that the switch did not alter disease control. In the group that were naïve to originator etanercept and were initiating treatment with SB4 the PASI score significantly reduced 12.5 3 6.2 at baseline to 7.8 3 3.7 at month 3 and to 6.7 3 2.2 at month 6 (p=0.03), indicating that initiating biosimilar etanercept resulted in a decrease in disease severity.

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ERYTHROPOIETIN

Stoppa et al: Comparative safety of originator and biosimilar epoetin alfa drugs: An observational prospective multicenter study [35]

SPONSOR: Non-commercial

LOCATION(S): 26 hospitals in Italy (Veneto, Liguria, Molise, and Sardegna)

DESIGN: Observational, multicenter, prospective cohort study

DATES: 1 October 2013 and 30 June 2015

OBJECTIVE(S): To compare the safety of originator versus biosimilar epoetin alfa drugs in patients with chronic kidney disease.

PATIENT CHARACTERISTICS: 867 patients, 423 (48.8%) received the originator epoetin and 444 (51.2%) the biosimilar (Binocrit® = 440, Reatcrit®=4), median duration of observation = 10.5 months (biosimilar) vs 8.5 months (originator).

OUTCOME(S): Three major categories of safety outcomes were agreed between the participating nephrologists; 'Problems related to the dialysis device', 'Cardio and cerebrovascular events' and 'Infections'.

RESULTS: After adjusting for confounding factors, the hazard ratio estimate was 1.0 (95% CI 0.7–1.3) for any outcome, 1.1 (95% CI 0.7–1.8) for problems related to the dialysis device, 0.9 (95% CI 0.6–1.5) for cardio and cerebrovascular events and 0.9 (95% CI 0.6–1.5) for infections.

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FILGRASTIM

Schwartzberg et al: Incidence of febrile neutropenia during chemotherapy among patients with nonmyeloid cancer receiving filgrastim vs a filgrastim biosimilar [36]

SPONSOR: Sandoz Inc

LOCATION(S): USA

DESIGN: Retrospective claims analysis of the Optum Research Database

DATES: 01 September 2014 through 31 July 2016

OBJECTIVE(S): To compare outcomes between biosimilar filgrastim(filgrastim-sndz) and originator filgrastim treated patients undergoing chemotherapy treatment for nonmyeloid malignancies in US clinical practice

PATIENT CHARACTERISTICS: Undergoing chemotherapy for nonmyeloid cancer who were treated with biosimilar filgrastim(filgrastim-sndz) or originator filgrastim in at least one completed cycle of a chemotherapy treatment regimen

OUTCOME(S): Incidence of neutropenia plus fever, neutropenia plus infection and neutropenia plus infection plus fever, as documented by relevant International Classification of Diseases codes. Equivalence between originator and biosimilar filgrastim considered if the 90% confidence interval for the between group difference in incidence were between -6% and +6%.

RESULTS: A total of 3459 patients were included of whom 162 received biosimilar filgrastim and 3370 received originator. The difference in incidence between biosimilar and originator groups was 0.2 (90%CI: -0.57 to.56) for neutropenia plus fever, -0.12 (90%CI: -1.17 to 2.28) for neutropenia plus infection and -0.14 (90% not calculated due to 0 incidence in biosimilar group) for neutropenia plus infection plus fever, all of which were within the equivalence criteria.

STAKEHOLDER PERCEPTIONS

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

HEALTH PROFESSIONALS

Aladul et al: Differences in UK healthcare professionals' knowledge, attitude and practice towards infliximab and insulin glargine biosimilars [37]

SPONSOR: None, investigator-initiated

LOCATION(S): Keele University, School of Pharmacy, UK

DESIGN: Anonymised, self-administered web-based survey

DATES: August 2016 – January 2017

OBJECTIVE(S): To investigate knowledge and attitudes of different healthcare professionals in UK towards infliximab and insulin glargine biosimilars

PARTICIPANTS: UK medical consultants/registrars (n=150), nurses (n=58) and pharmacists (n=26) specialised in dermatology, diabetology, gastroenterology or rheumatology were contacted via a variety of specialist clinical societies such as the British Society of Gastroenterology and asked to complete the online survey. Response rate = unable to be determined.

RESULTS: The majority of consultants / registrars (76.6%) and pharmacists (84.8%) identified biosimilars as "*a similar copy of a biological medicine*", whereas 53.4% of nurses identified with this definition of a biosimilar. 18.9% of nurses stated they either did not know what biosimilars are or have never heard of them, compared with 1.9% (n=3) of consultants / registrars and 3.8% (n=1) of pharmacists. Registrars / consultants and pharmacists were largely aware that biosimilars were available on their local drug formularies (80.7 and 80.9% respectively) compared with 57% of nurses. With regards to initiating patients on biosimilar medicines, nurses were more likely to have concerns with biosimilar safety (42%) that would prevent them from initiating a biosimilar when compared with the registrars / consultants (14%) and pharmacists (19%). A similar pattern was observed when questioned about efficacy with 54% of nurses stating that concerns with efficacy would prevent them from initiating a biosimilar, compared with 22% of registrar / consultants and 16% of pharmacists. This pattern was also observed for switching patients onto biosimilars from an originator product with 52% of nurses expressing concerns with biosimilar safety that would prevent them from switching, compared with 28% of registrars / consultants and 38% of pharmacists. Nearly all consultants / registrars and nurses (>91%) considered robust pharmacovigilance studies as the most important influence on the decision to prescribe a biosimilar medicine, whereas the majority of pharmacists (97%) weighted NICE (National Institute for Health and Care Excellence, UK) as more important. Consultants / Registrars and pharmacists considered increased patient acceptability as the least important influence on the decision to prescribe biosimilars (27 and 28% respectively) whereas 32% of nurses considered potential cost saving to be the least important factor on the decision to prescribe. The authors concluded that a difference in the level of biosimilar understanding existed between the health professions with a "*good understanding in medical consultants and pharmacists, but a lower level for nurses*". The authors stated that in the UK biologics cannot be automatically substituted by the dispensing pharmacist, "*Therefore, the decision to switch to biosimilars (or to originator) is a multi-disciplinary process involving the physician, patient, specialist nurse and pharmacist*".

REVIEWER COMMENTARY: The stated objectives were to investigate knowledge and attitudes towards biosimilar glargine insulin and infliximab, however the survey asked participants questions regarding biosimilars in general and did not specifically discuss infliximab or glargine insulin.

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Ismailov et al: Biosimilar knowledge among oncology/hematology team members in Colorado, USA: An educational initiative and follow-up survey [38]

SPONSOR: Pfizer Inc.

LOCATION(S): Oncology/Haematology physician offices in Colorado, USA

DESIGN: Education session, followed by online anonymous survey

DATES: Not stated

OBJECTIVE(S): Increase oncology/haematology team members' knowledge of biosimilars and various aspects related to biosimilars, such the approval process, safety, interchangeability, and the potential of biosimilars to enable optimal combination therapy for cancer.

PARTICIPANTS: 82 oncology/haematology teams were identified through the Colorado Department of Health Care, Policy and Financing. 62 team members responded, with participants consisting of oncology nurses or oncology nurse practitioners (73%), medical assistants (21%) and patient navigators (6%).

RESULTS: Participants were provided with a Pfizer representative led educational training session consisting of printed education materials supported by face-to-face discussion and then asked to complete an anonymous online survey. The majority of participants who undertook the education session and then completed the online survey displayed good knowledge regarding all topics related to biosimilars including definitions, regulation, safety, cost and interchangeability.

REVIEWER COMMENTARY: This Pfizer sponsored study did not evaluate participant prior knowledge and understanding of biosimilars. As such the value of the educational intervention described is difficult to evaluate.

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O'Callaghan et al: Knowledge of adverse drug reaction reporting and the pharmacovigilance of biological medicines: A survey of healthcare professionals in Ireland [39]

SPONSOR: None

LOCATION(S): Ireland

DESIGN: Anonymised, self-administered web-based survey

DATES: May – July 2017

OBJECTIVE(S): Assess the knowledge and general experience of adverse drug reporting knowledge, behaviours, and attitudes related to the pharmacovigilance of biologicals among healthcare professionals (HCPs) in Ireland.

PARTICIPANTS: Hospital doctors, GPs, nurses and pharmacists across Ireland were contacted via a variety of professional societies such as the Royal College of Physicians in Ireland and asked to complete the online survey.

RESULTS: 698 participants were included in the study and completed the survey. Familiarity with the term biosimilar varied between the respondents from the different health professions in Ireland. 73.1% of nurses stated they were unfamiliar with this term, compared with 52.8% of GPs, 30.7% of hospital doctors, 20.1% of community pharmacists and 4.6% of hospital pharmacists. Specific questions regarding pharmacovigilance issues related to biologics, including but not exclusive to biosimilars, was investigated. 92.1% of respondents were aware that "*ADRs associated with a patient changing between different brands of biological medicines should be reported*". 59.9% of respondents correctly identified that it is better to report an ADR involving a biological medicine by its brand name rather than by its non-propriety name. 75.2% of respondents were aware that a biosimilar is not the same as a generic medicine. 61.3% of respondents correctly stated that it is just as important to record the batch numbers of biological medicines as it is for non-biological medicines. The authors observed that "*statements relating to traceability of biologicals had the lowest proportions of correct answers. Knowledge gaps relating to the inclusion of brand names and batch numbers in biological ADR reports were identified.*" This finding was considered by the authors to be of particular importance "*the increasing availability of biological medicines, including biosimilars, make it necessary for HCPs to implement appropriate practice behaviours in order to ensure their traceability.*" The authors concluded that "*A substantial proportion of hospital doctors, GPs, nurses and community pharmacists were found to lack confidence in their own knowledge of ADR reporting, highlighting the importance of ongoing HCP education and training in the area of pharmacovigilance.*"

REVIEWER COMMENTARY: This manuscript discusses the importance of pharmacovigilance for biological medicines, it does not focus specifically on biosimilar medicines. However, the authors highlight that the need for robust pharmacovigilance practices such as recording biological medicines by brand name will be increasingly important as the number of biological and biosimilar medicines on the market expands.

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PATIENTS/HEALTH PROFESSIONALS

Tischer et al: Patients' and nurses' preferences for auto-injectors for rheumatoid arthritis: Results of a European survey [40]

SPONSOR: Sandoz

LOCATION(S): France, Germany, Italy, Spain, and the UK

DESIGN: A demonstration of a new auto-injector device was provided for participants, followed by a market research survey investigating user preferences of four auto-injector devices. The patient survey was conducted by trained interviewers through 20-minute face-to-face interviews using a structured questionnaire. The nurse survey was conducted by trained interviewers via 45-minute face-to-face interviews using a structured questionnaire.

DATES: June – October 2017

OBJECTIVE(S): Assess patients' rating of importance of eleven auto-injector attributes; determine patient and nurse educator preference for auto-injector device in patients with rheumatoid arthritis (RA)

PARTICIPANTS: The patient survey (n = 200) included adult patients with moderate–severe RA currently using etanercept (Enbrel), biosimilar etanercept (Benepali), or adalimumab (Humira). The nurse survey (n=100) included nurses who instruct patients with moderate–severe RA on the use of autoinjectors. Nurses were recruited if they had experience instructing patients on the use of etanercept autoinjectors (both MyClic and Molly) and the adalimumab autoinjector (Humira pen).

RESULTS: Both patients (9.2 / 10 on a Likert scale) and nurses (9.7 / 10 on a Likert scale) responded that the auto-injector attribute "*easy to perform the self-injection with the pen*" was the most important attribute. The second most important attribute was stated to be "*Easy to grip the pen*". Patients and nurses agreed that "*convenient starting of the injection by pushing a button*" was the least important attribute. When comparing the different auto-injector devices patients and nurses both stated that the new Erelzi/Sensoready formulation and device combination had the highest "*Overall satisfaction*" rating. Erelzi/Sensoready also rated the highest on the attribute considered to be the most important "*easy to perform the self-injection with the pen*". This is the device that was demonstrated by the trained interviewer and marketed by the sponsor of the study Sandoz. The authors concluded that "*Patients and nurses were most likely to recommend SensoReady over other autoinjectors to patients with RA. Main reasons for this preference were the buttonless injection, the large window offering a 360° view for the visual feedback that the full dose had been injected, and the triangular shape, which makes the autoinjector easy to grip.*"

REVIEWER COMMENTARY: Although caution must be taken when interpreting the findings of this market research exercise, this study highlights the importance of auto-injector design on biosimilar preference and uptake, particularly in patients with diseases which affect dexterity such as RA. Biosimilar initiation and switching must consider auto-injector attributes in addition to the efficacy and safety of the biosimilar drug being injected.

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

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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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