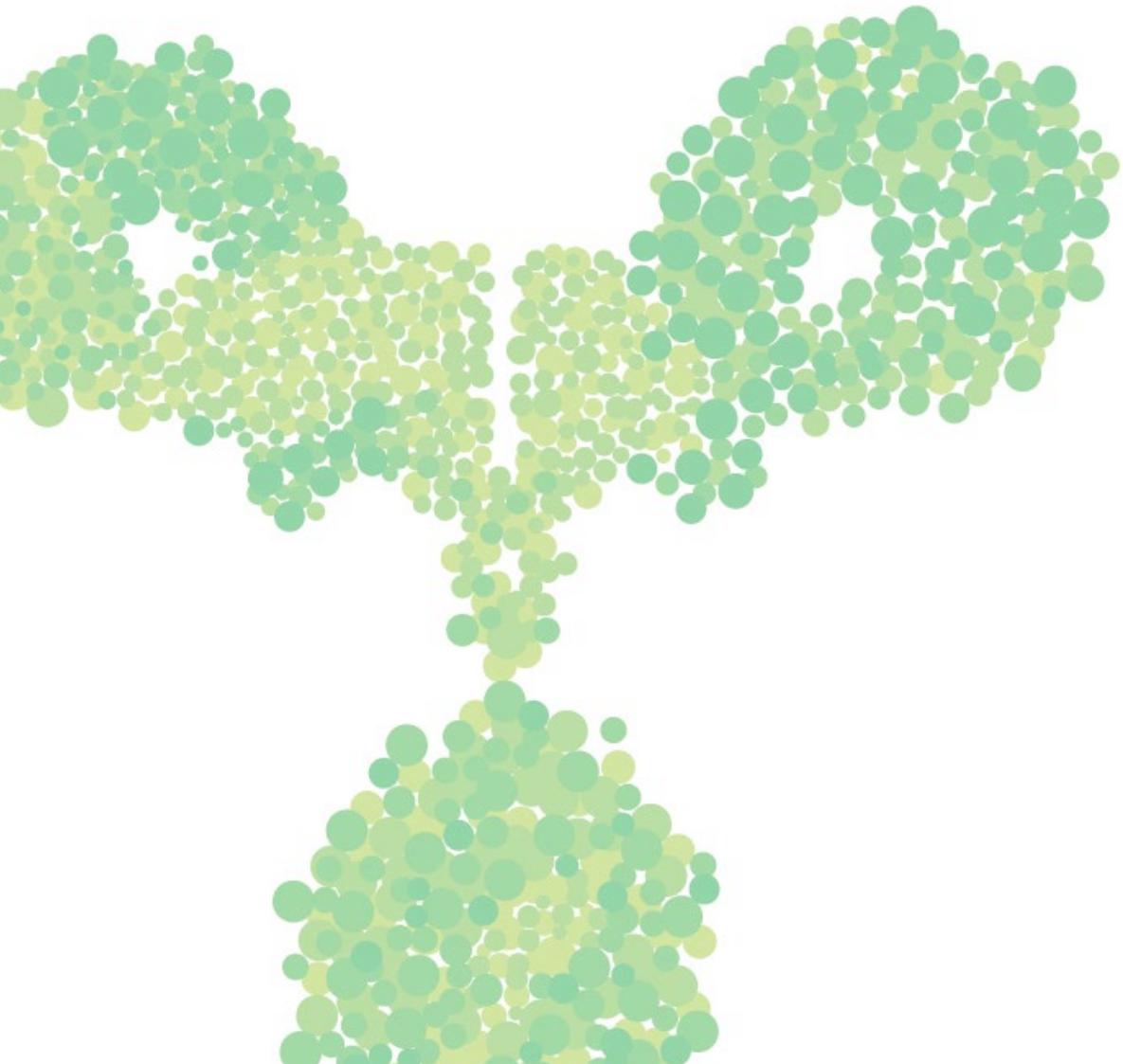
GBMA EDUCATION

University of South Australia | School of Pharmacy and Medical Sciences

International Biosimilar Medicines

Review of the Literature: Quarterly Update

July – September 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.

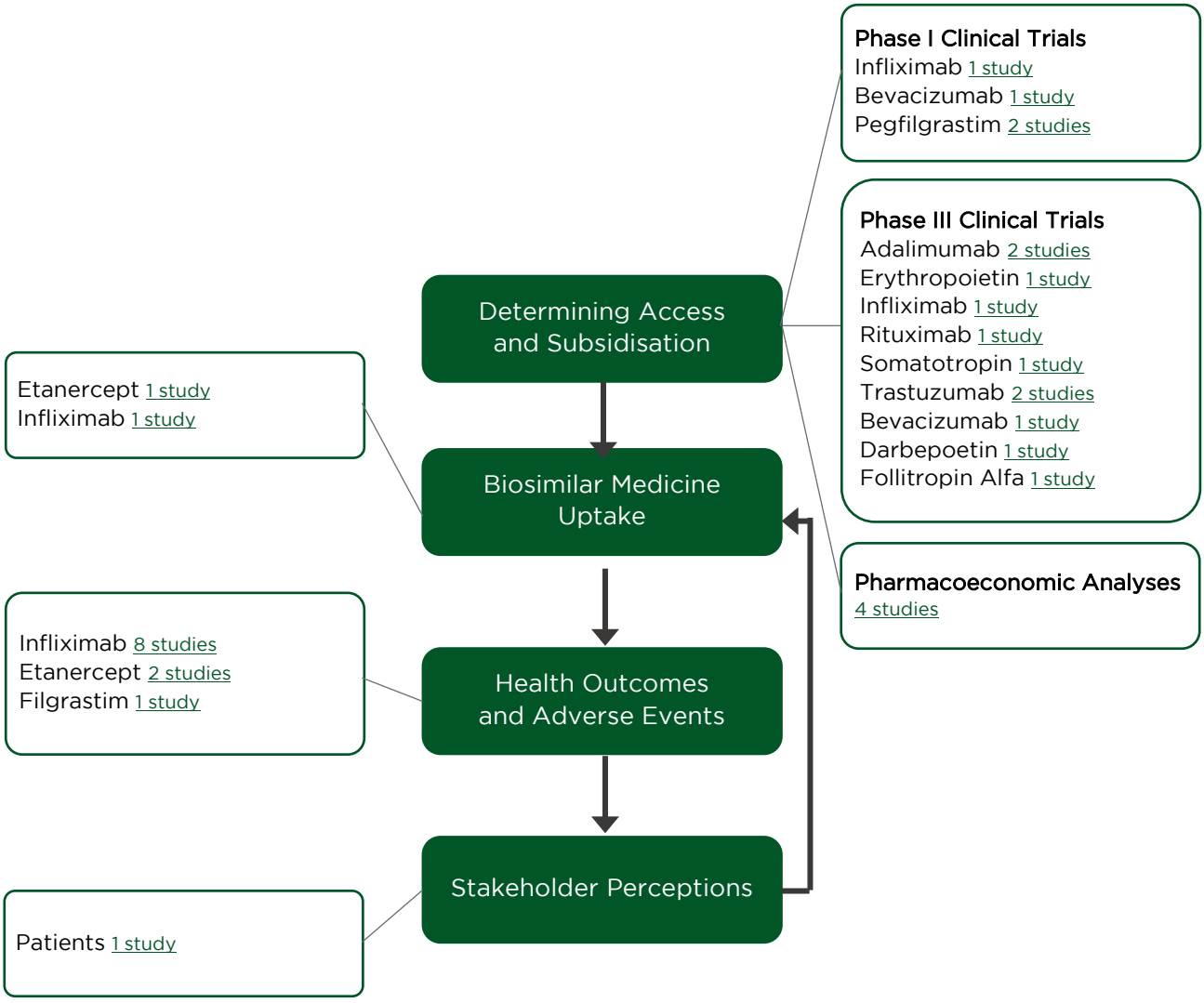
Stakeholder Perceptions

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 July 2019 and 30 September 2019.

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



Manuscripts provided for reference but not summarised

Appendix 1: Educational/Review Articles
41 manuscripts

Appendix 2: Technical
12 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 four papers that reported phase I and 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 and pharmacokinetic studies of potential biosimilar medicines

Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
INFLIXIMAB						
PF-06438179/GP1111 (combination with methotrexate)	Remicade® (EU) in combination with methotrexate	Randomised, double-blind, two-arm, parallel, multiple-dose study	Patients with moderate to severely active rheumatoid arthritis (n=650, randomised 1:1)	Undertaking a population pharmacokinetic approach, similar estimated pharmacokinetic parameters, and parameter variability were obtained for PF-06438179/GP1111 and EU Remicade® (CL 0.014L/hr vs 0.015L/hr; V_c 3.38L vs 3.3.57L; V_p 1.70L vs 1.65L, respectively).	Not reported.	Palaparthy et al[1]

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Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
BEVACIZUMAB						
TAB008	Avastin®	Randomised, double-blind, two-arm, parallel, multiple-dose study	Health adult Chinese 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 TAB008 with Avastin®.	Two subject showed positive ADA on days 15 and 85 (one subject in the TAB008 group, and one subject in the Avastin® group). No neutralising antibodies were detected.	Wang et al[2]

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Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
PEGFILGRASTIM						
B12019 (Pelmeg®)	Neulasta® (EU)	Randomised, double-blind, two-arm, crossover, single-dose study	Healthy adult males (n=171, randomised 1:1)	94.32% CI of the ratio of geometric least square means for PK ($AUC_{0\text{-last}}$ and C_{max}) and PD ($AUEC_{0\text{-last}}$) parameters were within the pre-defined equivalence interval of 80-125% for the comparison of Pelmeg® with EU Neulasta®.	No anti-filgrastim-reactive positive samples were detected in any subject. 19.9% of subjects had confirmed ADA positive reactivity with PEG, with no noted differences between the treatment groups.	Roth et al[3]

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Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
B12019 (Pelmeg®)	Neulasta® (EU)	Randomised, double-blind, three-period, two-arm, crossover, multiple-dose study	Healthy adult males (n=96, randomised 1:1)	95% CI of the ratio of geometric least square means for PD ($AUEC_{0\text{-last}}$) parameters were within the pre-defined equivalence interval of 80-125% for the comparison of Pelmeg® with EU Neulasta®. Descriptive analysis of PK ($AUC_{0\text{-}120}$ and C_{max}) and secondary PD (E_{max}, $t_{max,E}$) parameters noted results to be similar for Pelmeg® and EU Neulasta®.	No neutralising antibodies were detected. Two confirmed ADA positive samples were detected (Day 15, Period 1); one subject dosed with Neulasta® was positive for Pelmeg®, Neulasta® and PEG, and one subjects dosed with Pelmeg® was positive for Neulasta®. No difference in immunogenicity between Pelmeg® and Neulasta® was observed.	Wessels et al[4]

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 11 reports of phase III trials of potential biosimilars.

ADALIMUMAB

Cohen et al: Long-term safety, efficacy, and immunogenicity of adalimumab biosimilar BI 695501 and adalimumab reference product in patients with moderately-to-severely active rheumatoid arthritis: results from a phase 3b extension study (VOLTAIRE-RAext)[5]

SPONSOR: Boehringer Ingelheim

REFERENCE PRODUCT: Not applicable

OBJECTIVE(S): To describe the long-term safety, efficacy, and immunogenicity of biosimilar adalimumab (BI 695501) in participants with moderately-to-severely active rheumatoid arthritis (RA) who had completed 48 weeks of treatment with BI 695501 or 48 weeks of reference adalimumab or 24 weeks of reference adalimumab followed 24 weeks of BI 695501 in the VOLTAIRE-RA phase III study*.

DESIGN: 48 week open-label extension phase.

SAMPLE SIZE: 430 participants entered into the extension phase, participants previously treated with 48 weeks of BI 695501 = 225, participants previously treated with 48 weeks of reference product = 103, participants previously treated with 24 weeks of each of BI 695501 and reference product = 102.

PATIENT CHARACTERISTICS: Demographics and clinical characteristics were similar between groups; mean DAS28-ESR at baseline of extension period was 3.8 in all participant groups; mean DAS28-CRP at baseline of extension period = 3.22 to 3.24 across all groups.

PRIMARY ENDPOINT: The proportion of patients with investigator-assessed drug related adverse events during the treatment phase.

RESULTS: The mean duration of exposure to BI 695501 during the extension phase ranged from 313.1 days to 331.3 days across the three groups. Investigator-assessed drug related adverse events occurred in 21.3% of participants previously treated with BI 695501 for 48 weeks as compared with 20.4% of those previously treated with 48 weeks of reference product and 17.6% of those previously treated with reference product for 24 weeks followed by 24 weeks of BI 695501. In all three groups the ACR20/50/70 treatment responses were maintained across the 48-week extension period. At the end of the extension period 8.4% of participants previously treated with BI 695501 for 48 weeks were in remission (ACR/EULAR definition) as compared with 9.7% of those previously treated with 48 weeks of reference product and 6.9% of those previously treated with reference product for 24 weeks followed by 24 weeks of BI 695501 whilst a good response was achieved in 37.8%, 37.9% and 41.6% or participants respectively. There was "*minimal*" change in the rates of anti-drug antibody positivity across the three groups relative to the baseline of the extension period and were within the variability of the limits of the assay.

* Cohen SB, Alonso-Ruiz A, Klimiuk PA et al. Similar efficacy, safety and immunogenicity of adalimumab biosimilar BI 695501 and Humira reference product in patients with moderately to severely active rheumatoid arthritis: results from the phase III randomised VOLTAIRE-RA equivalence study. *Ann Rheum Dis* 2018; **77**: 914-21.

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Edwards et al: Safety of adalimumab biosimilar MSB11022 (acetate-buffered formulation) in patients with moderately-to-severely active rheumatoid arthritis[6]

SPONSOR: Merck KGaA and Fresenius Kabi

REFERENCE PRODUCT: Humira® (EU, citrate formulation)

OBJECTIVE(S): To compare the safety, immunogenicity, and efficacy of MSB11022 (acetate formulation) with reference adalimumab (citrate formulation) in participants with moderately-to-severely active rheumatoid arthritis with an inadequate response to methotrexate.

DESIGN: A phase 3 multi-centre, randomized, double-blind parallel group trial.

SAMPLE SIZE: 288 participants randomized, MSB11022 = 143, reference product = 145.

PATIENT CHARACTERISTICS: Aged at least 18 years with a clinical diagnosis of moderately-to-severely active RA with disease duration ≥ 6 months from confirmed diagnosis, treated with methotrexate for at least 12 weeks prior to baseline which was stable for at least 4 weeks prior to screening, adalimumab naïve.

EQUIVALENCE CRITERIA: The primary endpoint was the incidence of treatment emergent adverse events of special interest (hypersensitivity). The study was not powered to demonstrate equivalence with regards to efficacy and equivalence criteria were not defined.

RESULTS: Treatment emergent adverse events of special interest occurred in 6 (4.2%, 95%CI: 1.56 to 8.91) participants in the MSB11022 group as compared with 8 (5.5%, 95%CI: 2.41 to 10.58) participants in the reference product group. Within the MSB11022 group 80.4% of participants were positive for antidrug antibodies on at least one occasion as compared with 71.7% of participants in the reference product group and neutralising antidrug antibodies were detected at least once in 39.6% and 39.3% of participants respectively.

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ERYTHROPOIETIN

Fishbane et al: Randomized Controlled Trial of Subcutaneous Epoetin Alfa-epbx Versus Epoetin Alfa in End-Stage Kidney Disease[7]

SPONSOR: Pfizer Inc.

REFERENCE PRODUCT: Epogen®

OBJECTIVE(S): To evaluate the equivalence of epoetin alfa-epbx (Retacrit®) to epoetin reference in haemodialysis patients with ESKD and anaemia, who were receiving epoetin alfa maintenance treatment (SC or IV).

DESIGN: Multicentre, randomized, active comparator-controlled, double-blinded, parallel-group. Participants were randomised 1:1 for an 18-week SC titration phase, participants who achieved a stable dose wee then re-randomised for a further 16-week maintenance phase, followed by a 48-week open label extension.

SAMPLE SIZE: 320 participants entered titration phase (1:1); 246 participants were re-randomised for the maintenance phase (1:1); 213 completed the study Retacrit = 106, reference product = 105.

PATIENT CHARACTERISTICS: Participants mean age = 57.4 years (Retacrit) vs 56.5 years (reference); baseline weekly hemoglobin levels (g/dl) = 10.36 (0.78) (Retacrit) vs 10.28 (0.78) (reference); baseline weekly erythropoietin dose by body weight (U/kg) = 93.53 (112.45) (Retacrit) vs 85.91 (82.08) (reference).

EQUIVALENCE CRITERIA: Containment of the 95% confidence interval (CI) for the least squares mean difference between groups in weekly hemoglobin levels (g/dl) and erythropoietin dose by body weight (BW) (U/kg).

RESULTS: The primary efficacy endpoints of difference between the mean weekly haemoglobin levels (0.04 [-0.17 to 0.24] g/dl per week) and the mean weekly epoetin dose (2.34 [-14.51 to 9.82] U/kg per week) between the two treatment groups were contained within the prespecified equivalence margins during the last 4 weeks of the maintenance phase. As such the authors stated that "*the study met its prespecified co-primary efficacy endpoints*". The safety profiles observed across the two treatment groups were described the authors as similar and "*consistent with those expected for an ESKD population receiving epoetin*".

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INFLIXIMAB

Lila et al: A phase III study of BCD-055 compared with innovator infliximab in patients with active rheumatoid arthritis: 54-week results from the LIRA study[8]

SPONSOR: JSC BIOCAD

REFERENCE PRODUCT: Referred to only as "innovator infliximab"

OBJECTIVE(S): To demonstrate equivalent efficacy and safety of BCD-055 and reference infliximab in participants with active rheumatoid arthritis.

DESIGN: Multi-centre randomized (2:1) double-blind phase 3 clinical study.

SAMPLE SIZE: 426 participants were randomized, BCD-055 = 284, reference infliximab = 142; 345 completed the study, BCD-055 = 237, reference infliximab = 108.

PATIENT CHARACTERISTICS: Diagnosed with rheumatoid arthritis (ACR 2010 criteria) at least 6 months prior to consent, active disease despite standard disease-modifying antirheumatic drugs (methotrexate or other), median age = 53 years in both groups, median rheumatoid arthritis duration (years) = 3.8 (BCD-055) vs 6.0 (reference); median methotrexate dose = 15mg in both groups; baseline median DAS28-CRP(4) = 6.2 (BCD-055) vs 6.0 (reference).

EQUIVALENCE CRITERIA: Containment of the 95% confidence interval for the difference in ACR20 rates at week 14 within the range of – 15% to 15%.

RESULTS: The rate of ACR20 response at week 14 was 71.2% in the BCD-055 group as compared with 67.9% in the reference product infliximab group, equating to a difference of 3.2% with a 95% confidence interval of -7.0% to 13.5% which was within the prespecified equivalence criteria of – 15% to 15%. Therapy related adverse events occurred in 47.14% of participants in the BCD-055 group as compared with 40.58% of participants in the reference product group (p = 0.245). Hypertension occurred more frequently in the BCD-055 group as compared with the reference product group (28.28% vs 15.94%, $p < 0.05$) but there was no difference in the frequency grade 3 hypertension (p = 1.00, 6 participants in the BCD group as compared with 2 in the reference product group). Anti-drug antibodies were detected in 28.46% of participants in the BCD-055 group as compared with 26.56% of participants in the reference product group (p=0.786).

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RITUXIMAB

Candelaria et al: Rituximab biosimilar RTXM83 versus reference rituximab in combination with CHOP as first-line treatment for diffuse large B-cell lymphoma: a randomized, double-blind study[9]

SPONSOR: mAbxience Research S.L.

REFERENCE PRODUCT: MabThera® (source not specified)

OBJECTIVE(S): To compare the efficacy, pharmacokinetics, pharmacodynamics, safety, and immunogenicity of RTXM83 with reference product rituximab in combination with CHOP chemotherapy as first-line treatment in participants with diffuse large B-cell lymphoma (DLBCL).

DESIGN: Prospective, multi-centre, double-blind, randomized clinical study.

SAMPLE SIZE: 256 participants randomised 1:1 plus an additional extension cohort of 16 Iranian participants included in the safety analysis only (in accordance with specific local regulatory requirements); 239 participants were included in the intention to treat population, biosimilar group = 122, reference product = 117.

PATIENT CHARACTERISTICS: Participants aged 18 to 65 years with a newly confirmed pathologic diagnosis of stage I (only with bulky disease) or stages II to IV DLBCL (Cotswolds modification of the Ann Arbor classification).

EQUIVALENCE CRITERIA: The lower limit of the 95% confidence interval for the difference in overall response rate, defined as the proportion of participants achieving complete remission (CR) or a partial response (PR) in each treatment group after study treatment (chemotherapy cycle 6 or within 30 days after last administration), above -13%.

RESULTS: After six cycles of chemotherapy, the overall response rate was 82.9% in the reference product group as compared to 83.6% in the biosimilar group, equating to a difference of 0.7% (p=0.5109). The lower limit of the 95% confidence interval for the difference in overall response rate was -8.77% which was above the pre-defined non-inferiority criteria of -13%. Treatment interruption, predominantly due to skin reactions and other infusion related reactions, occurred in 11 (8%) participants in the biosimilar group as compared with 20 (15%) participants in the reference product group. A single participant in the reference product group discontinued due to infusion related reactions.

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SOMATOTROPIN

Czepielewski et al: Efficacy and safety of a biosimilar recombinant human growth hormone (r-hGH Cristalia) compared with reference r-hGH in children with growth hormone deficiency (CERES study): A randomized, multicentric, investigator-blind, phase 3 trial[10]

SPONSOR: Cristália Produtos Químicos Farmacêuticos Ltda (Brazil)

REFERENCE PRODUCT: Genotropin®

OBJECTIVE(S): To evaluate equivalence in efficacy and safety of recombinant human growth hormone (r-hGH Cristalia) compared to the reference product in prepubertal children with growth hormone deficiency.

DESIGN: Multicentre, randomized, active comparator-controlled, investigator-blinded, parallel-group.

SAMPLE SIZE: 97 participants randomised 1:1, r-hGH Cristalia = 49, reference product = 48

PATIENT CHARACTERISTICS: Participants age ranged 4-13 years, mean age = 8.3 (r-hGH Cristalia) vs 9.0 years (reference); all participants had peak serum growth hormone levels at baseline ≤7 ng/mL, treatment-naïve at enrolment, mean height at the beginning of treatment = 128.5cm (r-hGH Cristalia) vs 131.9cm (reference product)

EQUIVALENCE CRITERIA: Containment of the 95% confidence interval (CI) for the least squares mean difference between groups in the percent change in height velocity (primary efficacy endpoint) and height standard deviation score. Safety was assessed by monitoring all adverse events (AEs) at each study visit along with standard blood counts.

RESULTS: At 12 months the mean height velocity for the per protocol r-hGH Cristalia group was 9.5 ± 1.72 cm/year as compared with 9.4 ± 1.5 cm/year in the reference group. The 95% confidence limits for this difference were −0.71 and 0.74 cm/year, which were contained within the non-inferiority limit of −2.0 cm/year. No statistical difference was observed in the height standard deviation score gain between the two treatment groups (mean difference = −0.02, CI 95%: −0.33; 0.38). Anti-drug antibodies were detected in 7 (14.3%) participants in the biosimilar group as compared with 13 (27.1%) participants in the reference product group. Headache was the most common adverse event occurring in two participants in the biosimilar group and 3 participants in the reference product group.

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TRASTUZUMAB

Esteva et al: Efficacy and safety of CT-P6 versus reference trastuzumab in HER2-positive early breast cancer: updated results of a randomised phase 3 trial[11]

SPONSOR: CELLTRION, Inc.

REFERENCE PRODUCT: Herceptin® (source not specified)

OBJECTIVE(S): Following the prior demonstration of equivalence of CT-P6 and reference trastuzumab in the neoadjuvant setting in the treatment of participants with breast cancer[†], the objective was to provide additional efficacy outcomes from the adjuvant period, update the overall safety results and undertake a post-hoc subgroup analysis of the primary outcome (pathological complete response).

DESIGN: Randomised, double-blind, parallel group, active controlled phase 3 study.

SAMPLE SIZE: 549 participants randomised to commence neoadjuvant treatment, CT-P6 = 271, reference trastuzumab = 278; participants completing neoadjuvant treatment period and pathological complete response assessment = 258 (CT-P6) vs 261 (reference product); participants completing adjuvant treatment period = 243 (CT-P6) vs 249 (reference product).

PATIENT CHARACTERISTICS: Female participants, aged ≥ 18 years with pathologically confirmed, newly diagnosed, operable, HER2-positive early breast cancer (clinical stage I, II, or IIIA) receiving neoadjuvant trastuzumab, docetaxel and fluorouracil, epirubicin and cyclophosphamide followed by surgery adjuvant trastuzumab.

RESULTS: At 1 year, nine participants (3.3%) in the CT-P6 group had experienced recurrent or progressive disease as compared with 6 participants (2.2%) in the reference product group whilst treatment emergent serious adverse events occurred in 20 participants in the CT-P6 group (7.4%) as compared with 33 participants (11.9%) in the reference product group. Heart failure occurred in 10 participants (3.7%) in the CT-P6 group as compared with 7 participants (2.5%) in the reference product group with a significant decrease in left ventricular ejection fraction (a decrease of ≥ 10% from baseline value and below an absolute value of 50%) occurred in 9 (3.3%) and 7 (2.5%) participants, respectively. Post-infusion antidrug antibody results were negative at all time points. Sub-group analysis of the primary outcome of pathological complete response was not influenced by region (Europe/Middle East/Africa vs Asia vs America), participant age or disease stage.

[†] Stebbing J, Baranau Y, Baryash V et al. CT-P6 compared with reference trastuzumab for HER2-positive breast cancer: a randomised, double-blind, active-controlled, phase 3 equivalence trial. *Lancet Oncol* 2017; **18**: 917-28.

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Pivot et al: Three-year follow-up from a phase 3 study of SB3 (a trastuzumab biosimilar) versus reference trastuzumab in the neoadjuvant setting for human epidermal growth factor receptor 2-positive breast cancer[12]

SPONSOR: Samsung Bioepis Co., Ltd

REFERENCE PRODUCT: Herceptin®

OBJECTIVE(S): To investigate the long-term event-free survival, overall survival and cardiac safety in participants who received biosimilar trastuzumab (SB3) or reference trastuzumab and to investigate, post-hoc, the impact of changes reported to have occurred[‡] in the physicochemical characteristics ('drift') of reference trastuzumab on the outcomes observed.

DESIGN: Observational, treatment-free extension cohort study, post-hoc analysis. Participants that received reference trastuzumab were classified as having received a 'drifted' or 'non-drifted' product based upon the lot number and/or expiry date of the product that they had received. The classification of reference product as 'drifted' and 'non-drifted' was based upon antibody-dependant cell-mediated cytotoxicity (ADCC) activity results reported previously[‡]. Participants that received at least one vial of 'drifted' reference product during the neoadjuvant treatment period were classified as 'drifted' whilst patients who were not exposed to the 'drifted' product during the neoadjuvant period were classified as 'non-drifted'.

SAMPLE SIZE: 875 participants randomised in the main study; 367 participants enrolled in extension study, SB3 = 186, reference product = 181; 'non-drifted' reference product = 55, 'drifted' reference product = 126.

PATIENT CHARACTERISTICS: Participants who had completed neoadjuvant treatment, surgery and adjuvant treatment. Median duration of follow-up from enrolment in main study = 40.8 months (SB3) vs 40.5 months (reference product), breast cancer type: locally advanced = 30.1% (SB3) vs 27.3% ('non-drifted' reference product) vs 31.7% ('drifted' reference product), operable = 66.7% (SB3) vs 67.3% ('non-drifted' reference product) vs 65.9% ('drifted' reference product).

RESULTS: The 3-year event free survival rate was 91.9% in the SB3 group as compared with 92.7% in the 'non-drifted' reference product group and 81.7% in the 'drifted' reference product group. The event-free survival rate was not significantly different between the SB3 group and the 'non-drifted' group, hazard ratio (SB3/'non-drifted' reference product) = 0.93, 95%CI: 0.31 to 2.85. However, the event free survival was lower in the 'drifted' reference product group than in the 'non-drifted' reference product group, hazard ratio ('drifted'/'non-drifted') = 5.31 (95% CI: 1.74 to 16.25). Five (2.7%) deaths occurred in the SB3 group as compared with one (1.8%) in the 'non-drifted' reference product group and 12 (9.5%) in the 'drifted' reference product group. The hazard ratio for overall survival for SB3/ 'non-drifted' reference product was 0.53 (95%CI: 0.05 to 5.51) and 7.96 (95%CI: 0.95 to 67.00) for 'drifted'/'non-drifted' reference product. No cases of symptomatic congestive heart failure were reported during the study whilst significant but asymptomatic decreases in left ventricular ejection fraction occurred in a single participant in the SB3 group and in two participants in the reference product group (combined 'drifted' and 'non-drifted').

REVIEWER COMMENTARY: The foundation of the development of a biosimilar medicine is the detailed physicochemical and pharmacological characterisation of the reference product and subsequent comparison against the attributes of a proposed biosimilar, including comparison across multiple batches of product. During the development of SB3 it was noted that the physicochemical attributes of reference trastuzumab changed, or 'drifted', on two occasions. These changes in physicochemical attributes impacted reference trastuzumab product lots with expiry dates between August 2019 and December 2019. These drifts were characterised by changes in glycosylation of reference product trastuzumab and were associated with changes in the pharmacological activities of FcγRIIIa binding and ADCC but not cellular proliferation, consistent with known pharmacological impact of antibody glycosylation.

[‡] Kim S, Song J, Park S et al. Drifts in ADCC-related quality attributes of Herceptin(R): Impact on development of a trastuzumab biosimilar. *MAbs* 2017; **9**: 704-14.

During the phase III clinical trial comparing SB3 with reference product trastuzumab in the neoadjuvant setting[§] it was observed that the proportion of participants achieving pathological complete response in the primary breast tumour, the primary endpoint of the study and the basis for defining equivalence, was 51.7% (208/402) in the SB3 group as compared with 42.0% (167/398 participants) in the reference trastuzumab group. The adjusted rate difference was 10.70% (95% CI: 4.13% to 17.26%) with the lower margin contained within but the upper margin was outside the predefined equivalence criteria (± 13%). However, the adjusted ratio of breast pathological complete response was within the predefined equivalence margins (1.259, 95% CI: 1.085 to 1.460).

The current manuscript extends the period of observation and investigates the outcomes of event-free survival and overall-survival. The authors have specifically investigated (post-hoc) the potential impact of 'drift' within reference product trastuzumab. The results suggest that outcomes associated with SB3 are indistinguishable from of reference product trastuzumab manufactured prior to the drift occurring, referred to as 'non-drifted' product in the manuscript, and that there is a possibility that event-free survival and overall survival might be lower for the 'drifted' reference product trastuzumab. However, it must be noted that this analysis is based upon a subset of patients from the main study, that there are unequal numbers in each of the groups and that there is insufficient power to formally test the hypothesis.

[§] Pivot X, Bondarenko I, Nowecki Z et al. A phase III study comparing SB3 (a proposed trastuzumab biosimilar) and trastuzumab reference product in HER2-positive early breast cancer treated with neoadjuvant-adjuvant treatment: Final safety, immunogenicity and survival results. *Eur J Cancer* 2018; **93**: 19-27.

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BEVACIZUMAB

Reinmuth et al: PF-06439535 (a Bevacizumab Biosimilar) Compared with Reference Bevacizumab (Avastin®), Both Plus Paclitaxel and Carboplatin, as First-Line Treatment for Advanced Non-Squamous Non-Small-Cell Lung Cancer: A Randomized, Double-Blind Study[13]

SPONSOR: Pfizer

REFERENCE PRODUCT: Avastin® (EU)

OBJECTIVE(S): To assess whether biosimilar bevacizumab (PF-06439535) demonstrated similarity to reference product bevacizumab based on the confirmed objective response rate (ORR) when used in combination with paclitaxel and cisplatin (4-6 cycles) followed by blinded monotherapy with PF-06439535 or reference product in participants with advanced non-squamous non-small-cell Lung cancer (NSCLC).

DESIGN: Multi-national, double-blind, randomized (1:1), parallel-group study.

SAMPLE SIZE: 719 participants randomised, PF-06439535=358, reference product = 361.

PATIENT CHARACTERISTICS: Adult participants with newly diagnosed, histologically or cytologically confirmed, predominantly non-squamous, Stage IIIB or IV NSCLC or recurrent NSCLC at least 6 months since completing adjuvant or neoadjuvant treatment.

EQUIVALENCE CRITERIA: Based upon the objective response rate (defined as the percentage of patients within each treatment group who achieved a complete response or partial response by week 19 which was subsequently confirmed on a follow-up tumour assessment by week 25) with specific criteria depending upon jurisdiction; FDA: containment of the 90% confidence interval of the risk ratio within 0.73 to 1.37, PDMA: containment of the 95% confidence interval of the objective response rate risk ratio within 0.729 to 1.371 and EMA: containment of the 95% confidence interval of the objective response rate risk difference between -13% to 13%.

RESULTS: The objective response rate in the PF-06439535 group was 45.3% (95%CI: 40.01 to 50.57) as compared with 44.6% (95%CI: 39.40 to 49.89) in the reference product group. The unstratified objective response rate risk ratio was 1.015, with a 95%CI of 0.863 to 1.193 and a 90% CI of 0.886 to 1.163 which were within the FDA and PDMA equivalence criteria respectively. The unstratified objective response rate risk difference was 0.653%, with a 95%CI of −6.608% to 7.908% which was within the equivalence criteria of the EMA. Hypertension occurred in 9.6% of participants in the PF-06439535 as compared with 8.9% in the reference product group. Five participants in each group were positive for anti-drug antibodies (including one participant in the reference product group who was positive at baseline). No participants in the PF-06439535 group were positive for neutralising anti-drug antibodies as compared with three participants in the reference product group.

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DARBEPOETIN

Nishi et al: Long-term (52 weeks) safety and efficacy of JR-131, a biosimilar of darbepoetin alfa, in Japanese patients with renal anemia undergoing hemodialysis; Phase 3 prospective study[14]

SPONSOR: JCR Pharmaceuticals Co., Ltd. and Kissei Pharmaceutical Co., Ltd.

REFERENCE PRODUCT: none

OBJECTIVE(S): To evaluate the safety and efficacy of JR-131 for long-term treatment of renal anaemia patients undergoing haemodialysis.

DESIGN: Multi-centre, prospective, single arm study. After treatment with the first dose of JR-131, the dose was adjusted to maintain the haemoglobin (Hb) level within the target range (≥10.0 g/dL to <12.0 g/dL).

SAMPLE SIZE: 159 patients received JR-131, and 114 patients completed the 52-week treatment; 61 patients received darbepoetin alfa, 96 received recombinant human erythropoietin.

PATIENT CHARACTERISTICS: Patients undergoing maintenance haemodialysis three times a week for at least 12 weeks; receiving originator darbepoetin alfa for at least 4 weeks or recombinant human erythropoietin (epoetin alfa, beta or kappa) at a dose of ≤9000 IU/week two to three times a week for at least 4 weeks, a haemoglobin concentrations level of ≥ 10.0 g/dL to <12.0 g/dL measured before the first dialysis of the week during the observation period. All participants were Japanese.

RESULTS: During the treatment period the mean haemoglobin concentrations during were in the range of 10.7–11.1 g/dL, suggesting that the haemoglobin concentrations were maintained within the target range of 10.0–12.0 g/dL. In participants that were switched from originator darbepoetin alfa to JR-131, there was no notable change in haemoglobin concentrations over the treatment period. In participants that were changed from epoetin to JR-131, haemoglobin concentrations increased following the change in therapy which was managed through dose adjustment.

REVIEWER COMMENTARY: This study included participants that changed from epoetin to darbepoetin. This represents a change in their therapy as opposed to a switch from an originator to biosimilar of the same therapy. The change in therapy from epoetin to darbepoetin was accomplished through the use of 1:200 conversion ratio however this represents an estimate and requires further clinical adjustment. The rise in haemoglobin concentrations observed in the participants that changed from epoetin to JR131 reflects this fact and was managed through dose adjustment. Consistent with this, the final mean dose conversion ratio observed in this study was 1:237 which is consistent with the range of values that have previously been reported for the conversion of epoetin to darbepoetin.

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FOLLITROPIN ALFA

Barakhoeva et al: A multicenter, randomized, phase III study comparing the efficacy and safety of follitropin alpha biosimilar and the original follitropin alpha[15]

SPONSOR: IVFarma LLC

REFERENCE PRODUCT: Gonal-f®

OBJECTIVE(S): To assess the therapeutic equivalence between a potential follitropin alpha biosimilar and the reference product in women undergoing assisted reproductive technologies with controlled ovarian hyperstimulation using a gonadotropin-releasing hormone antagonist (GnRH-ant) protocol.

DESIGN: Multi-centre, randomized (1:1), parallel-group, comparative phase III study. Follitropin was administered at a dose of 150IU until day 5 at which time the dose could be adjusted according to a maximum of 450IU according to ultra-sound results. Ultrasound and dose adjustment was performed by an unblinded clinician. The clinician performing oocyte collection was blinded to the treatment allocation.

SAMPLE SIZE: 110 participants randomized 1:1, biosimilar follitropin (Primapur®) = 55, reference product (Gonal-F®)= 55, 6 participants in each group did not proceed to embryo transfer.

PATIENT CHARACTERISTICS: Mean age (years) = 31.3 (biosimilar) vs 30.0 (reference); mean duration of infertility (months) = 46.4 (biosimilar) vs 36.9 (reference); mean antral follicle count = 11.2 (biosimilar) vs 12.4 (reference); mean FSH (IU/L) = 6.46 (biosimilar) vs 6.76 (reference); mean oestradiol concentration (pg/ml) = 35.87 (biosimilar) vs 33.82 (reference).

EQUIVALENCE CRITERIA: A difference in the mean number of oocytes retrieved within the range of $_{\pm}$3.4.

RESULTS: A mean of 12.16 (± 7.28) oocytes were retrieved per participant in the biosimilar group as compared with 11.62(± 6.29) in the reference product group equating to a difference of difference of 0.546 (± 1.297) oocytes (95%CI: -2.026 to 3.116) which was within the equivalence criteria of ±3.4 oocytes. There was no evidence of the development of anti-FSH antibodies on the basis of the comparison of anti-FSH levels before and after controlled ovarian hyperstimulation.

REVIEWER COMMENTARY: Due to differences in the injector device it was not possible to double blind this study and as such only the embryologist, but not the participant, were blinded. The primary endpoint of the study was the number of oocytes retrieved by the embryologist.

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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, four publications were identified that examined the economic impact of the introduction of biosimilars

Catt et al: Value assessment and quantitative benefit-risk modelling of biosimilar infliximab for Crohn's disease[16]

SPONSOR: None

LOCATION(S): United Kingdom

DATES: 2015/16

OBJECTIVE(S): To explore how the price of biosimilar infliximab must decrease to offset hypothetical differences in immunogenicity relative to originator infliximab in order to remain the preferred option.

DESIGN: A 1-year decision-analytic model was developed to compare the incremental health benefit for biosimilar infliximab compared with originator. The model explored hypothetical scenarios of increased immunogenicity to biosimilar infliximab, which influenced rates of non-response and infusion reactions. Model parameters were taken from literature review of clinical trials and previous cost-effectiveness models. Drug cost were obtained from the British National Formulary. A two-way sensitivity analysis was conducted to assess the interaction between the development of anti-drug antibodies to biosimilar infliximab, and the price differential between the originator and biosimilar infliximab to identify the discount in vial price required to compensate for a range of hypothetical increases in the rate of anti-drug antibodies to biosimilar infliximab as compared to originator.

RESULTS: The base-case analysis that there is no difference in immunogenicity between originator and biosimilar, indicated a 0.04 incremental net health benefit for biosimilar infliximab relative to originator based upon the British National Formulary drug cost (originator infliximab = £420/vial, biosimilar infliximab = £378/vial). When it was assumed that 50% of patients would develop anti-drug antibodies to biosimilar infliximab compared with only 12.4% of patients who received originator infliximab, the biosimilar remained the preferred option compared to originator infliximab provided it was priced at or below £410/vial. In a worst-case scenario in which it was assumed that 100% of patients receiving biosimilar infliximab would develop anti-drug antibodies, the biosimilar infliximab would remain the treatment of choice with a positive incremental net health benefit if it were priced at up to £395/vial.

REVIEWER COMMENTARY: The authors explore the potential impact of a difference in immunogenicity between originator and biosimilar infliximab. However, the authors provide no evidence to support the specific scenarios that have been tested.

Tarallo et al: Costs associated with non-medical switching from originator to biosimilar etanercept in patients with rheumatoid arthritis in the UK[17]

SPONSOR: Pfizer

LOCATION(S): United Kingdom, France, Germany, Italy, Spain

DATES: Drug costs from 2010, resource costs from 2015-2016 and 2017

OBJECTIVE(S): To estimate the cost impact of non-medical switching from originator to biosimilar etanercept (SB4 or GP2015) in patients with stable rheumatoid arthritis in the UK over a 1-year period.

DESIGN: A cohort-based cost-decision model was developed with a 1-year time horizon, to examine non-medical switching from originator to biosimilar etanercept in patients with stable rheumatoid arthritis. The model explored patients undergoing a non-medical switch to an etanercept biosimilar. At 3-6 months non-responders could then switch back to originator etanercept, switch to a different etanercept biosimilar or change therapy to a different agent (adalimumab, tocilizumab or abatacept). Drug costs were obtained from the 2010 NICE British National Formulary data, and resource costs were obtained from published UK sources. Data on rates of switching and resource utilisation were based upon survey responses provided by 150 rheumatologists from Germany, France, Italy, Spain and the UK. Respondents were asked to estimate parameters to be included in the model such as;

- "*On average, how many of the following visits/tests/procedures per year form part of routine monitoring for stable RA patients on originator etanercept?",*
- "*On average, how many of the following visits/tests/procedures did patients who were initially stable on originator etanercept and switched to SB4/GP2015 for non-medical reasons receive in each of the below timeframes, (0–3 months and 4–6 months) post-switch to the biosimilar?*"
- *"On average, how many hospitalizations and emergency room visits per year did patients who were initially stable on originator etanercept and switched to SB4/GP2015 for non-medical reasons typically require in each of the below timeframes (0–3 months and 4–6 months) post-switch?*" and
- "*How many of your XXX patients who were initially stable on originator etanercept and switched to SB4/GP2015 for non-medical reasons have since required a subsequent change in therapy?".*

RESULTS: The model assumed that 5,000 patients were treated with originator etanercept and predicted that 875 patients would initially switch to SB4 and 384 would switch to GP2015. After 3 months, the model predicted that of the patients who switched treatment, 8.3% would switch back to the originator, 3.8% would switch to the alternate etanercept biosimilar and 14.2% would change therapy to another biologic. The model predicted that healthcare resource utilisation would increase for switchers compared to non-switcher. Despite lower biosimilar drug costs, the total annual health-care costs of the switching scenarios were found to be higher than continuous treatment with originator etanercept over a 1-year time period (2-9% higher).

REVIEWER COMMENTARY: The results of this study should be interpreted in the context of the following observations:

- The model assumes that all patients treated with originator etanercept will continue on this treatment for at least one year with no patients losing response and requiring a change to an alternative agent.
- The probability of a patient being a non-responder following switching was informed by the responses provided to the survey and as such is subjective, highly variable and maybe subject to responder bias and recall bias.
- The model provides for non-responding patients to switch from one etanercept biosimilar to another but provides no clear scientific or clinical rationale for this decision.

The inclusion of switching back from biosimilar etanercept to originator etanercept in this model, on the basis of the survey responses, is consistent with previous reports that postulate an influence of the nocebo effect in switching from originator to biosimilar in which participants report an increase in subjective symptoms, in the absence of objective measures of disease worsening, which then improve following switching back to the originator product. Patient education is considered an important element in reducing the risk of the nocebo effect. The survey asked if "*demonstrations/training sessions*" were provided but this may be limited to the device itself and may or may not include more detailed education about biosimilar medicines.

Guiliani et al: The economic impact of biosimilars in oncology and hematology: The case of trastuzumab and rituximab[18]

SPONSOR: None

LOCATION(S): Italy

DATES: Not reported

OBJECTIVE(S): To determine the cost of rituximab and trastuzumab biosimilar compared with originator for pivotal phase III clinical trials.

DESIGN: Pharmacological costs necessary to get the benefit in the cancer outcomes for biosimilar compared to originator rituximab and trastuzumab were calculated for 5 phase III clinical trials. Outcomes were taken as time to treatment failure (TTF) for rituximab, and pathological complete response (pCR) for trastuzumab. Drug costs were taken from local hospital drug costs and were assumed to be rituximab: originator €248/100mg, biosimilar €150/100mg and trastuzumab: €622/150mg, biosimilar €370/150mg.

RESULTS: The economic advantage of the biosimilar was estimated at approximately 40% lower costs in the case of both rituximab and trastuzumab biosimilars.

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Vasudevan et al: The Cost-effectiveness of Initial Immunomodulators or Infliximab Using Modern Optimization Strategies for Crohn's Disease in the Biosimilar Era[19]

SPONSOR: Non-commercial

LOCATION(S): United States

DATES: Drug costs from 2018

OBJECTIVE(S): To examine the cost-effectiveness from a US 3rd party payer perspective of initial treatment of moderate to severe Crohn's disease with infliximab monotherapy versus azathioprine monotherapy or a combination of azathioprine and infliximab.

DESIGN: A 1-year Markov model was used to examine how the change in price of infliximab may influence the treatment cascade for Crohn's disease, noting that there has already been discount due to the introduction of biosimilar infliximab. Drug costs were taken from the Red Book Online, with infliximab costs taken as the lowest cost of the available brands. Other treatment costs were based on published data and previous Markov models. The drug costs of biologics were reduced to 10% of their initial value as a part of the sensitivity analysis to determine the impact of cost reductions in anti-TNF therapy associated with biosimilar-related market competition.

RESULTS: The model incorporating a 10% reduction in biologic drug costs resulted in an improvement in the cost of all 3 strategies, with costs of $30,723, $38,761, and $46,164 per QALY gained for azathioprine, combination therapy, and infliximab monotherapy, respectively. In this model, the ICER for using infliximab with azathioprine compared with azathioprine monotherapy as initial therapy was $161,643, whereas infliximab was still >$500,000 per QALY gained. Based on the defined willingness-to-pay threshold of $100,000, azathioprine monotherapy remained the most cost-effective option.

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. During the update period, there were two papers published examining this theme.

ETANERCEPT

Chan et al: Implementing and delivering a successful biosimilar switch programme - the Berkshire West experience[20]

SPONSOR: None

LOCATION(S): United Kingdom

DATES: August 2016 - March 2017

OBJECTIVE(S): To evaluate a managed switching programme funded through a novel fixed price incentivisation model aimed to support the switch of rheumatic patients established on originator etanercept (Enbrel) to biosimilar Benepali.

DESIGN: A fixed price incentivisation model where government reimbursed price for all brands of etanercept were fixed price for 1 year. The fixed price was approximately 75% of the originator price leaving a gap of approximately 10% between the fixed price and the price of biosimilar brand. When patients were switched from originator to biosimilar, the local healthcare trust was able to realise 100% of savings.

RESULTS: 154 patients on Enbrel were identified and 113 patients switched to Benepali. Ninety-four responded to a survey on patient perceptions. The majority of respondents (81/94, 86%) recalled receiving written information and discussing them in clinic, 63% reported having no concerns about the switch program. Mean visual analogue score (Scale 1-10) for confidence in the biosimilar was 7.86. The authors reported that the Benepali switch program enabled the trust to receive a net income of over £95,000, with a reduction in local prescribing costs of £186,000. The cost of a pharmacist for 6 weeks and admin cost was reportedly £11,250.

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INFLIXIMAB

Hersanyi et al: Influence of biosimilar infliximab launch on the utilization pattern of biological medicines: the case of Hungary[21]

SPONSOR: None

LOCATION(S): Hungary

DATES: September 2012 and December 2016.

OBJECTIVE(S): This manuscript investigated efficiency of national policy on biosimilar uptake of multisource infliximab after originator infliximab lost market exclusivity.

DESIGN: Analysis of all biologic utilization (infliximab, abatacept, adalimumab, certolizumab pegol, etanercept, golimumab, rituximab, tocilizumab) for infliximab indications in Hungary (rheumatoid arthritis, Crohn's disease; paediatric Crohn's disease; ulcerative colitis; ankylosing spondylitis; psoriatic arthritis; psoriasis) using the National Institute of Health Insurance Fund Management (NIHIFM) database. Patient records were collected and processed by NIHIFM employees with aggregated data provided to academic investigators. All patients who received at least one biologic medicine in the study period were included. Inflectra (biosimilar infliximab) won a national procurement tender in September 2013, so data was grouped by this timepoint within the study. Biosimilar infliximab and originator biologic uptake were analysed at both initiation and switching among different biological medicines.

RESULTS: After the market introduction of biosimilar Inflectra, infliximab biologic market share increased in UC patients from 59.6% to 63.8%, CD patients from 49.7% to 51.3% and in psoriatic patients from 6.3 to 6.9% for newly initiated patients. Conversely infliximab market share decreased from 100% to 35.5% in paediatric CD during the same period. Switching between biologics was reported by the authors most frequently from originator infliximab to other biologics (70-76% of switching occurrences). Switching from originator infliximab to biosimilar was less frequently observed (7-16% of switches) and less frequent again if 3 or more biologics were available for an indication. The authors summarized that *"market launch of infliximab biosimilars in Hungary was not translated to increased utilization of more affordable multisource biologicals".*

REVIEWER COMMENTARY: The original aim of the study was not achievable with this study design. National policy during the study period was not explicit and no costings were available to the authors. The volume of biologic usage in the study period and the patient sample size was not presented. No statistical analysis of change in market share or switching was performed by the authors. Factors such as indication expansion of alternative biologic agents concurrent to the entry of biologic infliximab confound these findings. The reason for switching between biologics was not recorded, it is unclear whether switches were medical or non-medical.

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

Bronswijk et al: Evaluating Efficacy, Safety, and Pharmacokinetics After Switching From Infliximab Originator to Biosimilar CT-P13: Experience From a Large Tertiary Referral Center[22]

SPONSOR: Non-commercial

LOCATION(S): Belgium (single-centre)

DESIGN: Prospective observational cohort study

DATES: Mandated switch from originator to biosimilar infliximab at March 2017

OBJECTIVE(S): To investigate the pharmacokinetics, efficacy, and safety of a mandatory switch from originator infliximab to biosimilar infliximab (CT-P13) in patients with Crohn's disease and ulcerative colitis.

PATIENT CHARACTERISTICS: 361 patients, median disease duration = 7.0 years; median duration of originator infliximab treatment = 6.0 years; proportion with concomitant immunosuppression at time of switch = 6%; median CRP concentration at time of switch = 1.5 mg/L; proportion of patients with anti-drug antibodies detected prior to switching not reported.

OUTCOME(S): The primary endpoint was discontinuation for any reason within 6 months after the index infusion of biosimilar infliximab.

RESULTS: A total of 15 patients (4%) discontinued treatment with biosimilar infliximab within 6 months of switching, of whom eight discontinued due to loss of clinical remission and five discontinued due to adverse events. Four patients (1.1%) developed new anti-drug antibodies but this was not associated with a loss of clinical remission or the need to cease infliximab.

REVIEWER COMMENTARY: It is reported that overall 30% of the 361 patients were positive for anti-drug antibodies and that anti-drug antibodies were newly detected as switching in four patients (1.1%). The authors employed two different assays to detect anti-drug antibodies; one assay was sensitive to the infliximab concentration within the sample (requiring an infliximab concentration <0.5 μg/mL) and the other a drug tolerant assay (requiring infliximab concentrations <3 μg/mL). Of the four patients with newly detected anti-drug antibodies only one of these patients was detected by the drug sensitive assay. This highlights one of the challenges in interpreting real-world observational reports as a result of the complex relationship between the clinical practice of therapeutic drug monitoring, intended to maintain trough infliximab concentrations, and the assessment of anti-drug antibodies.

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Kaltsonoudis et al: Maintained Clinical Remission in Ankylosing Spondylitis Patients Switched from Reference Infliximab to Its Biosimilar: An 18-Month Comparative Open-Label Study[23]

SPONSOR: None

LOCATION(S): Greece (single-centre)

DESIGN: The study is described as a *"prospective observational cohort study"*. However, it is also stated that "*allocation of the patients was done randomly using an internet-based allocation program*".

DATES: Switching period: January 2017 until June 2017, followed-up until December 2018

OBJECTIVE(S): To compare the outcome of switching from originator infliximab to biosimilar infliximab with continuing treatment with originator infliximab in participants with ankylosing spondylitis who were in remission.

PATIENT CHARACTERISTICS: 88 patients agreed to participate, 45 patients randomised to switch to biosimilar infliximab, 43 patients randomised to continue originator infliximab, mean duration of remission (all patients) = 3.6 years, mean age = 36.1 years (switched to biosimilar) vs 35.7 years (continued originator), mean Bath Ankylosing Spondylitis Activity Index (BASDAI) at baseline = 3.7 (switched to biosimilar) vs 3.6 (continued originator), mean ESR (mm/hr) at baseline = 18.5 (switched to biosimilar) vs 19.3 (continued originator), mean CRP (mg/L) at baseline = 6.0 (switched to biosimilar) vs 5.8 (continued originator)

OUTCOME(S): Treatment continuation, disease activity as assessed by the Bath Ankylosing Spondylitis Activity Index (BASDAI) and the Ankylosing Spondylitis Activity Score (ASDAS)

RESULTS: Within the group that switched to biosimilar infliximab the mean BASDAI was 3.7 at conclusion of the study as compared with 3.7 at the time of switching. In the group that continued originator infliximab the BASDAI was 3.8 as compared with 3.6 at the time of allocation. During follow-up five participants from the group that switched to biosimilar infliximab and three participants from the group that continued originator infliximab discontinued the study. Amongst the five participants in the switching group who discontinued, one did so due to recurrent infection and the remaining four did so on the basis of "*…nonspecific, subjective complaints such as headache, somnolence, dizziness, arthralgias, fatigue and pain*" although "*…clinical examination of these patients was unremarkable, and the acute phase reactants were within normal limits*". Three of these participants responded well (details not provided) when switched back to originator infliximab and a single patient did not and was changed to an alternative therapy. Three participants in the group that continued originator infliximab discontinued as a result of recurrent infections (n=2) or disease flare (n=1).

REVIEWER COMMENTARY: The authors attribute 80% (4/5) of the discontinuation of biosimilar infliximab to the nocebo effect. Consistent with the experience reported by other authors, where a nocebo effect is suspected on the basis of non-specific, subjective symptoms in the absence of changes in objective measures such as inflammatory markers, a high proportion of participants, 75% (3/4) in this study, respond well switching back to originator product. Education is considered to be an important factor reducing the risk of the nocebo effect. The authors in this study indicate that a "*shared-decision making*" process was used and as this was a randomised trial; participants provided written informed consent, but further description of this content is not provided.

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Grøn et al: Comparative effectiveness of certolizumab pegol, abatacept and biosimilar infliximab in patients with rheumatoid arthritis treated in routine care. Observational data from the Danish DANBIO registry emulating a randomized trial[24]

SPONSOR: DANBIO registry has agreements with AbbVie, Biogen, BMS, Eli Lilly, MSD, Novartis, Pfizer, Roche and UCB.

LOCATION(S): Denmark (nationwide)

DESIGN: Observational cohort study using the DANBIO registry

DATES: Patients who initiated treatment with biosimilar infliximab between July 2014 and June 2016.

OBJECTIVE(S): To assess compliance to treatment guidelines and to compare the effectiveness of certolizumab pegol, abatacept and biosimilar infliximab (CT-P13) in patients treated according to guidelines.

Only the results describing the outcomes of biosimilar infliximab are relevant to this review and so included here.

PATIENT CHARACTERISTICS: 225 patients initiated treated with biosimilar infliximab; mean disease duration = 4 years; mean DAS28 at baseline = 4.5; mean CRP at baseline (mg/L) = 9.

OUTCOME(S): DAS28-remission-rates at 6 and 12-months, one-year treatment retention rate.

RESULTS: DAS28 remission was achieved in 94 (42%) patients treated with biosimilar infliximab at 6 months and in 78 (35%) patients at 12 months. The one-year retention rate was 69%.

REVIEWER COMMENTARY: This study aimed to compare outcomes amongst bDMARDs but there was no comparison of originator versus biosimilar infliximab. For this reason, the results included here are restricted to the descriptive outcomes observed for biosimilar infliximab.

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Guiotto et al: Switching from infliximab originator to a first biosimilar is safe and effective. Results of a case-control study with drug levels and antibodies evaluation[25]

SPONSOR: Fondazione IBD Onlus and Fondazione Scientifica Mauriziana

LOCATION(S): Italy (single-centre)

DESIGN: Observational

DATES: Patients initiated in biosimilar from 2015, switching to biosimilar mandated from April 2016.

OBJECTIVE(S): To compare the safety and effectiveness of switching from originator infliximab to biosimilar infliximab (CT-P13, Remsima) with initiating and continuing biosimilar infliximab in patients with Crohn's disease and ulcerative colitis.

PATIENT CHARACTERISTICS: 66 patients, switched group = 53, biosimilar group =13; Crohn's disease = 55% (n=29, switched group) vs 23% (n=3, biosimilar only group); concomitant immunosuppressants = 13% (switching group) vs 31% (biosimilar only group); remission at baseline of observation = 44% (switching group) vs 62% (biosimilar only group); median duration of infliximab treatment prior to enrolment = 4.0 years (switching group) vs 0.6 years (biosimilar only group), antidrug antibodies detected at baseline = 69% (switching group) vs 0 (biosimilar only group); p<0.0001; median duration of observation after study enrolment = 20.6 months (switching group) vs 12.4 months (biosimilar only group), p = 0.007.

OUTCOME(S): Rate of infliximab discontinuation.

RESULTS: During follow-up 14/53 (26%) patients in the group that switched from originator infliximab to biosimilar infliximab discontinued treatment due to adverse events or loss of efficacy as compared 8/13 patients in the biosimilar only group (p = 0.017). Treatment was discontinued due to deep remission in eight 8 patients in the group that switched from originator to biosimilar infliximab and in a single patient in the biosimilar only group with a median time after study entry of 10.5 months. At 12 months, antidrug antibodies were detected in 63% of patients in the switching group as compared with 57% of participants in the biosimilar only group.

REVIEWER COMMENTARY: Comparisons between the groups should be interpreted with caution. There are significant differences between the patient characteristics including the duration of treatment with infliximab and the duration of follow-up. The patients who initiated and continued biosimilar infliximab had a significantly shorter duration of treatment than those who switched from originator to biosimilar. It is not surprising that the discontinuation rate in a group of patients starting infliximab is greater than in a group of patients that have been stabilised on the treatment for a longer period of time.

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Kim et al: Retention rate and long-term safety of biosimilar CT-P13 in patients with ankylosing spondylitis: data from the Korean College of Rheumatology Biologics registry[26]

SPONSOR: Celltrion Healthcare Co., Ltd.

LOCATION(S): Korea (nationwide)

DESIGN: Korean College of Rheumatology Biologics (KOBIO) registry

DATES: December 2012 to December 2017

OBJECTIVE(S): To evaluate the long-term drug retention, efficacy, and safety of biosimilar infliximab (CT-P13) patients with ankylosing spondylitis.

PATIENT CHARACTERISTICS: 244 patients were identified.

OUTCOME(S): 4-year retention rate.

RESULTS: The retention rate after 4 years, as assessed by Kaplan-Meier curves, was 66%. The median duration of treatment with biosimilar infliximab observed was 2.05 years (range 0.04–4.18). A total of 38 (15.6%) patients changed therapy from biosimilar infliximab to another agent and 32 (13.1%) patients discontinued biologic treatment entirely. Infusion or injection-site reactions (n=8) and skin rash (n=2 events) were the most common adverse events resulting in discontinuation of biosimilar infliximab. After one year of treatment, a major improvement was seen in the ASDAS score in 56.5% of patients and a clinical important improvement in 82.2%. This was maintained at 2 years in 56.9% of patients that achieved a major improvement and 85.4% of patients that achieved a clinically important improvement.

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Nakagawa et al: Infliximab biosimilar CT-P13 is interchangeable with its originator for patients with inflammatory bowel disease in real world practice[27]

SPONSOR: None

LOCATION(S): Japan (nationwide)

DESIGN: Interim analysis of post-marketing surveillance registry

DATES: Enrolment between November 2014 and March 2017, analysis to July 2018

OBJECTIVE(S): To evaluate the safety and efficacy of biosimilar infliximab (CT-P13) in Japanese patients with inflammatory bowel disease.

PATIENT CHARACTERISTICS: 700 patients enrolled in the post-marketing surveillance registry; interim analysis of 523 patients, Crohn's disease = 267, ulcerative colitis = 256, mean observation period = 299 day; anti-TNF-α antibody naïve patients = 217; patients switched for nonmedical reasons such as institutional policy or economic reason = 219, patients switching to biosimilar infliximab from originator infliximab due to adverse events or insufficient efficacy = 38

OUTCOME(S): Incidence of adverse drug reactions, treatment retention

RESULTS: A total of 144 adverse drug reactions were reported in 106 patients. Infusion reactions occurred in 49 patients and were the most common adverse event. Infusion reactions occurred in 21/217 (9.7%) anti-TNF-α antibody naïve patients as compared with 10/219 (4.6%) of patients that switched from originator infliximab to biosimilar infliximab ($P < 0.01$). Infusion reaction occurred in 7/22 patients that were documented as having an allergy to infliximab. Approximately 80% of patients with Crohn's disease and approximately 70% of patients with ulcerative colitis (Kaplan-Meier plots but exact values provided) who were switched from originator infliximab to biosimilar infliximab for nonmedical reasons remained on biosimilar infliximab at 80 weeks as compared with approximately 70% of anti-TNF-α antibody naïve with Crohn's disease and 55% of patients with ulcerative colitis which was statistically significantly different ($P<0.05$).

REVIEWER COMMENTARY: It is notable that 38 patients were reported to have switched from originator infliximab to biosimilar infliximab due to adverse events or insufficient efficacy. The basis for making such a clinical decision is unclear. Unsurprisingly, the rate of adverse drug reactions in this group of patients was considered to be high. Interpretation of the results for the patients who were "*switched for medical reasons*" is difficult as this group included patients who were "*Switching to CT-P13 from infliximab (IFX) due to adverse events or insufficient efficacy*" and those who were changing therapy from adalimumab and who had previously discontinued originator infliximab due to remission of disease but were now restarting infliximab, this time with biosimilar infliximab, as a result of relapse.

Return to OVERVIEW

Kaniewska et al: Efficacy, tolerability, and safety of infliximab biosimilar in comparison to originator biologic and adalimumab in patients with Crohn disease[28]

SPONSOR: None

LOCATION(S): Poland (single-centre)

DESIGN: Retrospective

DATES: Patients hospitalised between March 2013 and September 2015 followed by up to 12 months treatment and 12 months additional follow-up. Patients treated before May 2014 received originator infliximab. Patients treated after May 2014 received either biosimilar infliximab or adalimumab.

OBJECTIVE(S): To compare the safety, efficacy and tolerability of biosimilar infliximab with originator infliximab and adalimumab in patients with Crohn's disease.

PATIENT CHARACTERISTICS: 286 consecutive adult patients with Crohn's disease, originator infliximab = 82, biosimilar infliximab = 109, adalimumab = 95, proportion with prior anti-TNF-α therapy = 36.6% (originator infliximab) vs 31.2% (biosimilar infliximab) vs 87.4% (adalimumab), proportion with thiopurine use = 92.7% (originator infliximab) vs 86.2% (biosimilar infliximab) vs 81.1% (adalimumab); median Crohn's Disease Activity Index (CDAI) score at baseline = 324 (originator infliximab) vs 323 (biosimilar infliximab) vs 322 (adalimumab), P = 0.95.

OUTCOME(S): Achievement of clinical response and remission, relapse rate, side effects.

RESULTS: Following induction therapy the median CDAI scores were 79 in group that received originator infliximab as compared with 74.5 in the biosimilar infliximab group and 86 adalimumab group ($P = 0.78$). A clinical response was achieved in 95% of patients that received originator infliximab as compared with 94% of those that received biosimilar infliximab and 87% of those that received adalimumab ($P = 0.35$) and clinical remission occurred in 76%, 81% and 70% respectively ($P = 0.49$). The relapse rate in those that received originator infliximab was 83% which was higher than both the biosimilar infliximab group (54%) and the adalimumab group (61%), $P<0.0001$. Allergic reaction occurred in two patients in the originator infliximab group and in three patients in the biosimilar infliximab group, all of whom had prior exposure to infliximab.

REVIEWER COMMENTARY: Details regarding prior anti-TNF-α are not provided. It is noted that treatment with originator infliximab versus biosimilar infliximab or adalimumab was determined by the date of hospitalisation. Accordingly, this may have impacted upon the specific details of prior anti-TNF-α therapy (infliximab versus adalimumab) and this may have influenced the results observed in this study.

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Nikkonen et al: Infliximab and its biosimilar produced similar first-year therapy outcomes in patients with inflammatory bowel disease[29]

SPONSOR: Non-commercial

LOCATION(S): Finland (single-centre)

DESIGN: Retrospective

DATES: Patients treated with originator infliximab during 2015 and early 2016 and patients treated with biosimilar infliximab during 2016, follow-up until 31 October 2018

OBJECTIVE(S): To compare the outcomes associated with biosimilar infliximab (Remsima®) with originator infliximab (Remicade®) in paediatric patients with inflammatory bowel disease.

PATIENT CHARACTERISTICS: 51 patients, originator infliximab = 23, biosimilar infliximab = 28; median age at commencement of induction therapy = 14.5 years (originator infliximab) vs 12.7 years (biosimilar infliximab); proportion with concomitant azathioprine at commencement of induction = 35% (originator infliximab) vs 50% (biosimilar infliximab); proportion with induction infliximab dose > 5mg/kg = 8.7% (originator infliximab) vs 57% (biosimilar infliximab), p<0.001; median faecal calprotectin at commencement of induction = 740 μg/g (originator infliximab) vs 650 μg/g (biosimilar infliximab)

OUTCOME(S): Treatment continuation, anti-drug antibodies resulting in discontinuation, faecal calprotectin

RESULTS: During the induction period, treatment was discontinued in two patients in the originator infliximab group as compared with a single patient in the biosimilar infliximab group. The median faecal calprotectin at week 6 was 182μg/g in the group that received originator infliximab as compared with 357μg/g in the biosimilar group (p > 0.05). During maintenance treatment, infliximab was discontinued due to side effects or loss of response in 9 patients (39%) in the originator infliximab group as compared with 10 patients (36%) in the biosimilar infliximab group. At 12 months, median faecal calprotectin levels were 113μg/g in the originator infliximab group and 166μg/g in the biosimilar group. Anti-drug antibodies resulted in treatment discontinuation in four patients that received originator infliximab and in a single patient that received biosimilar infliximab.

REVIEWER COMMENTARY: The greater proportion of patients receiving an induction dose >5kg/kg in the biosimilar group represents a change in practice in this institution which the authors attribute to publications in that time period that indicated higher doses were more effective. This change in practice confounds the interpretation of the results presented.

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ETANERCEPT

Madenidou et al: Switching patients with inflammatory arthritis from Etanercept (Enbrel) to the biosimilar drug, SB4 (Benepali): A single-centre retrospective observational study in the UK and a review of the literature[30]

SPONSOR: None

LOCATION(S): United Kingdom (single-centre)

DESIGN: Retrospective

DATES: Patients switched until April 2019

OBJECTIVE(S): To describe the outcomes in patients with rheumatoid arthritis (RA), axial spondyloarthritis (AxS) and psoriatic arthritis (PsA) who switched from originator etanercept to biosimilar etanercept (SB4).

PATIENT CHARACTERISTICS: 72 patients identified as switching to SB4; median duration of originator etanercept prior to switching = 3.8 years (RA) vs 5.2 years (AxS) vs 3.3 years (PsA).

ENDPOINT(S): Treatment continuation.

RESULTS: Within 6 months of switching to SB4, 19/72 (26.4%) of patients had switched back to originator etanercept as a result of loss of effect (n=11), adverse events (n=6), infection (n=1) and difficulty using the SB4 device (n=1). Adverse events resulting in switching back to originator etanercept included headache, dyspnoea, weight gain, hair loss, rash and fatigue. Loss of response was associated with statistically significant ($p<0.05$) increase in DAS-28, Patient Global Score, increase in tender joint count and an increase in C-reactive protein After a median follow-up of 12 months (IQR:7.5-15.5) all 19 patients who switched back to originator etanercept remained on originator etanercept.

REVIEWER COMMENTARY: The authors note that loss of response is mostly due to subjective disease activity measures with the exception of CRP and suggest that amongst patients with RA a request to switch back to originator etanercept was associated with statistically significant ($p<0.05$) increase in DAS-28, Patient Global Score, increase in tender joint count and an increase in CRP however the basis for this is unclear. The values for these parameters prior to switching are only provided for the entire RA group, not specifically for patients that who later requested to switch back to originator etanercept. The basis for claiming statistically significant associations is unclear. The prominence of subjective disease activity measures is consistent with a contribution of the nocebo effect. It is noted that a single patient was switched back to originator as a result of difficulties with the biosimilar device reinforcing the need for appropriate education on injection devices and that patients may have a preference for one device relative to another.

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Glintborg et al: Does a mandatory non-medical switch from originator to biosimilar etanercept lead to increase in healthcare use and costs? A Danish register-based study of patients with inflammatory arthritis[31]

SPONSOR: Partly funded by Pfizer

LOCATION(S): Denmark (nationwide)

DESIGN: Observation cohort study (registry)

DATES: Individuals who switched between 1 April 2016 to 1 January 2017 with 1-year pre and post periods for an individual's index date.

OBJECTIVE(S): To investigate if switching from originator etanercept to biosimilar etanercept (SB4) was associated with increased healthcare utilisation and costs.

PATIENT CHARACTERISTICS: 1620 individuals were identified.

ENDPOINT(S): Health utilisation measured as inpatient hospital services (hospital admissions, hospital days), outpatient visits and use of medication other than etanercept. Health costs were for inpatient, outpatient and primary sector contacts (general practitioners, other specialist doctors, physiotherapists, chiropractors and podiatrists) and prescription medications (note: etanercept costs, either originator or biosimilar are not included in this analysis).

RESULTS: Outpatient services accounted for the greatest proportion of total health costs before and after switching to biosimilar etanercept (mean number per patient = 12.3 visits pre-switch vs 13.3 visits post-switch), with an 8% increase post-switching (estimate 1.08, 95%CI: 1.05 to 1.11). There was an increase in outpatient health costs specifically during the first month after switching, including the date of the switch, which reflects that individuals received an outpatient service as part of switching to biosimilar etanercept. In the 52 weeks post switching there was a 7% increase in the cost of outpatient services which was due to a 24% increase for services other than those for 'Diseases of the musculoskeletal system and connective tissue' (estimate 1.24, 95%CI: 1.09 to 1.41). There was no change in pain medication use as assessed by defined daily doses (estimate 0.99, 95%CI: 0.96 to 1.03, P = 0.702) or 'other' medications (estimate 1.0, 95%CI: 1.00 to 1.05, P = 0.051).

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FILGRASTIM

Sato et al: Evaluation of a biosimilar granulocyte colony-stimulating factor for peripheral blood stem cell mobilization in Japanese healthy donors: a prospective study[32]

SPONSOR: Kyowa Hakko Kirin and Fuji Pharma (Japan)

LOCATION: Japan (two centres)

DESIGN: Prospective observational biosimilar group, historic originator control group

DATES: July 2014 to January 2017

OBJECTIVE(S): To evaluate efficacy, safety and economic benefit of biosimilar filgrastim for peripheral blood stem cell (PBSC) mobilisation in healthy donors.

PATIENT CHARACTERISTICS: 13 participants were mobilized with biosimilar filgrastim, 13 were mobilized with originator; mean age = 38 (biosimilar filgrastim) vs 38 years (originator); mean weight= 63 kg (biosimilar filgrastim) vs 63 kg (originator); all participants were Japanese.

OUTCOME(S): Total CD34+ cells yield from apheresis, treatment cost.

RESULTS: No statistical difference was observed between biosimilar filgrastim and originator with regards to; median total administered dose of filgrastim (biosimilar filgrastim = 2.4 [2.1 – 3.0] mg) vs originator 2.7 [2.1 – 3.0] mg) and total $CD34^+$ cells yield from all apheresis (biosimilar filgrastim = 4.87 [1.62-14.9] $x10^6$ /kg vs originator = 4.93 [1.68-8.23] $x10^6$ /kg). The authors reported no difference in non-haematological adverse events between the two groups, with all events being classified as 'transient and reversible'. A significant reduction ($p < 0.05$) in average total medical cost per donor was reported with use of filgrastim BS (479,680 ± 62,210 JPY, n = 9) in comparison with the originator (596,510 ± 55,580 JPY, n = 13).

REVIEWER COMMENTARY: This manuscript does not describe participant selection or randomisation procedures. It is not explicit whether the originator filgrastim is Gran M® however it is stated that this was the agent on which originator pricing was based. No explanation of why four participants from the biosimilar filgrastim group were not included in the costing analysis was provided.

STAKEHOLDER PERCEPTIONS

During the quarterly update period, one paper has explored the topic of evaluating and improving stakeholder awareness, confidence, attitudes and acceptance of biosimilar medicines.

PATIENTS

Rho et al: Usability of Prefilled Syringe and Autoinjector for SB4 (An Etanercept Biosimilar) in Patients with Rheumatoid Arthritis[33]

SPONSOR: Samsung Bioepis Co., Ltd.

LOCATION(S): Poland

DESIGN: Open-label, single-arm, cross over study. After education participants self-administered two weekly injections using the pre-filled Benepali device, followed by self-administration of six weekly injections using the auto-injector Brenzys device. The endpoints included change in injection site pain score, overall impression, and participant preference at week 3 (after change over).

DATES: May - September 2017

OBJECTIVE(S): Compare the usability, tolerability and patient preference between two devices, prefilled syringe (Benepali) and autoinjector (Brenzys) for the etanercept biosimilar SB4.

PARTICIPANTS: 54 biologic treatment naïve Adult participants (18 to 55 years, mean 43.6 years) diagnosed with RA for at least 6 months.

RESULTS: The mean difference in injection site pain between week 1 and week 3 was contained within the pre-defined equivalence margin, measured using an 11-point visual numerical scale. The authors reported that pain, measured both immediately and 15–30 min after injection, were comparable between the pre-filled period and auto-injector periods. It was noted that patient overall impression of the device, captured by a questionnaire administered at week 3, favoured the autoinjector device over the pre-filled injector and that 81.1% of surveyed participants preferred the auto-injector compared with 7.5% who preferred the pre-filled injector.

REVIEWER COMMENTARY: The authors acknowledged that sequence effects may be a source of bias in this single arm cross-over study.

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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.

1. Arvinte T, Palais C, Poirier E et al. Part 2: Physicochemical characterization of bevacizumab in 2mg/mL antibody solutions as used in human i.v. administration: Comparison of originator with a biosimilar candidate. Journal of Pharmaceutical & Biomedical Analysis 2019; 176: 112802.
2. Arvinte T, Palais C, Poirier E et al. Part 1: Physicochemical characterization of bevacizumab in undiluted 25mg/mL drug product solutions: Comparison of originator with a biosimilar candidate. Journal of Pharmaceutical & Biomedical Analysis 2019; 175: 112742.
3. Brekkan A, Lopez-Lazaro L, Plan EL et al. Sensitivity of Pegfilgrastim Pharmacokinetic and Pharmacodynamic Parameters to Product Differences in Similarity Studies. AAPS Journal 2019; 21: 85.
4. Brinson RG, Marino JP. 2D J-correlated proton NMR experiments for structural fingerprinting of biotherapeutics. Journal of Magnetic Resonance 2019; 307: 106581.
5. Chow SC, Lee SJ. Design and Analysis of Biosimilar Switching Studies. Pharmaceutical Medicine 2019.
6. Duivelshof BL, Jiskoot W, Beck A et al. Glycosylation of biosimilars: Recent advances in analytical characterization and clinical implications. Analytica Chimica Acta 2019.
7. Dyck YFK, Rehm D, Joseph JF et al. Forced Degradation Testing as Complementary Tool for Biosimilarity Assessment. Bioengineering 2019; 6: 21.
8. Habib MAH, Ismail MN. Characterization of erythropoietin biosimilars using mass spectrometric CID and HCD techniques. Journal of Liquid Chromatography and Related Technologies 2019; 42: 380-91.
9. Huo Y, He J, Li F. Sialic acids content analysis of the innovator and biosimilar darbepoetin alfa by fluorometric HPLC assay. Current Pharmaceutical Analysis 2019; 15: 333-7.
10. Misra SK, Orlando R, Weinberger SR et al. Compensated Hydroxyl Radical Protein Footprinting Measures Buffer and Excipient Effects on Conformation and Aggregation in an Adalimumab Biosimilar. AAPS Journal 2019; 21: 87.
11. Obianom ON, Thway TM, Schrieber SJ et al. Retrospective Analysis of Bioanalytical Method Validation Approaches in Biosimilar Biological Product Development. AAPS Journal 2019; 21: 105.
12. Paek K, Kim GW, Ahn SY et al. Assessment of the Molecular Mechanism of Action of SB3, a Trastuzumab Biosimilar. Biodrugs 2019; 23: 23.
13. Riccetti L, Sperduti S, Lazzaretti C et al. Glycosylation Pattern and in vitro Bioactivity of Reference Follitropin alfa and Biosimilars. Frontiers in Endocrinology 2019; 10: 503.
14. Thomas M, Thatcher N, Goldschmidt J et al. Totality of evidence in the development of ABP 215, an approved bevacizumab biosimilar. Immunotherapy 2019; 26: 26.