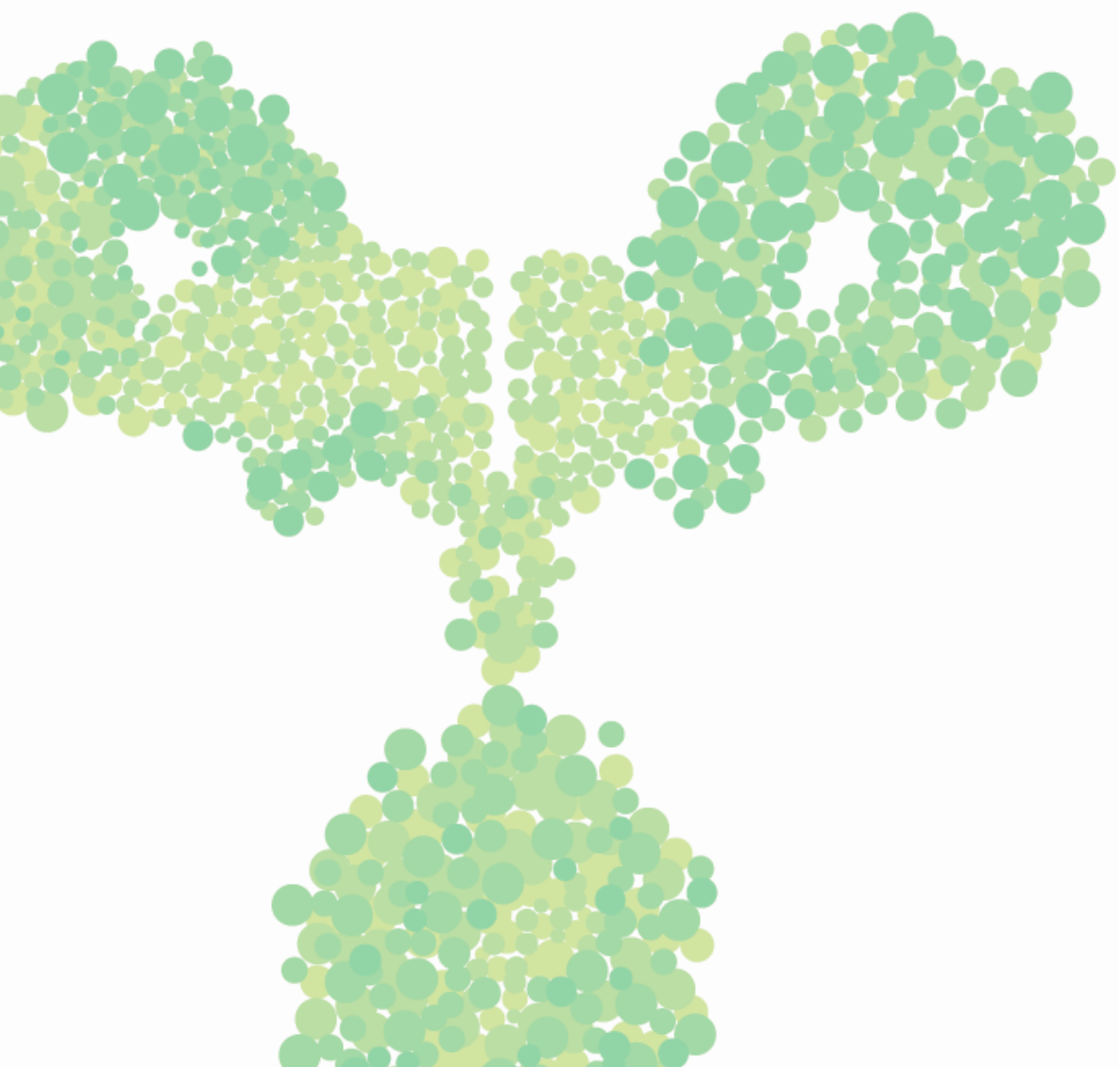
GBMA EDUCATION

University of South Australia | School of Pharmacy and Medical Sciences

International Biosimilar Medicines

Review of the Literature: Quarterly Update

October 2018 – December 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 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.

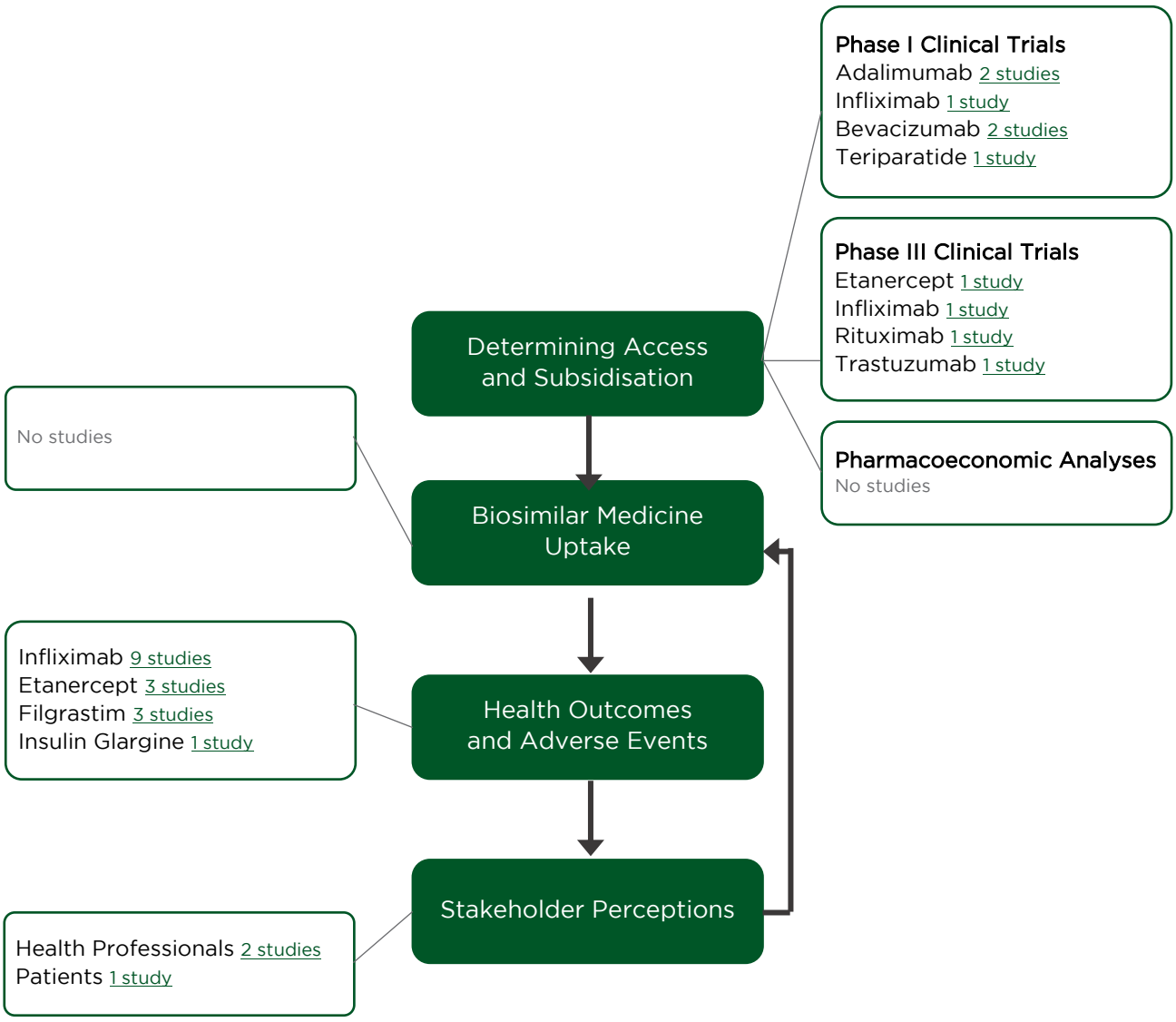
Stakeholder Perceptions

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 October 2018 and 31 December 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
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 six 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						
SB5 Autoinjector versus SB5 Pre-Filled Syringe	None	Randomised, open-label, two-arm, parallel, single-dose study	Healthy adults (n=189; 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 comparisons of SB5 administered via the auto-injector or pre-filled syringe.	Not reported.	Shin et al [1]

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Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
BI 695501 Autoinjector versus BI 695501 Pre-Filled Syringe administered to the abdomen	None	Randomised, open-label, two-arm, parallel, single-dose study	Healthy males (n=66; randomised 1:1)	90% CI of the ratio of geometric least square means for AUC_{0-1032}, AUC_{0-inf} and C_{max} were within the pre-defined equivalence interval of 80-125% for the comparisons of BI 695501 administered via the auto-injector or pre-filled syringe, with the exception of the 90% CI for C_{max} which extended slightly beyond the upper limit (125.44%).	Similar frequencies of ADA-positive subjects, ADA titres, and frequencies of neutralising ADA-positive subjects were observed across the treatment groups. By Day 42, the median ADA titres were 8 and 4 in the auto-injector and pre-filled syringe groups respectively.	Ramael et al [2]
BI 695501 Autoinjector versus BI 695501 Pre-Filled Syringe administered to the thigh	None	Randomised, open-label, two-arm, parallel, single-dose study	Healthy adults (n=162; randomised 1:1)	90% CI of the ratio of geometric least square means for AUC_{0-1368}, AUC_{0-inf} and C_{max} were within the pre-defined equivalence interval of 80-125% for the comparisons of BI 695501 administered via the auto-injector or pre-filled syringe.	Similar frequencies of ADA-positive subjects, ADA titres, and frequencies of neutralising ADA-positive subjects were observed across the treatment groups. By Day 57, the median ADA titre was 8 in both the auto-injector and pre-filled syringe groups.	

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Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
INFLIXIMAB						
GB242	Remicade	Randomised, double-blind, two-arm, parallel, single-dose study	Healthy Chinese adults (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 GB242 with Remicade.	Two subjects in the GB242 treatment group were positive for ADAs on Day 7 & 14; no ADAs were detected in any other subjects.	Zhang 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 Japanese males (n=46; 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]
BEVZ92	Avastin	Randomised, open-label, two-arm, parallel, multiple-dose study	Adult patients with metastatic colon cancer (n=140; randomised 1:1)	90% CI of the ratio of geometric least square means for $AUC_{0\text{-}336}$ and AUC_{ss} were within the pre-defined equivalence interval of 80-125% for the comparison of BEVZ92 with Avastin.	Occurrence of ADAs was low and similar in both groups (BEVZ92 n=2; Avastin n=1)	Romera et al [5]

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Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
TERIPARATIDE						
RGB-10	Forsteo	Randomised, double-blind, two-arm, crossover, single-dose study	Healthy adult females (n=54)	94.12% CI of the ratio of geometric least square means for PK ($AUC_{0\text{-last}}$, $AUC_{0\text{-inf}}$ and C_{max}) parameters were within the pre-defined equivalence interval of 80-125%for the comparison of RGB-10 with Forsteo. There were no statistical differences in PD (serum calcium $AUC_{0\text{-last}}$, C_{max} and T_{max}) parameters between the treatment groups.	Not reported	Takacs et al [6]

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 four reports of phase III trials of potential biosimilars.

ETANERCEPT

Matucci-Cerinic et al: Efficacy, safety and immunogenicity of GP2015, an etanercept biosimilar, compared with the reference etanercept in patients with moderate-To-severe rheumatoid arthritis: 24-week results from the comparative phase III, randomised, double-blind EQUIRA study [7]

SPONSOR: Hexal AG

REFERENCE PRODUCT: Enbrel®

OBJECTIVE(S): To demonstrate equivalent efficacy and to compare the safety and immunogenicity of a proposed etanercept biosimilar (GP2015) with reference etanercept (Enbrel) in patients with moderate-to-severe, active RA, who had an inadequate response to either conventional synthetic and/or biologic disease modifying antirheumatic drugs (DMARDs)

DESIGN: A 48-week, parallel-group, randomised, double-blind, two-period, phase III study. At week 24, participants from both treatment groups who achieved at least a moderate treatment response (EULAR response criteria) continued to receive GP2015 or were switched to GP2015 from reference product for an additional 24 weeks (not reported).

SAMPLE SIZE: A total of 186 and 190 patients were randomized to GP2015 and reference etanercept, respectively

PATIENT CHARACTERISTICS: Rheumatoid arthritis (ACR 1987 or ACR/EULAR 2010 Criteria) for ≥6 months before baseline, active disease (DAS28-CRP ≥3.2), CRP >5 mg/L or ESR ≥28 mm/h, inadequate clinical response to methotrexate at a dose of 10–25 mg/week, were on methotrexate therapy for ≥3 months and on a stable dose for ≥28 days prior to baseline, stable dose of folic acid (≥5 mg per week) for ≥28 days before baseline.

EQUIVALENCE CRITERIA: Containment of the 95% confidence interval (CI) for the difference in mean baseline-week 24 change in DAS28-CRP at week 24 within the interval −0.6 to 0.6.

RESULTS: The least squares mean difference (GP2015–reference) in change in DAS28-CRP from baseline up to week 24 was −0.07 with a 95% CI of −0.26 to 0.12 which was within the pre-defined equivalence criteria. Anti-drug antibodies occurred less frequently in the GP2015 group at 1.6% as compared with 22.7% in the reference product group with anti-drug antibodies being transient in both groups, peaking at week 4. No participants in the GP2015 group developed neutralising antibodies as compared with 1.6% and 0.6% of participants in the reference group at weeks 4 and 12 respectively. Injection-site reactions were reported in fewer participants in the GP2015 group (7.0%) as compared with the reference product group (18.4%).

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INFLIXIMAB

Matsuno et al: A randomized double-blind parallel-group phase III study to compare the efficacy and safety of NI-071 and infliximab reference product in Japanese patients with active rheumatoid arthritis refractory to methotrexate [8]

SPONSOR: Nichi-Iko Pharmaceutical Co., Ltd

REFERENCE PRODUCT: Remicade®

OBJECTIVE(S): To demonstrate equivalent efficacy of a proposed infliximab biosimilar (NI-017) to that of RP when administered to patients with active rheumatoid arthritis and an inadequate response to methotrexate.

DESIGN: A 54 week, randomized double-blind, two-period, phase III study. If the efficacy was insufficient at week 14 Dose increase and/or shortened dosing interval was allowed based on the investigator's discretion. After week 30 all participants received open-label NI-017 for a further 24 weeks at the same dose and interval as the previous 30 weeks.

SAMPLE SIZE: A total of 242 patients were randomized into the NI-017 (n = 126) and reference product (n = 116) groups of whom 238 completed the primary efficacy evaluation at 14 weeks.

PATIENT CHARACTERISTICS: Japanese patients with rheumatoid arthritis (ACR/EULAR 2010 Criteria), inadequate response to previous treatment with methotrexate and a stable dose of ≥6 mg/week during 4 weeks prior to the screening, DAS28-ESR score >3.2.

EQUIVALENCE CRITERIA: Containment of the 95% confidence interval (CI) of the difference in mean baseline-to-week 14 change of DAS28-ESR values within the range of -0.6 to 0.6.

RESULTS: The difference in mean baseline-to-week 14 change of DAS28-ESR values of was 0.02 with a 95% CI of -0.280 to 0.328 which was within the predefined equivalence criteria. Infusion-related reactions occurred in 8.7% of the biosimilar group as compared with 6.0% of the reference product group. At week 14, anti-drug antibodies were detected in 25.6 % of participants in the biosimilar group as compared with 18.6% in the preference product group (p=0.206). At week 54, anti-drug antibodies were detected in 17.2% in the group that received biosimilar for the duration of the study as compared with 22.8% in the group that switched from reference product to biosimilar at week 30.

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RITUXIMAB

Ogura et al: Efficacy, pharmacokinetics, and safety of the biosimilar CT-P10 in comparison with rituximab in patients with previously untreated low-tumour-burden follicular lymphoma: a randomised, double-blind, parallel-group, phase 3 trial [9]

SPONSOR: Celltrion, Inc

REFERENCE PRODUCT: MabThera (US)

OBJECTIVE(S): To assess the therapeutic equivalence of single-agent CT-P10 and rituximab in patients with newly diagnosed low-tumour-burden follicular lymphoma.

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

SAMPLE SIZE: 258 participants were randomised, CT-P10 = 130 vs reference product = 128; 231 patients completed up to month 7, CTP-10= 119 (92%) vs reference product = 112 (88%)

PATIENT CHARACTERISTICS: CD20-positive follicular lymphoma of grade 1–3a, histologically confirmed by central pathological review; at least one measurable tumour mass in two dimensions; Ann Arbor stage II–IV disease, low tumour burden according to Groupe D'Etude des Lymphomes Folliculaires (GELF) criteria.

EQUIVALENCE CRITERIA: Equivalence was shown if the two-sided 90% confidence interval (CI) for the treatment difference in the proportion of responders (defined as a complete response, unconfirmed complete response, or partial response) by 7 months between CT-P10 and rituximab within 17%.

RESULTS: In the ITT population, 83% of participants (108/130) in the CT-P10 group achieved an overall response by month 7 as compared with 81% of participants (104/128) in the reference product group rituximab equating to a difference estimate of 1·8% with a 90% CI of –6·43 to 10·20 which was within the predefined equivalence criteria of 17%. Infections occurred in 35 (27%) participants in the CT-P10 group and 27 (21%) participants in the reference product group. Anti-drug antibodies were detected in one participant in the CT-P10 group and three in the reference product group.

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TRASTUZUMAB

Pegram et al: PF-05280014 (a trastuzumab biosimilar) plus paclitaxel compared with reference trastuzumab plus paclitaxel for HER2-positive metastatic breast cancer: a randomised, double-blind study [10]

SPONSOR: Pfizer

REFERENCE PRODUCT: Herceptin® (EU)

OBJECTIVE(S): To compare the efficacy, safety and immunogenicity of biosimilar trastuzumab (PF-05280014) and reference trastuzumab (Herceptin®) when used in combination with paclitaxel as first-line treatment for patients with HER2+ metastatic breast cancer.

DESIGN: Randomised, double-blind, parallel-group study

SAMPLE SIZE: 707 patients were randomised to PF-05280014 plus paclitaxel (n = 352) or trastuzumab-EU plus paclitaxel (n = 355); 702 patients received study treatment; 538 (76.6%) were exposed to at least eight cycles of treatment, PF-05280014 = 266, trastuzumab-EU = 272

PATIENT CHARACTERISTICS: Females aged ≥ 18 years with metastatic, histologically confirmed breast cancer with at least one measurable lesion as defined by Response Evaluation Criteria in Solid Tumours (RECIST) 1.1, HER2+ status according to one of the following: HER2 gene amplification by fluorescent in-situ hybridisation (FISH), chromogenic in-situ hybridisation (CISH) or dual in-situ hybridisation (DISH), with amplification defined per the manufacturer's kit instruction; HER2 overexpression by immunohistochemistry (IHC) categorised as IHC3+; or HER2 overexpression by IHC categorised as IHC2+, with FISH, CISH or DISH confirmation. Prior trastuzumab exposure = 9.4% (PF-05280014) vs 11% (reference product). Forty-four participants were positive for anti-drug antibodies of whom three participants in the PF-05280014 group and one participant in the reference group had prior trastuzumab exposure.

EQUIVALENCE CRITERIA: Containment of the 95% confidence interval (CI) of the risk ratio for objective response rate (defined as the percentage of patients in each group with RECIST 1.1 complete or partial response by Week 25 that was confirmed by Week 33) within a pre-specified equivalence margin of 0.80–1.25.

RESULTS: The risk ratio for objective response rate by week 25 (confirmed by week 33) in the intention-to-treat population was 0.940 (PF-05280014 group over trastuzumab-EU group), with a 95% CI of 0.842–1.049 which was in the prespecified equivalence criteria of 0.80–1.25. The primary reason for discontinuing treatment was objective disease progression in 39.2% of the PF-05280014 as compared with 40.3% in the reference product group. Decreased ejection fraction was reported in 10.0% of participants in the PF-05280014 group and 11.0% reference product group. All participants were negative for anti-drug antibodies after study treatment initiation through 378 days post-randomisation, except one participant in each group.

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, no publications were identified that examined the economic impact of the introduction of biosimilars

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BIOSIMILAR MEDICINE UPTAKE

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

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

HEALTH OUTCOMES AND ADVERSE EVENTS

Within the period encompassed by this update, there have been 16 papers that have examined pharmacovigilance of biosimilar medicines, specifically the impact of substitution, switching and extrapolation of indication.

INFLIXIMAB

Bergqvist et al: Switching from originator infliximab to the biosimilar CT-P13 in 313 patients with inflammatory bowel disease [11]

SPONSOR: Non-commercial

LOCATION(S): County of Skåne, Sweden (4 hospitals)

DESIGN: Prospective observational open-label multicentre cohort study

DATES: Switching commenced October 2015

OBJECTIVE(S): To assess drug effectiveness, safety, immunogenicity, and drug concentrations, after a nonmedical switch from originator infliximab (Remicade) to the biosimilar infliximab (CT-P13) in patients with inflammatory bowel disease receiving maintenance therapy.

PATIENT CHARACTERISTICS: 313 IBD patients, 195 with CD, 118 with UC); median (range) age at diagnosis = 21 years (6–67) for CD and 27 (6–71) for UC; median (range) age at study inclusion = 37 (18–78) for CD and 38 (18–78) for UC, median time for treatment with originator infliximab prior to switch (years; range) = 4.6 (0.4–16.6) for CD and 3.6 (0.2–9.6) for UC, concomitant thiopurines = 47.3%, concomitant methotrexate = 2.9%, remission at baseline = 66.2% (100/151) for CD and 71.6% (73/102) for UC

OUTCOME(S): The primary endpoint was change in disease activity at 2, 6, and 12 months after the switch, evaluated by the symptom-based scores Harvey–Bradshaw Index (HBI) for CD and the Simple Clinical Colitis Activity Index (SCCAI) for UC.

RESULTS: A total of 250 patients completed 12 months of follow-up. Biosimilar infliximab was discontinued in 10 (3.2%) patients due to remission, 23 (7.4%) patients due to lack of sufficient effect, and 15 (4.8%) patients due to adverse events. There were no statistically significant differences in disease activity measures at 2, 6 or 12 months. At 12 months 68.2% (73/107) of CD and 78.9% (56/71) of CD patients were in remission. Of those in remission at baseline, 16.9% (11/65) of patients with CD and 8.3% (4/48) of patients with UC had lost remission at 12 months. Anti-drug antibodies were detected in six CD (3.2%) and two UC patients (1.8%) who were negative at the time of switching (analysis of anti-drug antibodies was limited to undetectable serum infliximab concentrations due to assay interference). Dose escalation occurred in increased disease activity in 6.8% (17/250) of the patients due to increased disease activity, 16.0% (40/250) due to low drug levels but without signs of increased disease activity and in 2.8% (7/250) for undocumented reasons but without signs of increased disease activity.

REVIEWER COMMENTARY: The result regarding dose modification following switching from originator to biosimilar infliximab should be interpreted with caution. The authors note that the timing of the switch coincided with a change in local clinical practice to include proactive therapeutic drug monitoring of infliximab and that "*…the 40 patients that were dose escalated due to low drug levels, although being asymptomatic, had in essence, developed low drug levels while treated with the originator product but not revealed as having low drug levels until subjected to the switch protocol…*".

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Condreanu et al: Assessment of effectiveness and safety of biosimilar infliximab (CT-P13) in a real-life setting for treatment of patients with active rheumatoid arthritis or ankylosing spondylitis [12]

SPONSOR: Egis Pharmaceuticals PLC

LOCATION(S): Bulgaria, Czech Republic, Romania

DESIGN: Multi-centre, non-interventional, observational study

DATES: December 2014 to October 2016

OBJECTIVE(S): To assess the effectiveness and safety of biosimilar infliximab (CT-P13) administered in a real-life setting to adult patients with active progressive rheumatoid arthritis (RA) and inadequate response to methotrexate or other conventional synthetic DMARDs or active progressive ankylosing spondylitis (AS) and inadequate response to non-steroidal anti-inflammatory drugs.

PATIENT CHARACTERISTICS: 151 subjects (RA=81, AS= 70, 47% male, 53% female); mean age = 49.1 ± 13.6 years, no previous exposure to anti-TNFa therapy = 66.7% (RA), 80.0% (AS)

OUTCOME(S): The primary end-point was the percentage of patients with a response to CT-P13 at 24 weeks, where response was defined as an improvement in the DAS-28-CRP score at week 24 consistent with moderate and good EULAR response criteria for patients with rheumatoid arthritis and an improvement of at least 50% in the BASDAI score or an absolute change of 2 units (on a 0–10 scale) relative to baseline for patients with ankylosing spondylitis.

RESULTS: Of the 151 patients, 19 terminated the study prematurely, and three patients were excluded due to missing efficacy measurements resulting in a total of 129 patients (RA: 67; AS: 62) eligible for inclusion in the efficacy analysis. At week 24 the overall response rate was 75.5% (RA=71.6%. AS=80%) with remission achieved in 44% of patients with RA and 31% of patients with AS. A total of seven patients discontinued biosimilar infliximab due to adverse events including five allergic infusion reactions (four definitely related, one probably related), one possibly-related hepatocellular injury and one unrelated ischemic stroke. Five patients stopped treatment due to therapeutic failure.

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Germain et al: Long-term follow-up after switching from originator infliximab to its biosimilar CT-P13: The weight of nocebo effect [13]

SPONSOR: None

LOCATION(S): Bordeaux, France

DESIGN: Prospective switching group, historic control group

DATES: Switching between November 2015 and October 2016, historic controls treated during 2013

OBJECTIVE(S): To assess the long-term retention rate of biosimilar infliximab (CT-P13) after switching from originator infliximab and to compare it with the retention rate observed in the historic cohort treated with originator infliximab.

Note: this study extends the previous report by Sherlinger et al [#]

PATIENT CHARACTERISTICS: Patients must have been receiving stable infliximab treatment for at least 6 months and "*there* (sic) *disease was controlled according to physician opinion*"

OUTCOME(S): Long-term retention rate

RESULTS: Treatment retention rates in the switching groups following a median of 120 weeks (range 6–145) was 56% (50/89) as compared with 67% (55/82) in the historic cohort after a median follow-up of 131 weeks (range 4–156). Of the 39 patients in the switching group that discontinued treatment, 14 did so after the previously reported 33 week time point. Of the 14 patients that stopped in this time period, five were due to objective clinical worsening, 6 for non-serious safety issues and 3 ceased treatment with stable remission. There was a trend towards more withdrawals in the switch group as compared with the historic controls (log-rank p=0.052) but this disappeared after excluding patients that did not have objective worsening of clinical activity (log-rank p=0.673).

[#] Scherlinger M, Germain V, Labadie C et al. Switching from originator infliximab to biosimilar CT-P13 in real-life: The weight of patient acceptance. *Joint Bone Spine* 2018; **85**: 561-7.

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Lopalco et al: Long-term effectiveness and safety of switching from originator to biosimilar infliximab in patients with Behcet's disease [14]

SPONSOR: None

LOCATION(S): Italy

DESIGN: Retrospective chart survey

DATES: Patients switched from originator to biosimilar infliximab between March 1st 2017 to May 31st 2017

OBJECTIVE(S): To evaluate the effectiveness and safety of switching from originator infliximab to biosimilar infliximab

PATIENT CHARACTERISTICS: 13 patients (ten male and three female patients); mean age = 39.77 ± 7.46 years), mean disease duration = 12.54 ± 4.21 years, mean duration of treatment with originator infliximab = 117.66 ± 48.01 months, 4/13 patients had symptoms at time of switch

OUTCOME(S): Disease activity as assessed with the BD current activity form (BDCAF)

RESULTS: At 3 months after switching, no patients had discontinued treatment with biosimilar infliximab and there were no significant differences in BDCAF when comparing the time of switching and 3 months after switching (p = 0.50). At 6 months after switching, two patients had ceased treatment due to disease recurrence, one of whom had previously experience disease flare whilst receiving originator infliximab and there were no differences in the BDCAF (p = 1.00).

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Plevris et al: Implementation of CT-P13 via a Managed Switch Programme in Crohn's Disease: 12-Month Real-World Outcomes [15]

SPONSOR: None

LOCATION(S) : Edinburgh, Scotland

DESIGN: Observational

DATES: From July 2015

OBJECTIVE(S): To prospectively evaluate the efficacy (clinical disease activity, CRP and faecal calprotectin), pharmacokinetics and safety of switching CD patients from originator infliximab to biosimilar infliximab (CT-P13) over 12 months.

PATIENT CHARACTERISTICS: 155 patients with disease status prior to switching: clinical remission = 91.7%, biochemical remission 51.3%, faecal biomarker remission = 71.2%; median trough infliximab level = 2.6 μg/mL (IQR 1.0–4.7); detectable antidrug antibodies (≥10AU/mL) = 47.7%

OUTCOME(S): Disease activity as assessed by the Harvey-Bradshaw Index, CRP and faecal calprotectin at 6 and 12months post switching

RESULTS: A total of 155 patients with Crohn's disease on maintenance treatment with originator infliximab were evaluated for switching. A total of 110 patients switched to biosimilar infliximab. Twenty patients changed treatment to adalimumab because of low IFX levels (< 3.0 μg/mL) plus presence of ATI (≥ 10 AU/mL) and 24 patients stopped therapy because of low IFX levels (< 3.0 μg/mL), presence of ATI (≥ 10 AU/mL) and remission. Of those that switched to biosimilar infliximab, treatment was intensified (increased dose or reduced interval) at the time of the switch in six patients. No significant differences were observed in the Harvey-Bradshaw Index scores (p = 0.0741), CRP (p = 0.1336) and faecal calprotectin (p = 0.2514) when comparing those levels before and after the switch. Trough infliximab concentrations were also not significantly different at 0, 6 and 12 months (p = 0.4706). The cost saving of switching to biosimilar infliximab was estimated at 46.4%.

REVIEWER COMMENTARY: In this study a number of patients that were initially considered for switching to biosimilar infliximab were changed to adalimumab as a result of factors that are associated with poor response to infliximab (eg. low infliximab concentrations and detectable anti-drug antibodies) and the issue of assigning causality in the case of poor response. Importantly in this context the authors note that "Furthermore, we recommend a baseline assessment of patients at their final Remicade [originator infliximab] infusion so that intervention can occur prior to switching to CT-P13 [biosimilar infliximab] to try to optimise treatment and prevent future disease deterioration, which patients may wrongly attribute to CT-P13." Whilst the authors frame this with respect to patients this must also be considered when interpreting the results of uncontrolled observational studies.

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Yazici et al: A descriptive analysis of real-world treatment patterns of innovator (Remicade) and biosimilar infliximab in an infliximab-naive Turkish population [16]

SPONSOR: Janssen Scientific Affairs

LOCATION(S): Turkey

DESIGN: Retrospective cohort, administrative claims database

DATES: Identification period: 1 Oct 2014–30 May 2015

OBJECTIVE(S): To compare the characteristics of infliximab-naïve patients with rheumatoid arthritis and inflammatory bowel disease who were initiated on biosimilar infliximab (CT-P13) with those who were initiated on originator infliximab and to describe the medication utilization patterns, including persistency and switching.

PATIENT CHARACTERISTICS: 779 patients with rheumatoid arthritis, originator infliximab = 73.8% (n=575), biosimilar infliximab= 26.2% (n=204); 581 patients with inflammatory bowel disease, originator infliximab = 87% (n=504), biosimilar infliximab= 13% (n=77)

OUTCOME(S): Retention rate

RESULTS: In patients with rheumatoid arthritis, the proportion of patients who discontinued treatment was lower in the originator group as compared with the biosimilar group (42.1% vs 62.8%; P<0.001) and the mean time to discontinuation was longer in the originator group than in the biosimilar group (263 days vs 207 days; P<0.001). Within the biosimilar group 20% of patients switched to originator infliximab as compared with 8% of patients in the originator group that switched to biosimilar. The proportion of patients in both groups changing to an alternative biologic was similar (~15%).

In patients with inflammatory bowel disease, the proportion of patients who discontinued treatment was lower in the originator group as compared with the biosimilar group (37.5% vs 62.3%; P<0.001) and the mean time to discontinuation was longer in the originator group than in the biosimilar group (288 days vs 177 days; P<0.001). Within the biosimilar group 42% of patients switched to originator infliximab as compared with 6.5% of patients in the originator group that switched to biosimilar. Of those who switched from originator to biosimilar, 36.2% switched back to the originator whilst 40.6% of those that switched from biosimilar to originator switched back to the biosimilar. The proportion of patients in both groups changing to an alternative biologic was similar (~10%).

REVIEWER COMMENTARY: The reasons for switching back to the originator are not provided in this study.

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Yazici et al: Analysis of real-world treatment patterns in a matched rheumatology population that continued innovator infliximab therapy or switched to biosimilar infliximab [17]

SPONSOR: Janssen Scientific Affairs

LOCATION(S): Turkey

DESIGN: Retrospective cohort, administrative claims database

DATES: December 2010 –June 2016

OBJECTIVE(S): To compare the treatment patterns of patients with rheumatoid arthritis (RA) who were treated with originator infliximab and switched to biosimilar infliximab (with a documented switch date) with those who continued treatment with originator (assigned a random date as a surrogate for the switch date).

PATIENT CHARACTERISTICS: Total of 697 patients, 605 continued originator, 92 switched to biosimilar; mean age = 41 years (continued originator) vs 43 years (switched); mean duration of originator infliximab treatment prior to switch/surrogate date = 422 days (continued originator) vs 438 days (switched); concomitant methotrexate = 27.6% (continued originator) vs 31.5% (switched); mean follow-up = 16.3 months (continued originator) vs 15.1 months (switched)

OUTCOME(S): Retention rate

RESULTS: 87% of patients in the switched group discontinued infliximab as compared with 33.9% of those in the continued group ($P<0.001$). The average time to discontinuation in the switched group was 98.4 days as compared with 117.1 days in the continued group ($P=0.032$). Within the switching group, 66 (72%) changed back to originator infliximab during the follow-up period. Nine patients (9.8%) in the switching group changed to an alternative biologic as compared 89 (14.7%) of the group that continued originator.

REVIEWER COMMENTARY: The authors state that "treatment persistence during the follow-up period was significantly higher for patients who continued IFX [originator] compared to patients who switched from IFX [originator] to CT-P13 [biosimilar]. However, it should be noted that a large proportion of the group that switched to biosimilar infliximab switched back to originator infliximab. No details are provided for why patients switched back to originator and the outcomes associated with switching back are not provided. It is likely that factors such as prescriber and patient attitudes toward biosimilar infliximab influenced this decision. The historical nature of the continued group, with an artificially assigned switch date surrogate, is not impacted by these factors limiting the comparability of the two groups. In this context 9% of the switched group changed to an agent other than infliximab as compared with 19% of the continued group.

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Meyer et al: Effectiveness and Safety of Reference Infliximab and Biosimilar in Crohn Disease: A French Equivalence Study [18]

SPONSOR: Non-commercial

LOCATION(S): France

DESIGN: Comparative equivalence cohort study using a nationwide health administrative database

DATES: Patients who received at least 1 infliximab infusion between 1 March 2015 and 30 November 2016

OBJECTIVE(S): To compare the effectiveness and safety of biosimilar infliximab (CT-P13) and originator infliximab (Remicade®) in a large nationwide observational equivalence cohort study of infliximab-naive patients with Crohn's Disease.

PATIENT CHARACTERISTICS: 5050 patients, originator infliximab = 2551 (50.5%), biosimilar infliximab = 2499 (49.5%); trend toward more severe disease in the biosimilar with more pelvic or abdominal computed tomography (48.1% vs. 42.5%) or magnetic resonance imaging (50.6% vs. 43.5%), hospitalizations (57.4% vs. 53.4%), and Crohn's Disease-related surgeries (17.7% vs. 14.8%) during the previous 12 months; concomitant thiopurine = 40.4%

OUTCOME(S): Primary outcome was a composite end point of death; Crohn's Disease-related surgery; all-cause hospitalization (except childbirth) for at least 1 night; or reimbursement of adalimumab, vedolizumab, or ustekinumab.

RESULTS: These was no significant difference in the primary outcome between the originator infliximab and biosimilar infliximab groups ($P > 0.20$). The cumulative incidence of the primary outcome was 29.6% (originator) as compared with 28.6% (biosimilar) at 6 months, 43.1% (originator) vs 41.6% (biosimilar) at 12 months and 51.5% (originator) vs 50.1% (biosimilar). Infliximab was discontinued in 18.6% of patients in the originator group as compared with 17.6% in the biosimilar group. Switching between infliximab products (originator to biosimilar or vice versa) occurred in 6.3% of patients initiated on originator infliximab as compared with 8.2% of those initiated on the biosimilar.

REVIEWER COMMENTARY: The reasons for switching are not provided.

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Scavone et al: Real World Data on the Utilization Pattern and Safety Profile of Infliximab Originator Versus Biosimilars in Italy: A Multiregional Study [19]

SPONSOR: Non-commercial

LOCATION(S): Italy (Campania, Lombardy, Sicily, Tuscany, and Veneto)

DESIGN: Analysis of reports in the Italian Pharmacovigilance Database

DATES: October 2015 to October 2017

OBJECTIVE(S): To compare the probability of reporting infections, infusion reactions, lack of efficacy, and hypersensitivity as ADRs as opposed to other types of ADRs between originator infliximab (Remicade®) and biosimilar infliximab (Remsima® and Inflectra®).

Outcomes: Reporting odds ratio between biosimilar infliximab and originator infliximab

RESULTS: Over the study period a total of 459 individual case safety reports for infliximab were identified of which 222 were for originator infliximab and 237 for biosimilar infliximab. Of the 459 cases reported 39 were considered preventable (eg. incorrect dose or inappropriate prescription for patient's underlying medical condition). Biosimilar infliximab had an increased probability of being reported as suspected for infusions reactions (ROR = 0.33, 95%CI: 0.12–0.89, p = 0.029), lack of efficacy (ROR = 0.35, 95%CI: 0.20–0.61, p < 0.001) and infusion reactions (ROR = 4.09; 95%CI: 1.26–13.32, p = 0.019).

REVIEWER COMMENTARY: This analysis is based upon spontaneous reporting and as the authors note, when considering the results for the comparison of originator and biosimilar infliximab there may be "a direct correlation between the increased attention that all biosimilars, including those of infliximab, have received from clinicians and patients and the increased reporting of ADRs induced by infliximab biosimilars cannot be excluded". The authors also note that "after reaching a peak, the reporting rate for infliximab biosimilars reduced substantially despite the distributed vials of infliximab increasing over time" consistent with an initial heightened awareness which subsided with time.

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ETANERCEPT

Scherlinger et al: Acceptance rate and sociological factors involved in the switch from originator to biosimilar etanercept (SB4) [20]

SPONSOR: None

LOCATION(S): Bordeaux University Hospital, France

DESIGN: Prospective, observational

DATES: Recruitment between 1 May and 31 October 2017

OBJECTIVE(S): To describe the uptake and outcomes associated with the offer to switch from originator to biosimilar etanercept (SB4) following the provision of information from their prescriber about biosimilars.

PATIENT CHARACTERISTICS: 52 patients with well-controlled rheumatic disease (rheumatoid arthritis = 20, spondyloarthritis = 32) and at least 6 months of treatment with originator etanercept; mean disease duration = 13.1 ± 11 years; mean duration of treatment with originator etanercept = 4.5 ± 3.3 years; originator etanercept was the first biologic = 40 (77%)

ENDPOINT(S): Switch acceptance rate (primary), description of patient attitudes and characteristics

RESULTS: 48/52 patients (92%) agreed to switch to biosimilar etanercept. The authors report that the *"main"* questions from patients related to "*drug similarity in term of efficacy and safety*" and that "*Many*" enquired about the "experience of the switch with other patients". The authors remark that amongst the four patients who declined the switch "*suspicious and defensive behaviour was noted when the prospect of switching to a biosimilar was raised*" and that these patients "*tended to have lower interest in biosimilar and to ask less questions on this subject*" but they do note that these observations were "*not objectively quantified*". Seven patients (15%) reported feeling pressured to accept the switch. Two patients that agreed to switch did not do so, attributed to the fact that "*contradictory and negative information had been given by their regular pharmacist*" and that in one instance the pharmacy continued to provide originator etanercept even though the prescription specifically stated SB4.

Three patients switched back to originator etanercept. One patient with RA reported increased arthralgia which was associated with moderate signs of disease activity on musculoskeletal ultrasound (before switch DAS28-VS = 2.1; after switch DAS28-VS = 4.2) but two months after switching back to the originator the authors considered that the patient displayed the "*same level of objective signs of activity*" (DAS28- VS = 3.0). One patient with AS reported increased pain and morning stiffness after the switch but the BASDAI was largely unchanged (6.0 pre-switch vs 6.2 post-switch) and there was no increase in either C-reactive protein or erythrocyte sedimentation rate. A third patient attributed a change in anticoagulant control (increased INR) to switching to biosimilar etanercept but the authors report that there was no change in control when the patient switched back to originator.

REVIEWER COMMENTARY: The authors note that two patients decided not to switch because "*contradictory and negative information had been given by their pharmacists*". No further details are provided. However, this should be viewed in the context that some patients reported feeling pressured to accept the switch. It is possible that the two patients who decided not to switch felt pressured and the discussion with their pharmacist empowered them to change their mind. These observations highlight the importance of shared decision making between patients and their healthcare providers.

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Glintborg et al: To switch or not to switch: results of a nationwide guideline of mandatory switching from originator to biosimilar etanercept. One-year treatment outcomes in 2061 patients with inflammatory arthritis from the DANBIO registry [21]

SPONSOR: Partly funded by Biogen

LOCATION(S): Denmark, nationwide

DESIGN: Observational cohort study using the DANBIO registry

DATES: Patients who switched from originator etanercept (Enbrel) to biosimilar etanercept (SB4) between 1 April 2016 and 1 January 2017, Danish national guideline issued in April 2016 that all patients with inflammatory arthritis treated with originator etanercept (Enbrel) must switch to biosimilar etanercept (SB4), historic comparison cohort of originator etanercept - treated patients by 1 January 2015

OBJECTIVE(S): To determine the proportion of patients treated with originator etanercept that switched to biosimilar etanercept (SB4) and amongst those that switched to; compare disease activity 3 months' prior to and after switching, compare the 1-year retention rates with that of a historic cohort of patients treated with originator etanercept and to describe the reasons for and patient characteristics associated with withdrawal or switch back to originator etanercept.

PATIENT CHARACTERISTICS: Patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and axial spondyloarthritis (AxSpA) treated with etanercept by 1 April 2016. Baseline was defined as fir first biosimilar dose for the switching group (−90 to +6 days) and as 1 April 2016 (±180 days) for the group that continued originator etanercept.

OUTCOME(S): Retention rate, change in disease activity measures (DAS28 for RA and PsA, BASDAI and ASDAS for AxSpA)

RESULTS: A total of 2183 patients were identified on whom 2061 were included. Of these 1621 (79%) switched to SB4. There was a trend toward some differences in the baseline characteristics between those that switched to biosimilar compared with those that continued originator including the duration of treatment with originator etanercept (switch vs non-switch) = 6.0 vs 5.3 years (RA), 4.3 vs 3.4 years (PsA), 4.6 vs 4.7 years (AxSpA), the concomitant use of methotrexate (switch vs non-switch) = 60% vs 49% (RA), 48% vs 30% (PsA), 15% vs 18% (AxSpA) and an etanercept dose of 25mg (switch vs non-switch) = 1% vs 43% (RA), 1% vs 18% (PsA), 1% vs 36% (AxSpA).

The 1-year adjusted retention rates in switchers was 83% (79% to 87%) as compared with 90% (88% to 92%) in the historic cohort and 77% (72% to 82%) in those who continued originator etanercept. During follow-up (median 401 days), 299 switchers (18%) and 145 of those who continued originator etanercept (33%) withdrew from treatment with biosimilar and originator etanercept, respectively, with lack of effect the most common reason for withdrawal. Amongst the switching group no clinically relevant differences in disease activity and flare rates 3 months pre-switch as compared with post- switch were observed. Amongst the 299 switchers who stopped biosimilar etanercept, 104 changed to an alternative agent, 120 switched back to originator etanercept and 65 ceased treatment with a biologic. Of those that switched back to originator etanercept, the median duration of treatment with biosimilar etanercept was median 120 (IQR 73 to 193) days with patients immediately resuming treatment with the originator (time interval between stopping biosimilar and restarting originator = 1 day). At the time of censoring, 87% (104/120) who switched back to originator etanercept were still receiving etanercept (median treatment duration = 236 days).

REVIEWER COMMENTARY: There is a trend toward some differences in the baseline characteristics between the patients that switched to biosimilar etanercept versus those that continued originator. One factor that appears to have impacted switching is the dose of etanercept that patients were receiving. In this case the originator was available in a prefilled pen/syringe that enabled convenient administration of a 25mg dose whilst the biosimilar was not available in this strength. This is reflected in the fact that of all non-switchers 185/440 were receiving 25mg highlighting the importance of considerations beyond the drug molecule itself.

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Sigurdardottir et al: Repeated switches between reference product etanercept and biosimilar do not affect disease activity or retention rate of etanercept over 24 months - a cohort study with historical controls [22]

SPONSOR: Not stated

LOCATION(S): Sweden, nation-wide

DESIGN: Swedish Rheumatology Quality Register

DATES: Not stated

OBJECTIVE(S): To compare the effects of switching from originator etanercept to biosimilar etanercept (SB4) and 18 months later re-switching to originator etanercept with a historic cohort

PATIENT CHARACTERISTICS: Switching cohort = 143, historic cohort = 97; median duration of etanercept use = 1.6 years (switching) vs 4.6 years (historic), p<0.0001

OUTCOME(S): Retention rate at 6 and 12 months

RESULTS: The retention rate in the group switched to biosimilar etanercept was 90% at 6 months and 78% at 12 months. At 18 months the retention rate in the biosimilar group had decreased to 69% which was significantly lower than the historic control group (p=0.0015). The most common reason for discontinuing biosimilar etanercept was patient request to switch back from biosimilar to originator (n=19). Reasons for requesting a re-switch are not provided but is noted that three patients reported "*problems using the biosimilar device*". The authors state that all patients were switched back to originator etanercept for "…*economical reasons as the price of RPE had then been reduced…*" and that this occurred "…*without any objective signs of disease worsening…*".

REVIEWER COMMENTARY: The reported 18 month retention rate for the biosimilar group includes patients that switched back to originator and so includes elements such as patient preference rather than purely clinical response.

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FILGRASTIM

Iino and Yamamoto: Efficacy and Safety of Biosimilar Filgrastim for Cord Blood Transplantation: A Single-Institution Retrospective Analysis [23]

SPONSOR: N/A

LOCATION: Japan

DESIGN: Retrospective analysis at single site

DATES: January 2015 through December 2016

OBJECTIVE(S): To compare outcomes between biosimilar filgrastim (Filgrastim BS, Fuji) and originator filgrastim treated patients with hematologic malignant tumours in the unrelated cord blood transplant (CBT) setting

PATIENT CHARACTERISTICS: Undergoing first CD34-positive stem cell allogeneic transplant. 12 consecutive patients who received biosimilar filgrastim were compared with a historical cohort of 10 consecutive patients who received originator

OUTCOME(S): Duration of filgrastim administration, total filgrastim dose, incidence of engraftment, time to hematopoietic recovery, incidence of febrile neutropenia, incidence of documented infection, adverse events, duration of hospitalization, 100 day and one year overall survival and cost of administration.

RESULTS: No statistical differences in clinical outcomes was observed between the biosimilar and originator groups. No statistical difference in the median dose and duration of filgrastim administration between the biosimilar group (9.68 mg [range: 5.40 - 12.60] and 22 days [range: 12-28] and the originator group (10.80 mg [range: 7.65 - 27.9] and 24 days [range: 17 - 62] was reported. No statistical difference in the median time to neutrophil recovery (ANC >0.5 x 10^9/L) was observed between the biosimilar group (22 days [range: 16-37] and originator (25 days [range: 18-38]. After ANC reached 1.0 x 10^9/L, the number of patients requiring additional filgrastim administration in the biosimilar group and originator group was 4 and 3, respectively. The probability of overall survival at 100 days and 1 year was 82.5% and 82.5%, respectively, for the biosimilar group, and 90% and 70%, respectively, for the originator group (P =0.62). A reduction in cost of approximately 464,000 yen (4100USD) per patient was reported for the treatment of the biosimilar group. The authors acknowledged limitations including the use of a historical originator group and a small sample size with heterogeneous transplant characteristics.

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Roche et al: Biosimilar filgrastim treatment patterns and prevention of febrile neutropenia: a prospective multicentre study in France in patients with solid tumours (the ZOHe study) [24]

SPONSOR: Sandoz

LOCATION: France

DESIGN: The Zohe study is a prospective, non-interventional multi-centre study of the use of biosimilar filgrastim (Zarzio, Sandoz) in routine clinical practice in patients at risk of chemotherapy induced neutropenia. The study included solid tumours and haematological malignancy. This manuscript reports the outcomes from solid tumour cohort, the data from the haematological cohort has been reported previously.

DATES: June 2013 through April 2014

OBJECTIVE(S): Describe the indications and characteristics of patients treated with biosimilar filgrastim and evaluate the use of biosimilar filgrastim in routine practice in patients receiving chemotherapy for solid tumours

PATIENT CHARACTERISTICS: Patients aged 18 years or older undergoing cytotoxic chemotherapy for solid tumours who received a first prescription for biosimilar filgrastim were included.

OUTCOMES: Data was collected using electronic case report form to collect patient characteristics, indication (primary or secondary prevention) in relation to European Organisation for Research and Treatment of Cancer (EORTC) recommendations, rates of febrile neutropenia and adverse events. Follow up visit data was collected at the three month end-point.

RESULTS: 1174 patients with solid tumours who received biosimilar filgrastim were recruited from 125 sites across France and included a representative sample of 60 oncologists, 35 haematologists and 30 other specialties. The mean age was 62.3 (±12.0) years with the most common tumours types being breast, lung and gastro-intestinal. The median initiation was day four of the chemotherapy cycle, the planned duration of biosimilar filgrastim for all tumour types was 5 days and no patients were treated for > 14 days. The majority of the solid tumour patients received biosimilar filgrastim during their first cycle at study inclusion, with the exception of GI and ovarian malignancies who were equally likely to be initiated on biosimilar filgrastim as primary or secondary prophylaxis. Almost all patients (99.1%) had at least one patient related risk factor for febrile neutropenia and, with the exception of ovarian tumours, very few patients were included with a febrile neutropenia risk <10%. As such the authors reported that biosimilar filgrastim use was largely in line with the EORTC guidelines and compliant with label indication. Severe neutropenia was observed in 7.6% (n=87) of patients during follow up. The incidence of febrile neutropenia varied from 7.7% in head and neck cancers to 0% in ovarian malignancy. 62 adverse events associated with biosimilar filgrastim were reported during the study occurring in 3.4% of patients. Of these 14 AEs were considered serious, with musculoskeletal and connective tissue disorders the most common. Discontinuation due to biosimilar filgrastim toxicity was observed in less than 5% of patients.

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Abboud et al: Real-world safety experience of tevagrastim/ratiograstim/biograstim and tbo-filgrastim, short-acting recombinant human granulocyte colony-stimulating factors [25]

SPONSOR: Teva

LOCATION: Global

DESIGN: Retrospective post-market analysis of periodic safety update reports for tbo-filgrastim.

DATES: From initial market entry 2008 (2012 US) through December 2016

OBJECTIVE(S): Present the real world cumulative post-market safety experience for tbo-filgrastim since market entry

OUTCOMES: Adverse events were collated from spontaneous reporting by health care professionals, consumers, competent authorities, literature, data collection systems and non-interventional studies.

RESULTS: 720 case reports were identified from the global safety database. 1432 adverse events associated with tbo-filgrastim use were recorded, of which 644 were serious. The most common adverse events were pyrexia, bone pain and back pain. The most common serious adverse events were febrile neutropenia, neutropenia, increased white blood cell count and increased neutrophils. Globally, 65 fatal outcomes were reported. The authors state that in the US reports of fatalities are automatically considered to be related for reporting purposes, so the incidence of causality is difficult to measure. During the reporting period 8 patients were tested for anti-drug antibodies. No binding or neutralizing antibodies were detected in testing performed by Teva. The authors summated that "*the safety profile for tbo-filgrastim/tevagrastim/ratiograstim /biograstim in the global postmarket setting is comparable to clinical trial experience*" and that "*no new signal emerged*".

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INSULIN GLARGINE

Ito et al: A comparison of the clinical courses of type 2 diabetic patients whose basal insulin preparation was replaced from insulin glargine 100 units/mL to insulin glargine biosimilar or 300 units/mL: a propensity score-matched observation study [26]

SPONSOR: None

LOCATION(S): Japan

DATES: April 2016 and April 2017

DESIGN: Retrospective observational study using propensity score matching

OBJECTIVE(S): To determine the clinical course of patients with type 2 diabetes whose basal insulin preparation was switched from originator insulin glargine 100units/mL (Lantus®, Sanofi) to biosimilar insulin glargine 100units/mL (LY2963016, Lilly) or to insulin glargine 300units/mL (Lantus XR®, Sanofi).

PATIENT CHARACTERISTICS: 34 patients switched from originator insulin glargine to biosimilar insulin glargine. Propensity scores included the following covariates; sex, age, duration of diabetes, body mass index (BMI), dose of basal insulin and bolus insulin, HbA1c level, occurrence of hypoglycaemia within the past 6 months, use of metformin, and use of dipeptidyl peptidase-4 (DPP-4) inhibitors. The distribution of propensity scores were similar between groups.

OUTCOMES: The primary outcome was change in HbA1c over 6 months and frequency of hypoglycaemia

RESULTS: No significant change in HbA1c level ($p = 0.48$) or body weight ($p = 0.18$) was observed 6 months after switching originator glargine biosimilar glargine. The rate of patients with a hypoglycaemic event within the last 6 months was not affected by switching to biosimilar glargine (12% at baseline vs 12% 6 months post switch).

REVIEWER COMMENTARY: This study included two groups of patients, one group that switched from originator insulin glargine to biosimilar insulin glargine and a second group that had a change in therapy from insulin glargine 100units/mL (Lantus®) to insulin glargine 300units/mL (Lantus XR®), both of which are produced by Sanofi. Only the group switching to biosimilar glargine is relevant to this review.

STAKEHOLDER PERCEPTIONS

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

HEALTH PROFESSIONALS

Lukasik and Nowicki: Knowledge and attitude of community pharmacy employees towards an automatic drug substitution of generics and biosimilars [27]

SPONSOR: Medical University of Lodz

LOCATION(S): Poland

DESIGN: Self designed anonymous questionnaire, one targeting professionals and one targeting patients. Pharmacy employees were recruited face to face across four 4 Polish provinces, patients were recruited from outpatient clinic waiting rooms in diabetology, cardiology and nephrology at a large academic hospital.

DATES: January – March 2017

OBJECTIVE(S): Evaluate knowledge, attitudes and opinion of pharmacy technicians, community pharmacists and patient's attitudes towards automatic substitution of generics and biosimilars.

PARTICIPANTS: Pharmacy employees were recruited face to face across four 4 Polish provinces, patients were recruited from outpatient clinic waiting rooms in diabetology, cardiology and nephrology at a large academic hospital.

RESULTS: A total of 260 pharmacy employees returned the questionnaire; 227 pharmacists and 33 pharmacy technicians of whom 9.1% of pharmacy technicians and 46.8% of pharmacists claimed to have "considerable knowledge" regarding biosimilar drugs. The response rate could not be determined. Most pharmacy employee respondents stated that the subject of biosimilars was insufficiently addressed in refresher courses and training conferences. The pharmacy employees evaluated biosimilars as carrying higher risk of adverse events than generics. Pharmacy employees in Poland stated that automatic substitution was available in approximately half of prescriptions in Poland.

REVIEWER COMMENTARY: The patient survey did not differentiate between generics and biosimilars, as such the results are not presented in this review. The pharmacy employee questionnaire separated the issue of biosimilars and generics rarely. The level of respondent understanding of biosimilars was undetermined. In general, the issue of automatic substitution addressed in this study included both generics and biosimilars.

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Aladul et al: Healthcare professionals' perceptions and perspectives on biosimilar medicines and the barriers and facilitators to their prescribing in UK: a qualitative study [28]

SPONSOR: None, investigator-initiated

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

DESIGN: 30 minute qualitative semi-structured interview of healthcare professionals (HCPs)

DATES: June – November 2017

OBJECTIVE(S): To investigate perceptions and perspectives of different HCPs in UK towards infliximab, etanercept and insulin glargine biosimilars and the barriers and facilitators to their uptake

PARTICIPANTS: HCPs were recruited from 5 hospital trusts in the Midlands of the UK. 22 interviews were conducted including pharmacists (n=4), consultants (n=11) and nurses (n=7).

RESULTS: The authors report the emergence of 5 major themes regarding biosimilars including perception, attitudes towards prescribing, evidence base, facilitators to prescribing and barriers to prescribing. With regards to perception and attitudes, all interviewed participants demonstrated an understanding of the biosimilar concept. The majority were content to initiate biosimilar drugs in their patients, however HCPs in rheumatology and diabetology expressed a concern that they were being pressured by their organisation to use biosimilars and that insufficient choice was given to patients. All gastroenterology participants were happy to switch patients from reference to biosimilar. Two (out of seven) rheumatology HCPs were happier to initiate than switch to a biosimilar in a stable patient for economic reasons. Diabetology HCPs were reluctant to switch to biosimilar insulin for cost reasons, stating that both the burden of monitoring and the cost savings would impact GP practices where the majority of insulin prescribing would occur post-discharge and hence the switch should occur in that setting. All HCPs who were comfortable with switching agreed that patients should be given the option. The majority of HCPs expressed a negative attitude towards automatic substitution of biosimilars at the pharmacy level. 50% of gastroenterology and rheumatology HCPs stated that any cost savings associated with biosimilar uptake should be shared between the clinical department and the commissioning group and that a 'gain share' approach would expand services and provide patient benefit. HCPs who worked in departments with no 'gain share' expressed a concern that biosimilar uptake increased workload and had a negative impact on the department. With regards to evidence base, gastroenterology HCPs expressed the greatest degree of confidence and fewer concerns regarding biosimilar usage. An initial concern was reported regarding indication extrapolation, but has now been addressed. A view was expressed that adalimumab uptake would be easier than infliximab due to the experience gained with infliximab. The rheumatology HCPs however expressed continued concern with indication extrapolation and were openly distrustful of biosimilars in comparison with the other specialties interviewed. Facilitators of biosimilar prescribing identified included NICE guidance, experience from other health care trusts and determining who benefits from any associated cost savings. Barriers identified included the development of an unexpected adverse event, strong negative opinions from patients and non-user-friendly administration devices. This was of particular importance to rheumatology HCPs who used the example of switching patients from reference etanercept (Enbrel) to the biosimilar Benepali where a difference in preservative ingredient has caused concern. It was also stated that many patients actually find the Benepali device easier to administer. The authors concluded that "*UK HCPs had a good understanding of biosimilars with subtle differences between specialties in their attitudes to using biosimilars*".

REVIEWER COMMENTARY: Much of the qualitative data is grouped by clinical specialty and it is unclear which profession's viewpoint is predominating within the specialty. The small sample size in this study limits data extrapolation and has questionable generalisability.

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PATIENTS

Ghil et al: Usability and safety of SB5 (an adalimumab biosimilar) prefilled syringe and autoinjector in patients with rheumatoid arthritis [29]

SPONSOR: Samsung Bioepis co Ltd

LOCATION(S): Poland

DESIGN: Phase II open-label single arm study. Participants self-injected with SB5 prefilled syringe at weeks 0 and 2, then were crossed over to the SB5 auto-injector and self-administered at weeks 4, 6, 8 and 10

DATES: August 2015 – March 2016

OBJECTIVE(S): Demonstrate comparability between administration of the adalimumab biosimilar, SB5, via prefilled syringe and autoinjector pen based on injection site pain, patient preference, and safety in rheumatoid arthritis

PARTICIPANTS: 48 adult patients with rheumatoid arthritis, considered to be candidates for self-administration of adalimumab, but were biologic and self-injection naïve.

RESULTS: No significant difference was reported in injection site pain scores at weeks 2 (pre-filled syringe) and 6 (auto-injector). Overall preference at week 6 for the auto-injector was 56.5%, 30.4% for the pre-filled syringe and 13% stated no preference. 22% of participants reported TEAEs after the first administration with the pre-filled syringe, compared with 12.2% after the first administration with the auto-injector.

REVIEWER COMMENTARY: The authors of study are employees of Samsung Bioepis. The single arm design of this study confounds comparison of device administration as the patients are being newly initiated on adalimumab, local tolerability of drug is likely to change during the course of the study. A cross-over study design should be employed to address any potential confounding factors and minimise risk of bias.

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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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