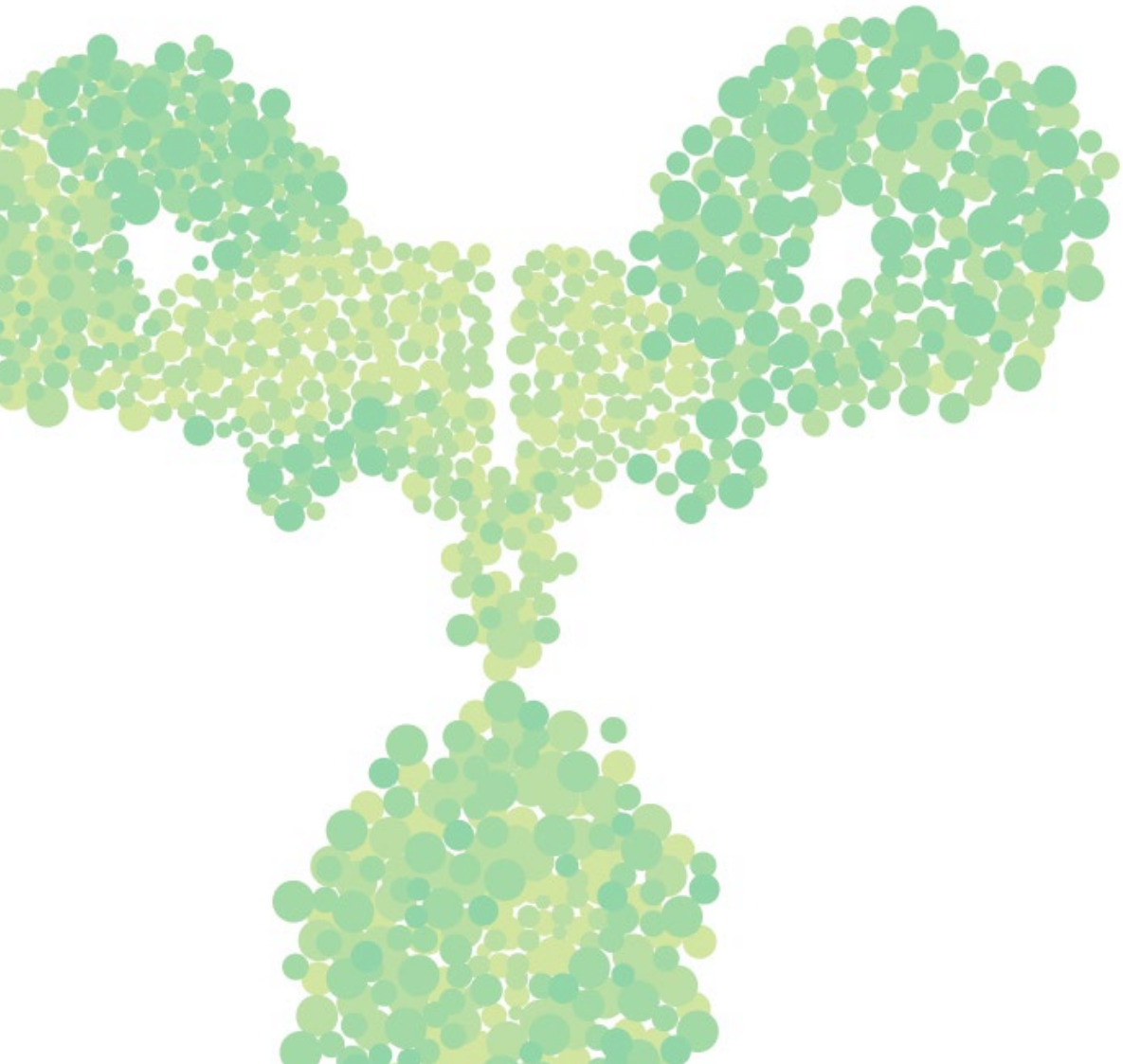
GBMA EDUCATION

UniSA Clinical & Health Sciences

International Biosimilar Medicines

Catalogue and Summary of Published Literature: Quarterly Update

July – September 2020



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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 catalogue and summary of the published literature examine all international and Australian clinical, academic and policy journals in relation to biosimilar medicines.

The catalogue and summary updates 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 catalogue and summary 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

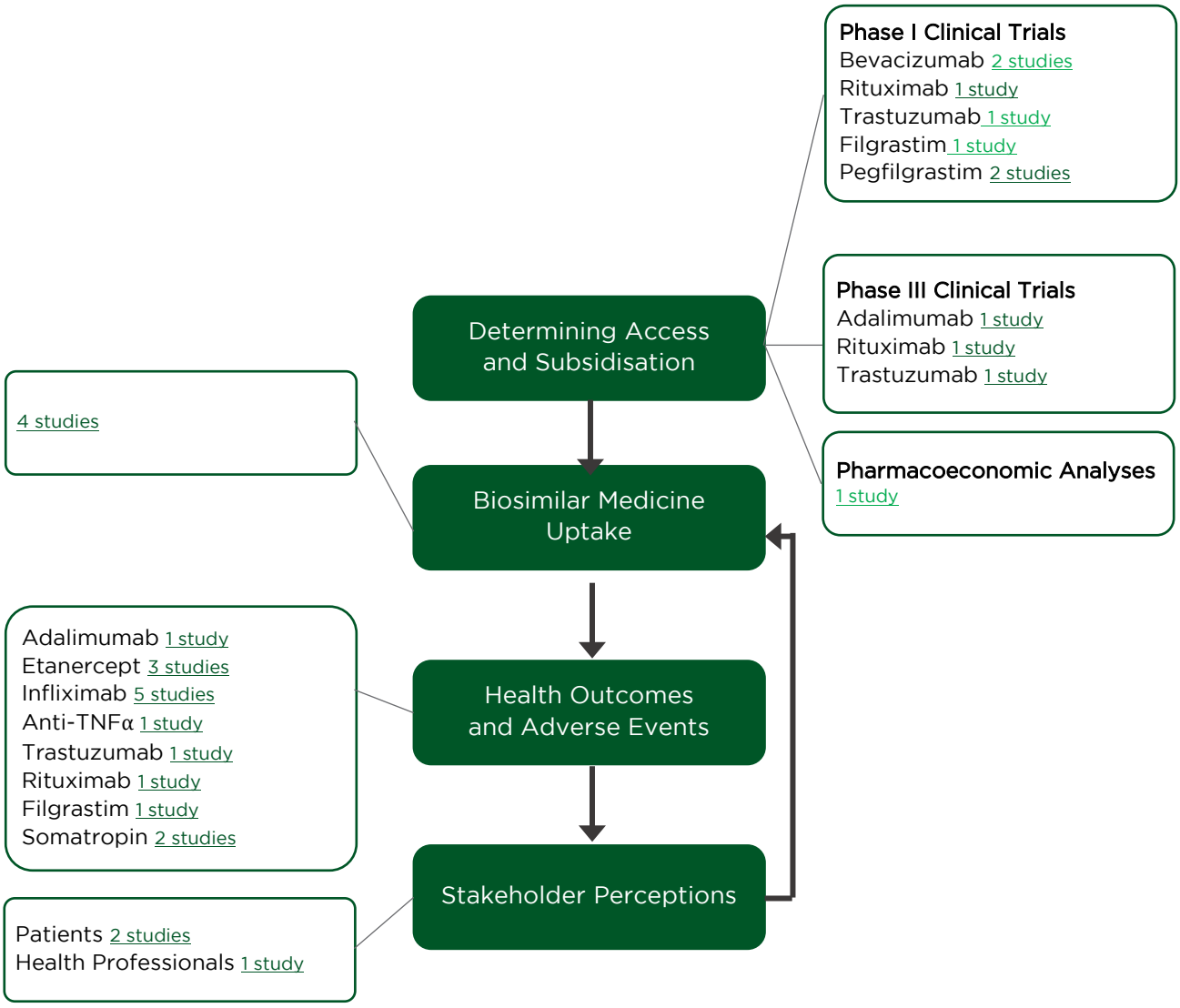
This theme encompasses the literature pertaining to evaluating and improving the awareness, confidence, attitudes and acceptance of biosimilar medicines by stakeholders, including literature that describes or evaluates any existing programs that aim to increase stakeholder understanding and confidence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

Please be advised that the reviewers have not graded the level of evidence for each study. The purpose of this report is to present information in a manner that facilitates the reader to make their own assessment of the literature. Reviewer commentary is only provided where it is considered that doing so may assist the reader in making this assessment

OVERVIEW OF THE LITERATURE

This report includes literature published between 01 July 2020 and 30 September 2020.

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



Manuscripts provided for reference but not summarised

Appendix 1: Educational/Review Articles
39 manuscripts

Appendix 2: Technical
16 manuscripts

DETERMINING ACCESS AND SUBSIDISATION

Phase I Clinical Trials

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

During the current update period, there were seven 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. An additional paper reported on an extension of a previous study.

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
BEVACIZUMAB						
SB8	Avastin-US and Avastin-EU	Randomised, double-blind, three-way, parallel, single-dose study	Healthy adult males (n=114, randomised 1:1:1)	90%CIs 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 SB8 & Avastin-US, SB8 & Avastin-EU and Avastin-US & Avastin-EU	The incidence of post-dose ADAs were similar between the treatment groups (SB8: 1/39 participants, Avastin-US: 1/38 participants, Avastin-EU: 4/39 participants). None of the participants has a positive result for neutralising ADAs.	Shin et al[1]

INTP24	Avastin-US and Avastin-EU	Randomised, double-blind, three-way, parallel, single-dose study	Healthy adult males (n=117, randomised 1:1:1)	90%CIs of the ratio of geometric least square means for $AUC_{0\text{-}inf}$ and C_{max} were within the pre-defined equivalence interval of 80-125% for the comparisons of INTP24 & Avastin-US, INTP24 & Avastin-EU	Anti-drug antibodies were detected in 3 (7.69%) participants in the INTP24 group, 4 (10.26%) in EU-bevacizumab, and 2 (5.13%) in US-bevacizumab.	Singh et al[2]

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Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
RITUXIMAB						
ABP 798	Rituxan(US) Mabthera (EU)	randomized, double-blind, active-controlled	Participants with rheumatoid arthritis 311 (randomized ABP 798, n = 104; rituximab EU, n = 104; rituximab US, n = 103)	90%CIs of the ratio of geometric least square means for $AUC_{0\text{-}inf}$ and C_{max} (following second infusion of first dose) were within the pre-defined equivalence interval of 80-125% for the comparison of ABP 798 & rituximab US and the comparison of ABP 798 & rituximab EU. The percentage of participants with complete CD19+ B-cell depletion from day 1 to day 3 was; ABP 798 = 92/97 (94.8%), rituximab EU = 93 /96 (96.9%) and rituximab US = 90/97 (92.8%)	Number of participants developing binding ADAs: ABP 798 = 13 (13.4%), rituximab EU = 10 (10.6%), rituximab US = 19 (19.6%) Number of participants developing neutralising ADAs: ABP 798 = 8 (8.2%), rituximab EU = 2 (2.1%), rituximab US = 8 (8.2%)	Burmester et al[3]

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Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
TRASTUZUMAB						
SIBP-01	Herceptin	Randomised, double-blind, two-way, parallel, single-dose study	Healthy adult males (n=100, randomised 1:1)	90%CIs 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 SIBP-01 & Herceptin	One participant in the SIBP-01 treatment group returned a positive ADA result on Day 35 (negative for neutralising ADAs). No participants in the Herceptin group returned a positive ADA result during the study.	Zhou et al[4]

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Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
FILGRASTIM						
Tinagrast	Neupogen (EU)	open-label, randomised, crossover, 2-sequence, and 2-period study	Healthy male adults (n=23, randomised 1:1:1)	90%CIs of the ratio of geometric least square means for PK (AUC_{0-inf} AUC_{0-12h}, C_{max}) and PD (maximum observed absolute neutrophil count effect, area under the effect on the absolute neutrophil count–time curve $AUEC_{0-96h}$) parameters were within the pre-defined equivalence interval of 80-125% for the comparisons of Tinagrast and Neupogen.		Khandoozi[5]

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Biosimilar Candidate	Reference Product	Study Design	Study Population	PK Outcomes (and PD where reported)	Immunogenicity Outcomes	Reference
PEGFILGRASTIM						
Pegfilgrastim-cbqv	Neulasta	Randomised, single-blind, three-way, crossover, reference-replicated, single-dose study	Healthy adults (n=122, randomised 1:1:1)	90%CIs of the ratio of geometric least square means for PK (AUC_{inf}, C_{max}) and PD (ANC $AUC_{0\text{-}last}$, ANC C_{max}) parameters were within the pre-defined equivalence interval of 80-125% for the comparisons of pegfilgratim-cbqv and Neulasta.	Similar percentages of subjects in each treatment group developed treatment-emergent ADAs after the first dose (period 1): 28.6% pegfilgrastim-cbqv and 33.3% Neulasta. No new participants developed ADAs after switching treatment in Periods 2 or 3. No treatment-emergent neutralising ADAs were detected.	Finck et al[6]
MSB11455	Neulasta	2-way, 2-sequence, group-sequential, crossover study	Healthy adults (n=292 subjects randomized, n=244 received both treatments)	90%CIs of the ratio of geometric least square means for PK (AUC_{last} AUC_{inf}, C_{max}) and PD (maximum observed effect on ANC) parameters were within the pre-defined equivalence interval of 80-125% for the comparisons of MSB11455 and Neulasta	ADAs were detected in 31 participants (21.2%) in the MSB11455/reference product sequence and 24 participants (16.4%) in the reference product/ MSB11455 treatment sequence at any time postdose. ADAs were mostly directed against the PEG portion and no filgrastim-specific neutralizing ADA were detected with either treatment sequence	Lickliter et al[7]

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RITUXIMAB

Smolen et al: Efficacy and safety of Sandoz biosimilar rituximab for active rheumatoid arthritis: 52-week results from the randomized controlled ASSIST-RA trial[8]

SPONSOR: Hexal AG and Sandoz

REFERENCE PRODUCT: Rituxan® (US)

OBJECTIVE(S): To descriptively compare the extent of B cell depletion and recovery, efficacy, safety and immunogenicity of the rituximab biosimilar (GP2013, Rixathon®) with reference rituximab (Ref-RTX) up to 52 weeks, extending upon the previous analysis of the primary endpoint at week 24*, and including the administration of a second dose of rituximab at the investigator's discretion.

DESIGN: 2 period randomised double blind study

SAMPLE SIZE: 290 of an initial 312 participants completed week 24 of the first period of the study and continued into the second period,GP2013 = 123, reference product = 167; 261 (83.3%) participants completed the second period; 218 participants received a second dose of rituximab, GP2013 = 91, reference product = 127

PATIENT CHARACTERISTICS:

RESULTS: The median time to administration of a second dose of rituximab was 197 days since the study start in both the GP2013 group and the reference product group. Amongst patients who received a second dose of rituximab, B cell levels remained low to week 52, with a similar extent of depletion observed in the GP2013 group as compared with the reference product group. Within this participant group significant interpatient variability in B cell levels is noted between weeks 24 and 38 due to interpatient variability in B cell recovery and the variability in the timing of the administration of the second dose which was at the discretion of the investigator but this was reduced by week 52 after all patients in this group had received a second dose. Amongst those who did not receive a second dose, B cell levels began to recover from week 12 through to week 52 with marked inter-patient variability observed in both the reference product group and the GP2013 group. At week 52, the mean DAS28 score was 3.3 in both the biosimilar rituximab group and the reference product group. Disease activity remained well controlled between weeks 24 and week 52 in both treatment groups. Infusion related reactions occurred in 6 participants who received a second dose of biosimilar rituximab as compared with 11 participants who received a second dose of reference product (5.0%). There was no increase in the proportion of participants with antidrug antibodies in either group between weeks 24 and 52.

* Smolen JS, Cohen SB, Tony HP et al. A randomised, double-blind trial to demonstrate bioequivalence of GP2013 and reference rituximab combined with methotrexate in patients with active rheumatoid arthritis. Ann Rheum Dis 2017; 76: 1598-602.

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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 three reports of phase III trials of potential biosimilars.

ADALIMUMAB

Alten et al: Immunogenicity of an adalimumab biosimilar, FKB327, and its reference product in patients with rheumatoid arthritis[9]

SPONSOR: Fujifilm Kyowa Kirin Biologics Co. Ltd.

REFERENCE PRODUCT: Humira® (US)

OBJECTIVE(S): To compare the long-term immunogenicity and safety in patients with rheumatoid arthritis of biosimilar adalimumab (FKB327) with the reference product adalimumab including patients who single- and double-switching between FKB327 and reference product, extending the previous 54 week report* to 104 weeks.

DESIGN: Open-label extension to a double blind phase III study. From week 54 all participants received open label FKB327 such that in the third period of the study there are four treatment groups; participants that received only FKB327 in all 3 study periods (F-F-F, no switch), participants that switched to FKB327 at week 54 having received reference product in period 1 and period 2 (RP-RP-F, single switch), participants that continued FKB327 in period 3 having switched from reference product at the end of period 1 (RP-F-F, single switch) and participants who have switched back to FBK327 from reference product having previously switched to reference product in period 2 from FKB327 in period 1 (F-RP-F, multiple switch).

SAMPLE SIZE: F-F-F (no switch) = 189, RP-RP-F (single switch) = 190, RP-F-F (single switch) = 93, F-RP-F = 100 (double switch)

PATIENT CHARACTERISTICS: Patients had to complete all 24 weeks of procedures in Period 1, with a minimum of 9 study drug doses received and a clinical response to treatment as determined by investigator opinion.

RESULTS: At the end of period 3, the proportion of participants who were anti-drug antibody (ADA) positive was 51.1% in the F-F-F (no switch) participants as compared with 48.1% in the RP-F-F (single switch) participants, 42.5% in the RP-RP-F (single switch) participants and 54.4%, F-RP-F (double switch) participants. During Period 3, no increases were reported for positive ADA status, ADA titer, or positive neutralizing ADA status through week 76 in any treatment sequence. As compared with the baseline of the open label extension periods, the proportion of ADA positive participants was significantly decreased at week 76 for patients in the F-F-F (P = .0039), RP-F-F (P = .0018) and RP-RP-F (P = .0002) groups. During period 3 treatment emergent adverse events occurred in 60.3% of participants in the F-F-F group as compared with 54.8% in the RP-F-F group, 60.0% in the RP-RP-F group, and 61% in the F-RP-F group. Adverse events resulted in treatment discontinuation during period 3 in 2.1% of participants in the F-F-F group as compared with 6.5% in the RP-F-F group, 5.3% in the RP-RP-F group and 5.0% in the F-RP-F group.

REVIEWER COMMENTARY: As noted by the authors, in this extension study it is possible that ADA-positive patients might drop out of the study, particularly as ADA-positivity may be associated with reduced efficacy, and this would serve to decrease the prevalence of ADA-positivity amongst those who continued to participate. However, it is reported that amongst those who dropped out of the study, 56.69% were ADA-positive which is similar to the rates observed in those who remained in the study.

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* Genovese MC, Glover J, Greenwald M et al. FKB327, an adalimumab biosimilar, versus the reference product: results of a randomized, Phase III, double-blind study, and its open-label extension. Arthritis Res Ther 2019; 21: 281.

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RITUXIMAB

Burmester et al: Efficacy and safety results from a randomized double-blind study comparing proposed biosimilar ABP 798 with rituximab reference product in subjects with moderate-to-severe rheumatoid arthritis[10]

SPONSOR: Amgen Inc

REFERENCE PRODUCT: Rituxan®(US), MabThera® (EU)

OBJECTIVE(S): To compare the clinical efficacy, safety, and immunogenicity of biosimilar rituximab (ABP 798) with reference product rituximab in participants with moderate to severe rheumatoid arthritis with an inadequate response or intolerance to other disease-modifying antirheumatic drugs including one or more tumour necrosis factor inhibitors, including switching from reference product to biosimilar.

DESIGN: Randomized, double-blind, active-controlled, 2 period study; in period 1 participants were randomised (1:1:1) to receive the first dose of either ABP 798, rituximab US, or rituximab EU; in period 2 participants in the ABP798 and rituximab EU received a second course of the same product whilst the rituximab US group switched to ABP 798.

SAMPLE SIZE: 301 participants randomised, ABP 798 = 104, rituximab EU = 104, rituximab US = 103; 289 participants completed period 2, continued ABP 798 = 97, continued rituximab EU = 99, switched from rituximab US to ABP 798 = 93; 55 participants (17.7%) received the first infusion of their second course between weeks 16 and 24, continued ABP798 = 21, continued rituximab EU = 22, switched from rituximab US to ABP 798 n = 12; proportion receiving concomitant oral corticosteroid = 55.8% (ABP 798) vs 50.0% (rituximab EU) vs 49.5% rituximab (US)

PATIENT CHARACTERISTICS: Mean age (years) = 54.6 (ABP 798) vs 56.8 (rituximab EU) vs 56.4 rituximab (US); mean duration of rheumatoid arthritis (years) = 11.37 (ABP 798) vs 11.69 (rituximab EU) vs 12.48 rituximab (US); mean DAS28-CRP at baseline = 6.09 (ABP 798) vs 5.84 (rituximab EU) vs 6.03 rituximab (US); mean baseline methotrexate dose (mg/week) = 15.8 (ABP 798) vs 16.6 (rituximab EU) vs 16.8 rituximab (US); number of participants with antidrug antibodies detected at baseline = 7 (ABP 798) vs 10 (rituximab EU) vs 6 rituximab (US)

EQUIVALENCE CRITERIA: Containment of the 2-sided 90% confidence interval for the difference in the mean change in DAS28-CRP at week 24 from baseline between ABP 798 and the reference product rituximab (pooled EU and US) within the range of −0.6 to 0.6 in the full analysis set (including all subjects randomised in the study)

RESULTS: At week 24 the mean decrease from baseline in DAS-CRP was −2.197 in the ABP 798 group as compared with −2.125 for rituximab reference group (pooled EU and US) with 90% confidence interval of −0.225 to 0.264 which was within the prespecified range of −0.6 to 0.6. Within the per protocol set the mean decrease from baseline in DAS-CRP was −2.207 in the ABP 798 group as compared with −2.123 for rituximab reference group (pooled EU and US) with 90% confidence interval of −0.242 to 0.255.

In the first treatment period infusion reactions occurred in 11.5% of participants in the ABP 798 group as compared with 6.7% in the rituximab EU group and 11.7% in the rituximab US group. At the end of study period 2 infusion reactions occurred in 15.4% of participants in the ABP 798 group as compared with 8.7% in the rituximab EU group and 15.5% in the group that switched from rituximab US to ABP 798. Grade ≥ 3 adverse reactions occurred in 4 participants in the ABP 798 group in period one as compared with 6 participants in the rituximab EU group and 4 participants in the rituximab US group. In study period 2 grade ≥ 3 adverse reactions occurred in 5 participants in the group that continued ABP 798 as compared with 9 participants in the group that continued rituximab EU and 9 participants in the group that switched from rituximab US to ABP 798.

From day one through to the end of study, anti-drug antibodies were detected in 14 (14.4%) participants in the group that continued ABP 798 as compared with 13 (13.8%) participants in the group that continued rituximab EU and 20 (20.6%) participants in the group what switched from

rituximab US to ABP 798 group. Anti-drug antibodies were transient in 8 (8.2%) participants in the group that continued ABP 798 as compared with 8 (8.5%) participants in the group that continued rituximab EU and 11 (11.3%) participants in the group what switched from rituximab US to ABP 798 group.

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TRASTUZUMAB

Alexeev et al: Randomized double-blind clinical trial comparing safety and efficacy of the biosimilar BCD-022 with reference trastuzumab[11]

SPONSOR: JSC BIOCAD

REFERENCE PRODUCT: Herceptin®

OBJECTIVE(S): To evaluate efficacy, safety and pharmacokinetics of a proposed biosimilar of trastuzumab (BCD-022) compared with reference trastuzumab when used in combinations with paclitaxel in the treatment of inoperable or metastatic HER2(+) breast cancer.

DESIGN: Multicentre, randomised, double blind

SAMPLE SIZE: 223 participants, BCD-022 = 113 participants, reference trastuzumab = 110 participants.

PATIENT CHARACTERISTICS: Female patients aged 18–75 with metastatic breast cancer, Grade 3+ HER2 overexpression confirmed by immunohistochemical (IHC) staining or grade 2+ HER2 overexpression accompanied by HER2 gene amplification confirmed by fluorescent hybridization in-situ (FISH); no statistically significant differences between groups with regards to estrogen and progesterone receptor status or prior therapy for breast cancer

EQUIVALENCE CRITERIA: Containment of the 95%CI for the difference in overall response rate (cumulative rate of complete and partial responses) between the originator trastuzumab group and the BCD-022 group within -20% to +20%

RESULTS: The overall response rate was 49.6% (95%CI: 40.08 to 59.07) in the BCD-022 group as compared with 43.6% (95%CI: 34.31 to 53.41) in the reference product group, equating to a difference of 6% with a 95%CI of – 8.05 to 19.89% which was within the pre-defined equivalence criteria of -20% to +20%. A complete response occurred in 4 participants in the BCD-022 group as compared with two in the reference product group whilst partial responses occurred in 52 and 46 participants, respectively. Grade 3-5 adverse events occurred in 94 participants in the BCD-022 group as compared with 95 participants in the reference product group. There were no statistically significant differences in the pharmacokinetic parameters $AUC_{(0\text{-}504)}$ and Cmax between the BCD-022 group and the reference product group at cycle 1 or cycle 6 with the 90%CI of ratio between groups for both values at both time points being within range of 80-125%.Neutralising anti-drug antibodies were detected in three participants in the BCD-022 group and in four participants in the reference product group.

REVIEWER COMMENTARY: It is stated that there were no significant differences in the occurrence of binding or neutralising anti-drug antibodies but only overall neutralising anti-drug antibody number are presented despite assessment at multiple time points and characterisation as binding or neutralising. A single participant was included in the BCD-022 group despite being listed as having “no data” for HER-2 expression. The basis for including this participant is unclear.

Note: BCD-022 was registered in Russia as Herticad® in 2015. The phase III clinical trial results for this product presented here are to be interpreted in the context of a proposed biosimilar medicine that would be subject to regulatory evaluation in accordance with published regulatory guidelines.

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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, one publication was identified that examined the economic impact of the introduction of biosimilars

Crosby et al: Potential cost implications of mandatory non-medical switching policies for biologics for rheumatic conditions and inflammatory bowel disease in Canada[12]

SPONSOR: Ontario Ministry of Health

LOCATION(S): Canada

DATES: June 2015 – December 2019

OBJECTIVE(S): To characterise biosimilar uptake of infliximab, etanercept and adalimumab and estimate the cost implications of mandatory non-medical switching across Canada.

DESIGN: The study examined biosimilar use of infliximab and etanercept, relative to use of originator, within provincial regions of Canada between June 2015 to December 2019. Based on 2019 data, costs savings were then estimated if mandatory non-medical switching policies were introduced in all provinces across Canada. Additional analysis also examined the potential impact of the introduction of an adalimumab biosimilar at 50% and 75% of the cost of the originator.

RESULTS: Despite a rise in biosimilar dispensing through public payers from June 2015 to December 2019, they represented only 15.5% of units of infliximab and etanercept dispensed nationally in 2019. However, biosimilar uptake in 2019 varied considerably by province (4.3% to 36.1%). In British Columbia where a mandatory non-medical switch policy was introduced for patients with rheumatic conditions in May 2019, the market share of biosimilars increased from 15.9% to 94.2% for etanercept, and 24.3% to 57.1% for infliximab between May to December 2019.

It was estimated that $239.61 million (24.2%) of cost savings would be realized if mandatory non-medical switching policies were introduced in all provinces across Canada in 2019; however this differed by province, ranging from $1.07 million (25.7%; Prince Edward Island) to $66.41 million (25.9%; Ontario).

The introduction of a mandatory non-medical switch policy in all provinces in Canada with the availability of an adalimumab biosimilar was predicted to result in national savings of $425.64 million (42.9%) at 50% of the innovator cost, and $332.61 million (33.5%) at 75% of the innovator cost.

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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 four papers were published examining this theme.

Agirrezabal et al: Real-World Budget Impact of the Adoption of Insulin Glargine Biosimilars in Primary Care in England (2015-2018)[13]

SPONSOR: none

LOCATION(S): England

DESIGN: Analysis of publicly available GP practice level prescribing data

DATES: August 2010 until December 2018

OBJECTIVE(S): To describe the adoption rates of insulin glargine biosimilars in primary care across Clinical Commissioning Groups (CCGs) in England and to estimate the savings realized and missed, since an insulin glargine biosimilar was first used.

RESULTS: By December 2018 biosimilar insulin glargine (Abasaglar) had attained an 8% market share with the highest rate of biosimilar adoption across the CCGs being 53.3% (NHS Swindon CCG) and 51.4% (NHS Kernow CCG) whilst the lowest was 0% (nine CCGs) with no clear geographical pattern identified in regards to adoption rates. The total savings attributed to biosimilar insulin glargine uptake between October 2015 and December 2018 was calculated to be £900,000 with total possible missed savings in England estimated at £25.6 million over that period.

REVIEWER COMMENTARY: When one of the CCGs amongst those with the highest adoption rates was contacted for additional information their response indicated that "… *NHS Kernow CCG has neither incentivized an increase in the use of biosimilars in Cornwall nor, more specifically, has it incentivized the uptake of biosimilar insulin glargine*" and as such the basis for the high adoption rate observed in this region relative to other regions is unclear.

Lee et al: Comparison of Utilization Trends between Biosimilars and Generics: Lessons from the Nationwide Claims Data in South Korea[14]

SPONSOR: Korea National Research Foundation

LOCATION(S): South Korea

DESIGN: Retrospective analysis of National Health Insurance Service claims data to assess total spending, utilization and unit price of second generation biosimilars infliximab, rituximab and trastuzumab. The data captured all usage in Korea during the study period.

DATES: January 2012 – December 2018

OBJECTIVE(S): Analysis of market penetration and associated cost saving of biosimilars in Korea

RESULTS: The introduction of biosimilar medicines resulted in reduction in originator price (cost per DDD) for infliximab (30.1%), rituximab (20.8%) and trastuzumab (21.2%) within 2 years of entry to the national formulary. Biosimilar market penetration (DDD utilization) was approximately 30% for biosimilar infliximab within 48 months of formulary entry, and 20% for both biosimilar rituximab and trastuzumab within 12 months of formulary entry. The authors compared this with first-generation biosimilars epoetin, filgrastim, and somatropin which achieved approximately 10% market penetration in Europe within 1 year of market entry. Simulated pricing models where biosimilars were not introduced and originator prices remained at pre-biosimilar unit prices, or where they were introduced but had no effect on originator price were conducted. The discrepancy between real and simulated total biologic spending was analysed. These simulations suggested that, over the 6 years since its market entry, biosimilar infliximab has resulted in savings of between US $82–114 million. The simulation estimated that the savings from the introduction of biosimilar rituximab and trastuzumab was between US $9 and US $14 million over 2 years for each biosimilar.

Al Tabaa et al: Doctor's aptitude for switching from innovator etanercept to biosimilar etanercept in inflammatory rheumatic diseases: experience from a single French rheumatology tertiary care center[15]

SPONSOR: Theradiag (for anti-drug antibodies assessment component only)

LOCATION(S): Single centre, France

DESIGN: Retrospective review of electronic medical records

DATES: Switching between October 2016 and April 2017

OBJECTIVE(S): To determine the proportion of eligible patients with rheumatoid arthritis and ankylosing spondylitis who switched from originator etanercept to biosimilar etanercept and to identify the patient and physician factors associated with switching.

Note: This section describes the factors associated with biosimilar uptake. The subsequent outcomes associated with switching are described within the section 'Health Outcomes and Adverse Events'.

RESULTS: A total of 304 patients were identified as being treated with originator etanercept. Of these, 121 patients were not eligible to switch (active disease, <6months treatment with originator, planned pregnancy etc) and 183 were candidates for switching. Of the 183 patients who were candidates for switching 94 patients were switched, equating to a switch rate amongst eligible patients of 51.6%. The mean disease duration in the switching group was 16.8 years as compared with 14.8 years in the group that did not switch (p=0.86). At baseline there was no statistically significant difference in the proportion of patients in remission (74.7% switching group vs 63.9% did not switch, p=0.34) or the mean value for the normalised disease activity score (1.8 in each group, p=0.86) but the patient-reported global activity was lower (better) in the group that did not switch (19.1) than in the group that switched (25.2) (p=0.02) and NSAID use was more common in the switching group (28.3% vs 12.3%, p<0.05). Amongst those who switched, 56.4% were treated by a physician with a full-time academic position as compared with 13.5% of patients that did not switch (p < 0.001) and the number of years of experience since completing their medical degree was higher in the switching group (21 years) than in the group that did not (15 years) (p < 0.01). None of the patient or physician factors were associated with switching on multivariate analysis.

REVIEWER COMMENTARY: The authors suggest that "…. *this study showed that the factors associated with this switch were likely related to physician and not patient characteristics", that "… physician characteristics might strongly depend on a local "school effect.""* and that as a result *"… the information/ education for the physicians should be more accurate and probably done on an individual level."* but that *"…. other studies aiming to evaluate the impact of educational programs for both the patient and the physician, on the switch from the reference product to its biosimilar, are necessary."*

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Kim et al: Uptake of Biosimilar Infliximab in the UK, France, Japan, and Korea: Budget Savings or Market Expansion Across Countries?[16]

SPONSOR: Not stated

LOCATION(S): UK, France, Japan, and Korea

DESIGN: MIDAS-IQVIA International database

DATES: October 2012 to March 2018 (22 quarters)

OBJECTIVE(S): To compare the market dynamics of biosimilar infliximab between UK, France, Japan, and Korea.

RESULTS: The infliximab market size remained relatively stable in the UK, France and Japan but increased 2.5 times in Korea. The market size for originator increased 1.7 times in Korea but decreased approximately 80% in the UK, 40% in France and 20% in Japan which was accompanied by substantial increases in the biosimilar product in the UK and France. By quarter one 2018 the market share for biosimilar infliximab was 89% in the UK, 48% in France, 35% in but only 6%. Japan had the lowest ex-factory price ratio for biosimilar relative to originator at 68% and remained consistent over the study period as compared with 99% in France and 95% in Korea which also remained consistent. In the UK the price ratio decreased from 87% at the start of the study period to 80% over the duration of the study.

REVIEWER COMMENTARY: The authors provide a summary of the regulatory and policy landscape in each of the four countries. The authors note that the results presented may be significantly impacted by confidential contract arrangements.

HEALTH OUTCOMES AND ADVERSE EVENTS

Within the period encompassed by this update, there have been 14 papers that have examined pharmacovigilance of biosimilar medicines, specifically the impact of substitution, switching and extrapolation of indication.

ADALIMUMAB

Nielsen et al: Effectiveness and safety of switching from originator to biosimilar adalimumab in patients with psoriasis[17]

SPONSOR: None

LOCATION(S): Single-centre, Denmark

DESIGN: Questionnaire and DERMBIO registry case note review

DATES: Patients switched from originator adalimumab to biosimilar adalimumab (Hyrimoz®) between November 1st 2018 and January 21st 2019

OBJECTIVE(S): To describe the outcomes associated with switching from originator adalimumab to biosimilar adalimumab in patients with psoriasis.

PATIENT CHARACTERISTICS: mean age = 53 years, average duration or originator adalimumab prior to switching = 6.3 years

OUTCOME(S): change in Psoriasis Area and Severity Index (PASI), change in Dermatology Life Quality Index (DLQI)

RESULTS: Three months post-switching there was no statistically significant change in mean PASI (Δ=0.21 points; CI: -0.32 to 0.76, p=0.42) or mean DLQI (Δ=1.09 points, CI: -0.46 to 2.63, p=0.16). A total of 27 patients reported experiencing the same or better effect from the biosimilar whilst 12 patients reported a worse effect with patients who reported a worse subjective effect scoring, on average, 0.92 points (CI 0.44-1.40,p=0.001) higher in the DLQI questionnaire compared with those who reported the same or better effect. Following switching, adverse events were reported in 17 patients (39.5%) as compared with 0 prior to switching with pruritus, flares and headache being most common.

REVIEWER COMMENTARY: The frequency of specific adverse events, particularly with respect to the proportion that are subjective in nature, is not reported. The authors note that "….*quality of life after switching deteriorates if a patient has a subjective feeling of worse effect even if PASI score remains unchanged*" reflecting the potential influence of these subjective events.

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ETANERCEPT

Ditto et al: Efficacy and safety of a single switch from etanercept originator to etanercept biosimilar in a cohort of inflammatory arthritis[18]

SPONSOR: None

LOCATION(S): Single-centre, Italy

DESIGN: Not clearly stated

DATES: Not clearly stated

OBJECTIVE(S): To describe the effect of switching from originator etanercept (Enbrel®) to biosimilar etanercept (SB4, Benepali®) in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS).

PATIENT CHARACTERISTICS: 107 patients identified, 16 patients ineligible to switch due to off-label use or age, four patients declined to switch, 87 patients switched to biosimilar, RA = 48, PsA = 26, AS = 13; median age = 63 years; median duration of treatment with originator etanercept = 7 years (RA) vs & years (PsA) vs 6 years (AS); proportion taking concomitant conventional synthetic DMARD = 72.9% (RA) vs 77.7% (PsA) vs 15.3% (AS)

OUTCOME(S): changes in disease activity measures (DAS28, DAPSA, BASDAI) evaluated during 12 months prior to switching and in the 12 months post-switching

RESULTS: Within each of the three disease groups there were no statistically significant changes in disease activity measures between baseline pre-switching and 6 and 12 months post switching (p = 0.205 – 0.750). Seven patients stopped treatment with biosimilar etanercept due to lack of efficacy of whom six changed to an alternative agent and one patient switched back to originator and was considered to have responded. Two patients stopped biosimilar etanercept due to subjective worsening or arthralgia, both of whom were switched back to originator and were considered to have responded. One patient with RA developed new onset psoriasis and one patient with PsA developed a cutaneous rash and were switched back to originator. Four patients did not agree to switching for "*psychological reasons*".

REVIEWER COMMENTARY: The authors report a high acceptance rate of switching from originator to biosimilar, with only four of 91 eligible patients declining to switch. This level of acceptance should be viewed in the context that it was achieved in the setting of a specific approach that was taken to switching patients such that *"At the time of the switch, every patient was informed about biosimilar properties, literature data and the possibility to return to originator if necessary"* ,that *"….we* [the authors] *properly discussed about these elements with every patient"* and that *"…. the shared decision between rheumatologists and patients was mandatory." The authors conclude that in their opinion "The physician–patient cooperation play a key role for a successful switch; therefore, it is critical to ensure that patients are informed about all the relevant information related to the switch as well as the respect for patients decisions and to make a strict follow-up to check any AE* [adverse event] *immediately".*

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Müskens et al: One-year results after transitioning from etanercept originator to biosimilar in a setting promoting shared decision-making in rheumatology[19]

SPONSOR: Non-commercial

LOCATION(S): Single-centre, Netherlands

DESIGN: Observational, historic controls

DATES: 1 June 2016 and 23 October 2017, historic controls: all patients treated with originator etanercept at 1 June 2015

OBJECTIVE(S): To compare the 1-year retention of biosimilar etanercept after open-label non-mandatory transitioning from originator etanercept in patients with stable inflammatory rheumatic disease in a setting promoting shared decision-making with that of historic controls

PATIENT CHARACTERISTICS: 79 patients identified who were eligible to switch, 70 (89%) agreed to switch; 89 patients identified as treated with originator etanercept on 1 June 2015 and included in historic control group; 56 patients were included in both the switching group and the historical cohort; median duration of treatment with etanercept = 5 years (switching group) vs 4 years (historical group); patients in each group had not received other biologics prior to etanercept

OUTCOME(S): 1-year treatment retention rate

RESULTS: The one-year retention rate switching group was 73% (95%CI: 0.62 to 0.83) as compared with the 89% (95%CI: 0.81 to 0.95) in the historical cohort (P = 0.013) equating to a higher risk of treatment discontinuation (HR = 2.56; 95% CI: 1.19, 5.49, P = 0.016) in the switching group. In the switching group, 19 patients ceased treatment with etanercept as compared with 10 patients in the historical group. However, within the switching group nine patients discontinued because of subjective health complaints, defined as worsening of disease perceived by the patient in the absence of changes in the disease activity score or in the clinical signs of arthritis according to the rheumatologist. After adjusting for the patients who discontinued for subjective reasons, the one-year retention rate in the switching group was 86% and was no longer statistically different from the 89% in the historical group (*P* = 0.51). Additionally, one patient that discontinued in the switching group did so on the basis of a suspected drug hypersensitivity reaction after switching, but this reaction also recurred after ceasing etanercept suggesting other causality.

REVIEWER COMMENTARY: The authors employed a shared decision making process in switching patients from originator to biosimilar involving "….*a standardized letter containing information on both the biosimilar and the proposed transition process to EB* [biosimilar etanercept]*"* with *"… the possibility of transitioning was discussed between the patient and the rheumatologist during the next outpatient visit" and "If the patient still had questions regarding, for instance, the transition or administration of the biosimilar, a consultation with the nurse specialist was planned to address these and any other questions".* Based upon the apparent impact of subjective discontinuation on the results the authors conclude that *"These findings imply that our method of transitioning does not seem to counter the nocebo effect sufficiently."*

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Al Tabaa et al: Doctor's aptitude for switching from innovator etanercept to biosimilar etanercept in inflammatory rheumatic diseases: experience from a single French rheumatology tertiary care center[15]

SPONSOR: Theradiag (for anti-drug antibodies assessment component only)

LOCATION(S): Single centre, France

DESIGN: Retrospective review of electronic medical records

DATES: Switching between October 2016 and April 2017

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

Note: other objectives of this study are provided within the section 'Biosimilar Medicine Uptake'.

PATIENT CHARACTERISTICS: 435 patients identified, 304 patients treated with etanercept, 183 patients eligible for switching, 94 patients switched

OUTCOME(S): 6-month retention rate post-switching

RESULTS: The 6-month retention rate post-switching was 83% (95% CI: 76 to 92). Biosimilar etanercept was discontinued in 26 (27.6%) patients, 13 discontinued on the basis of lack of efficacy and 12 discontinued due to adverse events (including injection site pain, headache, fatigue etc) but with no serious adverse events occurring. Of those who discontinued due to lack of efficacy only a single patient had objective signs of disease activity with that patient then changed to tocilizumab but with poor response before then being changed back to originator etanercept with good response. No anti-drug antibodies were detected amongst the 44 samples obtained at baseline prior to switching or in the 30 samples following 6 months of treatment with the biosimilar. The baseline normalized global disease activity was higher in patients that discontinued biosimilar etanercept (2.27 vs 1.67, $p<0.05$) and more patients who discontinued had objective signs of inflammation (7% vs 1.5%, $p<0.05$). On multivariate analysis, none of the patient or physician factors were independently associated with discontinuation of biosimilar etanercept.

REVIEWER COMMENTARY: The authors note that "*From our data, differentiating the discontinuation due to a side effect related to the drug, to a nocebo effect, or to a flare of the disease, independent of any treatment, is difficult*" but conclude that "Our study suggests that *a nocebo effect is probably the best explanation for bETN* [biosimilar etanercept] *failure*…"

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INFLIXIMAB

Jørgensen et al: Efficacy and Safety of CT-P13 in Inflammatory Bowel Disease after Switching from Originator Infliximab: Exploratory Analyses from the NOR-SWITCH Main and Extension Trials[20]

SPONSOR: Non-commercial

LOCATION(S): Nation-wide, Norway

DESIGN: Subgroup analysis of the 52-week, randomised, non-inferiority, double-blind study with a 26-week open extension (CT-P13) multicentre, phase 4 NOR-SWITCH study

DATES: Enrolment between October 2014 and July 2016

OBJECTIVE(S): To assess treatment efficacy, safety, and immunogenicity of originator and biosimilar infliximab, including switching from originator infliximab to CT-P13, in an explorative subgroup analysis of patients in the NOR-SWITCH trials with Crohn's disease (CD) and ulcerative colitis (UC).

PATIENT CHARACTERISTICS: 248 patients enrolled and randomised into the NORSWITCH main trial, CD= 155, UC = 93, switched from originator to CT-P13 = 123, continued originator = 125; 207 patients continued into the 26-week open extension study, CD = 127, UC = 80;

OUTCOME(S): Disease worsening during the 52-week main study and 26-week extension defined as a change in disease activity indices (Crohn's disease: a change from baseline of 4 points or more and a total score of 7 points or greater worsening in Harvey-Bradshaw Index, ulcerative colitis, a change from baseline of more than 3 points and a total score of 5 or greater) or a consensus on disease worsening between investigator and patient leading to major change in treatment.

RESULTS: At the conclusion of the randomised period there were no statistically significant changes in disease activity indices in either patients with Crohn's disease or ulcerative colitis. Disease worsening occurred in 36.5% (23/63) of patients with Crohn's disease in the CT-P13 group as compared with 21.2% (14/66) patients in the originator group, equating to an adjusted risk difference of −14.3% with a 95% confidence interval of −29.3 to 0.7. Amongst patients with ulcerative colitis, disease worsening occurred in 11.9% (5/42) in the CT-P13 group as compared with 9.1% (3/33) in the originator group equating to an adjusted risk difference of −2.6% with a 95% confidence interval of −15.2 to 10.0.

At conclusion of the extension study there were no statistically significant changes in disease activity indices in either patients with Crohn's disease or ulcerative colitis. Disease worsening occurred in 20.6% (13/63) of patients with Crohn's disease in the group that continued CT-P13 as compared with 13.1% (8/61) of patients in the group that switched from originator to CT-P13 in the extension period equating to an adjusted risk difference of 7.9% with a 95% confidence interval of −5.2 to 21. Disease worsening occurred for the first time during the extension period in 11 patients of whom five were in the group that switched from originator to CT-P13 six were in the group that continued CT-P13. Amongst patients with ulcerative colitis disease worsening occurred in 15.4% (6/39) of patients with Crohn's disease in the group that continued CT-P13 as compared with 2.9% (1/35) of patients in the group that switched from originator to CT-P13 in the extension period equating to an adjusted risk difference of 12.4% with a 95% confidence interval of −0.1 to 25. Disease worsening occurred for the first time during the extension period in six patients of whom one was in the group that switched from originator to CT-P13 five were in the group that continued CT-P13.

Adverse events leading to treatment discontinuation occurred in two participants with Crohn's disease treated with CT-P13 in the main study as compared with one who received originator and in two participants with ulcerative colitis treated with originator and none who received CT-P13. In the extension study a single participant with Crohn's disease in the switching group discontinued due to adverse events with no discontinuation from any other participants.

Anti-drug antibodies developed in four patients with Crohn's disease in the CT-P13 group as compared with three patients in the originator group and in eight patients with ulcerative colitis in the CT-P13 group as compared with five patients in the originator group during the randomised period. During the extension period one patient with Crohn's disease in the group that switched from originator to CT-P13 developed anti-drug antibodies with none in the group that continued CT-P13 and amongst patient with ulcerative colitis one patient in each of the continuing and switching groups developed anti-drug antibodies.

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Kim et al: Retention Rate and Efficacy of the Biosimilar CT-P13 Versus Reference Infliximab in Patients with Ankylosing Spondylitis: A Propensity Score–Matched Analysis from the Korean College of Rheumatology Biologics Registry[21]

SPONSOR: Celltrion Healthcare Co., Ltd

LOCATION(S): Korean, nationwide

DESIGN: Propensity score–matching analysis (age, sex, and baseline BASDAI score) of the Korean College of Rheumatology Biologics registry (KOBIO)

DATES: Patients who received originator or biosimilar infliximab between December 2012 and December 2017

OBJECTIVE(S): To compare the outcomes associated with the use of originator infliximab and biosimilar infliximab (CT-P13) in patients with ankylosing spondylitis who as first-line treatment or following failure of another tumor necrosis factor (TNF) inhibitor (criteria not defined).

PATIENT CHARACTERISTICS: A total of 256 patients were identified as receiving biosimilar infliximab and 143 received originator infliximab, of whom 124 biosimilar treated patients were propensity score matched with 124 originator infliximab treated patients. Ninety-eight of 124 patients (79.0%) in the biosimilar group and 81 of 124 patients (65.3%) in the originator infliximab group were treated in the first-line setting. The mean disease duration was longer in the biosimilar group than in the originator group ((3.9 years vs 2.5 years, $p = 0.01$) and mean baseline CRP was higher in the biosimilar group (2.5 vs 1.3 $p = 0.014$). A total of 26 patients received biosimilar infliximab and 43 patients received originator infliximab following prior treatment with another tumor necrosis factor (TNF) inhibitor including adalimumab, etanercept, originator infliximab or biosimilar infliximab. Amongst the 27 patients that had received an infliximab previously the reason for receiving the same or alternate product in this study period was *"unknown"* with one patient receiving biosimilar infliximab as a result of a lack of efficacy of originator infliximab. Amongst the patients who had had prior TNF inhibitor therapy the mean disease duration was shorter in the biosimilar infliximab group as compared with the originator group (5.4years vs 7.6yrs, $p = 0.005$), and the mean ASDAS-CRP score and (3.5 vs 2.9, $p< 0.001$) as were CRP levels (2.5 vs 1.3, $p = 0.004$) were higher in the biosimilar group.

OUTCOME(S): retention rates up to 4 years, major improvement in disease control (defined as improvement of at least 2 points between two consecutive Ankylosing Spondylitis Disease Activity Score [ASDAS] scores)

RESULTS: The retention rate overall was 64.2% (95%CI:53.5 to73.0) in the biosimilar group as compared with 55.6% (95%CI: 42.9 to 66.6) in the originator infliximab group ($p = 0.41$). Among patients receiving first-line therapy, the retention rate was 66.3% (95%CI: 54.3 to 75.8) in the biosimilar group as compared with 50.6% (95%CI: 34.7 to 64.6) originator group ($p = 0.15$). Amongst the group with prior TNF inhibitor treatment the retention rate was 55.6% (95%CI: 30.4 to 74.9) as compared with 64.6% (95%CI: 41.7 to 80.4) ($p = 0.45$). Within the biosimilar group 13 (of 105 evaluable patients) changed treatment due to lack of efficacy as compared with 9 (of 92 evaluable patients) in the originator group whilst eight changed treatment due to adverse events in the biosimilar group as compared with 5 in the originator group. Two patients changed from biosimilar infliximab to originator and three patients changed from originator infliximab to biosimilar due to adverse events of lack of efficacy.

There were no statistically significant differences in the proportion of patients achieving a major improvement in ASDAS scores (≥ 2-point) from baseline between the biosimilar group and originator group. Median CRP levels were statistically lower in the originator infliximab group compared with the biosimilar infliximab group CT-P13 group at 2 (0.09 vs 0.23, p = 0.02), 3 (0.08 vs 0.19, p=0.04), and 4 years (0.12 vs 0.5, p = 0.04, 6 versus 4 patients) were low and not clinically different.

A total of 60 adverse events considered to be drug related occurred in 23 patients (18.5%) in the biosimilar group as compared with 42 adverse events in 19 patients (15.3%) in the originator

infliximab group. Infusion related reactions occurred in nine participants in the biosimilar group as compared with eight participants in the originator group.

REVIEWER COMMENTARY: Despite some differences between the groups at baseline characteristics there was no difference in the overall retention rates and whilst CRP values may have been statistically different at some timepoints these values were low, based on small numbers and not clinically significant and there were no differences in the disease activity measure ASDAS. It should be noted that the treatment history provided for patients previously treated with infliximab is limited and the basis for re-treatment largely "*unknown*", particularly given the potential for these patients to have anti-drug antibodies following treatment with originator infliximab and the potential impact of this on subsequent infliximab treatment. The basis for a patient being treated with biosimilar infliximab in response to a lack of efficacy with originator infliximab is also unclear.

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Ollech et al: Efficacy of biosimilar infliximab CT-P13 among inpatients with severe steroid-refractory colitis[22]

SPONSOR: None

LOCATION(S): Single-centre, US

DESIGN: Retrospective cohort study

DATES: Patients admitted between January 2018 and December 2018

OBJECTIVE(S): To describe the outcomes associated with the use of biosimilar infliximab (CT-P13) in hospitalized patients with acute severe colitis who had not responded to three days of intravenous methylprednisolone

PATIENT CHARACTERISTICS: 21 patients, median age = 32.2 years, median disease duration = 4.25 years; number of patients receiving prior adalimumab = 6, number of patients receiving prior vedolizumab = 6, number of patients receiving prior ustekinumab = 1, median c-reactive protein on admission = 23, number patients with infliximab dose 5mg/kg = 14, number patients with infliximab dose 10mg/kg = 7; number of patients with concomitant azathioprine = 4, number of patients with concomitant methotrexate = 2. Dose escalation was recorded in 6 patients.

OUTCOME(S): colectomy-free survival at 6 months

RESULTS: Median duration of follow-up was 5.9 months. Seven patients proceeded to colectomy with a mean time to colectomy of 2.2 months with a colectomy-free survival rate at 6 months of 70.05%. Two patients developed anti-drug antibodies.

REVIEWER COMMENTARY: Details are not provided regarding which patients proceeded to colectomy with respect to factors such as treatment history and the infliximab dose that they received.

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Deaner et al: Recurrence rates of inflammation after switching from originator infliximab to biosimilar infliximab-abda for non-infectious uveitis[23]

SPONSOR: None

LOCATION(S): Single centre, US

DESIGN: Retrospective case series

DATES: Patients treated since April 24th 2017

OBJECTIVE(S): To describe the frequency of ocular flares in patients with non-infectious uveitis who switched for nonmedical reasons (eg. insurance) to biosimilar infliximab (Reflexis®) after receiving a minimum of 3 months of treatment with originator infliximab.

PATIENT CHARACTERISTICS: 34 patients identified as treated for uveitis with originator infliximab, 17 patients identified as eligible, 8 patients were excluded as they did not receive follow-up and, 9 patients were excluded as they had less than 3 months follow-up; average age = 43.6 years

OUTCOME(S): Frequency of uveitis flares, defined as new or worsening inflammatory activity on clinical exam, increased macular edema on optical coherence tomography (OCT) or leakage on fluorescein angiography (FA) as interpreted by a uveitis specialist

RESULTS: The average duration of treatment with originator infliximab prior to switching was 49.2 months but ranged from 3.4 to 170.3 months. Three flares occurred in two patients (11.8%) in the period preceding switching as compared with eight flares in six patients (35.3%) after switching, of which two flares occurred in a patient that had only been treated for 3.4 months prior to switching. The average flares per person-year while receiving biosimilar infliximab was calculated as 0.916 as compared with 0.192 in the preceding period (P=0.037). Three of the four patients who experienced a flare within the first 90 days after switching responded well and achieved disease control with increased dose of biosimilar infliximab. One patient discontinued biosimilar infliximab and was switched back to originator and one patient stopped infliximab for reasons unrelated to disease control (pregnancy).

REVIEWER COMMENTARY: The authors conclude that their results suggest that "… *patients who are unstable, requiring escalating dosing of originator infliximab or adjuvant therapies to control inflammation will likely not do well with a switch to biosimilar infliximab-abda* [biosimilar infliximab]" and suggest that *"… despite their "highly similar" molecular structures there are unique molecular differences between the originator and biosimilar products that may account for their clinical differences*". The results of this analysis should be interpreted with caution. Specific details are not provided regarding the basis on which each flare was identified or the severity of those events with the authors noting that "*our study was heterogenous in the types of inflammatory eye disease included, definition of uveitis flare, and frequency of ocular examinations*". The exact basis for the calculation of the per person-year flare rate post switching is unclear given that follow-up duration for patients post switching is provided but the duration of treatment with biosimilar infliximab is not, particularly for patients who ceased treatment. Additionally, a number of patients were followed-up for significantly less than 12 months after switching, some of whom experienced a flare in that period but remained on biosimilar infliximab indicating it was considered that, despite the flare, this therapy was still effective. In this context, there is significant uncertainty whether these patients would continue to flare at the same rate or whether their condition may have settled again had they been followed up for a longer duration and as noted by the authors "*Despite the early flares, these patients may go on to be well controlled on infliximab-abda* [biosimilar infliximab]*"*. The authors also report that they identified 17 additional patients who were treated for uveitis but were not included in the study including eight patients who didn't follow up after switching and nine patients who had less than 3 months follow-up after switching; noting that four of six patients included who flared did so within the first 90 days of switching and that three of those patients responded to infliximab.

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Xue et al: Are Patients at Risk for Recurrent Disease Activity After Switching from Remicade® to Remsima®? An Observational Study[24]

SPONSOR: none

LOCATION(S): Single centre, The Netherlands

DESIGN: Two phase prospective open label observational study, 6-month intensive monitoring phase post-switch and two year

DATES: patients switched to biosimilar infliximab (Remsima®) between June and July 2016 with 2-year follow-up

OBJECTIVE(S): To describe the outcomes associated with switching from originator infliximab to biosimilar infliximab (Remsima®) in patients with rare immune-mediated inflammatory diseases who were considered to have stable disease following treatment with originator infliximab for a minimum of 6 months.

PATIENT CHARACTERISTICS: 48 patients, sarcoidosis = 17, Behçet's disease = 12, non-infectious uveitis = 11, other diagnoses = 8; mean age = 51 years, mean duration or originator infliximab treatment = 48 months, number of patients with anti-drug antibodies prior to switch = 6

OUTCOME(S): Physicians perception of disease activity (PPDA) and patient self-reported outcomes (PSROs) at time of switch, 3, 6, 12, 18 and 24-months post-switch. Adverse event reports. Anti-drug antibodies at baseline, 3 and 6 months

RESULTS: During the first six months there were no statistically significant differences in the and patient self-reported outcomes. Physicians reported increased disease activity in seven patients and adverse events in five patients. Within the sarcoidosis patients 41% (7/14) were reported to have "*significantly increased disease activity or adverse events*". There were no statistically significant differences in the mean laboratory parameters between baseline, 3 months and 6 months post switching. Eight patients were reported to have been switched back from biosimilar infliximab to originator infliximab as a result of significant adverse events (angioedema, n=1, which did not recur after switching), disease relapses (n=3), progression of pre-existing symptoms (n=2) or other adverse events including headache and nausea (n=2, but these were later attributed to other causes including medication overuse headache and diaphragmatic hernia). Anti-drug antibodies developed in two patients during the two year follow-up but this was not associated with clinical worsening of those patients but treatment was changed pre-emptively to an alternative agent in these patients.

REVIEWER COMMENTARY: The authors conclude that *"…. among rare immune diseases in particular (neuro)sarcoidosis patients previously treated with Remicade® requires a well-considered decision-making and intensive monitoring due to a possibly higher incidence of disease worsening or exacerbation of (neurologic) symptoms*" and suggest that "*Remicade® and its biosimilar Remsima® might exert different biological actions in certain disease conditions such as sarcoidosis, and these might be related to differences in fucose content of the Fc fragment.".* Despite drawing these conclusions the authors acknowledge that *"…it is important to note that we did not had a control arm treated with the originator", that "evaluation of disease activity was based solely on physician perception and may therefore have been affected by differences in interpersonal interpretations"* and accordingly that *"…we could not rule out the possibility that the recurrent disease activity might be a part of the course of disease rather due to the switch to Remicade®".*

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ANTI-TNFα

Provenzano et al: Open-label non-mandatory transitioning from originators to biosimilars in routine clinical care[25]

SPONSOR: None

LOCATION(S): Single centre, Italy

DESIGN: Observational prospective

DATES: Since May 2018

OBJECTIVE(S): To describe the outcomes observed with switching from originator adalimumab, etanercept or infliximab to biosimilar in patients with rheumatoid arthritis (RA), psoriatic arthritis (PsA) and ankylosing spondylitis (AS) who had been treated for at least 2 years with the originator product and had achieved stable clinical remission or low disease activity for at least 6 months.

PATIENT CHARACTERISTICS: 145 patients, RA = 59 (41%), PsA = 45 (31%), AS = 41 (28%); mean age = 55 years; mean disease duration = 15 years; treatment: adalimumab = 39 (26.9%), etanercept = 85 (58.6%), infliximab = 21 (14.5%); median duration or treatment with originator = 10 years

OUTCOME(S): biosimilar switching acceptance rate, biosimilar retention rate

RESULTS: Of the eligible patients identified 98% agreed to switch from originator to biosimilar. Following at least 12 months of follow-up 84.8% of patients (123/145) were considered to be remain in clinical remission or have low levels of disease activity and remained on the biosimilar whilst 22 patients had ceased (including two patients with stable disease in whom death was unrelated). The median duration of biosimilar treatment prior to stopping was 6.5 months. Seven patients stopped the biosimilar within 3 months of switching due to increased disease activity of whom six were switched back to originator and one to an alternate agent. Of those that switched back to originator 5 were considered to have responded and one did not. Twelve patients were switched to an alternative agent after a minimum of 3 months post-switching (median 8 months) due to a reactivation of their disease.

REVIEWER COMMENTARY: The acceptance rate for switching to biosimilar in this study is high at 98% and the retention rate was 84%. The authors attribute these observations to the fact that they "*…adopted a physician-patient shared decision strategy that could have minimized the "nocebo effect" as compared with a mandatory switch policy*". Noting this, amongst 5 patients that were considered to have lost response within 3 months and were switched back to originator product, specific details defining the loss of response to the biosimilar and subsequent response to originator are not provided. It is possible that the nocebo effect contributes to this observation, particularly as "*…switchback to the originator was allowed according to medical judgement and clinical preference*".

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Trastuzumab

Mendes et al: Real-world intensive safety monitoring of biosimilars rituximab and trastuzumab in a Portuguese oncology hospital[26]

SPONSOR: None

LOCATION(S): Single centre, Portugal

DESIGN: Prospective observational study utilising a paper-based adverse drug reaction reporting form

DATES: 1 April to 30 September 2019

OBJECTIVE(S): To describe the safety profile of biosimilar trastuzumab (CT-P6)

PATIENT CHARACTERISTICS: 58 patients treated for HER2 positive breast cancer

RESULTS: Only one patient included experienced an adverse drug reaction. This individual experienced a total of five adverse drug reactions including headache, tremor, pain in extremity, back pain, tachypnoea.

REVIEWER COMMENTARY: The authors report that the single patient that experienced adverse drug reactions to biosimilar trastuzumab was switched to originator trastuzumab but details are not provided for the outcomes of this switch.

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Rituximab

Mendes et al: Title Real-world intensive safety monitoring of biosimilars rituximab and trastuzumab in a Portuguese oncology hospital[26]

SPONSOR: None

LOCATION(S): Single centre, Portugal

DESIGN: prospective observational study utilising a paper-based adverse drug reaction reporting form

DATES: 1 November 2018 to 30 September 2019

OBJECTIVE(S): to describe the safety profile of biosimilar rituximab (CT-P10)

PATIENT CHARACTERISTICS: 35 patients, diffuse large B-cell lymphoma (n = 17), B-cell lymphoma (n = 8), Mantle cell lymphoma (n=3)

RESULTS: A total of 16 adverse drug reactions were experienced by four patients. The most common event was chest discomfort (n=4). Rituximab was delayed in two patients on one occasion and then discontinued in one of these patients.

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FILGRASTIM

Parody et al: Mobilization of Hematopoietic Stem Cells into Peripheral Blood for Autologous Transplantation Seems Less Efficacious in Poor Mobilizers with the Use of a Biosimilar of Filgrastim and Plerixafor: A Retrospective Comparative Analysis[27]

SPONSOR: None

LOCATION(S): Single-centre, Spain

DESIGN: Retrospective

DATES: Consecutive patients from December 2013 to November 2017

OBJECTIVE(S): To compare the outcomes of originator filgrastim (Neupogen®) and biosimilar filgrastim (Zarzio®) for the mobilisation of hematopoietic stem cells for transplant in patients with multiple myeloma, non-Hodgkin's lymphoma and healthy donors, including in combination with plerixafor in individuals who did not attain minimum peripheral blood CD34+ cell levels on day +4.

PATIENT CHARACTERISTICS: 216 patients diagnosed with lymphoma (lymphoma = 102, multiple myeloma = 114); 163 patients did not require plerixafor, originator filgrastim = 105, biosimilar filgrastim = 58; 45 patients required plerixafor, originator filgrastim = 30, biosimilar filgrastim = 15; 56 related healthy donors were mobilized, originator filgrastim = 33, biosimilar filgrastim = 23

OUTCOME(S): Peripheral blood CD34+ cell counts day +4, day +5, total CD34+ cell collected, mobilization failure

RESULTS: Amongst patients who did not require plerixafor administration the median number of CD34+ cells in peripheral blood on day +4 was lower (p = 0.03) for patients in the biosimilar group (23.7 x10^3/mL) than in the originator product group (33.4 x10^3/mL) but there was no difference on day +5 (42.0 x10^3/mL vs 49.5 x10^3/mL) or total mobilised CD34+ cells (4.79 x10^6/mL vs 4.9 x10^6/mL). Mobilization failure occurred in two patients in the originator filgrastim group with none in the biosimilar group (p = ns).

As plerixafor is administered following a poor response to initial treatment with filgrastim, a multivariate analysis investigating sex, age, weight, basal disease, pre-mobilization status, number of prior lines of chemotherapy (<2), and originator or biosimilar filgrastim for association with a requirement for plerixafor was conducted. Only age (hazard ratio: 0.96, 95%CI:0.93 to 0.99, p= 0.04) basal disease (hazard ratio: 0.24, 95%CI:0.1 to 0.56, p= 0.001), and the number of prior lines of chemotherapy (<2) (hazard ratio: 0.32, 95%CI:0.17 to 0.61, p= 0.001) were identified with a require for plerixafor but not originator or biosimilar filgrastim.

Amongst patients who went on to require plerixafor, the median number of CD34+ cells in peripheral blood on day +4 was significantly lower (p = 0.02) in patients in the biosimilar group (2.4 x10^3/ml) as compared to those in the originator group (4.8 x10^3/ml) but not on day +5 (13.8 x10^3/ml vs 20.7 x10^3/ml, p = 0.08). A second dose of plerixafor was required by four patients in the biosimilar group as compared with one patient in the originator group (p = 0.02). Mobilization failure occurred in three patients in the biosimilar filgrastim group with none in the originator group (p = 0.01). Multivariate analysis identified biosimilar filgrastim as associated with risk of mobilization failure in patients receiving plerixafor with a hazard ratio of 10.3 with 95%CI of 1.3 to 77.8 (p = 0.02). Within those who received plerixafor, 12/15 who received biosimilar filgrastim had a history of 2 or more prior lines of prior chemotherapy as compared with 18/30 patients in the originator group.

Amongst the healthy donor group, there were no differences in peripheral blood CD34+ cells between those who received biosimilar filgrastim and originator filgrastim on days +4 (71.5 x10^3/ml vs 70 x10^3/ml, p = ns) and day +5 (100 x10^3/ml vs 97.7 x10^3/ml, p = ns). Three donors that received biosimilar filgrastim required more than one apheresis to achieve the minimum target, one of whom required plerixafor, as compared with none in the originator filgrastim group and mobilisation failure occurred in a single donor who had received originator filgrastim.

REVIEWER COMMENTARY: On the basis of the results identified the authors specifically conclude that in the GSF based mobilisation "*….the combination of PLEX + BIO* [plerixafor plus biosimilar filgrastim] *might be less efficacious than PLEX + NEU* [plerixafor plus originator filgrastim] *in patients defined as being poor mobilizers*". This conclusion should be interpreted in the context of the small number of patients who received plerixafor in combination with biosimilar filgrastim and that there were numerical imbalances with regards to the number of lines of prior chemotherapy between the originator and biosimilar group. It is widely established that prior chemotherapy can impact on the mobilisation of CD34+ cells, reflected in the fact that this was identified by the authors as a factor associated with a requirement for plerixafor. In contrast, biosimilar versus originator filgrastim was not identified as a factor associated with requiring plerixafor and there was no difference identified amongst healthy donors.

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SOMATROPIN

Pfaffle et al: Safety and Effectiveness of Omnitrope, a Biosimilar Recombinant Human Growth Hormone: More Than 10 Years' Experience from the PATRO Children Study[28]

SPONSOR: Hexal AG

LOCATION(S): hospitals and specialized endocrinology clinics across 14 countries including Austria, Canada, Czech Republic, France, Germany, Italy, Poland, Romania, Slovenia, Spain, Sweden, Taiwan, UK and US.

DESIGN: Open-label, longitudinal post-marketing surveillance study

DATES: Up to November 2017

OBJECTIVE(S): To investigate the long-term safety and effectiveness of biosimilar somatropin (Omnitrope®)

PATIENT CHARACTERISTICS: 6009 infants, children, and adolescents (PATRO children) from 298 centres receiving treatment with Omnitrope® for any diagnosis

RESULTS: The mean duration of Omnitrope® treatment was 33.1 months. A total of 10,360 adverse events were reported in 2750 patients (45.8% incidence) in the safety group, of 396 patients had adverse events with a suspected relationship to the study drug. 50 adverse events in 37 patients were serious and treatment related. The mean height standard deviation scores in patients who had not been pre-treated with rhGH were +1.85 (SD = 0.94) at 5 years in growth hormone deficiency (n=514), +1.76 (SD = 0.68) at 5 years in patients born small for gestational age (n=270) and +1.0 (SD = 0.57) at 5 years in patients with Turner syndrome (n=29). The authors concluded that "*All available data indicate that Omnitrope® does not differ from other rhGH medicines with regard to its effectiveness and safety profile in approved indications*."

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Beck-Peccoz et al: Malignancy risk in adults with growth hormone deficiency undergoing long-term treatment with biosimilar somatropin (Omnitrope®): data from the PATRO Adults study[29]

SPONSOR: Hexal AG

LOCATION(S): 8 European countries (Czech Republic, France, Germany, Italy, Netherlands, Spain, Sweden, UK)

DESIGN: Open-label, longitudinal post-marketing surveillance study

DATES: Up to July 2018

OBJECTIVE(S): To investigate the long-term risk, with a particular focus on malignancy risk of biosimilar somatropin (Omnitrope®)

PATIENT CHARACTERISTICS: 1293 adults from 76 centres receiving treatment with Omnitrope® for any diagnosis

RESULTS: The mean duration of Omnitrope® treatment was 39.7 [range 0 - 134] months. A total of 3828 adverse events were reported in 872 patients (incidence 67.4%), of which 702 adverse events in 353 patients (incidence 27.3%) were regarded as serious. 33 (20 male, 13 female) patients treated with Omnitrope® developed malignancies during the study period (incidence rate of 7.94 per 1000 patient-years). Of these patients 30 had prior history of malignancy and three had no prior history of malignancy. Two malignancies were considered as potentially related to Omnitrope® treatment and included basal cell carcinoma in a male patient who had previously received total body irradiation for ALL and a female patient with malignant melanoma. The authors concluded that "*Our findings are consistent with previously published data on the risk of malignancies in adult GHD patients receiving GH replacement therapy.*" and that the "*current analysis of PATRO Adults indicate that rhGH treatment in the form of Omnitrope® might not increase the risk of de novo malignancies or tumor recurrence in adult GHD patients.*".

STAKEHOLDER PERCEPTIONS

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

PATIENTS

PATIENTS

Macaluso et al: Biosimilars: The viewpoint of Italian patients with inflammatory bowel disease[30]

SPONSOR: No funding declared

LOCATION(S): Italy

DESIGN: 20-item anonymous online questionnaire

DATES: May 2018.

OBJECTIVE(S): Investigate the perspective and knowledge of Italian IBD patients regarding biosimilar medicines

PARTICIPANTS: 1749 members of the Italian inflammatory bowel disease patients' association

RESULTS: 4302 invitations to participate were sent, with a response rate of 40.7% obtained. 46.9% of respondents identified as having Crohn's disease, 51.3% ulcerative colitis and 1.8% unclassified. 15.7% of participants were currently using a biosimilar medicine, with 78.7% not currently using a biosimilar medicine, 5.5% responded that they did not know. 14.2% of respondents stated that they had previously used a biosimilar. When asked "*Have you ever been informed by your IBD specialist about of the existence of biosimilars?*", 45.2% of respondents answered "*No*". 40.3% of all respondents thought they had been sufficiently informed by their IBD specialist about biosimilars and 22.5% were unsure. Subgroup analysis showed this increased to 68.7% for respondents who have used a biosimilar medicine. 57.7% of all respondents rated their general knowledge around biosimilars as "*poor*". Subgroup analysis showed that this decreased to 28.9% for those currently being treated with a biosimilar medicine. When asked "*Do you think that biosimilars are the same as the originator products?*", from the discrete answer options 73.9% of all respondents selected "*I don't know*", 12.0% selected "*efficacy could be reduced*", 9.2% selected "*safety could be reduced*" and 10.6% selected "*yes*". Of the participants who stated they were currently taking a biosimilar the proportion who answered "*yes*" to this question increased to 18.8% and of those who stated they were sufficiently informed by their IBD specialist the proportion increased to 15.4%.

REVIEWER COMMENTARY: The authors concluded that the findings of the survey revealed an "*extensive lack of knowledge and information provided to patients by IBD specialists*" but it should be noted that respondents were asked whether they are sufficiently informed on biosimilars in IBD, but the actual level of understanding was not reported. Question design specifically referenced responder perception of the role of IBD specialists in providing awareness of biosimilars, rather than investigating their general awareness of the topic or education provided from other sources. Limitations identified by the authors include the potential for recruitment bias due to low response rate and the online format.

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Maucksch et al: Patient Satisfaction with the Etanercept Biosimilar SB4 Device, Among Rheumatoid Arthritis and Spondyloarthropathy Patients - A German Observational Study[31]

SPONSOR: Biogen GmbH

LOCATION(S): Multi-centre, Germany

DESIGN: Non-interventional, cross-sectional,

DATES: Participants recruited for the study between August 2017 and June 2018

OBJECTIVE(S): To assess patient satisfaction with the use of the biosimilar etanercept (SB4) pre-filled pen in those with Rheumatoid Arthritis (RA) or Spondyloarthropathy (SpA)

PARTICIPANTS: Participants who had been treated with SB4 pre-filled pen for a minimum of three months

RESULTS: A total of 492 participants were included. The median duration of use of SB4 pre-filled pens was 201 days (range 90 – 699 days). Overall, 193 patients (39%) were 'very satisfied' with the SB4 pre-filled pen, 233 (47%) were 'satisfied', 23 (5%) were 'neutral', 11 (2%) were 'dissatisfied', and 32 (7%) were 'very dissatisfied'. 89% of participants (n =439) reported that the pen was 'simple' or 'very simple' to use and 91% (n = 445) reported that the acoustic signal (click) was 'clear' or 'very clear'. With regards to device training, 175 participants (36%) reported being trained by their physician, 225 participants (46%) by a nurse or site staff, 11 participants (2%) by both physician and nurse or site staff and 77 (16%) reported not receiving training.

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PRESCRIBERS

Viscido et al: Use of biosimilars in inflammatory bowel diseases: A survey among the clinicians members of the Italian Group for the Study of Inflammatory Bowel Disease (IGIBD)[32]

SPONSOR: None

LOCATION(S): Italy

DESIGN: 18 question anonymous paper-based survey

DATES: 28 to 30 November 2019

OBJECTIVE(S): To investigate the knowledge of Italian physicians dedicated to the management of patients with inflammatory bowel disease about biosimilars

PARTICIPANTS: Attendees at the Xth National Congress of Italian Group for the study of Inflammatory Bowel Disease (IGIBD)

RESULTS: A total of 186 responses were received with an overall response rate of 62%. Only 1.6% of respondents had not prescribed a biosimilar in the previous year and 95.2% responded to have knowledge about biosimilars and their regulation. Biosimilars were considered to be as safe and efficacious as the originator by 45.2% of respondents with concerns about immunogenicity reported by 21.5% of respondents. When asked "*What is your view about the extrapolation across the indications?*", 31.7% agreed, 44.6% partially agreed, 15.6% disagreed and 8.1% were neutral. When asked "*What is your view about the switch to a biosimilar in a patient successfully treated with the originator?*" 50.5% agree, 41.4% selected a case-by-case basis, 7% disagreed and 1.1% were neutral. When asked "*What is your view about the interchangeability and substitution?*" 45.2% agreed, 38.2% partially agreed, 11.3% disagreed and 5.4% were neutral. Forty six percent of respondents considered that most patients do not know about biosimilars, with 74.4% of respondents informing all patients about them and 46.2% of respondents relying on a nurse to provide patient education.

REVIEWER COMMENTARY: The authors note that "… *physicians taking care of patients with IBD in Italy are confident with biosimilars and consider them a cost-effective version of the originator biologic, that can work with comparable safety and efficacy* …" and that this survey "… *performed at the end of 2019, seems to indicate that the clinicians' confidence with biosimilars is continuously growing.*"

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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. Asami Y, Pan J, Oh MS et al. Statistical Considerations on Clinical Efficacy Studies of Biosimilar for PMDA Submission. Therapeutic Innovation and Regulatory Science 2020; 54: 1134-7.
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1. Shin D, Lee YJ, Choi J et al. A phase I, randomized, single-dose pharmacokinetic study comparing sb8 (bevacizumab biosimilar) with reference bevacizumab in healthy volunteers. *Cancer Chemotherapy and Pharmacology* 2020; **86**: 567-75.
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