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A novel approach to support implementation of biosimilars within a UK tertiary hospital

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Key messages

What is already known on this subject?

- Biosimilars are considered therapeutically equivalent to originator medicines and can offer significant cost savings to the NHS.
- Clinicians and patients raise concerns over the efficacy and tolerability of the biosimilars when switching from established treatment with the respective originator.

What this study adds?

- A mechanism for clinical teams to raise concerns about switches from the originator to the biosimilar has supported rapid implementation of biosimilars whilst allowing individualised treatment decisions.
- A system to collect outcome data and review decisions made for each patient can report back to the clinicians to aid future decision making for switching to biosimilars.

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Abstract

Objectives

To assess the transfer of patients treated with originator biological therapies to biosimilar products in a large UK tertiary referral hospital reflecting practice within the National Health Service (NHS) using prospectively collected data by a hospital based registry administered by the Biologics Steering Group (BSG).

Methods

We analysed data collected prospectively in a hospital-based registry in a large NHS tertiary referral hospital in the United Kingdom. The registry was administered by the hospital's Biologics Steering Group (BSG), which considered requests for patients to remain on or revert to originator products. The registry contained prospectively collected data on patients switching therapy from an originator to a biosimilar. The data included clinical circumstances or rationale for each request, whether it was granted, and the results of clinical reviews at 3–6 months.

Results

In a twelve month period we identified 1299 patients who could switch to the respective biosimilar and of these, 1196 (92%) did so. Of the 260 patients taking infliximab, 250 (96% switched to infliximab biosimilar: of the 390 patients taking etanercept 50mg, 298 (76%) switched to etanercept 50 mg biosimilar; and of the 649 patients taking rituximab, 648 (99%) switched to rituximab biosimilar. The BSG received 39 applications: 12 (out of 39) applications were to remain on the originator and 27 (out of 39) were to switch back to the originator. Of the applications to remain on the originator 10 (out of 12) were approved. At 3–6 month review, 2 of these approvals reported continued efficacy, 3 switched to the biosimilar, 3 switched to an alternative therapy and 2 stopped treatment. 2 (out of 10) applications were not approved, both applicants reported efficacy with the biosimilar at follow up. Of the 27 applications to switch back to the originator, 16 (out of 27) applications were approved. At 3–6 months, 9 (out of 16) applicants reported regain of efficacy, 6 (out of 16) reported cessation of reported adverse effects and 1 (out of 16) switched to alternative therapy. 8 (out of 27) applications were not approved, and at point of follow up 50% reported efficacy with the biosimilar and 50% had switched to an alternative therapy. 3 (out of 27) applications were withdrawn by the clinical team as efficacy was achieved with the biosimilar.

Conclusion

We have set up a system within a busy NHS clinical practice to successfully switch patients to biosimilars, and established a mechanism to guide decisions on continuing with or reverting back to the originator. Such a system could be of use more broadly within the NHS and other health care systems.

Key words

Biologics, Biosimilars, Implementation, Service provision, Individualised treatment

Introduction

Biological therapies include, amongst others, vaccines, blood and blood components and gene therapy[1]. In the UK the term 'biologics' is now synonymous with monoclonal antibodies (mAbs) used to target specific pathological processes in a wide range of diseases[2]. The first of the monoclonal antibodies to be approved was the anti-CD3 specific mAb, approved by the Food and Drug Administration (FDA) in 1986 to treat kidney transplant rejection[3]. Since then the therapeutic use of antibodies has expanded rapidly, and changed the way in which cancer, autoimmune and inflammatory diseases are treated. Between 2005 and 2014 biologics accounted for 55 (20%) of the 269 new molecular entities approved by the US Food and Drug Administration (FDA)[4]. Important advances include antibodies that target tumour-necrosis factor (TNF), such as infliximab and adalimumab, now routinely used to treat rheumatoid arthritis, psoriasis and Crohn's disease; human epidermal growth factor receptor 2 (HER2) antibodies including trastuzumab used in the treatment of breast cancer; vascular endothelial growth factor (VEGF) receptor antibodies including bevacizumab used in several cancers and age-related macular degeneration and the CD20 specific antibody rituximab used to treat haematological and autoimmune diseases[5].

However this innovation has come with a financial pressure. The National Health Service (NHS) in the UK spent £16.8 billion on medicines in 2015/16[6]. In this period £815 million was spent on infliximab, etanercept, rituximab, trastuzumab and adalimumab[7] alone. These agents also account for five of the top ten drugs prescribed in the NHS by spend[7]. One way in which costs can be managed is by switching to biosimilars[8]. These are akin to generics for small molecular entities. To facilitate the approval of biosimilars the European Medicines Agency (EMA) created a regulatory pathway for the production of biosimilars and this has been supported by NHS England (NHSE) and the National Institute for Health and Care Excellence (NICE) to provide value for money[7,9,10]. Part of the regulatory pathway establishes that the biosimilar is highly similar and clinically indistinguishable in comparison to the originator with respect to efficacy, safety and tolerability, based on comprehensive comparability studies and pharmacovigilance activities[9]. Since the first EMA biosimilar approval in 2006 the EU monitoring system for safety concerns has not identified any relevant group difference in the nature, severity or frequency of adverse effects between biosimilars and the originators[9].

Biosimilar use offers potential savings of at least £200–300 million per year by 2020/21[7]. Switching to biosimilars has been advised by NHSE with the aim that at least 90% of new patients are prescribed the best value biosimilar within 3 months of launch, and at least 80% of existing patients switch within 12 months, so that the publically funded NHS can maximise the value it derives for patients from the money it spends on medicines[7]. However, patients and clinicians can be concerned about potential loss of efficacy, altered immunogenicity or unanticipated differences in adverse effects[11,12] when switching to a biosimilar.

Here we describe the process that has been undertaken to manage switching to biosimilars within the NHSE 12-month target at University College London Hospital NHS Foundation

Trust (UCLH) This task was taken on by the Drugs and Therapeutics Committee (DTC) which at UCLH oversees the governance of use of and introduction of new medicines to the hospital formulary. We describe how a sub-group of this committee, the Biosimilar Steering Group (BSG), established a multi-disciplinary model to provide a mechanism for clinicians to apply for individual patients to remain on or revert to an originator on the grounds of efficacy, safety, tolerability or social circumstances whilst ensuring cost-effectiveness.

Here we outline the decisions and their outcomes for each application submitted to the BSG during the switch to biosimilar infliximab, etanercept 50 mg and rituximab and describe a framework of how such mechanisms can be implemented into clinical care.

Methods

The Biosimilar Steering Group (BSG) was established as a multidisciplinary sub-committee of the DTC. Members of BSG included the DTC Chair, Chief Pharmacist, Lead Research & Medicines Optimisation Pharmacist, Consultants in Rheumatology, Dermatology and Gastroenterology and a Nurse Representative. This membership allowed a balance of (1) members who were independent of prescribing these medicines and provided experience of governance and optimisation of medicines and (2) clinicians with expert knowledge of the conditions and patient groups in question.

Terms of reference for the BSG were established which outlined criteria for application to the BSG. These included: loss of efficacy, changes in tolerability, or social circumstances. Applications could be made to continue on biologic originator or to switch back from the biosimilar to the originator. An application form was developed to simplify and standardise the application and included items that could inform the decision (Supplementary Table 1). This form was then used to review the cases submitted prior to development. These items included:

- Efficacy - clinical data of efficacy outcome measures, for example in rheumatology; Disease Activity Scores (DAS28) or Bath Ankylosing Spondylitis Disease Activity Index (BASDAI)
- Tolerability - a timeline of reported adverse effects and any changes in regular medication
- Social circumstances – evidence of exceptional individual circumstance; for example, students undertaking examinations or patients who work abroad for a significant period during the year in countries where biosimilars would not be readily available

Applications were not accepted if patients fell into one of the categories below:

- Requests related to loss of efficacy that was first noticed after patients had received biosimilar treatment for more than six months. In such situations, the BSG attributed loss of response to a class effect rather than specific to the biosimilar.
- Requests related to loss of efficacy where patients had missed doses of their treatment.

- Requests related to loss of efficacy where a patient had documented loss of response to the originator 6 months prior to initiation of the biosimilar. For example increased DAS28 or BASDAI scores, increased swollen joints or a flare.
- Requests because of reduced tolerability if a different device could be prescribed and was expected to be of benefit. For example changing administration with the Benepali pre-filled pen to the Benepali pre-filled syringe.

On receipt of applications the BSG had to decide whether a switch was clinically appropriate. The decision from the BSG was communicated electronically. Clinical teams were able to appeal against a decision in writing to the BSG, outlining in detail the reasons for the appeal for a second review.

For both approved and declined requests, details of each application was inputted onto a local registry including information on the BSG decision, clinical information submitted by the clinical team, and outcomes from the 3–6 month reviews following the decision using the electronic health record. Treatment success was defined as reduced disease scores such as DAS28 or BASDAI, reduction in swollen or tender joints or resolution of reported adverse effects.

The BSG reviewed applications for infliximab, rituximab and for etanercept 50 mg. As this was an audit of a service provision ethical approval was not required.

Nomenclature of Targets and Ligands

Key protein targets and ligands in this article are hyperlinked to corresponding entries in http://www.guidetopharmacology.org, the common portal for data from the IUPHAR/BPS Guide to PHARMACOLOGY.

Results

Altogether 1299 patients were eligible to switch to the respective biosimilar. The switch for infliximab and etanercept occurred from January 2016 to January 2017 and for rituximab from April 2017 to April 2018. Between January 2016 and July 2018 the BSG received 39 applications (3%) either to remain on or revert back to the originator (Table 1). The applications were submitted by three departments, 37/39 (95%) by rheumatology, 1/39 (3%) by gastroenterology and 1/39 (3%) by dermatology.

Within the 12-month time frame 103 (8%) patients did not switch, of whom 92 were treated with etanercept. Seventy-six percent of patients treated with etanercept switched, which was below the 80% target outlined by NHSE. After 21 months, this figure had improved to 95.5% of patients on etanercept being on the biosimilar. By October 2018, the percentage of patients prescribed biosimilars of infliximab, etanercept and rituximab at UCLH was 98.2%, 95.6% and 99.5% respectively, indicating that most patients were eventually prescribed the respective biosimilar.

The median age of the patients where applications were submitted to the BSG was 38.2 years, the majority of patients were diagnosed with rheumatoid arthritis and juvenile rheumatic conditions (table 2).

BSG received the most applications for etanercept (25/39, 64%) followed by infliximab (13/39, 33%) and then rituximab (1/39, 3%) respectively. Table 3 outlines the number of applications for each biologic therapy, the submission criteria and outcome from the BSG review.

Once the BSG had communicated the outcome to the clinical team each patient was reviewed after 3–6 months. Table 4 outlines the outcomes from the 3–6 month follow-up for all BSG decisions.

The BSG provided impartial advice to clinical teams when applications were submitted. Key examples include one application submitted under the criterion of clinical efficacy. The patient and clinical team had reported loss of efficacy with infliximab biosimilar. After a review of the information the BSG suggested that anti-infliximab antibodies should be assayed. Anti-infliximab antibodies were present and the patient was subsequently switched to an alternative treatment.

Another example includes an application submitted under the criteria of clinical tolerability. The patient had reported that the Benepali® pre-filled pen caused a painful injection site. The BSG reviewed the application and advised for the patient to trial the Benepali® pre-filled syringe as administration instructions differ between the two preparations. The patient tolerated the new device and did not require switching back to the originator.

Three applications, based on reduction of efficacy with the biosimilar, were withdrawn by the clinical team. Each application reported increased tender and swollen joints and flares; however, the clinical condition of these patients stabilised whilst continuing administration of the biosimilar during the period of time of the BSG review.

Discussion

We have described a mechanism that supports the successful implementation of the safe and effective switching from the originator to the biosimilar in large tertiary centre in the UK. We have developed a process that guides decisions to remain or revert to originator products resulting in a very high proportion of patients switching to biosimilars. This mechanism allowed UCLH to exceed the recommended targets for infliximab and rituximab of at least 80% of existing patients switching to the biosimilar within 12 months, with our results of successfully switching 96% and 99% of patients. This was not achieved for the biosimilar switch to etanercept 50 mg within 12 months; however, by October 2018, 95.6% of eligible patients were prescribed etanercept 50 mg.

Although the target switch for etanercept was not met within the 12-month time frame, the target was achieved at a later date. The primary challenge that slowed down switching to biosimilar etanercept was that this medicine was outsourced for homecare delivery rather than supplied from the hospital. As a result patients could have up to 2–3 months' supply delivered and were seen less often in hospital for face-to-face consultations to facilitate a switch. In comparison, patients received infliximab and rituximab infusions on a regular basis at the hospital, which enabled the switch to the respective biosimilar to be implemented quicker.

The BSG supported the clinical teams to switch to the respective biosimilar by enabling an independent framework for clinicians to raise concerns about switches which were reviewed by a multi-disciplinary sub-committee. This approach allowed consideration of multiple factors in which the clinical responsibility did not lie solely with the treating clinician. This holistic approach proved to be advantageous, enabling impartial advice to be provided to clinical teams for complex applications and ensuring outcomes of each application were recorded in a registry.

Patients who eventually stabilised with the biosimilar or required changes to an alternative therapy illustrate the non-inferiority between originators and biosimilars. Moreover, this highlights the fluctuations of chronic diseases which are being considered here. These fluctuations or indeed progression of disease may account for a perceived reduction in clinical efficacy by both treating clinician and individual receiving therapy. Progression of disease itself is therefore not an appropriate criterion for reversion to originator[13,14]. Similarly patients who achieved efficacy with the originator after switching from the biosimilar highlight potential within-patient variation as well as the waxing and waning nature of these chronic diseases[14]. Separately the BSG did not receive any applications from clinicians to switch patients to the originator who had only ever been initiated on the respective biosimilar.

The strength of establishing the BSG is first, providing institutional support for the implementation of biosimilars; secondly, facilitating shared multi-disciplinary decision-making; and thirdly, the establishment of an outcome registry documenting data which can be fed back to clinical teams, the DTC and to improve the reviewing process for future decisions. This process itself was supported by the institution.

Limitations in the BSG methods have been identified which will inform future developments. First, incomplete data submission with BSG applications; this has highlighted that records of objective efficacy and safety measures are not easily available and clinicians had to dedicate time to presenting a case to the BSG. Digital developments including use of the new electronic health record system and development of a BSG database will ease this administrative burden, including collection and review of disease indices. Secondly, clearer exclusion criteria for BSG requests would prevent clinicians expending effort in applications that are unlikely to be approved. In addition it is important to address misconceptions and support better understanding of biosimilars from the clinician and patient perspective. Thirdly, there remains a challenge in the objective assessment of disease activity or tolerance where these are based on patient-reported outcomes.

The experience gained and outcomes collected from the BSG for the infliximab, etanercept and rituximab biosimilar switch have enabled a clear pathway and forum to support the clinical teams.

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Authors' Contributions

K.S: provided the collection of data, analysis and interpretation of data and drafting of the manuscript; S.S, M.L, R.U: revised it critically for important intellectual content; R.E.F: revised it critically for important intellectual content and gave final approval of the version to be submitted; R.S, P.N.B: provided the conception and design of the study, revised it critically for important intellectual content and gave final approval of the version to be submitted.

Conflict of interest

The authors have no conflicts of interest to declare

Data availability statement

Research data are not shared

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Table 1: Number of patients that switched to the respective biosimilar or remained on the originator within the 12-month target and the type of requests received by the BSG

	Infliximab Total	**Etanercept Total**	**Rituximab Total**	**Total**
Number of patients prescribed the originator before the switch to biosimilar	260	390	649	1299
Number of patients who switched to the biosimilar	250	298	648	1196
Number of patients not yet switched to the biosimilar or reviewed by the BSG after 12 months	10	92	0	103
Number of applications to the BSG to switch back from the biosimilar to originator	6	20	1	27

Table 2: Patient characteristics

Patient characteristics	
Gender- no. of patients	
Female	25
Male	14
Median Age – years (range)	38.2 (18–72)
Diagnosis- no. of patients	
Rheumatoid arthritis	12
Juvenile rheumatic conditions*	13
Psoriasis	5
Miscellaneous~	9

*Juvenile rheumatic conditions represent a composite of juvenile idiopathic arthritis and juvenile dermatomyositis in order to prevent disclosing patient confidentially owing to the low numbers with each condition

~Miscellaneous represents a composite of ankylosing spondylitis, Bechet's disease and inflammatory bowel disease in order to prevent disclosing patient confidentially owing to the low numbers with each condition

Table 3: Number of applications for each biologic therapy, the submission criteria and outcome from the BSG decision.

	Infliximab	**Etanercept**	**Rituximab**
	Total number (%)	**Total number (%)**	**Total number (%)**
Total number of applications	**13 (100)**	**25 (100)**	**1 (100)**
Criteria of submitting applications			
Social circumstances to remain on the originator	5 (38)	5 (20)	0 (0)
Social circumstances to revert to the originator	0 (0)	1 (4)	0 (0)
Clinical efficacy to remain on the originator	2 (15)	0 (0)	0 (0)
Clinical efficacy to switch back to the originator	5 (38)	12 (48)	1 (100)
Clinical tolerability to remain on the originator	0 (0)	0 (0)	0 (0)
Clinical tolerability to switch back to the originator	1 (8)	7 (28)	0 (0)
Outcome for each application reviewed by the BSG			
Approved to remain on the originator	7 (54)	3 (12)	0 (0)
Not approved to remain on the originator	0 (0)	2 (8)	0 (0)
Applications to remain on the originator revoked by medical team	0 (0)	0 (0)	0 (0)
Approved to switch back from the biosimilar to originator	2 (15)	13 (52)	1 (100)
Not approved to switch back from the biosimilar to originator	3 (23)	5 (20)	0 (0)
Applications to switch back from the biosimilar to originator revoked by medical team	1 (8)	2 (8)	0 (0)

Table 4: The outcomes from the 3-6 months follow up for all BSG decisions.

	Infliximab	**Etanercept**	**Rituximab**
	Total number (%)	**Total number (%)**	**Total number (%)**
Total number of applications	**13 (100)**	**25 (100)**	**1 (100)**
Outcome of applications approved to remain on the originator			
Efficacy maintained with the originator	1 (8)	1 (4)	0 (0)
Switched to respective biosimilar	2 (15)	1 (4)	0 (0)
Switched to alternative therapy	3 (23)	0 (0)	0 (0)
Treatment stopped	1 (8)	1 (4)	0 (0)
Outcome of applications not approved to remain on the originator			
Efficacy with biosimilar	0 (0)	2 (8)	0 (0)
Switched to alternative therapy	0 (0)	0 (0)	0 (0)
Outcome of applications approved to switch back to the originator			
Efficacy regain with originator	1 (8)	7 (28)	1 (100)
Adverse effects ceased	1 (8)	5 (20)	0 (0)
Switched to an alternative therapy	0 (0)	1 (4)	0 (0)
Outcome of applications not approved to switch back to the originator			
Efficacy with biosimilar	1 (8)	3 (12)	0 (0)
Switched to an alternative therapy	2 (15)	2 (8)	0 (0)
Applications to switch back to the originator withdrawn by the clinical team			
Efficacy with biosimilar	1 (8)	2 (8)	0 (0)
Switched to an alternative therapy	0 (0)	0 (0)	0 (0)