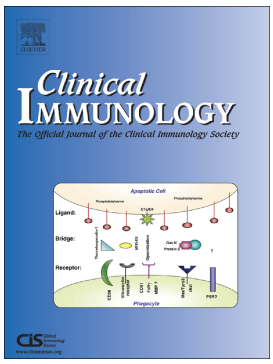

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PII: S1521-6616(20)30185-6

DOI: https://doi.org/10.1016/j.clim.2020.108447

Reference: YCLIM 108447

To appear in: *Clinical Immunology*

Received date: 17 March 2020

Revised date: 24 April 2020

Accepted date: 24 April 2020

Please cite this article as: O.A. Cuevas and C.M. Hedrich, Biosimilars in pediatric rheumatology and their introduction into routine care, *Clinical Immunology* (2019), https://doi.org/10.1016/j.clim.2020.108447

Biosimilars in Pediatric Rheumatology and their introduction into routine care

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Abstract:
Biosimilars are biologic medications that are slightly altered versions of already approved biologic disease modifying anti-rheumatic drugs (bDMARDs). They can be manufactured after the original product's patent protection expires. The advent of biosimilar use in pediatric rheumatology started with the biosimilar to infliximab in 2013. Since then, more biosimilars have been made available including etanercept, rituximab and adalimumab. This manuscript briefly reviews the history of biosimilar introduction to treatment and suggests strategies for the adoption of biosimilar drugs in services specialized in Pediatric Rheumatology, including potential barriers and solutions to their implementation into practice. The review covers general aspects relevant to all biosimilar drugs and specific examples covering individual drugs based on the experience of a large tertiary Pediatric Rheumatology service in the Northwest of England.

Keywords:
Biosimilar, Children, Rheumatology, Pediatrics, Treatment

Funding:
This research did not receive any specific grant from funding agencies in the public, commercial, or not-for-profit sectors

1. Introduction

The use of monoclonal antibodies (mAbs) has become a key component in the differential treatment of pediatric autoimmune/inflammatory conditions since the etanercept originator product Enbrel® was made available in the European market for the treatment of Juvenile Idiopathic Arthritis (JIA) in 1999. Biologic or biopharmaceutical products are defined by their synthesis being manufactured in, extracted from, or semi-synthesized from biological sources. Based on this, the European Medicines Agency (EMA) defines them as "*medicines derived from living cells or organisms, consisting of large highly complex molecular entities which may be difficult to characterize*"[1]. They are structurally complex, diverse between individual agents, and may have several functional domains within a single molecule. Biologics share key properties, including being toxic to target cells or neutralizing cytokines (e.g. TNF, IL-17, IL-6, IL-1, etc.), but may differ in aspects such as the mechanism of action. For instance, etanercept is a fusion protein of the Fc region of IgG1 and the extracellular domain of the human TNF 2 receptor. It acts as a soluble competitive antagonist of the TNF-alpha receptor and only binds to free and not receptor bound TNF. Adalimumab on the other hand is a recombinant anti-TNF antibody that binds specifically to freely available TNF-alpha, neutralizing the biological function of TNF by blocking its interaction with the cell surface TNF receptors. Thus, adalimumab can also inactivate already receptor bound TNF. These differences in chemical structure and mechanism of action can directly affect patient-related aspects of clinical care; patients and clinicians will have to choose anti-TNF therapies between etanercept (given subcutaneously twice a week) and adalimumab (given subcutaneously once every 2 weeks). Furthermore, some biologic medicines may be derived from animal cell lines, and other from human cell lines; this can lead to differences in the levels of immunogenicity within the available products [2,3].

Over the years, a constantly growing number of biologic disease-modifying anti-rheumatic drugs (bDMARDs) have joined etanercept and allow for (some level of) target-directed and individualized treatment. The effects of these drugs in inducing and maintaining remission have been tangible and in many superior when compared to conventional non-biologic DMARDs such as methotrexate or sulphasalazine [4-10]. As a result both rheumatologists and the general public have been demanding increased and faster access to these novel drugs. However, availability of bDMARDs needs to be considered carefully and balanced in the context of finite budgets of public health care systems [11-14]. However, it should be noted that, even with lower costs, the use of bDMARDs (may it be the originator or the biosimilar) requires critical decision making, taking side effects such as infections and tumor risk into consideration.

The introduction of biosimilar pharmaceuticals to the market in 2013 may have opened the door to more widespread access to these "high cost" medicines [11-14]. Biosimilars are biologic medications that are on the molecular level very similar to already approved bDMARDs and therefore are approved but slightly altered "versions" of the "innovator drug". They can be manufactured after the original product's patent protection expires [15]. The European Medicines Agency (EMA) defines a biosimilar medicine as "*a biological product that is highly similar but not identical, to the licensed originator biological medicine and shows no clinically meaningful difference in terms of quality, safety and efficacy*" [1]. From a licensing perspective, biosimilars are approved following similar standards of pharmaceutical quality, safety and efficacy that apply to all biological medicines. The process, however, is expedited and limited to clinical testing in one of the conditions (and age groups) the original product was licensed for [16].

Over the past 5 years, the number of tested and licensed biosimilar mAb products (ending with "-mab") and soluble protein receptor constructs (ending with "-cept") has increased exponentially as patents of originator bDMARDs have started to expire [17-21]. This article provides an overview of the introduction of biosimilar medicines in Pediatric Rheumatology using a large tertiary Pediatric service in the North West of England as an example (Alder Hey Children's NHS Foundation Trust). We suggest introduction strategies and discuss barriers to implementation with drug-specific examples and share a number of lessons learned over the last five years.

2. Biosimilar medicines in Pediatric Rheumatology: is extrapolation justified and feasible?

Pediatric practitioners have always been advocates of the sentence "*Children are not small adults*" [22]. We have sadly learned from examples where children have come to harm (grey-baby syndrome with chloramphenicol in neonates, phocomelia cases with thalidomide, respiratory depression in ultra-rapid codeine metabolizers) that extrapolation from adult dosage information is not always feasible. This is due to the potential of pharmacokinetic and pharmacodynamic differences in children when compared to young people (adolescents) and adults. These differences can lead to significant alterations in the process of drug absorption, distribution, metabolism and excretion, which ultimately, if ignored, can negatively affect pediatric patients [23-25].

For many years, children have been called "*therapeutic orphans*" due to the lack of investment in pediatric research and pediatric clinical trials. In the last 13 years both the Food and Drug Association (FDA) in the United States and the EMA, among others, aimed to address this imbalance by implementing a number of strategies to increase the number of pediatric clinical trials and research in novel medicines with potential pediatric applications. They have also encouraged pharmaceutical companies to re-visit traditional active ingredients via Pediatric Use Marketing Authorization (PUMA) where Pediatric clinical trials are not available by providing incentives such as renewal or extensions of patents [26-27]. However, while more Pediatric trials are being performed, advances have been disappointingly slow with still only a very small number of Pediatric clinical trials being planned and funded [28].

The principle of extrapolation claims that comparable structural attributes, biological functions, human (not necessarily pediatric) pharmacokinetic and pharmacodynamics (PK/PD) between a reference originator product and a biosimilar in a homogenous population of patients falling within a sensitive indication allows to apply the principle of "similarity" also to all other indications (figure 1) [29,30]. Because of the aforementioned historical struggle with Pediatric medicines and challenges associated, a majority of Pediatric practitioners found the "principle of extrapolation" a difficult pill to swallow.

A number of assays allow for in-depth characterization of complex proteins, both on a physicochemical and a functional level [31]. Through these, structural attributes of the originator molecules can be compared and contrasted to biosimilars. Minor alterations and resulting differences may be accepted as long as the biological functions of the drug remain the same. The basis to support this approach lies in the fact that originator molecules have indeed been changed substantially during their patented life [29,30]. For instance, the originator molecule infliximab (Remicade®) underwent at least 3 "high risk" manufacturing changes that led to variability on the original protein while not resulting in a new licensing process and/or clinical trial. In a real-life-scenario, (minor) alterations did not affect the efficacy or toxicity of the originator product. Therefore, we may assume that a similar degree of variability will not necessarily affect the efficacy and toxicity of biosimilars.

Nonetheless, and due to the added complexity that pharmaceutical companies face replicating complex protein structures, biosimilar medicines need to undergo a more rigorous development approach, much closer to the one required for originator medicines than generic medicines (figure 2). PK and PD equivalence needs to be demonstrated in humans, and biosimilars have to be tested in a clinical trial with a large enough sample population with a known indication for the drug.

Unfortunately, the need for like-for-like comparison in children and young people (CYP) was not deemed necessary by either the FDA or the EMA. Because of this, Pediatric clinicians across the world have been left to deal with these uncertainties as part of real clinical practice.

Another risk that many clinicians feel may be undetected by the suggested development strategy for biosimilars is the potential of patients developing cross-immunogenicity when swapping from an originator product to a biosimilar, or switching between two biosimilars. To address this, the UK's NICE advised that interchangeability of the products cannot be assumed, and therefore recommends prescribing of these drugs by brand, avoiding automatic substitutions and, in Pediatrics, close clinical monitoring for an initial undefined period [32]. A number of studies suggested that the most common switch (i.e. from originator molecule to biosimilar) does not affect drug efficacy and safety [33,34]. However, additional data from clinical and real-world studies (especially of switching between biosimilars) are required, as is continued pharmacovigilance. Thus, any switching between drugs should remain a clinical decision made jointly by the treating physician and patients and their families on an individual basis supported by scientific evidence, not just resemble a cost-saving exercise [32]. To address remaining concerns, prospective immunogenicity testing, long-term pharmacovigilance plans and post-marketing studies are needed to, among others, capture late adverse events.

3. Suggestion for a pathway to safely implement biosimilar medicine use

The adoption of biosimilars will help provide much needed savings to national health systems and/or insurers and further benefit individualized patient care. However, introduction should not be driven purely by financial considerations.

The purpose of creating a document to guide the adoption of new biosimilar medicines by Children's Hospitals/Trusts is to outline the process involved in the early adoption phase that allows early assessment of benefits and potential risks for patients, prescribers and Hospitals/Trusts. The ultimate aim is to ensure that the care provided to patients remains unaltered, and that the patient experiences no change in the treatment tolerability and efficacy [35]. However, we will describe some examples further on where this premise was not fully adhered to. A graphical summary of the suggested adoption process is available on *Appendix A*. We suggest that, before initiating adoption of a new biosimilar medicine in the department's portfolio, the pediatric rheumatology multidisciplinary team (MDT), including a pharmacist (purchasing and contracts), specialist nurses (administration details) and at least one responsible clinician (Pediatric Rheumatologist), review the flowchart and assess if the plausibility for the introduction of the drug.

3.1 Initial considerations

One of the considerations prior to adoption of new biosimilars relevant to pediatric practice should include whether the available biosimilar covers the required licensed indications. Generally, by definition, biosimilars can only be approved and used for the indications covered by the originator drug. For example, etanercept biosimilars were approved by the

EMA and the FDA for the treatment of juvenile idiopathic arthritis (JIA) and therefore adoption for this indication should be prioritized. When the new biosimilars for adalimumab became available, the FDA and the EMA approved some of them for JIA but not for pediatric uveitis, while being approved for anterior uveitis in adults [36]. The indications included were reflective of the approved indications of the originator product at the time of initiation of biosimilar development. Indeed, licensed indications for a product drive the choice of biosimilar (or no biosimilar) adoption, as pediatric good practice prescribing rules advise that licensed products should be used first, unless there are individual patient-centered circumstances affecting the prescriber's decision process [37]. Cost reduction should generally not be considered as a valid reason on their own to favor off-label and unlicensed use of medicines in children over licensed ones [37]. However, pressure from insurers/funders, health systems and Hospitals/Trusts certainly influence thought processes in real life.

On the other hand, in cases where the originator product has been used off-label outside licensing (examples are rituximab and infliximab in Pediatric Rheumatology), biosimilar products (as of now) also will not cover these indications and cannot contribute to the generation of evidence towards approval in the respective patient population [32]. However, at the same time, the use and clinical assessment of biosimilars for pediatric patients should and cannot necessarily be reduced to the license of the originating product as a host of treatments are tolerated in children, have proven efficacious in practice while not being formally approved. As such, biosimilar medicines may be used off-label in the future for non-approved conditions. The availability of these drugs to treat non-approved conditions will be directly affected by the commissioning processes in the respective countries where the drug is being used. Furthermore, even when the biosimilar medicine has been granted a pediatric license, this does not necessarily mean that the product is suitable for pediatric use. This could be due to the inclusion of inappropriate excipients in the formulation or due to the choice of devices that have been made available. Pharmaceutical companies producing etanercept biosimilars to date, for example, have not developed a 10mg strength vial and as such are not suitable for use in the younger population group of patients [38,39]. Therefore, the type of preparation available (strength, concentrations, formulation, route, administration details) also needs to come into play. Tables 1 and 2 show examples of an in-depth assessment of the biosimilar products available (etanercept and adalimumab) at the time.

Lastly, embarking in the process of biosimilar adoption is a resource heavy endeavor. Departments need to ensure that they factor in time for their relevant multidisciplinary team members (specialist nurses, pharmacists, etc.) to develop information and educational tools for families and other members of staff, guideline updates and/or amendments and deal with any queries from patients and their families pertaining the novel use of biosimilar medicines. Some of these tools may be available from pharmaceutical companies. However, in the authors' experience (as Pediatrics is usually a small market) child-friendly educational and informative tools do not exist for all originating drugs and/or biosimilars and it may be years before become are available.

3.2 Provision of medicines

In order to maximize potential cost savings associated with the adoption of biosimilars into clinical routines, a number of actions may be agreed. In the UK, supplying the drug via homecare companies maximizes the cost-efficiency for these expensive drugs (biologics and biosimilars alike). Services in the UK will need to establish whether a pharma-funded homecare service is offered by manufacturers and whether any extended services are included, or (for non-pharma-funded services) a homecare service provider within the

regional framework is suitable [35]. Moreover, it is imperative to ascertain whether product-associated support services available are acceptable to CYP. Most homecare service providers will offer some type of community nursing support for administration education, but their staff are rarely trained in Pediatrics. Thus, the clinical team and pharmacy providers need to assess carefully how important they perceive this is for their specific patient groups. More importantly, a homecare team or service should already be available in the Rheumatology Service/Hospital/Trust and be able to take on additional patient numbers every time a biosimilar product is adopted in the hospital formulary. However, even in well-established homecare departments and services, the process of initiating a homecare contract may be lengthy and the service level agreements drafted by individual homecare companies may need to be altered multiple times.

For drugs that are not suitable for home administration, further checks are necessary. This particularly applies to drugs that require being prepared in the Aseptic Services Unit (ASU). It has to be considered whether data on drug stability, storage and expiration of the biosimilar are the same or comparable to the originator. The Pharmacy Aseptic Team will need to develop new worksheets for intravenous biosimilars approved for use within the Hospital/Trust. In most cases, extended stability data for the biosimilar may be available from the manufacturers and they should always be the first port of call to obtain this information [35].

Finally, close liaison with the Pharmacy Purchasing Team is required to discuss practical matters including anticipated launch dates, regional contracts and pricing information (including aforementioned homecare provision services).

3.3 Target patient population

A decision requires to be made on whether individual biosimilars should be introduced for existing patients (switch), new patients only, or both. The authors department's approach has been to trial the biosimilar product in new patients first to gather real-life data on whether a small pilot patient population tolerates the new product and shows comparable response rates expected from originator drugs. If the trial period (this could be any length of time, in the case of bDMARDs usually between 3 to 6 months, depending on the number of patients started on these drugs within the service) delivers positive results (with the focus on tolerability much for than long term efficacy at this stage), consideration to switch existing patients can go ahead. Moots *et al* recently reviewed published experience with switching from originator biologic to biosimilar evaluating 12 studies that ranged in observation length from 24 to 56 weeks [34]. The authors concluded that initial data suggests maintenance of efficacy and safety in the absence of increased immunogenicity. Recently, a total of 265 patients were switched from an originator bDMARD to the respective biosimilar and followed for 3 years. After 2 years, 140 patients were switched to a second biosimilar while 26 remained on the first biosimilar and 55 reverted back to the originator. Analysis showed that the number of biosimilars received did not affect antidrug antibodies development [40]. Further studies have suggested similar results for most biosimilar drugs [41,42].

However, continued pharmacovigilance is imperative as, with added biosimilars entering the market and potentially different centers purchasing different ones, individual patients may be switched between preparations when changing address (for example, transitioning to adult services, moving to university or moving to other postcodes or counties). The authors expect that once the first disease cohort of patients has successfully switched from originator drug to biosimilar, it will be difficult to argue against switching patients when new biosimilars come into the market as all these drugs work on similar premises. However, small modifications to complex proteins may have variable and potentially unpredictable immunogenic potential.

Thus, the inclusion of patients treated with biosimilars in the available cohort studies such as the 'Biologics for Children with Rheumatic Diseases' (BCRD) and BSPAR Etanercept Study (BSPAR ETN) in the UK (https://sites.manchester.ac.uk/bcrdbspar/) or the BIKER registry in Germany (http://www.biker-register.de/). is imperative to obtain a long-term view on whether patients on biosimilar medicines indeed clinically respond in a similar way to patients on the originator medicines [43].

3.4 Governance and local approval

Forms for the use of new drugs should be submitted to local clinical committees. The submission document should cover all the points addressed above. Experience from other services, published evidence (where available), clinical opinion or reviews should be included as evidence [35]. As explained above, it is unlikely that pediatric data will be available through randomized controlled trials. At this point a decision should be made on which biosimilar the department will be adopting if more than one is available. As a useful collateral effect, submitting the evidence to request the addition of a new bDAMRD may trigger a review and improvement of the current practice.

3.5 Informing and involving patients

The UK NICE guidance suggests that the "*decision on the requirement to inform new patients rests with the individual clinical team once the biosimilar has been approved and adopted at the Trust*". It is important to note that, for new patients, the use of a biosimilar will not be a change in therapy they need to be informed of, but a recommended treatment like any other started by a clinician. Thus, no additional information is needed on top of the usual drug related education given to the patient and their families. The focus of developing information and educational materials for biosimilar medicines should be for patients switching from an originator product to a biosimilar product [35]. How the information/education is carried out will be specific for the therapy in question. For example, for patients who are coming to the hospital for their treatments, face to face education and information should be prioritized. For patients who are being treated at home, a number of possibilities are available (see table 3).

Box 1: Authors' experience with patient involvement.

Whether face to face or via letter, a number of points that should be discussed with patients and families when switching from an originator medicine to a biosimilar, or between to biosimilars:

1) Explain the reasoning behind the change. Be honest if the change has been driven mainly by financial considerations but present it in the context of wider health benefits for the whole population if relevant

2) Explain, in lay terms, what a biosimilar medicine is and how it compares in efficacy and safety to the originator molecule or the other biosimilar

3) Signpost the patient and their family to higher organisms supporting the switch and any educational sites they can access to gain further information

4) Lay out any differences in care the child might expect as a result of the switch

5) Offer them sufficient time to read and access the information and contact the team with any queries or worries they might have. Re-assure them if possible that they will not be forced to switch, but make sure that any resistance to change is based on accurate facts and not misunderstanding of information. Ultimately, if the families refused to switch, a patient centered approach was favored and no patient who was not willing to switch was forced to do so.

(For an exemplary information sheet see Appendix 2).

3.6 Transition to adult services

The transitioning process should take into consideration the commissioning position of biosimilar pharmaceuticals in adult Rheumatology. Young adults should be supported in potential (and likely) switching between drugs whenever possible before the actual transition happens. For some young adults, changing teams and care environment may already cause concern and/or anxieties. Adding an alteration of the drug and/or device they are using at the same time should be avoided whenever possible. However, ultimately this will be the decision of the young person, and some of them will choose to stay on their 'Pediatric initiated preparation' until transition occurs. While this option should certainly be respected, patients and families should be informed about the possibility that adult services may not have a choice but to switch treatment after transition. Of note, the patient's treatment (including brand names) should be clearly communicated to the adult service to ensure continuity of treatment and supply [35].

3.7 Prescribing requirements and IT readiness

Another practical aspect to secure a smooth transition to biosimilar medicines includes ensuring electronic prescribing systems have been updated to include the new medicines in the hospital formulary. NICE in the UK and the EMA have suggested to prescribe biosimilars by brand name [1,32]. In the authors' service biosimilars and any originator medicines are prescribed by both their active drug name (international non-proprietary name INN) and the brand name in brackets, for example, "Infliximab (Remsima®)".

3.8 Pharmacovigilance and clinical outcomes monitoring

By nature, all biologics require close clinical monitoring for safety, and any suspected adverse drug reaction (ADR) should be reported to national drug safety authorities providing the brand and batch number.

Box 2: Practical safety monitoring in a clinical setting.

1) Black triangle drugs: biosimilar medicines are new medicines (black triangle), so any (suspected) ADRs need to be reported.

2) Our team has completed a "yellow card report" for every patient experiencing an injection site reaction or pain/stinging after administering the adalimumab biosimilar Amgevita®. Our service incorporated this as a necessary requirement in patients who do not tolerate the biosimilar medicine and wish to switch back to the originator drug.

As with all biologic medicines, collection of clinical outcomes should take place and prospectively be assessed to ensure quality of outcomes. Individual clinical teams should agree on the mechanisms of outcome data recording and collecting. Loss of biological activity after a switch from originator to biosimilar agent should be documented in a detailed fashion and, wherever possible, include anti-drug antibody monitoring.

Box 3: Practical efficacy monitoring.

1) Consider testing anti-drug antibody status (if the test is available) before switching to the new biosimilar medicine to allow future analysis of loss of efficacy in patients. Other factors, such as co-prescription of traditional DMARD or adherence to treatment should also be recorded.

2) Monitor the reasons if patients request a switch back to the original molecule. In our center's experience (supplement table 1) the main reasons leading to failure of biosimilar

treatment were issues with device acceptability and/or patients experiencing nocebo effects [44].
3) Nocebo effects may occur in any care setting and highlight the importance of communicating treatment changes clearly, including originator to biosimilar switched in practice [45-49].

However, testing for anti-drug antibodies causes added cost and thus may not be a viable option to allow this aspect of pharmacovigilance in all patients.
Lastly, a patient experience survey in the form of a short questionnaire may be carried out before and after the implementation of biosimilar treatment to ensure that patient experience has not been negatively impacted. Findings should be shared nationally/internationally and used to support future commissioning decisions when relevant [35].

3.9 Tracking of savings and biosimilar adoption rate

Although the establishment of biosimilar medicines should not be done solely for the purpose of cost saving, the potential drug budget savings are one of the main reasons behind biosimilar adoption across services and health care systems.

Box 4: Practical considerations in the UK.

In the UK, Medicines Optimization Commissioning for Quality and Innovation (CQUIN) targets agreed by Hospitals/Trusts will drive the adoption of biosimilar medicines into routine care.
1) Percentage targets: a defined percentage target for mAbs naïve patients and (usually) a different (lower) percentage target for switching patients. These percentages may increase over time and Hospitals/Trusts who fail to meet these agreements will incur financial penalties [32,50]
2) The patient should be at the center of all care, and as such the Regional Medicines Optimization Committee (RMOC) issued a statement with regards to the adalimumab biosimilar product and suggests that [45]:
a) Where severe discomfort at the injection site is of significant concern, transition to another product may be appropriate.
b) Where disease flares occur after switching to a biosimilar these are unlikely to reflect a failure of the biosimilar. Disease flares and a lack of sustained response happen commonly during treatment with the same product. Logically any lack of responsiveness (regardless of a recent switch) should prompt a discussion about changing the drug completely to a different biologic agent, but reverting to the originator drug is a possible initial step. If a flare is due to disease progression rather than lack of effect of the biosimilar (which is likely to be the majority of cases), going back to the originator will not make much difference and sooner or later the patient will move on to a different biologic agent.

4. Effects of biosimilar introduction on prescribing behavior and access to treatment

Looking at the process described above, it is apparent that adoption of biosimilar medicines is not a simple and straightforward process. Some services/centers may delay or avoid adoption of biosimilars, although potential financial penalties imposed are considerable deterrents. Nonetheless, offering "incentives" affecting our patient population may increase biosimilar use in Pediatrics. One of these incentives could be long-awaited increased access to biologic agents earlier in the treatment of JIA and/or other pediatric autoimmune/inflammatory conditions. Other incentives may target centers that are fast in adopting new biosimilar medicines, rewarding them with increments in budgets to employ staff needed in specific areas or expand their patient experience services [44]. However, this requires to be married

with concise and effective mechanisms for monitoring drug safety and outcomes. Unfortunately, to date, the adoption of biosimilar medicines has not translated to faster access to these medicines in Pediatric Rheumatology (at least in the UK and Germany, but likely also in other regions).

Box 5: Prescribing and access to biosimilars in the UK.

Rheumatology clinical teams spent a lot of time and effort switching patients to biosimilar medicines in the last years working on the premise that cost-efficiencies would lead to improved access to medicines. However, in the experience of the authors, it would seem unwise to expect changes in the near future with regards to early access to mAbs

1) The NHS England pathway to treat JIA is unlikely to change the approach that (in most cases) a non-biologic DMARD requires to be trialed first [51].

2) Financial rewards for meeting Trust CQUIN targets, if available, often have to be shared between teams or need to be diverted to the individual Trust's annual cost improvement targets.

3) For Pediatric conditions rarer than JIA, where randomized clinical trials are not available to evaluate the efficacy of treatments, access to NHS England funded drugs has become even more complex over the past years. Individual Funding Requests (IFR) are rarely accepted based on the lack of "exceptionality" and therefore will be rejected [52]. Requests for Urgent Policy Proposals are likely to be rejected with "low levels of quality evidence", which directly impacts Pediatric patients with rare conditions. Commissioning Through Evaluation might be available, but the overall process tends to be significantly time-consuming for the clinicians putting these requests forward and may take a long time to translate into access to medicines.

4) The NHS (as other healthcare systems) is under significant financial strain with new high cost treatments being recently approved for pediatric patients with non-rheumatology conditions, such as the CFTR modulator drugs for cystic fibrosis and nusinersen for certain types of spinal muscular atrophy (SMA).

Changes in the choice for first- or second-line biologic medicines may be more likely to occur. UK NICE guidelines for example state in the vast majority of their reviews that, where head to head trials determining efficacy between medicines are not available (and this is usually the case in Pediatric Rheumatology), the most cost-effective option should be used first [32].

Box 6: Potential short-term changes in access to biologic drugs

A small number of examples of increased access to high cost drugs have materialized since the adoption of biosimilar medicines.

1) Adalimumab may become the first line anti-TNF of choice, as it is now more cost-effective than etanercept (especially in younger patients where biosimilar etanercept formulations are not available).

2) Access to rituximab has increased in conditions such as juvenile dermatomyositis, where it is no longer necessary for patients to be treated with IV immunoglobulins in order to be eligible for rituximab.

3) When the IL-6 inhibitor tocilizumab will become available as a biosimilar in the near future, and always guided by available clinical evidence, clinicians may find themselves able to choose freely between TNF-blockers and e.g. IL-6 inhibitors as first line treatments for JIA and other conditions., according to patient preferences and individual disease phenotype and progression or directed by pharmacogenomics.

4) Individual Hospitals/Trusts are more likely to approve treatments for rare conditions not funded by NHS England using biosimilar mAbs if the cost is reasonable and potentially off-set with inpatient bed stays.

5. Conclusions

Biosimilar pharmaceuticals have been introduced to Pediatric Rheumatology and are here to stay. We suggest a pathway the pediatric rheumatology MDT can use for the assessment and implementation of biosimilar medicines in individual Children's Hospitals/Trusts, highlighting areas of importance in Pediatrics such as drug licensing, excipient analysis and administration device availability. Pharmacovigilance programs and patient satisfaction surveys should be considered as methods to monitor biosimilar safety, efficacy and acceptance in the Pediatric patient population. Ultimately, the more biosimilar medicines are made available, and the more competitive their prices become, the more likely the utopia of universal access to mAb medicines will come true in the future.

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7. Figure legends

Figure 1: ***The principle of extrapolation and application of similarity*** *(Reproduced with permission from [29] by courtesy of Springer Verlag GmbH).* If a biosimilar product matches the originator molecule in its structural attributes, tested biological functions, PK and PD studies in humans for a sensitive indication, then, assuming similarity for all other non-tested indications can be justified.

Figure 2: ***Development approach of biosimilar medicines compared to generic and originator biologic product***. Reproduced with permission by courtesy of Springer Verlag Gmb. The figure shows how the development required for biosimilar products is much closely related to that of the originator medicine compared to that of a generic medicine.

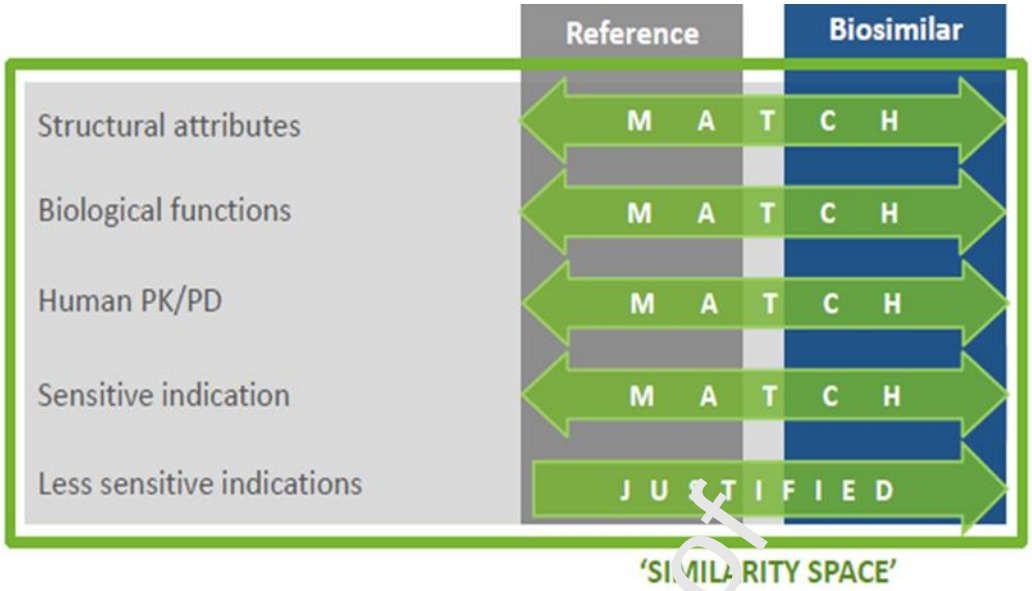

Figure 1: ***The principle of extrapolation and application of similarity*** *(Reproduced with permission from [29] by courtesy of Springer Verlag GmbH). If a biosimilar product matches the originator molecule in its structural attributes, tested biological functions, PK and PD studies in humans for a sensitive indication, then, assuming similarity for all other non-tested indications can be justified.*

	Generic	New biologic	Biosimilar
Time to market (years)	2–3	8–10	7–8
Clinical studies	Bioequivalence studies in healthy volunteers	Phase I, II, III efficacy and safety studies	Comparative phase I pharmacokinetic and Phase III study
Patients (n)	20–50	800–1000	~500
Post-approval activities	Pharmacovigilance, Risk Management Plan in special situations	Phase IV, Risk Management Plan including Pharmacovigilance	Phase IV, Risk Management Plan including Pharmacovigilance

Figure 2: ***Development approach of biosimilar medicines compared to generic and originator biologic product***. *Reproduced with permission by courtesy of Springer Verlag Gmb. The figure shows how the development required for biosimilar products is much closely related to that of the originator medicine compared to that of a generic medicine.*

***Table 1:* Etanercept biosimilar product assessment**. *Source: European Public Assessment Report (EMA); "soft" intelligence from PMSG and UKMI Written by S M Wong*

	Benepali®	**Erelzi®**
Manufacturer	Biogen	Sandoz
Preparation	25mg pre-filled syringe (PFS) 50mg Pen, PFS	25mg PFS 50mg Pen, PFS
Pens NB: Enbrel pen involves pressing a button; 27 gauge needles	Auto-injector device (pressing the pen against the skin) Needle sheath is latex-free Needle size – 27 Gauge ½ inch	Senso-ready pen (pressing the pen against the skin) Needle sheath contains a derivative of latex Needle size –27 Gauge ½ inch
License	As Enbrel® preparations	As Enbrel® preparations
Clinical study	Phase III, randomized, double-blind, study in 596 subjects with moderate to severe RA despite methotrexate therapy No pediatric reference studies	The PIII EGALITY trial comparing product with Enbrel® in 531 patients with moderate-severe chronic plaque psoriasis completed in March 2015. No pediatric reference studies
Safety	Similar between the two treatment groups and in line with the well-characterized safety profile of Enbrel®	The incidence of treatment-emergent adverse events up to week 52 was comparable between biosimilar product (59.8%) and Enbrel® (57.3%)
Homecare	- Pharma-funded service - Details of homecare services provided with each provider	- Pharma-funded service - Details of homecare services provided with each provider
Excipients <u>Enbrel®</u> Sucrose, WFI Sodium chloride L-Arginine hydrochloride Sodium phosphate monobasic dihydrate Sodium phosphate dibasic dihydrate	- Sucrose - Sodium chloride - Sodium dihydrogen phosphate monohydrate - Disodium hydrogen phosphate heptahydrate - Water for injections NB: Unlike Enbrel®, Benepali® does not contain L-arginine	- Citric acid anhydrous - Sodium citrate dihydrate - Sodium chloride - Sucrose - L-Lysine hydrochloride - Sodium hydroxide (for pH adjustment) - Hydrochloric acid (for pH adjustment) - Water for injections **NB: citric acid and sodium citrate are known to cause discomfort on injection**
Existing issues	Despite full pediatric license granted to both products, no pediatric formulation has been developed (10mg vial or 25mg powder and solvent vial) for smaller/younger patients. If biosimilar is adopted, the originator should still be offered to some patients	
Outcome	Benepali® biosimilar of choice due to excipients Current recommendations for BRAND choice are as follows: • Patients (new and old) who need doses <25mg: use Enbrel® (10mg or 25mg vials as appropriate) • Any new patient on a dose of 25mg and above will be offered Benepali® • Existing patients on an Enbrel® PFS or PEN will be informed on the Trust switching initiative and will be switched to Benepali® if agreed • Existing patients on a dose of 25mg of Enbrel® powder and solvent	

	preparation will be consulted about the possibility of switching to a 25mg Benepali® PFS • Any patients over 16 years of age and a dose of 25mg or over will be switched to Benepali® to facilitate transition to adult care. • This guidance will be reviewed as new biosimilar preparations come into the UK market. *****Unlicensed use of the biosimilar (i.e. decanting from the 25mg of 50mg formulations to give doses under 25mg) is not recommended*****

***Table 2:* Adalimumab biosimilar product assessment.** *Source: European Public Assessment Report (EMA); "soft" intelligence from PMSG and UKMI Written by S M Wong*

	Amgevita®	**Imraldi®**	**Cyltezo®**
Manufacturer	Amgen	Biogen	Boehringer
Presentation	Sureclick Pen 40mg in 0.8mL 27G 20mg in 0.4mL and 40mg in 0.8mL PFS, 27 and 29G Needle sheath in Pen contains a latex derivative	40mg in 0.8mL Pen 40mg in 0.8mL PFS No 20mg preparation	40mg Autoinjector pen in 0.8mL 40mg in 0.8mL PFS No 20mg preparation Needle sheath in Pen contains a latex derivative
License	As Humira® except pediatric uveitis	As Humira® except pediatric uveitis	As Humira® except pediatric uveitis
Clinical studies	Available via EMA in RA patients No paediatric reference studies	Available via EMA in RA patients No paediatric reference studies	Available via EMA in RA patients No paediatric reference studies
Safety	As above Comparable (compared to old Humira® formulation)	As above Comparable (compared to old Humira® formulation)	As above Comparable (compared to old Humira® formulation)
Homecare	Pharma-funded	Pharma-funded	Pharma-funded
Excipients	Glacial acetic acid, sucrose, polysorbate 80, sodium hydroxide quantum Citrate free	Sodium citrate, citric acid monohydrate, histidine buffer, sorbitol, polysorbate 20, water	Sodium acetate trihydrate, glacial acetic acid. Trehalose dehydrate, polysorbate 80 and water Citrate free
Existing issues	Amgevita® only product with 20mg pediatric preparation None of them licensed in pediatric uveitis: potential use off-label or keep originator Pain/device comparison studies used Humira® old preparation for comparison Concentration: half of Humira® = larger volume of injection Humira® introduced 3 changes to their formulation: 27 to 29G needle, removal of citrate and reduction of injection volume. Pediatric patients consistently reported better tolerability of this formulation VS the old one in our unit. Amgevita® and Cyltezo® are citrate free, however, needle gauge in some of the products is still 27G and the volume remains the same as the old Humira® formulation. It remains to be seen whether removing the citrate alone will lead to a similar patient experience as with the new Humira® formulation		
Outcome	Trial of Amgevita® (citrate free and pediatric formulations) in new patients. If no issues reported, offer switch to existing patients. Monitor for reports of discomfort on injection		

Table 3: ***Available options to inform patients who are switching from originator products to biosimilar products.*** *An example of a patient information letter can be found in Appendix B*

Option	Positive aspects	Negative aspects
Focus groups prior to adoption	Open, face to face	Difficult to organize Could be costly if facilities or catering need to be booked Logistic issues if large number of patients on the drug
One to one patient/carer consultation with trained clinician	Face to face Opportunity to ask questions in a private environment	Time consuming (could take away time from clinic review) Patients might take a long time to be due a clinic visit delaying biosimilar implementation Availability of rooms for consultation
Distribution of patient information leaflets with contact details of relevant professionals within the MDT (nurse specialists, pharmacists)	Suitable for large patient numbers Suitable for patients who are being treated at home Avoid delays in implementation of biosimilar	Not face to face Relays on the patient to contact team if there are any issues/worries Does not capture potential technique training needs (new administration device)

Highlights:

- Biologic therapeutics are manufactured in biological sources
- Biosimilars are altered versions of the not patent protected innovator drug
- Significant concerns exist in the adoption of drugs not trialed in children
- Real-life data on drug safety and efficacy need to be collected to increase evidence base
- Despite all concerns, biosimilars may improve access to biologics in Pediatric rheumatology