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Prescribing biosimilars: when reluctance overcomes evidence

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Generic formulations of small molecules are usually as effective as originators, have similar harms, and are cheaper to prescribe. The same should be true of biosimilars, which are generic equivalents of originator biological medicines (biologics).[1]

Two years ago[2] we cited an article in the *Financial Times,*[3] whose author claimed that the UK had been slow to adopt biosimilars. Here we provide evidence that that is so, based on the limited publicly available information on NHS prescribing of biosimilars.

Biosimilars are biologics that are highly similar to other already approved biologics and are themselves approved according to the same standards of pharmaceutical quality, safety, and efficacy.[4] They are not necessarily identical. Consider, for example, monoclonal antibodies. Although a biosimilar is likely to preserve the primary amino acid sequence of the originator, differences in glycosylation, deamination, oxidation, or three-dimensional structure can occur. These can affect interactions with target molecules, which could lead to differences in benefits, harms, or both, between biosimilars and the corresponding originators. This may be the case, for example, with epoetins.[5,6]

Clinicians face two problems: choosing between an originator or a biosimilar when starting therapy and whether to switch from one to the other during established therapy.

There are principles to ensure that biosimilars are similar enough,[7] and US and European regulators demand that biosimilars should be "highly similar to the reference medicinal product in physicochemical and biological terms".[8] This includes, for example, pharmacokinetic and pharmacodynamic similarity, and being used in the same dosages as the originator product. Furthermore, "any observed differences have to be duly justified with regard to their potential impact on safety and efficacy." The principles are included in guidance from the US Food and Drug Administration,[9] and NICE has provisions for recommending biosimilars when appropriate.[10]

There is some reassuring evidence of equivalence. For example, two infliximab biosimilars, Remsima and Inflectra[11,12,13] are identical to the originator, Remicade, in pharmaceutical form, strength, composition, and route of administration. The biological actions of Remsima are essentially identical to those of Remicade, apart from minor pharmacodynamic differences that appear to be clinically insignificant.[14] The pharmacokinetics are almost identical, and clinical markers of disease activity respond equally well to originator and biosimilar products in rheumatoid arthritis and ankylosing spondylitis.

The WHO plans to prequalify biosimilars for cancer therapy, giving them a global stamp of approval.[15] Comparability of quality, safety, and efficacy will make them eligible for procurement by UN agencies. This should increase assurance of equivalence.

However, showing that two products are of equal efficacy does not prove that switching them maintains the balance of benefits and harms in individual patients. For example, in an 18-month study in inflammatory bowel disease, switching from originator infliximab to a biosimilar did not affect efficacy, but 13/143 patients dropped out because of adverse events.[16]

A systematic review of 58 studies, including 12 clinical trials, mostly involving infliximab or epoetins, suggested that the expected cost savings of switching

outweighed the risks of anticipated harms.[17] A later review of 57 studies, covering a wider range of compounds (infliximab and epoetins, but also adalimumab, etanercept, filgrastim, follicle stimulating hormone, genotropin, insulin glargine, and rituximab), reported that safety and efficacy were mostly unchanged after switching.[18] However, the data were limited, and the authors commented that well powered and appropriately analysed clinical trials and pharmacovigilance studies, with long-term follow-up and multiple switches, were needed.

We sought evidence about UK prescribing of biosimilars in two publicly accessible sources: OpenPrescribing.net, a freely available website containing detailed current data on all prescribing in individual English general practices[19]; and the NHS Medicines Optimisation Dashboard, which contains a limited number of prespecified measures at the individual NHS Trust level.[20] Insulin glargine is commonly prescribed in primary care, and detailed data are available through OpenPrescribing.net: the originator, Lantus, still accounts for 90% of GP prescriptions (Figure 1); the biosimilar Abasaglar accounts for around 60% of the increased number of prescriptions since it was licensed in September 2015. This suggests that 40% of new patients are still receiving the originator, whose NHS indicative price is 7% higher, and that switching is rare. No other biosimilars are commonly prescribed in primary care, and hospital prescribing data are limited: from the large number of biosimilars now available (Table 1), the Medicines Optimisation Dashboard gives information on only three (Table 2). Uptake has been incomplete. This may have substantial cost implications, as prices are high and originators typically cost about 10% more than biosimilars.[21]

Reasons for the poor uptake of biosimilars may include lack of familiarity, therapeutic inertia, concern about patient confusion over different brand names and different looking formulations, perceived lack of efficacy, the nocebo effect,[22] and apparently modest percentage price differences.

When a biosimilar has been licensed, there should be no concerns about starting treatment with it rather than the originator. Switching to a cheaper product in a patient who is already taking an originator can also be recommended when there is high quality

evidence of equivalence of the benefits and harms, provided progress is then carefully monitored.

Table 1. Examples of biosimilars currently approved in the EU and/or USA

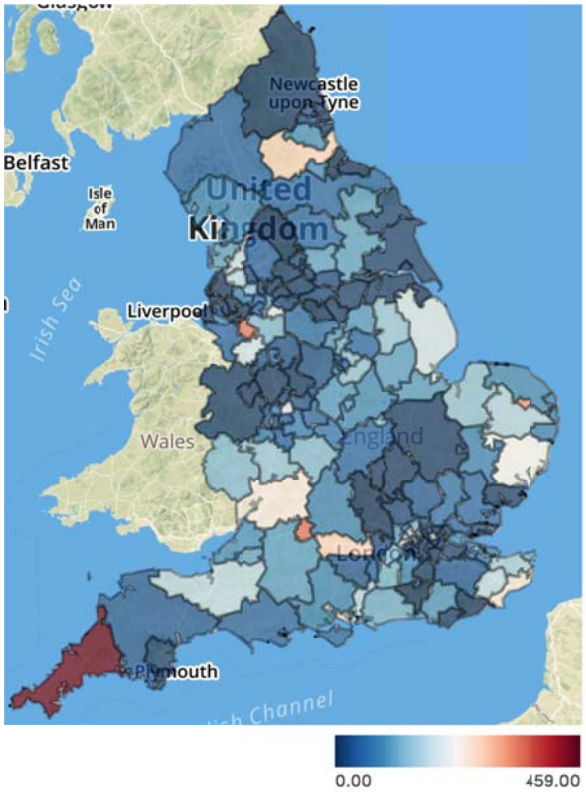
Generic name*	Originator brand name (company)	Examples of biosimilar brand names (company)
Adalimumab[a]	Humira (AbbVie)	Imraldi (Samsung Bioepis/Merck)
Darbepoetin[b]	Aranesp (Amgen)	Retacrit (epoetin zeta; Hospira) Silapo (epoetin zeta; Stada Arzneimittel)
Epoetin alfa[b]	Epogen/Eprex/Procrit (epoetin alfa; Amgen/ Johnson & Johnson)	Abseamed (Medice Arzneimittel Pütter) Binocrit (Sandoz)
Etanercept[c]	Enbrel (Amgen/Pfizer)	Brenzys/Benepali (Samsung Bioepis/Merck) Erelzi (Sandoz)
Filgrastim[b]	Neupogen (Amgen)	Biograstim (CT Arzneimittel) Filgrastim Hexal (Hexal) Grastofil (Apotex)
Infliximab[a]	Remicade (Johnson & Johnson/Merck)	Flixabi/Renflexis (Samsung Bioepis/Merck) Remsima/Inflectra/Flammegis (Celltrion/Hospira)
Insulin glargine[d]	Lantus (Sanofi)	Abasaglar/Basaglar (Eli Lilly/Boehringer Ingelheim) Semglee (Mylan/Biocon)
Rituximab[a]	MabThera/Rituxan (Roche)	Truxima/Blitzima/Ritemvia/Rituzena (Celltrion/Hospira)
Teriparatide[d]	Forteo/Forsteo (Eli Lilly)	Movymia (Stada Arzneimittel) Terrosa (Gedeon Richter/Mochida Pharmaceutical)
Trastuzumab[a]	Herceptin (Roche)	Ontruzant (Samsung Bioepis/Merck)

*Hyperlinks are to entries in the GaBi (Generics and Biosimilars Initiative) website (last accessed 15 June 2018)
[a]Monoclonal antibodies; [b]Glycoproteins; [c]Fusion protein; [d]Polypeptide hormones

Table 2. Current percentage uptakes of three biosimilars in hospitals

Drug	Percentage uptake	
	Median	Interquartile range
Etanercept	76%	60–90%
Infliximab	90%	85–98%
Rituximab	60%	42–76%

Figure 1. Numbers of items prescribed as Abasaglar per 1000 items of insulin glargine, in English Clinical Commissioning Group as at April 2018



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