

UNCHARTERED TERRITORY: NICE, BIOSIMILARS AND GROWTH HORMONE



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In February a summit was convened in Parliament to discuss the introduction of 'biosimilar' medicines to the treatment area of restricted growth in children and the implications this might have on the current review by the National Institute for Health and Clinical Excellence (NICE) on the use of growth hormone (GH) in children (2009). GH prescribing in children was originally appraised and approved by NICE in 2002 prior to the introduction of 'biosimilar' medications. This summit provided an opportunity to explore the implications for NICE in its reappraisal of the use of GH in children, which for the first time will include a 'biosimilar' medicine.

Human GH is manufactured using recombinant biotechnology and has been used to treat restricted growth in children for over 25 years, when it was first introduced to clinical practice. Many hundreds of thousands of children have been treated with recombinant human GH (rhGH) worldwide, and through continuing pharmacovigilance, to date, such technology has been demonstrated to be remarkably safe. This has been a great success but only achieved by strict monitoring as no medicine or treatment should ever be

considered completely risk free. Prescribers still have a significant number of responsibilities in counselling and advising parents and children about the possibilities of adverse effects whilst reassuring them of the benefits of treatments. Furthermore, doctors prescribing rhGH have ultimate responsibility for patient outcomes and a statutory responsibility of reporting Adverse Drug Reactions (ADRs). In the UK it is important that prescribers are fully supported in this role. To date, regulatory bodies have taken a rigorous and robust approach to the use of biotechnology treatments. Current regulation in the UK is through the European Medicines Agency (EMA), who have responsibility for licensing treatments and the Medicines and Healthcare products Regulatory Agency (MHRA), the 'health watchdog' who are responsible for monitoring quality and safety of treatments.

The patent for many of the rhGH brands has now expired and today we face an issue that has yet to become relevant to most other health areas, that of 'follow-on' or 'copy' biotechnology treatments. Due to the nature of biotechnology these treatments can only ever be similar, and never the same as the reference products. As

such, they are referred to as 'biosimilars' under European guidance.

For the prescriber, 'biosimilar' medicines pose difficult questions for a number of reasons. As with any new treatment, and particularly any new biotechnology treatment, it is essential that rigorous and robust safety procedures are put in place as they are introduced. This is particularly important as, despite being unique biotechnology products in their own right, due to their similar nature to originator products, the manufacturers of 'biosimilar' treatments have negotiated a different route to market. The EMA has introduced a unique pathway for 'biosimilars', relinquishing their robust stance on the need for extensive studies on long term efficacy and allowing the use of new rhGH preparations without submitting them to their standard trials of efficacy and safety. Whilst requiring less data to prove quality, safety and efficacy, this 'biosimilar pathway' is robust and rigorous enough to meet the safety requirements of the EMA. Despite this, a number of European countries, including France and Spain, have introduced additional precautions in the form of legislation to safeguard patients during the introduction of 'biosimilars'.

A number of steps have been taken at a national level to ensure patient safety whilst we learn the similarities and differences of these medicines,

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such as any potential difference in efficacy or dosage. Actions taken in the UK include: inclusion of guidance about 'biosimilar' medicines in the 'general guidance' section of the British National Formulary (BNF) and the flagging of all 'biosimilars' with a black triangle, highlighting that the treatment is new and is being intensely monitored; strict guidance on non-substitution and non-switching from originally prescribed products; inclusion of the issue in the MHRA Drug Safety Update; and heightened campaigns on pharmacovigilance protocols such as the yellow card system.

Dr Brian Iddon MP invited Professor Peter Littlejohns, Clinical and Public Health Director of NICE, to attend the recent Parliamentary Summit on 'biosimilar' rhGH and to discuss the forthcoming review. Professor Littlejohns highlighted how the remit of NICE is to look at clinical and cost effectiveness of treatments and as such, safety recommendations fall outside of their remit. Despite this, there remains a significant need among clinicians to understand the new 'biosimilar' technology. Currently, there is a distinct lack of knowledge in this area and it is essential that this be considered by the NICE appraisal committee and that every avenue is taken to explain to users the safety issues related to any treatment in a clear, frank and up front way. Many of the concerns arise from a lack of information or understanding about the differences between 'biosimilar' and originator medicines, and this opinion was voiced at the meeting.

Michael Ranke¹ (a paediatric endocrinologist based in Germany) advocates a '*premium nihil nocere*' (first do no harm) stance be taken requiring strict pharmacovigilance

and collection of more robust research data before 'biosimilars' are used in growth disorders. Ranke argues that the 'biosimilar' label just denotes that it is a treatment which has been approved by a unique process and the final prescription of any treatment must be made from an independent and informed position¹. It is now crucial that all sectors of the community responsible for treating growth disorders with rhGH including 'biosimilars' are fully informed so that information is freely made available to clinicians, patients and their carers.

Taking this advice into consideration, there are a number of steps that should be taken to ensure the safe introduction of 'biosimilars' to the treatment of growth disorders, as follows:

Do not switch: In the treatment of growth disorders, switching between different brands of rhGH is not recommended. This becomes more pertinent with the introduction of 'biosimilars', as there is no certainty that the dosage or efficacy will be equal between the originator product and any 'biosimilar'. For this reason strict, non-switching regulations must be maintained. It is important that all prescribers are made aware of this.

Prescription by brand name only: Similar to the strict regulations on non-switching, prescribers must be made aware that prescription by brand name is essential and prescribing by the International Nonproprietary Name (INN) must always be avoided. Due to the possible and unforeseen differences, we cannot afford to take the same approach to biotechnology products as we do with generic medicines.

Patient education and Patient Information Leaflets: Currently, there is no information easily available to patients about 'biosimilars' and their unique route to market. Such information should be made available on Patient Information Leaflets for any 'biosimilar' treatment, in a noticeable and easily understandable way. This is particularly important in helping patients to understand the importance of reporting ADRs. Additionally, patient information should be made available, through the prescriber, at the time at which treatment is chosen and agreed.

Clear and distinct packaging: Each biotechnology treatment is unique and, as such, this information should be easily visible to the pharmacist, patient and prescriber to avoid inadvertent switching.

Clinician awareness: Everyone who is either able to prescribe or dispense 'biosimilar' treatments needs to be fully aware of the difference in technology from originator products and the regulatory process. It is also important that clinicians using 'shared care' arrangements with GPs for rhGH prescribing, need to ensure that GPs are familiar with such treatments being received by patients under their care as they are the people most likely to be on the front line when patients present with ADRs.

The yellow card system: This system is crucial in raising awareness is the role of the MHRA in ensuring there are high levels of awareness around the yellow card and reporting mechanisms for ADRs.

Pharmacovigilance: Currently a number of manufacturers of rhGH have invested in a rigorous post marketing surveillance scheme to collect and share data. All

producers of 'biosimilar' medicines should put in place their own post marketing surveillance schemes and publish their findings.

Inclusion in NICE: Whilst we have a number of avenues through which awareness of 'biosimilar' treatments is increased it is clear that a major part of the community remains unfamiliar with 'biosimilars'. To ameliorate this situation, the NICE appraisal committee should consider including information about 'biosimilar' technology and this should be reflected in any final recommendations on the use of products.

It is important that our patients receive the very best levels of care. Essential in this is awareness of all of the treatments available, what is different, what is the same; understanding how and why regulatory agencies have taken the steps they have to date and what role we have as prescribers and users in ensuring a safe introduction of these unique, but similar, biotechnology treatments to clinical practice. Whilst it is not within the remit of NICE to consider safety, they should reflect the regulations already in place, at least until we know a good deal more about these new products. In examining 'biosimilar' medicines alongside other biotechnology treatments, NICE are in uncharted territory. Whilst this should not hold any of us back from exploring all possible courses of action, we should proceed with caution and from a fully informed position.

Footnote

1 Ranke, M. B. (2008) New Preparations Comprising Recombinant Human Growth Hormone: Deliberations on the Issue of Biosimilars. *Hormone Research* [online]. 69 (1) 22-28. Available at: <http://content.karger.com/ProdukteDB/produkte.asp?typ=pdf&doi=111791>