BMJ Open

What drives the prescribing of biosimilars in England?

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-013730
Article Type:	Research
Date Submitted by the Author:	05-Aug-2016
Complete List of Authors:	Chapman, Stephen; Keele University, School of Pharmacy Fitzpatrick, Raymond; Keele University, School of Pharmacy Aladul, Mohammed; Keele University, School of Pharmacy
Primary Subject Heading:	Health policy
Secondary Subject Heading:	Health services research
Keywords:	EPIDEMIOLOGY, THERAPEUTICS, HEALTH SERVICES ADMINISTRATION & MANAGEMENT

What drives the prescribing of biosimilars in England?

Stephen R Chapman, Professor of Prescribing[1], Raymond W Fitzpatrick, Professor of Clinical Pharmacy[1], Mohammed I Aladul, PhD student in Pharmacy Practice[1]

[1] School of Pharmacy, Keele University, Hornbeam Building, Newcastle-under-Lyme, Staffordshire, ST5 5BG, United Kingdom.

* Correspondence to: Stephen R Chapman

School of Pharmacy, Keele University, Hornbeam Building 3.06, Newcastle-under-Lyme, Staffordshire, ST5 5BG, United Kingdom.

Tel: +44 (0)1782 734131

Fax: +44 (0)1782 733326

E-mail: s.r.chapman@keele.ac.uk

KEY WORDS- growth hormone, prescribing trends, patient preferences, cost, biosimilar

RUNNING HEAD- Impact of formulation on growth hormone prescribing

WORD COUNT: 2505

What drives the prescribing of biosimilars in England?

ABSTRACT

Objective: The patent expiry of a number of biological medicines and the advent of biosimilars, raised the expectations of healthcare commissioners that biosimilars would reduce the high cost of these medicines and produce potential savings to the NHS. We aimed to examine the prescribing pattern of different growth hormone preparations in both primary and secondary care in England to determine relative rates of decrease or increase and identify the possible factors influencing prescribing.
Design: Longitudinal observational study.
Setting and data sources: Primary care prescribing cost and volume data was derived from the NHS business services authority website, and for secondary care from the DEFINE database, between April 2011 and December 2015.
Outcomes: Quarterly prescribing analysis to examine trends and measure the relationship between utilisation and price.
Results: Expenditure and utilisation of growth hormone in primary care decreased by 17.91% and 7.29% respectively, whereas expenditure and utilisation in secondary care increased by 68.41% and 100% respectively between April 2011 and December 2015. The utilisation of reconstitution requiring products significantly declined in primary care (R^2 = 0.9292) and slightly increased in use in secondary care (R^2 = 0.139). In contrast, the utilisation of ready to use products significantly increased in use in both primary (R^2=0.7526) and secondary care (R^2=0.9633) respectively. Weak or no correlation existed between utilisation and price of growth hormone preparations in primary and secondary care.
Conclusion: The price of growth hormone products was not the key factor influencing prescribing of the biologic medicines. The main driver for specific product selection was the ease of use and the number of steps in dose preparation. Prescribers appear to be taking into account patient preferences rather than cost in their prescribing decisions.

Strengths and limitations of study

- This study includes cost and volume analysis of all available growth hormone preparations in England.
- The study analyses longitudinal observational dataset reflecting “real life“ prescribing in primary and secondary care.
- The analysis shows which factors drive prescribing of growth hormone.
- Time period for analysis was limited to five years.
- Segmented regression of interrupted time series analysis of the data was considered but cannot be applied.

INTRODUCTION

Biological medicines can be defined as biotechnological products whose active ingredient is developed from living cells by one or more of recombinant deoxyribonucleic acid (DNA), controlled gene expression and antibody production methods.[1] These medicines represent an advance in the treatment of patients with chronic and life-threatening diseases such as diabetes, growth hormone deficiency and cancer.[2] Biological medicines are expensive compared to conventional drugs, mainly due to the cost of research and development and their complicated biosynthesis and handling techniques.[3] As a consequence, they potentially place a heavy burden on health care budgets even in developed countries with high resources.[4] In a free at the point of need health system funded through general taxation, such as the UK NHS, there is always pressure to remain within budget and provide value for money for tax payers.[5] According to the Health and Social Care Information Centre report in 2015, the expenditure on medicines in England was £15.5 billion with hospital expenditure growing at a higher rate than primary care.[6] The Five Year Forward View of the NHS England predicted a budget

deficit of nearly £30 billion a year by 2020-2021 if the increasing demand was met by no further annual efficiencies and funding remained flat in real terms.[7] NHS Health care policy makers' aim to reduce the acquisition cost of the drugs without affecting the clinical outcome by increasing the uptake of less expensive generic alternatives to branded medicines.[8]

The patent expiry of a number of biological medicines and the establishment of regulatory frameworks by the European Medicines Agency to register similar biological medicines termed "biosimilars", raised the expectations of healthcare commissioners that biosimilars would reduce the high cost of these medicines and produce potential savings to the NHS. The UK is a relatively large market for biological and generic medicines, so represents a potentially attractive market for the biosimilars manufacturers.[9] Recent data has revealed that the uptake of biosimilars in the UK is low compared to Germany and Sweden.[10] Possible reasons behind this low uptake were healthcare prescribers and patients concerns regarding quality, safety and efficacy of biosimilars and brand loyalty.[11]

Human recombinant growth hormone is a biological medicine where a biosimilar has been available since 2006.[12] An IMS Health report in 2014 showed that uptake of biosimilar growth hormone varies considerably across the different European markets, with highest use in Poland (99%) and lowest in Norway (3%) and the UK (5%). In Poland, the implementation of a strict tendering procurement system has resulted in the evolution of growth hormone biosimilar market share.[10 13]

The UK Medicines and Healthcare products Regulatory Agency (MHRA) guidance on biosimilars is that products should not be assumed to be identical due to the high molecular weight and structural differences between biological medicines. Thus, biological medicines and biosimilars are prescribed by brand names rather than by their International Non-propriety Name.[14] UK policymakers may have anticipated that the lower price of biosimilars compared to branded biological medicines (15-30%) would lead to a rapid uptake in the same way as conventional small molecule generic medicines, even though the price differential is far greater for generic small molecule medicines (50-90%).[15] The high unit cost of biological medicines means the small percentage price differential could result in significant annual savings.[16] The extent to which savings on prescribing for conventional small molecule medicines can be realised is a function of multifactorial influences on prescribing in the UK.[17] It is not clear whether this is universally applicable to biological medicines. The main objectives of this study were to undertake a detailed analysis of the pattern of use of human recombinant growth hormone in primary and secondary care settings in England and to determine possible factors influencing its prescribing.

METHODS

Data source

The study was a retrospective analysis of primary and secondary care usage of growth hormone in England. Primary care monthly prescription cost analysis data was derived from the NHS business services authority website,[18] for prescriptions dispensed in primary care in England from April 2011 to December 2015. Monthly secondary care data were taken from DEFINE Software for 2011-2016 since this prescribing database did not exist before April 2011. DEFINE Software is a NHS prescribing database of medicines usage in approximately 120 hospitals who subscribe to the software package. Data were at gross national level not at institutional or patient level. The volume comparator was the defined daily dose (DDD), defined by the World Health Organisation (WHO) as the mean maintenance daily dose of a medicine for its principal indication in adults. The DDD index for growth hormone is 2U.[19] Primary care data were number of items issued and amount of drug in units. This was converted into defined daily doses using the following formula:

Drug usage (DDDs) = (items issued ×amount of drug per item)/DDD

Secondary care data were already available in defined daily doses. Prices of the individual preparations were expressed as price per defined daily dose (£/DDD).

Statistical analysis

Prescribing trends were examined for growth hormone in primary and secondary care over the period April 2011– December 2015. Linear regression analyses were used with a quarter (three months) as the independent variable and prescription DDD as dependent variable, using quarterly data from each in primary and secondary care. The regression coefficient values were divided by the baseline

prescription DDD (in April 2011) to calculate the average quarterly percentage increase or decrease in prescribing of growth hormone. Correlation analyses were used between prescription DDD and cost/DDD, using quarterly data from each in primary and secondary care. All calculations were performed using Microsoft Excel 2013 and SPSS 21.

RESULTS

Pricing and Expenditure

In primary care, prices of branded growth hormone preparations did not change between April 2011 and December 2015 with the exception of Genotropin® preparations which decreased by 25%. Biosimilar growth hormone (Omnitrope® preparations) prices decreased by 15% over this period (Table 1). Over the same time period there were higher price reductions in secondary care, including all Genotropin® preparations, Humatrope Cart®, Norditropin SimpleXx®, Omnitrope SurePal® and Zomacton Inj® (Table 1).

Expenditure on growth hormone preparations in primary care in England decreased by 17.91% between April 2011 and December 2015, whereas expenditure in secondary care increased by 68.41% during the same period.

Table 1 Prices of growth hormone preparations

	Price per DDD in primary care			Price per DDD in secondary care		
	Apr 2011	Dec 2015	% dif	Apr 2011	Dec 2015	% dif
Genotropin Cart®	15.45	11.59	-25	18.55	13.4	-27.75
Genotropin GoQuick®	15.45	11.59	-25	18.55	13.91	-25
Genotropin MiniQuick®	15.45	11.59	-25	18.55	13.91	-25
Humatrope Cart®	12.00	12.00	0	13.20	12.00	-9
Norditropin NordiFlex®	15.45	15.45	0	18.55	18.55	0
Norditropin SimpleXx®	14.18	14.18	0	17.02	14.55	-14.5
NutropinAq Cart®	13.53	13.53	0	14.37	15.34	6.75
Omnitrope Cart®	11.69	9.83	-16	11.52	11.52	0
Omnitrope SurePal®	11.56**	9.83	- 15	13.46**	10.92	-19
Saizen Cart®	15.45	15.45	0	18.55	18.55	0
Saizen Click.easy®	15.45	15.45	0	18.55	18.55	0
Zomacton Inj®	13.28	13.28	0	15.946	13.95	-12.5

*Omnitrope® and Omnitrope SurePal® are growth hormone biosimilars
**Omnitrope SurePal® was marketed in June 2013 in secondary care and October 2013 in primary care

Volume of utilisation

Growth hormone utilisation in primary care declined from 764,877 DDDs in second quarter 2011 to 709,054 DDDs in the fourth quarter 2015. Regression analysis indicates that this decline of on average 0.45% per quarter (95% confidence interval 0.70 to 0.21) is statistically significant. Genotropin Cart®, Norditropin SimpleXx® and Saizen Click.easy® dominated the growth hormone market by volume, accounting for 30%, 24% and 17.5% respectively of prescribed growth hormone in second quarter 2011 (Figure 1). By the fourth quarter 2015, Genotropin Cart®, Norditropin SimpleXx® still had the highest share of the growth hormone market at 22% for both but Saizen Cart® had replaced Saizen Click.easy at 14.5% (Figure 1).

In contrast to primary care, secondary care utilisation of growth hormone doubled from 152,457 DDDs in second quarter 2011 to 304,443 DDDs in fourth quarter 2015 representing a statistically

significant rise of on average 5.8% (95% confidence interval 4.71 to 6.89) per quarter. As in primary care Genotropin Cart® and Norditropin SimpleXx® dominated the growth hormone market by volume, accounting for 18%, 23% respectively of prescribed growth hormone in second quarter 2011. By the fourth quarter 2015, Genotropin Cart®, had decreased to 12% Norditropin SimpleXx® increased slightly to 25% but Omnitrope Cart® and Saizen Cart® also accounted for 11% and 12% of the market respectively (Figure 2).

The correlation analysis between price per DDD and product utilisation in primary care revealed that for Norditropin NordiFlex®, Saizen Cart®, Saizen Click.easy® there was no correlation. For Genotropin Cart® there was an intermediate positive correlation (R^2=0.5023), for Genotropin MiniQuick®, Humatrope Cart® , Norditropin SimpleXx®, Zomacton Inj® there were weakly positive correlation (R^2=0.1081, R^2=0.075, R^2=0.2313 and R^2=0.0006 respectively). For remaining products there were weakly negative correlations (NutropinAq Cart® R^2=0.2066, Omnitrope Cart® R^2=0.0764, Omnitrope SurePal® R^2=0.3614), with the exception of Genotropin GoQuick® there was an intermediate negative correlation.

In secondary care, a similar diverse pattern of correlation between price/DDD and product utilisation was seen. Norditropin NordiFlex® and Omnitrope Cart® showed no correlation. For Genotropin GoQuick®, NutropinAq Cart® and Saizen Cart® there were weakly positive correlation (R^2=0.2535, R^2=0.0873, R^2=0.0004 respectively). For remaining products there were weakly negative correlations (Genotropin Cart® R^2=0.0128, Genotropin MiniQuick® R^2=0.1622, Humatrope Cart® R^2=0.0155, Omnitrope SurePal® R^2=0.4973 and Zomacton Inj® R^2=0.3766), with the exception of Norditropin SimpleXx® there was an intermediate negative correlation.

Figure 3 shows the utilisation trends for products requiring reconstitution and those in a ready to use formulation in primary and secondary care settings. The utilisation of products requiring reconstitution (Genotropin Cart®, Genotropin GoQuick®, Genotropin MiniQuick®, Humatrope Cart®, Saizen Click.easy® and Zomacton Inj®) all showed a very clear decline in use in primary care (R^2=0.9292) and a very slight increase in use in secondary care (R^2 = 0.139). In stark contrast, the utilisation of ready to use products (Norditropin NordiFlex®, Norditropin SimpleXx®, NutropinAq Cart®, Omnitrope Cart®, Omnitrope SurePal®, Saizen Cart®) showed a very clear increase in use in both primary and secondary care (R^2=0.7526) and (R^2=0.9633) respectively.

DISCUSSION

The long established principles of good prescribing practice and medicines optimisation suggest that clinicians aim to prescribe to maximise effectiveness, minimise risks and take into account the patients experience.[20] At the same time, in a health system free at the point of need funded by general taxation, prescribers consider relative costs of medicines and NHS policy and NICE guidance whilst still respecting the patient's choice.[21] [22] Balancing between these conflicting aims and recommendations result in good prescribing to achieve maximum effectiveness, minimum risk and cost and respecting.

In England, there are currently seven preparations of growth hormone. Although these preparations differ in their injecting device for the delivery of growth hormone, these preparations are equal in terms of clinical effectiveness.[23] With the availability of such a variety of preparations endocrinologists and other healthcare professionals prescribing growth hormone are being asked to make some complex decisions regarding the selection of the preparation for each patient.. The latest NICE guidelines in 2010 for treatment with growth hormone stated that the product selection should be based on a discussion between the prescriber and the patient or the patients' parents, taking into account the advantages and disadvantages of each device. If more than one option is suitable the less expensive one should be chosen.[23]

In this study, we classified growth hormone delivery devices according to the formulation into reconstitution requiring agents and ready to use agents. Ready to use agents were characterised by fewer steps and time required for dose preparation by patients and potentially a reduction in user errors that may occur during the reconstitution process. Studies have identified that premixed solution devices (ready to use devices) are more acceptable to patients and/or parents than reconstitution requiring devices. The simplicity and the least steps required for preparation and administration of growth hormone doses are considered among the most desirable attributes of administration devices.[24 25]

Interestingly, the utilisation of the growth hormone market leader in primary care Genotropin Cart® decreased over the study period despite a 25% price reduction (Figure 1). Over the same time period Saizen Cart® (ready to use product) replaced Saizen Click.easy® (reconstitution requiring agent) although it was the same price (Figure 1). The pattern of product utilisation in secondary care was more diverse (Figure 2). In this sector Genotropin Cart® usage decreased despite a 27.75% price reduction over the study period (Figure 2). The market leader in secondary care, Norditropin SimpleXx® (ready to use agent), grew only slightly despite a 14.5% price reduction. Omnitrope Cart® and Siazen Cart® (both ready to use agents) increased their share of the secondary care market although in both cases the price did not change. These findings suggest ease of use rather than price is the key influence on the prescribing decision. The analysis of price and product utilisation supports this observation. A number of products both in primary and secondary care showed no correlation between price and production utilisation. Indeed some showed a positive correlation indicating that the higher price was associated with higher use. A negative correlation would suggest that price was influencing use. However, in both primary and secondary care all the negative correlations were weak $R^2<0.5$, with the exception of Genotropin GoQuick® in primary care and Norditropin SimpleXx® in secondary care which were intermediate $R^2>0.5<0.75$. This complete diversity of correlations in both sectors indicates price is not the driver for product use.

The use of ready to use agents increased in both sectors during the study period (Figure 3). This explains the slight overall decrease in growth hormone in primary care as it comprises a growth in the use of the ready to use agents counteracted by a significant decrease in the use of the reconstitution requiring agents. Furthermore, the overall growth in secondary care comprises a significant (almost tripling) growth in the ready to use agents and a flattening use of the reconstitution requiring agents (Figure 3). This indicates that ease of use rather than price is the key driver for growth hormone product selection in both primary and secondary care. The findings from this study agree with previous studies of branded growth hormone that outlined that ease of use and convenience (premixed formulations) were the most important product characteristics from patients' perspective.[25 26 27] This may have been because the patients are adolescents who will be in full-time education and require formulations which are quick and easy to use.

Previous literature on this subject has focused on patient preferences in relation to specific devices. This study is the first to show that these preferences are translated into prescriber product selection. Implicitly this suggests that for growth hormone, prescribers, whilst following the principles of medicines optimisation take more account of patient preferences than central guidance on cost efficiency. This contrasts with other health economies were mandated switching to biosimilars meant that 90% of prescribing was the less expensive biosimilar.[28]

Our study has several limitations, firstly, the time period for analysis was limited to five years as we wanted to explore the utilisation of growth hormone in both primary and secondary care. We could only access monthly data for primary and secondary care since 2011. Secondly, segmented regression of interrupted time series analysis of the data was considered but growth hormone prices change were not linked to a single point of time and NICE guidance on growth hormone was not changed during

the study period. Visual analyses of Figures 1 and 2 showed no abrupt change in the pattern of utilisation of growth hormone over the study period required for this type of analysis.

CONCLUSION

This study has demonstrated that the price of growth hormone products is not the key influencing factor in prescribing of biologic medicines. The main driver for specific product selection is the ease of use and fewer steps in dose preparation. Prescribers are clearly taking into account patient preferences rather than cost in their prescribing decisions, in line with national guidance.

Contributors: All authors have contributed to this study and all authors reviewed and approved the final version of the manuscript. SRC designed the study, interpreted the results and reviewed the manuscript and corrected the final version of the manuscript. RWF participated in the study design, interpreted the results and reviewed the manuscript and corrected the final version of the manuscript. MIA participated in the study design, data collection, and interpretation of results, prepared the manuscript draft, and performed all analytical testing and manuscript review.

Funding: This research was not funded or sponsored by any organisation and the researchers are independent of any funding bodies.

Access to data: All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: No ethical approval was required for this research.

Data sharing statement: No additional data are available.

REFERENCES

1. Nowicki M. Basic facts about biosimilars. *Kidney Blood Press Res* 2007;*30*(5):267-272.
2. Farfan-Portet MI, Gerkens S, Lepage-Nefkens I, et al. Are biosimilars the next tool to guarantee cost-containment for pharmaceutical expenditures? *Eur J Health Econ* 2014;15(3):223.
3. Blackstone EA, Joseph PF. The economics of biosimilars. *Am Health Drug Benefits* 2013;6(8):469.
4. McCamish M, Woollett G. The rise of the biosimilar. *Expert Rev Clin Pharmacol* 2012;5(6):597-599.
5. Harker R. NHS funding and expenditure. 2012. [Online] Available: http://www.nhshistory.net/parlymoneypapter.pdf. (Accessed 16 May 2016).
6. HSCIC. Prescribing Costs in Hospitals and the Community. 2015. [Online] Available: http://www.hscic.gov.uk/catalogue/PUB18973/hosp-pres-eng-201415-report.pdf. (Accessed 27 May 2016).

7. NHS England. Five Year Forward View. 2014. [Online] Available: https://www.england.nhs.uk/wp-content/uploads/2014/10/5yfv-web.pdf. (Accessed 24 May 2016).
8. Spoors J, Kusel J. The uptake of non-branded medicines: Fact, fiction and biosimilarities. *BJHCM* 2015;21(7):331-342.
9. Megerlin F, Lopert R, Taymor K, et al. Biosimilars and the European experience: implications for the United States. *Health Aff* 2013;32(10):1803-1810.
10. IMS Institute for Healthcare Informatics. Assessing biosimilar uptake and competition in European markets. 2014. [Online] Available: https://www.imshealth.com/files/web/IMSH%20Institute/Healthcare%20Briefs/Assessing_biosimilar_uptake_and_competition_in_European_markets.pdf. (Accessed 26 May 2016).
11. Antonini P, Murphy M. Assuring patient adoption during biosimilar development and commercialization. Worldwide clinical trials. 2015. [Online] Available: https://www.worldwide.com/getattachment/3908b310-3d7b-40af-9a42-1f878d54b1ca/Assuring-Patient-Adoption-during-Biosimilar-Develo/Assuring-Patient-Adoption-during-Biosimilar-Develo. (Accessed 25 May 2016).
12. Lee J, Davis M, Clark J, et al. Estimated cost-effectiveness of growth hormone therapy for idiopathic short stature. *Arch Pediatr Adolesc Med* 2006;160(3):263-269.
13. IMS Institute for Healthcare Informatics. The Impact of Biosimilar Competition. 2015. [Online] Available: http://ec.europa.eu/DocsRoom/documents/14547/attachments/1/translations/en/renditions/native. (Accessed 20 June 2016).
14. Medicines and Healthcare Products Regulatory Agency (MHRA). Biosimilar products, Drug Safety Update. 2008. [Online] Available: https://www.gov.uk/drug-safety-update/biosimilar-products. (Accessed 25 May 2016).
15. Zuniga L, Calvo B. Biosimilars-the way forward. *Biotechnology* 2010;5:42.
16. Rana P, Roy V. Generic medicines: issues and relevance for global health. *Fundam Clin Pharmacol* 2015;29(6):529-542.
17. Prosser H, Walley T. A qualitative study of GPs' and PCO stakeholders' views on the importance and influence of cost on prescribing. *Soc Sci Med* 2005;60(6):1335-1346.
18. NHS Prescription Services. Prescription Cost Analysis (PCA) Data. 2016. [Online] Available: http://www.nhsbsa.nhs.uk/PrescriptionServices/3494.aspx. (Accessed 1 May 2016).
19. WHOCC. Definition and general considerations. 2015. [Online] Available: http://www.whocc.no/ddd/definition_and_general_considera/. (Accessed 1 May 2016).
20. Royal Pharmaceutical Society. Medicines Optimisation: Helping patients to make the most of medicines. 2013. [Online] Available: http://www.rpharms.com/promoting-pharmacy-pdfs/helping-patients-make-the-most-of-their-medicines.pdf. (Accessed 16 Jun. 2016).
21. Ess M, Schneeweiss S, Szucs D. European healthcare policies for controlling drug expenditure. *Pharmacoeconomics* 2003;21(2):89-103.
22. Barber N. What constitutes good prescribing?. *BMJ* 1995;310(6984):923.
23. NICE. Human growth hormone (somatropin) for the treatment of growth failure in children. 2010. [Online] Available: https://www.nice.org.uk/guidance/ta188. (Accessed 15 Jun. 2016).
24. Stanhope R, Buchanan C, Butler G, et al. An open-label acceptability study of Norditropin SimpleXx-a new liquid growth hormone formulation. *J Pediatr Endocrinol Metab* 2001;14(6):735-740.
25. Wickramasuriya N, Casey A, Akhtar S, et al. Factors determining patient choice of device for GH therapy. *Horm Res Paediatr* 2006;65(1):18-22.
26. Ahmed F, Smith A, Blamires C. Facilitating and understanding the family's choice of injection device for growth hormone therapy by using conjoint analysis. *Arch Dis Child* 2008;93(2):110-114.

27. Dumas H, Panayiotopoulos P, Parker D, et al. Understanding and meeting the needs of those using growth hormone injection devices. *BMC Endocr Disord* 2006;6(1):1.
28. Dörner T, Strand V, Cornes P, et al. (2016). The changing landscape of biosimilars in rheumatology. *Ann Rheum Dis* 2016;75(6), 974-982.

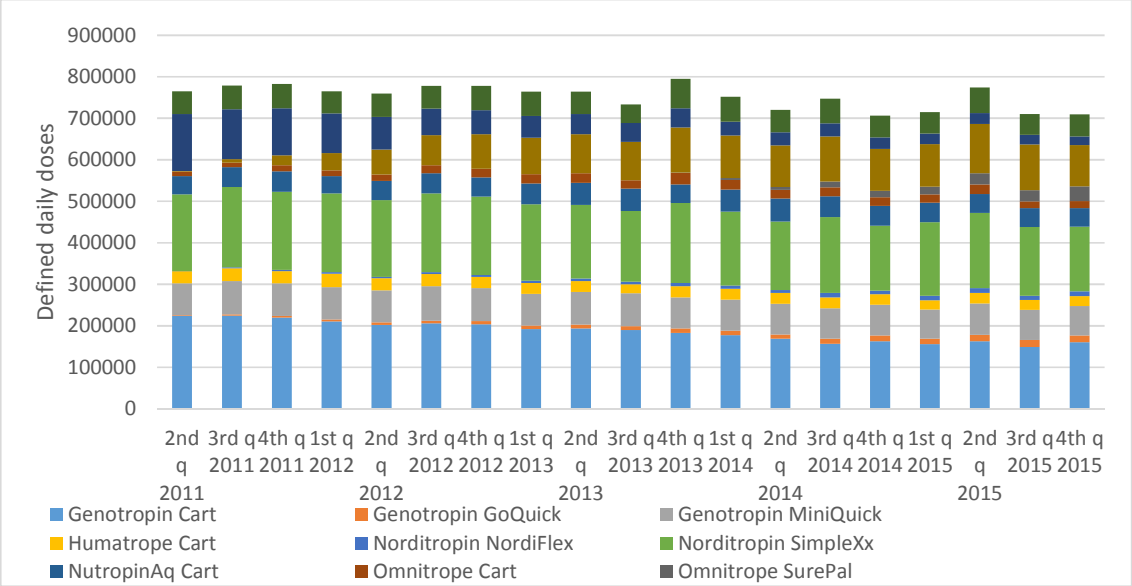

Figure 1 Quarterly utilisation of growth hormone preparation in primary care between April 2011 and December 2015

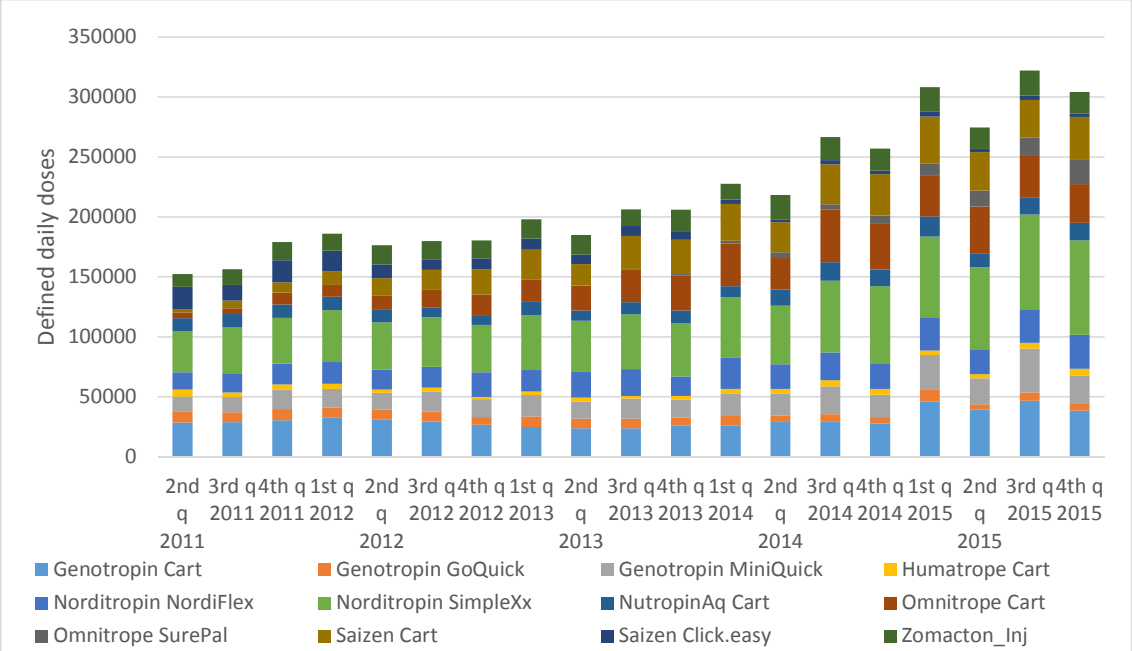

Figure 2 Quarterly utilisation of growth hormone preparation in secondary care between April 2011 and December 2015

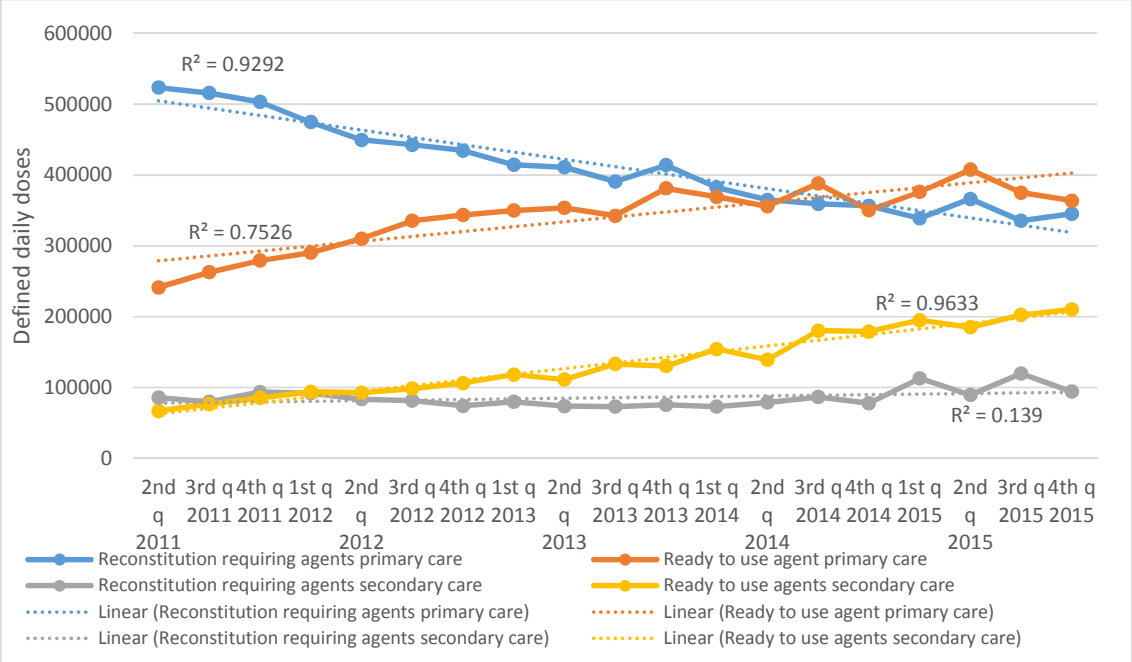

Figure 3 Comparison between reconstitution requiring agents and ready to use agents in primary and secondary care

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	P2	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	P2 P2 N/A
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	P2		
Objectives	3	State specific objectives, including any prespecified hypotheses	P3		
Methods					
Study Design	4	Present key elements of study design early in the paper	P3		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P3		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the	N/A	RECORD 6.1: The methods of study population selection (such as codes or	N/A

		sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	N/A	algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	N/A N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	P3	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	P3
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P3		
Bias	9	Describe any efforts to address potential sources of bias	N/A		
Study size	10	Explain how the study size was	P3		

		arrived at			
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	P3		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	P3		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	P3 P3
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-	P3

				level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	N/A	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	N/A
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	N/A		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	P4		
Main results	16	(a) Give unadjusted estimates	P4, P5		

		and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	P5		
Discussion					
Key results	18	Summarise key results with reference to study objectives	P5		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P6	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	N/A
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P6		
Generalisability	21	Discuss the generalisability (external validity) of the study results	P6		

Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P7		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	P8

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

BMJ Open

What drives the prescribing of growth hormone preparations in England? Prices versus patient preferences

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-013730.R1
Article Type:	Research
Date Submitted by the Author:	02-Dec-2016
Complete List of Authors:	Chapman, Stephen; Keele University, School of Pharmacy Fitzpatrick, Raymond; Keele University, School of Pharmacy Aladul, Mohammed; Keele University, School of Pharmacy
Primary Subject Heading:	Health policy
Secondary Subject Heading:	Health services research
Keywords:	EPIDEMIOLOGY, THERAPEUTICS, HEALTH SERVICES ADMINISTRATION & MANAGEMENT

What drives the prescribing of growth hormone preparations in England? Prices versus patient preferences

Stephen R Chapman, Professor of Prescribing[1], Raymond W Fitzpatrick, Professor of Clinical Pharmacy[1], Mohammed I Aladul, PhD student in Pharmacy Practice[1]

[1] School of Pharmacy, Keele University, Hornbeam Building, Newcastle-under-Lyme, Staffordshire, ST5 5BG, United Kingdom.

* Correspondence to: Stephen R Chapman

School of Pharmacy, Keele University, Hornbeam Building 3.06, Newcastle-under-Lyme, Staffordshire, ST5 5BG, United Kingdom.

Tel: +44 (0)1782 734131

Fax: +44 (0)1782 733326

E-mail: s.r.chapman@keele.ac.uk

KEY WORDS- growth hormone, prescribing trends, patient preferences, cost, biosimilar

RUNNING HEAD- Impact of formulation on growth hormone prescribing

WORD COUNT:

What drives the prescribing of growth hormone preparations in England? Prices versus patient preferences

ABSTRACT

Objective: The patent expiry of a number of biological medicines and the advent of biosimilars, raised the expectations of healthcare commissioners that biosimilars would reduce the high cost of these medicines and produce potential savings to the NHS. We aimed to examine the prescribing pattern of different growth hormone preparations (ready to use and reconstitution requiring) in both primary and secondary care in England to determine relative rates of decrease or increase and identify the possible factors influencing prescribing following the introduction of biosimilar growth hormone in 2008.

Design: Longitudinal observational study.

Setting and data sources: Primary care prescribing cost and volume data was derived from the NHS business services authority website, and for secondary care from the DEFINE database, between April 2011 and December 2015.

Outcomes: Quarterly prescribing analysis to examine trends and measure the relationship between utilisation and price.

Results: Expenditure and utilisation of growth hormone in primary care decreased by 17.91% and 7.29% respectively, whereas expenditure and utilisation in secondary care increased by 68.41% and 100% respectively between April 2011 and December 2015. The utilisation of reconstitution requiring products significantly declined in primary care (R^2 = 0.9292) and slightly increased in use in secondary care (R^2 = 0.139). In contrast, the utilisation of ready to use products significantly increased in use in both primary (R^2=0.7526) and secondary care (R^2=0.9633) respectively. Weak or no correlation existed between utilisation and price of growth hormone preparations in primary and secondary care.

Conclusion: The price of growth hormone products was not the key factor influencing prescribing of the biologic medicines. The main driver for specific product selection was the ease of use and the number of steps in dose preparation. Prescribers appear to be taking into account patient preferences rather than cost in their prescribing decisions.

Strengths and limitations of study

- This study includes cost and volume analysis of all available growth hormone preparations in England.
- The study analyses longitudinal observational dataset reflecting “real life“ prescribing in primary and secondary care.
- The analysis shows which factors drive prescribing of growth hormone.
- Time period for analysis was limited to five years.
- Segmented regression of interrupted time series analysis of the data was considered but cannot be applied.

INTRODUCTION

Biological medicines can be defined as biotechnological products whose active ingredient is developed from living cells by one or more of recombinant deoxyribonucleic acid (DNA), controlled gene expression and antibody production methods.[1] These medicines represent an advance in the treatment of patients with chronic and life-threatening diseases such as diabetes, growth hormone deficiency and cancer.[2] Biological medicines tend to be expensive compared to conventional drugs, mainly due to the cost of research and development and their complicated biosynthesis and handling techniques.[3] For example, Remicade® (infliximab) costs £12,584 per year per patient for the treatment of Crohn’s disease.[4] As a consequence, they potentially place a heavy burden on health care budgets even in developed countries with high resources.[5] In a free at the point of need health system funded through general taxation, such as the UK NHS, there is always pressure to remain within budget and provide value for money for tax payers.[6] According to the Health and Social Care Information Centre

report in 2015, the expenditure on medicines in England was £15.5 billion with hospital expenditure growing at a higher rate than primary care.[7] The Five Year Forward View of the NHS England predicted a budget deficit of nearly £30 billion a year by 2020-2021 if the increasing demand was met by no further annual efficiencies and funding remained flat in real terms.[8] NHS Health care policy makers' aim to reduce the acquisition cost of the drugs without affecting the clinical outcome by increasing the uptake of less expensive generic alternatives to branded medicines.[9]

The patent expiry of a number of biological medicines and the establishment of regulatory frameworks by the European Medicines Agency to register similar biological medicines termed "biosimilars", raised the expectations of healthcare commissioners that biosimilars would reduce the high cost of these medicines and produce potential savings to the NHS. The UK is a relatively large market for biological and generic medicines, so represents a potentially attractive market for the biosimilars manufacturers.[10] Recent data has revealed that the uptake of biosimilars in the UK is low compared to Germany and Sweden.[11] Possible reasons behind this low uptake were healthcare prescribers and patients concerns regarding quality, safety and efficacy of biosimilars and brand loyalty.[12]

Human recombinant growth hormone is a biological medicine where a biosimilar has been available since 2006.[13] An IMS Health report in 2014 showed that uptake of biosimilar growth hormone varies considerably across the different European markets, with highest use in Poland (99%) and lowest in Norway (3%) and the UK (5%). In Poland, the implementation of a strict tendering procurement system has resulted in the evolution of growth hormone biosimilar market share.[11 14] In 2015, growth hormone preparations cost £35,742,128 which represent 0.385% of the overall medicine bill in primary care.[7]

Although the concept of generics and biosimilars is the same, biosimilars cannot be considered generics, since they are similar but not identical to the branded biotherapeutics due to the high molecular weight and complexity of biotherapeutics and the difference in synthesis process.[15] This has been recognised by the European Medicine Agency (EMA) in specific legislation for biosimilars approval.[16] The UK Medicines and Healthcare products Regulatory Agency (MHRA) guidance on biosimilars is that products should not be assumed to be identical due to the high molecular weight and structural differences between biological medicines. Thus, biological medicines and biosimilars are prescribed by brand names rather than by their International Non-propriety Name.[17] UK policymakers may have anticipated that the lower price of biosimilars compared to branded biological medicines (15-30%) would lead to a rapid uptake in the same way as conventional small molecule generic medicines, even though the price differential is far greater for generic small molecule medicines (50-90%).[18] The high unit cost of biological medicines means the small percentage price differential could result in significant annual savings.[19] The extent to which savings on prescribing for conventional small molecule medicines can be realised is a function of multifactorial influences on prescribing in the UK.[20 22] It is not clear whether the same influences which apply to generic medicines are universally applicable to biological medicines. Since 2006, the EMA has approved 23 biosimilars in different therapeutic areas, including growth hormone, erythropoietins, granulocyte-colony stimulating factors, monoclonal antibody and insulin. The European experience during this ten years, identified that the uptake and market penetration of potential biosimilar depend on therapeutic area, geographic area and patient acceptance. The uptake and market penetration of biosimilars are also governed by price variations, local market dynamics, competitors, stakeholder knowledge and experience with products and marketing efforts by companies.[23]

The main objectives of this study were to undertake a detailed analysis of the pattern of use of human recombinant growth hormone in primary and secondary care settings in England and to determine possible factors influencing its prescribing. A priori hypothesis was set, that, similar to generic medicines, price would be the dominant influencing factor in the use of these medicines.

METHODS

Data source

The study was a retrospective analysis of primary and secondary care usage of growth hormone in England. Primary care monthly prescription cost analysis data was derived from the NHS business services authority website,[24] for prescriptions dispensed in primary care in England from April 2011 to December 2015. Monthly secondary care data were taken from DEFINE Software for 2011-2016

since this prescribing database did not exist before April 2011. DEFINE Software is a NHS prescribing database of medicines usage in approximately 120 hospitals (covering over 90% of NHS hospitals throughout the UK including Specialist Centres and Mental Health Trusts) who subscribe to the software package.[25] Data were at gross national level not at institutional or patient level. The volume comparator was the defined daily dose (DDD), defined by the World Health Organisation (WHO) as the mean maintenance daily dose of a medicine for its principal indication in adults. The DDD index for growth hormone is 2 international units.[26] Primary care data were number of items issued and amount of drug in units. This was converted into defined daily doses using the following formula:

Drug usage (DDDs) = (items issued ×amount of drug per item)/DDD

Secondary care data were already available in defined daily doses.

Prices of the individual preparations were expressed as price per defined daily dose (£/DDD). Primary care prices were the basic price of a drug excluding value-added tax (VAT) (the price listed in the national Drug Tariff or in standard price lists). Secondary care prices were the average net prices for different trusts throughout the UK including VAT.

Statistical analysis

Regression analysis were used to understand and explore the association (relation) between the independent variables and the dependent variable, and the forms of these relationships.[27 28]

Prescribing trends were examined for growth hormone in primary and secondary care over the period April 2011– December 2015. Linear regression analyses were used with a quarter (three months) as the independent variable and prescription DDD as dependent variable, using quarterly data from each in primary and secondary care. The regression coefficient values were divided by the baseline prescription DDD (in April 2011) to calculate the average quarterly percentage increase or decrease in prescribing of growth hormone. Correlation analyses were used between prescription DDD and cost/DDD, using quarterly data from each in primary and secondary care. All calculations were performed using Microsoft Excel 2013 and SPSS 21.

RESULTS

Pricing and Expenditure

In primary care, prices of branded growth hormone preparations did not change between April 2011 and December 2015 with the exception of Genotropin® preparations which decreased by 25%. Biosimilar growth hormone (Omnitrope® preparations) prices decreased by 15% over this period (Table 1). Over the same time period there were higher price reductions in secondary care, including all Genotropin® preparations, Humatrope Cart®, Norditropin SimpleXx®, Omnitrope SurePal® and Zomacton Inj® (Table 1).

Expenditure on growth hormone preparations in primary care in England decreased by 17.91% between April 2011 and December 2015, whereas expenditure in secondary care increased by 68.41% during the same period.

Table 1 Change in price/DDD (in GB pounds) of growth hormone in primary and secondary care between April 2011 and December 2015

	Primary care						Secondary care					
Drug Name	2011	2012	2013	2014	2015	% Dif.	2011	2012	2013	2014	2015	% Dif.
Genotropin Cart®	15.45	11.76	11.59	11.59	11.59	-25	18.55	15.38	13.4	13.4	13.4	-27.75
Genotropin GoQuick®	15.45	11.76	11.59	11.59	11.59	-25	18.55	13.91	13.91	13.91	13.91	-25
Genotropin MiniQuick®	15.45	11.76	11.59	11.59	11.59	-25	18.55	13.91	13.91	13.91	13.91	-25
Humatrope Cart®	12.00	12.00	12.00	12.00	12.00	0	13.20	13.20	12.00	12.00	12.00	-9
Saizen Click.easy®	15.45	15.45	15.45	15.45	15.45	0	18.55	18.55	18.55	18.55	18.55	0
Zomacton_Inj®	13.28	13.28	13.28	13.28	13.28	0	15.94	15.94	13.95	13.95	13.95	-12.5
Norditropin NordiFlex®	15.45	15.45	15.45	15.45	15.45	0	18.55	18.55	18.55	18.55	18.55	0
Norditropin SimpleXx®	14.18	14.18	14.18	14.18	14.18	0	17.02	17.02	15.17	14.55	14.55	-14.5

NutropinAq Cart®	13.53	13.53	13.53	13.53	13.53	0	14.37	14.37	15.34	15.34	15.34	6.75
Omnitrope Cart®	11.69	11.69	11.69	11.69	9.83	-16	11.52	11.52	11.52	11.52	11.52	0
Omnitrope SurePal®			11.56	11.56	9.83	-15			13.46	10.92	10.92	-19
Saizen Cart®	15.45	15.45	15.45	15.45	15.45	0	18.55	18.55	18.55	18.55	18.55	0

*Omnitrope® and Omnitrope SurePal® are growth hormone biosimilars
**Omnitrope SurePal® was marketed in June 2013 in secondary care and October 2013 in primary care
% Dif.: % of difference between 2011 and 2015 price/DDD

Volume of utilisation

Growth hormone utilisation in primary care declined from 764,877 DDDs in second quarter 2011 to 709,054 DDDs in the fourth quarter 2015. Regression analysis indicates that this decline of on average 0.45% per quarter (95% confidence interval 0.70 to 0.21) is statistically significant. Genotropin Cart®, Norditropin SimpleXx® and Saizen Click.easy® dominated the growth hormone market by volume, accounting for 30%, 24% and 17.5% respectively of prescribed growth hormone in second quarter 2011 (Figure 1). By the fourth quarter 2015, Genotropin Cart®, Norditropin SimpleXx® still had the highest share of the growth hormone market at 22% for both but Saizen Cart® had replaced Saizen Click.easy at 14.5% (Figure 1).

In contrast to primary care, secondary care utilisation of growth hormone doubled from 152,457 DDDs in second quarter 2011 to 304,443 DDDs in fourth quarter 2015 representing a statistically significant rise of on average 5.8% (95% confidence interval 4.71 to 6.89) per quarter. As in primary care Genotropin Cart® and Norditropin SimpleXx® dominated the growth hormone market by volume, accounting for 18%, 23% respectively of prescribed growth hormone in second quarter 2011. By the fourth quarter 2015, Genotropin Cart®, had decreased to 12%, Norditropin SimpleXx® increased slightly to 25% but Omnitrope Cart® and Saizen Cart® also accounted for 11% and 12% of the market respectively (Figure 2).

The correlation analysis between price per DDD and product utilisation in primary care revealed that for Norditropin NordiFlex®, Saizen Cart®, Saizen Click.easy® there was no correlation. For Genotropin Cart® there was an intermediate positive correlation (R^2=0.5023), for Genotropin MiniQuick®, Humatrope Cart®, Norditropin SimpleXx®, Zomacton Inj® there were weakly positive correlation (R^2=0.1081, R^2=0.075, R^2=0.2313 and R^2=0.0006 respectively). For remaining products there were weakly negative correlations (NutropinAq Cart® R^2=0.2066, Omnitrope Cart® R^2=0.0764, Omnitrope SurePal® R^2=0.3614), with the exception of Genotropin GoQuick® there was an intermediate negative correlation.

In secondary care, a similar diverse pattern of correlation between price/DDD and product utilisation was seen. Norditropin NordiFlex® and Omnitrope Cart® showed no correlation. For Genotropin GoQuick®, NutropinAq Cart® and Saizen Cart® there were weakly positive correlation (R^2=0.2535, R^2=0.0873, R^2=0.0004 respectively). For remaining products there were weakly negative correlations (Genotropin Cart® R^2=0.0128, Genotropin MiniQuick® R^2=0.1622, Humatrope Cart® R^2=0.0155, Omnitrope SurePal® R^2=0.4973 and Zomacton Inj® R^2=0.3766), with the exception of Norditropin SimpleXx® there was an intermediate negative correlation.

Table 2 Growth hormone preparations characteristics

Reconstitution requiring agent		Ready to use agents	
Agent	Description	Agent	Description
Genotropin Cart®	Cartridge needed, needs fridge after reconstitution, dose cannot pre-set	NutropinAq Cart®	Cartridge needed, needs fridge, dose cannot pre-set
Genotropin GoQuick®	Pre-filled, needs fridge after reconstitution	Norditropin NordiFlex®	Pre-filled, dose cannot pre-set
Genotropin MiniQuick®	Pre-filled syringe, single dose, preservative free, portable, can be kept outside the fridge before use.	Norditropin SimpleXx®	Cartridge needed, dose cannot pre-set, can be kept at room temperature for 3 weeks after first use, auto-injector
Humatrope	Cartridge needed, needs fridge before and	Omnitrope	Cartridge needed, needs fridge, dose cannot

Cart®	after reconstitution, dose cannot pre-set	Cart®	pre-set
Zomacton Inj®	Needle free, vial needed, may cause skin reaction, dose cannot be pre-set	Omnitrope SurePal®	Cartridge needed, needs fridge, dose pre-set, hidden needle
Saizen Click.easy®	Automatic needle insertion, cartridge needed, needs fridge during use, dose cannot pre-set	Saizen Cart®	Electronic - automatic injector, dose pre-set, records of dose history, hidden needle, on-screen for instruction of use, control of comfort parameters (injection depth, time, speed), cartridge needed.

Table 2 summarises the main characteristics of reconstitution requiring agents and ready to use growth hormone preparations. Figure 3 shows the utilisation trends for products requiring reconstitution and those in a ready to use formulation in primary and secondary care settings. The utilisation of products requiring reconstitution (Genotropin Cart®, Genotropin GoQuick®, Genotropin MiniQuick®, Humatrope Cart®, Saizen Click.easy® and Zomacton Inj®) all showed a clear decline in use in primary care (R^2=0.9292) and a slight increase in use in secondary care (R^2 = 0.139). In stark contrast, the utilisation of ready to use products (Norditropin NordiFlex®, Norditropin SimpleXx®, NutropinAq Cart®, Omnitrope Cart®, Omnitrope SurePal® and Saizen Cart®) showed a very clear increase in use in both primary and secondary care (R^2=0.7526) and (R^2=0.9633) respectively.

Figure 4 shows that in primary care the utilisation of 5 out of 6 ready to use agents increased between 2011 and 2015 irrespective to the price. The utilisation of 4 of 6 of reconstitution requiring agents decreased during the same period although their prices have decreased. Figure 5 shows that in secondary care that utilisation of all ready to use agents increased between 2011 and 2015 irrespective of price. The utilisation of 3 out of 6 reconstitution requiring agents increased during the same period when their prices decreased. The utilisation of remaining three reconstitution requiring agents decreased despite price reduction.

DISCUSSION

The long established principles of good prescribing practice and medicines optimisation suggest that clinicians aim to prescribe to maximise effectiveness, minimise risks and take into account the patients experience.[29] At the same time, in a health system free at the point of need funded by general taxation, prescribers consider relative costs of medicines and NHS policy and NICE guidance whilst still respecting the patient's choice.[30] [31] Balancing between these conflicting aims and recommendations result in good prescribing to achieve maximum effectiveness, minimum risk and cost, although it is recognised that financial and non-financial incentives may also be needed to encourage best practice.[32]

In the UK, growth hormone prescribing follows a shared care protocol between primary and secondary care. In hospital, a consultant endocrinologist first diagnoses the patient requiring growth hormone. An endocrine specialist nurse demonstrates the available growth hormone devices to the patient, then trains the patient on the use of their chosen device. The patient is then provided with an initial supply. The primary care GP continues prescribing growth hormone for the patient in accordance with the local agreed shared care protocol.[33]

In England, there are currently seven preparations of growth hormone. Although these preparations differ in their injecting device for the delivery of growth hormone, these preparations are equal in terms of clinical effectiveness.[34] With the availability of such a variety of preparations endocrinologists and other healthcare professionals prescribing growth hormone are being asked to make some complex decisions regarding the selection of the preparation for each patient. The latest NICE guidelines in 2010 for treatment with growth hormone stated that the product selection should be based on a discussion between the prescriber and the patient or the patients' parents, taking into account the advantages and disadvantages of each device. If more than one option is suitable the less expensive one should be chosen.[34]

In this study, we classified growth hormone delivery devices into reconstitution requiring agents and ready to use agents. Ready to use agents were characterised by fewer steps and time required for dose preparation by patients and potentially a reduction in user errors that may occur during the reconstitution process. Reconstitution can be quite complex since each preparation requires a special reconstitution kit. The cartridge containing lyophilised growth hormone is reconstituted using only the diluent syringe that accompanies the cartridge. The diluent syringe is placed into the reconstitution kit, the needle cover of the diluent syringe is removed, and the cartridge inserted. When the diluent needle is inserted inside the cartridge, the plunger of the diluent is pushed until all the diluent is transferred into the cartridge. The cartridge is then removed from the kit, with gentle rotary movement (mixing) but not shaking until the solution became clear.[35]

Studies have identified that premixed solution devices (ready to use devices) are more acceptable to patients and/or parents than reconstitution requiring devices. The simplicity and the least steps required for preparation and administration of growth hormone doses are considered among the most desirable attributes of administration devices.[36 37] Ready to use agents are associated with less pain than reconstitution requiring agents due to the higher concentration of these products and, therefore, smaller volumes of GH injected. Furthermore, added preservative and buffer to the premixed solution of GH decrease the injection pain.[38]

Interestingly, the utilisation of the growth hormone market leader in primary care Genotropin Cart® decreased over the study period despite a 25% price reduction (Figure 1). Over the same time period Saizen Cart® (ready to use agent) replaced Saizen Click.easy® (reconstitution requiring agent) although it was the same price (Figure 1). This challenges policy assumptions that cheaper drugs will dominate. It also shows that perceived preference may outweigh national guidance to select lowest cost agents. The results have implications for those considering effectiveness of implementation of national guidance. Furthermore, the results has implications for NHS budget mangers when they consider which medicines to make available within local health economies.

The pattern of product utilisation in secondary care was more diverse (Figure 2). In this sector Genotropin Cart® usage decreased despite a 27.75% price reduction over the study period (Figure 2). The market leader in secondary care, Norditropin SimpleXx® (ready to use agent), grew only slightly despite a 14.5% price reduction. Omnitrope Cart® (the less expensive option) and Siazen Cart® (the most expensive option) (both ready to use agents) increased their share of the secondary care market although in both cases the price did not change. These findings suggest ease of use rather than price is the key influence on the prescribing decision. Within the NHS in the UK medicines are reimbursed differently in primary and secondary care. In primary care community pharmacies are reimbursed by the government for the medicines they dispense at a basic NHS price which is set nationally, whereas in hospitals the prices paid for medicines are negotiated with manufacturers through regional and local contracting processes. These discounts are sometimes offset since hospital medicines attract VAT whereas primary care medicine do not. This means that the cost of medicines are often different in secondary care.

The analysis of price and product utilisation supports this observation. A number of products both in primary and secondary care showed no correlation between price and production utilisation. Indeed some showed a positive correlation indicating that the higher price was associated with higher use. A negative correlation would suggest that price was influencing use. However, in both primary and secondary care all the negative correlations were weak $R^2<0.5$, with the exception of Genotropin GoQuick® in primary care and Norditropin SimpleXx® in secondary care which were intermediate $R^2>0.5<0.75$. This complete diversity of correlations in both sectors indicates price is not the driver for product use.

The use of ready to use agents increased in both sectors during the study period (Figure 3). This explains the slight overall decrease in growth hormone in primary care as it comprises a growth in the

use of the ready to use agents counteracted by a significant decrease in the use of the reconstitution requiring agents. Furthermore, the overall growth in secondary care comprises a significant (almost tripling) growth in the ready to use agents and a flattening use of the reconstitution requiring agents (Figure 3). Figure 3 also shows that reconstitution requiring agents dominated until 2014, but were overtaken by ready to use agents. This is perhaps a reflection of the more conservative rate of change of prescribing patterns in the UK, since the reconstitution requiring agents were available since 1987,[39] whereas the first ready to use agents only became available in the UK in 2000 and the newer devices from 2011 (Norditropin Nordiflex® and Saizen Cart® were launched in 2011 and Omnitrope Surepal® was launched in 2013).[40 41] This is supported in the literature, which has identified the UK market as one of the slowest markets in Europe in taking up new medicines.[42] Furthermore, stable patients will most likely have remained on the product they were initiated on since if all is well, both patients and prescribers may be disinclined to switch. Thus, given the nature of this therapy it takes time for new products to get market traction.

Figure 4 and 5 also suggest that the quantity or the utilisation of growth hormone preparations is not price dependent in both primary and secondary care settings. The utilisation of ready to use agents increased in both sector irrespective to the change in price (decreased or unchanged).

This suggests that ease of use rather than price is the key driver for growth hormone product selection in both primary and secondary care. The findings from this study agree with previous studies of branded growth hormone that outlined that ease of use and convenience (premixed formulations) were the most important product characteristics from patients' perspective.[37 43 44] This may have been because the patients are adolescents who will be in full-time education and require formulations which are quick and easy to use.

Previous literature on this subject has focused on patient preferences in relation to specific devices. This study focused on whether these preferences are translated into prescriber product selection. Implicitly this suggests that for growth hormone, prescribers, whilst following the principles of medicines optimisation take more account of patient preferences than central guidance on cost efficiency. This contrasts with other health economies were mandated switching to GH biosimilar meant that 99% of prescribing was the less expensive biosimilar.[14]

Our study has several limitations, firstly, the time period for analysis was limited to five years as we wanted to explore the utilisation of growth hormone in both primary and secondary care. We could only access monthly data for primary and secondary care since 2011. Secondly, segmented regression of interrupted time series analysis of the data was considered but growth hormone prices change were not linked to a single point of time and NICE guidance on growth hormone was not changed during the study period. Visual analyses of Figures 1 and 2 showed no abrupt change in the pattern of utilisation of growth hormone over the study period required for this type of analysis.

CONCLUSION

This study has suggests that the price of growth hormone products is not the key influencing factor in prescribing of biologic medicines. The main driver for specific product selection is the ease of use and fewer steps in dose preparation. Prescribers are clearly taking into account patient preferences rather than cost in their prescribing decisions, in line with national guidance.

Contributors: All authors have contributed to this study and all authors reviewed and approved the final version of the manuscript. SRC designed the study, interpreted the results and reviewed the manuscript and corrected the final version of the manuscript. RWF participated in the study design, interpreted the results and reviewed the manuscript and corrected the final version of the manuscript. MIA participated in the study design, data collection, and interpretation of results, prepared the manuscript draft, and performed all analytical testing and manuscript review.

Funding: This research was not funded or sponsored by any organisation and the researchers are independent of any funding bodies.

Access to data: All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: No ethical approval was required for this research.

Data sharing statement: No additional data are available.

REFERENCES

1. Nowicki M. Basic facts about biosimilars. *Kidney Blood Press Res* 2007;*30*(5):267-272.
2. Farfan-Portet MI, Gerkens S, Lepage-Nefkens I, et al. Are biosimilars the next tool to guarantee cost-containment for pharmaceutical expenditures? *Eur J Health Econ* 2014;15(3):223.
3. Blackstone EA, Joseph PF. The economics of biosimilars. *Am Health Drug Benefits* 2013;6(8):469.
4. National Institute for Clinical Excellence. Infliximab (review) and adalimumab for the treatment of Crohn's disease. 2010. [Online]. Available at: https://www.nice.org.uk/guidance/ta187/resources/guidance-infliximab-review-and-adalimumab-for-the-treatment-of-crohns-disease-pdf. (Accessed 14 Nov. 2016).
5. McCamish M, Woollett G. The rise of the biosimilar. *Expert Rev Clin Pharmacol* 2012;5(6):597-599.
6. Harker R. NHS funding and expenditure. 2012. [Online] Available: http://www.nhshistory.net/parlymoneypapter.pdf. (Accessed 16 May 2016).
7. HSCIC. Prescribing Costs in Hospitals and the Community. 2015. [Online] Available: http://www.hscic.gov.uk/catalogue/PUB18973/hosp-pres-eng-201415-report.pdf. (Accessed 27 May 2016).
8. NHS England. Five Year Forward View. 2014. [Online] Available: https://www.england.nhs.uk/wp-content/uploads/2014/10/5yfv-web.pdf. (Accessed 24 May 2016).
9. Spoors J, Kusel J. The uptake of non-branded medicines: Fact, fiction and biosimilarities. *BJHCM* 2015;21(7):331-342.
10. Megerlin F, Lopert R, Taymor K, et al. Biosimilars and the European experience: implications for the United States. *Health Aff* 2013;32(10):1803-1810.
11. IMS Institute for Healthcare Informatics. Assessing biosimilar uptake and competition in European markets. 2014. [Online] Available: https://www.imshealth.com/files/web/IMSH%20Institute/Healthcare%20Briefs/Assessing_biosimilar_uptake_and_competition_in_European_markets.pdf. (Accessed 26 May 2016).
12. Antonini P, Murphy M. Assuring patient adoption during biosimilar development and commercialization. Worldwide clinical trials. 2015. [Online] Available: https://www.worldwide.com/getattachment/3908b310-3d7b-40af-9a42-1f878d54b1ca/Assuring-Patient-Adoption-during-Biosimilar-Develo/Assuring-Patient-Adoption-during-Biosimilar-Develo. (Accessed 25 May 2016).
13. Lee J, Davis M, Clark J, et al. Estimated cost-effectiveness of growth hormone therapy for idiopathic short stature. *Arch Pediatr Adolesc Med* 2006;160(3):263-269.
14. IMS Institute for Healthcare Informatics. The Impact of Biosimilar Competition. 2015. [Online] Available: http://ec.europa.eu/DocsRoom/documents/14547/attachments/1/translations/en/renditions/native. (Accessed 20 June 2016).
15. Misra A. Are biosimilars really generics? Expert Opin Biol Ther 2010;10(4):489-494.
16. Roger D, Goldsmith D. Biosimilars: it's not as simple as cost alone. J Clin Pharm Ther 2008;33(5):459-464.
17. Medicines and Healthcare Products Regulatory Agency (MHRA). Biosimilar products, Drug Safety Update. 2008. [Online] Available: https://www.gov.uk/drug-safety-update/biosimilar-products. (Accessed 25 May 2016).
18. Zuniga L, Calvo B. Biosimilars-the way forward. *Biotechnology* 2010;5:42.
19. Rana P, Roy V. Generic medicines: issues and relevance for global health. *Fundam Clin Pharmacol* 2015;29(6):529-542.

20. Prosser H, Walley T. A qualitative study of GPs' and PCO stakeholders' views on the importance and influence of cost on prescribing. Soc Sci Med 2005;60(6):1335-1346.
21. Grabowski H. G., Ridley D. B., Schulman, K. A. Entry and competition in generic biologics. *MDE Manage Decis Econ* 2007;28(4□5): 439-451.
22. Mestre-Ferrandiz J, Towse A, Berdud M. Biosimilars: how can payers get long-term savings? *Pharmacoeconomics* 2016;34(6):609-616.
23. QuintilesIMS. Biosimilar Use and Uptake in Europe. 2015. [Online]. Available at: http://www.quintiles.com/blog/biosimilar-use-and-uptake-in-europe (Accessed 14 Nov. 2016).
24. NHS Prescription Services. Prescription Cost Analysis (PCA) Data. 2016. [Online] Available: http://www.nhsbsa.nhs.uk/PrescriptionServices/3494.aspx. (Accessed 1 May 2016).
25. Rx Info. Define. 2016. [Online]. Available at: http://www.rx-info.co.uk/products/define.ashx (Accessed at 14 Nov. 2016).
26. WHOCC. Definition and general considerations. 2015. [Online] Available: http://www.whocc.no/ddd/definition_and_general_considera/. (Accessed 1 May 2016).
27. Bowers D. Medical statistics from scratch: an introduction for health professionals. John Wiley & Sons 2008.
28. Bewick V, Cheek L, Ball J. Statistics review 7: Correlation and regression. *Critical Care* 2003;7(6):1.
29. Royal Pharmaceutical Society. Medicines Optimisation: Helping patients to make the most of medicines. 2013. [Online] Available: http://www.rpharms.com/promoting-pharmacy-pdfs/helping-patients-make-the-most-of-their-medicines.pdf. (Accessed 16 Jun. 2016).
30. Ess M, Schneeweiss S, Szucs D. European healthcare policies for controlling drug expenditure. *Pharmacoeconomics* 2003;21(2):89-103.
31. Barber N. What constitutes good prescribing?. *BMJ* 1995;310(6984):923.
32. Karlsberg-Schaffer S, Sussex J, Feng Y. Incentives to Follow Best Practice in Health Care. OHE Briefing. 2015. [Online]. Available at: https://www.ohe.org/publications/incentives-follow-best-practice-health-care (Accessed 18 Nov. 2016).
33. Bujanova J, Cummings H. Management of growth hormone deficiency in adults. *Prescriber* 2015;26(23):29-33.
34. NICE. Human growth hormone (somatropin) for the treatment of growth failure in children. 2010. [Online] Available: https://www.nice.org.uk/guidance/ta188. (Accessed 15 Jun. 2016).
35. Eli Lilly Humatrope®: Information and Patient Instructions. 2011. [Online]. Available at: http://pi.lilly.com/us/humatrope-ppi_newrecon.pdf (Accessed 14 Nov. 2016).
36. Stanhope R, Buchanan C, Butler G, et al. An open-label acceptability study of Norditropin SimpleXx-a new liquid growth hormone formulation. *J Pediatr Endocrinol Metab* 2001;14(6):735-740.
37. Wickramasuriya N, Casey A, Akhtar S, et al. Factors determining patient choice of device for GH therapy. *Horm Res Paediatr* 2006;65(1):18-22.
38. Kirk J. Developments in growth hormone delivery. *Curr Drug ther* 2010;5(1): 43-47.
39. European Medicine Agency. Questions and answers on Genotropin and associated names (somatropin injection). 2010. [Online] Available: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Genotropin_6_12/WC500093962.pdf. (Accessed 14 Nov. 2016).
40. HSCIC. Prescription Cost Analysis England 2011. 2012. [Online] Available: http://content.digital.nhs.uk/catalogue/PUB05807/pres-cost-anal-eng-2011-rep.pdf. (Accessed 15 Nov. 2016).
41. HSCIC. Prescription Cost Analysis England 2013. 2014. [Online] Available: http://content.digital.nhs.uk/catalogue/PUB13887/pres-cost-anal-eng-2013-rep.pdf. (Accessed 15 Nov. 2016).
42. Chaplin S. Is the UK too slow in the uptake of new medicines? *Prescriber* 2015;26:29-30.

43. Ahmed F, Smith A, Blamires C. Facilitating and understanding the family's choice of injection device for growth hormone therapy by using conjoint analysis. *Arch Dis Child* 2008;93(2):110-114.
44. Dumas H, Panayiotopoulos P, Parker D, et al. Understanding and meeting the needs of those using growth hormone injection devices. *BMC Endocr Disord* 2006;6(1):1.

Figure 1. Quarterly utilisation of growth hormone preparations in primary care between April 2011 and December 2015. DDD: defined daily dose.

Figure 2. Quarterly utilisation of growth hormone preparations in secondary care between April 2011 and December 2015. DDD: defined daily dose.

Figure 3. Comparison between reconstitution requiring agents and ready to use agents in primary and secondary care between April 2011 and December 2015. DDD: defined daily dose.

Figure 4. Utilisation versus cost/DDD of reconstitution requiring agents and ready to use agents of growth hormone preparations in primary care. DDD: defined daily dose.

Figure 5. Utilisation versus cost/DDD of reconstitution requiring agents and ready to use agents of growth hormone preparations in secondary care. DDD: defined daily dose.

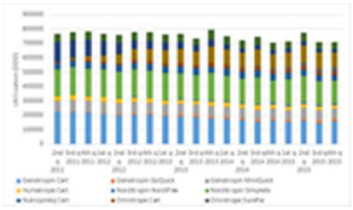

Figure 1. Quarterly utilisation of growth hormone preparations in primary care between April 2011 and December 2015. DDD: defined daily dose.

14x8mm (300 x 300 DPI)

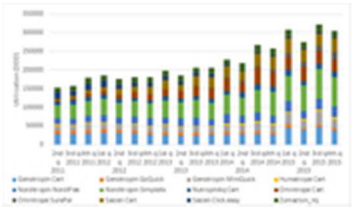

Figure 2. Quarterly utilisation of growth hormone preparations in secondary care between April 2011 and December 2015. DDD: defined daily dose.

14x8mm (300 x 300 DPI)

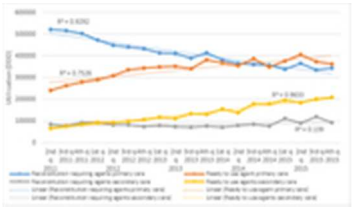

Figure 3. Comparison between reconstitution requiring agents and ready to use agents in primary and secondary care between April 2011 and December 2015. DDD: defined daily dose.

14x8mm (300 x 300 DPI)

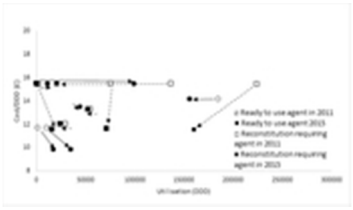

Figure 4. Utilisation versus cost/DDD of reconstitution requiring agents and ready to use agents of growth hormone preparations in primary care. DDD: defined daily dose.

14x8mm (300 x 300 DPI)

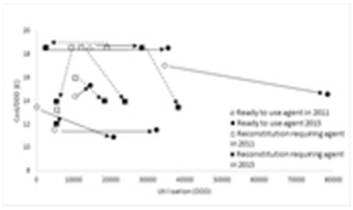

Figure 5. Utilisation versus cost/DDD of reconstitution requiring agents and ready to use agents of growth hormone preparations in secondary care. DDD: defined daily dose.

14x8mm (300 x 300 DPI)

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	P2	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	P2 P2 N/A
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	P2		
Objectives	3	State specific objectives, including any prespecified hypotheses	P3		
Methods					
Study Design	4	Present key elements of study design early in the paper	P3		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P3-4		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the	N/A	RECORD 6.1: The methods of study population selection (such as codes or	N/A

		sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	N/A	algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	N/A N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	P4	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	P3
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P4		
Bias	9	Describe any efforts to address potential sources of bias	N/A		
Study size	10	Explain how the study size was	P4		

		arrived at			
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	P4		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	P4		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	P4 P4
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-	P4

				level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	N/A	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	N/A
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	N/A		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	P4		
Main results	16	(a) Give unadjusted estimates	P4-6		

		and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	P5-6		
Discussion					
Key results	18	Summarise key results with reference to study objectives	P5-6		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P8	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	N/A
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P6-7		
Generalisability	21	Discuss the generalisability (external validity) of the study results	P7		

Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P9		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	P9

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.

BMJ Open

What drives the prescribing of growth hormone preparations in England? Prices versus patient preferences

Journal:	*BMJ Open*
Manuscript ID	bmjopen-2016-013730.R2
Article Type:	Research
Date Submitted by the Author:	20-Jan-2017
Complete List of Authors:	Chapman, Stephen; Keele University, School of Pharmacy Fitzpatrick, Raymond; Keele University, School of Pharmacy Aladul, Mohammed; Keele University, School of Pharmacy
Primary Subject Heading:	Health policy
Secondary Subject Heading:	Health services research
Keywords:	EPIDEMIOLOGY, THERAPEUTICS, HEALTH SERVICES ADMINISTRATION & MANAGEMENT

What drives the prescribing of growth hormone preparations in England? Prices versus patient preferences

Stephen R Chapman, Professor of Prescribing[1], Raymond W Fitzpatrick, Professor of Clinical Pharmacy[1], Mohammed I Aladul, PhD student in Pharmacy Practice[1]

[1] School of Pharmacy, Keele University, Hornbeam Building, Newcastle-under-Lyme, Staffordshire, ST5 5BG, United Kingdom.

* Correspondence to: Stephen R Chapman

School of Pharmacy, Keele University, Hornbeam Building 3.06, Newcastle-under-Lyme, Staffordshire, ST5 5BG, United Kingdom.

Tel: +44 (0)1782 734131

Fax: +44 (0)1782 733326

E-mail: s.r.chapman@keele.ac.uk

KEY WORDS- growth hormone, prescribing trends, patient preferences, cost, biosimilar

RUNNING HEAD- Impact of formulation on growth hormone prescribing

WORD COUNT:

What drives the prescribing of growth hormone preparations in England? Prices versus patient preferences

ABSTRACT

Objective: The patent expiry of a number of biological medicines and the advent of biosimilars, raised the expectations of healthcare commissioners that biosimilars would reduce the high cost of these medicines and produce potential savings to the NHS. We aimed to examine the prescribing pattern of different growth hormone preparations (ready to use and reconstitution requiring) in both primary and secondary care in England to determine relative rates of decrease or increase and identify the possible factors influencing prescribing following the introduction of biosimilar growth hormone in 2008.

Design: Longitudinal observational study.

Setting and data sources: Primary care prescribing cost and volume data was derived from the NHS business services authority website, and for secondary care from the DEFINE database, between April 2011 and December 2015.

Outcomes: Quarterly prescribing analysis to examine trends and measure the relationship between utilisation and price.

Results: Expenditure and utilisation of growth hormone in primary care decreased by 17.91% and 7.29% respectively, whereas expenditure and utilisation in secondary care increased by 68.41% and 100% respectively between April 2011 and December 2015. The utilisation of reconstitution requiring products significantly declined in primary care (R^2 = 0.9292) and slightly increased in use in secondary care (R^2 = 0.139). In contrast, the utilisation of ready to use products significantly increased in use in both primary (R^2=0.7526) and secondary care (R^2=0.9633) respectively. Weak or no correlation existed between utilisation and price of growth hormone preparations in primary and secondary care.

Conclusion: The price of growth hormone products was not the key factor influencing prescribing of the biologic medicines. The main driver for specific product selection was the ease of use and the number of steps in dose preparation. Prescribers appear to be taking into account patient preferences rather than cost in their prescribing decisions.

Strengths and limitations of study

- This study includes cost and volume analysis of all available growth hormone preparations in England.
- The study analyses longitudinal observational dataset reflecting “real life“ prescribing in primary and secondary care.
- The analysis shows which factors drive prescribing of growth hormone.
- Time period for analysis was limited to five years.
- Segmented regression of interrupted time series analysis of the data was considered but cannot be applied.

INTRODUCTION

Biological medicines can be defined as biotechnological products whose active ingredient is developed from living cells by one or more of recombinant deoxyribonucleic acid (DNA), controlled gene expression and antibody production methods.[1] These medicines represent an advance in the treatment of patients with chronic and life-threatening diseases such as diabetes, growth hormone deficiency and cancer.[2] Biological medicines tend to be expensive compared to conventional drugs, mainly due to the cost of research and development and their complicated biosynthesis and handling techniques.[3] For example, Remicade® (infliximab) costs £12,584 per year per patient for the treatment of Crohn’s disease.[4] As a consequence, they potentially place a heavy burden on health care budgets even in developed countries with high resources.[5] In a free at the point of need health system funded through general taxation, such as the UK NHS, there is always pressure to remain within budget and provide value for money for tax payers.[6] According to the Health and Social Care Information Centre

report in 2015, the expenditure on medicines in England was £15.5 billion with hospital expenditure growing at a higher rate than primary care.[7] The Five Year Forward View of the NHS England predicted a budget deficit of nearly £30 billion a year by 2020-2021 if the increasing demand was met by no further annual efficiencies and funding remained flat in real terms.[8] NHS Health care policy makers' aim to reduce the acquisition cost of the drugs without affecting the clinical outcome by increasing the uptake of less expensive generic alternatives to branded medicines.[9]

The patent expiry of a number of biological medicines and the establishment of regulatory frameworks by the European Medicines Agency to register similar biological medicines termed "biosimilars", raised the expectations of healthcare commissioners that biosimilars would reduce the high cost of these medicines and produce potential savings to the NHS. The UK is a relatively large market for biological and generic medicines, so represents a potentially attractive market for the biosimilars manufacturers.[10] Recent data has revealed that the uptake of biosimilars in the UK is low compared to Germany and Sweden.[11] Possible reasons behind this low uptake were healthcare prescribers and patients concerns regarding quality, safety and efficacy of biosimilars and brand loyalty.[12]

Human recombinant growth hormone is a biological medicine where a biosimilar has been available since 2006.[13] An IMS Health report in 2014 showed that uptake of biosimilar growth hormone varies considerably across the different European markets, with highest use in Poland (99%) and lowest in Norway (3%) and the UK (5%). In Poland, the implementation of a strict tendering procurement system has resulted in the evolution of growth hormone biosimilar market share.[11 14] In 2015, growth hormone preparations cost £35,742,128 which represent 0.385% of the overall medicine bill in primary care.[7]

Although the concept of generics and biosimilars is the same, biosimilars cannot be considered generics, since they are similar but not identical to the branded biotherapeutics due to the high molecular weight and complexity of biotherapeutics and the difference in synthesis process.[15] This has been recognised by the European Medicine Agency (EMA) in specific legislation for biosimilars approval.[16] The UK Medicines and Healthcare products Regulatory Agency (MHRA) guidance on biosimilars is that products should not be assumed to be identical due to the high molecular weight and structural differences between biological medicines. Thus, biological medicines and biosimilars are prescribed by brand names rather than by their International Non-propriety Name.[17] UK policymakers may have anticipated that the lower price of biosimilars compared to branded biological medicines (15-30%) would lead to a rapid uptake in the same way as conventional small molecule generic medicines, even though the price differential is far greater for generic small molecule medicines (50-90%).[18] The high unit cost of biological medicines means the small percentage price differential could result in significant annual savings.[19] The extent to which savings on prescribing for conventional small molecule medicines can be realised is a function of multifactorial influences on prescribing in the UK.[20 22] It is not clear whether the same influences which apply to generic medicines are universally applicable to biological medicines. Since 2006, the EMA has approved 23 biosimilars in different therapeutic areas, including growth hormone, erythropoietins, granulocyte-colony stimulating factors, monoclonal antibody and insulin. The European experience during this ten years, identified that the uptake and market penetration of potential biosimilar depend on therapeutic area, geographic area and patient acceptance. The uptake and market penetration of biosimilars are also governed by price variations, local market dynamics, competitors, stakeholder knowledge and experience with products and marketing efforts by companies.[23]

The main objectives of this study were to undertake a detailed analysis of the pattern of use of human recombinant growth hormone in primary and secondary care settings in England and to determine possible factors influencing its prescribing. A priori hypothesis was set, that, similar to generic medicines, price would be the dominant influencing factor in the use of these medicines.

METHODS

Data source

The study was a retrospective analysis of primary and secondary care usage of growth hormone in England. Primary care monthly prescription cost analysis data was derived from the NHS business services authority website,[24] for prescriptions dispensed in primary care in England from April 2011 to December 2015. Monthly secondary care data were taken from DEFINE Software for 2011-2016

since this prescribing database did not exist before April 2011. DEFINE Software is a NHS prescribing database of medicines usage in approximately 120 hospitals (covering over 90% of NHS hospitals throughout the UK including Specialist Centres and Mental Health Trusts) who subscribe to the software package.[25] Data were at gross national level not at institutional or patient level. The volume comparator was the defined daily dose (DDD), defined by the World Health Organisation (WHO) as the mean maintenance daily dose of a medicine for its principal indication in adults. The DDD index for growth hormone is 2 international units.[26] Primary care data were number of items issued and amount of drug in units. This was converted into defined daily doses using the following formula:

Drug usage (DDDs) = (items issued ×amount of drug per item)/DDD

Secondary care data were already available in defined daily doses.

Prices of the individual preparations were expressed as price per defined daily dose (£/DDD). Primary care prices were the basic price of a drug excluding value-added tax (VAT) (the price listed in the national Drug Tariff or in standard price lists). Secondary care prices were the average net prices for different trusts throughout the UK including VAT.

Statistical analysis

Regression analysis were used to understand and explore the association (relation) between the independent variables and the dependent variable, and the forms of these relationships.[27 28]

Prescribing trends were examined for growth hormone in primary and secondary care over the period April 2011– December 2015. Linear regression analyses were used with a quarter (three months) as the independent variable and prescription DDD as dependent variable, using quarterly data from each in primary and secondary care. The regression coefficient values were divided by the baseline prescription DDD (in April 2011) to calculate the average quarterly percentage increase or decrease in prescribing of growth hormone. Correlation analyses were used between prescription DDD and cost/DDD, using quarterly data from each in primary and secondary care. All calculations were performed using Microsoft Excel 2013 and SPSS 21.

RESULTS

Pricing and Expenditure

In primary care, prices of branded growth hormone preparations did not change between April 2011 and December 2015 with the exception of Genotropin® preparations which decreased by 25%. Biosimilar growth hormone (Omnitrope® preparations) prices decreased by 15% over this period (Table 1). Over the same time period there were higher price reductions in secondary care, including all Genotropin® preparations, Humatrope Cart®, Norditropin SimpleXx®, Omnitrope SurePal® and Zomacton Inj® (Table 1).

Expenditure on growth hormone preparations in primary care in England decreased by 17.91% between April 2011 and December 2015, whereas expenditure in secondary care increased by 68.41% during the same period.

Table 1 Change in price/DDD (in GB pounds) of growth hormone in primary and secondary care between April 2011 and December 2015

	Primary care						Secondary care					
Drug Name	2011	2012	2013	2014	2015	% Dif.	2011	2012	2013	2014	2015	% Dif.
Genotropin Cart®	15.45	11.76	11.59	11.59	11.59	-25	18.55	15.38	13.4	13.4	13.4	-27.75
Genotropin GoQuick®	15.45	11.76	11.59	11.59	11.59	-25	18.55	13.91	13.91	13.91	13.91	-25
Genotropin MiniQuick®	15.45	11.76	11.59	11.59	11.59	-25	18.55	13.91	13.91	13.91	13.91	-25
Humatrope Cart®	12.00	12.00	12.00	12.00	12.00	0	13.20	13.20	12.00	12.00	12.00	-9
Saizen Click.easy®	15.45	15.45	15.45	15.45	15.45	0	18.55	18.55	18.55	18.55	18.55	0
Zomacton_Inj®	13.28	13.28	13.28	13.28	13.28	0	15.94	15.94	13.95	13.95	13.95	-12.5
Norditropin NordiFlex®	15.45	15.45	15.45	15.45	15.45	0	18.55	18.55	18.55	18.55	18.55	0
Norditropin SimpleXx®	14.18	14.18	14.18	14.18	14.18	0	17.02	17.02	15.17	14.55	14.55	-14.5

NutropinAq Cart®	13.53	13.53	13.53	13.53	13.53	0	14.37	14.37	15.34	15.34	15.34	6.75
Omnitrope Cart®	11.69	11.69	11.69	11.69	9.83	-16	11.52	11.52	11.52	11.52	11.52	0
Omnitrope SurePal®			11.56	11.56	9.83	-15			13.46	10.92	10.92	-19
Saizen Cart®	15.45	15.45	15.45	15.45	15.45	0	18.55	18.55	18.55	18.55	18.55	0

*Omnitrope® and Omnitrope SurePal® are growth hormone biosimilars
**Omnitrope SurePal® was marketed in June 2013 in secondary care and October 2013 in primary care
% Dif.: % of difference between 2011 and 2015 price/DDD

Volume of utilisation

Growth hormone utilisation in primary care declined from 764,877 DDDs in second quarter 2011 to 709,054 DDDs in the fourth quarter 2015. Regression analysis indicates that this decline of on average 0.45% per quarter (95% confidence interval 0.70 to 0.21) is statistically significant. Genotropin Cart®, Norditropin SimpleXx® and Saizen Click.easy® dominated the growth hormone market by volume, accounting for 30%, 24% and 17.5% respectively of prescribed growth hormone in second quarter 2011 (Figure 1). By the fourth quarter 2015, Genotropin Cart®, Norditropin SimpleXx® still had the highest share of the growth hormone market at 22% for both but Saizen Cart® had replaced Saizen Click.easy at 14.5% (Figure 1).

In contrast to primary care, secondary care utilisation of growth hormone doubled from 152,457 DDDs in second quarter 2011 to 304,443 DDDs in fourth quarter 2015 representing a statistically significant rise of on average 5.8% (95% confidence interval 4.71 to 6.89) per quarter. As in primary care Genotropin Cart® and Norditropin SimpleXx® dominated the growth hormone market by volume, accounting for 18%, 23% respectively of prescribed growth hormone in second quarter 2011. By the fourth quarter 2015, Genotropin Cart®, had decreased to 12%, Norditropin SimpleXx® increased slightly to 25% but Omnitrope Cart® and Saizen Cart® also accounted for 11% and 12% of the market respectively (Figure 2).

The correlation analysis between price per DDD and product utilisation in primary care revealed that for Norditropin NordiFlex®, Saizen Cart®, Saizen Click.easy® there was no correlation. For Genotropin Cart® there was an intermediate positive correlation (R^2=0.5023), for Genotropin MiniQuick®, Humatrope Cart®, Norditropin SimpleXx®, Zomacton Inj® there were weakly positive correlation (R^2=0.1081, R^2=0.075, R^2=0.2313 and R^2=0.0006 respectively). For remaining products there were weakly negative correlations (NutropinAq Cart® R^2=0.2066, Omnitrope Cart® R^2=0.0764, Omnitrope SurePal® R^2=0.3614), with the exception of Genotropin GoQuick® there was an intermediate negative correlation.

In secondary care, a similar diverse pattern of correlation between price/DDD and product utilisation was seen. Norditropin NordiFlex® and Omnitrope Cart® showed no correlation. For Genotropin GoQuick®, NutropinAq Cart® and Saizen Cart® there were weakly positive correlation (R^2=0.2535, R^2=0.0873, R^2=0.0004 respectively). For remaining products there were weakly negative correlations (Genotropin Cart® R^2=0.0128, Genotropin MiniQuick® R^2=0.1622, Humatrope Cart® R^2=0.0155, Omnitrope SurePal® R^2=0.4973 and Zomacton Inj® R^2=0.3766), with the exception of Norditropin SimpleXx® there was an intermediate negative correlation.

Table 2 Growth hormone preparations characteristics

Reconstitution requiring agent		Ready to use agents	
Agent	Description	Agent	Description
Genotropin Cart®	Cartridge needed, needs fridge after reconstitution, dose cannot pre-set	NutropinAq Cart®	Cartridge needed, needs fridge, dose cannot pre-set
Genotropin GoQuick®	Pre-filled, needs fridge after reconstitution	Norditropin NordiFlex®	Pre-filled, dose cannot pre-set
Genotropin MiniQuick®	Pre-filled syringe, single dose, preservative free, portable, can be kept outside the fridge before use.	Norditropin SimpleXx®	Cartridge needed, dose cannot pre-set, can be kept at room temperature for 3 weeks after first use, auto-injector
Humatrope	Cartridge needed, needs fridge before and	Omnitrope	Cartridge needed, needs fridge, dose cannot

Cart®	after reconstitution, dose cannot pre-set	Cart®	pre-set
Zomacton Inj®	Needle free, vial needed, may cause skin reaction, dose cannot be pre-set	Omnitrope SurePal®	Cartridge needed, needs fridge, dose pre-set, hidden needle
Saizen Click.easy®	Automatic needle insertion, cartridge needed, needs fridge during use, dose cannot pre-set	Saizen Cart®	Electronic - automatic injector, dose pre-set, records of dose history, hidden needle, on-screen for instruction of use, control of comfort parameters (injection depth, time, speed), cartridge needed.

Table 2 summarises the main characteristics of reconstitution requiring agents and ready to use growth hormone preparations. Figure 3 shows the utilisation trends for products requiring reconstitution and those in a ready to use formulation in primary and secondary care settings. The utilisation of products requiring reconstitution (Genotropin Cart®, Genotropin GoQuick®, Genotropin MiniQuick®, Humatrope Cart®, Saizen Click.easy® and Zomacton Inj®) all showed a clear decline in use in primary care (R^2=0.9292) and a slight increase in use in secondary care (R^2 = 0.139). In stark contrast, the utilisation of ready to use products (Norditropin NordiFlex®, Norditropin SimpleXx®, NutropinAq Cart®, Omnitrope Cart®, Omnitrope SurePal® and Saizen Cart®) showed a very clear increase in use in both primary and secondary care (R^2=0.7526) and (R^2=0.9633) respectively.

Figure 4 shows that in primary care the utilisation of 5 out of 6 ready to use agents increased between 2011 and 2015 irrespective to the price. The utilisation of 4 of 6 of reconstitution requiring agents decreased during the same period although their prices have decreased. Figure 5 shows that in secondary care that utilisation of all ready to use agents increased between 2011 and 2015 irrespective of price. The utilisation of 3 out of 6 reconstitution requiring agents increased during the same period when their prices decreased. The utilisation of remaining three reconstitution requiring agents decreased despite price reduction.

DISCUSSION

The long established principles of good prescribing practice and medicines optimisation suggest that clinicians aim to prescribe to maximise effectiveness, minimise risks and take into account the patients experience.[29] At the same time, in a health system free at the point of need funded by general taxation, prescribers consider relative costs of medicines and NHS policy and NICE guidance whilst still respecting the patient's choice.[30] [31] Balancing between these conflicting aims and recommendations result in good prescribing to achieve maximum effectiveness, minimum risk and cost, although it is recognised that financial and non-financial incentives may also be needed to encourage best practice.[32]

In the UK, growth hormone prescribing follows a shared care protocol between primary and secondary care. In hospital, a consultant endocrinologist first diagnoses the patient requiring growth hormone. An endocrine specialist nurse demonstrates the available growth hormone devices to the patient, then trains the patient on the use of their chosen device. The patient is then provided with an initial supply. The primary care GP continues prescribing growth hormone for the patient in accordance with the local agreed shared care protocol.[33]

In England, there are currently seven preparations of growth hormone. Although these preparations differ in their injecting device for the delivery of growth hormone, these preparations are equal in terms of clinical effectiveness.[34] With the availability of such a variety of preparations endocrinologists and other healthcare professionals prescribing growth hormone are being asked to make some complex decisions regarding the selection of the preparation for each patient. The latest NICE guidelines in 2010 for treatment with growth hormone stated that the product selection should be based on a discussion between the prescriber and the patient or the patients' parents, taking into account the advantages and disadvantages of each device. If more than one option is suitable the less expensive one should be chosen.[34]

In this study, we classified growth hormone delivery devices into reconstitution requiring agents and ready to use agents. Ready to use agents were characterised by fewer steps and time required for dose preparation by patients and potentially a reduction in user errors that may occur during the reconstitution process. Reconstitution can be quite complex since each preparation requires a special reconstitution kit. The cartridge containing lyophilised growth hormone is reconstituted using only the diluent syringe that accompanies the cartridge. The diluent syringe is placed into the reconstitution kit, the needle cover of the diluent syringe is removed, and the cartridge inserted. When the diluent needle is inserted inside the cartridge, the plunger of the diluent is pushed until all the diluent is transferred into the cartridge. The cartridge is then removed from the kit, with gentle rotary movement (mixing) but not shaking until the solution became clear.[35]

Studies have identified that premixed solution devices (ready to use devices) are more acceptable to patients and/or parents than reconstitution requiring devices. The simplicity and the least steps required for preparation and administration of growth hormone doses are considered among the most desirable attributes of administration devices.[36 37] Ready to use agents are associated with less pain than reconstitution requiring agents due to the higher concentration of these products and, therefore, smaller volumes of GH injected. Furthermore, added preservative and buffer to the premixed solution of GH decrease the injection pain.[38]

Interestingly, the utilisation of the growth hormone market leader in primary care Genotropin Cart® decreased over the study period despite a 25% price reduction (Figure 1). Over the same time period Saizen Cart® (ready to use agent) replaced Saizen Click.easy® (reconstitution requiring agent) although it was the same price (Figure 1). This challenges policy assumptions that cheaper drugs will dominate. It also shows that perceived preference may outweigh national guidance to select lowest cost agents. The results have implications for those considering effectiveness of implementation of national guidance. Furthermore, the results has implications for NHS budget mangers when they consider which medicines to make available within local health economies.

The pattern of product utilisation in secondary care was more diverse (Figure 2). In this sector Genotropin Cart® usage decreased despite a 27.75% price reduction over the study period (Figure 2). The market leader in secondary care, Norditropin SimpleXx® (ready to use agent), grew only slightly despite a 14.5% price reduction. Omnitrope Cart® (the less expensive option) and Siazen Cart® (the most expensive option) (both ready to use agents) increased their share of the secondary care market although in both cases the price did not change. These findings suggest ease of use rather than price is the key influence on the prescribing decision. Within the NHS in the UK medicines are reimbursed differently in primary and secondary care. In primary care community pharmacies are reimbursed by the government for the medicines they dispense at a basic NHS price which is set nationally, whereas in hospitals the prices paid for medicines are negotiated with manufacturers through regional and local contracting processes. These discounts are sometimes offset since hospital medicines attract VAT whereas primary care medicine do not. This means that the cost of medicines are often different in secondary care.

The analysis of price and product utilisation supports this observation. A number of products both in primary and secondary care showed no correlation between price and production utilisation. Indeed some showed a positive correlation indicating that the higher price was associated with higher use. A negative correlation would suggest that price was influencing use. However, in both primary and secondary care all the negative correlations were weak $R^2<0.5$, with the exception of Genotropin GoQuick® in primary care and Norditropin SimpleXx® in secondary care which were intermediate $R^2>0.5<0.75$. This complete diversity of correlations in both sectors indicates price is not the driver for product use.

The use of ready to use agents increased in both sectors during the study period (Figure 3). This explains the slight overall decrease in growth hormone in primary care as it comprises a growth in the

use of the ready to use agents counteracted by a significant decrease in the use of the reconstitution requiring agents. Furthermore, the overall growth in secondary care comprises a significant (almost tripling) growth in the ready to use agents and a flattening use of the reconstitution requiring agents (Figure 3). Figure 3 also shows that reconstitution requiring agents dominated until 2014, but were overtaken by ready to use agents. This is perhaps a reflection of the more conservative rate of change of prescribing patterns in the UK, since the reconstitution requiring agents were available since 1987,[39] whereas the first ready to use agents only became available in the UK in 2000 and the newer devices from 2011 (Norditropin Nordiflex® and Saizen Cart® were launched in 2011 and Omnitrope Surepal® was launched in 2013).[40 41] This is supported in the literature, which has identified the UK market as one of the slowest markets in Europe in taking up new medicines.[42] Furthermore, stable patients will most likely have remained on the product they were initiated on since if all is well, both patients and prescribers may be disinclined to switch. Thus, given the nature of this therapy it takes time for new products to get market traction.

Figure 4 and 5 also suggest that the quantity or the utilisation of growth hormone preparations is not price dependent in both primary and secondary care settings. The utilisation of ready to use agents increased in both sector irrespective to the change in price (decreased or unchanged).

This suggests that ease of use rather than price is the key driver for growth hormone product selection in both primary and secondary care. The findings from this study agree with previous studies of branded growth hormone that outlined that ease of use and convenience (premixed formulations) were the most important product characteristics from patients' perspective.[37 43 44] This may have been because the patients are adolescents who will be in full-time education and require formulations which are quick and easy to use.

Previous literature on this subject has focused on patient preferences in relation to specific devices. This study focused on whether these preferences are translated into prescriber product selection. Implicitly this suggests that for growth hormone, prescribers, whilst following the principles of medicines optimisation take more account of patient preferences than central guidance on cost efficiency. This contrasts with other health economies were mandated switching to GH biosimilar meant that 99% of prescribing was the less expensive biosimilar.[14]

Our study has several limitations, firstly, the time period for analysis was limited to five years as we wanted to explore the utilisation of growth hormone in both primary and secondary care. We could only access monthly data for primary and secondary care since 2011. Secondly, segmented regression of interrupted time series analysis of the data was considered but growth hormone prices change were not linked to a single point of time and NICE guidance on growth hormone was not changed during the study period. Visual analyses of Figures 1 and 2 showed no abrupt change in the pattern of utilisation of growth hormone over the study period required for this type of analysis.

CONCLUSION

This study has suggests that the price of growth hormone products is not the key influencing factor in prescribing of biologic medicines. The main driver for specific product selection is the ease of use and fewer steps in dose preparation. Prescribers are clearly taking into account patient preferences rather than cost in their prescribing decisions, in line with national guidance.

Contributors: All authors have contributed to this study and all authors reviewed and approved the final version of the manuscript. SRC designed the study, interpreted the results and reviewed the manuscript and corrected the final version of the manuscript. RWF participated in the study design, interpreted the results and reviewed the manuscript and corrected the final version of the manuscript. MIA participated in the study design, data collection, and interpretation of results, prepared the manuscript draft, and performed all analytical testing and manuscript review.

Funding: This research was not funded or sponsored by any organisation and the researchers are independent of any funding bodies.

Access to data: All authors had full access to all of the data (including statistical reports and tables) in the study and can take responsibility for the integrity of the data and the accuracy of the data analysis.

Transparency declaration: The lead author affirms that the manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

Competing interests: All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

Ethical approval: No ethical approval was required for this research.

Data sharing statement: No additional data are available.

REFERENCES

1. Nowicki M. Basic facts about biosimilars. *Kidney Blood Press Res* 2007;*30*(5):267-272.
2. Farfan-Portet MI, Gerkens S, Lepage-Nefkens I, et al. Are biosimilars the next tool to guarantee cost-containment for pharmaceutical expenditures? *Eur J Health Econ* 2014;15(3):223.
3. Blackstone EA, Joseph PF. The economics of biosimilars. *Am Health Drug Benefits* 2013;6(8):469.
4. National Institute for Clinical Excellence. Infliximab (review) and adalimumab for the treatment of Crohn's disease. 2010. [Online]. Available at: https://www.nice.org.uk/guidance/ta187/resources/guidance-infliximab-review-and-adalimumab-for-the-treatment-of-crohns-disease-pdf. (Accessed 14 Nov. 2016).
5. McCamish M, Woollett G. The rise of the biosimilar. *Expert Rev Clin Pharmacol* 2012;5(6):597-599.
6. Harker R. NHS funding and expenditure. 2012. [Online] Available: http://www.nhshistory.net/parlymoneypapter.pdf. (Accessed 16 May 2016).
7. HSCIC. Prescribing Costs in Hospitals and the Community. 2015. [Online] Available: http://www.hscic.gov.uk/catalogue/PUB18973/hosp-pres-eng-201415-report.pdf. (Accessed 27 May 2016).
8. NHS England. Five Year Forward View. 2014. [Online] Available: https://www.england.nhs.uk/wp-content/uploads/2014/10/5yfv-web.pdf. (Accessed 24 May 2016).
9. Spoors J, Kusel J. The uptake of non-branded medicines: Fact, fiction and biosimilarities. *BJHCM* 2015;21(7):331-342.
10. Megerlin F, Lopert R, Taymor K, et al. Biosimilars and the European experience: implications for the United States. *Health Aff* 2013;32(10):1803-1810.
11. IMS Institute for Healthcare Informatics. Assessing biosimilar uptake and competition in European markets. 2014. [Online] Available: https://www.imshealth.com/files/web/IMSH%20Institute/Healthcare%20Briefs/Assessing_biosimilar_uptake_and_competition_in_European_markets.pdf. (Accessed 26 May 2016).
12. Antonini P, Murphy M. Assuring patient adoption during biosimilar development and commercialization. Worldwide clinical trials. 2015. [Online] Available: https://www.worldwide.com/getattachment/3908b310-3d7b-40af-9a42-1f878d54b1ca/Assuring-Patient-Adoption-during-Biosimilar-Develo/Assuring-Patient-Adoption-during-Biosimilar-Develo. (Accessed 25 May 2016).
13. Lee J, Davis M, Clark J, et al. Estimated cost-effectiveness of growth hormone therapy for idiopathic short stature. *Arch Pediatr Adolesc Med* 2006;160(3):263-269.
14. IMS Institute for Healthcare Informatics. The Impact of Biosimilar Competition. 2015. [Online] Available: http://ec.europa.eu/DocsRoom/documents/14547/attachments/1/translations/en/renditions/native. (Accessed 20 June 2016).
15. Misra A. Are biosimilars really generics? Expert Opin Biol Ther 2010;10(4):489-494.
16. Roger D, Goldsmith D. Biosimilars: it's not as simple as cost alone. J Clin Pharm Ther 2008;33(5):459-464.
17. Medicines and Healthcare Products Regulatory Agency (MHRA). Biosimilar products, Drug Safety Update. 2008. [Online] Available: https://www.gov.uk/drug-safety-update/biosimilar-products. (Accessed 25 May 2016).
18. Zuniga L, Calvo B. Biosimilars-the way forward. *Biotechnology* 2010;5:42.
19. Rana P, Roy V. Generic medicines: issues and relevance for global health. *Fundam Clin Pharmacol* 2015;29(6):529-542.

20. Prosser H, Walley T. A qualitative study of GPs' and PCO stakeholders' views on the importance and influence of cost on prescribing. Soc Sci Med 2005;60(6):1335-1346.
21. Grabowski H. G., Ridley D. B., Schulman, K. A. Entry and competition in generic biologics. *MDE Manage Decis Econ* 2007;28(4□5): 439-451.
22. Mestre-Ferrandiz J, Towse A, Berdud M. Biosimilars: how can payers get long-term savings? *Pharmacoeconomics* 2016;34(6):609-616.
23. QuintilesIMS. Biosimilar Use and Uptake in Europe. 2015. [Online]. Available at: http://www.quintiles.com/blog/biosimilar-use-and-uptake-in-europe (Accessed 14 Nov. 2016).
24. NHS Prescription Services. Prescription Cost Analysis (PCA) Data. 2016. [Online] Available: http://www.nhsbsa.nhs.uk/PrescriptionServices/3494.aspx. (Accessed 1 May 2016).
25. Rx Info. Define. 2016. [Online]. Available at: http://www.rx-info.co.uk/products/define.ashx (Accessed at 14 Nov. 2016).
26. WHOCC. Definition and general considerations. 2015. [Online] Available: http://www.whocc.no/ddd/definition_and_general_considera/. (Accessed 1 May 2016).
27. Bowers D. Medical statistics from scratch: an introduction for health professionals. John Wiley & Sons 2008.
28. Bewick V, Cheek L, Ball J. Statistics review 7: Correlation and regression. *Critical Care* 2003;7(6):1.
29. Royal Pharmaceutical Society. Medicines Optimisation: Helping patients to make the most of medicines. 2013. [Online] Available: http://www.rpharms.com/promoting-pharmacy-pdfs/helping-patients-make-the-most-of-their-medicines.pdf. (Accessed 16 Jun. 2016).
30. Ess M, Schneeweiss S, Szucs D. European healthcare policies for controlling drug expenditure. *Pharmacoeconomics* 2003;21(2):89-103.
31. Barber N. What constitutes good prescribing?. *BMJ* 1995;310(6984):923.
32. Karlsberg-Schaffer S, Sussex J, Feng Y. Incentives to Follow Best Practice in Health Care. OHE Briefing. 2015. [Online]. Available at: https://www.ohe.org/publications/incentives-follow-best-practice-health-care (Accessed 18 Nov. 2016).
33. Bujanova J, Cummings H. Management of growth hormone deficiency in adults. *Prescriber* 2015;26(23):29-33.
34. NICE. Human growth hormone (somatropin) for the treatment of growth failure in children. 2010. [Online] Available: https://www.nice.org.uk/guidance/ta188. (Accessed 15 Jun. 2016).
35. Eli Lilly Humatrope®: Information and Patient Instructions. 2011. [Online]. Available at: http://pi.lilly.com/us/humatrope-ppi_newrecon.pdf (Accessed 14 Nov. 2016).
36. Stanhope R, Buchanan C, Butler G, et al. An open-label acceptability study of Norditropin SimpleXx-a new liquid growth hormone formulation. *J Pediatr Endocrinol Metab* 2001;14(6):735-740.
37. Wickramasuriya N, Casey A, Akhtar S, et al. Factors determining patient choice of device for GH therapy. *Horm Res Paediatr* 2006;65(1):18-22.
38. Kirk J. Developments in growth hormone delivery. *Curr Drug ther* 2010;5(1): 43-47.
39. European Medicine Agency. Questions and answers on Genotropin and associated names (somatropin injection). 2010. [Online] Available: http://www.ema.europa.eu/docs/en_GB/document_library/Referrals_document/Genotropin_6_12/WC500093962.pdf. (Accessed 14 Nov. 2016).
40. HSCIC. Prescription Cost Analysis England 2011. 2012. [Online] Available: http://content.digital.nhs.uk/catalogue/PUB05807/pres-cost-anal-eng-2011-rep.pdf. (Accessed 15 Nov. 2016).
41. HSCIC. Prescription Cost Analysis England 2013. 2014. [Online] Available: http://content.digital.nhs.uk/catalogue/PUB13887/pres-cost-anal-eng-2013-rep.pdf. (Accessed 15 Nov. 2016).
42. Chaplin S. Is the UK too slow in the uptake of new medicines? *Prescriber* 2015;26:29-30.

43. Ahmed F, Smith A, Blamires C. Facilitating and understanding the family's choice of injection device for growth hormone therapy by using conjoint analysis. *Arch Dis Child* 2008;93(2):110-114.
44. Dumas H, Panayiotopoulos P, Parker D, et al. Understanding and meeting the needs of those using growth hormone injection devices. *BMC Endocr Disord* 2006;6(1):1.

Figure 1. Quarterly utilisation of growth hormone preparations in primary care between April 2011 and December 2015. DDD: defined daily dose.

Figure 2. Quarterly utilisation of growth hormone preparations in secondary care between April 2011 and December 2015. DDD: defined daily dose.

Figure 3. Comparison between reconstitution requiring agents and ready to use agents in primary and secondary care between April 2011 and December 2015. DDD: defined daily dose.

Figure 4. Utilisation versus cost/DDD of reconstitution requiring agents and ready to use agents of growth hormone preparations in primary care. DDD: defined daily dose.

Figure 5. Utilisation versus cost/DDD of reconstitution requiring agents and ready to use agents of growth hormone preparations in secondary care. DDD: defined daily dose.

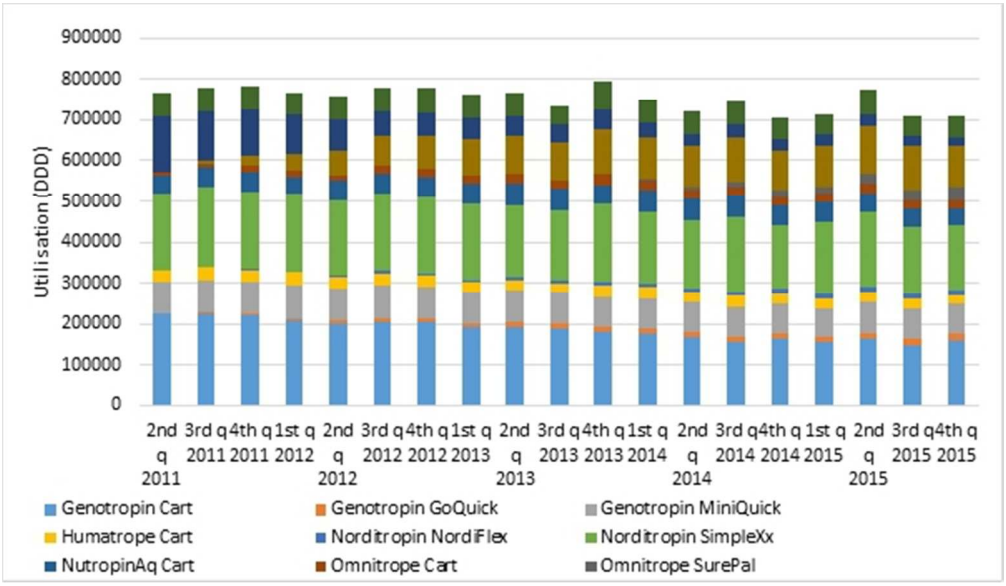

Figure 1. Quarterly utilisation of growth hormone preparations in primary care between April 2011 and December 2015. DDD: defined daily dose.

50x29mm (300 x 300 DPI)

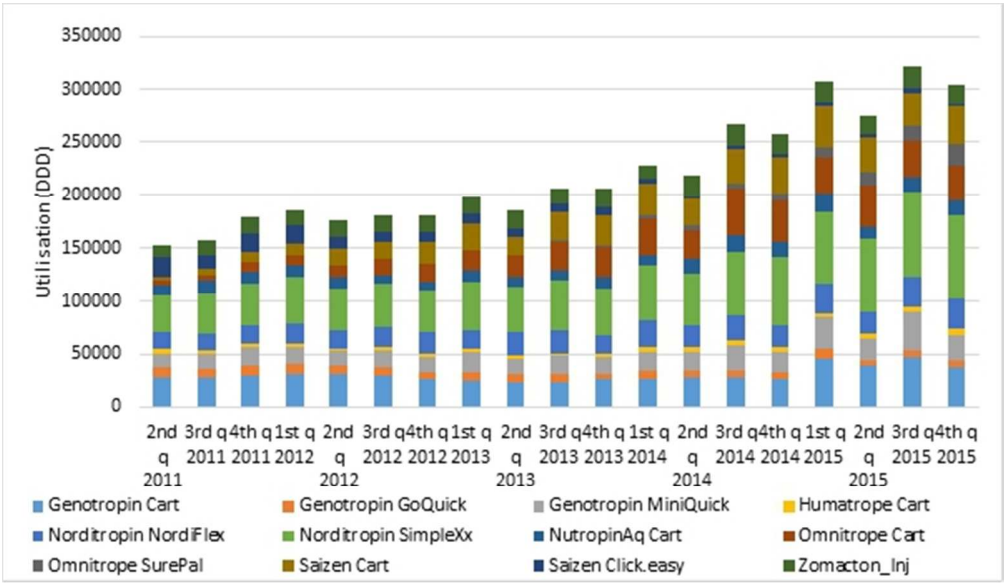

Figure 2. Quarterly utilisation of growth hormone preparations in secondary care between April 2011 and December 2015. DDD: defined daily dose.

50x29mm (300 x 300 DPI)

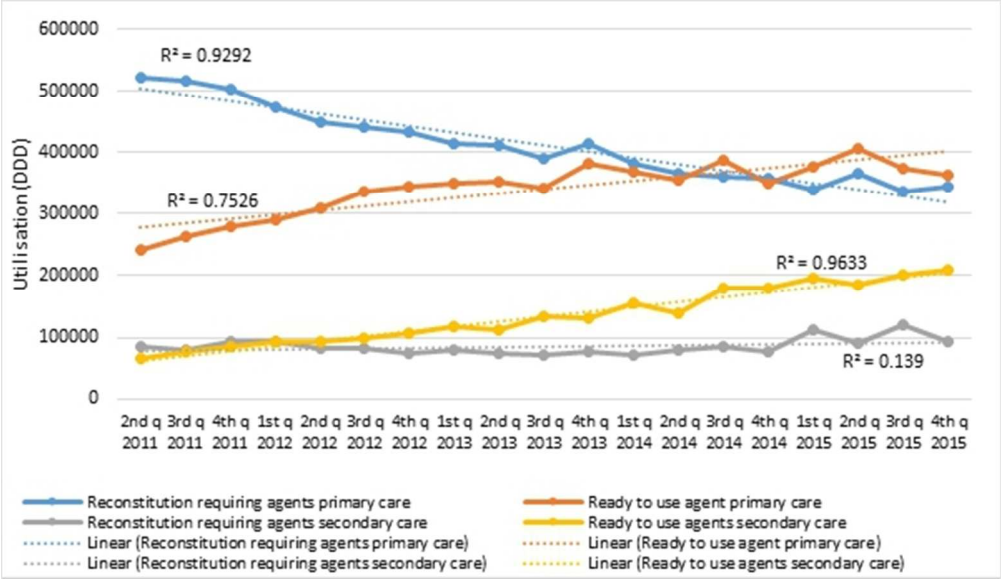

Figure 3. Comparison between reconstitution requiring agents and ready to use agents in primary and secondary care between April 2011 and December 2015. DDD: defined daily dose.

50x29mm (300 x 300 DPI)

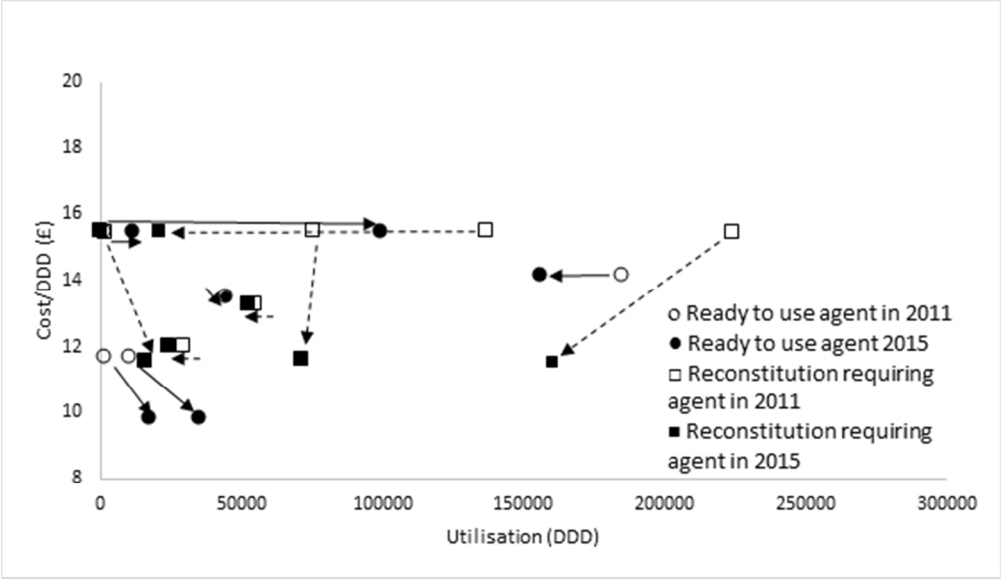

Figure 4. Utilisation versus cost/DDD of reconstitution requiring agents and ready to use agents of growth hormone preparations in primary care. DDD: defined daily dose.

50x29mm (300 x 300 DPI)

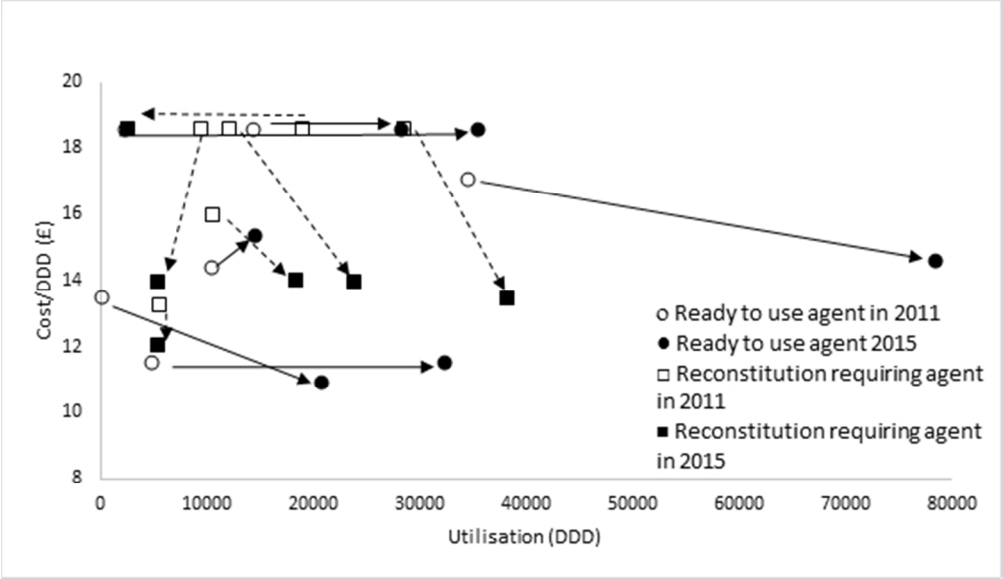

Figure 5. Utilisation versus cost/DDD of reconstitution requiring agents and ready to use agents of growth hormone preparations in secondary care. DDD: defined daily dose.

50x29mm (300 x 300 DPI)

The RECORD statement – checklist of items, extended from the STROBE statement, that should be reported in observational studies using routinely collected health data.

	Item No.	STROBE items	Location in manuscript where items are reported	RECORD items	Location in manuscript where items are reported
Title and abstract					
	1	(a) Indicate the study's design with a commonly used term in the title or the abstract (b) Provide in the abstract an informative and balanced summary of what was done and what was found	P2	RECORD 1.1: The type of data used should be specified in the title or abstract. When possible, the name of the databases used should be included. RECORD 1.2: If applicable, the geographic region and timeframe within which the study took place should be reported in the title or abstract. RECORD 1.3: If linkage between databases was conducted for the study, this should be clearly stated in the title or abstract.	P2 P2 N/A
Introduction					
Background rationale	2	Explain the scientific background and rationale for the investigation being reported	P2		
Objectives	3	State specific objectives, including any prespecified hypotheses	P3		
Methods					
Study Design	4	Present key elements of study design early in the paper	P3		
Setting	5	Describe the setting, locations, and relevant dates, including periods of recruitment, exposure, follow-up, and data collection	P3-4		
Participants	6	*(a) Cohort study* - Give the eligibility criteria, and the	N/A	RECORD 6.1: The methods of study population selection (such as codes or	N/A

		sources and methods of selection of participants. Describe methods of follow-up *Case-control study* - Give the eligibility criteria, and the sources and methods of case ascertainment and control selection. Give the rationale for the choice of cases and controls *Cross-sectional study* - Give the eligibility criteria, and the sources and methods of selection of participants *(b) Cohort study* - For matched studies, give matching criteria and number of exposed and unexposed *Case-control study* - For matched studies, give matching criteria and the number of controls per case	N/A	algorithms used to identify subjects) should be listed in detail. If this is not possible, an explanation should be provided. RECORD 6.2: Any validation studies of the codes or algorithms used to select the population should be referenced. If validation was conducted for this study and not published elsewhere, detailed methods and results should be provided. RECORD 6.3: If the study involved linkage of databases, consider use of a flow diagram or other graphical display to demonstrate the data linkage process, including the number of individuals with linked data at each stage.	N/A N/A
Variables	7	Clearly define all outcomes, exposures, predictors, potential confounders, and effect modifiers. Give diagnostic criteria, if applicable.	P4	RECORD 7.1: A complete list of codes and algorithms used to classify exposures, outcomes, confounders, and effect modifiers should be provided. If these cannot be reported, an explanation should be provided.	P3
Data sources/ measurement	8	For each variable of interest, give sources of data and details of methods of assessment (measurement). Describe comparability of assessment methods if there is more than one group	P4		
Bias	9	Describe any efforts to address potential sources of bias	N/A		
Study size	10	Explain how the study size was	P4		

		arrived at			
Quantitative variables	11	Explain how quantitative variables were handled in the analyses. If applicable, describe which groupings were chosen, and why	P4		
Statistical methods	12	(a) Describe all statistical methods, including those used to control for confounding (b) Describe any methods used to examine subgroups and interactions (c) Explain how missing data were addressed (d) *Cohort study* - If applicable, explain how loss to follow-up was addressed *Case-control study* - If applicable, explain how matching of cases and controls was addressed *Cross-sectional study* - If applicable, describe analytical methods taking account of sampling strategy (e) Describe any sensitivity analyses	P4		
Data access and cleaning methods		..		RECORD 12.1: Authors should describe the extent to which the investigators had access to the database population used to create the study population. RECORD 12.2: Authors should provide information on the data cleaning methods used in the study.	P4 P4
Linkage		..		RECORD 12.3: State whether the study included person-level, institutional-	P4

				level, or other data linkage across two or more databases. The methods of linkage and methods of linkage quality evaluation should be provided.	
Results					
Participants	13	(a) Report the numbers of individuals at each stage of the study (*e.g.*, numbers potentially eligible, examined for eligibility, confirmed eligible, included in the study, completing follow-up, and analysed) (b) Give reasons for non-participation at each stage. (c) Consider use of a flow diagram	N/A	RECORD 13.1: Describe in detail the selection of the persons included in the study (*i.e.,* study population selection) including filtering based on data quality, data availability and linkage. The selection of included persons can be described in the text and/or by means of the study flow diagram.	N/A
Descriptive data	14	(a) Give characteristics of study participants (*e.g.*, demographic, clinical, social) and information on exposures and potential confounders (b) Indicate the number of participants with missing data for each variable of interest (c) *Cohort study* - summarise follow-up time (*e.g.*, average and total amount)	N/A		
Outcome data	15	*Cohort study* - Report numbers of outcome events or summary measures over time *Case-control study* - Report numbers in each exposure category, or summary measures of exposure *Cross-sectional study* - Report numbers of outcome events or summary measures	P4		
Main results	16	(a) Give unadjusted estimates	P4-6		

		and, if applicable, confounder-adjusted estimates and their precision (e.g., 95% confidence interval). Make clear which confounders were adjusted for and why they were included (b) Report category boundaries when continuous variables were categorized (c) If relevant, consider translating estimates of relative risk into absolute risk for a meaningful time period			
Other analyses	17	Report other analyses done—e.g., analyses of subgroups and interactions, and sensitivity analyses	P5-6		
Discussion					
Key results	18	Summarise key results with reference to study objectives	P5-6		
Limitations	19	Discuss limitations of the study, taking into account sources of potential bias or imprecision. Discuss both direction and magnitude of any potential bias	P8	RECORD 19.1: Discuss the implications of using data that were not created or collected to answer the specific research question(s). Include discussion of misclassification bias, unmeasured confounding, missing data, and changing eligibility over time, as they pertain to the study being reported.	N/A
Interpretation	20	Give a cautious overall interpretation of results considering objectives, limitations, multiplicity of analyses, results from similar studies, and other relevant evidence	P6-7		
Generalisability	21	Discuss the generalisability (external validity) of the study results	P7		

Other Information					
Funding	22	Give the source of funding and the role of the funders for the present study and, if applicable, for the original study on which the present article is based	P9		
Accessibility of protocol, raw data, and programming code		..		RECORD 22.1: Authors should provide information on how to access any supplemental information such as the study protocol, raw data, or programming code.	P9

*Reference: Benchimol EI, Smeeth L, Guttmann A, Harron K, Moher D, Petersen I, Sørensen HT, von Elm E, Langan SM, the RECORD Working Committee. The REporting of studies Conducted using Observational Routinely-collected health Data (RECORD) Statement. *PLoS Medicine* 2015; in press.