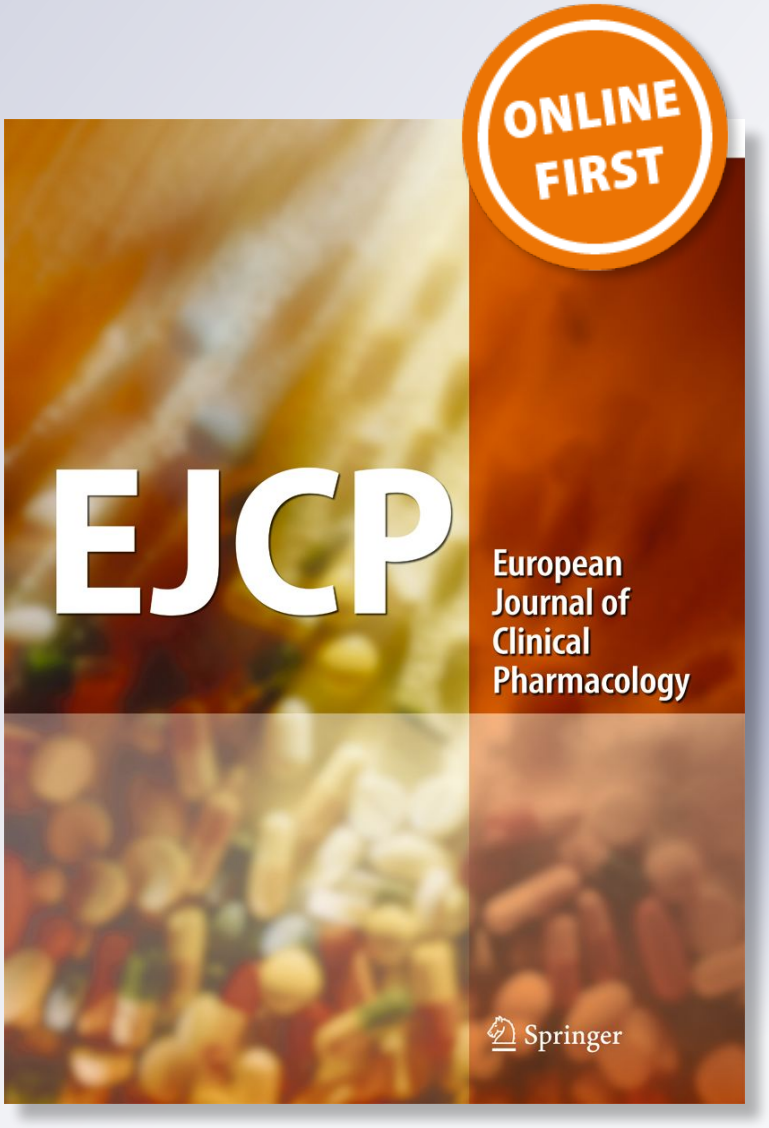
Towards preventive pharmacovigilance through medicine misuse identification: an example with recombinant human growth hormone for aesthetic purposes

Alfredo J. Rodrigues-Neto, Camila Biazoni-Albaricci, Adalton Ribeiro, Silvana Lima & Albert Figueras

European Journal of Clinical Pharmacology

ISSN 0031-6970

Eur J Clin Pharmacol
DOI 10.1007/s00228-018-2510-9



Springer

European Journal of Clinical Pharmacology
https://doi.org/10.1007/s00228-018-2510-9

PHARMACOEPIDEMIOLOGY AND PRESCRIPTION

Towards preventive pharmacovigilance through medicine misuse identification: an example with recombinant human growth hormone for aesthetic purposes

Alfredo J. Rodrigues-Neto[1] · Camila Biazoni-Albaricci[1] · Adalton Ribeiro[2] · Silvana Lima[2] · Albert Figueras[3,4]

Received: 12 February 2018 / Accepted: 22 June 2018

Abstract

Purpose Historically, somatropin has been used for conditions related with ageing, but since the marketing of recombinant human growth hormone (rhGH), increasing promotional pressure has prompted aesthetic uses, despite lack of evidences about its efficacy and safety for those purposes.

Methods A routine analysis of the Pharmacovigilance Center of São Paulo (Brazil) showed reports of suspected adverse reactions in young adults and mature patients receiving rhGH. After presuming an off-label use of this expensive product, a drug utilisation study within the pharmacovigilance database has been carried out.

Results The analysis showed a bimodal age distribution of the rhGH reports. Up to 17.1% of the 1289 reports ($n = 220$) involved patients aged ≥ 20 years taking rhGH for off-label uses.

Conclusions This information was the basis to design interventions in order to reduce inappropriate utilisation of this expensive product. Analyses of how medicines are being used through pharmacovigilance databases are a way to identify its irrational utilisation, thus facilitating preventive actions to improve how medicines are used and reducing avoidable adverse effects.

Keywords Pharmacovigilance · Medicines utilisation · Off-label · Somatropin

Introduction

The importance of growth hormone (GH) was recognised early after its discovery in the nineteenth century. The potential effects of GH in preventing ageing were suggested in the 1920s, but the interest on its use really increased after the synthesis and marketing of recombinant human growth hormone (rhGH) [1, 2].

In addition to its efficacy in GH-deficient children and adolescents, some endocrine syndromes, and short stature, GH deficiency in adults (GHD-A) was described and defined. Studies began to show the potential benefits of GH replacement in these patients, although sound evidences for a reduction in cardiovascular events as well as mortality continue to be lacking [3]. Additionally, several results in animals and few observations in humans suggested the use of rhGH as an anti-ageing product, in muscle wasting or even decreased bone mineral density. A careful recent review of the available evidences highlighted that results of clinical trials are lacking and, in some cases, the real clinical relevance of the physiological effects observed after the use of rhGH are at best controversial [4–6].

In Brazil, as in many other countries, rhGH has been approved for use in children presenting GH deficit, Turner or Prader-Willi syndromes, and short stature for the gestational age. In adults, the approved indications of use are clinical diagnosis of GHD-A [7]. The EMA has also approved its

Electronic supplementary material The online version of this article (https://doi.org/10.1007/s00228-018-2510-9) contains supplementary material, which is available to authorized users.

✉ Albert Figueras
afs@icf.uab.cat

[1] Faculdade de Ciências Farmacêuticas, Universidade de São Paulo, São Paulo, Brazil

[2] Núcleo de Farmacovigilância, Centro de Vigilância Sanitária de São Paulo, São Paulo, Brazil

[3] Fundació Institut Català de Farmacologia, Departament de Farmacologia, Universitat Autònoma de Barcelona, Barcelona, Spain

[4] Fundació Institut Català de Farmacologia, Hospital Vall d'Hebron, Passeig Vall d'Hebron, 119-129, 08035 Barcelona, Spain

Published online: 23 July 2018

use in acromegaly [8] and the FDA for muscle wasting from HIV and short bowel syndrome [9]. Although these are precise indications, off-label utilisation of rhGH is expected due to historical non-evidence-based uses of non-recombinant GH, the high cost of rhGH preparations (that increases commercial pressure), and the growing attention in the so-called biomedical enhancement and anti-ageing currents, thus pushing off-label utilisation despite the lack of information about the safety of its long-term use, and even evidences found in studies in transgenic mice suggesting that massive chronic elevations of GH levels could accelerate rather than prevent ageing [10].

In Brazil, a specific regulation defines the guidelines to prescribe and sell rhGH [11]. A medical prescription is required before the dispensation, and pharmacists keep the original prescription when they sell the product.

During a routine assessment of some reports of suspected adverse drug reactions (ADR) in search for signals, consumption of rhGH among young adults was observed. As this use could go against its approved indications, a study was designed and carried out. So, the main purpose of the present analysis was to describe the indications of use of rhGH after a careful revision of the reports of suspected ADR involving this product received by the São Paulo Pharmacovigilance System.

Methods

The present study was designed as a drug utilisation study (DUS) of rhGH use in real practice taking the information spontaneously filled in the reports of the pharmacovigilance database of São Paulo (Brazil). Brazil was accepted in the International Drug Monitoring Program of the WHO in 2001. Later, the minimum requirements concerning the compulsory reporting of any suspicion of severe adverse event by the market authorization holders were established in 2005, and regulations following the international standards were published in 2009. In May 2005, the Pharmacovigilance Centre of the Centro de Vigilância Sanitária de São Paulo (PvC-SP) (in Portuguese, Núcleo de Farmacovigilância) implemented an electronic reporting system called Periweb. Since then to May 31, 2017 (when the present study was conducted), up to 250,000 reports have been sent and included in the PvC-SP database.

Study sample

All products containing rhGH marketed in Brazil were identified through the National Health Surveillance Agency (ANVISA) [7]. In May 2017, seven different products were marketed, so all reports of suspected ADR involving rhGH received and included in Periweb between May 1, 2005 and May 31, 2017 were identified and retrieved for future analysis. All these reports were analysed in order to ensure that no duplicated cases had been included.

Evaluation of the reports and indications of use

Taking into account the main objective of the present study, only the following variables were identified and retrieved from each report: 'age', 'sex', and 'indication of use'. When the variable 'indication of use' was not filled, the information included as free text in the original report was analysed in order to look for the description of additional data regarding the reason to use rhGH. Additionally, as our focus was off-label use of rhGH, only patients aged 20 years or older were analysed in detail.

Two of us independently reviewed all the included reports in order to classify the declared indications of use according to the description written in the report. The following categories were identified: (1) reduced GH levels, (2) osteoporosis, (3) aesthetic uses (including 'building-up muscle mass', 'weight reduction', 'burning fat', 'obesity', and 'rejuvenation'), (4) other uses ('diabetes', 'tissue repair', or combination with concomitant products that lead to suspect aesthetic use), and (5) miscellanea (without information, non-classifiable, or suspected technical complaint). In case of discordance among both evaluators, a third opinion was searched and consensus was reached.

Results

During the study period, 1289 reports of suspected ADR in patients being treated with rhGH were received. There were 646 men (50.1%), 578 women (44.8%), and 65 reports that did not specify patient's sex (5.1%). The age distribution was as follows: 782 reports (60.7%) of patients younger than 20 years old, 223 (17.3%) patients between 20 and 50 years old, and 50 (3.9%) reports involving patients older than 51 years; in the remaining 234 reports (18.2% of the study sample), information on age was not filled (Supplementary material).

Indications of use

Figure 1 shows the age distribution of the reports involving patients using rhGH (Supplementary material). One aspect that should be highlighted is the bimodal distribution of the reports according to the age of the involved patients. A more detailed analysis of the reported indications of use for rhGH was carried out for the 273 patients aged ≥ 20 years in order to identify potential off-label uses. Only 46 out of 273 (16.8%) were using rhGH for reduced levels of GH, and two patients (0.7%) received the medicine for osteoporosis; interestingly,

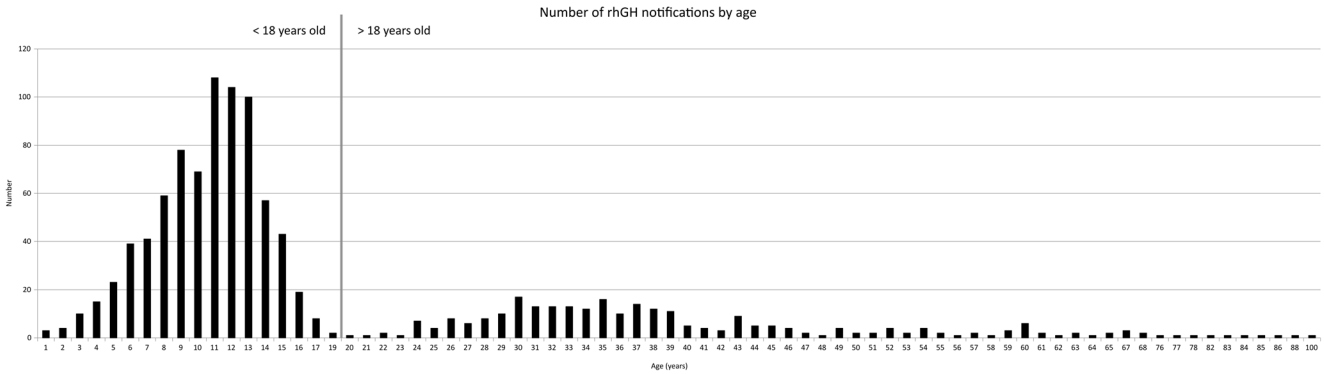


Fig. 1 Age distribution of the reports of suspected adverse drug reactions describing the use of rhGH received at the Periweb database

124 patients (45.4%) were taking rhGH for aesthetic purposes, and 59 patients (21.6%) were taking it for other off-label uses (Table 1). The remaining 42 reports (15.4%) were classified as "miscellanea" (see "Methods").

Taking into account that 234 reports (18.2% of the study sample) did not include information about the age of the patient, the additional analysis of the indication of use of rhGH among those reports showed that 41 patients (17.5% of them) took rhGH for an approved indication, while 19 (8.1%) used it for aesthetic purposes and 18 (7.7%) for other off-label use. No information was available for the remaining 156 reports (66.7%) (Table 1).

Thus, up to 220 reports (17.1% of the study sample) described an ADR after using rhGH for aesthetic purposes (143) or other off-label uses (77).

Discussion

Although the main objectives of the pharmacovigilance programmes are to identify previously unknown ADR and help to define the safety profile during the postmarketing period of any medicine, careful analyses of pharmacovigilance databases could also give some interesting clues to concomitant problems related with medicines and their use that eventually could produce an ADR. This was the case of the present study, which showed that at least 17% of the reports involving rhGH received at the PvC-SP described a suspected ADR that appeared after an off-label indication of the product, including aesthetic uses. Thus, implementing interventions to reduce the inappropriate use of some specific medicines could also result in a reduction of unnecessary adverse effects.

Two reports describing the use of rhGH for osteoporosis in patients over 50 years were also observed in our sample. A meta-analysis showed a significant increase in the femur and lumbar spine bone density in adult patients with GH deficit treated with rhGH, an increase time-, genre-, and age-dependent. These effects were observed in case of daily treatments during at least 1 year were more accentuated in men, and a small negative correlation between benefit and age was found [12]. Notwithstanding this, osteoporosis is not an indication of use for rhGH and more evidences are needed.

Most of this uncovered use in the adult population sample of this study was aesthetic, for muscle mass increase and body weight reduction. Uses of GH to mitigate the effects of ageing had been proposed soon after the discovery of this hormone, and the interest has been boosted since the availability of the human recombinant somatropin. In Brazil, the existence of a wide demand of rhGH for those uses had already originated several criminal actions that are bringing about 475,000 US$/month losses to the public health system (Sistêma Único de Saúde, SUS) [13, 14].

The present analysis proposed a simple drug utilisation study methodology based on a selected sample of patients, those that were reported as having a potential adverse effect to a pharmacovigilance database. This is a biased sample of the real population exposed to the medicine of interest (rhGH), but to our opinion, it is a quick and easy method that although it does not allow quantifying inappropriate consumption, at

Table 1 Distribution of the indications of use of rhGH described for the adult population (≥ 20 years old; $n = 273$ reports) and for those patients with no age reported ($n = 234$)

Age group	Use	*n*	%
Adults (≥ 20 years old)	GH deficiency (label use)	46	16.8
	Osteoporosis	2	0.7
	Aesthetic uses	124	45.4
	Other off-label uses	59	21.6
	Miscellanea	42	15.4
	Total	273	100.0
Not reported	GH deficiency (label use)	41	17.5
	Aesthetic uses	19	8.1
	Other off-label uses	18	7.7
	Miscellanea	156	66.7
	Total	234	100.0

least it is useful to confirm the existence of a problem related with the use of a given medicine. Based on this basis, it is possible to justify an intervention addressed to health professionals and the population or to design an intervention to quantify and characterise the extension of the identified problem among consumers that have neither presented an ADR nor presented non-reported ADRs. In the case described herein, in addition to the number of reports in patients using off-label rhGH (220), the distribution of the study sample depicted in Fig. 1 showing a big sample of reports from children and adolescents besides the smaller but not insignificant number of reports in adults helped to arise a reasonable doubt that added to previous evidences found in Brazil and helped to design informative interventions by health authorities.

In addition to the detection of previously unknown adverse effects of medicines, pharmacovigilance databases can actually help to identify inappropriate or off-label uses of medicines, thus contributing to alert health authorities and work towards a more preventive pharmacovigilance that will benefit the whole population.

Compliance with ethical standards

Conflict of interest The authors declare that they have no conflict of interest.

References

1. Ayyar VS (2011) History of growth hormone therapy. Indian J Endocrinol Metabol 15:162. https://doi.org/10.4103/2230-8210.84852
2. Conrad P, Potter D (2004) Human growth hormone and the temptations of biomedical enhancement. Sociol Health Illn 26:184–215
3. Gasco V, Caputo M, Lanfranco F, Ghigo E, Grottoli S (2017) Management of GH treatment in adult GH deficiency. Best Pract Res Clin Endocrinol Metab 31:13–24
4. Samaras N, Papadopoulo MA, Samaras D, Ongaro F (2014) Off-label use of hormones as an antiaging strategy: a review. Clin Interv Aging 9:1175–1186
5. von Haeling S, Ebner N, dos Santos MR, Springer J, Anker SD (2017) Muscle wasting and cachexia in heart failure: mechanisms and therapies. Nat Rev Cardiol 14:323–341. https://doi.org/10.1038/nrcardio.2017.51
6. Tritos NA (2017) Focus on growth hormone deficiency and bone in adults. Best Pract Res Clin Endocrinol Metab 31:49–57
7. Agência Nacional De Vigilância Sanitária - Anvisa (2004) Available at: http://consultas.anvisa.gov.br/#/medicamentos/q/?substancia=22433. Accessed 19 June 2017
8. European Medicines Agency (EMA). Available at: http://www.ema.europa.eu/ema/index.jsp?curl=pages%2Fincludes%2Fmedicines%2Fmedicines_landing_page.jsp&searchkwByEnter=false&quickSearch=growth+hormone&keywordSearch=Submit. Accessed 22 May 2018)
9. Food and Drug Administration (FDA). Somatropin information. Available at: https://www.fda.gov/Drugs/DrugSafety/PostmarketDrugSafetyInformationforPatientsandProviders/ucm237839.htm Accessed 24 May 2018
10. Bartke A (2003) Can growth hormone (GH) accelerate aging? Evidence from GH-transgenic mice. Neuroendocrinology 78:210–216
11. Brazilian Health Ministry (2010) Portaria N° 110, de 10 de Março de 2010. Protocolo Clínico e Diretrizes Terapêuticas–Hipopituitarismo. Available at: http://bvsms.saude.gov.br/bvs/saudelegis/sas/2010/prt0110_10_03_2010.html. Accessed 23 May 2018)
12. Barake M, Klibanski A, Tritos NA (2014) Effects of recombinant human growth hormone therapy on bone mineral density in adults with growth hormone deficiency: a meta-analysis. J Clin Endocrinol Metab 99:852–860
13. Anonymous (2016) Grupo desviou R$ 1,6 mi em remédio vendido como 'bomba', diz polícia. Available at: http://g1.globo.com/sao-paulo/sorocaba-jundiai/noticia/2016/01/grupo-desviou-r-16-mi-em-remedio-vendido-como-bomba-diz-policia.html. Accessed 23 May 2018
14. Anonymous (2017) Polícia flagra casal suspeito de desviar remédios de hospital estadual. Available at: http://g1.globo.com/sp/bauru-marilia/noticia/2017/03/policia-flagra-casal-suspeito-de-desviar-remedios-de-hospital-estadual.html. Accessed 23 May 2018