



EDITORIAL

Two decades of growth hormone treatment in adulthood[☆]



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Dos décadas de tratamiento con hormona de crecimiento en la edad adulta

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Adult growth hormone deficiency (AGHD) has been recognized for almost 20 years as a specific syndrome¹ consisting of changes in body composition, increased cardiovascular risk and mortality, decreased exercise tolerance, and impaired bone mineral composition and health-related quality of life (HRQoL).

AGHD has multiple causes, among which tumors are the most common. Other associated pituitary hormone deficiencies are found in a majority of cases. AGHD also includes cases of GHD starting in childhood that persist into adulthood.

The availability of recombinant GH (rGH) from 1985 led to early studies on its benefits in adulthood, and showed that most manifestations of the syndrome improved with replacement therapy.² Based on these studies, treatment with rGH of adults with GHD was approved by the European Medicine Agency in 1995, by the US FAD in 1996, and in Spain one year later.

In the subsequent 20 years of use of rGH, a very high number of patients have been treated, and efficacy and safety data additional to those collected in pre-approval clinical trials are therefore available.

Favorable short- and mid-term effects, up to the first three years of treatment, on body composition, lipid profile,

muscle strength, bone mineral remodeling and density, cognitive function, and HRQoL have been clearly established.³ Many studies are available on the short-term benefits, and there is little doubt in this regard. By contrast, few long-term studies with at least five years of treatment have been conducted. Most data come from observational post-marketing studies, mainly the Pfizer International Metabolic Database and the Hypopituitary Control and Complications Study, some national registers, and some series, usually retrospective.^{4–6}

Long-term benefits include those related to body composition, including increased lean mass and decreased fat mass as measured by DEXA, which has been shown to be the best method currently available, despite the fact that it does not allow for calculating the body water compartment. This improved body composition results in increased muscle strength during the first five years of treatment which does not persist in some studies, but may provide these patients with some protection against the general effects of decline characteristic of aging. These changes are more marked in males as compared to females, with similar IGF-1 levels.

As regards bone mineral density, the increases reported range from 4% to 10% depending on the series, mainly occur in trabecular bone, and are more marked in males. Ten-year studies continue to show this positive effect, but the femoral neck appears to stabilize from the fifth year. Unfortunately, no randomized, controlled studies are available showing fracture rate reductions in patients treated with rGH.

Improvement in HRQoL and psychological well-being was another aspect in which the treatment was considered positive, given that it was approved. The experience

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accumulated over this period suggests that the effects on HRQoL are very heterogeneous: there are both patients with normal HRQoL scores at baseline who do not therefore improve, and others with great initial impairments who show dramatic responses. Overall, it may be stated that patients with poorer baseline scores will experience the greatest improvements, and that patients with GHD starting in childhood usually have normal scores, and no improvement is thus achieved.

The increased cardiovascular morbidity and mortality reported in patients with GHD has been related to an unfavorable pattern in both traditional and emerging cardiovascular risk factors.⁷ In most studies reported, treatment with rGH has a beneficial effect on most factors, especially on lipid profile, with reductions in both total and LDL cholesterol and improved HDL and triglyceride levels.^{3,8} Using the Framingham and European Cardiology Society scoring systems, cardiovascular risk has been found to be reduced by up to a half after two years of treatment.

Few studies have been reported relating treatment with rGH to cardiovascular and cerebrovascular morbidity and mortality, and their conclusions regarding the benefits achieved are far from being unanimous.⁹ Unexpectedly, the four studies with the largest patient samples found no decrease in morbidity and mortality as compared to the untreated group. These results have created some controversy and have been attributed to multiple reasons, including study duration, lack of information about other factors, and even concomitant medications. Despite the limitations of the available data, there is currently insufficient evidence to recommend treatment with rGH based on the cardiovascular status of patients.

As regards the safety of treatment with rGH, the greatest concern is its potential to increase or promote the occurrence of cancer. Although there have been some reports suggesting a potential increase in some tumor types in adults treated with GH during childhood,¹⁰ most follow-up studies have not shown such an increase,^{11,12} but longer studies will be required to confirm this.

There has also been concern about the effect on carbohydrate metabolism. Although treatment with rGH decreases visceral fat, it also causes decreased insulin sensitivity in the short term. Although this is not a generalized effect, rGH may induce in some patient subgroups impaired blood glucose levels, and even the occurrence of diabetes in a small proportion of patients.^{13,14} This requires special monitoring during treatment, and the use of rGH is not recommended in diabetic patients.

In pharmacoeconomic terms, the benefits of replacement therapy in deficient adult patients result in improvements in quality of life tests. Various studies, particularly those related to large long-term follow-up registers such as the Pfizer International Metabolic Database, have found a positive economic evaluation related to the decreased use of healthcare system resources and the reduction in work time lost and disability in these patients. These data support the value of this treatment also from the economic viewpoint.¹⁵

In Spain, the prescription of rGH to both children and adults has been subject to special regulation and control by regional departments of health because of its high price and potential misuse. Thus, the different regional authorities created advisory committees or boards of experts intended

to verify that prescriptions were for the approved indications and were based on the established diagnostic criteria, and to ensure monitoring of their efficacy. A second control mechanism was added at national level by which the drug could only be dispensed by hospital pharmacies. This surveillance by the corresponding committees was generally very well accepted by the prescribing professionals, whose prescriptions were supported. The governments of some regions, such as Catalonia, have now eliminated their advisory committees and have transferred prescription and expense control to each hospital.

In recent years, biosimilar drugs, copies of biotechnological preparations whose patent has expired, have been approved for clinical use. Approval is based on the consideration that they are therapeutic equivalents to the innovative agents in terms of both safety and efficacy. The first such drug approved by the European Medicines Agency was a biosimilar for Genotropin® in 2006, and according to regulations it is approved for all indications of the original drug in both children and adults.

The main doubts about these preparations relate to safety, as biosimilars have not undergone the long drug surveillance periods that the original drugs did. In the PATRO Adults (SAN-SOM-2011-02) postmarketing surveillance study, currently ongoing, it is planned to recruit 1500 adults with hypopituitarism treated for a period of 5 years. On the other hand, the advent of these preparations, with the resultant price competition, has caused adjustments in the market and decreased the high costs, which will undoubtedly contribute to the financial sustainability of healthcare systems. It should be noted in this regard that the applicable Spanish regulations prevent the automatic replacement of an innovative drug by a biosimilar, and only the prescribing physician may make such a replacement if deemed appropriate.

The experience accumulated over almost 20 years of treatment with rGH in adults, and in a shorter time in children, confirms its benefits in patients with GHD. Moreover, rGH has a good safety profile and does not usually cause adverse effects when used in individualized doses and with adequate monitoring. Future challenges include a deeper understanding of its efficacy, especially as regards mortality reduction, long-term safety, and improvements in the selection of patients who may benefit from this treatment.

Conflict of interests

None.

References

1. Cuneo TRC, Salomon F, MacGauley GA, Sonksen PH. The growth hormone deficiency syndrome in adults. *Clin Endocrinol (Oxf)*. 1992;37:387-97.
2. Abs R, Bengtsson B-A, Hernberg-Stahl E, Monson JP, Tauber JP, Wilton P, et al. GH replacement in 1034 growth hormone deficient adults: demographic and clinical characteristics, dosing and safety. *Clin Endocrinol*. 1999;50:703-13.
3. Maison P, Griffin S, Nicoue-Beglah M, Haddad N, Balkau B, Chanson P. Impact of growth hormone (GH) treatment on cardiovascular risk factors in GH-deficient adults: a metaanalysis of blinded, randomized, placebo-controlled trials. *J Clin Endocrinol Metab*. 2004;89:2192-9.

4. Wilhelm B, Kann PH. Long-term effects of 7-year growth hormone substitution on bone metabolism, bone density, and bone quality in growth hormone-deficient adults. *Med Klin (Munich)*. 2004;99:569–77.
5. Götherström G, Svensson J, Koranyi J, Alpsten M, Bosaeus I, Bengtsson B, et al. A prospective study of 5 years of GH replacement therapy in GH-deficient adults: sustained effects on body composition, bone mass, and metabolic indices. *J Clin Endocrinol Metab*. 2001;86:4657–65.
6. Cabo D, Lecube A, Barrios M, Mesa J. Terapia sustitutiva a largo plazo con hormona de crecimiento en la edad adulta. *Med Clin (Barc)*. 2011;136:659–64.
7. Abs R, Feldt-Rasmussen U, Mattson A, Monson J, Bengtsson B, Got M, et al. Determinants of cardiovascular risk in 2,589 hypopituitary GH-deficient adults – a KIMS database analysis. *Eur J Endocrinol*. 2006;155:79–90.
8. Gazzaruso C, Gola M, Karamouzis I, Giubbini R, Giustina A. Cardiovascular risk in adult patients with growth hormone (GH) deficiency and following substitution with GH – an update. *J Clin Endocrinol Metab*. 2014;99:18–29.
9. van Bunderen CC, van Varsseveld NC, Erfurth EM, Ket JC, Drent ML. Efficacy and safety of growth hormone treatment in adults with growth hormone deficiency: a systematic review of studies on morbidity. *Clin Endocrinol (Oxf)*. 2014;81:1–14.
10. Carel JC, Ecosse E, Landier F, Meguellati-Hakkas D, Kaguelidou F, Rey G, et al. Long-term mortality after recombinant growth hormone treatment for isolated growth hormone deficiency or childhood short stature: preliminary report of French SAGHe study. *J Clin Endocrinol Metab*. 2012;97:416–25.
11. van Bunderen CC, van Nieuwpoort C, Arwert LI, Heymans MW, Franken AAM, Koppeschaar HPF, et al. Does growth hormone replacement therapy reduce mortality in adults with growth hormone deficiency? Data from the Dutch national registry of growth hormone treatment in adults. *J Clin Endocrinol Metab*. 2011;96:3151–9.
12. Hartman ML, Xu R, Crowe BJ, Robison LL, Erfurth EM, Kleinberg DL, et al. Prospective safety surveillance of GH-deficient adults: comparison of GH-treated vs untreated patients. *J Clin Endocrinol Metab*. 2013;98:980–8.
13. Attanasio AF, Jung H, Mo D, Chanson P, Bouillon R, Ho KKY, et al. Prevalence and incidence of diabetes mellitus in adult patients on growth hormone replacement for growth hormone deficiency: a surveillance database analysis. *J Clin Endocrinol Metab*. 2011;96:2255–61.
14. Parra PA, Barquiel B, Fernández A, Pérez L, Lecumberri B, Llaro MG, et al. Comportamiento de la hemoglobina glicada en adultos con déficit de GH en tratamiento sustitutivo. *Endocrinol Nutr*. 2015;62:240–5.
15. Koltowska-Häggström M, Mattsson AF, Shalet SM. Assessment of quality of life in adult patients with GH deficiency: KIMS contribution to clinical practice and pharmacoeconomic evaluations. *Eur J Endocrinol*. 2009;161:S51–64.