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ORIGINAL ARTICLE

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Growth hormone treatment does not to lead to insulin resistance nor excessive rise in IGF-1 levels, while improving height in patients small for gestational age A long-term observational study

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Abstract

Objective: In children born small for gestational age (SGA), the relationship between growth hormone (GH) treatment and insulin resistance (IR) has only been investigated for a short period, necessitating a longer observation period. This study aimed to evaluate the long-term (10 years) effect of GH to SGA-children on IR and safety during treatment.

Design: This was a multicenter observational study.

Patients: SGA-children who received GH treatment in Spain (stratified by Tanner-stage and age at GH onset [two groups: ≤6 years old or >6 years old]).

Measurements: The analysed variables (yearly measures) included auxologic, metabolic (insulin-like growth factor-1 (IGF-1), height velocity [HV], weight and homeostatic model assessment-IR [HOMA-IR]) and safety data. Data were collected prospectively (since the study approval: 2007) and retrospectively (since the initiation of GH treatment: 2005–2007).

Results: A total of 389 SGA children (369 Tanner-I) were recruited from 27 centres. The mean age (standard deviation) of the children at GH treatment onset was 7.2 (2.8) years old. IGF-1 (standard deviation score [SDS]) and HOMA-IR values tended to increase until the sixth year of GH-treatment, with significant differences being observed only during the first year, while these remained stable in the later years (within normal ranges). Height (SDS) increased significantly (basal: −3.0; tenth year: −1.13), and the maximum HV (SDS) occurred during the first year (2.75 ± 2.39).

Conclusions: HOMA-IR values increased significantly in SGA-children during the first year of GH-treatment, remained stable and were within normal ranges in all cases. Our 10-year data suggests that long-term GH treatment does not promote IR and is well-tolerated, safe and effective.

KEYWORDS
efficacy, growth hormone, homeostatic model assessment, insulin resistance, long-term follow-up, safety, small for gestational age

1 | INTRODUCTION

Small for gestational age (SGA), defined as infants born with a weight and/or height that is two standard deviations (SDs) below the mean for their gestational age (at term or preterm),[1] affects approximately 3%–10% of live births.[2] Most children born SGA show catch-up growth during the first years of life, but 10% will continue with a pathologically short stature throughout childhood and adolescence.[3]

SGA syndrome affects glucose metabolism and insulin sensitivity (IS),[4] which entails the subsequent risk of developing type-2 diabetes mellitus (DM) and other interrelated metabolic disorders, such as dyslipidemia, cardiovascular diseases and hypertension.[5] SGA children with short stature show reduced levels of insulin-like growth factor-1 (IGF-1),[3] a protein involved in foetal growth, development and metabolism regulation.[5] IGF-1 levels are associated with IS, but this association seems to be complex[6] and has not yet been well characterized. Several studies on children have shown cut-off values of insulin resistance (IR) between 2.5 and 3.2, according to the homeostatic model assessment of IR (HOMA-IR).[7,8]

The only standard therapy approved for SGA syndrome is based on recombinant human growth hormone (rhGH), which leads to an increase in the growth rate and enables infants to grow according to the normal limits and have a normal adult height.[9] The rhGH therapy has been shown to induce transient IR in children; therefore, there is a concern regarding the diabetogenic potential of rhGH therapy in children born with SGA.[10] However, a recent review has revealed that, while rhGH treatment could pose a risk factor for the development of DM, family history could have more impact in its development.[11]

Although monitoring glucose homeostasis is recommended, there is no consensus on the appropriate method.[10] A larger number of patients undergoing longer follow-up periods are needed to elucidate the relationship between IS patients and GH-treated SGA patients. Therefore, we carried out the first multicenter study in Spain to determine the long-term evolution of IR from the beginning of GH treatment in a larger population of SGA-children receiving rhGH treatment. The secondary endpoints of this study included the determination of the auxological and metabolic rhGH treatment effects to identify potential predictive factors and assess the treatment's safety profile.

2 | METHODS

2.1 | Study design and population

This prospective study was performed in 27 Spanish centres.

The patients included in the study were Spanish SGA-children (age ≥ 4 years) born at term and treated with rhGH (Saizen®; Merck-Serono. European authorization: September 2005)

All procedures performed during the study were in accordance with the Declaration of Helsinki and were approved by the Ethics Committee of Hospital Materno Infantil Carlos Haya of Málaga. The patients (≥12 years old) or their parents or legal representatives provided written informed consent.

The children were recruited between February 2007 and November 2012. Data from the patients' medical records were collected both prospectively and retrospectively, with the latter being collected at the start of the treatment and before the study authorisation (2005–2007).

The inclusion criteria were as follows: children with a current height < −2.5 SD; height adjusted to parental stature < −1 SD; born SGA at term (after Week 37 of gestation); weight and/or length at birth < −2 SD for their gestational age; aged ≥4 years old; and receiving rhGH treatment (daily dose: 0.035 mg/kg body weight; subcutaneously). The exclusion criteria were as follows: closed epiphysis, rhGH-hypersensitivity, active neoplasia, genetic or malformation syndromes and evidence of progression or recurrence of any underlying intracranial lesion.

The cessation treatment criteria were height velocity (HV) < 2 cm/year and bone age (BA) > 14 years in females and ≥15 years in males.

The sample size required for assessing the posttreatment safety profile (200 patients after 10 years of treatment, based on the SEPAGE study [NCT01082354] and our study [SER-GH-2005-01]) was determined based on the Saizen® Long Term Observational study (SALTO).[12]

The estimated sample size was 450 subjects, as calculated based on the SEPAGE (poor accrual and loss of 35% of patients who were to participate in SALTO) and SALTO (potential refusal of our patients to participate, and estimated loss of the participating patients; 12% during treatment and 35% during the follow-up) studies.

The safety population included all patients who received ≥1 rhGH dose. The evaluable population was defined as the safety population who had undergone ≥1-year of follow-up from the start of treatment.

Children were stratified according to the Tanner stage (Stage I or ≥I [II/III/IV, and adult]) and the age at treatment onset (6 years old [early start], or ≥6 years old [late start]). The second stratification was due to the differentiation and avoidance of children entering puberty during the first year of treatment, taking into account that some of them could have had advanced or precocious puberty. The stratification was established at 6 years of age to ensure a 3-year period before reaching puberty as the time for catch-up growth. Patients with Tanner stage >I were excluded from the analyses according to the start time of treatment to ensure the initial prepubertal situation.

2.2 | Measurements; analysis/statistics

All variables were measured at least once a year, following the standard procedures of each centre. Only children with Tanner stage-I underwent analyses, thus ensuring their prepubertal state at the onset of treatment. Standardized (standard deviation score [SDS]) values were used to avoid variability in measurements among the centres.

The IR development/progression (primary endpoint) was calculated using the HOMA-IR index (mass units): fasting insulin (μu/ml) × fasting glucose (mmol/L)/22.5.

The auxological effects of treatment were assessed according to the following parameters: HV (cm/year), weight (kg) and height (cm) as SDS (chronological age [CA] and sex reference values obtained from Carrascosa),[13] BA (assessed using the Greulich and Pyle atlas)[14] and Tanner-stage (testicular size or breast development). The potential predictor value of body mass index (BMI) (SDS) for IR was calculated.

The metabolic effects of treatment were assessed according to the following parameters: fasting plasma IGF-I (ng/ml) (SDS) (reference values from Elmlinger et al.),[15] plasma triglycerides (mg/dl), high-density lipoprotein cholesterol (mg/dl), HbA1c (% of total haemoglobin) and thyroid hormones. Assessments were carried out following different methods and at different local laboratories, and measures (reference values) were standardized for the comparative analyses.

Nonresponders to rhGH treatment were defined as a growth rate < +1 SDS during the first year of treatment.

Safety variables included adverse events (AEs; Medical Dictionary for Regulatory Activities), physical examination, vital signs and blood and urine tests.

Categorical variables are expressed as absolute and relative frequencies (%), while continuous variables are expressed as mean, SD, 95% confidence interval (95 % CI) and SDS. Continuous variables were analysed using the *t*-test or Wilcoxon test.

TABLE 1 Characteristics of the evaluable population (*n* = 393)

	Patients (*N* = 393)
Male, *n* (%)	198 (50.4)
Age, mean (years ± SD)	
At study inclusion	7.8 ± 3.1
At treatment initiation	7.2 ± 2.8
Gestational age at birth, mean (weeks ± SD)	37.6 ± 3.2
Missing (*n*) = 3	
Genetic target height size, mean (cm ± SD); [SDS]	163.1 ± 7.9
Male ≤ 6 years	169.3 ± 4.8; [1.3]
Female ≤ 6 years	156.9 ± 5.1; [−1.2]
Male > 6 years and Tanner I	169.3 ± 4.2; [1.5]
Female > 6 years and Tanner I	156.0 ± 4.3; [−1.6]
Missing (*n*) = 29	
Birth height, mean (cm ± SD)	43.6 ± 4.0
Missing (*n*) = 21	
Birth weight, mean (kg ± SD)	2.2 ± 0.6
Missing (*n*) = 2	
Relevant medical history at baseline, *n* (%)	50 (12.7)
Past medical history	12 (24.0)
Current ongoing[a]	38 (76.0)
Mild–moderate[a]	35 (92.1)
Familiar clinical history, *n* (%) (brother/sister diagnoses SGA)	
Missing (*n*) = 13	
Yes	34 (9.0)
No	277 (72.9)
NA	56 (14.7)

Abbreviations: NA, not applicable; SD, standard deviation; SDS, standard deviation score; SGA, small for gestational age.

[a]Calculated on the number of patients with current relevant medical history at baseline.

Regression analysis was performed on the direct endpoints. A correlation analysis was performed to determine the association between changes in HOMA-IR and HV (Spearman's correlation coefficient). Statistical significance was set at $p \leq .05$. If the CI did not include the zero-effect value, it could be assumed that there was a statistically significant result. All statistical procedures were performed using the SAS 9.2 statistical software (SAS Institute).

3 | RESULTS

At the time of the final analysis in October 2018, a total of 410 patients from 27 centres constituted the safety population, of which 393 were considered to be in the evaluable population (Table 1).

The sample was sex-balanced (Table 1), with a mean age at treatment onset of 7.2 ± 2.8 years old.

Treatment was completed in 150 patients (38.17%). The reasons for discontinuation among the 200 (50.89%) patients with early withdrawal included the following: lack of efficacy (at the investigator's discretion), $n = 15$ (7.5%); inability to follow treatment, $n = 10$ (5.0%); AEs, $n = 6$ (3.0%); and administrative causes (follow-up data not reported), $n = 137$ (68.5%). Missing data occurred in 43 patients (10.94%). A total of 8.95% of the patients had an SGA sibling. Arterial hypertension and type-II DM were the most common familiar clinical histories (11.32% and 12.1%, respectively). Other types of familiar clinical history included cancer (10.0%), familial hyperlipidemia (9.47%), obesity (5.79%), gestational diabetes (2.37%), type-I DM (1.05%) and myocardial infarction or stroke before the age of 40 years (0.53% for each case).

3.1 | Insulin resistance

The mean HOMA-IR increased significantly during the first year of treatment: overall, 0.62 ± 1.47 (Table 2; Figure 1A); Tanner-I ≤ 6 years old, 0.40 ± 0.8 and >6 years old, 0.80 ± 1.65 (Table 3); and Tanner-II, 0.99 ± 3.16 (Table 3). Overall, no significant differences were observed thereafter, although an increasing trend was observed until visit 6 (Figure 1A). The HOMA-IR values were maintained within normal ranges and were similar in both age groups (≤6 years old and >6 years old; Table 3). The increase was higher in children ≤6 years old because their values from baseline to Visit 3 were significantly lower than those in the >6 years old group. Nevertheless, the values were similar in both groups at Visit 6 (normal range).

The changes in *height velocity*, *height and weight*, *BMI*, *ratio of BA and CA*, *and IGF-1* can be seen in Tables 2 and 3 and in Figure 1B,C.

3.2 | HOMA-IR relations

No relationship was found between the HOMA-IR index and HV, except for the second year (Spearman's correlation coefficient = 0.19; $p < .05$).

3.3 | Multiple correlation analysis

The HOMA-IR values increased proportionally with baseline age and BMI, and inversely with baseline HOMA-IR and weight values. These four variables explained 21% of the change in the HOMA-IR values (Table 4).

3.4 | Metabolic parameters

No significant changes in plasma triglycerides, high-density lipoprotein cholesterol, HbA1c and thyroid hormones were observed during rhGH treatment.

3.5 | Safety

A total of 411 patients were included in the safety population, of which 16 (3.9%) reported AEs. In 14 of them, the event was due to the treatment. Furthermore, six (2.9%) patients discontinued treatment because of AEs. The AEs were musculoskeletal and connective tissue disorders (back pain, osteochondrosis, osteonecrosis and scoliosis), which were considered to be moderate, except for one mild AE (osteochondrosis; Table 5).

There were four serious AEs (SAEs), none was severe. Two were categorized as probably related to treatment—two patients developed significant IR and T2DM. When treatment was withdrawn the T2DM was resolved and the IR returned to baseline. In both cases not specific treatment for IR and T2DM was required. In both cases the evolution was favourable.

One patient had a SAE categorized as possibly related to treatment, osteochondrosis (Phertes), the rhGH treatment continued and the subject was derived to Traumatology Department. One patient had a serious AE, chronic renal failure, categorized as not related to treatment and the subject continued with the rhGH treatment. The evolution of these two patients in unknown.

4 | DISCUSSION

This study that was carried out in a large population of SGA infants treated with rhGH showed that, despite a significant increase in the mean HOMA-IR values during the first year of treatment, the values remained stable within the normal range. Similar results were observed by Jensen et al.[16] in the North European Small for Gestational Age Study (NESGAS), in which the IR, IGF-I and height values increased during the first year of rhGH treatment in the 110 SGA infants. Moreover, Horikawa et al.[17] showed an increase in the mean HOMA-IR values after 260 weeks of GH treatment, which was similar to that observed in our study until Visit 6. This increase was related to the dose administered, which was also similar to the one we used. A rapid increase in IR could lead to a significant increase in fasting blood glucose, as observed Sas et al.[18] in 78 SGA children (mean age, 7.3 years)

TABLE 2 Annual evolution by the visit of HOMA-IR and auxologic and metabolic variables, up to the 10th year of rhGH-treatment

N mean ± SD (95% CI)	HOMA-IR (mass units)	HV (cm/year)	HV (SDS)	Height (SDS)	Weight (SDS)	BMI (SDS)	BA/CA Ratio	IGF-1 (SDS)
Basal	1.19 ± 1.14 (1.05, 1.32)	–	–	−3.00 ± 0.61 (−3.06, −2.93)	−1.72 ± 0.56 (−1.78, −1.67)	−0.70 ± 0.80 (−0.78, −0.62)	0.71 ± 0.17 (0.70, 0.73)	−0.31 ± 1.06 (−0.41, −0.20)
V1	**282** 1.91 ± 2.58 (1.60, 2.21)	8.59 ± 2.33 (8.35, 8.83)	2.75 ± 2.39 (2.50, 2.99)	−2.35 ± 0.71 (−2.42, −2.28)	−1.47 ± 0.55 (−1.53, −1.42)	−0.76 ± 0.70 (−0.83, −0.69)	0.79 ± 0.15 (0.78, 0.81)	0.99 ± 1.20 (0.87, 1.12)
V2	**235** 2.09 ± 1.61 (1.88, 2.30)	6.80 ± 1.48 (6.64, 6.97)	1.09 ± 1.40 (0.94, 1.25)	−2.02 ± 0.73 (−2.10, −1.94)	−1.35 ± 0.60 (−1.42, 1.29)	−0.77 ± 0.74 (-0.85 ± −0.69)	0.85 ± 0.14 (0.83, 0.87)	1.21 ± 1.21 (1.07, 1.35)
V3	**192** 2.21 ± 1.40 (2.01, 2.41)	6.51 ± 1.66 (6.30, 6.72)	0.88 ± 1.22 (0.73, 1.04)	−1.60 ± 2.74 (−1.93, −1.26)	−1.06 ± 3.01 (−1.43, −0.69)	−0.75 ± 0.70 (−0.84, −0.67)	0.89 ± 0.13 (0.88, 0.91)	1.37 ± 1.40 (1.20, 1.55)
V4	**149** 2.40 ± 1.33 (2.19, 2.62)	5.97 ± 2.66 (5.59, 6.35)	0.82 ± 3.08 (0.38, 1.27)	−1.59 ± 0.81 (−1.70, −1.47)	−1.18 ± 0.58 (−1.26, −1.10)	−0.76 ± 0.72 (−0.86, −0.66)	0.92 ± 0.11 (0.91, 0.94)	1.14 ± 1.35 (0.94, 1.35)
V5	**97** 2.67 ± 2.28 (2.21, 3.13)	5.42 ± 4.26 (4.68, 6.16)	0.30 ± 45.40 (−0.64, 1.24)	−1.66 ± −1.37 (−1.70, −1.47)	−1.17 ± 0.63 (−1.28, −1.06)	−0.77 ± 0.72 (−0.90, −0.65)	0.95 ± 0.10 (0.94,0.97)	1.09 ± 1.40 (0.84, 1.34)
V6	**61** 2.74 ± 1.57 (2.34, 3.15)	5.42 ± 2.10 (4.95, 5.89)	0.68 ± 3.97 (−0.21, 1.57)	−1.50 ± 0.88 (−1.68, −1.31)	−1.22 ± 0.62 (−1.35, −1.08)	−0.83 ± 0.67 (−0.97, −0.68)	0.95 ± 0.09 (0.93, 0.97)	1.00 ± 1.42 (0.67, 1.33)
V7	**38** 2.39 ± 1.26 (1.98, 2.81)	5.67 ± 2.23 (5.05, 6.28)	0.33 ± 1.26 (−0.02, 0.68)	−1.39 ± 0.88 (−1.62, −1.17)	−1.14 ± 0.70 (−1.32, −0.97)	−0.76 ± 0.72 (−0.95, −0.58)	0.96 ± 0.09 (0.94, 0.99)	0.86 ± 1.23 (0.51, 1.21)
V8	**31** 2.37 ± 1.40 (2.21, 3.24)	5.54 ± 2.82 (4.54, 6.39)	0.39 ± 1.67 (−0.16, 0.94)	−1.38 ± 0.79 (−1.62, −1.15)	−1.25 ± 0.55 (−1.42, −1.09)	−0.89 ± 0.60 (−1.07, −0.71)	0.97±0.08 (0.94,1.00)	0.79 ± 1.05 (0.45, 1.12)
V9	**14** 2.46 ± 0.98 1.89, 3.032	4.38 ± 2.97 (3.18, 5.58)	−0.01 ± 1.24 (−0.51, 0.49)	−1.25 ± 0.73 (−1.55, 0.96)	−1.19 ± 0.62 (−1.44, −0.94)	−0.84 ± 0.72 (−1.13, −0.55	0.97 ± 0.08 (0.94, 1.00)	0.60 ± 0.57 (0.37, 0.84)
V10	**9** 2.11 ± 0.51 1.72, 2.50	4.44 ± 3.01 (2.29, 6.60)	0.44 ± 1.17 (−0.39, 1.27)	−1.13 ± 0.64 (−1.54, −0.72)	−1.00 ± 0.79 (−1.50, −0.50)	−0.64 ± 0.88 (−1.20, −0.08)	0.97 ± 0.06 (0.92, 1.02)	0.64 ± 0.54 (0.26, 1.03)

Note: Evaluable population ($n = 393$). [a]The bold values are intended to indicate the *N* of patients.

Abbreviations: BA, bone age; BMI, body mass index; CA, chronological age; CI, confidence interval; HOMA-IR, homeostatic model assessment of insulin resistance; HV, height velocity; IGF-I, insulin-like growth factor-I; rhGH, recombinant human growth hormone; SD, standard deviation; SDS, standard deviation score.

[a]The difference between the 393 patient (evaluable population size) and the number of patients with data in each visit are 'missing' patients. It includes those patients that had complete/discontinued the treatment.

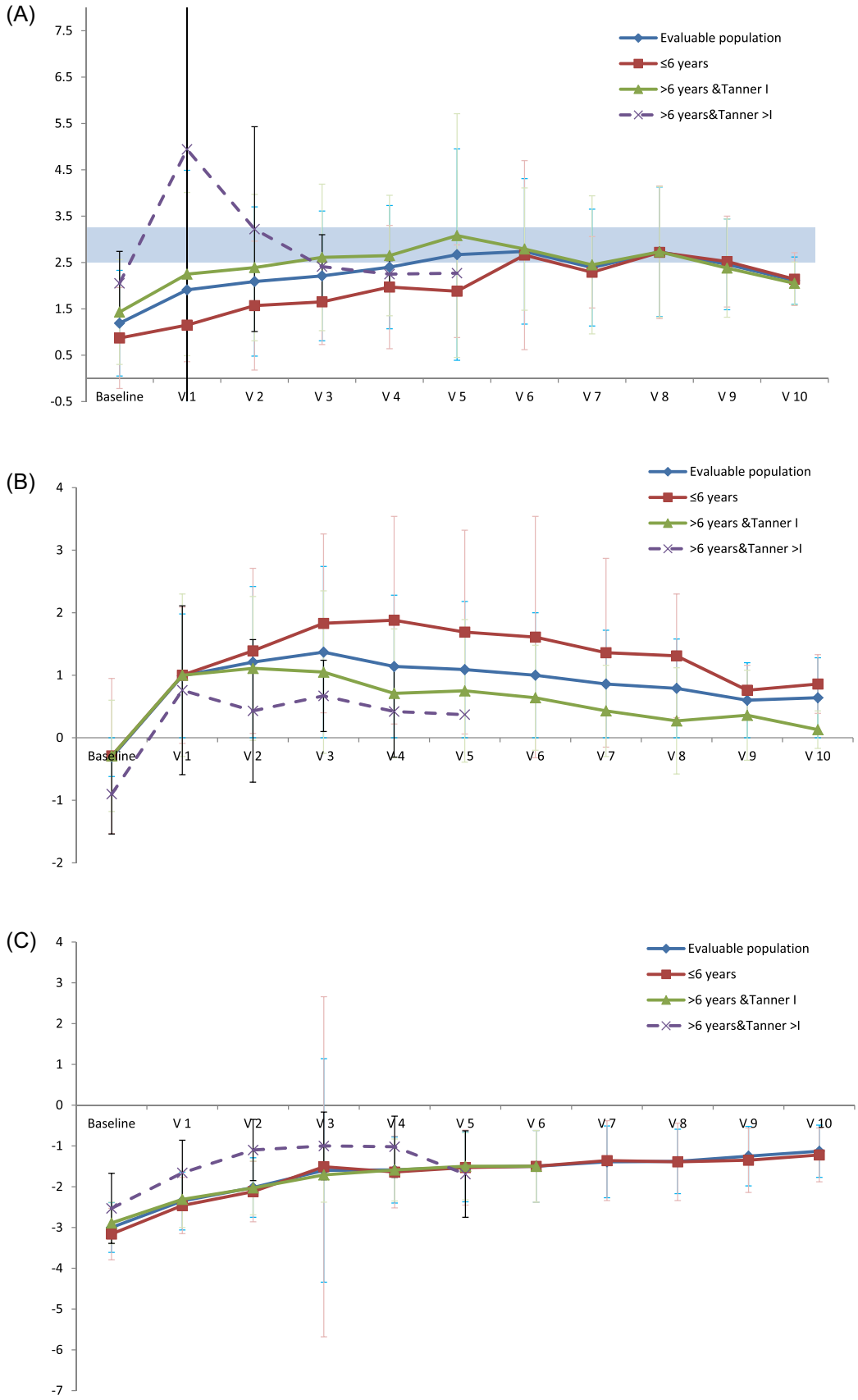

FIGURE 1 (A) HOMA-IR index by visit (from baseline to Visit 10) and by age at start of treatment—(Tanner I and Tanner II) (evaluable population). (B) IGF index by visit (from baseline to Visit 10) and by age at start of treatment (evaluable population). (C) htSDS index by visit (from baseline to Visit 10) and by age at start of treatment (evaluable population). HOMA-IR, homeostatic model assessment of insulin resistance; IGF, insulin-like growth factor [Color figure can be viewed at wileyonlinelibrary.com]

TABLE 3 Change from baseline to HOMA-IR and height measured every year versus previous year by age and Tanner stage at start of treatment

N Mean ± SD (95% CI)	Change HOMA-IR Early start (≤6 years) Tanner I	Late start (>6 years) Tanner I	Tanner II	Change height Change in HSDS	Gain in HSDS
V1 – basal	0.40 ± 0.84 (0.23, 0.57)	**100** 0.80 ± 1.65 (0.47, 1.12)	**11** 0.99 ± 3.16 (−1.13, 3.12)	0.65 (0.48) (0.60, 0.70)	**387** 3.53 (2.75) (3.26, 3.81)
V2 – V1	**76** 0.41 ± 1.28 (0.12, 0.70)	**98** 0.07 ± 2.00 (−0.33, 0.47)	**10** −0.02 ± 1.21 (−0.89, 0.84)	0.30 (0.34) (0.27, 0.34)	**323** 1.77 (2.06) (1.54, 2.00)
V3 – V2	**63** 0.15 ± 1.30 (−0.18, 0.47)	**85** 0.03 ± 1.66 (−0.33, 0.38)	**8** −0.05 ± 0.76 (−0.69, 0.58)	0.42 (2.67) (0.09, 0.75)	**256** 1.88 (4.88) (1.28, 2.48)
V4 – V3	**41** 0.31 ± 1.32 (−0.11, 0.73)	**71** 0.04 ± 1.45 (−0.31, 0.38)	**2** −0.08 ± 1.16 (−10.52, 10.35)	0.18 (0.43) (0.12, 0.24)	**195** 1.08 (2.62) (0.70, 1.45)
V5 – V4	**27** 0.02 ± 1.16 (−0.44, 0.48)	**54** 0.66 ± 2.56 (−0.04, 1.36)	**1** 0.07 (–)	0.12 (0.51) (0.03, 0.21)	**131** 0.87 (3.20) (0.32, 1.42)
V6 – V5	**15** 0.54 ± 1.80 (−0.46, 1.54)	**33** 0.11 ± 1.35 (−0.37, 0.59	**0**	0.09 (0.30) (0.03, 0.16)	**86** 0.68 (2.09) (0.23, 1.13)
V7 – V6	**11** −0.27 ± 2.39 (−1.88, 1.33)	**21** −0.03 ± 1.36 (−0.65, 0.59)	**0**	0.10 (0.34) (0.02, 0.19)	**60** 0.75 (2.41) (0.13, 1.37)
V8 – V7	**10** 0.63 ± 1.25 (−0.27, 1.52)	**12** 0.05 ± 0.96 (−0.56, 0.66)	**0**	0.08 (0.40) (−0.04, 0.20)	**44** 0.56 (2.95) (−0.34, 1.46)
V9 – V8	**6** 0.17 ± 1.06 (−.94, 1.28)	**4** −0.61 ± 2.49 (−4.57, 3.34)	**0**	0.02 (0.28) (−0.09, 0.14)	**25** 0.22 (2.13) (−0.67, 1.10)
V10 – V9	**5** −0.38 ± 0.97 (−1.58, 0.82)	**2** −1.62 ± 0.07 (−2.27, −0.98)	**0**	0.08 (0.27) (−0.10, 0.26)	**11** 0.59 (1.99) (−0.74, 1.93)

Note: Descriptive statistics. Evaluable population. The bold values are intended to indicate the *N* of patients.

Abbreviations: CI, confidence interval; HOMA-IR, homeostatic model assessment of insulin resistance; HSDS, height standard deviation score; SD, standard deviation.

TABLE 4 Factors influencing the change of HOMA-IR

Parameter	Estimate	Standard error	*t*	Pr > |*t*|
Intercept	−5.1530	1.2605	−4.09	<.0001
Basal insuline resistance (HOMA-IR)	−0.5003	0.1034	−4.84	<.0001
Age at start of treatment	0.5659	0.1329	4.26	<.0001
Basal weight	−0.2170	0.0646	−3.36	0.0009
Basal BMI	0.4066	0.0987	4.12	<.0001
R^2	0.2138			

Note: Multiple linear regression model. Evaluable population.
Abbreviations: BMI, body mass index; HOMA-IR, homeostatic model assessment of insulin resistance.

reporting relative IR (increased fasting and glucose-stimulated insulinemia). Additionally, although the HOMA-IR index could be attributed to rhGH treatment, García Cuartero et al.[19] in the normal population showed a progressive increase in glucose, insulin, C-peptide and HOMA index values in relation to age, with statistically significant differences between prepubertal and pubertal stages for both sexes. Although Seino et al.[20] have revealed that patients with HOMA-IR values ≥2.5 are regarded as being resistant to insulin, Arellano-Ruiz et al.[21] has shown that HOMA-IR have a moderate diagnostic accuracy when measuring IR in children and adolescents, establishing values between 2.30 and 3.59 as the cut-off points to avoid the risk of metabolic syndromes. In our study, the highest HOMA-IR value within that range was observed at the sixth year (2.74), without significant differences related to age being observed at the beginning of treatment. A similar increase in the HOMA-IR values within the normal range was observed by Güemes Hidalgo et al.[22] in a different study carried out in SGA children treated for 3 years (from 0.72 to 1.67) that had initiated treatment at the mean age of 5.9 years old. Despite this, Horikawa et al.[17] showed that including a dose of 0.067 mg/kg/day did not influence glucose tolerance and did not affect glucose metabolism.

Furthermore, our study showed a significant increase in IGF-1 (SDS) values during the first year and a less significant increase between Visits 1 and 2. Similar results were obtained at 24 months by Qie and Yang[23] in Chinese SGA children treated with rhGH. Afterward, the increase was approximately 1 SDS until Visit 7. At Visit 7, following discontinuation of treatment, the IGF levels progressively decreased to normal levels as described Sas et al.[18] In SGA children, Gaddas et al.[24] have shown that IGF-I is a useful biomarker of the short-term response to rhGH as it increases with treatment. In the final analysis of this study, the increase in the IGF-I (SDS) levels during the first year was +1.30. This was 2.4 points below than the value observed by Jensen et al.[16] in the NESGAS study that used a dose that was twice that of our study (0.035 mg/kg/day [our study] vs. 0.067 mg/kg/day [NESGAS's study]). In addition, the basal IGF-I (SDS) level (−0.32) was higher in the 2516 SGA patients (−0.7; Brabant's reference values) than in any other study of Blankenstein et al.[25] in whom an increase in IGF-I levels during the first year was observed. The response of IGF-1 to rhGH is directly related to the value of basal IGF-1[16] and inversely related to that of the basal total body fat as described Thankamony et al.[26] Both variables could explain the difference in the increase in IGF-1 levels compared to those observed in our study. Additionally, Rustogi et al.[27] showed a positive correlation between an increase in IGF-I levels and catch-up growth by 18 months in SGA children. In this sense, our study showed a higher HV (SDS) during the first year of rhGH treatment (2.75 ± 2.39). Furthermore, the mean HV (SDS) was greater than 2 SDS, which coincides with the largest increase in IGF-I levels in our study. The HV was constantly greater than zero in every evaluation (5.5 cm/year). After the first year, the HV SDS started to decrease with respect to the first year. Accordingly, Rhie et al.[28] showed similar results, with the highest increase being observed during the first year of rhGH treatment, and then it gradually decreased, although it remained above 5 cm. Moreover, height was found to be normal with rhGH treatment in short SGA children with a safe metabolic profile as described Labarta et al.[29]

Regarding the children's growth, the mean BA–CA ratio increased significantly during rhGH treatment from baseline to Visit 4 and then stabilized until the end of the study. BA increases over time, as suggested by the increase in the BA–CA ratio (close to 1 after 6 years of treatment). This result is consistent with the change from 0.8 (basal) to 1 (after 5 years of rhGH) observed by Ross et al.[30] in 481 SGA children and in other conditions requiring rhGH.

Our IGF-I, HV (SDS) and BA results increased during the first year of rhGH treatment and then normalized over time. In this respect, Zhao et al.[31] showed that following GH therapy in small children, there was a positive association between IGF-1 (SDS) and the BA–CA ratio when the IGF-1 level was lower than 2 SDS, as observed in our study, suggesting that a low level of IGF-1 could contribute to BA delay in short children and adolescents. Moreover, a moderate but significant BA acceleration during rhGH treatment as the BA–CA ratio increased in SGA children who experienced an increase in IGF-1 levels, although it remained within the normal range.[29] Taken together, the increase in IGF-I levels due to rhGH treatment could potentiate catch-up growth and normal BA maturation in SGA children.

The weight increased during the first 3 years and then stabilized. The mean weight change was greater than 0 SDS, though it was close to 0 SDS in every evaluation. After the first year, the weight increase began to diminish. Similar results were obtained by Rodríguez et al.[32] on 152 SGA children. In line with this finding, the BMI was stable during treatment but decreased in the late phase of follow-up. This BMI stability has already been described by Krebs et al.[33] at 1 year of rhGH. In this sense, Reinehr et al.[34] in other disorders requiring rhGH, BMI reductions have been observed in sizes close to adult values. Xu et al.[4] has shown that glucose metabolism and IS are affected in SGA patients, with the subsequent risk of developing type-2 DM and other interrelated metabolic disorders.[5] BMI reduction implies a decrease in overweight and a reduction in cardiovascular risk factors. Pfäffle et al.[35] utilized a biosimilar rhGH in the subgroup of SGA patients, osteochondrosis and type-I DM. In a study carried out by Rhie et al.[28] in Korea using rhGH in a subgroup of 208 SGA children, one case of glucose intolerance and one case of scoliosis were reported.

TABLE 5 Treatment emergence adverse events according to organ/system classification and preferred terms[a]

Adverse event	Events (*n*)	Severity	Serious	Related to treatment
Congenital, familial and genetic disorders				
Congenital hypothyroidism	1	Mild	No	Not related
Endocrine disorders				
Autoimmune thyroiditis	1	Mild	No	Not related
General disorders and administration site conditions				
Oedema peripheral	1	Mild	No	Unlikely
Hepatobiliary disorders				
Cholelithiasis	1	Mild	No	Not related
Hypertransaminasaemia	1	Mild	No	Unlikely
Investigations				
IGF	1	Mild	No	Probable
IGF increase	4	Mild	No	Probable
Metabolism and nutrition disorders				
Hyperglycaemia	1	Moderate	Yes	Possible
Type 2 diabetes mellitus	1	Moderate	Yes	Probable
Musculoskeletal and connective tissue disorders				
Back pain	1	Moderate	No	Probable
Osteochondrosis	2	Mild/moderate	No	Unlikely
Osteonecrosis	1	Moderate	Yes	Possible
Scoliosis	1	Moderate	No	Possible
Psychiatric disorders				
Anxiety	1	Moderate	No	Probable
Renal and urinary disorders				
Renal failure chronic	1	Moderate	Yes	Unlikely
Reproductive system and breast disorders				
Gynaecomastia	1	Mild		Not related
Varicocele	1	Mild	No	Not related
Skin and subcutaneous tissue disorders				
Dermatitis allergic	1	Mild	No	Unlikely
Surgical and medical procedures				
Osteotomy	1	Moderate	No	Unlikely
Total	23			

Abbreviation: IGF, insulin-like growth factor.

[a]Intention to treat population ($N = 411$).

The adverse effects related to hydrocarbon metabolism found in our study have been mild and transitory, although to detect them it is sometimes necessary to perform an oral glucose overload, since neither the HbA1c value nor the HOMA-R index have been useful. Osteochondrosis and other alterations related to cartilage ischaemia are presented by pain and inflammatory signs. In all cases, long-term follow-up during and after GH treatment, as performed in the SALTO study,[12] is useful.

One limitation of this study was its observational nature. Age, a possible confounding factor, was evaluated by stratifying the sample according to age at the beginning of treatment in ≤6 or >6 years of age, without finding significant differences in the HOMA-IR values between both groups. Due to this observational nature, a comparative normal age- and sex-matched population was not included. Another limitation was its multicenter nature, which increases the variability in measurements, procedures and normal ranges at each

centre. This bias was minimized by standardising the values (SDS). Another limitation was the reduction in the number of patients during long-term follow-up, especially from the fourth year onward.

In conclusion, treatment with rhGH for 1 year in SGA children showed an increase in the HOMA-IR and IGF-I values, which remained stable and within the normal limits. The initial increase in the IGF-I levels due to rhGH treatment could potentiate catch-up growth and normal BA maturation in SGA children. The BMI reduction at the end of the follow-up period suggests a reduction in the risk of cardiovascular diseases and diabetes. Although there was an increase in the values of HOMA-IR during follow-up, it always remained within the normal range, suggesting that long-term rhGH treatment does not result in IR and that it is effective in normalized adult height and safety. More studies are necessary to assess the role of rhGH treatment in IR.

SGA STUDY INVESTIGATOR COLLABORATIVE GROUP

Other members of the SGA collaborative group who have contributed to this study in the same way are as follows: José Gómez Vida (Hospital Universitario Clínico San Cecilio), Rafael Espino Aguilar (Hospital Universitario Virgen de Valme), Francisco José Macías López (Hospital SAS Jerez de la Frontera), M. Ángeles Santos Mata (Hospital SAS Jerez de la Frontera), Pablo Prieto Matos (Hospital Universitario de Salamanca), Cristina Rodriguez Dehli (Hospital San Agustín, Avilés), Isolina Riaño Galán (Hospital Universitario Central de Asturias), Francisco Rivas Crespo (Hospital Universitario Central de Asturias), Nuria Cabrinety Pérez (Hospital Sagrado Corazón), María Caimari Jaume (Hospital Son Espases), Raquel Corripio Collado (Consorcio Corporación Sanitaria Parc Taulí), Albert Feliu Rovira (Hospital Universitario Sant Joan de Reus), Jacinto Guillén (Hospital Don Benito-Villanueva), Manuela Núñez Estévez (Hospital Materno Infantil de Badajoz), Jesús Barreiro Conde (Hospital Clínico Universitario de Santiago), Lidia Castro Feijoo (Hospital Clínico Universitario de Santiago), Isabel González Casado (Hospital Universitario La Paz), Amparo González Vergaz (Hospital Universitario Severo Ochoa), Joaquín Ramírez Fernández (Hospital Universitario Príncipe de Asturias), María Chueca Guindulain (Hospital Virgen del Camino), Sara Berrade Zubiri (Hospital Virgen del Camino), Amaia Vela Desojo (Hospital Universitario de Cruces), Miguel Ángel Fuentes Castello (Hospital General Universitario de Elche), Fernando Aleixandre Blanquer (Hospital General universitario de Elda), Lorea Ruiz Pérez (Hospital General Universitario de Alicante), Arancha Escribano Muñoz (Hospital Clínico Universitario Virgen de la Arrixaca), José M[a] Martos Tello (Hospital Clínico Universitario Virgen de la Arrixaca), Manuel Carranza Ferrer (Hospital Nuestra Señora de Meritxell).

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CONFLICT OF INTERESTS

The authors belong to the Merck-funded 'SGA Research Collaborative Group6'. Bosh J. received honoraria as a lecturer from Merck, Lilly, Ipsen, Pfizer and Sandoz. Alfonso M. Lechuga-Sancho is a consultant member of several promoted studies and an advisor to several pharmaceutical companies. Juan P. López-Siguero has received honoraria as a lecturer and advisor from Merck, Sandoz and Lilly. Maria J. Martínez-Aedo and Jose Antonio Bermúdez de la Vega do not declare any conflict of interests. Triana Villalobos is an employee from Merck, S.L.U.

DATA AVAILABILITY STATEMENT

The data that support the findings of this study are available from the corresponding author upon reasonable request.

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