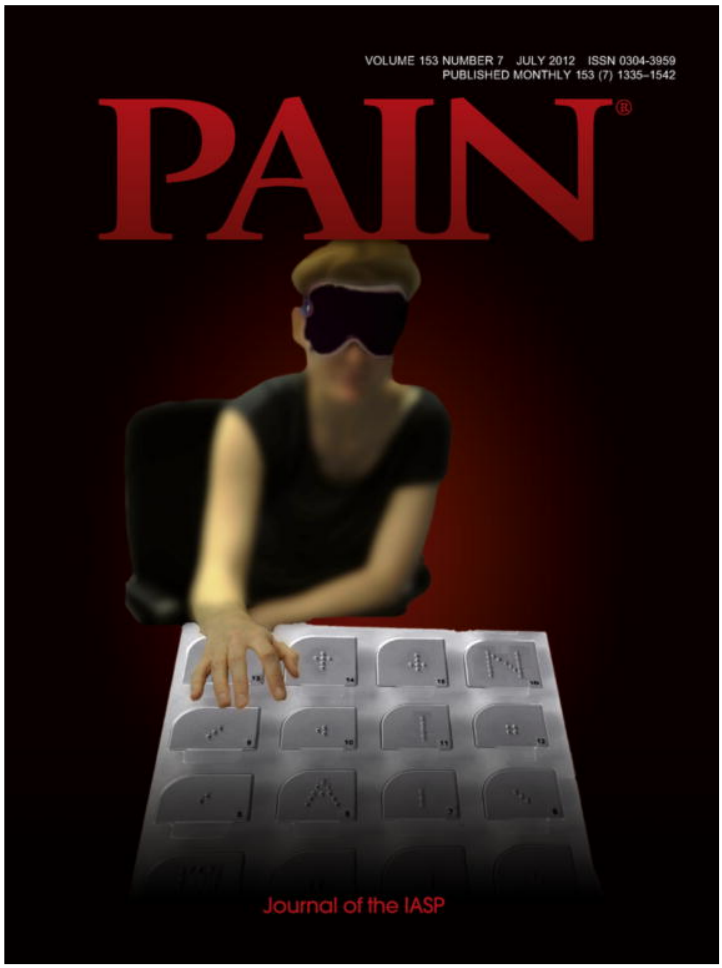

PAIN® 153 (2012) 1382–1389

www.elsevier.com/locate/pain

Growth hormone treatment for sustained pain reduction and improvement in quality of life in severe fibromyalgia

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Sponsorships or competing interests that may be relevant to content are disclosed at the end of this article.

ARTICLE INFO

Article history:
Received 27 September 2011
Received in revised form 7 February 2012
Accepted 13 February 2012

Keywords:
Growth hormone
GH
Fibromyalgia
Pain
Fatigue
IGF-1
FIQ
VAS
EQ5D
Adult growth hormone deficiency
Safety

ABSTRACT

Functional defects in growth hormone (GH) secretion and its efficacy as a complementary treatment have been suggested for fibromyalgia. This study investigated the efficacy and safety of low-dose GH as an add-on therapy in patients with both severe FM and low insulin-like growth factor 1 levels. A total of 120 patients were enrolled in a multicenter, placebo-controlled study for 18 months. They were randomly assigned to receive either 0.006 mg/kg/day of GH subcutaneously (group A, n = 60) or placebo (group B, n = 60) for 6 months (blind phase). The placebo arm was switched to GH treatment from month 6 to month 12 (open phase), and a follow-up period after GH discontinuation was performed until month 18. Standard treatment for fibromyalgia (selective serotonin re-uptake inhibitors, opioids, and amitriptyline) was maintained throughout the study. Number and intensity of tender points, Fibromyalgia Impact Questionnaire (FIQ) with its subscales, and EuroQol 5 dimensions test (EQ5D) with visual analogue scale (VAS) were assessed at different time points. At the end of the study, 53% of group A patients obtained fewer than 11 positive tender points, vs 33% of group B patients ($P < .05$). 39.1% vs 22.4% reached more than 50% improvement in VAS ($P < .05$). Group A patients showed significantly improved FIQ scores ($P = .01$) compared with group B. Although GH discontinuation worsened all scores in both groups during follow-up, impairment in pain perception was less pronounced in the GH-treated group ($P = .05$). In this largest and longest placebo-controlled trial performed in FM (NCT00933686), addition of GH to the standard treatment is effective in reducing pain, showing sustained action over time.

1. Introduction

Fibromyalgia is a chronic, non articular, and non inflammatory pain syndrome characterized by widespread increased sensitivity in tender points, and is frequently accompanied by profound tiredness [28]. According to the 1990 diagnosis criteria of the American College of Rheumatology (ACR), used at the time when our patients were randomized and treated, fibromyalgia pain should involve

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[1] Steering Committee, On behalf of the CT27560 Spanish Multicenter trial participants.

0304-3959/$36.00
http://dx.doi.org/10.1016/j.pain.2012.02.012

both sides of the body above and below the waist, 11 or more trigger points among 9 pairs of specified sites should be affected, and for a period of at least 3 months [28]. In 2010, new ACR fibromyalgia diagnostic criteria were published abandoning the tender point count and placing an increased emphasis on patient symptoms [29]. Because of its high prevalence (2.4% to 3.4% of the total population [8,9], 0.6% to 0.75% in Scandinavian countries [23]) and the high medical costs involved [2,16], better treatment is urgently needed.

Despite its classification in the World Health Organization International Classification of Disease (M79.7 in the ICD-10 2007 version) as a single entity, fibromyalgia should be regarded as a syndrome [14] with different etiologies. Endocrinological disturbances have been observed, involving the thyroid [4], the pituitary-adrenal axis [26], or the growth hormone (GH)/insulin-like growth factor 1 (IGF-1) axis [7,18,21] as potential participants in the pathophysiology of fibromyalgia. As recently documented, 50% of fibromyalgia patients have GH abnormalities, including low IGF-1 serum levels in more than 30%, classic adult GH deficiency (AGHD) in fewer than 20%, and in a few patients some degree of normoglycemic GH resistance (high GH levels) (10). Whether these changes are causative or rather the adaptation to chronic stress and pain remains unclear [10].

Current consensus guidelines based on data from clinical trials state that the best available fibromyalgia treatment should include drugs, rehabilitation, and psychological support [8,9]. Therapies with proven efficacy in fibromyalgia include tricyclic antidepressants, selective serotonin reuptake inhibitors, and opioid analgesics [5]. Some drugs have been recently approved in the United States for the former indication of fibromyalgia: duloxetine [24], pregabalin [3], and milnacipram [20]. More recently, sodium oxybate was submitted for registration [19]. Fibromyalgia treatment is far from optimal, and a search for new therapies is needed.

Twelve years ago, results of a 9-month placebo-controlled study were published showing GH administration to be well tolerated and effective [6]. Later, our group conducted a 12-month pilot trial with GH as an adjuvant agent in a very homogeneous population with severely symptomatic fibromyalgia and low IGF-1 levels [12]. The aim of the present study was to perform a larger placebo-controlled trial over a longer period of 18 months.

2. Methods

2.1. Patients and study design

CT27560 (NCT00933686) is a Spanish multicenter clinical trial to explore the efficacy and safety of GH as an add-on treatment to the standard drugs used in fibromyalgia. The trial was conducted in Spain in 5 tertiary hospitals from different regions. It was designed as a prospective, randomized, semi–cross-over study with a double-blind, placebo-controlled trial for the first 6 months, and as an open-label design thereafter (all patients being treated with GH for 6 months). The 12- to 18-month period was the follow-up after GH discontinuation was carried out (Fig. 1). From the start of the study to the end of the open phase with GH treatment, neither patients nor investigators knew in which group (placebo or GH) they were allocated, blinded to cumulative time (6 or 12 months) elapsed on active therapy.

A total of 493 women with fibromyalgia (mean age 50 ± 9.4 years and mean body mass index 27.2 ± 4.1 kg/m^2) were screened. All patients fulfilled the 1990 ACR diagnostic criteria [28]. To be eligible for the trial, patients had to be age 18 years old or older, have a confirmed diagnosis of fibromyalgia of more than 1 year, with more than 16 tender points and a Fibromyalgia Impact Questionnaire (FIQ) score of more than 75, and with a baseline serum IGF-1 value lower than 150 ng/mL (34% of the 493 screened patients). All patients had been receiving stable doses of intensive treatment including amitriptyline (10 to 50 mg/day), selective serotonin reuptake inhibitors (10 to 40 mg/day) and tramadol (100 to 400 mg/day) for at least 6 months before the study. These criteria were used to define the severity of fibromyalgia in our population. The body mass index had to be <35 kg/m^2. Premenopausal or postmenopausal status was recorded. Exclusion criteria included: disabling physical or mental status, previous or current malignancies either active or inactive, intracranial occupying lesion, any relevant endocrine disorder including diabetes mellitus, history of pituitary disorder, previous treatment with growth hormone, other systemic or inflammatory rheumatic conditions, and hypersensitivity to somatotropin or any excipients. Pregnant women, nursing mothers, or women with child bearing potential were also excluded.

An insulin tolerance test (IT) or glucagon test and pituitary magnetic resonance imaging (MRI) were performed as screening procedures and have been reported elsewhere [11]. Partial or total GH-deficient patients were excluded from the study (17%). A modified IGF-1 generation test was performed to rule out patients not prone to respond to GH (6.8%) [11].

A total of 120 women were enrolled in the study [11], with 60 patients randomly assigned to receive GH for 12 months (group A) and 60 patients to receive placebo for 6 months followed by GH for 6 additional months (open-label phase) (group B). All of the 120 patients were studied in the 12- to 18-month follow-up extension after GH discontinuation.

The study was conducted in accordance with the Declaration of Helsinki and received approval from ethics local institutional review boards and the Spanish Drug Agency (n°27560). The trial has been registered (NCT00933686) at Clinical Trials.gov. All patients gave written informed consent prior to their inclusion in the study.

Study medication was human GH produced by recombinant DNA technology (r-hGH) in a mammalian cell line (Saizen 8 mg Click-easy), using the one-click auto injector. The placebo consisted of sucrose, phosphoric acid, sodium hydroxide, and metacresol 0.3% in water for injection (Saizen excipients).

Patients were randomly assigned, according to a computer-generated randomization table, to receive either 0.006 mg/kg/day of r-hGH subcutaneously or placebo added to their standard and homogenized intensive therapy. Doses of r-hGH were adjusted after months 1, 3, 7, and 9 according to centralized IGF-1 plasma levels and/or the appearance of adverse events possibly related to GH. The adjustments consisted of increments of 0.2 mg/day if the percentage of increment of IGF-1 from baseline was lower than 50%, until reaching the maximum upper normal limit. To maintain the blind condition during the IGF-1 titration, couples of groups A and B were established: any dose change in group A lead to a placebo volume adjustment in group B. GH dosage adjustment and side effects were evaluated by the endocrinologist.

Follow-up visits were scheduled at months 1, 3, 6, 7, 9, and 12. Data from the follow-up study were recorded at months 13, 15, and 18. At baseline and follow-up visits, the number of tender points and their intensity were evaluated according to the 1990 ACR criteria. Patients also completed the FIQ (with subscales), and EuroQol 5 dimensions test (EQ5D) with VAS. Blood samples to determine IGF-1 dose were drawn at 1-, 3-, 6-, 7-, and 9-month follow-up visits. At baseline and 6 months, blood cell count, biochemical profile, and other laboratory tests were also performed, including thyroid-stimulating hormone (TSH), thyroxine (free T4), triiodothyronine (free T3), cortisol, insulinemia, triglycerides, high-density lipoprotein and low-density lipoprotein cholesterol, C-reactive protein, erythrocyte sedimentation rate, rheumatoid factor, aldolase, and creatinkinase. Adverse events, concomitant

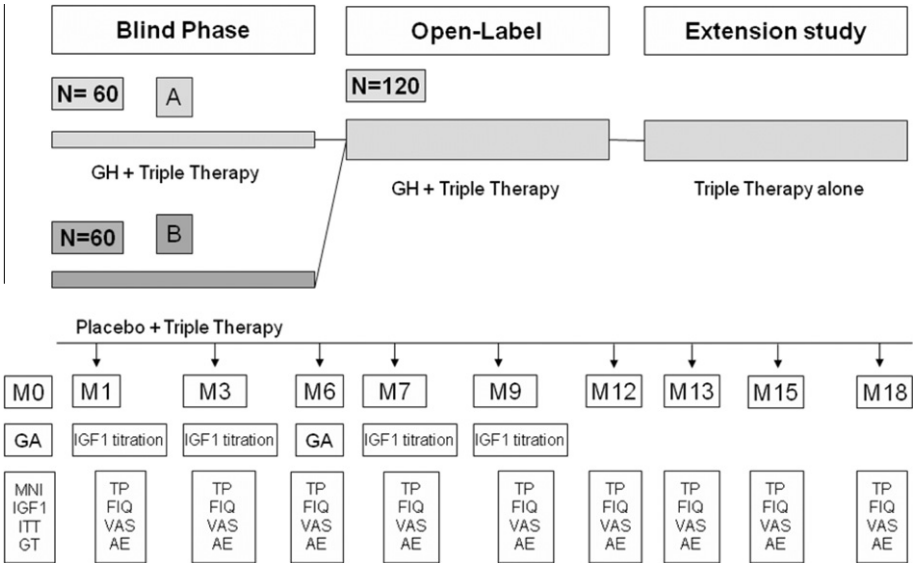

Fig. 1. Study design and flowchart. M0 = prescreening procedures (flowchart previously published); AE = adverse events; GA = general analysis; GT = insulin-like growth factor 1 generation test; FIQ = Fibromyalgia Impact Questionnaire; IT = insulin-induced hypoglycemia; MNI = pituitary magnetic nuclear imaging; TP = tender points; VAS = visual analogue scale. Data about Month 0- Screening period, previously published, have been authorised by the first and corresponding author, G. Cuatrecasas MD.

medication, and treatment compliance were recorded at each follow-up visit. Fig. 1 shows a flowchart of the study.

2.2. Efficacy assessments

The primary efficacy endpoint was the rate (%) of fibromyalgia patients with a reduction in the number of positive tender points to fewer than 11 (cut-off for diagnosis of fibromyalgia) at 12 months compared with baseline. Other measures of pain, such as mean number of tender points and average pain intensity, were also evaluated. Fibromyalgia trigger points were assessed by a rheumatologist blinded to the treatment group using the protocol described by Wolfe et al. [28] using 18 (9 bilateral) standardized sites. Secondary efficacy end points included (1) Spanish validated versions of the FIQ (a 10-item questionnaire that measures physical impairment, well being, missed work, pain, fatigue, rest, stiffness, anxiety, and depression), measured from 0 (best result) to 100 (worse result) [24]; (2) 5-dimension EQ5D used in GH deficiency patients and also in multiple musculoskeletal diseases, and (3) VAS, which is a 20-cm visual analogue scale in which the respondents rate their health state that day between 0 (worst imaginable) and 100 (best imaginable) [22]. VAS results are shown as >30% and >50% improvement to compare GH efficacy with some registered drugs.

2.3. Laboratory assays

Serum GH, IGF-1, TSH, free T4, free T3, and insulin levels were determined by automated chemi luminescent immunoassay system using a commercially available kit (immulite 2000, DPC, Los Angeles, CA for GH and IGF-1). GH and IGF-1 were measured in a central laboratory (Unilabs Reference Lab, Fundación Jimenez Diaz, Madrid, Spain). The interassay coefficient of variation of GH and IGF-1 assays were 4.52% and 3.04%, respectively. The analytical sensitivities of GH and IGF-1 assays were 0.05 ng/mL and <25 ng/mL, respectively. Serum cortisol levels were also determined by chemi luminescence using the Liason Analizer (Sorin Diagnostics SpA, Milan, Italy). Normal IGF-1 values were adjusted for age and weight, and an upper limit of 340 μg/mL was used.

2.4. Safety

Safety was assessed by every investigator using physical examination, performing hematological and biochemical laboratory testing, reporting adverse events, and looking at injection site reactions. To minimize the occurrence of adverse events, GH doses were individually adjusted during the study according to age-adjusted IGF-1 serum levels (Fig. 2) and investigator discretion.

2.5. Statistics

The number of patients included in the study was calculated to provide 90% power to detect a 35% absolute difference in the proportion of patients with fewer than 11 positive tender points, using a 2-sided test. Quantitative end points are presented as mean and standard deviation. The 95% confidence interval was used to indicate the precision of an estimate. The homogeneity of variances was analyzed by the Levene test, and the within-group comparisons used a *t* test and the nonparametric Mann-Whitney or Wilcoxon tests when necessary. Categorical data are presented as absolute numbers and percentages. A χ^2 analysis or Fisher exact test was used to compare these variables when applicable. Regarding the main variable, the differences between groups were analyzed by analysis of covariance, with the baseline number of tender points as a covariate. The time course within-group comparisons were analyzed by repeated-measurements analysis of variance. All *P* values were based on a 2-tailed distribution, and a 5% level of significance was considered. The statistical analysis was based on the intention-to-treat population. The SPSS statistical software package (version 12.0) was used for statistical analysis.

3. Results

The recruited population was well balanced (Table 1) in terms of baseline characteristics, including anthropometric, baseline laboratory characteristics, and specific fibromyalgia items.

At the end of the blind phase, no differences were seen between the placebo and the GH arm in the percentage of patients showing fewer than 11 positive tender points, mean number of tender

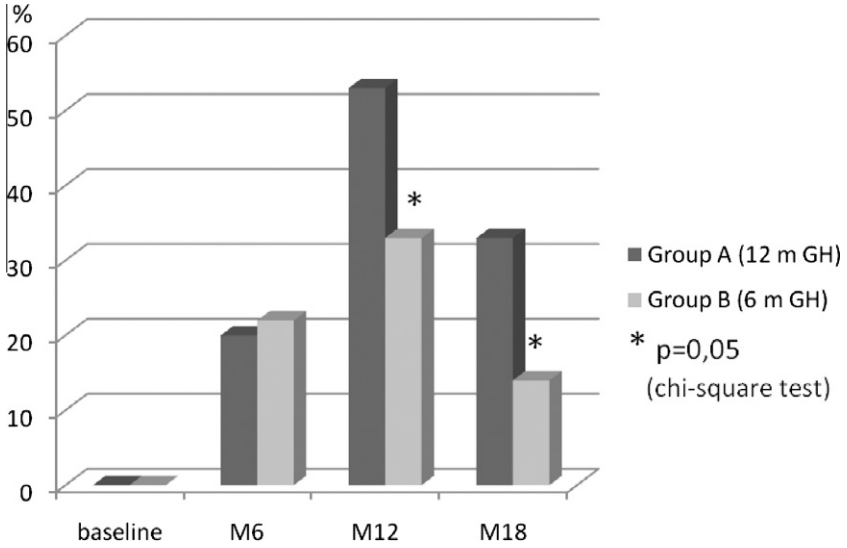

Fig. 2. Percent of patients with fewer than 11 positive tender points.

Table 1
Baseline characteristics.

	n	Group A	N	Group B	
		Mean ± IC		Mean ± IC	*P* value
SAP	53	120.9 ± 4.1	56	118.3 ± 4.0	.374
DAP	53	81.2 ± 2.9	56	76.9 ± 2.4	.021
Pulse	48	76.6 ± 3.2	54	76.6 ± 2.6	.981
Waist (cm)	49	91.7 ± 3.1	53	89.2 ± 3.3	.260
Height (cm)	55	158.2 ± 1.7	58	158.6 ± 1.5	.700
Weight (kg)	55	69.4 ± 2.7	58	66.8 ± 2.6	.168
BMI (kg/m^2)	55	27.7 ± 1.0	58	26.6 ± 1.1	.127
GHbaseline	48	2.65 ± 2.81	49	1.46 ± 0.79	.414
GH after IT	55	15.1 ± 2.7	58	13.6 ± 2.9	.454
IGF-1 baseline	54	108.4 ± 7.7	58	109.7 ± 7.1	.804
ΔIGF-1 (%) generation test	54	102.7 ± 9.3	57	114.1 ± 11.4	.125
FM diagnosis (mo)	53	57.8 ± 10.6	58	57.3 ± 13.3	.949
Tender points	54	17.1 ± 0.3	57	17.1 ± 0.3	.953
Pain intensity (/18 TP)	52	7.67 ± 0.33	53	7.36 ± 0.30	.166
Pain intensity (/+ TP)	52	8.04 ± 0.3	53	7.70 ± 0.26	.088
FIQbaseline	54	85.9 ± 2.4	58	85.8 ± 1.8	.961
AVSbaseline	54	72.7 ± 3.5	58	74.9 ± 3.1	.339

AVS = analogic visual scale; BMI = body mass index; DAP = diastolic arterial pressure; FIQ = Fibromyalgia Impact Questionnaire; FM = fibromyalgia; GH = growth hormone; IGF = insulin-like growth factor; IT = insulin tolerance test; SAP = systolic arterial pressure; TP = tender points.

points, intensity of pain in every point evaluated, total FIQ scores and subscales, EQ5D, and VAS.

At the end of the open phase, 53% of the patients treated with GH for 12 months (group A) reached fewer than 11 positive tender points (primary endpoint) compared with 33% of those treated for 6 months (group B) ($P < .05$) (Fig. 2). Furthermore, group A showed a trend in the reduction of the mean number of positive tender points, 40% (difference between evaluation at 12 months and baseline: 6.84 ± 1.74) compared with 28% in group B (4.67 ± 1.60) ($P = .07$), and pain intensity was also lower in group A (5.2 ± 0.72 vs 6.21 ± 0.56; $P = .03$). Similar improvements were observed at 12 months in FIQ score (53 ± 6.5 in group A vs 65 ± 6.5 in group B; $P = .02$) (Fig. 3), EQ5D score (9.09 ± 0.64 in group A vs 9.94 ± 0.56 in group B; $P = .047$), and VAS scale (45 ± 6.9 in group A vs 60.6 ± 6 in group B; $P = .01$) (Fig. 4). At 12 months, 56.5% of patients in group A vs 36.7% of group B patients obtained an improvement of more than 30% in VAS, and 39.1% in group A vs 22.4% of group B reached more than 50% ($P < .05$). All FIQ-specific subscales showed better scores among group A patients compared with group B (item 1: physical dysfunction [$P = .05$], item 3: working absenteeism [$P = .06$], item 4: pain [$P = .02$], item 5: professional activity [$P = .01$], item 6: fatigue [$P = .05$], item 8: tenderness [$P = .03$], and item 10: depression [$P = .05$]). The observed improvement at 12 months in EQ5D was due to a significant change in pain/well-being ($P = .017$) and anxiety/depression ($P = .037$). No changes were seen in movement, personal care, or daily activities EQ5D dimensions.

GH treatment discontinuation in the extension phase of the study worsened all the scores in both groups from the 1-month follow-up ($P < .05$), but group A showed a trend to fewer positive tender points than the 6-month GH-treated group ($P = .06$) at 18 months.

We found negative correlations between peak GH after IT and IGF-1 after generation test ($r = -0.24$), and between peak GH and mean number of tender points at the 6-month ($r = -0.23$) and 12-month ($r = -0.25$) evaluation point. Positive correlations were found between the mean number of tender points and pain intensity ($r = 0.86$), total FIQ score ($r = 0.46$), VAS score ($r = 0.41$), and EQ5D ($r = 0.51$) at the end of the study (12 month). No correlations between main outcomes and baseline IGF-1 levels, peak GH, or IGF-1 generation test were found.

No significant differences were seen in the main variables measured in the 5 hospitals. No differences were seen when analyzing separately premenopausal or postmenopausal women, either with or without estrogen substitution treatment. Both groups showed similar anthropometric data at baseline, and no significant changes were observed throughout the study. These groups were also comparable in terms of IGF-1, peak GH after IT, and percentage of IGF-1 increment when performing the IGF-1 generation test (Fig. 1).

IGF-1 was significantly higher in group A (191 ± 19 ng/mL) compared with group B patients (114 ± 8) in the blind phase, whereas in the open-label phase, IGF-1 was higher in group A (209 ± 23 ng/mL vs 180 ± 19 ng/mL; $P = .056$) only at 9 months. No significant differences were seen at 12 months between groups. IGF-1 was always in the normal range (Fig. 5).

Thirteen patients were stable at 16 to 18 positive tender points throughout the study. This non responder population was analyzed separately, and significant differences were only found for fibromyalgia severity (baseline + tender points 16.9 ± 0.3 in GH responders vs 17.7 ± 0.3 in non responders) and pain intensity (7.38 ± 0.24 vs 8.11 ± 0.49). No differences were seen in fibromyalgia duration or GH secretion/resistance status. No changes in serum cortisol, TSH, free T3, free T4, or insulin were seen through the study.

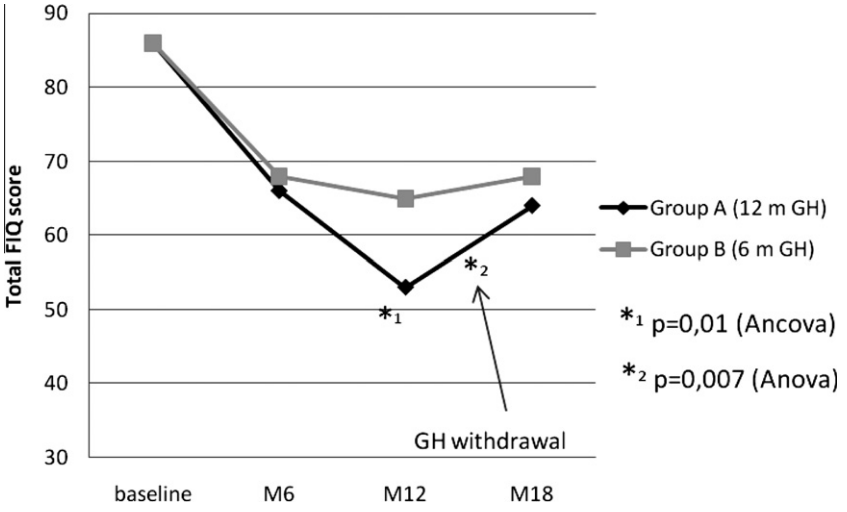

Fig. 3. Mean (confidence interval) total score of Fibromyalgia Impact Questionnaire.

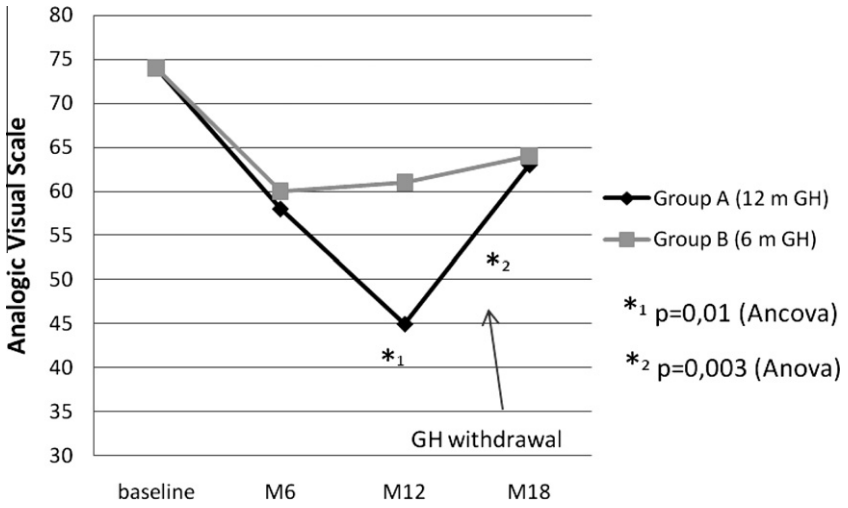

Fig. 4. Mean (confidence interval) score of visual analogue scale.

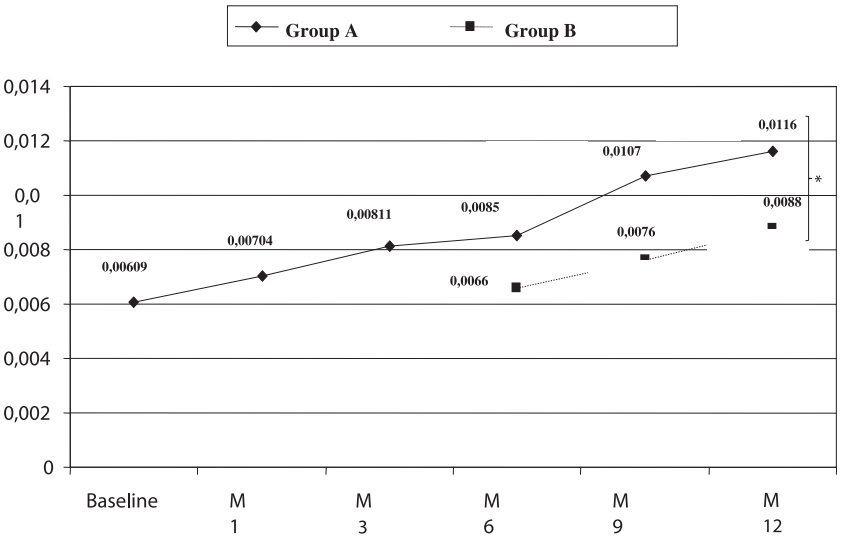

Fig. 5. Growth hormone dose titration.

In relation to safety, the concomitant administration of GH and standard therapy was well tolerated. No relevant changes in any of the clinical or laboratory parameters were observed in the 2 groups. A total of 4 serious adverse events were reported in 4 patients, all of them in group A (GH treatment for 12 months). One was considered GH-related: sleep apnea syndrome (the other 3 cases required hospitalization for abdominal pain, hospitalization for suspected cervix neoplasm not confirmed, and hospitalization due to allergic food reaction). GH was not permanently withdrawn in any of these cases. Table 2 shows all reported adverse events (432 adverse events in 45% for group A and 55% for group B. Headache (7.9%) (retinal fundoscopy was done in all cases, and benign cranial hypertension was discarded), edema in lower extremities (7.4%), and carpal tunnel syndrome (3.5%) were the most prevalent GH-related adverse events (Table 3).

4. Discussion

Because of the wide range of symptoms in fibromyalgia patients, evaluation of efficacy of any treatment is complex. To date, reports have shown improvements in pain intensity as the most common outcome measurement, evaluated with VAS or self-rating pain diaries [3,19,20,27]. However, we chose manual trigger point examination by an observer who was blinded to the treatment to assess pain intensity [9]. We are aware that ACR diagnosis criteria were changed in 2010, after our trial had been authorized by the regulatory authorities (2007), abandoning the tender point count and placing increased emphasis on patient symptoms [29]. In spite of this, the important end points of fatigue and global well being were assessed with self-rating instruments (FIQ and its subscales or EQ5D, a multidimensional test widely used in AGHD) [13,22,24]. The positive correlations found in our study between these composite end points indicate the concordance and usefulness of these tests.

The efficacy of GH in fibromyalgia was first suggested in one 9-month, randomized, double-blind study [6]. The population studied (n = 50) had, as in our study, low IGF-1 baseline values, but was not homogeneous enough in terms of GH secretion status and concomitant medication. In our previous pilot study [12], which lasted 12 months to take into account the effects of seasonal variation in pain, GH treatment was effective in pain relief, improvement of fatigue scores, and VAS in a highly selected fibromyalgia population, but these effects seemed to be more pronounced and faster than found in earlier studies [6]. However, because of the small number of patients (n = 24) and the lack of a placebo control group, results were inconclusive. The CT27560 trial was then designed to address those fibromyalgia patients highly homogeneous for GH axis status (low IGF-1 but normal GH response to IT to avoid overlap of patients with classic AGHD, and positive IGF-1 generation test to avoid non responders to GH treatment), active medication, and severity of the disease. As far as we know, our study is the largest and longest lasting placebo-controlled GH treatment study with fibromyalgia patients.

At the end of the study, a significant and clinically relevant difference was observed between patients treated for 12 months with GH and those treated for only 6 months in all quality of life scores (FIQ, EQ5D, and subscales). Almost 40% of the 12-month GH-treated patients showed more than 50% pain improvement, and more than half reached more than 30% improvement, assessed by VAS. This is the cut-off required by the US Food and Drug Administration for drug registry approval in the treatment of fibromyalgia [3,20,27]. Our data are similar to those obtained with duloxetine, pregabalin, milnacitram, or sodium oxybate, but GH seems to have a more sustained action throughout the first 12 months [24]. Pain may be evaluated as the number of positive tender points or intensity of tenderness, but we decided to express the percentage of patients reaching fewer than 11 positive tender points, the minimum number for fibromyalgia diagnosis, as our primary endpoint. More than half of the patients treated for 12 months fell below that given cut-off criteria.

Compared with previously published data [6], our study did not show differences between the groups at 6 months of treatment, neither in the mean number of tender points nor in the percentage of patients reaching fewer than 11 positive tender points. A possible explanation for the lack of efficacy in the short term could be the fact that 6 months is sufficiently long enough to see an effect with our dose regime. Both absolute dosage and frequency of GH increase in dose toward a defined maximum have to be taken into account, 6-month blind-phase only allowing changes in dose in 2 visits (1- and 3-month visits). Previous studies used a starting dose that was double the one used in the present trial (average dose 0.0125 mg/kg/day vs 0.006 mg/kg/day) [6,12]. Only at the end of the open-label phase in those patients being continuously treated for 12 months (group A) (again up-titrated at 7- and 9-month visits), the average dose approached the one used in previously published studies [6,12] (Fig. 5). Although this study was not designed as a dose-controlled study, the results of this trial suggest the need for higher doses of GH in fibromyalgia than those used in classic adult GH deficiency. The need for higher doses might because of the GH resistance described in this population (high plasma GH levels or insufficient increase in IGF-1 in the IGF-1 generation test [11]). The fact that about half of the fibromyalgia population is premenopausal women with some estrogen capacity [15] may also account for this GH resistance. Previously published studies [6,12] did not perform dynamic testing of GH secretion, therefore including patients having a true AGHD, who are more prone to respond to GH with clear improvement of symptoms much earlier after treatment initiation.

The placebo effect must be taken into account. It is well known that invasive procedures delivered in a supportive environment, particularly in an undertreated disease such as fibromyalgia, may result in beneficial effects [25], especially in the open phase of the study. Nevertheless, our patients, despite receiving GH

Table 2
Reported adverse events.

	Group A/Total (%)	Group B/Total (%)
Headache	10.9	5.4
Edema	8.8	6.3
Paresthesia	6.7	2.5
Insomnia	4.7	0.8
Carpal tunnel syndrome	4.1	2.9
Urinary tract infection	3.6	0.4
Back pain	3.1	0.0
Upper respiratory tract infection	3.1	0.0
Impaired work ability	2.6	2.9
Nausea	2.6	0.4
Anxiety	2.6	0.0
Arthralgia	2.1	3.3
Neck pain	2.1	1.3
Hypertension	2.1	0.4
Abdominal distension	2.1	0.0
Vaginal candidiasis	2.1	0.0
Skin reaction to injection	1.7	2.5
Hyperhidrosis	1.6	0.8
Abdominal pain	1.6	0.4
Hypercholesterolemia	1.6	0.0
Somnolence	1.0	1.7
Depression	1.0	0.4
Weight increase	1.0	0.4
Breast pain	1.0	0.0
Hyperglycemia	0.5	1.3
Anemia	0.5	0.0
Hypothyroidism	0.0	0.8
Nasopharyngitis	0.0	0.8

Table 3
Drug-related adverse events.

	Group A		Group B		Group A + B (open phase)	
Adverse events	N = 32	%(N = 120)	N = 22	%(N = 120)	N = 33	%(N = 120)
Carpal tunnel syndrome	4	3.3	2	1.7	8	6.6
Paresthesias	7	5.8	2	1.7	9	7.5
Peripheral Edema	11	8.7	4	3.4	8	7.5
Headache	10	8.3	14	11.6	6	5

treatment from the 6-month point, did not know to which regime they had been assigned in the first part of the study.

Finally, after GH withdrawal (while maintaining amitriptyline, selective serotonin re-uptake inhibitors, and opioids) our patients showed a clear impairment in all quality of life scores and pain, as early as the first month. However, at the 18-month evaluation, patients previously treated with GH for 1 year (group A) showed fewer positive tender points than those only treated for 6 months (group B) ($P = .05$). This sustained beneficial effect of GH after its withdrawal suggests a memory effect, raising the possibility of discontinuous GH treatment regimes.

Why does GH show such an analgesic effect? So far, little attention has been paid to the presence of pain in AGHD [13]. A recent study showed that patients with Turner syndrome treated with GH for their growth impairment experienced less pain [1]. GH, IGF-1, and IGF-2 receptors, present in the hippocampus and limbic cortex, where pain sensation is processed and modulated [17], might drive the effect of GH in pain relief.

The lack of correlation between IGF-1 and clinical improvement may be in part due to the dose given to avoid adverse events. There was a positive correlation between peak GH and higher mean number of tender points at the 6- and 12-month points, suggesting a more aggressive and painful clinical presentation of the fibromyalgia syndrome if GH secretion is low.

In terms of safety, the concomitant administration of GH with standard therapy for fibromyalgia was well tolerated. No patients withdrew from the study, and all patients followed the prescribed medication. Some of the adverse events (Table 2) are related with fibromyalgia symptoms themselves (e.g., back pain, impaired work obligations, insomnia), and the difference between the 2 groups is difficult to evaluate because of the possible slight clinical difference between the 2 groups that were present at baseline. The high frequency of headaches has not previously been reported in fibromyalgia trials using GH. Despite using a low starting dose of GH, the high frequency of edema in lower extremities should be taken into account. Carpal tunnel syndrome also shows a significant prevalence throughout the study, but lower than in previous trials [6,12]. However, its presence in the placebo group suggests that fibromyalgia itself could be partially responsible for this symptom. The low GH-related side effects might be partly due to the safety IGF-1 upper limit used at up- or down-titration visits.

Conflict of interest statement

MPD and GC are scientific advisors for Merck SL, Spain. GC received honoraria for related lectures in November 2008 and February 2009. CA, MJG and JFS received fees from steering committee advisory. JPI and EG are employees of the medical department of Merck SL, Spain.This study was supported by a grant from Merck SL, Spain as part of the trial CT27560 (NCT00933686).

Acknowledgements

The authors thank R. Huguet, A. Leal, P. Lopez-Mondéjar, G. Prats, M. Ramentol, and B. Yoldi, investigators in the Merck Seronotrial CT27560; S. Burgues, A. Peiró, J. Cabrera, J.C. Gil, and L. Gonzalez-Molero from Merck SL, Spain; and A. Esteban and F. Yunta from Cabyc SL (CRO), Spain, for monitoring and statistical assistance.

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