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


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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
both sides of the body above and below the waist, 11 or more trig- 
ger points among 9 pairs of specified sites should be affected, and 
for a period of at least 3 months [28]. In 2010, new ACR fibromyal-
gia 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 pop-
ulation [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. Endoclinological distur-
bances have been observed, involving the thyroid [4], the piti-
itary-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 lower
levels and/or the appearance of adverse events possibly related 
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 pla-
como 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, bio-
chemical 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 
baseline serum IGF-1 value lower than 150 ng/mL (34% of the 
gressed 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 fibromyal-
gia in our population. The body mass index had to be <35 kg/m². 
Premenopausal or postmenopausal status was recorded. Exclusion 
criteria included: disabling physical or mental status, previous or 
current malignancies either active or inactive, intracranial occupi-
ining lesion, any relevant endocrine disorder including diabetes mel-
litus, 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 modi-
fied 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 re-
view boards and the Spanish Drug Agency (n=27560). The trial 
has been registered (NCT00933686) at Clinical Trials.gov. All pa-
tients 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 con-
sisted of sucrose, phosphoric acid, sodium hydroxide, and metacre-
sol 0.3% in water for injection (Saizen excipients).

Patients were randomly assigned, according to a computer-gen-
erated 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 pla-
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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, bio-
chemical 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
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 Liaison Analyzer (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 χ2 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 points, and average pain intensity.
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 7.38 ± 0.24) compared with group B (4.67 ± 0.33 vs 8.11 ± 0.49). No differences were seen at 12 months between groups. IGF-1 was always in the normal range (Fig. 5).

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.

### Table 1
Baseline characteristics.

<table>
<thead>
<tr>
<th>Variable</th>
<th>Group A N</th>
<th>Group B N</th>
<th>Mean ± IC</th>
<th>Mean ± IC</th>
<th>P value</th>
</tr>
</thead>
<tbody>
<tr>
<td>SAP</td>
<td>53</td>
<td>56</td>
<td>120.9 ± 4.1</td>
<td>118.3 ± 4.0</td>
<td>.374</td>
</tr>
<tr>
<td>DAP</td>
<td>53</td>
<td>56</td>
<td>81.2 ± 2.9</td>
<td>76.9 ± 2.4</td>
<td>.021</td>
</tr>
<tr>
<td>Pulse</td>
<td>48</td>
<td>54</td>
<td>76.6 ± 3.2</td>
<td>76.6 ± 2.6</td>
<td>.981</td>
</tr>
<tr>
<td>Waist (cm)</td>
<td>49</td>
<td>53</td>
<td>91.7 ± 3.1</td>
<td>89.2 ± 3.3</td>
<td>.260</td>
</tr>
<tr>
<td>Height (cm)</td>
<td>55</td>
<td>58</td>
<td>158.2 ± 1.7</td>
<td>158.6 ± 1.5</td>
<td>.700</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>55</td>
<td>58</td>
<td>69.4 ± 2.7</td>
<td>66.8 ± 2.6</td>
<td>.168</td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>55</td>
<td>58</td>
<td>27.7 ± 1.0</td>
<td>26.6 ± 1.1</td>
<td>.127</td>
</tr>
<tr>
<td>GH baseline</td>
<td>48</td>
<td>49</td>
<td>6.84 ± 1.74</td>
<td>6.84 ± 1.74</td>
<td>.953</td>
</tr>
<tr>
<td>Pain intensity (+/TP)</td>
<td>52</td>
<td>53</td>
<td>7.67 ± 0.33</td>
<td>7.70 ± 0.26</td>
<td>.260</td>
</tr>
<tr>
<td>Tender points</td>
<td>54</td>
<td>57</td>
<td>30.3 ± 0.3</td>
<td>29.8 ± 0.3</td>
<td>.593</td>
</tr>
<tr>
<td>IGF-1 baseline</td>
<td>54</td>
<td>57</td>
<td>108.4 ± 7.7</td>
<td>109.7 ± 7.1</td>
<td>.804</td>
</tr>
<tr>
<td>IGF-1 (%) generation test</td>
<td>54</td>
<td>57</td>
<td>102.7 ± 9.3</td>
<td>114.1 ± 11.4</td>
<td>.125</td>
</tr>
<tr>
<td>FM diagnosis (ms)</td>
<td>53</td>
<td>58</td>
<td>57.8 ± 10.6</td>
<td>57.3 ± 13.3</td>
<td>.949</td>
</tr>
<tr>
<td>Pain intensity (/18 TP)</td>
<td>46</td>
<td>53</td>
<td>7.67 ± 0.33</td>
<td>7.36 ± 0.30</td>
<td>.166</td>
</tr>
<tr>
<td>Pain intensity (/+ TP)</td>
<td>52</td>
<td>53</td>
<td>8.04 ± 0.33</td>
<td>7.70 ± 0.26</td>
<td>.088</td>
</tr>
</tbody>
</table>

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.


![Fig. 2. Percent of patients with fewer than 11 positive tender points.](image)

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 7.38 ± 0.24) compared with group B (4.67 ± 0.33 vs 8.11 ± 0.49). No differences were seen at 12 months between groups. IGF-1 was always in the normal range (Fig. 5).

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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 cervical 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 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, milnacipran, 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

<table>
<thead>
<tr>
<th>Event</th>
<th>Group A/Total (%)</th>
<th>Group B/Total (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>10.9</td>
<td>5.4</td>
</tr>
<tr>
<td>Edema</td>
<td>8.8</td>
<td>6.3</td>
</tr>
<tr>
<td>Paresthesia</td>
<td>6.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Insomnia</td>
<td>4.7</td>
<td>0.8</td>
</tr>
<tr>
<td>Carpal tunnel syndrome</td>
<td>4.1</td>
<td>2.9</td>
</tr>
<tr>
<td>Urinary tract infection</td>
<td>3.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Back pain</td>
<td>3.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Upper respiratory tract infection</td>
<td>3.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Impaired work ability</td>
<td>2.6</td>
<td>2.9</td>
</tr>
<tr>
<td>Nausea</td>
<td>2.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Anxiety</td>
<td>2.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Arthralgia</td>
<td>2.1</td>
<td>3.3</td>
</tr>
<tr>
<td>Neck pain</td>
<td>2.1</td>
<td>1.3</td>
</tr>
<tr>
<td>Hypertension</td>
<td>2.1</td>
<td>0.4</td>
</tr>
<tr>
<td>Abdominal distension</td>
<td>2.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Vaginal candidiasis</td>
<td>2.1</td>
<td>0.0</td>
</tr>
<tr>
<td>Skin reaction to injection</td>
<td>1.7</td>
<td>2.5</td>
</tr>
<tr>
<td>Hyperhidrosis</td>
<td>1.6</td>
<td>0.8</td>
</tr>
<tr>
<td>Abdominal pain</td>
<td>1.6</td>
<td>0.4</td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>1.6</td>
<td>0.0</td>
</tr>
<tr>
<td>Somnolence</td>
<td>1.0</td>
<td>1.7</td>
</tr>
<tr>
<td>Depression</td>
<td>1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Weight increase</td>
<td>1.0</td>
<td>0.4</td>
</tr>
<tr>
<td>Breast pain</td>
<td>1.0</td>
<td>0.0</td>
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<tr>
<td>Hyperglycemia</td>
<td>0.5</td>
<td>1.3</td>
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<tr>
<td>Anemia</td>
<td>0.5</td>
<td>0.0</td>
</tr>
<tr>
<td>Hypothyroidism</td>
<td>0.0</td>
<td>0.8</td>
</tr>
<tr>
<td>Nasopharyngitis</td>
<td>0.0</td>
<td>0.8</td>
</tr>
</tbody>
</table>
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 amitryptiline, 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 withdrawal suggests a memory effect, raising the possibility of discontinuous GH treatment regimes.

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 IGFI-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).

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References


