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Safety and Tolerability of Growth Hormone Therapy in Multiple System Atrophy: A Double-Blind, Placebo-Controlled Study

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Abstract: The objective of this study was to investigate tolerability and possible neurotrophic effects of growth hormone (GH) in treatment of multiple system atrophy (MSA). In this double-blind pilot study, MSA patients were randomized to recombinant human growth hormone (r-hGH, n = 22), 1 mg every second day (6 months) followed by alternating daily injections of 1 mg and 0.5 mg (6 months), or matched placebo (n = 21). Safety analysis demonstrated no obvious between-group differences. In both groups, there was progressive worsening of Unified Parkinson's Disease Rating Scale total score, which tended to be less in r-hGH-treated patients (12.9% at 6 months, 25.3% at 12 months) than in placebo (17.0% and 35.7%). Similarly, there was a trend to less worsening in Unified MSA Rating Scale total score with r-hGH (13.2% and 21.2%) than with placebo (21.1% and 36.5%). Cardiovascular reflex autonomic testing also tended to show less deterioration with r-hGH than with placebo at 12 months. However, 95% CI did not indicate treatment differences for any efficacy measures. In conclusion, r-hGH administration in MSA patients for up to 1 year appears safe and might influence disease symptoms, signs and, possibly, progression. The results support further studies utilizing higher doses in more patients. © 2007 Movement Disorder Society

Key words: multiple system atrophy; growth hormone treatment; UPDRS; UMSARS; autonomic testing.

Multiple system atrophy (MSA) is a neurodegenerative disease of the central and autonomic nervous systems. Neuronal loss occurs in striatum, nigra, olives, pons, cerebellum, and spinal cord. This causes varying combinations of parkinsonism, cerebellar and autonomic dysfunction, with symptoms including akinesia, rigidity, postural stability, loss of balance and incoordination, orthostatic faintness, erectile dysfunction in men, urinary incontinence, and incomplete bladder emptying. MSA typically presents in the fifth to seventh decade of life, with a slightly higher incidence in men[1] and patients usually show only a modest response to levodopa (L-dopa) treatment.[2,3] While degeneration in Parkinson's disease is primarily in the nigrostriatal pathway, MSA involves multiple neuronal systems, and the symptoms are related to this progressive neuronal degeneration.[4] Disease progression is rapid, and mean survival is only about 7 years following onset.[5] The etiological cause of MSA has not yet been established and there is no known cure. Current treatment is symptomatic, mainly involving therapies for parkinsonian symptoms, orthostatic hypotension, and urogenital dysfunction.

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Members of the Growth-Hormone MSA Study Group and the European MSA Study Group are listed as an Appendix

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TABLE 1. *Baseline demographic characteristics and multiple system atrophy (MSA) clinical history*

	r-hGH-treated (n = 22)	Placebo (n = 21)	Total (n = 43)
Male (n)	11 (50.0)[a]	15 (71.4)	26 (60.5)
Female (n)	11 (50.0)	6 (28.6)	17 (39.5)
Age (years)			
Mean ± SD	58.4 ± 9.0	62.0 ± 7.4	60.1 ± 8.4
Range	36–79	48–73	36–79
Body weight (kg)			
Mean ± SD	72.9 ± 17.5	73.3 ± 15.6	73.1 ± 16.4
Body mass index (kg/m^2)			
Mean ± SD	25.1 ± 4.8	24.7 ± 4.3	24.9 ± 4.5
Range	17.6–36.3	16.7–35.7	16.7–36.3
Time since MSA diagnosis (months)			
Mean ± SD	16.5 ± 11.4	26.8 ± 27.8	22.4 ± 22.6
Range	3.1–38.4	0.2–85.6	0.2–85.6
MSA subtypes (n)			
MSA-P	14 (63.6)	12 (57.1)	26 (60.5)
MSA-C	8 (36.4)	9 (42.9)	17 (39.5)

[a]Values in parentheses indicate percentages.

r-hGH, recombinant human growth hormone; SD, standard deviation; MSA-P, parkinsonian-type MSA; MSA-C, cerebellar-type MSA.

During normal physiological development, endogenous growth hormone (GH) promotes numerous key events and functions in virtually every tissue in the body, acting either directly or indirectly through the second messenger insulin-like growth factor-I (IGF-I). GH has been shown to have several important neurotrophic actions, including stimulating neuronal and glial proliferation, increasing myelination, and increasing brain size.[6,7] GH and IGF-I receptors have been demonstrated in all regions of the adult human brain, including neurons and glial cells, and GH deficiency is associated with impaired survival of new neurons[8] and deficits in brain development and function.[9] Experimental studies in rodents have established that GH administration stimulates neuronal and glial proliferation as well as myelination in the brain, and systemic administration of IGF-I induces neurogenesis in the hippocampus.[10] These findings suggest that GH or IGF-I or both might influence repair of damaged neurons or attenuate further neuronal loss. Most neurons are terminally differentiated and not replaced after neuronal death. However, neural stem cells, which have been identified in the adult brain, generate new neurons throughout life in several species, including humans. The proliferation and differentiation of adult neural stem cells are affected by factors such as age, growth factors, and excitatory input.

We hypothesized that GH and IGF-I might act as "survival factors" for neurons at risk of degeneration in MSA patients. In addition, patients with MSA have been shown to have impaired secretion of GH in response to clonidine[11] and arginine,[12] although the response to L-dopa is normal. In a placebo-controlled study in GH-deficient adults, subcutaneous recombinant human growth hormone (r-hGH) administration was shown to induce an average 10-fold increase in GH concentration, as well as increased concentrations of IGF-I and β-endorphin immunoreactivity, in the CSF.[13] This pilot study was carried out to explore the safety and potential clinical benefits in terms of stabilization of clinical parameters of treatment with r-hGH in MSA patients. The study used laboratory assessments of the disease course in combination with clinical rating. Heart rate variability (HRV) during forced respiration and blood pressure response to head-up tilt (MAP%) were assessed to measure cardiovascular reflex function in the autonomic nervous system.

PATIENTS AND METHODS

Patients

Patients with clinically probable MSA, according to the criteria proposed by Gilman et al.[2] and judged by the responsible neurologist to have an anticipated survival of at least 1 year, were enrolled into the study. Patients were recruited through the European MSA Study Group (EMSA-SG).[14] Patients were excluded if they were wheelchair-bound, had any concomitant infection/inflammation of blood or CSF, had evidence of renal or liver dysfunction, or had diabetes mellitus, active malignancy, or any clinically relevant condition that would preclude GH treatment. Patients who were receiving symptomatic treatment for MSA maintained stable doses of medications from 4 weeks before study entry until at least 6 months of study treatment (Table 1).

Study Design

This was an international, multicenter, double-blind, randomized, placebo-controlled study designed as a preliminary examination of r-hGH treatment of patients with MSA to see if the treatment was tolerated and could provide clinical stabilization, compared with placebo. The dose of r-hGH chosen was similar to that used for replacement therapy in adult GH-deficient patients. The study was approved by the appropriate ethical review boards, and all patients gave written informed consent. On entry to the study, medical history and demographic data were assessed, and functional assessment of disease was performed. The patients were centrally randomized to receive injections of either r-hGH (Saizen®) at a dose of 1.0 mg every second day or matched placebo, in a double-blind manner for 6 months. At the end of the first 6 months, for patients who tolerated the initial dose, the dose was escalated to daily injections of r-hGH, at 1.0 mg and 0.5 mg on alternate days, or matched placebo, for a further 6 months. Thus, during the first 6 months the weekly r-hGH dose was 4 mg for a week and 3 mg the next, and from 6 to 12 months the total dose was 5.5 mg for a week and 5 mg the next. Study medication was administered at bedtime by subcutaneous injection, with rotation of the injection sites on the abdomen, arms, and legs; the time of injection and amount injected were recorded by the patients on diary cards. The patients were subsequently followed-up for an additional 3 months after treatment cessation. Saizen and placebo was provided by Serono International S.A. (Switzerland). Placebo contained phosphoric acid 85%, diluted phosphoric acid or sodium hydroxide (q.s), and *meta*-cresol 0.3% (w/v), which was reconstituted diluent containing *meta*-cresol in water for injection.

Study Assessments

Adverse event data were obtained from information volunteered by the patient or via patient questioning and through the use of diary cards.

Efficacy was assessed from measurement of Unified Parkinson Disease Rating Scale (UPDRS—primary outcome measure), Unified MSA Rating Scale (UMSARS—secondary outcome measure)[15] and autonomic testing (primary outcome measure), at baseline, and after 6 and 12 months of treatment. UPDRS was chosen as the primary outcome measure rather than UMSARS, because at the time the study started, UMSARS had been designed but had not yet been validated, although this has since been done.[15]

All autonomic tests were performed based on heart rate and blood pressure changes in time domain. Patients were placed and secured on a tilting table, and recordings of heart rate and blood pressure were initiated. An electrocardiogram was recorded with standard chest leads. Sinus arrhythmia was evaluated during 60-second periods of controlled deep breathing (six respiratory cycles per period) and was calculated according to the following formula:

$$\mathrm{HRV} = \frac{\frac{1}{N}\sum_{J=1}^{N}(\mathrm{RRmax}_j - \mathrm{RRmin}_j)}{60/\mathrm{HR}} \times 100$$

where J indicates the respiratory cycles, HRV indicates heart rate variability, HR indicates heart rate, and RR indicates heart beat interval. Orthostatic tests were performed subsequently, with the time used for raising the tilt table from the horizontal position to 75° head-up tilt limited to 2 seconds. Quantitative blood pressure changes during 8 minutes of tilt were based on sphygmomanometric data.

Data Analysis

This was a pilot study and 43 patients (22 randomized to r-hGH, 21 to placebo) were included. This number was an arbitrary decision, based on the fact that it was considered as (i) a reasonable expectation for recruiting patients affected by an orphan disease and (ii) sufficient to test the concept of r-hGH use in MSA primarily from a safety perspective. With this number, it was not expected to be able to demonstrate a statistically significant treatment effect on efficacy. In fact, as an indication, assuming a spontaneous progression of the total UMSARS score of 17 points within 1 year (standard deviation 10) and a treatment effect size of seven points with an α risk of 5% and a β risk of 10% (assumptions based on the EMSA-SG data on the natural history of MSA[16]) and considering the large number of premature discontinuations to be expected in this population, twice as many patients would have been necessary. Such a number was considered inappropriate for this type of pilot proof-of-concept trial.

Statistical analyses

All patients were included in the analysis of efficacy on an intention-to-treat (ITT) basis; in addition, data were analyzed for the per-protocol population (PP), defined as those still participating in the trial at 12 months, with no major protocol deviations and $\geq$75% compliance. Results were tabulated as mean, SD, and median, with 95% CI calculated for means for each treatment group; differences between treatments were assessed

TABLE 2. *Reasons for which 16 patients discontinued the study during the 12 months treatment period*

Reason for discontinuation	r-hGH-treated group (n = 22)	Placebo (n = 21)	All patients (n = 43)
Death	3	2	5
Adverse event	3	1	4
Protocol violation	1	1	2
Patient decision	2	2	4
Unspecified	1	0	1
Total	*10 (45.5)*[a]	*6 (28.6)*	*16 (37.2)*

[a]Values in parentheses indicate percentages.

from overlap of the 95% CI values. The last observation carried forward (LOCF) strategy was used to impute for missing values (mainly due to deaths and loss of follow-up).

RESULTS

Patient Disposition

There were 43 patients randomized in the study (22 to r-hGH and 21 to placebo); 34 patients (17 and 17) completed 6 months of treatment and 27 patients (12 and 15) completed 12 months. Of the 16 patients discontinued, 5 were due to the death of the patient from causes associated with MSA. Reasons for discontinuation of the 16 patients are given in Table 2. One patient on r-hGH was not compliant for ~7 weeks before the 6-month clinic visit and received <75% of treatment overall; therefore, the PP population comprised 11 patients in the r-hGH group and 15 patients in the placebo group. Of the 26 patients who completed the 12-month treatment without protocol violations, 13 had the parkinsonian type of MSA (MSA-P) and 13 had the cerebellar type (MSA-C). Twenty patients completed the HRV test and 17 completed the orthostatic provocation test. All 43 patients were receiving concomitant medications during the study, mostly antiparkinsonian drugs (81.4% of the patients). There were no obvious differences between treatment groups for disease duration or for any of the concomitant medications. During the 3-month follow-up, there were further three deaths caused by MSA in the two groups.

Efficacy Assessments

At baseline, the UPDRS scores were similar for both treatment groups, with mean total scores of 65.9 for r-hGH and 62.4 for placebo (Table 3). During the study, the mean total UPDRS score increased in both groups, indicating deterioration of the disease, at 6 and further at 12 months. The 95% CI for the changes did not indicate a difference between treatments (Table 3); however, there was a trend for the increase from baseline, shown as percentage change in Figure 1, to be less for the r-hGH-treated group than for the placebo-treated group. The percentage change was similar for the ITT population (Fig. 1) and the PP population (12 month change: r-hGH, 29.0%; placebo, 37.4%).

The results for UMSARS scores (Table 3) were very similar to those for UPDRS, indicating a worsening of MSA symptoms and signs over time. The increase in mean UMSARS total score was less at both 6 and 12 months for the group treated with r-hGH than for those given placebo, but the 95% CI did not indicate any difference. The percentage change from baseline for UMSARS total score for the ITT population was similar to that for the PP population (12 month change: r-hGH, 25.3%; placebo, 38.0%; Fig. 1).

HRV and MAP% (Table 4) also showed progressive deterioration during the study. The mean decrease in HRV at 6 months was slightly greater in the r-hGH group than placebo, but at 12 months, the mean change was greater in the placebo group. For MAP%, the mean decrease was less for the r-hGH group than the placebo group at both 6 and 12 months, although the 95% CI values did not show any differences.

TABLE 3. *Total scores evaluated from the unified Parkinson's disease rating scale (UPDRS) and the unified multiple system atrophy rating scale (UMSARS) at baseline and after 6 and 12 months of treatment, with either recombinant human growth hormone (r-hGH) or placebo*

	r-hGH	Placebo
UPDRS total score		
Baseline	65.9 ± 19.6 (22)[a]	62.4 ± 25.3 (21)
6 months		
Total score	73.9 ± 20.6 (17)	72.8 ± 25.7 (17)
Change from baseline	8.5 ± 12.6 (17)	10.6 ± 12.5 (17)
95% CI for change	2.0:15.0	4.2:17.1
12 months		
Total score	78.6 ± 28.6 (12)	81.9 ± 24.9 (15)
Change from baseline	16.7 ± 23.0 (12)	22.3 ± 14.7 (15)
95% CI for change	2.1:31.3	14.1:30.4
UMSARS total score		
Baseline	49.9 ± 13.8 (22)	46.9 ± 13.7 (21)
6 months		
Total score	55.1 ± 15.6 (17)	56.7 ± 16.7 (17)
Change from baseline	6.6 ± 8.6 (17)	9.9 ± 6.5 (17)
95% CI for change	2.2:11.0	6.5:13.2
12 months		
Total score	55.8 ± 18.0 (12)	62.1 ± 15.9 (15)
Change from baseline	10.6 ± 11.8 (12)	17.1 ± 8.6 (15)
95% CI for change	3.1:18.1	12.4:21.9

Values are mean ± standard deviation (SD).
[a]Values in parentheses indicate number of patients.
CI, confidence interval.

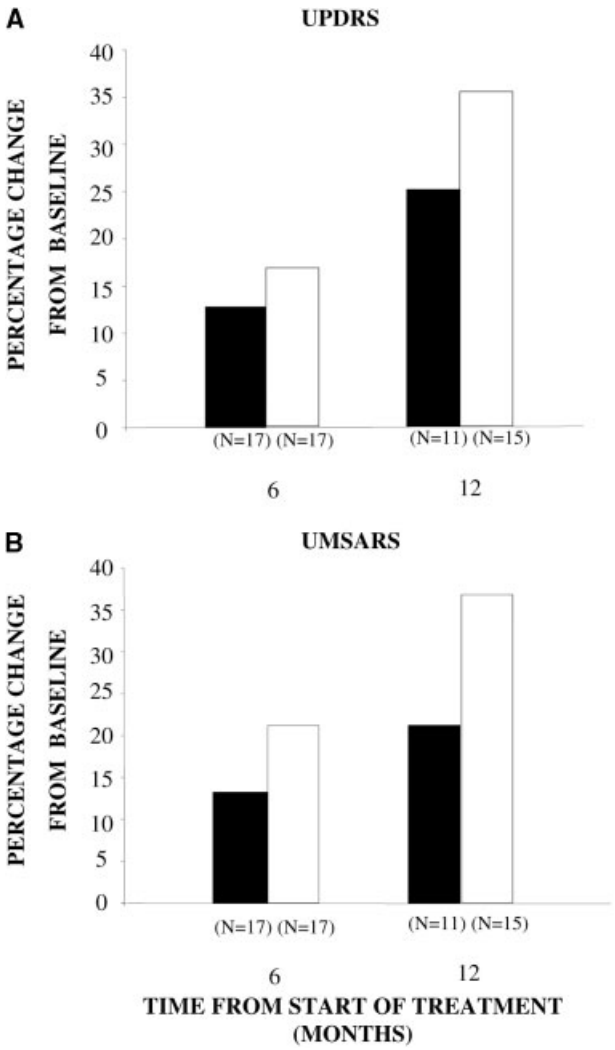

FIG. 1. Clinical signs of disease progression measured as mean percentage change from baseline in (a) unified Parkinson's disease rating scale (UPDRS) and (b) Unified multiple system atrophy (MSA) rating scale (UMSARS) in MSA patients after 6 and 12 months of treatment, with either recombinant human growth hormone (r-hGH) (filled bars) or placebo (open bars).

Safety Analysis

Serious adverse events were reported for 8 patients in the r-hGH group and 10 in the placebo group; only one event, an acute myocardial infarction, was thought to be possibly related to the study medication, but this patient was receiving placebo. During the study, adverse events were reported by 21 of 22 patients (95.5%) receiving r-hGH and 19 of 21 patients (90.5%) receiving placebo. The most common events were headache in six patients in the r-hGH group and five patients in the placebo group, urinary tract infection (five and six patients), constipation (five and three patients), fall (five and three patients), peripheral edema (five and three patients), and syncope (five and two patients). Overall, the reported adverse events, the system organ classes for the events, and the classification of relationship of events to the study medication were similar for both treatment groups. Four patients discontinued due to an adverse event: three in the r-hGH-treated (two hyperglycemia, one MSA worsening) and one in the placebo-treated (MSA worsening) groups. Eight patients died of MSA-related causes during the study. Five deaths had occurred by the per protocol analysis at 12 months (three patients receiving r-hGH, two receiving placebo) and three occurred thereafter.

One r-hGH-treated patient had an adverse event of hyperglycaemia, which was classified as probably related and the affected patient was subsequently discontinued. Fasting glucose at baseline for this patient was 4.7 mmol/l and increased to 6.6 mmol/l after 3 months of r-hGH. Fasting glucose concentration did not increase in the r-hGH-treated group from a mean of 5.49 mmol/l at baseline to 5.36 mmol/l at 12 months, with similar values for the placebo group.

DISCUSSION

GH is closely involved in the growth and development of the normal CNS. GH-deficient mice exhibit a microcephalic cerebrum with hypomyelination, retarded neuronal growth, and poor synaptogenesis. The hypomyelination is due to arrested glial proliferation, suggesting that the action of GH on the proliferation and maturation of both glial and neuronal cells is necessary for myelin

TABLE 4. *Laboratory signs of disease progression, evaluated by decrease in heart rate variability at forced respiration (HRV) and decrease in blood pressure response to head-up tilt (MAP%), of multiple system atrophy (MSA) patients treated with recombinant human growth hormone (r-hGH) or placebo*

	r-hGH	Placebo
Heart rate variability (%)		
Baseline	13.3 ± 16.0	12.7 ± 18.3
Change from baseline to 6 months	−3.5 ± 16.3	−0.4 ± 3.8
95% CI for change	−13.3:6.4	−2.7:2.0
Change from baseline to 12 months	−3.1 ± 15.5	−4.3 ± 9.1
95% CI for change	−14.2:8.0	−10.4:1.8
Mean arterial blood pressure after head-up tilt (%)		
Baseline	85.4 ± 21.0	81.6 ± 16.8
Change from baseline to 6 months	−0.5 ± 11.0	−5.4 ± 11.1
95% CI for change	−8.4:7.3	−13.3:2.6
Change from baseline to 12 months	−2.3 ± 10.6	−7.9 ± 12.4
95% CI for change	−11.2:6.5	−16.8:1.0

None of the differences between r-hGH and placebo are significant.
CI, confidence interval.

formation.[17] Following brain injury, IGF-I mRNA is induced primarily within reactive microglia. The resultant IGF-I protein appears to have a dual role, first as an endogenous neurotrophic and antiapoptotic agent acting directly on stressed cells and second as a prohormone for generation of the N-terminal tripeptide of IGF-I, glycine-proline-glutamate and the resulting des-*N*-1–3-IGF-I, both of which have specific neuroprotective properties.[18] GH and IGF-I have also been suggested to promote memory and cognitive capabilities.[19] Patients with MSA have a decreased GH response, the mechanism of which may be related to a lack of α-2-adrenergic stimulation of GH releasing hormone secretion from the hypothalamus.[11] Although MSA patients do not appear to be GH-deficient, it is possible that exogenous GH administration might affect the progression of the disease.

The study aimed to evaluate the effects of r-hGH at a dose similar to that used for replacement therapy in adult GH-deficient patients; the alternating 4 and 3 mg weekly doses for the first 6 months were similar to the average dose recommended for adult GH deficiency (1–2 mg weekly), while the increased dose for the second 6-month period was toward the higher level of the recommended dose (7 mg weekly). Common undesirable effects associated with r-hGH administration in adults include injection site reactions, localized lipoatrophy, and fluid retention (peripheral edema, stiffness, arthralgia, myalgia, paresthesia; usually transient and dose-dependent). Uncommonly, carpal tunnel syndrome and idiopathic intracranial hypertension can occur and, rarely, hypothyroidism, insulin resistance, and hyperglycaemia. Antibodies to GH, the clinical significance of which is unknown, can form in some patients. In this study, r-hGH treatment was generally well tolerated, and the safety analysis essentially reflected the seriousness of the underlying disease, with no obvious differences between r-hGH and placebo in terms of adverse events.

In a recently published study examining the rate of deterioration in patients with MSA, an annual increase of 28.6% was observed in UPDRS-III scores.[20] This section of the UPDRS relates to motor function, and the data illustrated the rapid progression of motor impairment in MSA patients, particularly during the early stages of disease. r-hGH treatment in the present study was associated with a trend to slow the worsening of UPDRS and UMSARS motor evaluation, and total scores and autonomic function. However, the clinical trial involved a relatively small number of patients. Each primary endpoint in the study was chosen to give unrelated information about disease progression. UPDRS scores obtained by different clinical examiners reflect some of the clinical disability in MSA. UMSARS scores, although having some overlap with UPDRS items, capture additional aspects of MSA. The use of objective and reproducible laboratory tests, however, served as an important complement. HRV and blood pressure response to tilt usually show pathological results in MSA.[21] HRV reflects autonomic function, including brain stem centers such as the dorsal vagal nucleus. In patients with coronary arteriosclerosis, decreased HRV may indicate increased risk for cardiovascular mortality.[22,23] Blood pressure response to tilt reflects a combination of sympathetic peripheral blood vessel control and the ability to respond with tachycardia to maintain blood pressure.

This study is the first to report the effects of GH treatment of patients with MSA. As yet, no drug has been shown to reduce progression of MSA. At the time this study was designed, no reliable data were available on spontaneous evolution in MSA patients of the clinical scales used to assess disease progression. Thus, when designing the study, it was impossible to make a reliable sample size calculation for detection of a positive effect. In addition, 37% of the patients discontinued prematurely during the study owing to the aggressive nature of the underlying disease. The number of drop-outs was even larger for the laboratory tests, so that only 21 patients completed HRV testing according to the study protocol and only 17 patients completed all three orthostatic provocation tests. The study was under-powered to demonstrate evidence of efficacy. Based on the treatment effect observed in this pilot trial, the number of patients needed to show a statistically significant effect would need to be in the order of 90, which should be feasible. The high rate of drop-out and death within 1 year also needs to be taken into account, since this will further influence power calculations for future studies. Since more patients were lost (due to death or other reasons) from the r-hGH group (10 of 22) than from the placebo group (6 of 15) during the study, and since those who did not complete the study were more likely to be deteriorating more rapidly, the use of the LOCF strategy might have artificially reduced the deterioration recorded in the r-hGH group, and so might not be the best choice.

The results of this study, therefore, suggest that a larger dose of r-hGH could be tolerated and may be necessary to demonstrate improvements in patients with MSA. With the benefit of additional information on the evolution of MSA gleaned in the present study and others,[16] further trials utilizing higher doses of r-hGH may be justified, since they could then be adequately powered to demonstrate efficacy in terms of the UPDRS/UMSARS evaluation scales. Future trials should also be more focused on early disease were beneficial effects could be easier to demonstrate.

APPENDIX

The following investigators also participated in the clinical study that generated the basis of these results: K. Bleasdale-Barr, L. Mason, M. Edwards, J. Hooker, T. Scaravilli, and H.-T. Kim, Institute of Neurology, London, UK; C. Thalamas, H. Delabaere, N. Poey, A. Canales, and M. Bertrand, Laboratoire de Pharmacologie Médicale et Clinique and Centre d'Investigation Clinique, Toulouse, France; R. Josep, Hospital Clinic de Barcelona, Spain.

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