Efficacy and safety of leuprorelin in patients with spinal and bulbar muscular atrophy (JASMITT study): a multicentre, randomised, double-blind, placebo-controlled trial

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Summary

Background Spinal and bulbar muscular atrophy is a hereditary motor neuron disease caused by the expansion of a polyglutamine tract in the androgen receptor. At present there are no treatments for spinal and bulbar muscular atrophy, although leuprorelin suppressed the accumulation of pathogenic androgen receptors in a phase 2 trial. We aimed to assess the efficacy and safety of leuprorelin for spinal and bulbar muscular atrophy.

Methods The Japan SBMA Interventional Trial for TAP-144-SR (JASMITT) was a 48-week, randomised, double-blind, placebo-controlled trial done at 14 hospitals between August, 2006, and March, 2008. Patients with spinal and bulbar muscular atrophy were randomly assigned (1:1) by minimisation to subcutaneous 11·25 mg leuprorelin or identical placebo every 12 weeks. Patients and investigators were masked to treatment allocation. The primary endpoint was pharyngeal barium residue, which indicates incomplete bolus clearance, measured at week 48 by videofluorography. All patients who were randomly assigned and who were assessed with videofluorography at least once were included in the analyses. This study is registered with the JMACCT clinical trials registry, number JMA-IIA00009, and the UMIN clinical trials registry, number UMIN000000465.

Findings 204 patients were randomly assigned and 199 started treatment: 100 with leuprorelin and 99 with placebo. At week 48, the pharyngeal barium residue after initial swallowing had changed by −5·1% (SD 21·0) in the leuprorelin group and by 0·2% (18·2) in the placebo group (difference between groups −5·3%; 95% CI −10·8 to 0·3; p=0·063). The mean difference in pharyngeal barium residue after piecemeal deglutition at week 48 was −3·2% (−6·4 to 0·0; p=0·049), but there was no significant difference between the groups after covariate adjustment for the baseline data (−4·1 to 1·6; p=0·392). In a predefined subgroup analysis, leuprorelin treatment was associated with a greater reduction in barium residue after initial swallowing than was placebo in patients with a disease duration less than 10 years (difference between groups −9·8, −17·1 to −2·5; p=0·009). There were no significant differences in the number of drug-related adverse events between groups (57 of 100 in the leuprorelin group and 54 of 99 in the placebo group; p=0·727).

Interpretation 48 weeks of treatment with leuprorelin did not show significant effects on swallowing function in patients with spinal and bulbar muscular atrophy, although it was well tolerated. Disease duration might influence the efficacy of leuprorelin and thus further clinical trials with sensitive outcome measures should be done in subpopulations of patients.

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Introduction

Spinal and bulbar muscular atrophy (SBMA), also known as Kennedy's disease, is an adult-onset, X-linked motor neuron disease characterised by muscle atrophy; limb, trunk, and facial weakness; contraction fasciculations; and bulbar involvement.[1–3] The prevalence of SBMA has been estimated to be 1–2 per 100 000, although a substantial number of patients with the disorder might have been misdiagnosed with other neuromuscular diseases such as amyotrophic lateral sclerosis.[4] Disease progression is usually slow, but life-threatening respiratory tract infections often occur in the advanced stage, resulting in premature death.[5] SBMA is caused by the expansion of a CAG triplet repeat, which encodes a polyglutamine tract, within the first exon of the androgen receptor gene.[6] Patients with SBMA have 38–62 CAG repeats, whereas individuals without the disorder have 9–36 CAG repeats.[4,6] Accumulation of the pathogenic androgen receptor protein in the nuclei of lower motor neurons is thought to lead to induction of neuronal cell dysfunction and eventual degeneration.[7] Deposition of pathogenic androgen receptors also occurs in non-neuronal tissues such as scrotal skin and can be used as a histopathological

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biomarker for SBMA.[8] Most patients also have high serum concentrations of creatine kinase.[1,3]

SBMA is a male-specific disease; even homozygous females do not display symptoms.[9,10] The sex dependency of the disorder seems to stem from the testosterone-dependent toxicity of the pathogenic androgen receptor.[10–14] In mouse models of SBMA, surgical castration delays disease onset and progression and reverses the neuromuscular phenotype.[11,14] Similar effects emerge when the mice are treated with leuprorelin, a luteinising hormone-releasing hormone (LH-RH) agonist that reduces testosterone release from the testes by downregulating LH-RH receptors in the pituitary gland.[12] A phase 2 randomised controlled trial of leuprorelin in patients with SBMA suggested a short-term improvement of swallowing function and long-term suppression of deterioration in motor function with a high tolerability.[15] These promising results, together with the well known tolerability of LH-RH agonists, led us to undertake a randomised, placebo-controlled clinical trial of leuprorelin in SBMA.

Methods

Patients

The Japan SBMA Interventional Trial for TAP-144-SR (JASMITT) study was a randomised, double-blind, placebo-controlled, parallel-group, multicentre trial at 14 hospitals in Japan. Patients were enrolled between August, 2006, and March, 2007; the study ended in March, 2008. Inclusion criteria were a clinical diagnosis of SBMA with more than one motor symptom (muscle weakness, muscle atrophy, bulbar palsy, and hand tremor); confirmation of androgen receptor CAG repeat expansion (>38 repeats); age 30–70 years at the time of informed consent; no desire to father a child; serum aspartate aminotransferase less than four times the upper limit of normal; serum alanine aminotransferase less than four times the upper limit of normal; ability to stand for 6 min with or without support; and ability to attend ambulatory hospital visits. Exclusion criteria were treatment with LH-RH agonists, testosterone drugs, 5-alpha-reductase inhibitors, antiandrogen drugs, anabolic-androgenic steroids, progesterone, or oestrogen drugs within 48 weeks before informed consent; previous treatment with LH-RH agonists for more than 48 weeks; history of surgical androgen deprivation (eg, orchiectomy); depression diagnosed by the mini-international neuropsychiatric interview Japanese version 5.0.0 major depression episode; coexisting severe disease besides SBMA; known allergy to leuprorelin, synthetic LH-RH, or LH-RH derivatives; and participation in other clinical trials within 12 weeks before informed consent.

Patients provided written informed consent before enrolment. The protocol was approved by the institutional review board at each participating centre and the Japanese regulatory authority (Pharmaceuticals and Medical Devices Agency, Japan). The study was done in accordance with the Declaration of Helsinki and good clinical practice.[16,17]

Randomisation and masking

Patients were randomly assigned (1:1) to receive either leuprorelin or an identical placebo by an independent registration centre (Clinical Trial Coordinating Center, Research Center for Clinical Pharmacology, The Kitasato Institute, Tokyo, Japan). Dynamic random allocation was done with minimisation on the basis of the patients' age (≤54 years or ≥55 years) and CAG repeat length (≤49 repeats or ≥50 repeats) to reduce bias.[18] The cutoff values were chosen on the basis of the mean age and CAG repeat length of the patients enrolled in the phase 2 trial.[15] Patients were assigned to a computer-generated randomisation list. Patients and investigators were masked to treatment allocation. An independent safety monitoring committee could request the unmasking of trial participants if necessary. The drug codes were broken and made available for data analysis when the study was completed and the data files had been verified.

Procedures

Leuprorelin (leuprorelin acetate) or placebo was subcutaneously injected at a dose of 11·25 mg every 12 weeks. Placebo was supplied as a vial containing microcapsule powder without leuprorelin, which was suspended in the same solution as the active drug for injection. We did not do a dose-response study because previous studies suggested that leuprorelin-mediated androgen deprivation is incomplete at doses lower than 3·75 mg every 4 weeks in adult men.[19] In a phase 2 trial of leuprorelin for prostate cancer, doses higher than 3·75 mg every 4 weeks led to a greater occurrence of adverse effects with no further reduction in serum testosterone concentrations.[20] A 3-month formulation of leuprorelin was effective at reducing testosterone concentration in patients with prostate cancer.[21] Therefore, we gave patients 11·25 mg every 12 weeks, which corresponds to 3·75 mg every 4 weeks.

The primary endpoint was pharyngeal barium residue at 48 weeks, visualised by videofluorography according to a standardised method.[22,23] This variable was selected because, although there is no established endpoint for clinical trials of SBMA, previous studies suggested that dysphagia and aspiration most strongly affect prognosis.[5] Among the various parameters of videofluorography, pharyngeal barium residue, which indicates incomplete bolus clearance, is directly associated with aspiration, and is the most common abnormal finding in patients with SBMA. Pharyngeal barium residue visualised by videofluorography is a predictive factor for aspiration and is associated with residues that are quantified by scintigraphy, suggesting that this measurement can be used to assess swallowing function reliably in patients with neuromuscular disorders.[24,25] In the phase 2

randomised controlled trial, only 22% of patients had dysphagia but 62% had pharyngeal residue.[15] In addition, swallowing function decreased as the disease progressed. The results of initial analyses of the phase 2 randomised trial, which involved videofluorography quantification by one investigator, suggested that the effect size would be big enough with pharyngeal barium residue for the effect to be obvious with fewer patients than it would with other measures such as the revised amyotrophic lateral sclerosis functional rating scale (ALSFRS-R). Neither the results of subsequent analyses by two independent videofluorography assessors nor the data from the follow-up study of the phase 2 trial[15] were available when we planned the present trial and chose pharyngeal barium residue as the primary outcome measure.

Secondary outcome measures were frequency of anti-polyglutamine (1C2) antibody-positive cells in scrotal skin biopsies; serum concentrations of creatine kinase; motor function, as measured by the ALSFRS-R, Japanese edition,[26] five components of the quantitative myasthenia gravis (QMG) score (without ptosis or diplopia sections),[27] and the 6-min walk test (6MWT);[28,29] temporal parameters of videofluorography, such as stage transition duration, duration of maximum laryngeal elevation, and duration of cricopharyngeal opening; and quality of life (amyotrophic lateral sclerosis assessment questionnaire 5 [ALSAQ-5], Japanese edition).[30] To assess safety, standard laboratory parameters were checked every 12 weeks and bone mineral density was monitored at weeks 0 and 48. Primary and secondary endpoints were measured at weeks 0, 24, and 48.

We measured the frequency of anti-polyglutamine (1C2) antibody-positive cells in scrotal skin biopsies because this parameter is associated with the number of 1C2-positive spinal motor neurons in autopsy specimens and is inversely associated with the limb Norris scale.[8] Three scrotal punch biopsies were taken from each patient at each timepoint under local anaesthesia and were processed for immunohistochemical analysis using the 1C2 antibody to detect accumulation of the pathogenic androgen receptor (webappendix p 1). We used the QMG and 6MWT to assess motor function because these parameters can be measured in a multicentre setting without any particular equipment.

In the videofluorography examinations, patients were instructed to swallow 3 mL of 40% weight/volume barium sulphate twice while standing. Pharyngeal barium residue was measured by the first 3 mL swallowed because the first residue directly affects the second one. All of the parameters were measured by three masked independent investigators according to standard procedures.[22,31] Briefly, pharyngeal residue was measured using a semi-quantitative scale: 0, 2, 5, 10, 20, 30, 40, 50, 60, 70, 80, 90, and 100%. We trained the evaluators to use this method, and the kappa statistic in the validation of pharyngeal barium residue was 0·80 before the trial, 1·0 during, and 1·0 after the end of the trial. Previous studies have also shown high intra-rater and inter-rater reliabilities for measurement of videofluorographic swallowing,[32] although little is known about the reproducibility of this parameter. Piecemeal deglutition—multiple repeated swallows to empty a bolus from the oral cavity—is often observed with videofluorography in patients with SBMA, and thus we measured pharyngeal residues not only after

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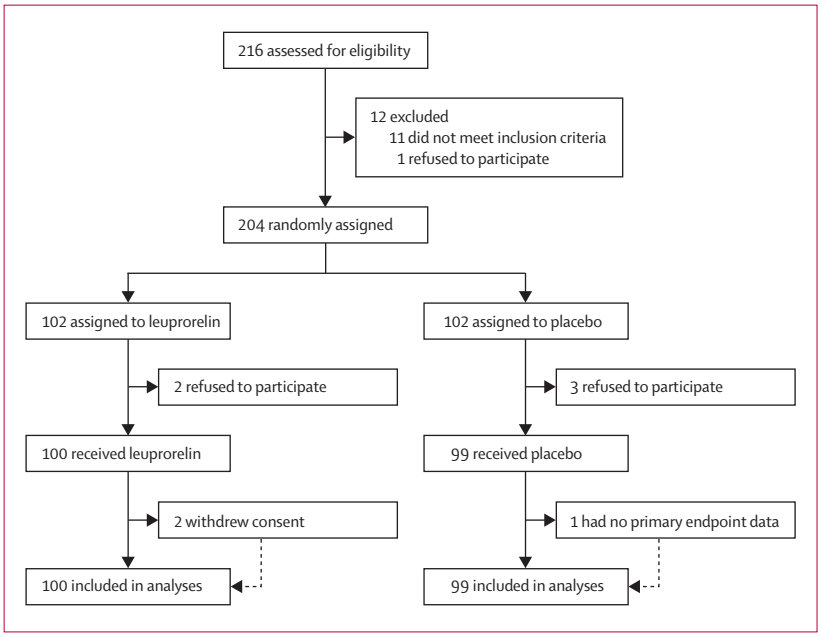

Figure 1: **Trial profile**

	Total study population		Subset group (duration of disease <10 years)	
	Leuprorelin (n=100)	Placebo (n=99)	Leuprorelin (n=44)	Placebo (n=37)
Age (years)	53·6 (9·2)	54·2 (9·2)	52·2 (9·6)	52·6 (9·9)
Duration of disease (years)	12·7 (8·4)	13·3 (7·3)	6·1 (2·4)	6·1 (2·6)
CAG repeat length	48·6 (4·0)	48·2 (3·2)	48·3 (4·4)	47·3 (2·6)
Weight (kg)	62·7 (9·4)	63·8 (11·2)	62·8 (10·5)	65·8 (12·0)
Residue after piecemeal deglutition (%)	10·6 (13·5)	6·7 (7·2)	9·6 (10·7)	4·6 (4·7)
Residue after initial swallowing (%)	20·3 (27·1)	18·7 (26·6)	21·5 (28·9)	12·0 (19·9)
Duration of cricopharyngeal opening (s)	0·4 (0·1)	0·4 (0·1)	0·4 (0·1)	0·4 (0·1)
Stage transition duration (s)	0·1 (0·3)	0·2 (0·3)	0·1 (0·2)	0·1 (0·1)
Laryngeal elevation duration (s)	0·2 (0·1)	0·3 (0·1)	0·3 (0·1)	0·3 (0·2)
ALSFRS-R score	40·8 (3·6)	41·0 (3·7)	42·2 (2·6)	42·5 (3·3)
6MWT (m)	323·2 (141·9)	303·7 (132·0)	378·4 (109·1)	372·2 (111·9)
Modified QMG score	7·2 (3·0)	6·8 (2·8)	6·5 (2·8)	5·6 (2·7)
ALSAQ-5 score	10·1 (3·4)	10·7 (3·8)	9·8 (3·4)	9·6 (4·0)
1C2-positive cells (%)	20·6 (15·0)	20·7 (14·0)	22·0 (16·4)	19·9 (12·8)
Creatine kinase (IU/L)	754·2 (443·2)	784·4 (479·8)	765·8 (488·7)	1019·5 (533·0)
Testosterone (ng/mL)	7·8 (3·0)	7·7 (2·6)	8·3 (2·9)	7·8 (2·6)

Data are mean (SD). ALSFRS-R=revised amyotrophic lateral sclerosis functional rating scale. 6MWT=6-min walk test. QMG=quantitative myasthenia gravis. ALSAQ-5=amyotrophic lateral sclerosis assessment questionnaire 5.

Table 1: **Demographics and baseline characteristics**

initial swallowing but also after piecemeal deglutition. The stage transition duration (also known as pharyngeal delay time) was defined as the interval from the bolus passing the base of the tongue to the onset of laryngeal elevation, and the duration of maximum laryngeal elevation was the length of time during which the larynx was maximally raised from its rest position. The duration of cricopharyngeal opening (also known as the duration of opening of the upper oesophageal sphincter) was defined as the length of time for which the cricopharyngeal sphincter was open. The mean values of the first and the second doses of barium sulphate were calculated for all the temporal parameters of videofluorography.

	n	Baseline	48 weeks	Difference	Between-group difference (95% CI)	p value*
Primary endpoint						
Pharyngeal barium residue after initial swallowing (%)						
Leuprorelin	98	20·3 (27·1)	15·2 (20·4)	−5·1 (21·0)	..	..
Placebo	96	18·7 (26·6)	18·8 (24·6)	0·2 (18·2)	−5·3 (−10·8 to 0·3)	0·063
Pharyngeal barium residue after piecemeal deglutition (%)						
Leuprorelin	97	10·6 (13·5)	9·0 (11·3)	−1·6 (12·9)	..	..
Placebo	96	6·7 (7·2)	8·3 (11·2)	1·7 (9·3)	−3·2 (−6·4 to 0·0)	0·049†
Secondary endpoints						
Duration of cricopharyngeal opening (s)						
Leuprorelin	98	0·43 (0·07)	0·46 (0·08)	0·03 (0·07)	..	..
Placebo	98	0·43 (0·09)	0·46 (0·08)	0·02 (0·06)	0·00 (−0·02 to 0·02)	0·68
Stage transition duration (s)						
Leuprorelin	98	0·14 (0·25)	0·19 (0·26)	0·04 (0·25)	..	..
Placebo	98	0·17 (0·28)	0·17 (0·28)	−0·01 (0·19)	0·05 (−0·01 to 0·11)	0·12‡
Laryngeal elevation duration (s)						
Leuprorelin	98	0·24 (0·11)	0·21 (0·09)	−0·03 (0·11)	..	..
Placebo	98	0·25 (0·12)	0·23 (0·11)	−0·02 (0·11)	−0·01 (−0·04 to 0·02)	0·52
ALSFRS-R score						
Leuprorelin	100	40·8 (3·6)	40·5 (4·1)	−0·4 (2·8)	..	..
Placebo	99	41·0 (3·7)	40·8 (3·4)	−0·1 (2·4)	−0·2 (−1·0 to 0·5)	0·54
6MWT (m)						
Leuprorelin	100	323·2 (141·9)	298·9 (144·6)	−24·2 (48·8)	..	..
Placebo	99	303·7 (132·0)	289·7 (139·1)	−14·0 (46·8)	−10·2 (−23·6 to 3·1)	0·13
Modified QMG score						
Leuprorelin	100	7·2 (3·0)	7·1 (3·1)	−0·1 (1·9)	..	..
Placebo	99	6·8 (2·8)	7·0 (2·9)	0·2 (1·8)	−0·3 (−0·8 to 0·2)	0·20
ALSAQ-5 score						
Leuprorelin	100	10·1 (3·4)	11·1 (3·8)	1·0 (2·9)	..	..
Placebo	99	10·7 (3·8)	10·9 (3·7)	0·1 (2·9)	0·9 (0·1 to 1·7)	0·033
1C2-positive cells (%)						
Leuprorelin	100	20·6 (15·0)	8·7 (8·3)	−11·9 (13·0)	..	..
Placebo	98	20·6 (14·0)	23·4 (14·3)	2·7 (12·1)	−14·7 (−18·2 to −11·2)	<0·0001§
Creatine kinase (IU/L)						
Leuprorelin	100	754·2 (443·2)	632·7 (398·7)	−121·5 (245·1)	..	..
Placebo	98	786·3 (481·9)	766·7 (494·9)	−20·0 (273·2)	−101·9 (−174·6 to −29·2)	0·006§

Data are mean (SD). ALSFRS-R=revised amyotrophic lateral sclerosis functional rating scale. 6MWT=6-min walk test. QMG=quantitative myasthenia gravis. ALSAQ-5=amyotrophic lateral sclerosis assessment questionnaire 5. *Two sample *t* test. †Wilcoxon rank sum test p=0·044. ‡Wilcoxon rank sum test p=0·012. §Wilcoxon rank sum test p<0·0001.

Table 2: **Primary and secondary endpoints**

All patients gave written informed consent for the genetic analyses. The results of genetic analyses of CAG repeat number were reported to the registration centre for dynamic allocation but were not disclosed to patients or investigators. Serum creatine kinase and testosterone concentrations were assessed in a central laboratory so that the patients and investigators were masked to the results.

All data related to the trial were recorded on case report forms that were reviewed with the patients' examination results by the independent trial monitor. After validation, all results were double entered into an SQL Server 2005 database. Data entry was controlled for consistency by use of SAS (version 9.1.3), according to the protocol and data management plan. An independent safety monitoring committee reviewed the adverse events that occurred during the trial.

Statistical analysis

In analyses of the phase 2 randomised trial of leuprorelin in patients with SBMA that were done 6 months after the last patient completed the trial, the standard deviation (SD) of pharyngeal barium residue was 9·34% and the standardised difference was −3·8%. We calculated that a sample size of 76 patients per group would provide 80% power to detect a −3·8% difference for pharyngeal barium residue between treatment groups (two sample *t* test), with a two-sided α level of 0·10 and an SD of 9·34% in both groups. We chose this α level on the basis of advice from the Japanese regulatory authority during our planning of the trial, which took into consideration the severity and rarity of SBMA. There is no effective treatment or established outcome measure for this disease; therefore the regulatory authority used the International Conference on Harmonization E9 guideline statement[33] that alternative values to the conventional level of type I error (5%) might be acceptable in some cases. The number of patients needed was estimated to be 85 per group (total 170 patients) to allow for dropouts. All patients who were randomised and who were assessed with videofluorography at least once were included in the analyses. Patients who discontinued treatment prematurely were encouraged to attend assessments, and the results of these assessments were used for efficacy analyses; we used the last-observation-carried-forward method to impute values that were not available at the final assessment.

The primary endpoint was assessed by use of the two sample *t* test. We used analysis of covariance to adjust for baseline differences of the respective covariates.[34] For the secondary endpoints, we used the two sample *t* test and the Wilcoxon rank sum test to calculate the differences between the groups. We noted adverse events and other safety information (laboratory tests and bone mineral density) for safety analyses. Each adverse event was coded to a preferred term and associated organ system according to an established and validated adverse reaction dictionary (MedDRA/J,

version 11.0). The endpoints for adverse events were the number of patients with at least one event or an event under each recorded preferred term.

We also investigated the efficacy of leuprorelin in a prespecified subgroup analysis of patients who had a disease duration of less than 10 years, because previous studies have suggested that motor function in patients with SBMA is inversely associated with disease duration.[5,29,35] The cutoff of 10 years was chosen because the mean disease duration was 11·9 years in the previous phase 2 randomised controlled trial[15] and the median duration from the onset of weakness to death was about 20 years in a large retrospective study on the natural history of SBMA.[5] All primary and secondary endpoints were assessed in the subgroup analyses and differences between groups were calculated by use of the two sample *t* test and the Wilcoxon rank sum test.

Statistical analyses were done using SAS (version 9.1.3). Two-sided p values less than 0·05 were deemed statistically significant. This study is registered in the JMACCT clinical trials registry, number JMA-IIA00009 and the UMIN clinical trials registry, number UMIN000000465.

Role of the funding source

The sponsors of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report. All authors had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results

204 patients were randomly assigned to leuprorelin or placebo (figure 1). 199 received at least one dose of the study drug (100 received leuprorelin, 99 placebo). 196 patients completed 48 weeks of treatment; two patients in the leuprorelin group refused to participate and two withdrew consent, and three patients in the placebo group refused to participate and one had no primary endpoint data. Demographics and baseline characteristics were similar between the two groups (table 1), except for barium residue after piecemeal deglutition (p=0·013). To examine the reliability of outcome measures and the effects of serum testosterone concentrations on these measures, we did cross-sectional analyses of the baseline data. ALSFRS-R score was associated with the duration of disease (p<0·0001), 6MWT (p<0·0001), modified QMG score (p<0·0001), ALSAQ-5 (p=0·0057), and pharyngeal barium residue (after initial swallowing p=0·0278; after piecemeal deglutition p=0·0409; webappendix p 3). However, the pretreatment serum concentrations of testosterone were not significantly associated with outcome measures of motor or swallowing function.

In the leuprorelin group, one patient's testosterone concentration was accidentally measured at week 48 on site and two investigators noticed the result. After the incident, the record was deleted from the hospital database and other investigators examined this patient.

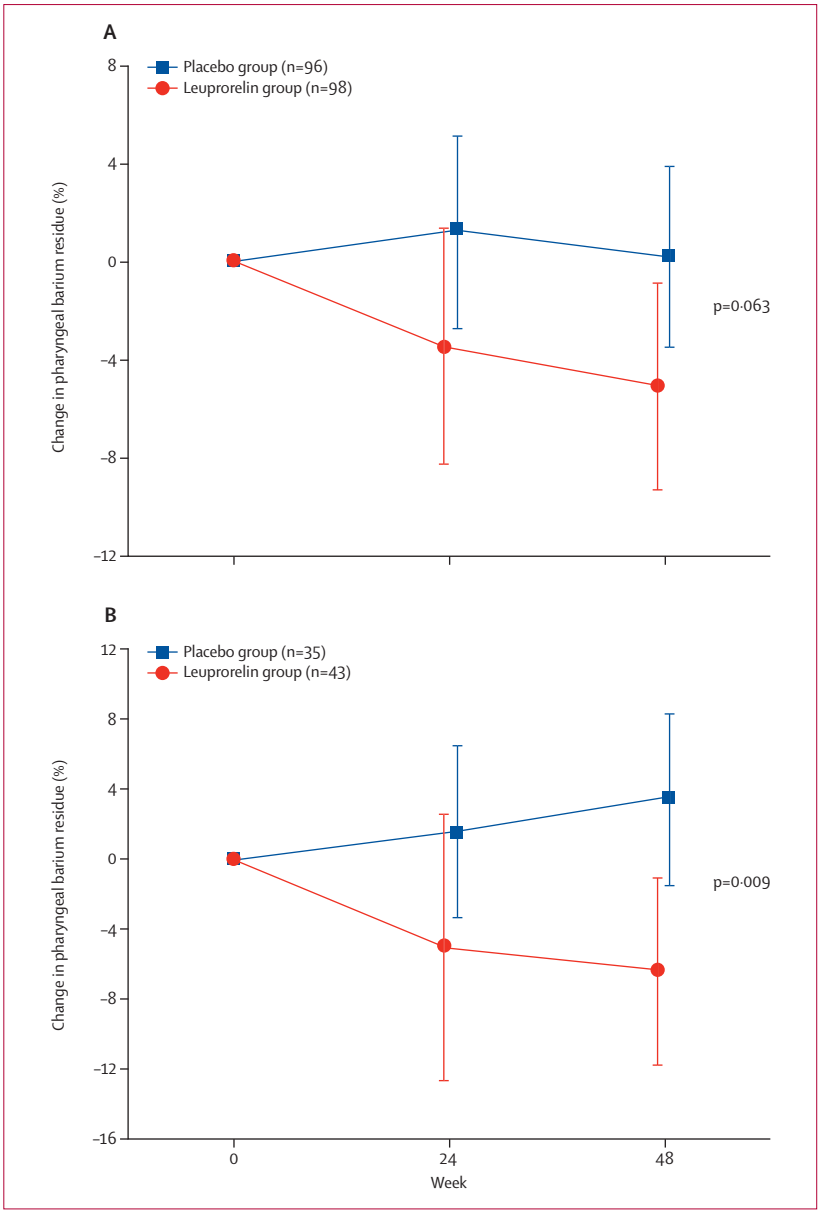

Figure 2: **Mean change in pharyngeal barium residue after initial swallowing**
(A) All patients. (B) Patients with disease duration <10 years. Bars=95% CI.

The two investigators who knew the concentration of testosterone had no contact with the patient and did not reveal the result until the end of the statistical analyses, to keep other investigators and the patient masked to treatment allocation.

At week 48, the difference in pharyngeal barium residue after initial swallowing between the leuprorelin group and the placebo group was –5·3% (95% CI –10·8 to 0·3; 90% CI –9·92 to –0·60; p=0·063; table 2; figure 2). The difference in pharyngeal barium residue after piecemeal deglutition was –3·2% (95% CI –6·4 to 0·0; 90% CI –5·89 to –0·52; p=0·049), but there was no

	Leuprorelin (n=100)		Placebo (n=99)	
	Patients	Events	Patients	Events
Any	76	380	77	273
Nasopharyngitis	36	55	32	41
Pharyngitis	5	5	3	4
Dizziness	5	7	1	1
Headache	7	8	3	3
Hot flush	10	10	2	3
Upper respiratory tract inflammation	4	5	6	6
Constipation	10	11	5	6
Gastritis	4	4	5	5
Abnormal hepatic function	6	6	3	3
Arthralgia	8	10	3	3
Back pain	8	10	10	11
Myalgia	5	5	3	3
Injection site induration	7	11	5	8
Increased blood triglycerides	5	5	2	2
Contusion	13	16	4	6
Post-procedural haemorrhage	3	3	6	6

Table 3: **Adverse events reported in at least 5% of patients in either group, irrespective of cause**

significant difference between the groups after covariate adjustment for baseline data (95% CI –4·09 to 1·62; 90% CI –4·13 to 0·59; p=0·392).

There were significant differences between the groups for the mean change in frequency of 1C2-positive cells (p<0·0001), the mean change in serum creatine kinase concentrations (p=0·006), and the mean change in ALSAQ-5 score (p=0·033; table 2). For the other secondary outcomes, no significant differences were seen between the groups at week 48. In patients who received leuprorelin, mean serum testosterone concentration decreased from 7·8 (SD 3·0) ng/mL to 0·3 (0·2) ng/mL in the first 12 weeks. Mean serum testosterone concentration at week 48 was 0·5 (1·3) ng/mL in the leuprorelin group compared with 7·6 ng/mL in the placebo group (2·7; p<0·0001).

Drug treatment was well tolerated and the incidence of adverse events was similar between the groups (76% in the leuprorelin group and 78% in the placebo group; table 3). There were no significant differences between the groups for drug-related adverse events (57 of 100 in the leuprorelin group and 54 of 99 in the placebo group; p=0·727). Six patients had serious adverse events that required admission to hospital: four in the placebo group (contusion, gastrointestinal neoplasm, dyspnoea, and foot fracture) and two in the leuprorelin group (dyspnoea and neoplasm). The drug-related adverse event hot flush was seen more often in the leuprorelin group compared with the placebo group (p=0·03). Although bone mineral density decreased by 6% in the leuprorelin group (data not shown), there were no marked exacerbations compared with previous reports of leuprorelin treatment (3–6%).[36–38] No drug-related adverse events were reported as the reason for treatment withdrawal.

In patients with disease duration less than 10 years, the baseline characteristics did not differ between the leuprorelin and placebo subgroups (table 1), except for barium residue after piecemeal deglutition (p=0·011) and serum creatine kinase (p=0·028). The mean difference in pharyngeal barium residue after initial swallowing between the groups was –9·8% (95% CI –17·1 to –2·5; p=0·009; table 4; figure 2). This difference was significant after covariate adjustment for the baseline data (p=0·037), although there was no significant difference between the patients included in the subgroup analysis and patients with a disease duration of 10 years or more for this endpoint by test for interaction (p=0·210). In a test of interaction, quality of life seemed to be less affected by leuprorelin in patients with a disease duration of less than 10 years than in those with a disease duration of 10 years or more (p=0·075). Secondary endpoints did not differ between groups in this subgroup analysis, except for the frequency of 1C2-positive cells (between-group difference –15·5, 95% CI –21·4 to –9·6; p<0·0001; table 4).

Discussion

Pharyngeal barium residue after piecemeal deglutition decreased by 1·6% between baseline and week 48 in the leuprorelin group and increased by 1·7% in the placebo group. Although this finding suggests that leuprorelin might improve swallowing function, the change in this primary outcome measure was not significant after covariate adjustment for the difference in baseline data between groups. Pharyngeal barium residue after initial swallowing also seemed to decrease in the leuprorelin group, but no significant difference was detected between the groups. Among the secondary outcome measures, the frequency of 1C2-positive cells and the serum concentrations of creatine kinase decreased by more in the leuprorelin group than in the placebo group, but we did not observe any significant differences in the temporal parameters of videofluorography, ALSFRS-R, 6MWT, or the modified QMG score. The ALSAQ-5 score showed a greater increase in patients in the leuprorelin group than in those in the placebo group. There was no difference in adverse events between the groups except for hot flush, which was more common in the leuprorelin group, and all of the drug-related adverse events had already been documented in the treatment of prostate cancer with leuprorelin.[19] No drug-related adverse effects were given as reasons for patients withdrawing from the study.

The results of all of the previous clinical trials that are relevant to this study are summarised in table 5. Phase 2 trials of leuprorelin reported a decreased frequency of 1C2-positive cells in scrotal skin, reduced serum concentrations of creatine kinase, and extended cricopharyngeal opening in patients with SBMA who were treated with leuprorelin compared with those given

placebo, together with a high tolerability.[15] The present study confirmed that leuprorelin treatment reduces accumulation of the pathogenic androgen receptor proteins and reduces serum concentrations of creatine, a marker of SBMA. We also confirmed that leuprorelin was well tolerated in patients with SBMA, but we were unable to verify the previous observation that leuprorelin extends the duration of cricopharyngeal opening.[15] This discrepancy might be because the phase 2 trial included only 50 patients in total and therefore the positive result could have been due to chance. The result of the previous trial should also be interpreted with caution because the duration of cricopharyngeal opening seemed to differ between the treatment groups at baseline.[15]

Several factors probably contribute to the absence of a significant effect of leuprorelin on the primary endpoint in our study. First, the videofluorography parameters we chose might not have been sensitive enough. Although standard videofluorography parameters for outcome measures in clinical trials have not been formally established, pharyngeal barium residue better represents overall swallowing function than do other temporal measurements.[23,41] Moreover, analyses of baseline data suggest a weak association between ALSFRS-R and the pharyngeal barium residue after initial swallowing. However, our data suggest that pharyngeal barium residue is highly variable between patients, which leads to a decreased sensitivity in the detection of disease-modifying effects of leuprorelin. Furthermore, in piecemeal deglutition—a possible compensatory mechanism against slowly progressive bulbar palsy—patients repeat multiple swallows and thus pharyngeal residue might be measured after each swallow, leading to multiple measurements for one patient; in this situation, the decision of which residue to quantify can vary among investigators. This suggests that the method of examination and evaluation of pharyngeal barium residue should be improved if it is to be used as the primary endpoint in future multicentre clinical trials. Specifically, calculation of the mean value of repetitive measurements or development of effective quantification methods might provide more accurate measurements.

Second, the antianabolic effects of leuprorelin might interfere with the improvement of motor function in patients with SBMA. Although a previous study reported a potential risk of androgen deprivation treatment for patients with SBMA because of an association between muscle strength and serum testosterone concentrations,[35] in our study, none of the baseline values for outcome measures were associated with hormone concentrations. Therefore, the balance between potential neuroprotection by leuprorelin and negative effects on muscles caused by androgen deprivation should be investigated in future studies.

Third, 48 weeks might not be long enough to assess the therapeutic effects of leuprorelin in SBMA. The neuromuscular symptoms of this disease progress for 15–20 years and thus the power of short-term trials is probably limited.[5] Patients who completed this double-blind trial will be followed up for 96 weeks in an open-label study. Trials with a longer follow-up period would be of benefit, but such studies could face problems such as poor patient recruitment and financial support.

Fourth, the disease duration of the patients might have influenced the results. Although we excluded patients with severe disease, the period from disease onset ranged from 4 months to 38 years in the enrolled patients. A disease-modifying treatment that prevents the accumulation of abnormal proteins might be more powerful before downstream molecular events have

	n	Baseline	48 weeks	Difference	Between-group difference (95% CI)	p value*
Primary endpoint						
Pharyngeal barium residue after initial swallowing (%)						
Leuprorelin	43	21·5 (28·9)	15·1 (23·4)	−6·4 (17·4)	..	..
Placebo	35	12·0 (20·2)	15·4 (22·4)	3·4 (14·2)	−9·8 (−17·1 to −2·5)	0·009
Pharyngeal barium residue after piecemeal deglutition (%)						
Leuprorelin	42	9·6 (10·7)	9·1 (14·5)	−0·6 (12·3)	..	..
Placebo	35	4·4 (4·7)	7·4 (10·3)	2·9 (8·6)	−3·5 (−8·4 to 1·4)	0·16†
Secondary endpoints						
Duration of cricopharyngeal opening (s)						
Leuprorelin	43	0·42 (0·07)	0·45 (0·09)	0·03 (0·07)	..	..
Placebo	36	0·44 (0·10)	0·46 (0·09)	0·02 (0·07)	0·01 (−0·02 to 0·04)	0·59
Stage transition duration (s)						
Leuprorelin	43	0·11 (0·15)	0·18 (0·20)	0·08 (0·17)	..	..
Placebo	36	0·09 (0·13)	0·12 (0·16)	0·04 (0·14)	0·04 (−0·03 to 0·11)	0·26
Laryngeal elevation duration (s)						
Leuprorelin	43	0·25 (0·12)	0·21 (0·08)	−0·05 (0·11)	..	..
Placebo	36	0·28 (0·16)	0·27 (0·14)	−0·02 (0·14)	−0·03 (−0·09 to 0·03)	0·28
ALSFRS-R score						
Leuprorelin	44	42·2 (2·6)	42·2 (2·9)	0·1 (2·7)	..	..
Placebo	37	42·5 (3·3)	42·4 (2·8)	0·0 (2·6)	0·1 (−1·1 to 1·3)	0·87
6MWT (m)						
Leuprorelin	44	378·4 (109·1)	363·5 (115·9)	−14·8 (52·2)	..	..
Placebo	37	372·2 (111·9)	362·7 (114·9)	−9·5 (53·0)	−5·3 (−28·7 to 18·0)	0·65
Modified QMG score						
Leuprorelin	44	6·5 (2·8)	6·0 (2·9)	−0·5 (1·9)	..	..
Placebo	37	5·6 (2·7)	5·6 (2·6)	0·0 (1·5)	−0·5 (−1·3 to 0·3)	0·19
ALSAQ-5 score						
Leuprorelin	44	9·8 (3·4)	10·4 (3·7)	0·6 (3·1)	..	..
Placebo	37	9·6 (4·1)	10·2 (3·7)	0·5 (3·0)	0·1 (−1·3 to 1·4)	0·94
1C2-positive cells (%)						
Leuprorelin	44	22·0 (16·4)	9·0 (8·2)	−13·0 (13·7)	..	..
Placebo	36	19·5 (12·8)	22·0 (15·3)	2·5 (12·6)	−15·5 (−21·4 to −9·6)	<0·0001‡
Creatine kinase (IU/L)						
Leuprorelin	44	765·8 (488·7)	666·9 (426·3)	−98·9 (242·1)	..	..
Placebo	36	1031·1 (535·8)	993·5 (602·9)	−37·6 (25·6)	−61·3 (−174·5 to 51·8)	0·28

Data are mean (SD). ALSFRS-R=revised amyotrophic lateral sclerosis functional rating scale. 6MWT=6-min walk test. QMG=quantitative myasthenia gravis score. ALSAQ=amyotrophic lateral sclerosis assessment questionnaire. *Two sample *t* test. †Wilcoxon rank sum test p=0·022. ‡Wilcoxon rank sum test p<0·0001.

Table 4: **Subgroup analyses in patients with disease duration <10 years**

	Patients	Interventions	Follow-up	Outcomes	Results	Quality rating*
Banno et al, 2006[8]						
Open-label single-site trial	5 patients with SBMA. Patients with desire to father a child were excluded	3·75 mg leuprorelin or placebo every 4 weeks	24 weeks	Serum creatine kinase and testosterone; mutant androgen receptor accumulation in scrotal skin biopsy	Decrease of mutant androgen receptor accumulation, serum creatine kinase, and testosterone	1
Banno et al, 2009[15]						
Randomised, placebo-controlled, single-site trial	50 patients with SBMA. Patients who were younger than 30 years, older than 70 years, or with desire to father a child were excluded	3·75 mg leuprorelin or placebo every 4 weeks	48 weeks	ALSFRS-R; serum creatine kinase, testosterone, aspartate aminotransferase, and alanine aminotransferase; mutant androgen receptor accumulation in scrotal skin biopsy; videofluorography parameters (duration of cricopharyngeal opening, pharyngeal delay time, pharyngeal barium residue, duration of maximal laryngeal elevation); lung function	No improvement in ALSFRS-R; extension of duration of cricopharyngeal opening; decrease of mutant androgen receptor accumulation, serum creatine kinase, and testosterone	5
Open-label, single-site follow-up trial	49 participants with SBMA who had participated in 48-week randomised controlled trial	12·25 mg leuprorelin every 12 weeks or no treatment	96 weeks	ALSFRS-R; videofluorography parameters (duration of cricopharyngeal opening, pharyngeal delay time, pharyngeal barium residue, duration of maximal laryngeal elevation)	Improvements in total and bulbar subscores of ALSFRS-R; extension of duration of cricopharyngeal opening	1
Preisler et al, 2009[39]						
Open-label, single-site trial	8 patients with SBMA. Patients younger than 18 years, older than 65 years, or receiving regular exercise training were excluded	Regular cycling exercise	12 weeks	Maximum oxygen uptake; maximum work capacity; activities of daily living; muscle morphology; citrate synthesis activity; body composition; electromyogram; static strength measurements; lung function; plasma creatine kinase, testosterone, luteinising hormone, follicle-stimulating hormone, prolactin, and albumin	No improvements in activities of daily living or maximum oxygen uptake; increase in maximum work capacity and citrate synthesis activity	1

SBMA=spinal and bulbar muscular atrophy. ALSFRS-R=revised amyotrophic lateral sclerosis functional rating scale. *Jadad scale score (range 0–5).[40]

Table 5: **Summary of relevant clinical trials on spinal and bulbar muscular atrophy, by method**

irreversibly damaged neurons: for example, vaccines against amyloid β might be effective in patients with presymptomatic or early-stage Alzheimer's disease.[42] The results of the subgroup analysis in patients with a disease duration of less than 10 years were not conclusive, and thus the effect of disease duration on outcome measures should be further investigated in clinical trials.

Finally, the extent of decline in motor function in the placebo group was smaller than in previous non-interventional reports.[5,29] Potent placebo-associated improvements have been detected in clinical trials for neurological diseases, including Parkinson's disease, and thus the occurrence of this effect in SBMA would not be surprising. Quantitative data on the natural history of motor functions in patients with this disease will be indispensable for designing future clinical trials.

Similar to a study of leuprorelin in the treatment of prostate cancer,[43] the quality of life score deteriorated in patients treated with leuprorelin in this trial. The mental, emotional, and physical aspects of quality of life are lower in men who have had androgen deprivation treatment, including leuprorelin, probably because of hormonal imbalance and drug-related depression.[19] The decreased quality of life in leuprorelin-treated patients, despite the improvement of pharyngeal barium residue, suggests that factors other than dysphagia, such as depression and loss of libido, can also influence quality of life in patients with SBMA. Although we did not report a significant increase in the frequency of depression in this study, the effects of leuprorelin on quality of life should be taken into account when planning trials of androgen deprivation in SBMA.

48-week treatment with leuprorelin is safe and well tolerated in patients with SBMA. The results of this trial were not definitive and therefore our findings should be validated in other health-care settings and in patients from other ethnic backgrounds. In addition, functional scales with sensitivity to detect disease progression specifically in SBMA should also be developed. The results of this study might contribute to the selection of the outcome measures, observation periods, and inclusion criteria in future clinical trials for patients with SBMA.

Research in context

Systematic review

Studies were identified by searches of Medline (1950 to July, 2010), Embase (1980 to July, 2010), and the Cochrane Central Register of Controlled Trials (*The Cochrane Library* issue 3, 2010) with the search terms "spinal and bulbar muscular atrophy", "spinobulbar muscular atrophy", "bulbospinal muscular atrophy", "bulbospinal neuronopathy", and "Kennedy's disease". Searches were restricted to human studies. All types of trial designs with at least three patients were included. All included clinical trials were assessed for methodological quality—in terms of the randomisation generation, double blinding, and proportion of patients lost to follow-up—with the Jadad scale (range, 0–5; the higher the score, the higher the quality).[40]

Interpretation

This study confirms that leuprorelin reduces accumulation of the pathogenic androgen receptor proteins and serum creatine kinase in patients with spinal and bulbar muscular atrophy, but there was no evidence that leuprorelin extended the duration of cricopharyngeal opening, as reported in the previous phase 2 randomised trial.[15] Neither the 48-week phase 2 randomised trial nor the present study reported a significant improvement of motor function in patients with spinal and bulbar muscular atrophy.

Contributors

MaK, HB, KS, YT, MoK, and GS were members of the steering committee. MaK, HB, KS, and GS were involved in study concept and design, data analysis, and writing of the manuscript. MaK, HB, KS, YT, MoK, IY, HS, MA, MM, IN, KK, SI, KI, HidM, ToY, ST, KH, TS, MN, HirM, FK, YW, KN, AT, TaY, and MU recruited patients, conducted the study, and collected data. YF and FT assessed the data. All authors had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

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Conflicts of interest

HS, HidM, ST, KN, and GS have received research grants from Takeda Pharmaceuticals. KN and GS have received honoraria from Takeda Pharmaceuticals. All other authors have no conflicts of interest.

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