Efficacy and safety of dutasteride in patients with spinal and bulbar muscular atrophy: a randomised placebo-controlled trial

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Summary

Background **Spinal and bulbar muscular atrophy (SBMA) is caused by polyglutamine expansion in the androgen receptor, which results in ligand-dependent toxicity. Animal models have a neuromuscular deficit that is mitigated by androgen-reducing treatment. We aimed to assess the efficacy and safety of the 5α-reductase inhibitor dutasteride in patients with SBMA, and to identify outcome measures for use in future studies of the disease.**

Methods **We undertook a randomised, double-blind, placebo-controlled, single-site clinical trial in ambulatory, symptomatic men with genetically confirmed SBMA. Participants were assigned by random number table to receive dutasteride (0·5 mg per day) or placebo orally for 24 months. Patients and investigators were masked to treatment allocation. The primary outcome measure was quantitative muscle assessment (QMA). The final efficacy analysis included all patients who were compliant with study treatment at 24 months. This trial was registered with ClinicalTrials.gov, NCT00303446.**

Findings **50 men were randomly assigned to treatment groups (25 dutasteride, 25 placebo), and 44 were included in the efficacy analysis (21 dutasteride, 23 placebo). At 24 months, the placebo group showed a decrease of 4·5% (–0·30 kg/kg) from baseline in weight-scaled muscle strength as indicated by QMA, and the dutasteride group had an increase in strength of 1·3% (0·14 kg/kg); the difference between groups (5·8%, 95% CI –5·9 to 17·6; p=0·28) was not significant. Prespecified secondary outcome measures of creatine kinase, muscle strength and function, motor nerve conduction, activities of daily living, and erectile function did not show a significant difference between the study groups in change from baseline. Quality of life, as measured by the physical component summary of the Medical Outcomes Study 36-item Short Form version 2, favoured dutasteride (change in score from baseline: placebo, –3·6%, *vs* dutasteride, 2·1%; p=0·01), whereas the mental component summary favoured placebo (3·3% *vs* –3·2%; p=0·03). The dutasteride group had fewer patients reporting falls than did the placebo group (9 *vs* 16; p=0·048); there were no other significant differences in reported adverse events.**

Interpretation **Our study did not show a significant effect of dutasteride on the progression of muscle weakness in SBMA, although there were secondary indications of both positive and negative effects compared with placebo. A longer trial duration or larger number of patients might be needed to show an effect on disease progression. Performance testing, QMA, and quality of life measures were identified as potentially useful endpoints for future therapeutic trials.**

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Introduction

Spinal and bulbar muscular atrophy (SBMA; Kennedy's disease) is an uncommon neurodegenerative disease that is characterised by muscle weakness.[1] The disease is progressively disabling and can be fatal. There is currently no effective treatment. In addition to bulbar and extremity muscle weakness, patients with SBMA can have manifestations of androgen insensitivity.[2] The cause of SBMA is a repeat expansion in the androgen receptor gene, which results in a toxic gain of function in the receptor protein and leads to a loss of spinal and bulbar motor neurons.[3]

The toxic effects of the mutant androgen receptor in SBMA depend on androgens. This ligand dependence is shown by prevention of the SBMA phenotype with castration in male transgenic mice and by induction of the phenotype in female mice with androgen administration.[4] These findings led to recent randomised clinical trials of leuprorelin, which reduces androgen concentrations. At 48 weeks, leuprorelin was associated with significantly improved swallowing function in a phase 2 study,[5] but not in a subsequent phase 3 trial.[6]

Inhibitors of 5α-reductase have not been tested before in SBMA. These agents block the conversion of the androgen testosterone to dihydrotestosterone[7] and offer the opportunity to decrease the toxic effects of dihydrotestosterone while sparing the anabolic effects of testosterone. We investigated the safety and efficacy of the 5α-reductase inhibitor dutasteride in patients with SBMA. Another aim of this study was to evaluate outcome measures for future studies of the disease.

Methods

Patients

We undertook a randomised, double-blind, placebo-controlled, single-site study at the National Institutes of Health (NIH) Clinical Center in Bethesda, MD, USA. Patients with SBMA were recruited between May and November, 2006, with the help of a patient organisation, the Kennedy's Disease Association. Inclusion criteria were genetically confirmed SBMA with neurological symptoms, ability to walk 100 feet (30 m), willingness to participate in the trial design, and male sex. Exclusion criteria were: age less than 18 years; female sex; history of hypersensitivity to dutasteride or 5α-reductase inhibitors; exposure to 5α-reductase inhibitors, antiandrogens, testosterone, or steroids in the preceding 6 months; history of taking potent CYP3A4 inhibitors for longer than 4 weeks; any pre-existing liver disease; serum alkaline phosphatase, γ-glutamyl transferase, or direct bilirubin greater than 1·5 times the upper limit of normal; serum transaminases greater than 1·5 times the upper limit of normal in patients with normal creatine kinase concentrations; creatinine greater than 1·5 times the upper limit of normal; platelet count, white blood cell count, or haemoglobin below the lower limit of normal; and other clinically significant medical disease that, in the judgment of the investigators, would expose the patient to undue risk of harm or prevent the patient from completing the study.

The National Institute of Neurological Disorders and Stroke (NINDS) institutional review board and a data and safety monitoring board approved and oversaw the study, and all patients gave written informed consent before enrolment.

See Online for webappendix

Randomisation and masking

Patients were assigned to treatment groups by use of a random number table in blocks of four or six patients by the NIH Clinical Center Pharmacy, which dispensed dutasteride or placebo according to the patient's enrolment number. Dutasteride and placebo were identical in appearance and taste. The patients were enrolled by CJC and NADP, who remained masked to the assignment and hormone concentrations, as were the patients and their families and all those who collected the data and did the final analysis.

Procedures

A comprehensive report of the baseline data for this study has been published elsewhere.[8] Patients received either 0·5 mg per day of dutasteride or placebo orally for 24 months between May, 2006, and November, 2008. There was no open-label extension. All patients had physical, respiratory, and speech and swallow therapy evaluations at the NIH Clinical Center. There was no difference between the groups in the evaluations that were done, and no therapy was offered during the course of the study. Primary-care physicians assessed patients between visits to NIH, providing an assessment of general physical health every 3 months during the trial. Patients reported the severity and type of adverse events at each visit. Patients were given supplies of study drug at each visit, and compliance was based on residual pill counts.

Quantitative muscle assessment (QMA) was the primary outcome measure. Additional outcome measures included a bulbar strength scale and manual muscle testing, performance testing and 2-min timed walk, self-assessed quality of life, electromyography and nerve conduction studies, and biochemical profiles. After the study started, barium swallow and pulmonary function studies were added. Primary and secondary efficacy outcome measures were evaluated at the initial, 12-month, and 24-month visits.

QMA was done with a fixed frame dynamometer, a strain gauge tensiometer, and a computer-aided acquisition system (Aeverl Medical, Gainesville, GA, USA). Maximal voluntary isometric muscle contractions were measured twice by two experienced examiners (EWL and JAS), and the average was calculated. Before the start of the study, QMA procedures were practised for 8–10 h for consistency between examiners, and the testing of ten healthy control individuals matched for age and sex was separate from both the practise and the actual study. Intrarater and inter-rater reliability was high (intraclass correlation coefficient [ICC]=0·93). We standardised QMA by testing the patients at the same time of day and with the same order of muscle group testing, by setting the joint angles with a goniometer, and by zeroing the load cells before each muscle group test.

The bulbar rating scale includes eight domains each rated on a 1–4 scale, abnormal to normal (web-appendix pp 1–2). Previous bulbar assessments were used to tailor the rating scale to SBMA.[9] The original 8–32 point scale was transformed to percentage of maximum score (0–100%).

Three experienced examiners (NADP, CJC, ADK) did manual muscle testing using a modified Medical Research Council scale (webappendix p 3); the average muscle score was based on 22 muscle groups. Muscle performance was measured with the Adult Myopathy Assessment Tool (AMAT), which includes seven timed functional tasks and six endurance tasks (webappendix pp 4–5), with high inter-rater and intrarater reliability (ICCs=0·95–0·98)[10] and correlation with other physical assessments such as QMA, gait speed, and the physical quality of life (Harris-Love and colleagues, unpublished).

Timed walk tests have been used previously in SBMA.[11] In the current study, the patients did a 2-min walk in a 15-m corridor three times, and the distance covered in the third of the three attempts was entered.[12] Patients were allowed to use an assistive device and to rest for up to 2 min between the trials.

At each visit, patients rated their daily activity with a modified nine-question Activities of Daily Living (ADL)

questionnaire (0–4, fully impaired to normal).[13] Patients completed the Medical Outcomes Study Short Form version 2 (SF-36v2; QualityMetric, Lincoln, RI, USA), in which they rated their quality of life over the preceding 4 weeks. We converted raw SF-36v2 scores to norm-based scales (0–100) and physical and mental component summaries using the scoring code provided by QualityMetric (SAS version 9.1.3). Sexual function was rated using the International Index of Erectile Function (IIEF). The total IIEF score (5–75) was reported as the percentage of maximum (0–100%).[14]

SBMA involves sensory as well as motor neurons.[8] Nerve conduction studies were therefore done on four sensory nerves (median, ulnar, radial, and sural) and two motor nerves (median and peroneal) using standard methodology and department-based normal values.[15] Motor unit number estimation (MUNE) was done with a statistical MUNE program, a Nicolet Viking Select machine (Cardinal Health, Dublin, OH), and Shefner modification[16] on the abductor pollicis brevis.[17] All patients were evaluated on the right side unless severe atrophy produced very low compound muscle action potentials (CMAPs), in which case the left side was used or the abductor digiti minimi was substituted.

Blood samples were drawn after overnight fasting. Baseline total and free testosterone testing was done at Mayo Medical Laboratories (Rochester, MN, USA) by high-performance liquid chromatography or tandem mass spectrometry and equilibrium dialysis (reference ranges of 240–950 ng/dL and 9–30 ng/dL, respectively). The 12-month and 24-month assays were done at the NIH Clinical Center Chemistry Department (Bethesda, MD, USA) with a chemiluminescence immunoassay for total testosterone (reference ranges were 262–1593 ng/dL for ages 20–49 years and 181–758 ng/dL for >49 years) and free testosterone calculated based on the total testosterone and albumin levels (reference range was 7·5–22·6 ng/dL). Dihydrotestosterone concentrations were measured by Esoterix (Calabasas Hills, CA, USA). Biochemical panels and blood counts were done by the NIH Clinical Center Chemistry Department.

After the start of the study, an effect on swallowing was reported in another study of leuprorelin in SBMA;[5] as a result of this finding, we opted to include swallowing evaluations in our study. Patients who presented at baseline with complaints of bulbar impairment received initial speech and swallow evaluations (n=15). Modified barium swallow studies were done at 12 and 24 months on all patients. 25 domains were assessed, and six were chosen for final analysis based on the abnormal findings in patients evaluated at baseline. All other domains were within normal range. Abnormal findings included vallecular pooling and repeated swallow, each assessed with thin liquids, purees, and solids. The domains were rated by the speech language pathologist using a Likert rating scale of 1–4 (1=severe difficulty, 2=moderate difficulty, 3=mild difficulty, 4=normal).

After the study started, one patient developed serious respiratory difficulties; as a result, the data and safety monitoring board recommended that we include pulmonary function tests as an additional safety measure. Forced vital capacity (FVC) was measured by respiratory therapists at 12 and 24 months, and the percentage of the reference value was calculated.[18]

Statistical analysis

The number of patients for enrolment was chosen before the start of the study to detect a 50% decrease in the estimated 5% per year rate of reduction in muscle strength. The rate of reduction in muscle strength had not previously been established for SBMA, so the rate was estimated on the basis of clinical experience. A power analysis showed that 20 individuals would be needed for each group to achieve 80% power for a two-

	Placebo (n=25)	Dutasteride (n=25)
Age (years)	53·5 (9·2; 39–71)	51·9 (10·5; 37–79)
CAG repeat length (n)	46·5 (2·0; 44–51)	47·1 (2·8; 43–53)
Duration of weakness (years)	11·4 (7·0; 0·0–28·1)	12·0 (9·4; 1·0–42·2)
Body-mass index (kg/m²)	27·8 (4·1; 22·5–40·6)	28·1 (5·8; 17·3–40·2)

Data are mean (SD; range). Baseline data for outcome measures are reported in tables 3 and 4.

Table 1: **Baseline characteristics**

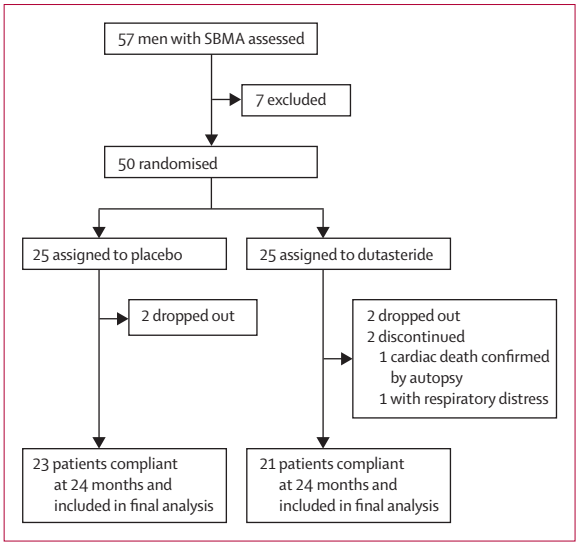

Figure 1: **Trial profile**

Four patients dropped out of the study in the first 6 months because of difficulties in travelling to the National Institutes of Health from elsewhere in the USA and Canada. One patient died between his 3-month and 6-month visits; an autopsy was consistent with a cardiac cause of death. One patient developed respiratory distress and his health declined rapidly during his 6 months of enrolment. He was removed from the study and admitted to hospital until his vital capacity and symptoms stabilised. No other cause for his respiratory failure was identified. His health subsequently continued to decline and he died about a year later. Thus, whereas the safety analysis included 25 patients in each group, the efficacy analysis at 24 months was done on 23 patients in the placebo group and 21 in the dutasteride group. SBMA=spinal and bulbar muscular atrophy.

	Placebo		Dutasteride		p value
	Mean (SD)	n	Mean (SD)	n	
Total testosterone (ng/dL)					
Baseline	627 (181)	25	625 (329)	25	..
12 months	497 (226)	23	602 (299)	21	..
24 months	542 (192)	23	566 (241)	21	0·77
Free testosterone (ng/dL)					
Baseline	14·5 (4·8)	25	13·2 (5·2)	25	..
12 months	10·5 (3·7)	23	11·5 (6·2)	21	..
24 months	10·0 (3·0)	23	9·8 (4·1)	21	0·68
Dihydrotestosterone (ng/dL)					
Baseline	44·6 (18·4)	25	45·7 (31·6)	25	..
12 months	44·2 (23·3)	23	5·3 (2·3)	21	<0·0001
24 months	41·8 (19·1)	23	5·3 (3·2)	21	<0·0001

p values shown for total and free testosterone are for the comparison of the placebo and dutasteride groups during the study (baseline to 12 and 24 months) on the basis of generalised estimating equation models; p values for dihydrotestosterone are for the comparison of the groups at 12 and 24 months by *t* test.

Table 2: **Hormone profile of patients during the study**

	Placebo		Dutasteride		Difference between groups (95% CI)	p value
	Mean (SD)	n	Mean (SD)	n		
Weight-scaled total force (kg/kg)						
Baseline	4·06 (1·39)	25	3·42 (1·77)	25	0·64 (–0·26 to 1·55)	..
12 months	3·90 (1·26)	22	3·60 (1·80)	21	0·30 (–0·64 to 1·26)	..
24 months	3·76 (1·31)	23	3·56 (1·75)	21	0·20 (–0·73 to 1·14)	0·19
Percentage change in weight-scaled total force						
12 months	–2·2% (9·4)	22	3·1% (27·1)	21	5·2% (–7·1 to 17·4)	..
24 months	–4·5% (13·5)	23	1·3% (24·2)	21	5·8% (–5·9 to 17·6)	0·28

p values are for comparison of the placebo and dutasteride groups during the study on the basis of generalised estimating equation models. One patient in the placebo group was not assessed at 12 months because of pain from a recent fall. Data for specific muscle groups and composites are shown in webappendix pp 6–9.

Table 3: **Primary outcome measure (quantitative muscle assessment)**

sided *t* test with a 0·05 significance level. To allow for dropout, the target enrolment was 25 individuals per group.

The data and safety monitoring board, which was unmasked to the group assignments, assessed an interim analysis after all patients had completed 12 months of the study. The 12-month values for the primary outcome measure were compared by *t* test. The predetermined plan was to stop the study if the p value was less than 0·005 favouring dutasteride or less than 0·05 favouring placebo. The analysis gave a p value of 0·49 and thus did not meet either of these criteria, and the study was continued until all patients reached the 24-month endpoint. The final analysis of the primary outcome was adjusted for the interim analysis to restrict the chance of falsely recording benefit at either 12 or 24 months to a p value of less than 0·05 overall. The final efficacy analysis included all patients who were compliant with study treatment at 24 months.

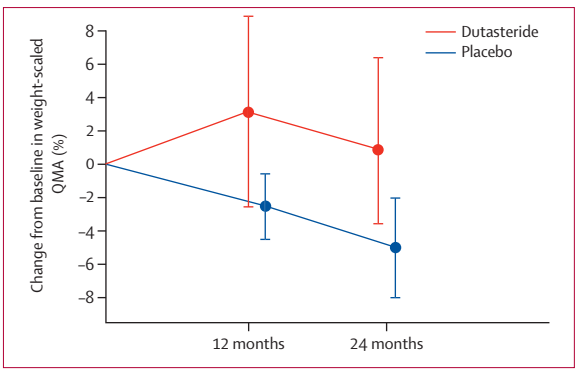

Figure 2: **Percentage change from baseline in the primary outcome measure, quantitative muscle assessment**
The difference between treatment groups was not significant. Bars show standard error of the mean. QMA=quantitative muscle assessment.

Generalised estimating equation (GEE) models were used to examine the effect of the study drug on the percentage change from baseline in weight-scaled QMA total force as well as on the secondary outcome measures. A covariance structure for multiple measurements of change per patient was modelled, to take into account repeated measures of the same patient. The first GEE model contained three predictors: time, treatment, and interaction between time and treatment. Using the first model, we made inferences regarding whether or not rates of change were different between placebo and dutasteride groups. Second, if there was no significant interaction between time and treatment, only the second GEE model containing time and treatment was used to test whether there was a consistent difference between treatment groups. If there was significant interaction between time and treatment, then a two-sample *t* test with Satterthwaite approximation (if necessary) was used at each timepoint.[19]

Descriptive statistics such as mean, SD, and SE were calculated to characterise the outcome measures. χ^2 tests were used to compare the number of patients on placebo and dutasteride who reported adverse events. Paired *t* tests were used to compare timepoints within the placebo group. All p values reported are two-sided. All statistical analyses, including PROC GENMOD for GEE models, were done with SAS software (version 9.1.3).

This trial was registered with ClinicalTrials.gov, NCT00303446.

Role of the funding source

The authors maintained sole control over the study design, execution, analysis, and interpretation. The investigators had free and unrestricted access to the data, and all authors participated in the writing and final decision to submit this work for publication. The sponsor and funding organisation had no role in the writing of the report or the decision to submit for publication.

Results

57 patients were recruited, of whom seven were excluded from the trial because of raised blood liver enzyme concentrations or haemoglobin concentrations below the lower limit of normal. Table 1 summarises the baseline characteristics of the 50 patients randomly allocated to placebo or dutasteride. The treatment groups were balanced with respect to age, CAG repeat length, disease duration, and body-mass index. Six patients did not complete the study (figure 1); the remaining 44 patients were compliant at 24 months and were included in the final analysis. At 12 months, the placebo group took 1 (SD 3) additional capsule and the dutasteride group missed 3 (3) capsules per 100 (p=0·04). At the 24-month visit, the placebo and dutasteride groups missed 1 (3) and 3 (4) pills, respectively; this difference was not significant. Testosterone concentrations were unchanged with dutasteride administration (table 2). Dihydrotestosterone concentrations decreased significantly in the dutasteride-treated group compared with placebo (p<0·0001, table 2), as expected.

Between baseline and 24 months there was a 4·5% average decrease in weight-adjusted total QMA in the placebo group and a 1·3% increase in the dutasteride group (table 3). Because of variability in the outcome, the change from baseline did not differ significantly between the two groups (figure 2). Post-hoc analysis showed no difference between the groups when the patients were separated according to whether their values were greater or less than the median in duration of weakness, age, CAG repeat length, or baseline QMA (webappendix p 10). Similarly, creatine kinase, manual muscle testing, AMAT, timed 2-min walk, bulbar rating scale, sensory nerve action potential amplitudes (SNAPs) of the median, ulnar, radial, and sural nerves, the SNAP average, CMAPs of the median and peroneal nerves, MUNE, ADL, IIEF, and FVC did not show a significant difference between the study groups in change from baseline (table 4, webappendix pp 11–22). Of the four sensory nerves tested for conduction velocity, only the radial nerve showed a difference favouring dutasteride (webappendix pp 11–22). A subset of 15 patients underwent initial barium swallow studies. These patients showed no significant difference between cohorts in their swallow score, which was an average of six domains (table 4).

The SF-36v2 physical component summary (PCS) favoured dutasteride over placebo at 24 months as percentage change from baseline (p=0·004; webappendix p 23) and as absolute change from baseline (p=0·01; table 4). There was a 6% difference at 24 months, with the placebo group falling 4% and the dutasteride group increasing 2% from baseline. Conversely, the mental component summary (MCS) favoured placebo over dutasteride at 24 months (p=0·03; webappendix p 23). The placebo group increased 3% in MCS score, and the dutasteride group fell 3% (table 4).

The only type of adverse event to differ between the groups was falls, for which fewer patients in the dutasteride group reported events than in the placebo group (p=0·048; table 5). Nine adverse events were categorised as serious, five in the placebo group and four in the dutasteride group (webappendix p 24). In the placebo group, two patients were admitted to hospital after falls. In the dutasteride

	Placebo					Dutasteride					Difference in change at 24 months (95% CI)	p value
	Baseline		Change at 24 months*			Baseline		Change at 24 months*				
	n	Mean (SD)	n	Mean (SD)	%	n	Mean (SD)	n	Mean (SD)	%		
Creatine kinase (U/L)	25	1181 (761)	23	−19 (494)	−1·6%	25	1041 (781)	21	−62 (472)	−6·0%	−43 (−338 to 251)	0·86
Manual muscle testing average	25	9·10 (0·75)	23	0·02 (0·74)	0·2%	25	8·68 (1·04)	21	0·01 (0·51)	0·1%	−0·01 (−0·39 to 0·39)	0·47
AMAT total	25	31·2 (8·8)	23	−2·8 (4·2)	−9·1%	25	27·0 (11·5)	21	−1·5 (3·9)	−5·6%	1·3 (−1·2 to 3·8)	0·13
Timed 2-min walk (m)	25	85·4 (37·0)	23	15·2 (30·7)	17·8%	25	77·6 (38·8)	20	26·9 (35·9)	34·6%	11·7 (−8·8 to 32·2)	0·28
Swallow score average	6	3·67 (0·35)	5	−0·53 (0·46)	−14·5%	9	3·69 (0·37)	7	−0·14 (0·54)	−3·8%	0·39 (−0·28 to 1·06)	0·11
Bulbar rating scale (%)	25	89·8% (6·5)	23	6·4% (5·8)	7·1%	25	91·2% (7·0)	21	3·9% (4·6)	4·2%	−2·5% (−5·7 to 0·7)	0·08
SNAP average (μV)	25	4 (3)	23	0 (1)	0·0%	25	4 (2)	21	0 (1)	0·0%	0 (−0·7 to 0·5)	0·73
Median CMAP (mV)	25	7·23 (2·37)	22	−0·23 (1·84)	−4·1%	25	5·28 (3·52)	21	0·24 (1·89)	4·6%	0·48 (−0·67 to 1·63)	0·37
Peroneal CMAP (mV)	25	3·18 (1·72)	22	0·15 (1·37)	6·8%	25	2·44 (2·32)	21	0·04 (0·81)	1·6%	−0·11 (−0·80 to 0·59)	0·65
MUNE (n)	25	48·4 (20·8)	23	−2·2 (23·3)	−4·4%	25	40·0 (24·1)	19	−2·6 (17·5)	−7·0%	−0·4 (−13·5 to 12·8)	0·99
Activities of Daily Living total	24	26·3 (4·1)	22	1·2 (3·3)	4·4%	25	25·5 (6·1)	21	1·1 (4·2)	4·4%	−0·1 (−2·3 to 2·3)	1·00
SF-36v2 PCS (%)	24	35·2% (9·9)	22	−3·6% (8·4)	−10·3%	24	34·0% (12·8)	21	2·1% (6·1)	6·3%	5·7% (1·2 to 10·3)	0·01
SF-36v2 MCS (%)	24	50·9% (12·7)	22	3·3% (9·3)	6·5%	24	52·4% (11·1)	21	−3·2% (10·2)	−6·2%	−6·5% (−12·6 to −0·5)	0·03
IIEF (%)	24	47·6% (38·3)	20	−0·3% (16·4)	−9·5%	25	43·9% (37·8)	21	−3·5% (6·9)	−11·4%	−3·2% (−11·1 to 4·6)	0·61

Additional biochemical tests and subscores for secondary outcome measures can be found in webappendix pp 11–22. p values are for comparison of placebo and dutasteride groups during the study on the basis of generalised estimating equation models. AMAT=Adult Myopathy Assessment Tool. SNAP=sensory nerve action potential. CMAP=compound muscle action potential. MUNE=motor unit nerve estimation. SF-36v2=Medical Outcomes Study 36-item Short Form version 2. PCS=physical component summary. MCS=mental component summary. IIEF=International Index of Erectile Function. *Mean and percentage change from baseline to 24 months within the study group.

Table 4: **Secondary measures of efficacy**

	Placebo (n=25)	Dutasteride (n=25)	p value
Bone fractures	4 (5)	3 (3)	0·684
Diarrhoea	0	3 (9)	0·074
Dyspepsia	1 (1)	3 (5)	0·297
Falls	16 (63)	9 (40)	0·048
Fatigue	1 (2)	4 (11)	0·157
Gastrointestinal	6 (8)	4 (6)	0·480
Headache	9 (27)	11 (35)	0·564
Muscle cramps	5 (12)	5 (10)	1·000
Muscle weakness	4 (6)	2 (3)	0·384
Myalgia	5 (21)	4 (17)	0·713
Numbness	4 (5)	6 (8)	0·480
Other infections	4 (6)	1 (1)	0·157
Pain	10 (33)	9 (23)	0·771
Shortness of breath	0	3 (3)	0·074
Upper respiratory infections	12 (33)	14 (32)	0·571

Data are the number of patients reporting each adverse event, with the number of events shown in parentheses. p values are for comparison of the number of patients reporting adverse events on placebo and dutasteride, based on χ^2 analysis.

Table 5: **Adverse events reported by more than 10% of patients in either group**

	Rate of decrease*	Paired *t* test, p value†	*Z* score‡
AMAT total	4·5%	0·004	0·68
SF-36v2 PCS	5·2%	0·054	0·43
Weight-scaled QMA	2·3%	0·116	0·34
Median CMAP	1·6%	0·553	0·13
MUNE	2·3%	0·654	0·09
IIEF	0·3%	0·946	0·02

AMAT=Adult Myopathy Assessment Tool. SF-36v2 PCS=physical component summary of the Medical Outcomes Study 36-item Short Form version 2. QMA=quantitative muscle assessment. CMAP=compound muscle action potential. MUNE=motor unit nerve estimation. IIEF=International Index of Erectile Function. *Calculated as the mean percentage change per year in the placebo group divided by the mean baseline value for the placebo group. †A paired *t* test was used to assess the significance of the change from baseline to 24 months. ‡Calculated as the absolute value of the mean change from baseline divided by the SD of the change.

Table 6: **Post-hoc analysis of selected outcome measures that showed a reduction in the placebo group between baseline and 24 months**

group, one patient died with autopsy-confirmed hypertensive and arteriosclerotic cardiovascular disease, and another developed serious respiratory difficulties and discontinued the study drug (figure 1).

Biochemical profiles showed only minor differences between the groups (webappendix pp 11–22). There was a relative increase in γ-glutamyl transferase in the dutasteride group compared with placebo, although the mean value after 24 months (33 [SD 21] U/L) was still less than the mean reported value in age-matched healthy controls (40 [3] U/L).[20] No differences between the dutasteride and placebo groups were seen with other liver function tests.

To assess the usefulness of the various outcome measures in characterisation of disease progression, we did a post-hoc analysis of measures that decreased between baseline and 24 months in the 23 patients who completed the study on placebo (table 6). The SF-36v2 PCS showed the greatest rate of reduction at 5·2% per year, followed by the AMAT, which fell at 4·5% per year. Only the AMAT showed a significant fall from baseline at 24 months (p=0·004).

The *Z* score indicates the power of an outcome measure to detect disease progression and can be used to guide the selection of endpoints in future trials. The AMAT score showed less variability than did the other measures, and had the best *Z* score, followed by the SF-36v2 PCS, weight-scaled QMA, and median CMAP (table 6). The slow rate of reduction in QMA is such that a study would have to run for much longer to detect a 50% benefit in a randomised clinical trial. By contrast, the AMAT and SF-36v2 PCS would require a shorter study period to detect a beneficial effect on disease progression.

In the five patients who received placebo and for whom barium swallow studies were done at baseline, there was a 7·2% per year fall in the average score from baseline to 24 months (table 4). A 2·4% decrease was seen also in the 21 patients taking placebo who were followed up from 12 to 24 months only (12 months, mean 3·44 [SD 0·70]; 24 months, 3·29 [0·65]).

Discussion

In our study, dutasteride had no significant effect on muscle strength at 2 years' follow-up. Several findings implicating androgens in SBMA provided the rationale for the study. First, dihydrotestosterone caused neurodegeneration in a fly model of SBMA.[21] Second, male transgenic mice developed progressive weakness, whereas female mice were comparatively unaffected; furthermore, motor function improved in the male mice with androgen reduction, and their female counterparts developed weakness with androgen administration.[4,22] Third, two sisters who were homozygous for the androgen receptor repeat expansion had only mild manifestations of the disease, suggesting that SBMA in human beings as in mice is limited to males, presumably because of their higher androgen concentrations.[23] Together, these findings provided impetus for testing of androgen-reducing therapy in SBMA.

Leuprorelin has shown benefit in mouse models of SBMA, and more recently has had some indications of efficacy in patients.[5] Leuprorelin decreases testicular testosterone production. Dutasteride offers a more selective approach to androgen reduction: differential expression of 5α-reductase in skeletal muscle and motor neurons suggests that dihydrotestosterone might be the primary ligand for the androgen receptor in motor neurons, whereas testosterone serves this role in skeletal muscle.[24,25] Thus, suppression of dihydrotestosterone production should decrease the toxic activation of the mutant androgen

receptor in motor neurons without disrupting the beneficial anabolic action of testosterone in muscle.

In our study, dihydrotestosterone concentrations decreased substantially in the dutasteride group, indicating an appropriate pharmacological effect. QMA, an outcome measure previously used in studies of amyotrophic lateral sclerosis and muscular dystrophy,[26] did not show a significant difference at 12 or 24 months between the study groups. There was no open-label extension, which might have given an indication of a longer term effect, albeit without a blinded control group for comparison. In retrospect, this study was underpowered. In view of the slow progression of weakness in the placebo group, more time or a larger number of patients might be needed to show a decrease in the rate of progression with QMA. Of the secondary measures, AMAT and SF-36v2 PCS might be better for use in future trials.

Analysis of the SF-36v2 PCS and MCS revealed positive and negative effects. Patients receiving dutasteride had an increase in PCS scores at 24 months, whereas PCS scores for the placebo group decreased. By contrast, MCS scores for the dutasteride group at 24 months showed a decrease from baseline, whereas placebo MCS scores increased. Other self-assessed parameters, including ADL and IIEF, did not show a significant difference.

Dysphagia is an important source of morbidity in SBMA. The six barium swallow measures assessed here represent the common areas of difficulty in this population. The average swallow score did not show a significant difference at 12 or 24 months. However, we were unable to draw a clear conclusion from this subset because of selection bias. In the phase 2 leuprorelin trial, Banno and colleagues[5] reported increased cricopharyngeal opening time with leuprorelin. However, a later phase 3 study[6] did not confirm a significant effect on swallow function.

Dutasteride was generally well tolerated in our population, with a low dropout rate and high compliance. There was a difference in the number of patients reporting musculoskeletal adverse events, with fewer patients taking dutasteride reporting events in this category. Most of this difference is attributable to falls, which, similar to the findings for SF-36v2 PCS, might suggest a benefit of dutasteride that was not detected as significant with QMA and the other secondary measures. In other studies, the most common adverse effects of dutasteride included impotence and decreased libido;[27] these effects might have contributed to the lower MCS scores in the dutasteride group compared with the placebo group.

The data obtained in this trial provide an indication of the rate of decline in various measures during 24 months in a placebo group. The SF-36v2 PCS, AMAT, and swallow scores showed the greatest percentage reduction per year. These data can be used in future trials of other drugs, such as HSP90 inhibitors,[28] ASC-J9,[29] and IGF-1,[30] which have been shown to improve motor function in mouse models.

The finding that dutasteride had no significant effect on muscle strength as measured by QMA after 24 months probably reflects the complex role of androgens in SBMA as well as the sensitivity of the test. Whereas androgens contribute to the toxic effects of the mutant androgen receptor in mouse models of SBMA, high blood androgen concentrations were correlated with increased muscle strength in a cross-sectional study of this patient population.[8] On the basis of these results, we do not currently recommend dutasteride as treatment for SBMA. Nevertheless, there are indications of potential benefit that point to the need for further investigation of androgen-lowering therapy. Our study contributes to the understanding of SBMA (panel) and suggests that future clinical trials need to take into account the rate of decline and use clinically meaningful outcome measures that can reliably predict a therapeutic benefit.

***Panel:* Research in context**

Systematic review

A review of the literature with PubMed was done from 1947 to December, 2010, with the search terms "Kennedy's disease", "spinal and bulbar muscular atrophy", "spinal bulbar muscular atrophy", "spinobulbar muscular atrophy", and "bulbospinal muscular atrophy", and limited to human studies and clinical trials. This review shows only two previously published randomised, placebo-controlled therapeutic trials in patients with spinal and bulbar muscular atrophy (SBMA), both investigating the androgen-reducing agent leuprorelin.[5,6] The first study did not show a benefit in the primary measure of muscle function, but suggested efficacy in a secondary measure of swallow function. The second, larger study did not find a significant effect on swallow function or muscle function.

Interpretation

Our study, which is the third randomised, placebo-controlled trial to be reported, investigated another androgen-reducing agent with a different mechanism of action, dutasteride. Again there was no significant effect on the change in muscle strength during a 2-year period, although there were indications of efficacy with secondary measures. Taken together, the three trials do not show a significant benefit of androgen-reduction treatment on the loss of muscle strength in SBMA. In all three studies, the rate of progression in the placebo group was slow, suggesting that increases in numbers of patients or length of follow-up might be needed if studies designed to show a significant slowing in the progression of muscle weakness are to be adequately powered.

Contributors

LEFR was involved in the study conduct and data collection. With the guidance of CJC and NADP, ADK was primarily responsible for conducting the study and collecting and preparing the clinical data. LEFR, MJW, SA, and KHF were involved in data interpretation and manuscript preparation. CAW helped with the manuscript preparation. SA and NOJ conducted the statistical analyses. JAS and EWL gathered

the data for the primary outcome measure. TJL, LL, JER, and BIS collected data for the secondary outcome measures. JAS and MOHL were involved in the interpretation of physical functioning outcome data. ALP and ABS facilitated confirmatory genetic testing and served as unmasked facilitators for the interim analysis. CJC, NADP, and KHF were involved in the study concept and design.

Conflicts of interest

ADK owns stock in GlaxoSmithKline. MJW's stipend was paid by a fellowship from the NIH Clinical Research Training Program, which is supported in part by funds paid to the NIH Foundation by Pfizer. NADP is employed by and receives stock options from Johnson and Johnson. KHF serves as an unpaid member of advisory boards for Biogen Idec and Prosensa. All other authors declare that they have no conflicts of interest.

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