Riluzole in patients with hereditary cerebellar ataxia: a randomised, double-blind, placebo-controlled trial

Silvia Romano, Giulia Coarelli, Christian Marcotulli, Luca Leonardi, Francesca Piccolo, Maria Spadaro, Marina Frontali, Michela Ferraldeschi, Maria Chiara Vulpiani, Federica Ponzelli, Marco Salvetti, Francesco Orzi, Antonio Petrucci, Nicola Vanacore, Carlo Casali, Giovanni Ristori

Summary

Background Our previous study in patients with cerebellar ataxias of different causes showed significant benefit of riluzole after 8 weeks. We aimed to confirm these results in patients with spinocerebellar ataxia or Friedreich's ataxia in a 1-year trial.

Methods Patients with spinocerebellar ataxia or Friedreich's ataxia (2:1 ratio) from three Italian neurogenetic units were enrolled in this multicentre, double-blind, placebo-controlled trial, and randomly assigned to riluzole (50 mg orally, twice daily) or placebo for 12 months. The randomisation list was computer-generated and a centralised randomisation system was implemented. Participants and assessing neurologists were masked to treatment allocation. The primary endpoint was the proportion of patients with improved Scale for the Assessment and Rating of Ataxia (SARA) score (a drop of at least one point) at 12 months. An intention-to-treat analysis was done. This trial is registered at ClinicalTrials.gov, number NCT01104649.

Findings Between May 22, 2010, and Feb 25, 2013, 60 patients were enrolled. Two patients in the riluzole group and three in the placebo group withdrew their consent before receiving treatment, so the intention-to-treat analysis was done on 55 patients (19 with spinocerebellar ataxia and nine with Friedreich's ataxia in the riluzole group, and 19 with spinocerebellar ataxia and eight with Friedreich's ataxia in the placebo group). The proportion with decreased SARA score was 14 (50%) of 28 patients in the riluzole group versus three (11%) of 27 in the placebo group (OR 8·00, 95% CI 1·95–32·83; p=0·002). No severe adverse events were recorded. In the riluzole group, two patients had an increase in liver enzymes (less than two times above normal limits). In two participants in the riluzole group and two participants in the placebo group, sporadic mild adverse events were reported.

Interpretation Our findings lend support to the idea that riluzole could be a treatment for cerebellar ataxia. Longer studies and disease-specific trials are needed to confirm whether these findings can be applied in clinical practice.

Funding Agenzia Italiana del Farmaco.

Lancet Neurol 2015; 14: 985–91

Published Online August 26, 2015 http://dx.doi.org/10.1016/S1474-4422(15)00201-X

See Comment page 968

Center for Experimental Neurological Therapies, Sant'Andrea Hospital, Neurosciences, Mental Health, and Sensory Organs (NESMOS), Sapienza University of Rome, Rome, Italy (S Romano MD, G Coarelli MD, M Ferraldeschi MD, F Ponzelli BPT, F Orzi MD, M Salvetti MD, G Ristori MD); **Physical Medicine and Rehabilitation Unit, Sant'Andrea Hospital, Sapienza University of Rome, Rome, Italy** (M C Vulpiani MD); **Department of Medical Sciences and Biotechnologies, Sapienza University of Rome, Rome, Italy** (C Marcotulli MD, L Leonardi MD, F Piccolo MD, C Casali MD); **National Research Council, Institute of Translational Pharmacology, Rome, Italy** (M Spadaro MD, M Frontali MD); **Neuromuscular and Neurological Rare Diseases Center ASO San Camillo-Forlanini, Rome, Italy** (A Petrucci MD); **and National Centre of Epidemiology, National Institute of Health, Rome, Italy** (N Vanacore MD)

Correspondence to:
Dr Giovanni Ristori, Center for Experimental Neurological Therapies, Sant'Andrea Hospital, Neurosciences, Mental Health, and Sensory Organs (NESMOS), Sapienza University of Rome, Via di Grottarossa 1035-1039, 00189 Italy
giovanni.ristori@uniroma1.it

or

Dr Marco Salvetti, Center for Experimental Neurological Therapies, Sant'Andrea Hospital, Neurosciences, Mental Health, and Sensory Organs (NESMOS), Sapienza University of Rome, Via di Grottarossa 1035-1039, 00189 Italy
marco.salvetti@uniroma1.it

Introduction

Hereditary ataxias are genetic disorders characterised by progressive postural and gait disturbances associated with poor coordination of limbs and eye movements, and impaired speech. The disorders can include other neurological and non-neurological symptoms and are classified according to their mode of inheritance: autosomal dominant or recessive, X-linked, and mitochondrial. Among this group of heterogeneous diseases, the autosomal dominant spinocerebellar ataxias and Friedreich's ataxia are the most frequently encountered in clinical practice. Affecting young people (from children to young adults) and being almost invariably disabling, these illnesses have a severe effect on patients and their families (which often have more than one affected member). The economic burden is also heavy and was recently estimated to be about €19 000 per year in patients with spinocerebellar ataxia.[1]

Unfortunately, treatment options for most hereditary ataxias are virtually nil, and much effort is in progress to find therapies, especially for the more common diseases. In 2014 a number of drugs were investigated for the treatment of Friedreich's ataxia, including nicotinamide and another histone deacetylase inhibitor (2-aminobenzamide histone deacetylase inhibitor [109]),[2,3] the iron chelator deferiprone,[4] and triple therapy with deferiprone, idebenone, and riboflavin.[5] Randomised trials of varenicline and lithium were done in Machado-Joseph disease (spinocerebellar ataxia type 3),[6,7] and the widely used antibiotic ceftriaxone was studied in a mouse model of spinocerebellar ataxia.[8] However, the clinical effect of these treatments has not been established (some studies were done in experimental models, others are in an exploratory phase in human beings, with partial or uncertain clinical benefits), and the latest results do not confirm the clinical effectiveness of some potential therapies, such as idebenone and erythropoietin.[9,10]

We reported encouraging data on the effects of riluzole in patients with cerebellar ataxias of different causes in a double-blind, placebo-controlled trial.[11] The rationale of this study was based on experimental evidence showing a beneficial role of small-conductance potassium channel openers (including riluzole)[12] in the pathophysiology of ataxia, a research path that is still being followed.[13–17] The side-effects were consistent with the established risk

Research in context

Evidence before the study

We searched PubMed up to April 30, 2015, for the following terms without language restriction: "cerebellar ataxia", "riluzole", "clinical trials", "spinocerebellar ataxia (SCA)", and "Friedreich's ataxia (FA)". We did not find studies on riluzole in cerebellar ataxia other than our pilot study of a brief course (8 weeks) of riluzole in patients with chronic cerebellar ataxia of different causes; despite the several other therapeutic approaches being under investigation, no treatment of proven efficacy is currently inferable from published reports.

Added value of the study

We confirmed safety and a significant benefit of riluzole in inherited forms of cerebellar ataxia. The trial allowed us to verify the effects of riluzole for a longer period (12 months), in a larger sample size of patients, and with more stringent diagnostic criteria (inherited forms of ataxia) than in our previous pilot study.

Implications of all the available evidence

This trial supports our attempt to investigate whether riluzole can be repurposed for use in cerebellar ataxia (many ongoing efforts in spinocerebellar ataxia and Friedreich's ataxia include repositioning approaches). Given the well known safety profile of riluzole and the need for new treatments for hereditary cerebellar ataxias, this trial might have potential implications for clinical practice, if further studies in larger and disease-specific populations support our findings.

profile of riluzole, and no major adverse event occurred, at least during the brief duration of the trial (8 weeks). We planned a new trial to verify the effects of riluzole for a longer period (12 months), in a larger sample size of patients, with more stringent diagnostic criteria (inherited forms instead of ataxias of any origin). Based on the results of our pilot study, and the fact that riluzole is thought to affect shared mechanisms underlying cerebellar ataxia, irrespective of disease cause,[11] we designed a trial with the aim of therapeutically targeting the most common types of hereditary ataxia in our population of patients.

Methods

Study design and participants

Patients with hereditary cerebellar ataxia were enrolled in a 12-month, randomised, double-blind, placebo-controlled trial of riluzole (100 mg/day). Enrolment was done at three Italian neurogenetic units: the Centre for Experimental Neurological Therapies (CENTERS), Neurology and Department of Neurosciences, Mental Health and Sensory Organs (NESMOS), Sapienza University of Rome; Department of Medical Sciences and Biotechnologies, Sapienza University of Rome; and the Neuromuscular and Neurological Rare Diseases Center, ASO, San Camillo-Forlanini. Eligible patients were between the ages of 14 and 70 years, with genetically confirmed cerebellar ataxia. Exclusion criteria were ataxic syndromes other than spinocerebellar ataxia or Friedreich's ataxia, serious systemic illnesses or conditions known for enhancing the side-effects of riluzole (ie, cardiac arrhythmias, haematological and hepatic diseases with serum values of alanine aminotransferase, aspartate aminotransferase, or bilirubin more than 1·5 times above the normal limit), and pregnancy (women of childbearing potential who agreed to use contraception were eligible) or breastfeeding.

The trial was done according to Good Clinical Practice guidelines and the Declaration of Helsinki. The local ethics committee approved the protocol and each patient provided written informed consent at the screening visit before the start of the study.

Randomisation and masking

Participants were randomly assigned (1:1) to riluzole or placebo. Riluzole (Rilutek; Aventis Pharma SA, Antony Cedex, France) 50 mg or placebo was given orally every 12 h for 12 months. The investigational drug was packaged and labelled by an independent contract research organisation (Pierrel Research IMP srl, Cantù, Italy). A list of randomisation numbers and corresponding treatment numbers was computer-generated by the contract research organisation before the start of the study. A centralised randomisation system was organised at the Centre for Experimental Neurological Therapies. The assignment of the patient to the treatment or placebo group was determined using randomly permuted blocks in each stratum; to match enrolment to the population of patients at the three enrolling centres, which includes more patients with spinocerebellar ataxia than Friedreich's ataxia, we stratified randomisation on the basis of the clinical form of ataxia. The spinocerebellar ataxia to Friedreich's ataxia ratio was 2:1.

Participants and assessing neurologists were masked to treatment allocation. A two-physician treating and assessing model was used; the treating physician was responsible for supervision, drug administration, recording of adverse events, and safety assessments. We had no independent data safety monitor; the treating physician was considered appropriate by the principal investigators and other authors to oversee safety issues because the risk–benefit profile of riluzole in patients with amyotrophic lateral sclerosis is well known, and our previous trial in cerebellar ataxia showed only sporadic and mild adverse events. The assessing physician was exclusively responsible for neurological assessments.

Procedures

After a screening visit to assess eligibility, baseline assessment included general clinical history, electrocardiogram (ECG) and neurological assessment, including the Scale for the Assessment and Rating of

Ataxia (SARA).[18] Quality of life was measured by the Italian version of the 36-item short form health survey questionnaire (SF-36).[19] The Beck Depression Inventory was used to assess mood status.[20] Blood samples were obtained for routine laboratory tests. The following procedures were repeated at different timepoints over the study period: clinical assessments, ECG, and laboratory tests every 3 months; SARA at months 3 and 12; and SF-36 and Beck Depression Inventory after 12 months. The participants' treatments preceding recruitment were maintained during the trial: three patients in the riluzole group and two patients in the placebo group (all with Friedreich's ataxia) were taking idebenone (5 mg/kg per day); all participants, except one individual in the placebo group and one in the treated group, were receiving physical therapy. During the study any adverse event (any untoward medical occurrence, including an abnormal laboratory finding, regardless of its causal relation to the study treatment) was recorded. The severity of the adverse event was graded as mild (minimal or no treatment required and no interference with the patient's daily activities); moderate (low level of inconvenience or concern, might need treatment and cause some interference with functioning); severe (patient's daily activities interrupted and systemic drug therapy or other treatment needed, usually incapacitating); and life-threatening (immediate risk of death).

Outcomes

The primary endpoint was the difference between the riluzole and placebo groups in the proportion of patients with an improvement of SARA score at the end of the trial with respect to the baseline. A drop of at least one point of SARA score was considered clinically relevant on the basis of the reported annual progression in patients with spinocerebellar ataxia; in a previous study, at 1 year follow-up no more than 5% of patients were judged to be better, whereas 25% were stable, and the rest were worse.[21] Annual changes of SARA scores in patients with Friedreich's ataxia that were reported[22] after the design of this study were in accord with these progression rates and support the choice of the endpoint. Secondary endpoints were differences between the two study groups in the following: proportion of patients with improved SARA score at month 3; mean changes in SARA scores from baseline to months 3 and 12; changes in SF-36 scores at 12 months; changes in Beck Depression Inventory scores at 12 months; number, type, and severity of adverse events; and a baropodometric analysis at 12 months. To assess the clinical efficacy of riluzole, we did two post-hoc analyses, of the proportion of patients reaching SARA scores of 5·5 or lower (ie, mild dependency in activities of daily living)[23] and the proportion of patients with an improvement in at least four SF-36 dimensions (an arbitrary operational approach based on the best change in the placebo group) after 12 months.

Statistical analysis

We assumed that a sample size of 27 patients per group (a total of 54 patients) had 80% power and an α value of 5% to detect a difference between the two groups of 35% in the proportion of patients with SARA scores improved by at least one point after 12 months. This calculation took into account previous results: the annual proportion of patients who were expected to improve (5%), according to the natural history of the most common genotypes;[21] the most conservative approach based on the lowest value found in our pilot study (improvement in 5·3% of the control group);[11] and the best correlation between International Cooperative Ataxia Rating Scale (which was used in our pilot trial) and SARA score (r=0·953).[24] A final sample size of 60 was chosen taking into account possible dropouts. Data were expressed as mean (SD) for continuous variables and as proportions for categorical variables. Comparisons between the riluzole and placebo groups were assessed using the t test for unpaired data for continuous variables and odds ratio (OR) with a relative 95% CI for categorical data. An intention-to-treat analysis was done adopting a last observation carried forward method. A logistic regression model was done at 12 months to adjust the results for the main baseline characteristics (age, sex, and genetic form of ataxia [spinocerebellar ataxia or Friedreich's ataxia]; this model was not prespecified in the protocol). p values less than 0·05 were considered significant. All the analyses were done using SPSS (version 22.0). This trial is registered at ClinicalTrials.gov, number NCT01104649.

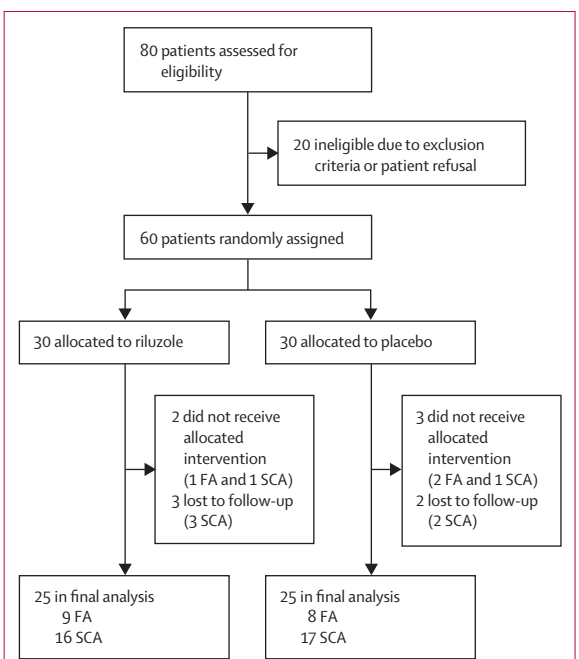

Figure 1: **Trial profile**
55 participants (28 in the riluzole group and 27 in the placebo group) were included in primary (intention-to-treat) and safety analyses. SCA=patient with spinocerebellar ataxia. FA=patient with Friedreich's ataxia.

See Online for appendix

	Riluzole group (n=30)	Placebo group (n=30)
Sex		
Male	17	14
Female	13	16
Age, years	46·2 (11·9)	43·1 (11·5)
Age at onset, years	34·0 (15·7)	31·4 (11·9)
Ataxia type		
Friedreich's ataxia	10	10
Spinocerebellar ataxia	20	20
SARA score	15·3 (8·9)	16·5 (8·7)
Beck Depression Inventory score	6·36 (4·02)	8·69 (7·25)
SF-36 (physical component score)*	44·95 (20·95)	48·93 (21·01)
SF-36 (mental component score)*	54·62 (15·53)	56·92 (29·55)

Data are n or mean (SD). For more details on participant characteristics, including ataxia subtypes, see appendix. SARA=Scale for the Assessment and Rating of Ataxia. *SF-36 results were obtained in 30 patients (15 from the riluzole group and 15 from the placebo group) that were similar to the rest of the study population for other baseline characteristics.

Table 1: **Demographic and baseline characteristics**

	Riluzole group (n=28)	Placebo group (n=27)	OR (95% CI) or mean difference (95% CI)	p value
Primary endpoint				
Proportion of patients with improved SARA score at month 12				
Yes	14 (50%)	3 (11%)	8·00 (1·95–32·83)	0·002
No	14 (50%)	24 (89%)		
Secondary endpoints				
Proportion of patients with improved SARA score at month 3				
Yes	14 (50%)	7 (26%)	2·86 (0·92–8·89)	0·066
No	14 (50%)	20 (74%)		
Changes in SARA score from baseline to months 3 and 12				
Month 3	−1·00 (1·75)	0·50 (2·28)	−1·50 (−2·59 to 0·40)	0·008
Month 12	−1·02 (2·15)	1·67 (2·63)	−2·68 (−3·98 to 1·39)	0·001
Beck Depression Inventory score at month 12	5·6 (4·6)	7·2 (6·2)	..	0·29
SF-36 (physical component score) at month 12*	51·3 (21·3)	43·4 (21·3)	..	0·29
SF-36 (mental component score) at month 12*	63·4 (21·3)	48·5 (28·2)	..	0·11

Values are n (%) or mean (SD) unless otherwise specified. *SF-36 results were obtained in 30 patients (15 from the riluzole group and 15 from the placebo group) that were similar to the rest of the study population for other baseline characteristics.

Table 2: **Primary and secondary outcomes**

	Riluzole group (n=28)	Placebo group (n=27)	p value
Total adverse events*	4 (14%)	2 (7%)	0·70
Severe adverse events	0	0	
Increase of liver enzymes	2 (7%)	0	0·50

Data are n (%).*In addition to the increase in liver enzymes, sporadic mild side-effects were reported: headache and abdominal pain by one patient each in the riluzole group and somnolence and diarrhoea by one patient each in the placebo group.

Table 3: **Adverse events**

Role of the funding source

The Agenzia Italiana del Farmaco funded the study. The funder had no role in the trial design, data collection, analysis, and interpretation, or writing the paper. The corresponding author (GR) and the study biostatisticians (MFe and NV) had full access to all the data, and all authors had access to the data if they wished. The corresponding author had final responsibility for the decision to submit for publication.

Results

60 of 80 patients assessed for eligibility were enrolled between May 22, 2010, and Feb 22, 2013, and randomly assigned to receive riluzole or placebo (figure 1). Five patients (two in the riluzole group and three in the placebo group) withdrew their consent before receiving treatment, and five patients (three in the riluzole group and two in the placebo group) were lost to follow-up; the analysis was done on the 28 patients who received riluzole and the 27 patients who received placebo. The demographic and baseline characteristics of the two groups did not differ (table 1). The clinical details of participants are reported in the appendix. Results for SF-36 dimensions were obtained in 15 patients from the riluzole group and 15 from the placebo group because the remaining participants declined to answer the questionnaire. The baseline characteristics of this subgroup did not differ from the rest of the population under study, except for a significantly higher score on the Beck Depression Inventory (9·55 [SD 6·07] *vs* 5·08 [4·64]; p=0·04; appendix), suggesting that patients with better mood status had more propensity to provide informative SF-36 questionnaires.

For the primary endpoint, the proportion of patients with a decreased SARA score after 12 months in the riluzole group was significantly higher than that in the placebo group (OR 8·00, 95% CI 1·95–32·83; p=0·002; table 2). The difference remained significant after the post-hoc logistic regression analysis that adjusted for sex, age, and clinical form of ataxia (OR 9·76, 95% CI 2·08–45·80; p=0·004). At month 3 the proportion of patients with decreased SARA scores did not differ significantly between the groups (table 2). The mean changes of SARA score compared with baseline were significantly different between the two groups at both 3 and 12 months, with negative mean changes for treated patients and positive mean values for the placebo group (table 2). Changes in Beck Depression Inventory scores did not differ between the riluzole and placebo groups. Mean physical and mental component scores of SF-36 did not differ between the riluzole and placebo groups after 12 months (table 2). The mean score for the social role functioning dimension of SF-36 was significantly higher in the riluzole group (71·4 [24·8] *vs* 45·7 [34·3]; p=0·02) but mean scores in the other dimensions did not differ between the groups (data not shown). The changes in SARA score at 3 and 12 months for each participant are

shown in figure 2. The proportion of patients with increased SARA scores (a post-hoc outcome showing deterioration of cerebellar ataxia) was greater in the placebo than the riluzole group: 10 (37%) of 27 versus 4 (14%) of 28 patients at 3 months; 13 (48%) of 27 versus 4 (14%) of 28 patients at 12 months (OR 5·39, 95% CI 1·51–22·54, p=0·006).

Two patients in the riluzole group showed an increase in liver enzymes (less than two times above normal limits), which has been shown before in patients receiving riluzole.[25] The values of aminotransferases reached maximum values after 3 months, then decreased to less than 1·5 times over the normal limit after 6 months, and persisted above normal limits until the end of the trial. In two participants in the riluzole group and two in the placebo group sporadic, mild side-effects were reported (table 3). No severe adverse events occurred. No problem with treatment compliance was recorded.

To assess the clinical relevance of the effects of riluzole, we did post-hoc analyses of SARA and SF-36 scores. The proportion of patients reaching a score of 5·5 or lower (indicative of mild dependency in the performance of daily living)[23] at 12 months was significantly different between the treated (9/28, 32·1%) and placebo (2/27, 7·4%) groups after adjustment for baseline characteristics (OR 5·87, 95% CI 1·07–32·35; p=0·04; appendix). The proportion of patients with an improvement in at least four SF-36 dimensions was significantly higher in the riluzole group (9/15, 60·0% *vs* 1/15, 6·7%; OR 21·71, 95% CI 1·67–281·61; p=0·019; adjusted for baseline variables; appendix).

We were not able to obtain results from the baropodometric analysis, which was not applicable or too stressful for the participants.

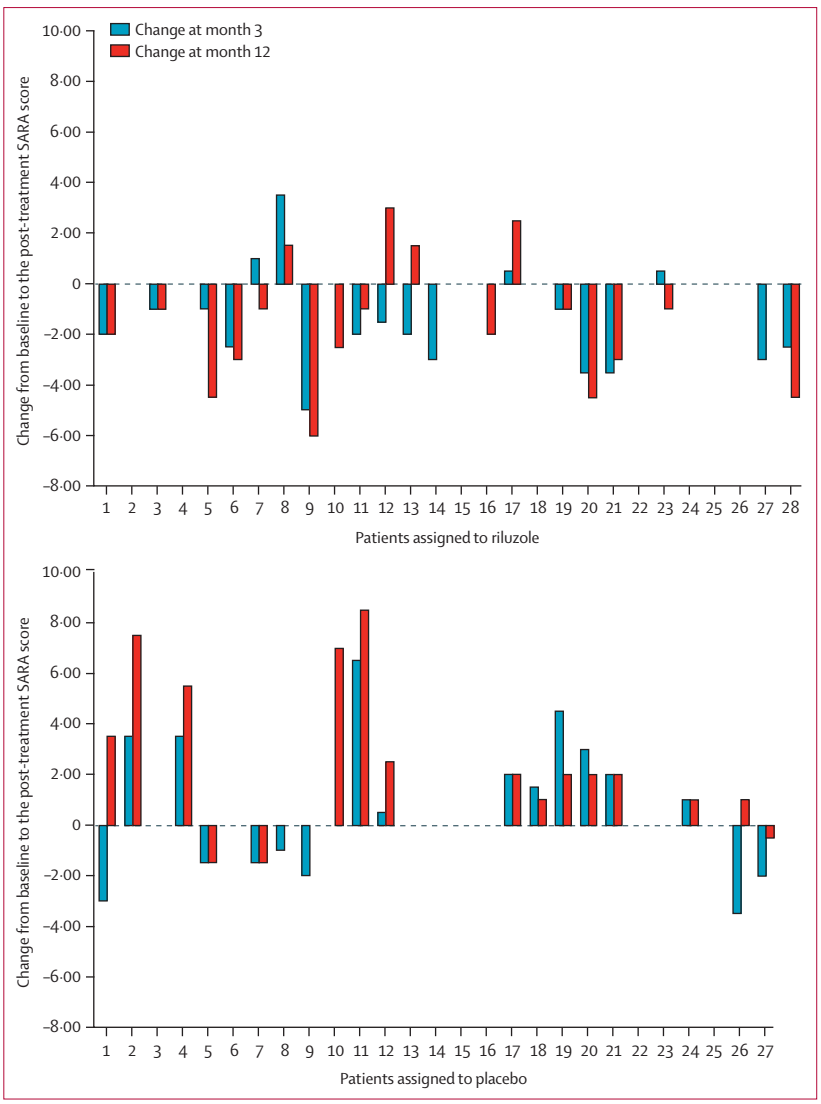

Figure 2: **Changes in SARA scores after 3 and 12 months**
Data are mean SARA score changes (positive values show deterioration of cerebellar ataxia, negative values show improvement, and zero values show no change), after treatment (3 and 12 months), for 28 patients in the riluzole group and 27 in the placebo group.

Discussion

This study confirms the findings of our previous, short duration study on the potential beneficial effect of riluzole in cerebellar ataxia.[11] In patients with inherited forms of ataxia the drug seemed safe and potentially beneficial in this 1-year protocol. An effect on disease progression is suggested by the changes in SARA scores in the riluzole-treated patients: the proportion of patients with decreased (50%) and increased (14%) values remained stable at 3 and 12 months. By contrast, patients taking placebo deteriorated at the end of the trial; the drop in patients with decreased SARA values (from 26% at month 3 to 11% at month 12) and the increase of those with increased SARA values (from 37% to 48%) are consistent with the reported natural history of the most common genotypes.[21,22,26,27] At the end of the trial, riluzole seemed to have a clinical effect in the post-hoc analyses of activities of daily living and quality of life (appendix). Potential confounding by unintended effects on mood (riluzole is being investigated for depression)[17,28] or by combination of rehabilitation and pharmacological treatments is unlikely; the changes in Beck Depression Inventory scores and the proportion of patients receiving physical therapy or idebenone (in the case of Friedreich's ataxia) during the trial were similar in both study groups.

The mechanism of action of riluzole in cerebellar ataxia is not fully understood. The action of small-conductance potassium channel openers is a plausible working hypothesis that is being investigated.[12–17] However, a more pleiotropic effect seems likely;[29] the drug enhances the uptake of glutamate by astrocytes and reduces the release of glutamate from active synapses, counteracting damage by excitotoxicity, so antiglutamatergic-mediated neuroprotection might play a long-term part in antagonising cerebellar degeneration in different forms of ataxia, as suggested by our previous study.[11] Moreover, riluzole enhances activity of the TWIK-related potassium

channel-1 (TREK-1), and intracellular expression of heat-shock proteins that have a neuroprotective role and counteract blood–brain barrier dysfunction (a trigger of the inflammatory component underlying several neurodegenerative diseases).[30]

Many of the limitations of this trial stem from the demanding features of some secondary outcome measures that were ill-suited to patients with progressive disability but without motivational support from friends or family members. Although there were no compliance issues with taking the drug, some patients found the protocol assessment stressful. As a result, several problems occurred during the trial: a planned collection of baropodometric parameters was not possible in most cases, or provided uninformative results; the flow of participants through the trial (figure 1) resulted in a relatively high (17%) loss of patients with respect to the randomisation; and the SF-36 questionnaire was obtained in only a subgroup of participants. These limitations could have affected the interpretation of the clinical effect of riluzole in inherited cerebellar ataxias. However, they are unlikely to detract from the overall results obtained for SARA scores (at the end of the trial a response was about ten times more frequent in the riluzole group [OR=9·76], the absolute risk difference was 39%, and the number needed to treat was 2·6).

Overall, this trial lends support to the idea that riluzole might be efficacious in the treatment of patients with cerebellar ataxia, in addition to its present indication for amyotrophic lateral sclerosis. The drug effect seems to be unaffected by adjustment for the different clinical forms of ataxia. Our findings suggest that riluzole could eventually be used in clinical practice, but confirmatory studies on larger and disease-specific populations, for a longer observation period (to reduce the effects of fluctuations in slowly evolving diseases) are needed. The virtual absence of effective therapies for the inherited forms of cerebellar ataxia, which affect a large number of patients and at-risk individuals worldwide, warrants further investigation of riluzole as a candidate treatment.

Contributors

GR and SR were the principal investigators. GR, SR, MFr, MSp, FO, MSa, AP, and CC conceived and designed the study. GC, MFe, MSp, LL, CM, FPi, MCV, and FPo followed up the patients and acquired the data. SR oversaw study implementation. All the authors were involved in the analysis and interpretation of the data. The statistical analyses were done by MFe and NV. GR, NV, MFr, FO, MSa, AP, and CC contributed to the writing of the manuscript.

Declaration of interests

MSa receives research support and has received fees as a speaker from Teva, Biogen, Bayer Schering, and Merck Serono. All other authors declare no competing interests.

Acknowledgments

This study was funded by the Agenzia Italiana del Farmaco (grant number FARM7KAJM7). We thank the patients and their families for their collaboration and help. The activity of the Centre for Experimental Neurological Therapies is supported, as a special project, by the Fondazione Italiana Sclerosi Multipla.

References

1 López-Bastida J, Perestelo-Pérez L, Montón-Alvarez F, Serrano-Aguilar P. Social economic costs and health-related quality of life in patients with degenerative cerebellar ataxia in Spain. *Mov Disord* 2008; **23:** 212–17.

2 Libri V, Yandim C, Athanasopuolos S, et al. Epigenetic and neurological effects and safety of high-dose nicotinamide in patients with Friedreich's ataxia: an exploratory, open-label, dose-escalation study. *Lancet* 2014; **384:** 504–13.

3 Soragni E, Miao W, Iudicello M, et al. Epigenetic therapy for Friedreich ataxia. *Ann Neurol* 2014; **76:** 489–508.

4 Pandolfo M, Arpa J, Delatycki MB, et al. Deferiprone in Friedreich ataxia: a 6-month randomized controlled trial. *Ann Neurol* 2014; **76:** 509–21.

5 Arpa J, Sanz-Gallego I, Rodriguez-de-Rivera FJ, et al. triple therapy with deferiprone, idebenone, and riboflavin in Friedreich's ataxia—open-label trial. *Acta Neurol Scand* 2014; **129:** 32–40.

6 Zesiewicz TA, Greenstein PE, Sullivan KL, et al. A randomized trial of varenicline (CHANTIX) for treatment of spinocerebellar ataxia type 3. *Neurology* 2012; **78:** 545–50.

7 Saute JA, de Castilhos RM, Monte TL, et al. A randomized phase 2 clinical trial of lithium carbonate in Machado-Joseph disease. *Mov Disord* 2014; **29:** 568–73.

8 Maltecca F, Baseggio E, Consolato F, et al. Purkinje neuron Ca^{2+} influx reduction rescues ataxia in CSA28 model. *J Clin Invest* 2015; **125:** 263–74.

9 Lagedrost SJ, Sutton MS, Cohen MS, et al. Idebenone in Friedreich ataxia cardiomyopathy—results from a 6-month phase III study (IONIA). *Am Heart J* 2011; **161:** 639–45.

10 Mariotti C, Fancellu R, Caldarazzo S, et al. Erythropoietin in Friedreich's ataxia: no effect on frataxin in a randomized controlled trial. *Mov Disord* 2012; **27:** 446–49.

11 Ristori G, Romano S, Visconti A, et al. Riluzole in cerebellar ataxia: a randomized, double-blind, placebo-controlled pilot trial. *Neurology* 2010; **74:** 839–45.

12 Cao YJ, Dreixler JC, Couey JJ, Houamed KM. Modulation of recombinant and native neuronal SK channels by the neuroprotective drug riluzole. *Eur J Pharmacol* 2002; **449:** 47–54.

13 Shakkottai VG, Chou CH, Oddo S, et al. Enhanced neuronal excitability in the absence of neurodegeneration induces cerebellar ataxia. *J Clin Invest* 2004; **113:** 582–90.

14 Shakkottai VG, do Carmo Costa M, Dell'Orco JM, Sankaranarayanan A, Wulff H, Paulson HL. Early changes in cerebellar physiology accompany motor dysfunction in the polyglutamine disease spinocerebellar ataxia type 3. *J Neurosci* 2011; **31:** 13002–14.

15 Gao Z, Todorov B, Barrett CF, et al. Cerebellar ataxia by enhanced Ca(V)2.1 currents is alleviated by Ca2+-dependent K+-channel activators in Cacna1a(S218L) mutant mice. *J Neurosci* 2012; **32:** 15533–46.

16 Kasumu AW, Hougaard C, Rode F, et al. Selective positive modulator of calcium-activated potassium channels exerts beneficial effects in a mouse model of spinocerebellar ataxia type 2. *Chem Biol* 2012; **26:** 1340–53.

17 Lam J, Coleman N, Garing A, Wulff H. The therapeutic potential of small-conductance Kca2 channels in neurodegenerative and psychiatric diseases. *Expert Opin Ther Targets* 2013; **17:** 1203–20.

18 Schmitz-Hübsch T, du Montcel ST, Baliko L, et al. Scale for the assessment and rating of ataxia: development of a new clinical scale. *Neurology* 2006; **66:** 1717–20.

19 Apolone G, Mosconi P, Ware JE. SF-36 Questionario sullo stato di salute. Manuale d'uso e guida all'interpretazione dei risultati. Milan: Guerini & Associati Editore, 1997.

20 Beck AT, Steer RA. Manual for the Beck Depression Inventory. San Antonio, TX: The Psychological Corporation, 1993.

21 Schmitz-Hubsh T, Fimmers R, Rakowicz M, et al. Responsiveness of different rating instruments in spinocerebellar ataxia patients. *Neurology* 2010; **74:** 678–84.

22 Marelli C, Figoni J, Charles P, et al. Annual change in Friedreich's ataxia evaluated by the scale for the assessment and rating of ataxia (SARA) is independent of disease severity. *Mov Disord* 2012; **27:** 135–38.

23 Kim BR, Lim JH, Lee SA, et al. Usefulness of the Scale for the Assessment and Rating of Ataxia (SARA) in ataxic stroke patients. *Ann Rehabil Med* 2011; **35:** 772–80.

24 Burk K, Malzig U, Wolf S, et al. Comparison of three clinical rating scales in Friedreich ataxia (FRDA). *Mov Disord* 2009; **24:** 1779–84.

25 Bensimon G, Doble A. The tolerability of riluzole in the treatment of patients with amyotrophic lateral sclerosis. *Expert Opin Drug Saf* 2004; **3:** 525–34.

26 Jacobi H, Bauer P, Giunti P, et al The natural history of spinocebellar ataxia 1, 2, 3 and 6: a 2-year follow-up study. *Neurology* 2011; **77:** 1035–41.

27 Reetz K, Dogan I, Costa AS, et al. Biological and clinical characteristics of the European Friedreich's ataxia consortium for translational studies (EFACTS) cohort: a cross-sectional analysis of baseline data. *Lancet Neurol* 2015; **14:** 174–82.

28 Pittenger C, Coric V, Banasr M, Bloch M, Krystal JH, Sanacora G. Riluzole in the treatment of mood and anxiety disorders. *CNS Drugs* 2008; **22:** 761–86.

29 Cifra A, Mazzone GL, Nistri A. Rilzole: what it does to spinal and brainstem neurons and how it does it. *Neuroscientist* 2012; **19:** 137–44.

30 Bittner S, Ruck T, Schuhmann MK, et al. Endothelial TWIK-related potassium channel-1 (TREK1) regulates immune-cell trafficking into the CNS. *Nat Med* 2013; **19:** 1161–65.