Safety and efficacy of riluzole in spinocerebellar ataxia type 2 in France (ATRIL): a multicentre, randomised, double-blind, placebo-controlled trial

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Summary

Background Riluzole has been reported to be beneficial in patients with cerebellar ataxia; however, effectiveness in individual subtypes of disease is unclear due to heterogeneity in participants' causes and stages of disease. Our aim was to test riluzole in a single genetic disease, spinocerebellar ataxia type 2.

Methods We did a randomised, double-blind, placebo-controlled, multicentre trial (the ATRIL study) at eight national reference centres for rare diseases in France that were part of the Neurogene National Reference Centre for Rare Diseases. Participants were patients with spinocerebellar ataxia type 2 with an age at disease onset of up to 50 years and a scale for the assessment and rating of ataxia (SARA) score of at least 5 and up to 26. Patients were randomly assigned centrally (1:1) to receive either riluzole 50 mg orally or placebo twice per day for 12 months. Two visits, at baseline and at 12 months, included clinical measures and 3T brain MRI. The primary endpoint was the proportion of patients whose SARA score improved by at least 1 point. Analyses were done in the intention-to-treat population (all participants who were randomly assigned) and were done with only the observed data (complete case analysis). This trial is registered at ClinicalTrials.gov (NCT03347344) and has been completed.

Findings Between Jan 18, 2018, and June 14, 2019, we enrolled 45 patients. 22 patients were randomly assigned to receive riluzole and 23 to receive placebo. Median age was 42 years (IQR 36–57) in the riluzole group and 49 years (40–56) in the placebo group and 23 (51%) participants were women. All participants presented with moderate-stage disease, characterised by a median SARA score of 13·5 (IQR 9·5–16·5). The primary endpoint, SARA score improvement of at least 1 point after 12 months, was observed in seven patients (32%) in the treated group versus nine patients (39%) in the placebo group, with a mean difference of –10·3% (95% CI –37·4% to 19·2%; p=0·75). SARA score showed a median increase (ie, worsening) of 0·5 points (IQR –1·5 to 1·5) in the riluzole group versus 0·3 points (–1·0 to 2·5) in the placebo group (p=0·70). No serious adverse event was reported in the riluzole-treated group whereas four patients in placebo group had a serious adverse event (hepatic enzyme increase, fracture of external malleolus, rectorrhagia, and depression). The number of patients with adverse events was similar in both groups (riluzole 16 [73%] patients *vs* placebo 19 [83%] patients; p=0·49).

Interpretation We were able to recruit 45 patients moderately affected by spinocerebellar ataxia type 2 for this trial. Riluzole did not improve clinical or radiological outcomes in these patients. However, our findings provide data on progression of spinocerebellar ataxia type 2 that might prove to be valuable for the design of other clinical trials.

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Introduction

Spinocerebellar ataxias are a group of autosomal dominantly inherited progressive neurological diseases that are clinically and genetically heterogeneous,[1] with 48 subtypes. A subgroup of seven subtypes is caused by pathological expansions of a polymorphic CAG repeat and most commonly affects adults in midlife. These seven subtypes are spinocerebellar ataxia type 1 (associated with pathogenic variants in *ATXN1*), spinocerebellar ataxia type 2 (*ATXN2*), spinocerebellar ataxia type 3 (*ATXN3*), spinocerebellar ataxia type 6 (*CACNA1A*), spinocerebellar ataxia type 7 (*ATXN7*), spinocerebellar ataxia type 17 (*TBP*), and dentatorubral pallidoluysian atrophy (*ATN1*). For these seven subtypes, mean age at onset and severity are closely and negatively correlated with the expanded CAG repeat size: the longer the pathological repeat, the earlier the age at onset. Paediatric and juvenile forms of the disease can also occur, especially for spinocerebellar ataxia type 2 and spinocerebellar ataxia type 7. The natural history of the disease for subtypes 1, 2, and 3 is well established, including the annual progression rate of the scale for the assessment and rating of ataxia (SARA) score.[2] No curative treatment exists for these diseases, although antisense

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Research in context

Evidence before this study

We searched PubMed from inception to Nov 23, 2021, for the following terms without language restriction: "cerebellar ataxia", "spinocerebellar ataxias (SCAs)", "riluzole", and "clinical trials". We found two clinical trials with evidence of clinical improvement after riluzole treatment. The first, a pilot study, included 40 patients affected by genetic and other forms of ataxias with a treatment duration of 8 weeks (NCT00202397), and the second trial included 60 patients with different causes of inherited cerebellar ataxias and disease stages treated for 12 months (NCT01104649) .

Added value of this study

The ATRIL study assessed the safety and efficacy of riluzole in patients with spinocerebellar ataxia type 2. We enrolled a homogeneous cohort of patients with spinocerebellar ataxia type 2 recruited by the French network of rare neurogenetic diseases. This choice for replication was justified by three facts: patients with spinocerebellar ataxia type 2 are among those included in previous ataxia studies; spinocerebellar ataxia type 2 can present an amyotrophic lateral sclerosis-like phenotype, and riluzole is widely used to treat amyotrophic lateral sclerosis; and intermediate *ATXN2* alleles (27–32 CAG repeats) are a risk factor for amyotrophic lateral sclerosis. In addition, we used pretrial cerebral MRI scans (cerebellum and brainstem volumes), added a quantitative measure of ataxia (the composite cerebellar functional severity score), and carefully analysed motor neuron involvement and quality-of-life measures. The ATRIL results showed no clinical or radiological improvement after riluzole treatment in patients with spinocerebellar ataxia type 2. However, we were able to measure significant volume loss over 12 months for specific brain regions in these patients.

Implications of all the available evidence

We report the absence of improvement of clinical or radiological outcomes under riluzole treatment, despite satisfactory treatment compliance and absence of serious adverse events. However, our longitudinal imaging results might provide valuable biomarkers for upcoming clinical trials.

oligonucleotides have produced encouraging results in several mouse models.[3,4]

Several disease-modifying treatments have been tested in hereditary ataxias, such as valproic acid or lithium, without demonstrated efficacy to support their clinical use. However, the effect of riluzole has been reported as beneficial in two trials. The first trial, which was a pilot study with 40 patients affected by genetic and other forms of ataxia,[5] showed a decrease of 5 points on the international cooperative ataxia rating scale score after 4 weeks and 8 weeks of treatment with riluzole (100 mg/day) compared with placebo. The second trial, which was a placebo-controlled, randomised, double-blind study included 40 patients with spinocerebellar ataxias (spinocerebellar ataxia types 1, 2, 6, 8, or 10) and 20 patients with Friedreich ataxia, treated for 12 months.[6] That study confirmed the beneficial effect of riluzole with a 1 point decrease on the SARA score after 1 year. However, these two studies included patients with different forms of disease-causing variants and different disease stages, as well as presymptomatic carriers. This heterogeneity makes the generalisability of the positive effect unclear in individual disease subgroups. For this reason, we decided to do a trial in a population that was homogeneous in terms of genotype. Riluzole is widely used in amyotrophic lateral sclerosis with beneficial effects on survival,[7] patients with spinocerebellar ataxia type 2 frequently present with involvement of motor neurons,[8] and intermediate *ATXN2* alleles (27–32 CAG repeat expansion) are a risk factor for amyotrophic lateral sclerosis,[9] predisposing patients to more rapid progression.[10] We therefore did a placebo-controlled trial with riluzole for 12 months in patients with spinocerebellar ataxia type 2, the same primary clinical endpoint as the previously reported 1 year trial.[6]

Methods

Study design and participants

For this multicentre, double-blind, randomised, placebo-controlled study (the ATRIL study), patients were recruited from eight national reference centres for rare diseases in France. Eligible patients were aged at least 18 years, with a genetically confirmed diagnosis of spinocerebellar ataxia type 2 (CAG repeat lengths ≥33 in the *ATNX2* gene), a SARA score of at least 5 and up to 26, and an age at onset of up to 50 years. Patients received physiotherapy as standard care before and during the trial. Patients also all had to be able to give their informed consent and be covered by social security. Key exclusion criteria included ataxic syndromes other than spinocerebellar ataxia type 2, previous riluzole treatment, serious systemic illnesses or conditions known for enhancing the side-effects of riluzole (ie, severe cardiac or renal insufficiency, haematological and hepatic diseases with serum alanine amino transferase concentrations greater than or equal to twice the upper limit of normal, or abnormal values of several other hepatic markers), hypersensitivity to the active substance or to any of the excipients (dibasic calcium phosphate anhydrous, microcrystalline cellulose, croscarmellose sodium, colloidal silica anhydrous, magnesium stearate, hypromellose, or titanium dioxide [E171] macrogol 400), hypersensitivity to any of the placebo ingredients (lactose monohydrate, microcrystalline cellulose, colloidal silica, anhydrous, magnesium stearate, or Opadry II HP85F18422 White), contraindications for MRI examination, participation in another therapeutic trial (within the past

3 months), pregnancy or breastfeeding, non-abstinence or absence of effective contraception for women, inability to understand information about the protocol, and adults under legal protection or otherwise unable to consent.

Deviations from the protocol, which were minor, concerned the scheduling windows of the visits. Because of the COVID-19 pandemic, disease progression, or patient personal constraint, follow-up visits for two patients (one visit each) could not be scheduled as per protocol (12 months, 2 weeks before the scheduled date).

The trial was done according to Good Clinical Practice guidelines, the Declaration of Helsinki, and in line with French regulations. The study was approved by the French Ethics Committee and all participants provided written informed consent at the first visit before any study procedures or assessments. This trial is registered at ClinicalTrials.gov, number NCT03347344.

Randomisation and masking

Randomisation was centralised and done by the Clinical Research Unit at Pitié-Salpêtrière University Hospital, under the supervision of the Agence Générale des Equipements et Produits de Santé (AGEPS) via the electronic reporting form. We used a block-randomisation scheme and a centralised procedure for randomisation, with stratification of participants included in Paris versus those recruited in other centres. After written consent and after checking inclusion and exclusion criteria, eligible patients were randomly assigned in a 1:1 ratio to receive either riluzole or placebo. AGEPS sent labelled pill boxes to the pharmacies of the eight different centres. Patients, investigators, and the trial team of the sponsor involved in the analysis remained masked to the randomised treatment assignments until the last study visit of each patient, with the exception of serious adverse events or medical emergency instances that required immediate unblinding.

Procedures

Riluzole 100 mg was administered orally (50 mg every 12 h) for 12 months. Placebo 50 mg was presented as a round, biconvex, 8 mm in diameter, nearly-white film-coated tablet matching the appearance of the riluzole used in this study. The shipment was overseen by the clinical department of AGEPS, the central pharmacy of the Pitié-Salpêtrière Hospital. Treatments were stored at ambient temperature in a secured storage area and presented in numbered boxes, labelled for this study according to Good Manufacturing Practices by the AGEPS. Each numbered box contained 6 months of treatment: 20 blister packs of 20 active or placebo tablets. Patient compliance was checked by clinical research associates during monitoring throughout the study (amount of treatment returned used or unused and doses administered).

Eligible patients had blood analyses to check for normal liver function and blood cell count (bilirubin, aspartate transaminase [ASAT], alanine transaminase [ALAT], γ glutamyl transferase, alkaline phosphatases, albumin, and blood-cell count) less than 1 month before the baseline visit. The baseline visit (visit 1) included a clinical examination (weight, height, and blood pressure) and patient medical history (age, alcohol consumption, caffeine consumption, tobacco consumption, concomitant treatment, comorbidities, and frequency of physical therapy). Cerebellar function was assessed by SARA[11] and quantitatively measured by the composite cerebellar functional severity score (CCFS).[12] Neurological examination used the inventory of non-ataxia signs (INAS)[13] to report on motor neuron involvement and other signs. 3T cerebral MRI was done on site-specific MRI scanners. We assessed quality of life using the French version of the 36-item short-form health survey questionnaire (SF-36).[14]

At visit 2 (12 months, 2 weeks before or after the scheduled date), a clinical and neurological examination was done (SARA and CCFS scores and INAS count), as well as an evaluation of compliance, collection of adverse events, collection of concomitant medication, assessment of quality of life (SF-36 questionnaire), and cerebral MRI.

The severity of adverse events was evaluated using the Common Terminology Criteria for Adverse Events. The investigators also assessed the causal relationship between adverse events and the investigational medicinal product or the study procedures.

Hepatic measurements (bilirubin, ASAT, ALAT, γ glutamyl transferase, alkaline phosphatases, and albumin) and blood-cell counts were monitored in a local laboratory at month 1, month 2, month 3, a week before month 6, month 9, and a week before month 12. Women also underwent a urine pregnancy test at month 0 and a blood pregnancy test at month 1, month 2, month 3, month 6, month 9, and month 12 to exclude any possibility of pregnancy. Examinations were done locally, always in the same laboratory for each patient.

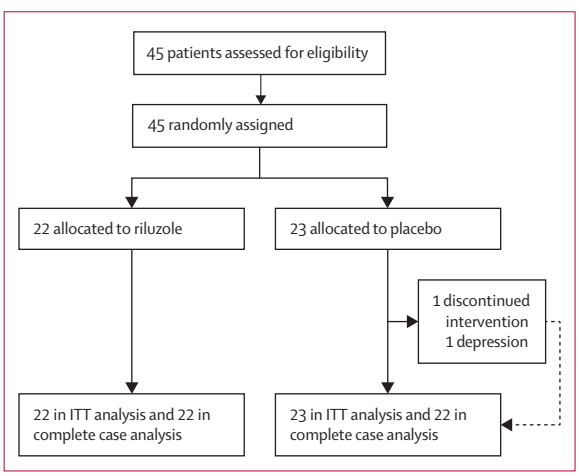

Figure 1: **Trial profile**
45 patients were included in the primary intention-to-treat and safety analyses, and 44 patients were included in the complete case analysis. ITT=intention to treat.

	Riluzole (n=22)	Placebo (n=23)
Sex		
Women	8 (36%)	15 (65%)
Men	14 (64%)	8 (35%)
Age	42 (36–57)	49 (40–56)
Age at onset	32 (25–43)	38 (29–44)
Disease duration	11 (5–12)	11 (6–18)
Repeat length of expanded alleles	39 (39–41)	39 (38–40)
Repeat length of short alleles	22 (22–22)	22 (22–22)
SARA score (maximum value 40)	15·3 (10·0–20·5)	12·5 (9·0–16·0)
CCFS	1·089 (1·004–1·226)	1·075 (1·008–1·185)
INAS count	4 (3–6)	4 (3–5)†
Sensory symptoms	18 (82%)	17 (74%)
Areflexia	14 (64%)	18 (78%)
Upper motor neuron signs*	11 (55%)	10 (43%)
Extensor plantar	7 (35%)	6 (26%)*
Spasticity	6 (27%)	6 (26%)‡
Hyperreflexia	4 (18%)	4 (17%)
Lower motor neuron signs*	8 (36%)	7 (32%)
Fasciculations	6 (27%)	4 (18%)‡
Paresis	2 (9%)	2 (9%)
Muscle atrophy	2 (9%)	2 (9%)
Cramps	16 (73%)	17 (74%)
Urinary dysfunction	8 (36%)	12 (52%)
(Continued from previous column)		
Extrapyramidal signs*	8 (36%)	5 (23%)
Dystonia	6 (27%)	4 (17%)
Resting tremor	5 (23%)	1 (5%)‡
Rigidity	1 (5%)	1 (4%)
Chorea/dyskinesia	3 (14%)	2 (9%)
Myoclonus	3 (14%)	2 (9%)
Brainstem oculomotor signs	9 (41%)	10 (45%)
Abnormal saccades*	20 (91%)	22 (96%)
Saccadic dysmetria*	18 (86%)†	18 (78%)
Double vision	3 (14%)	9 (39%)
Nystagmus*	3 (14%)	8 (9%)
Dysarthria	21 (95%)	21 (91%)
Dysphagia	13 (59%)	13 (57%)
Vertigo	7 (32%)	6 (26%)
Problems with handwriting	22 (100%)	22 (96%)
Cognitive dysfunction	0	2 (9%)
Alcohol consumption (at least once a week)	1 (4%)	4 (17%)
Physiotherapy	17 (77%)	15 (65%)
Number of hours per week	1 (1–3)	1 (1–2)

Data are n (%) or median (IQR). Ethnic background was not assessed. Upper motor neuron signs are defined as extensor plantar (unilateral or bilateral), spasticity, or hyperreflexia. Lower motor neuron signs are defined as fasciculations, paresis, or muscle atrophy. Brainstem oculomotor signs are defined as ophthalmoparesis on horizontal gaze, ophthalmoparesis on vertical gaze, or slowing of saccades. Extrapyramidal signs are defined as dystonia, resting tremor, or rigidity. Abnormal saccades are defined as broken up smooth pursuit or slowing saccades. Saccadic dysmetria is defined as hypometric saccades or hypermetric saccades. Nystagmus is defined as downbeat nystagmus on fixation, horizontal gaze-evoked nystagmus, or vertical gaze-evoked nystagmus. Other clinical characteristics have been defined in previous publications. SARA=scale for the assessment and rating of ataxia. CCFS=composite cerebellar functional severity score. INAS=inventory of non-ataxia signs. *N=20. †N=21. ‡N=22.

Table 1: **Clinical and genetic characteristics at baseline**

Outcomes

The primary outcome was a 1 point improvement of the SARA score after 12 months, as used by Romano and colleagues.[6] Prespecified secondary endpoints were: to evaluate the quantitative progression of cerebellar symptoms by showing a decrease in the SARA score; decrease in the SARA score compared with the natural evolution (this analysis is based on results of a previous study combined with results of the ATRIL trial); decrease in the CCFS score; change in the INAS score, including signs of involvement of lower motor neurons (presence of fasciculations, muscle atrophy, or paresis); decrease in or stabilisation of the rate of atrophy in the cerebellum and brainstem (midbrain, pons, and medulla oblongata), measured using volumetric 3T MRI; patient quality of life assessed using the SF-36 questionnaire; long-term tolerance of riluzole confirmed by clinical examination at study visits and by blood analysis (hepatic measurements, blood cell count) every month during the first 3 months of treatment, then every 3 months; and survival. Post-hoc endpoints concerned the baseline comparison with healthy controls of cerebellar and brainstem volumes, the correlation of baseline clinical scores with MRI data, and preinclusion progression of atrophy on MRI in patients for whom data were available.

Statistical analysis

On the basis of Romano and colleagues' report,[6] we expected a positive effect in both groups. The primary criterion was a decrease in SARA score of at least 1 point after 12 months of treatment. We expected that 5% of patients in the placebo group would improve their SARA score and 45% of the patients in the treated group would improve their score. Using a two-sided Fisher's exact test (bilateral test), and an α of 5%, the inclusion of 21 patients in each group allows for 80% power with a 40% δ between the two groups.

Quantitative variables were described by their mean and SE or SD or their median (IQR) for each treatment group separately. Frequency, percentage, and a 95% CIs were used to describe qualitative variables for each treatment group separately. A Fisher's exact test was used to compare the proportion of patients with an improvement in SARA score of at least 1 point at 12 months between the

	Riluzole (n=22)	Placebo (n=22)	Mean difference (95% CI)	p value
Primary outcome: SARA score improvement of at least 1 point at month 12	7 (32%)	9 (39%)*	−10·3% (−37·4 to 19·2)	0·75
Secondary outcomes				
Change in the SARA score between inclusion and month 12	0·5 (−1·5 to 1·5)	0·3 (−1·0 to 2·5)	0·23 (−1·06 to 1·51)	0·70
Change in the CCFS between inclusion and month 12	0·055 (0·014 to 0·086)	0·004 (−0·040 to 0·020)	0·064 (0·015 to 0·110)	0·0050
Change in the INAS between inclusion and month 12	0 (−1 to 1)	−1 (−2 to 0)	−0·8 (−1·7 to 0·0)	0·070
Change in SF-36 PCS				
between inclusion and month 12	−1·9 (−6·2 to 11·1)	0·7 (−5·4 to 8·6)	−2·1 (−6·4 to 2·3)	0·89
Change in SF-36 MCS between inclusion and month 12	−0·8 (−4·7 to 3·5)	−4·7 (−6·8 to 3·2)	−1·5 (−8·4 to 5·5)	0·31
Percentage of MRI volume variation between inclusion and month 12				
Vermis	−4·86 (−7·32 to −0·03)	−3·35 (−6·36 to −0·25)	−0·79 (−4·52 to 2·94)	1·00
Left cerebellum	−1·73 (−3·95 to −1·25)	−1·27 (−3·29 to −0·33)	−0·83 (−2·45 to 0·79)	1·00
Right cerebellum	−1·25 (−3·03 to −0·47)	−1·58 (−2·23 to −0·35)	−0·83 (−2·57 to 0·9)	1·00
Midbrain	−1·63 (−3·44 to 0·96)	−3·34 (−5·82 to −0·69)	0·58 (−2·44 to 3·61)	1·00
Pons	−1·92 (−3·51 to −1·28)	−2·28 (−3·13 to −1·07)	0·45 (−1·1 to 2·01)	1·00
Medulla oblongata	1·59 (−5·20 to 6·77)	−1·41 (−6·72 to 2·75)	5·18 (−0·45 to 10·82)	1·00

Data are reported as n (%) or median (IQR) unless otherwise stated. The progression of brain atrophy for each region at month 12 is reported as median (IQR) of percentage change. Only one patient discontinued, and therefore secondary outcome results were presented by complete case analysis. SARA=scale for the assessment and rating of ataxia. CCFS=composite cerebellar functional severity score. INAS=inventory of non-ataxia signs. SF-36=36-item short-form health survey questionnaire. PCS=physical component score. MCS=mental component score. *The primary endpoint analysis was done by intention to treat, with n=23 in the placebo group.

Table 2: **Primary and secondary outcomes**

two treatment groups. The primary analysis was done on an intention-to-treat (ITT) basis with missing data for one patient replaced by values for the worst evolution in the treatment group and by mean values for evolution in the placebo group. An additional analysis of the primary endpoint and analyses of secondary endpoints were done with only the observed data (complete case analysis). Changes in quantitative scores (CCFS, INAS, SF-36, and MRI data) between baseline and month 12 were first calculated and then compared using a Mann-Whitney test. In addition to the month 0 and month 12 data from the trial, for the quantitative evolution of the SARA score compared with its expected natural evolution, a mixed model including the 2 years of pretrial data when available was used to test differences in progression between groups. Frequency of adverse events was compared between groups using Fisher's exact test. P values of less than 0·05 were considered significant, except for in MRI analysis, in which the Holm step-down Bonferroni method was used to consider multiple comparisons.

The prespecified MRI analyses included analysis of volume loss at month 12 compared with baseline in the placebo group and comparison between the two groups. Post-hoc analyses were as follows: comparison of baseline volumes between the ATRIL population and a healthy control group of 18 individuals acquired from the Paris Center and involved in the study PHRC AOM03059 (they had no neurological disease history and a normal neurological examination; the atrophy rates for cerebellum and pons as well as changes in white-matter density at month 12 were compared between both groups and between patients with spinocerebellar ataxia type 2 and healthy controls with Student *t* test); the correlations between baseline clinical scores, SARA, CCFS, and brain MRI data were determined using a linear-regression model adjusted for age at the baseline visit and the CAG repeat on the expanded allele, with p values being adjusted for multiple comparisons (Holm); and the atrophy progression for patients in the riluzole group, for whom two previous brain MRI scans had been acquired before the start of the trial. Statistical analyses were done with SAS software (version 9.4).

Role of the funding source

The funder of the study had no role in study design, data collection, data analysis, data interpretation, or writing of the report.

Results

Between Jan 18, 2018, and June 14, 2019, we enrolled 45 patients with spinocerebellar ataxia type 2 recruited in eight national reference centres for rare disease: the Pitié-Salpêtrière University Hospital in Paris (n=26), the Purpan University Hospital in Toulouse (n=5), the Pellegrin University Hospital in Bordeaux (n=3), the Pierre Wertheimer Neurological Hospital in Bron (n=3), the University Hospital of Angers (n=2), the University Hospital of Lille (n=2), the La Timone Hospital in

Marseille (n=2), and the Hautepierre University Hospital in Strasbourg (n=2).

22 patients were randomly assigned to receive riluzole and 23 patients to receive placebo (figure 1). In the placebo group, one patient left the study because of depression.

Clinical characteristics at baseline are shown (table 1). Participants complained about handwriting difficulties (44 [98%] of 45 patients) and cramps (33 [73%] of 45 patients). Median SARA score was 13·5 of 40 (IQR 9·5–16·5) with a median disease duration of 11 years (IQR 6–16); the most prevalent signs were cerebellar ataxia (45 [100%]), dysarthria (43 [93%]), brainstem involvement (with abnormal saccades in 43 [93%]) and dysphagia in 26 [58%]), neuropathy (areflexia in 32 [71%]), and deep sensory decrease (35 [78%]). Upper motor neuron signs were found in 21 (49%) patients and lower motor neuron signs were found in 15 (34%).

For the primary endpoint (ie, the proportion of patients with a 1-point SARA-score improvement, meaning a decrease in SARA score), no significant variations in SARA score were found between treated and untreated patients on the basis of the ITT analysis (seven [32%] *vs* nine [39%]; p=0·75; table 2). Complete case analysis confirmed this result (seven [32%] *vs* nine [41%]; p=0·75).

See Online for appendix

No significant differences in SARA improvement were found in patients with or without motor neuron involvement (table 2). The SARA score after 12 months was not significantly different between the riluzole and placebo groups and showed a median increase (meaning worsening) of 0·5 (IQR –1·5 to 1·5) in the riluzole group versus 0·3 (–1·0 to 2·5) in the placebo group (p=0·70; table 2).

The quantitative change of SARA compared with the extended pretrial 2-year slope of SARA (analysed in all participants for whom at least one SARA score was available, n=43) showed no significant change in SARA progression before and during the trial for both groups (figure 2).

CCFS worsened significantly in the riluzole group compared with the placebo group (0·055, IQR 0·014 to 0·086, *vs* 0·004, –0·040 to 0·020; p=0·0050; table 2). INAS change was similar (0, IQR –1 to 1 *vs* –1 to –2 to 0; p=0·070) in both groups (table 2). We did not detect a statistically significant upper or lower motor neuron improvement in the riluzole group compared with the placebo group (table 2).

Quality of life, as assessed by the SF-36 questionnaire, showed that for all dimensions except pain, patients had lower scores in physical and mental states than the French General Population (appendix p 3). At month 12, a tendency towards worsening of the composite SF-36 score was observed in both groups compared with baseline. This difference from baseline was not significant in either group (table 2; appendix p 3).

In the riluzole group, no patient had clinically significant blood-analysis abnormalities. Liver enzymes did not increase with treatment except in one patient (ALAT increase less than two times the normal value at month 2 of treatment followed by regression at month 3). In the placebo group, one patient had an ALAT increase (five times the normal value). No serious adverse event was reported in the riluzole group whereas four patients in the placebo group had a serious adverse event. The number of patients with adverse events was similar in both groups (riluzole 16 [73%] *vs* placebo 19 [83%]; p=0·49]). No death occurred during the trial. All adverse events are listed (table 3). Treatment compliance was high in both groups, 94% (SD 9·75) in the riluzole group and 94% (5·77) in the placebo group.

All patients underwent brain MRI at baseline and at 12 months. One patient was excluded from brainstem analysis because of suboptimal segmentation. Baseline cerebellum and brainstem volumes are reported in the appendix (pp 4–5). Compared with healthy controls, baseline volumes were significantly lower in patients with spinocerebellar ataxia type 2, with the exception of the superior cerebellar peduncle (appendix pp 4–5). No significant difference was found between the two groups in percentage of volume change between baseline and the 12 month visit (table 2; appendix pp 6–7). A significant change of volume at month 12 compared with baseline was found in the placebo group for the left lobule crus I (Holm p=0·0013) and pons (Holm p=0·0002) appendix pp 6–7).

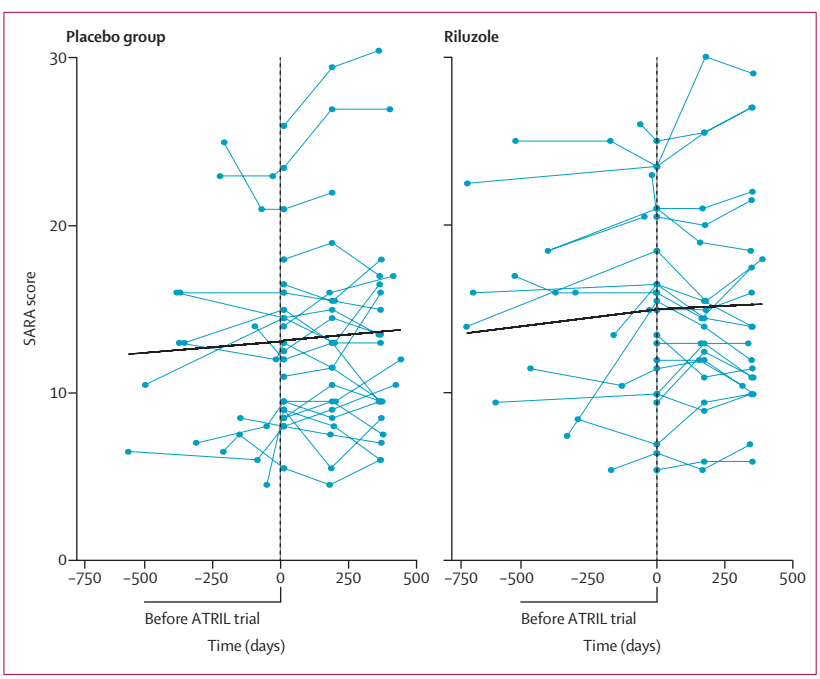

***Figure 2*: Change in SARA score 2 years before and during ATRIL**
Change in SARA score in the placebo (A) and riluzole (B) groups. Each blue line represents a single patient. The black lines for each group represent the mean line of SARA progression estimated from the model (a mixed model including the 2 years of pre-trial data when available to test differences in progression between groups). Time in days is represented on the x-axis, with 0 indicating the beginning of the ATRIL study. The negative values represent time before the ATRIL study. For SARA score, 0 indicates least severe impairment and 40 most severe impairment. SARA=Scale for the Assessment and Rating of Ataxia.

In post-hoc analyses, we investigated the correlations between baseline SARA and CCFS scores and MRI data. Cerebellar and brainstem atrophy was greater in patients with higher SARA scores at baseline, but the change from baseline was not significant after adjustment for age and pathological CAG repeat length (appendix p 8). Higher CCFS scores were significantly correlated with higher vermis grey-matter atrophy (appendix p 10), even after adjustment (Holm p=0·044; appendix p 9).

For five patients in the riluzole group, two previous brain MRI scans at 2-year intervals were available. The progression of atrophy for each region on the basis of two previous MRI scans and the two clinical trial MRI scans is shown in the appendix (p 11). On the basis of these data, mean annual volume loss showed significant progression over the course of the 12 months for the pons (–277 mm³ [SE 41] per year, p<0·0001) and for the left lobule crus I (–171 mm³ [SE 24] per year, p<0·0001).

	Riluzole (n=22)	Placebo (n=23)	p value
Patients with serious adverse events	0	4 (17%)*	0·10
Patients with adverse events	16 (73%)	19 (83%)	0·49
Number of adverse events	2 (1–3·5)	3 (1·5–4)	..
Severity of the adverse event			0·32
Slight	24 (69%)	43 (61%)	..
Moderate	11 (31%)	23 (32%)	..
Severe	0	5 (7%)	..
Treatment stopped because of adverse event	0	3 (13%)†	0·23
Types of adverse events			
Blood and lymphatic system disorders	0	4 (17%)	0·10
Hepatic disorders	1 (5%)	3 (13%)	0·60
Cardiac disorders	1 (5%)	2 (9%)	1·00
Skin disorders	3 (14%)	1 (4%)	0·34
Musculoskeletal disorders	1 (5%)	7 (30%)	0·040
Gastrointestinal disorders	2 (9%)	6 (26%)	0·24
Infections	4 (18%)	5 (22%)	1·00
Nervous system disorders	4 (18%)	6 (26%)	0·72
Ear and labyrinth disorders	0	2 (9%)	0·48
Other	9 (41%)	11 (48%)	0·76

Data are n (%) or median (IQR). *Hepatic enzymes increase, fracture of external malleolus, rectorrhagia, and depression. †Depression, an alanine transaminase increase greater than five times the reference value, and one patient had hair loss and limb tremor.

Table 3: **Adverse and serious adverse events**

Discussion

A regimen of 50 mg of riluzole twice per day for 12 months in adults with spinocerebellar ataxia type 2 did not result in a 1 point decrease of the SARA score at month 12 more often than did placebo. Therefore, we could not confirm a beneficial effect of riluzole, as has been previously reported.[6]

The mechanism of action of riluzole is not yet clear. This molecule has a pleiotropic effect on several ion channels and neurotransmitters. Riluzole seems to have a neuroprotective action enhancing the synaptic reuptake of glutamate and decreasing its release,[15] thereby preventing excitotoxicity; it also regulates the release of other excitatory neurotransmitters such as acetylcholine, dopamine, and serotonin by reducing cellular Ca^{2+} influx.[15] The most interesting potential mechanism for improving cerebellar ataxia is linked to its function as an opener of small-conductance Ca^{2+}activated K+ channels, regulating the increased firing frequency of deep cerebellar nuclei neurons resulting from loss of Purkinje cells. When considering patients with Friedreich's ataxia separately from those with spinocerebellar ataxias in the trial by Romano and colleagues,[6] the improvement in SARA score was not different between patients from the treated and placebo groups. The absence of benefit from riluzole in Friedreich's ataxia could be explained by the prominent loss of deep cerebellar nuclei neurons with spared Purkinje cells. Furthermore, in a mouse model of spinocerebellar ataxia type 3, treatment with riluzole for 10 months showed decreased motor performance.[16] This study revealed a reduction of soluble normal ataxin 3 in riluzole-treated mice associated with an increased accumulation of mutated ataxin 3 protein.[16]

Even though patients with spinocerebellar ataxia type 2 represented the third largest group (n=16 of 60) after those with spinocerebellar ataxia 1 and those with Friedreich's ataxia in the previous trial,[6] the heterogeneous nature of the cohort could have affected previous results. For this reason, we chose to enrol only patients with spinocerebellar ataxia type 2 with similar disease stages and did not include presymptomatic carriers (defined by a SARA score of less than 3 of 40). We included patients with a moderate stage of disease and a median SARA score of 13·5 of 40. We chose to enrol only patients with an age at onset up to 50 years, given that previous studies showed that patients with a later age at onset have a slower disease progression.[2,17] This choice would reduce the power for assessment of efficacy of the drug given the rare nature of this disease and the consequent small number of patients available.

In addition to the primary outcome, we evaluated the quantitative change of SARA score after 12 months that was not significantly different between the two groups. SARA is a validated assessment of cerebellar ataxia with a linear progression,[2] allowing us to do the analyses at only two timepoints. However, SARA is rater dependent and patient dependent (eg, it can be affected by physiotherapy, concomitant treatments or diseases, examination at different times of day)[18] and variations in scores could have potentially masked the beneficial effect of riluzole. For this reason, we used the CCFS, a validated, quantitative, and age-adjusted outcome measure that is rater independent, to assess upper-limb dysfunction.[12] Unexpectedly, CCFS measures significantly worsened in the riluzole-treated group. However, this measure did not

differ between baseline and 1 year follow-up in the placebo group, indicating that CCFS was not sensitive enough to pick up upper-limb disease progression within the time of the study. We also investigated motor neuron involvement but treatment was not accompanied by an improvement of the upper and lower motor neuron signs.

For brain MRI volumetry, which is reported to be more sensitive in detecting changes than clinical scores,[19] we used new automated tools (CEREbellum Segmentation [CERES] from the volBrain online platform) to obtain an accurate segmentation of the brainstem and a lobule-based parcellation of the cerebellum. Cerebellar and brainstem volumes decreased over 12 months in the placebo group, as expected and previously reported in other longitudinal studies.[19,20] Moreover, it has been previously reported that for for carriers of the SCA2 mutation in *ATXN2* atrophy is already present at a presymptomatic stage in the brainstem,[21] especially the pons,[20] and in the cerebellum.[21] In this trial, volume loss was not prevented by riluzole, and volume changes did not differ between the two groups after 1 year. Two regions showed a significant decrease in volume compared with baseline, the pons and the left lobule crus I. The first region is one of the most important for oculomotor control. Saccade abnormalities, such as slow saccades, are common in spinocerebellar ataxia type 2.[22] In fact, more than one third of patients had oculomotor abnormalities at baseline and these did not improve after riluzole treatment. Lobule crus I has been implicated in cerebellar cognitive tasks, such as working memory and executive functions. Even though cerebellar motor alterations are usually the first signs observed in patients with spinocerebellar ataxia type 2, cerebellar cognitive affective syndrome (CCAS)[23] is common. However, we did not use a specific scale to assess CCAS. The presence of advanced atrophy at baseline could explain why we did not find a significant difference in volume change after 12 months for the other cerebellum or brainstem regions. We might explain this by a floor effect for change in the cerebellum, as has already been suggested, meaning that if the volume is already low at baseline, significant changes over time are not detected.[24]

For the **volBrain: Automated MRI Brain volumetry system** see https://volbrain.upv.es

CCFS score correlated significantly with vermis grey-matter atrophy, by contrast with SARA scores, which did not correlate with brain volume loss. However, the anatomical and physiological link between the vermis and upper-limb dysmetria is not established.

Future trials of gene therapy will likely be done in a multicentre setting because of the low prevalence of spinocerebellar ataxias. For this reason, objective and quantitative biomarkers rather than clinical measures are necessary to monitor drug effects and avoid inter-rater variability. We and others have shown that blood neurofilament light-chain concentrations correlate with clinical and radiological outcomes.[25] The absence of neurofilament measurement, which was not validated in spinocerebellar ataxias when this study began, represents a limitation of this study, as does the absence of other objective biomarkers (eg, oculomotor recording or wearable sensors) that might have provided more accurate readouts. Cognitive assessment by the CCAS scale[26] could also have been useful for exploring correlations with specific cerebellum lobule volumes. Another limitation of our study is the low number of enrolled patients (45 patients) compared with the sample size calculations from the EUROSCA cohort (172 patients with spinocerebellar ataxia type 2 would be needed to detect a 50% reduction in SARA progression rate with a power of 80% in a 1 year trial).[2] The inclusion of 172 patients with same-stage spinocerebellar ataxia type 2 seems to not be feasible except for in a multicentre international setting. The ATRIL sample size estimation was based on the study by Romano and colleagues.[6] Considering their primary endpoint, the ATRIL sample size was sufficiently powered to show a difference between groups on the basis of the reported 50% of patients with SARA score improved by at least 1 point after 12 months.[6] However, with a 95% CI between −37·4% and 19·2%, our data are consistent with a wide range of potential effects and do not exclude potential benefits (or harms) of riluzole.

In conclusion, using the same dose and duration of riluzole, and the same and additional readouts as Romano and colleagues,[6] in a large clinically and genetically homogeneous group of patients with spinocerebellar ataxia type 2, we found no improvement in clinical and radiological outcomes, despite satisfactory treatment compliance and an absence of serious adverse events. Although this result does not exclude a possible positive effect of riluzole on other forms of cerebellar ataxia, it illustrates the need to evaluate treatments in a homogeneous groups of patients, even in rare diseases.

Contributors

AD was the principal investigator. GC, STdM, and AD conceived and designed the study. GC, AH, CE, MLM, FC, PC, CG, ST, MA, KN, DD, CV, and AD followed up the patients and acquired the data. CF, MC, VR, and JFM analysed the radiological data. The statistical analyses were done by STdM. All authors reviewed, contributed to, and approved the final manuscript. All authors had full access to and verified the data and had final responsibility for the decision to submit the manuscript for publication.

Declaration of interests

We declare no competing interests.

Data sharing

Individual anonymised participant data and relevant clinical study documents (study protocol, statistical analysis plan, informed consent form, and clinical study report) will be available for qualified scientific and medical researchers as necessary for doing legitimate research. To request access to the data and submit a research proposal, please send a request to alexandra.durr@icm-institute.org.

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References

1 Durr A. Autosomal dominant cerebellar ataxias: polyglutamine expansions and beyond. *Lancet Neurol* 2010; **9:** 885–94.
2 Jacobi H, du Montcel ST, Bauer P, et al. Long-term disease progression in spinocerebellar ataxia types 1, 2, 3, and 6: a longitudinal cohort study. *Lancet Neurol* 2015; **14:** 1101–8.

3 Scoles DR, Meera P, Schneider MD, et al. Antisense oligonucleotide therapy for spinocerebellar ataxia type 2. *Nature* 2017; **544:** 362–66.

4 Moore LR, Rajpal G, Dillingham IT, et al. Evaluation of antisense oligonucleotides targeting ATXN3 in SCA3 mouse models. *Mol Ther Nucl Acid* 2017; **7:** 200–10.

5 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.

6 Romano S, Coarelli G, Marcotulli C, et al. Riluzole in patients with hereditary cerebellar ataxia: a randomised, double-blind, placebo-controlled trial. *Lancet Neurol* 2015; **14:** 985–91.

7 Fang T, Khleifat AA, Meurgey J-H, et al. Stage at which riluzole treatment prolongs survival in patients with amyotrophic lateral sclerosis: a retrospective analysis of data from a dose-ranging study. *Lancet Neurol* 2018; **17:** 416–22.

8 Pulst SM. Degenerative ataxias, from genes to therapies: the 2015 Cotzias Lecture. *Neurology* 2016; **86:** 2284–90.

9 Elden AC, Kim H-J, Hart MP, et al. Ataxin-2 intermediate-length polyglutamine expansions are associated with increased risk for ALS. *Nature* 2010; **466:** 1069–75.

10 Chiò A, Calvo A, Moglia C, et al. ATXN2 polyQ intermediate repeats are a modifier of ALS survival. *Neurology* 2015; **84:** 251–8.

11 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.

12 du Montcel ST, Charles P, Ribai P, et al. Composite cerebellar functional severity score: validation of a quantitative score of cerebellar impairment. *Brain* 2008; **131:** 1352–61.

13 Jacobi H, Rakowicz M, Rola R, et al. Inventory of non-ataxia signs (INAS): validation of a new clinical assessment instrument. *Cerebellum* 2013; **12:** 418–28.

14 Ware JE, Sherbourne CD. The MOS 36-item short-form health survey (SF-36). I. Conceptual framework and item selection. *Med Care* 1992; **30:** 473–83.

15 Bellingham MC. A review of the neural mechanisms of action and clinical efficiency of riluzole in treating amyotrophic lateral sclerosis: what have we learned in the last decade? *CNS Neuro Ther* 2011; **17:** 4–31.

16 Schmidt J, Schmidt T, Golla M, et al. In vivo assessment of riluzole as a potential therapeutic drug for spinocerebellar ataxia type 3. *J Neurochem* 2016; **138:** 150–62.

17 Diallo A, Jacobi H, Cook A, et al. Survival in patients with spinocerebellar ataxia types 1, 2, 3, and 6 (EUROSCA): a longitudinal cohort study. *Lancet Neurol* 2018; **17:** 327–34.

18 Grobe-Einsler M, Taheri Amin A, Faber J, et al. Development of SARAhome, a new video-based tool for the assessment of ataxia at home. *Mov Disord* 2021; **36:** 1242–46.

19 Adanyeguh IM, Perlbarg V, Henry P-G, et al. Autosomal dominant cerebellar ataxias: imaging biomarkers with high effect sizes. *Neuroimage Clin* 2018; **19:** 858–67.

20 Nigri A, Sarro L, Mongelli A, et al. Progression of cerebellar atrophy in spinocerebellar ataxia type 2 gene carriers: a longitudinal MRI study in preclinical and early disease stages. *Front Neurol* 2020; **11:** 616419.

21 Jacobi H, Reetz K, du Montcel ST, et al. Biological and clinical characteristics of individuals at risk for spinocerebellar ataxia types 1, 2, 3, and 6 in the longitudinal RISCA study: analysis of baseline data. *Lancet Neurol* 2013; **12:** 650–58.

22 Federighi P, Cevenini G, Dotti MT, et al. Differences in saccade dynamics between spinocerebellar ataxia type 2 and late-onset cerebellar ataxias. *Brain* 2011; **134:** 879–91.

23 Schmahmann JD. The cerebellum and cognition. *Neurosci Lett* 2019; **688:** 62–75.

24 Koscik TR, Sloat L, van der Plas E, et al. Brainstem and striatal volume changes are detectable in under 1 year and predict motor decline in spinocerebellar ataxia type 1. *Brain Commun* 2020; **2:** fcaa184.

25 Coarelli G, Darios F, Petit E, et al. Plasma neurofilament light chain predicts cerebellar atrophy and clinical progression in spinocerebellar ataxia. *Neurobiol Dis* 2021; **153:** 105311.

26 Hoche F, Guell X, Vangel MG, Sherman JC, Schmahmann JD. The cerebellar cognitive affective/Schmahmann syndrome scale. *Brain* 2018; **141:** 248–70.