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

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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.

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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