Riluzole in spinocerebellar ataxia type 7: report on two families and a granted project.

Ferraldeschi M [1], Tzekov R. [2] , Romano S. [1], Pegoraro E. [3], Sato G. [4] , Maritan V. [5] (5), Paderni C. [6], Suppiej A. [7], Zesiewicz T. [8], Ristori G. [1]

1. Department of Neurosciences, Mental Health and Sensory Organs (NESMOS Department), Center for Experimental Neurological Therapies (CENTERS), S. Andrea Hospital-site, "Sapienza" University of Rome;
2. Department of Ophthalmology, Advanced Visual Function Testing Service , University of South Florida , Tampa, FL, USA
3. Institute of Neurology, University of Padua
4. Center for Low Vision Rehabilitation of adult, ULSS 16. Padua
5. Center for Low Vision Rehabilitation of childhood. Pediatric clinic. Padua
6. Robert Hollman Foundation. Padua
7. Child Neurology, Clinical Neurophysiology and Neuroophthalmology, Paediatric University Hospital Padua.
8. Department of Neurology, USF Ataxia Research Center, University of South Florida, Tampa, FL, USA

BACKGROUND

Spinocerebellar ataxia type 7 (SCA7) is one of the rarest dominant forms of cerebellar ataxias (ADCAs). It is caused by the expansion of a CAG repeat within the ataxin 7 (ATXN7) gene on chromosome 3p12-p21.1, leading to a pathogenic polyglutamine tract within the ataxin 7 protein.
We reported encouraging data on riluzole effects in patients with cerebellar ataxias of different etiologies (1), and in patients with hereditary cerebellar ataxia other than SCA7 (2). These works prompted us to try an off-label use of riluzole in an Italian and an American family with SCA7.

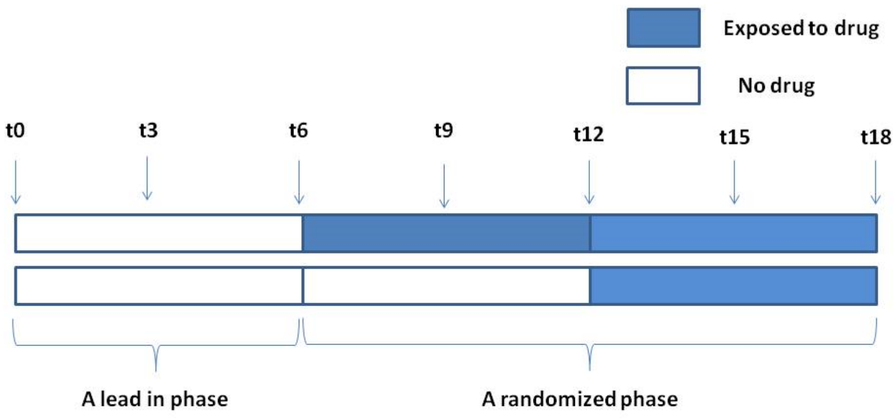
METHODS AND RESULTS

A 41-year old woman, followed at Padua Center, had 40 triplets at ATXN7 gene and was referred at age 36 with visual deterioration and cerebellar signs with progressive course. She started riluzole in late 2014 when visual loss was overt, and SARA score was 30. After 2 years of riluzole therapy SARA score was 16, while no improvement in vision occurred (deterioration from 1/100 in both eyes to light perception). Her 22-year old daughter started riluzole in the past four months, and she is currently stable with a SARA score of 16.
Two female siblings (63 and 73 year-old), assessed at USF (US) reported visual disturbances and were diagnosed as SCA7 (40 and 39 repeats, respectively). They were followed up by ophthalmological examinations and neurological examination for several years. In late 2010 they started riluzole. After one year of therapy cerebellar and visual functions improved (respectively from 8 to 6 at SARA score and from 0.6 to 0.4 at logMAR) in both siblings. SARA score remained stable for 3 years and then started to increase (13 at the last evaluation - 6 years after the beginning of the treatment in both siblings), while visual acuity and OCT lesions remained practically stable in both siblings, since they started the drug.

CONCLUSIONS

SCA7 has no therapeutic options, so that the relentless course, the important visual deficit that accompanies cerebellar ataxia, and the possibility of disease development in childhood are pressing unmet needs.
Data from these families suggest some efficacy and safety even on long-term follow-up.
This and the published data on riluzole in cerebellar ataxia (1-2) prompted us to propose to the Agenzia Italiana del Farmaco (AIFA – Italian Drug Agency) a randomized, double-blind, placebo-controlled pilot trial with a lead-in phase(see flow diagram; figure 1), aimed at verifying the effects of the drug in an informative number of SCA7 people (now accepted). The objective of the trial will be a serial evaluation of riluzole effects on stringent outcome measures: ophthalmological metrics, scale for the assessment and rating of ataxia (SARA), and safety biomarkers (see flow chart of the study; Figure 2).

Figure 1: Flow diagram



A randomized , double-blind, placebo-controlled pilot trial with a lead in phase

The co-primary endpoints were the proportion of patients with stable Scale for the Assessment and Rating of Ataxia (SARA) and the Visual Acuity in log MAR units at 18 months, calculated as mean of t0-t3-t6 evaluations.

Figure 2: Flow-chart

	Visit 1		Visit 2	Visit 3-7
Activity	T0 Baseline Randomization Treatment		T3 Follow-up visit	T6-T9-T12-T15-T18 Follow-up visit
Informed Consent	x			
Inclusion / Exclusion Criteria	x			
Demographic data	x			
Medical History	x			
Concomitant medications	x		x	x
Physical examination	x		x	x
Neurological examination(SARA score)	x		x	x
Electrocardiogram	x		x	x
Ophthalmological exams	x		x	x
Hematology and Blood Chemistry	x		x	x
Randomization		x		
Study drug/placebo				x
Adverse Events			x	x

REFERENCES

1.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.
2.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(10):985-91

giovanni.ristori@uniroma1.it; michela.ferraldeschi@gmail.com; silvia.romano@uniroma1.it

S. Andrea Hospital-site, "Sapienza" University of Rome;+39 06/33776044