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Short report

The effect of the neuroprotective agent riluzole on MRI parameters in primary progressive multiple sclerosis: a pilot study

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Progressive axonal loss is the most likely pathologic correlate of irreversible neurologic impairment in primary progressive multiple sclerosis. In a run-in versus treatment trial, we show that the neuroprotective agent riluzole seems to reduce the rate of cervical cord atrophy and the development of hypointense T1 brain lesions on magnetic resonance imaging.
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Key words: *multiple sclerosis; neuroprotection; riluzole*

Introduction

Most currently available treatments for multiple sclerosis (MS) are aimed at suppressing the inflammatory component of the disease. Their main clinical impact is on relapses, whereas an effect on permanent disability so far has been less well established. Patients with primary progressive (PP) MS show less inflammatory activity – the reason why they are typically excluded from treatment trials, despite clear clinical progression. Recent evidence suggests that axonal loss in MS may occur earlier in the course of the disease and is the most likely correlate of irreversible neurologic impairment.[1–4] Suppression of disease activity and reduction of axonal damage were shown in an animal model of MS, when using the AMPA/kainate antagonist NBQX.[5,6] These observations support the pursuit of neuroprotective therapeutic strategies in MS.

We performed a pilot study investigating the effects of the neuroprotective agent riluzole in PP MS patients. Riluzole is an approved treatment for amyotrophic lateral sclerosis (ALS), providing a greater probability of survival.[7] The drug appears to act through the inhibition of glutamate transmission, an excitotoxin participating in the process of neuronal damage. Since the magnetic resonance imaging (MRI) correlates of axonal loss, atrophy of the spinal cord, and T1 hypointense brain lesions are sensitive enough to measure disease progression in short periods of time,[8] we used these measures as primary outcome parameters.

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Methods

We selected nine women and seven men (aged 30–66 years), with documented progression during the 24 months before inclusion, from a natural history study. Kurtzke's EDSS scores were between 3.0 (inclusive) and 7.5 (inclusive). All adverse events were documented; safety laboratory consisted of serum transaminases (monthly for three months and every three months thereafter) and haematology (CBC and differential every six months) after the start of treatment. The study was approved by the hospital ethics committee, and all patients gave informed consent. During the first year, no specific treatment was given; during the second year, all patients were treated with riluzole (2×50 mg daily). MRI scanning consisted of six monthly inversions prepared by 3D gradient echo sequence of the cervical cord, and yearly T1- and T2-weighted spin-echo sequences of the brain. The main efficacy parameter was the change in spinal cord cross-sectional area, obtained from 10 contiguous 3-mm axial slices perpendicular to the cord above the center of the C2–C3; the coefficient of variation for this method in our hands was 1.3%. Scans were analysed in a randomized and blinded fashion, and since this was an explorative study, no formal statistics were performed.

Results

Two patients discontinued treatment because of side effects (headache in one, increase in spasticity in the other); since they also discontinued to follow-up their data, these patients were excluded from analysis. Five patients needed intermittent reduction in dosage of riluzole. In 14 patients who took medication for over three months, severe adverse effects were not observed. Adequate MRI data could not be obtained at multiple time points in one patient (who was

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Table 1 Baseline data for spinal cord area, T1 and T2 lesion load, and the percentage change during the first and second year of follow-up

MRI parameter	*Baseline*	*1 year*	*2 years*	*Change during first year[a] (without treatment) [%]*	*Change during second year[a] (with treatment) [%]*
Spinal cord area[b]	66.7 (9.1)	65.4	65.2	−2.0	−0.2
T1 lesion load[c]	271 (0–7032)	403 (0–9393)	369 (129–9243)	+15	+6
T2 lesion load[c]	2160 (513–32892)	3343 (540–28008)	4206 (600–28800)	+7.0	+10

[a]Median change of all evaluable scans. [b]Mean, mm^2 (SD); SD=standard deviation. [c]Median, mm^3 (range).

therefore excluded from analysis), while five others had one missing data point. In the first year, an average decrease of 2.0% in cord area was found, and an increase in T1 and T2 lesion loads, as expected (Table 1). In the second year, we saw a stabilization in cord diameter (−0.2%), as illustrated in Figure 1. While the increase in T2 lesion load in the brain continued under treatment, the accumulation of T1 hypointense lesions showed a trend towards stabilization.

Discussion

The results from this pilot study, as far as we know the first neuroprotective treatment in MS, suggest a favourable effect on MRI parameters of axonal loss during 12 months of treatment with riluzole in the absence of an effect on total brain lesion load. Remarkably, another study applying novel MRI techniques in monitoring the effect of treatment on the pathologic process in MS found the same dissociation, although mirrored; treatment with the lymphocyte-depleting humanized monoclonal antibody Campath 1H strongly reduced the number of new inflammatory lesions, without an effect on progression of atrophy and T1 lesion load as markers of axonal loss.[9] Our observations are in line with the hypothesis that riluzole does not affect new lesion formation, but does have an impact on subsequent mechanisms involving lesion evolution and axonal loss, and thereby stimulates further placebo-controlled studies in (PP) MS. Obvious limitations of our study are the small sample size and the lack of a randomized cross-over design. Despite the small size of the group, the reduction of the spinal cord cross-sectional area is of the same magnitude as that reported in the paper by Stevenson *et al.*[8] In a recently published study, a correlation between glutaminase expression and axonal damage was confirmed experimentally in animals.[6] White matter from other inflammatory neurologic diseases displayed glutaminase reactivity, whereas normal and non-inflammatory conditions showed none, implicating that imbalanced glutamate homeostasis contributes to axonal and oligodendroglial pathology in MS, and that manipulation of this imbalance may have a therapeutic impact.

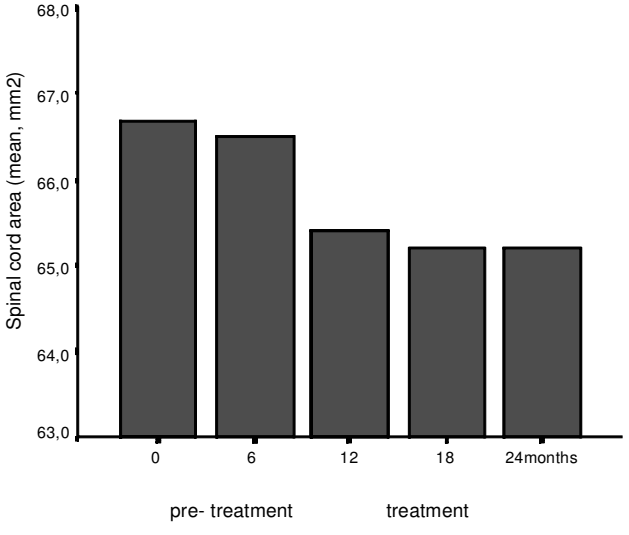

Figure 1 *Spinal cord area (mean, mm^2); months 0–12 without treatment, months 12–24 with treatment*

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References

1 Ferguson B, Matyszak MK, Esiri MM, Perry VH. Axonal damage in acute multiple sclerosis lesions. *Brain* 1997; **120(Pt 3):** 393–99.
2 Trapp BD, Peterson J, Ransohoff RM, Rudick R, Mork S, Bo L. Axonal transection in the lesions of multiple sclerosis. *N Engl J Med* 1998; **338:** 278–85.
3 Scolding N, Franklin R. Axon loss in multiple sclerosis. *Lancet* 1998; **352:** 340–41.
4 van Waesberghe JH, Kamphorst W, De Groot CJ, *et al.* Axonal loss in multiple sclerosis lesions: magnetic resonance imaging insights into substrates of disability. *Ann Neurol* 1999; **46:** 747–54.
5 Pitt D, Werner P, Raine CS. Glutamate excitotoxicity in a model of multiple sclerosis. *Nat Med* 2000; **6:** 67–70.
6 Werner P, Pitt D, Raine CS. Multiple sclerosis: altered glutamate homeostasis in lesions correlates with oligodendrocyte and axonal damage. *Ann Neurol* 2001; **50:** 169–80.
7 Bensimon G, Lacomblez L, Meininger V, ALS/Riluzole Study Group. A controlled trial of riluzole in amyotrophic lateral sclerosis. *N Engl J Med* 1994; **330:** 585–91.
8 Stevenson VL, Leary SM, Losseff NA, *et al.* Spinal cord atrophy and disability in MS: a longitudinal study. *Neurology* 1998; **51:** 234–38.
9 Coles AJ, Wing MG, Molyneux P, *et al.* Monoclonal antibody treatment exposes three mechanisms underlying the clinical course of multiple sclerosis. *Ann Neurol* 1999; **46:** 296–304.