MRS study of the Effects of Minocycline on Markers of Neuronal and Microglial Integrity in ALS

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INTRODUCTION

Amyotrophic lateral sclerosis (ALS) is a rare neurodegenerative disease characterized by progressive loss of cortical, bulbar and spinal motor neurons. No effective pharmacological treatment currently exists for ALS and the only FDA-approved treatment is riluzole, an antiglutamate neuroprotector, which can extend life by no more than 2-3 months. Several other drug candidates are presently under investigation, including the antiapoptotic agent minocycline, a tetracycline antibiotic which has been shown to prolong life by a few weeks in a transgenic mouse model of ALS.[1] Recent human studies indicate that minocycline exerts neuroprotective effects and the drug has already been in phase III trials. Several MRS studies have reported reduced NAA in the precentral gyrus and brainstem areas.[2,3] In this study, MRS was used to monitor the effect of minocycline administration for a short period to ALS patients under no other treatment.

METHODS

Ten ALS patients (62.5 ± 10.3 years; 8 men, 2 women) newly diagnosed according to the El Escorial criteria for definite or probable ALS were recruited. Patients were submitted to MRS examination before minocycline administration (t = 0) and at times 3 and 6 weeks after onset of minocycline treatment (200 mg/day). Single-voxel MRS data were acquired in the motor cortex (precentral gyrus) and in the brainstem on a GE Signa 1.5 T imager using the PRESS sequence with TE = 30 ms or 135 ms, TR = 1500 ms, a voxel size of 2 x 2 x 2 cm^3 and 128 acquisitions. The NAA/Cr, Cho/Cr, mI/Cr, Glx/Cr, NAA/mI and NAA/(Cr+Cho) metabolite ratios were quantified with LCModel. Statistical analyses were performed using one way repeated measures ANOVA followed by a Tukey test for pairwise multiple comparisons.

RESULTS

Metabolite ratios determined by LCModel are presented in Table 1 for spectra acquired with TE = 30 ms for 10 SLA patients. In the precentral gyrus, none of the metabolite ratios showed any significant variation in the six week period following minocycline administration. Larger variations were measured in the brainstem at t = 6 weeks relative to t = 0 for NAA/Cr (+8.7%), Cho/Cr (+15%), mI/Cr (+20%) and NAA/mI (-11%), but only mI/Cr showed a tendency toward statistical significance (p = 0.061) at 6 weeks. No lactate was detected in any case.

Table 1. MRS metabolite ratios for ALS patients

Metabolite ratio	Precentral gyrus			Brainstem		
	t = 0	t = 3 wk	t = 6 wk	t = 0	t = 3 wk	t = 6 wk
NAA/Cr	1.52 ± 0.14	1.49 ± 0.16	1.52 ± 0.13	2.06 ± 0.36	2.13 ± 0.51	2.24 ± 0.40
Cho/Cr	0.31 ± 0.02	0.29 ± 0.04	0.32 ± 0.03	0.53 ± 0.07	0.58 ± 0.09	0.61 ± 0.12
mI/Cr	0.91 ± 0.10	0.93 ± 0.11	0.94 ± 0.09	1.14 ± 0.29	1.27 ± 0.24	1.37 ± 0.34
Glx/Cr	1.81 ± 0.28	1.83 ± 0.25	1.73 ± 0.32	2.31 ± 0.52	2.40 ± 0.55	2.46 ± 0.67
NAA/mI	1.69 ± 0.28	1.63 ± 0.33	1.64 ± 0.29	1.90 ± 0.50	1.72 ± 0.56	1.68 ± 0.29
NAA/(Cho+Cr)	1.13 ± 0.16	1.16 ± 0.15	1.16 ± 0.12	1.35 ± 0.21	1.38 ± 0.23	1.40 ± 0.23

DISCUSSION

The fact that the previously reported decreases in NAA/Cr and NAA/(Cho+Cr) in the precentral gyrus and brainstem for ALS patients are not observed after six weeks of minocycline treatment suggests that the drug may prevent neuronal loss. The increased mI/Cr ratio in the brainstem is consistent with glial activation. These results suggest that minocycline treatment may have beneficial effects on brain regions affected by ALS.

References

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