The treatment impact of minocycline on quantitative MRI in acute spinal cord injury

Y. Zhang[1], V. Yong[1], R. Hurlbert[1], and S. Casha[2]
[1]University of Calgary, Calgary, AB, Canada, [2]Dalhousie University, Halifax, Nova Scotia, Canada

Introduction

The impact of acute spinal cord injury (SCI) remains catastrophic. However, there is no treatment proven to significantly reduce disability following this devastating condition. Pathological changes in acute SCI include instant cell death as a result of direct mechanical attack and secondary injury to the mildly or undamaged neuronal tissue following primary insult[1]. Currently, improving recovery of partially injured spinal cord tissue is considered as a practical therapeutic approach[2]. As a tetracycline derivative minocycline has been shown to reduce injury bulk and improve functional outcomes in mice subjected to SCI[3]. Recently, a pilot placebo-controlled, randomized clinical trial has been undertaken to test the potential of minocycline in human SCI. The purpose here was to assess the treatment impact of minocycline using quantitative MRI.

Method

Fifty-two patients were randomized within 12 hours of injury to either intraveneous minocycline or placebo therapy, twice daily, for 1 week. Patients were included if they were: ≥16 years old; had motor complete or motor incomplete or central cord injury in the cervical or thoracic spine; able to provide informed consent. MR imaging was performed at a single site using a 1.5T scanner (Avanto or Sonata, Siemens Medical Systems, Germany) within 24 hours of injury (day 1), and at day 7, week 4, and week 52 after acute SCI. MRI protocols included: sagittal T1-weighted (T1W) spin echo (SE) (TR=433 ms, TE=13 ms); sagittal T2W fast SE (TR=3340 ms, TE=95 ms) and sagittal short time inversion recovery (STIR) MRI (TR=4360 ms, TE=70 ms) with FOV=240x240 mm^2, slice thickness=3 mm, and matrix=896x896. Axial images included T1W, T2W or 3D gradient echo MRI.

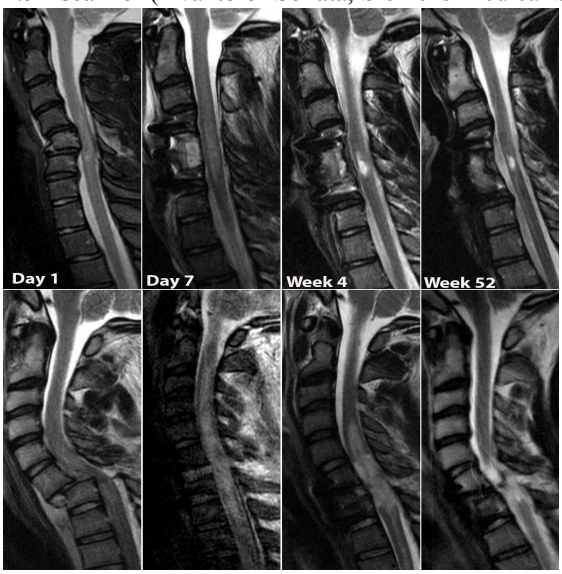

Fig1: The SCI lesion treated with minocycline (top) appears more confined than that with placebo over time.

Maximum canal compromise (MCC) and maximum spinal cord compression (MSCC) at the injury epicenter was quantified on the sagittal T1W and T2W images respectively based on a published method[4]. The length and area of overall T2 hyperintensity were assessed on the sagittal T2W MRI using a semi-automatic region-growing program (Osirix 3.6) (Fig. 1). Neurological outcomes were evaluated simultaneously. The difference between groups was analyzed using Wilcoxon Rank sum test (Stata 10) ($p \leq 0.05$ as significance).

Results

Fifty patients were followed by MRI: 24 (14 cercival) in the minocycline and 26 (20 cervical) in the placebo arms. The injury pattern assessed as motor complete vs motor incomplete vs central cord injury was 16 : 4 : 4 in the minocycline group and 18 : 6 : 2 in the placebo group. Thirty-one patients had MR images available throughout the study. Overall, the minocycline group tended to have much less (negative) MSCC indicating less cord expansion, and smaller T2 lesion length and area than the placebo group ($p>0.05$). Similar tread was observed in the motor complete and cervical only subgroups, which formed the majority of this SCI cohort. Area under the curve comparison showed the same changing pattern between treatment groups ($p>0.05$) (Fig. 2).

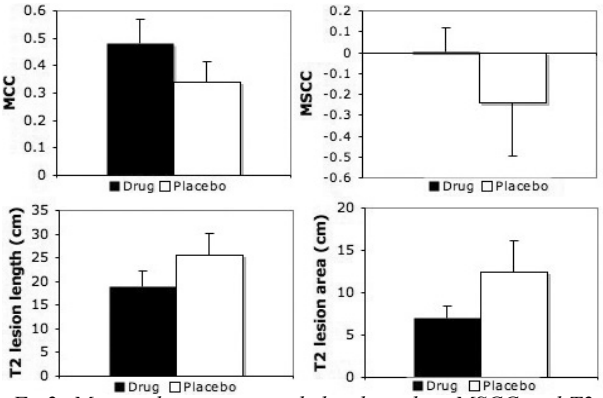

Fig2: Minocycline group tended to have less MSCC and T2 lesion length and area than the placebo group ($p>0.05$). Greater MCC may reflect worse fracture (data not shown).

Discussions

This pilot study showed that minocycline appeared to decrease the severity of cord swelling during acute injury or myelomalasia at chronic SCI (negative MSCC), and reduce the territory of T2 hyperintensity. This may be related to the therapeutic mechanisms of minocycline which is evidenced to suppress neuroinflammation, reduce excitotoxicity, lipid peroxidation and apoptotic cell death in experimental models[2,3]. These favorable MRI findings are consistent with clinical outcomes showing improved motor recovery in a subset of the minocycline group (unpublished). However, the benefits of minocycline are subject to further confirmation. Quantitative MRI assessments may be useful to evaluate treatment impacts in acute SCI.

References

[1] Lammertse D et al. *J Spinal Cord Med*. 2007; 30: 205-214. [2] Kwon BK, et al. *J Neurotrauma* DOI: 10.1089/neu.2009.1149. [3] Wells J et al. *Brain* 2003; 126: 1628-1637. [4] Fehlings MG, et al. *Spine* 1999; 24: 605-13.