

Results of a phase IIa clinical trial using minocycline in acute spinal cord injury.

When a car crash or a fall are resulting in the damage of the spinal cord, the injury does not stop there. On the contrary, tissues continue to produce toxic compounds for hours, even days and weeks. These compounds kill and disable the tissue surrounding the injury, damaging even distant nerve cells and finally increasing the area of damage (see figure 1). This so called secondary damage will result in a stronger functional impairment and might render rehabilitation much harder to achieve. Reducing this damage could have a deep impact on rehabilitation. The spinal cord is showing some degree of tolerance to damage, meaning that you don't need all of its functions all of the time to control the arms and legs. Rehabilitation works on this fundamental principle. Unfortunately, secondary damage can destroy nerve cells far from the initial injury, therefore partly or completely destroying any residual movement. In such devastating cases, any small benefit resulting from a drug treatment could greatly improve the quality of life. Secondary nerve degeneration may also produce chronic pain and muscle spasms. Reducing these debilitating consequences would also greatly improve the quality of life for those who survive severe spinal damage.

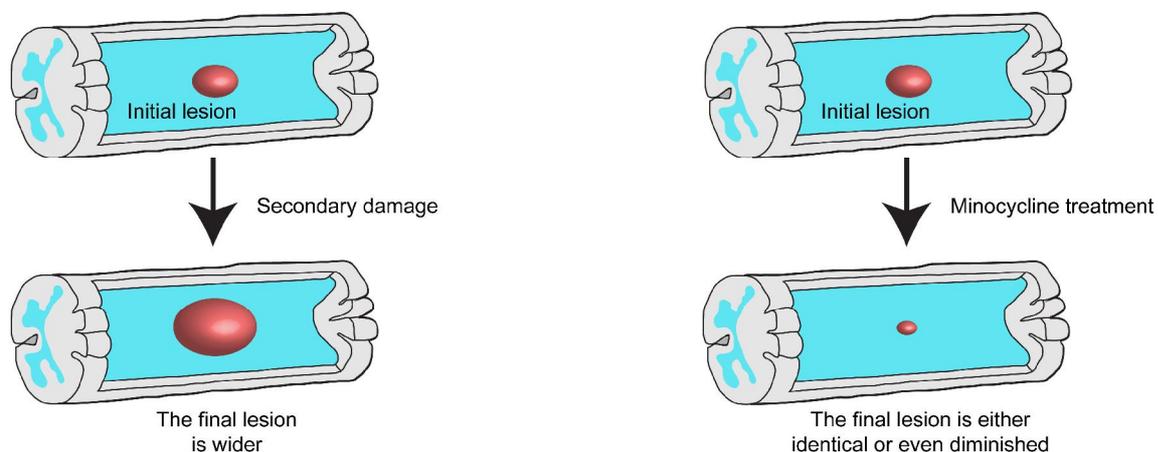


Fig. 1 and 2: Schematized concept of a neuroprotective strategy after acute spinal cord injury. Minocycline has been shown to exert neuroprotective functions in pre-clinical SCI models

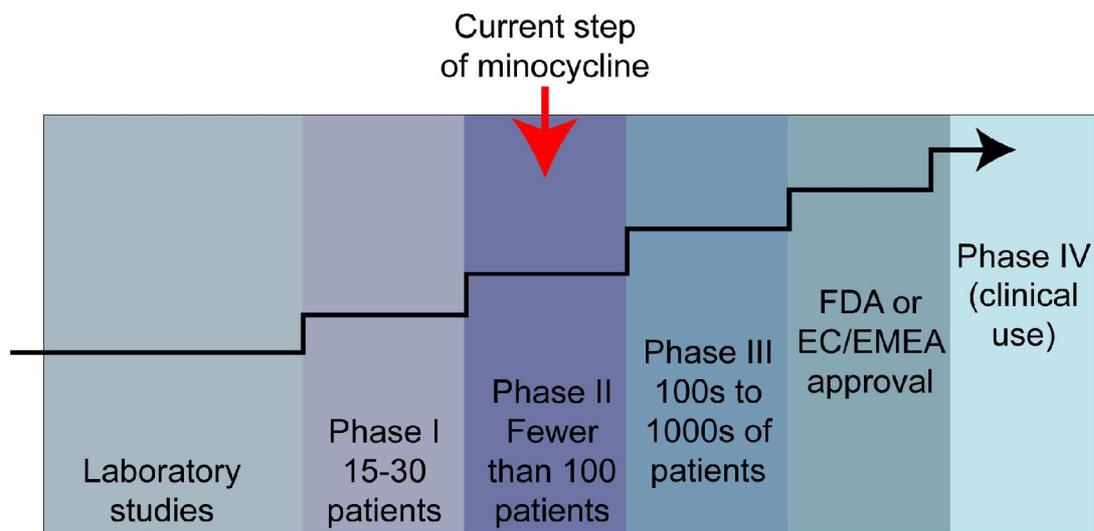
Numerous preclinical studies have shown that the compound minocycline had a neuroprotective effect, reducing the extent of progressive tissue loss (Wells et al., 2003). This structural preservation, which allowed the survival of neurons and oligodendrocytes, resulted in an improved functional outcome. Interestingly the time window for treatment was slightly delayed, compared to traditional neuroprotective therapies, which made the clinical application of minocycline more realistic. Indeed one of the problems with spinal cord injury is that the subjects won't be able to reach an emergency room before hours after the injury. Additionally minocycline is an antibiotic already approved by the American Food and Drug Administration, commonly used to treat acne, as well as other ailments, and has very few, well documented side effects.

Based on these facts the University of Calgary initiated a "randomized controlled clinical trial" (RCT) that started recruiting spinal cord injured patients in 2004. Subjects who experienced a high level traumatic spinal cord injury (above the eleventh thoracic vertebra), that could start the treatment within 12 h after injury and who met other inclusion criteria were administered 7 days of intravenous minocycline.

This clinical trial is focused on a single center (University of Calgary) in order to minimize any differences in the delivery of the compound and the following clinical observations. Based on state of the art rules as it contains a placebo group that will not receive any minocycline and both the treating doctors and patients are blinded on whether they will receive the treatment or the placebo to avoid any bias observation.

This clinical trial was on a so-called “phase IIa” (see figure 3) intended mostly to assess the safety of the treatment (meaning the absence of undesired side effects). Since spinal cord injury subjects have, for a comparable injury, a great variability of functional outcome (for example how much mobility a subjects is having one year after the injury) large number of subjects are necessary to rule out a clear effect on a functional recovery. For this study, 27 subjects received an intravenous minocycline treatment for seven days and were compared to 25 subjects that received a placebo compound. The degree of functional recovery was assessed using the motor recovery over 1 year using the American Spinal Cord Injury Association examination.

The minocycline regimen established in this study proved to be feasible, safe, since no severe adverse effects were reported (one patient showed transient liver enzyme increase). Although this study does not establish the efficacy of minocycline in spinal cord injury, the findings are encouraging and warrant further investigation in a multi-centre phase III trial, in which a higher number of subjects will be enrolled.



For more details on the clinical trial please visit the following homepage:
<http://clinicaltrials.gov/ct2/show/NCT0055949>

Ref:

Wells JE, Hurlbert RJ, Fehlings MG, Yong VW. Neuroprotection by minocycline facilitates significant recovery from spinal cord injury in mice. *Brain*. 2003 Jul;126(Pt 7):1628-37. Epub 2003 Jun 4

Casha S, Zygun D, McGowan MD, Bains I, Yong VW, John Hurlbert R: Results of a phase II placebo-controlled randomized trial of minocycline in acute spinal cord injury. *Brain*. 2012 Apr;135(Pt 4):1224-36