

First clinical trial of chronic spinal cord injury treated with a single drug

Kang Lu^{1,2} and Ying Wang^{3,*}

¹Department of Laboratory Medicine, Zhejiang Provincial Hospital of Chinese Medicine, Hangzhou 310006, China

²The First Affiliated Hospital of Zhejiang Chinese Medical University, Hangzhou 310006, China

³Department of Clinical Research Center, Hangzhou First People's Hospital, Hangzhou 310006, China

*Correspondence: wangying@hmc.edu.cn

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CALLING FOR NEW THERAPY, THE SPINAL CORD INJURY

Spinal Cord Injury (SCI) is a devastating neurological condition that can lead to physical paralysis, psychological stress, and financial burden.¹ SCI is not only a health condition that severely affects the quality of life of patients and their families, but also has important socioeconomic implications, so there is an urgent need to improve the clinical management of patients with SCI. SCI can result in nerve disconnection and persistent neurological deficits, so restoring the neural network through axonal growth is an important strategy to achieve significant neurological recovery. Electrical stimulation therapy, cell therapy, stem cell transplantation, and the use of exoskeleton robots

have all been attempted to treat SCI. However, clinical trials of these therapies in patients have not yet provided reproducible evidence of clinical efficacy. Although many targeted preclinical drugs have been evaluated in clinical trials, but few have been made into clinical practice.² SCI may remain a challenging condition, there have been no trails using drugs to improve nerve repair after SCI. Excitingly, in the last few days, Stephen M Strittmatter team published in The Lancet Neurology a landmark randomized trial for the first time that demonstrated that a drug can promote nerve repair in chronic SCI.³ This research may be a breakthrough, indicating drug treatment for SCI is no longer out of reach.

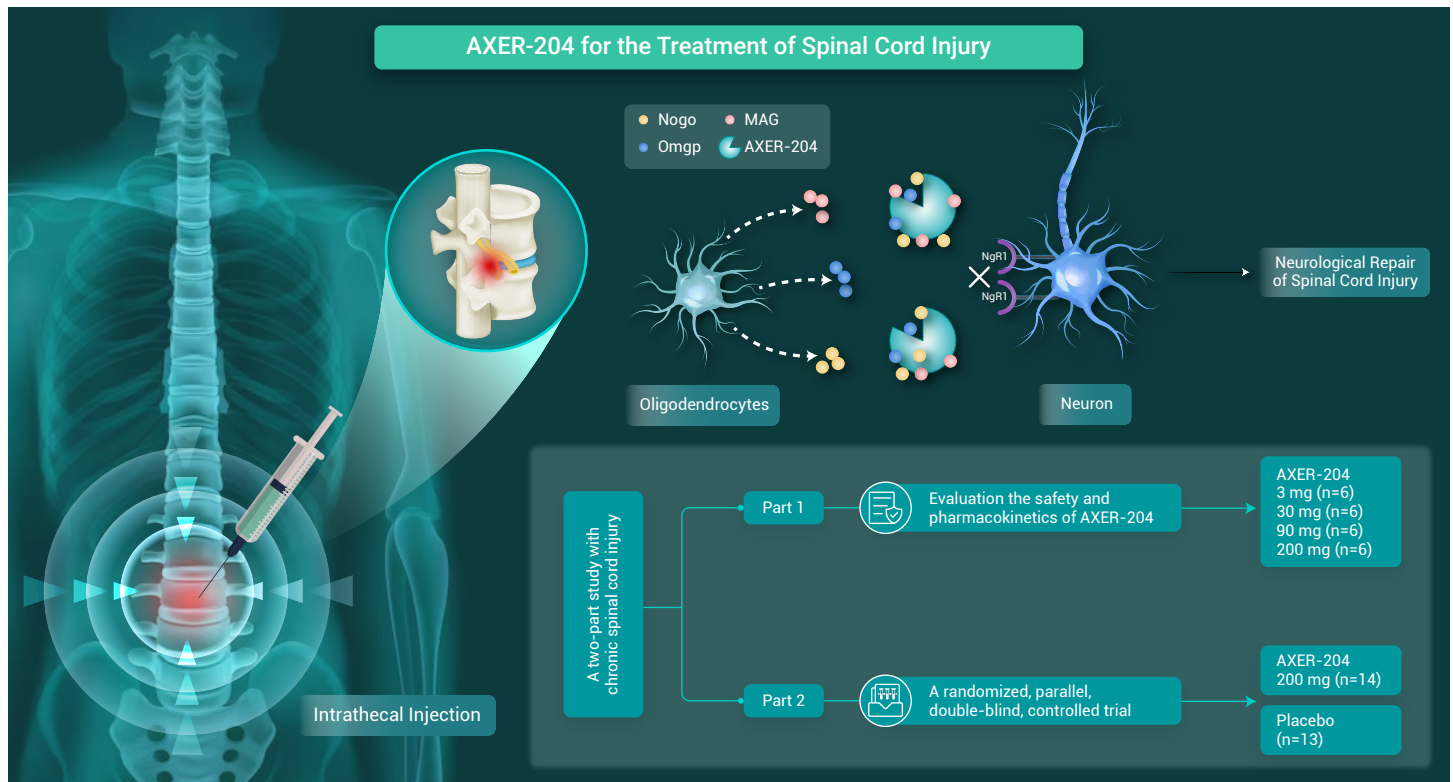


Figure 1. AXER-204 for the treatment of spinal cord injury AXER-204 inhibited axon growth through binding to Nogo, MAG, and Omgp proteins secreted by oligodendrocytes and inhibiting their binding to NgR1 receptors on neuronal membranes. This clinical study consisted of two parts. In part 1, participants received intrathecal injections of 3, 30, 90, or 200 mg of AXER-204, with the aim of evaluating the safety and pharmacokinetics of AXER-204. The part 2 was a randomized, double-blind, controlled trial to compare the efficacy of AXER-204 with placebo and to further assess the safety and pharmacokinetics of AXER-204.

AXER-204 IN SCI

Many affecting factors are the obstacles to potential therapeutic strategies, such as weak neuronal cell ability and multiple extracellular environmental factors that inhibit axonal regeneration. Among this, it has been proved that oligodendrocytes can inhibit axonal regeneration in the microenvironment, thus has been called one of the culprits in the treatment of SCI. Oligodendrocytes inhibit axon growth in the injury area by secreting Nogo, MAG, and Omgp, which bind to the NgR1 receptor on neuronal membranes. AXER, a NgR1 (310) ento-Fc, which a soluble decoy receptor that contains the ligand binding domain of NgR1 fused to the Fc portion of IgG1 to maintain protein stability.⁴ AXER-204 blocks the three oligodendrocyte ligands, thereby

protecting the cognate receptor of neurons from activation. The preclinical therapeutic effects have been demonstrated in a variety of rat central nervous system injury models and non-human primate SCI studies.⁵

DESIGN OF CLINICAL TRIAL

This randomized clinical trial in humans (NCT 03989440) was an ongoing, randomized, double-blind, placebo-controlled study over three years. The results indicated that AXER-204 was safe and achieved target cerebrospinal fluid concentrations. There were no serious adverse events associated with AXER-204 throughout the study. The trial was divided into two parts. Each subject received separate intrathecal injections of AXER-204 at different doses in Part 1. To further assess the safety and pharmacokinetics of AXER-

204, a randomized, double-blind, controlled trial comparing the therapeutic differences between AXER-204 and placebo was conducted in Part 2. The aim of the study was to evaluate the safety and preliminary efficacy of AXER-204. On this basis, they also evaluated the pharmacokinetics and safety of AXER-204 in chronic SCI patients and explored preliminarily therapeutic efficacy. The general mechanism of AXER-204 for the treatment of SCI was shown in Figure 1. Nogo, MAG, and Omgp were secreted by oligodendrocytes, which bind to NgR1 receptors on neuronal membranes and thus inhibit axon growth. AXER-204 inhibited axon growth by blocking the three proteins from binding to the NGR1 receptor, with the aim of promoting the recovery of neurological function after spinal cord injury.

EFFICACY AND SAFETY

However, in a post-hoc subgroup analyses of incomplete injury patients who did not receive AXER-204 treatment in the first part, the AXER-204 group showed a 4-point improvement in ISNCSCI UEMS and a 9-point improvement in ISNCSCI total motor score, while the placebo group did not show any changes in these indicators. This indicated that incomplete injury was more suitable for treatment aimed at promoting axonal growth and neural plasticity compared to complete injury.

The unique novel innovation of this study lies in its patient population and mechanistic hypothesis. As we known, improvement of neurological function via neural repair hasn't been the basis of randomized clinical trials in patients with chronic SCI in previous studies. Therefore, this scientific study also lays the groundwork for future development by providing baseline data on the variability of outcomes in multicenter trials, thus supporting the design of additional trials in the future. In Part 1, no serious adverse events occurred in patients. In Part 2, four serious adverse events were reported in four patients (29%) and two patients (15%) in the AXER-204 and placebo groups, respectively. Pharmacokinetic measurements showed high cerebrospinal fluid concentrations of AXER-204, minimal systemic exposure, and no accumulation during repeated dosing. The CSF of AXER-204 at the 200 mg dose were higher than those reported to be successful in stimulating axon growth and nerve recovery in animal studies. Data from the first part of the trial indicated that AXER-204 didn't accumulate in vivo at cerebrospinal fluid and serum concentrations. The half-life of CSF AXER-204 was approximately 12 h, and the concentration of AXER-204 in CSF on day 8 was undetectable. However, animal studies showed that the residence time of AXER-204 CSF was significantly shorter than that in the central nervous system.⁵ These above suggested that intrathecal injection of AXER-204 was safe and feasible. Finally, the researchers also conducted an exploratory analysis of the therapeutic efficacy of AXER-204. In Part 1, a total of 17 patients (including those receiving single doses of 30mg, 90mg, or 200mg AXER-204) underwent efficacy assessment. Among them, 5 patients (29%) showed a ≥ 3 -point increase in ISNCSCI UEMS scores from baseline at day 29. However, none of the 6 patients who received a single 3-mg treatment dose showed a ≥ 3 -point increase. Moving on to Part 2, the AXER-204 group experienced a 1.5-point increase in ISNCSCI UEMS score from baseline at Day 169, which was

slightly higher than the 0.9-point increase observed in the placebo group. However, this difference did not reach statistical significance ($p=0.59$).

CONCLUSION

To the best of our knowledge, this was the first clinical study to investigate a drug that promoted nerve repair in chronic SCI, and this study confirmed that intrathecal injection of 200 mg of AXER-204 was safe and feasible, with no serious adverse events reported. These results give rise to optimism that the current lack of an effective drug therapy for spinal cord injury can be overcome in the future. However, this clinical trial also has several limitations that need to be acknowledged. Firstly, the inclusion of patients of injury severities provided extensive security data but may result in masking of potential benefits in patients with incomplete SCI. Since the outcome of pharmacokinetic and proteomic were originated from single-dose analyses, multidose therapy may not repercussion well. Another limitation was that the dosing regimen of AXER-204 in this trial consisted of repeated administrations at predetermined intervals. It would be beneficial to explore the effects of more frequent or individualized dosing regimens to optimize the blockade of NgR1 ligands in CNS tissues and potentially enhance therapeutic outcomes. Moreover, in the second part of the study, AXER-204 didn't demonstrate an advantage over placebo and didn't reach statistical significance. It's promising in patients with incomplete SCI who were not treated with AXER-204. Larger clinical studies are necessary to confirm these findings and establish the true efficacy of AXER-204 in this specific patient population. AXER-204 attained nerve injury repair by inhibiting Nogo, MAG and Omgp secreted by oligodendrocytes, but it is also important to consider that this behavior may lead to inhibition of myelin regeneration factors. Therefore, it may also be necessary to combine AXER-204 with other drugs to complete the repair of nerve function in SCI.

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DECLARATION OF INTERESTS

The authors declare no competing interests.