Intrathecal Administration of Recombinant Human Hepatocyte Growth Factor for Acute Spinal Cord Injury: Road from Bench to Clinical Trial and Future Perspective

Kazuya Kitamura, MD, PhD, Tokyo, Japan
Akio Iwanami, MD, PhD, Tokyo, Japan
Hiroki Iwai, MD, PhD, Tokyo, Japan
Jun-ichi Yamane, MD, PhD, Tokyo, Japan
Kanehiro Fujiyoshi, MD, Tokyo, Japan
Yoshiaki Toyama, MD, Tokyo, Japan
Morio Matsumoto, MD, PhD, Tokyo, Japan
Hideyuki Okano, Tokyo, Japan
Masaya Nakamura, MD, Tokyo, Japan

Introduction: Hepatocyte growth factor (HGF) has been highlighted as a potent organotrophic and angiogenic factor in the central nervous system, as well as in other solid organs. We first revealed that endogenous up-regulation of HGF in injured spinal cord was insufficient, compared with sharp increase of c-Met (HGF receptor) expression during acute phase of spinal cord injury (SCI) and introduction of exogenous HGF into spinal cord by HSV injection significantly promoted the survival of neurons and oligodendrocytes, angiogenesis and axonal regeneration, thereby reducing the damaged area and promoting functional recovery after SCI. We have also reported efficacy of intrathecal infusion of recombinant human HGF (rhHGF) in thoracic SCI model of rats and cervical SCI model of non-human primate (common marmoset). The purpose of this study is to investigate its therapeutic time window, confirm its efficacy in clinically-relevant severe cervical SCI model of marmosets and establish novel treatment by conducting clinical trial.

Methods: 1) To investigate therapeutic time window of intrathecal rhHGF, contusive SCI was induced at Th10 level in adult rats and 200 mg of rhHGF or PBS was infused intrathecally from Th12 level for 4 weeks from right after, 4 days, 2 or 6 weeks after SCI (n = 6 for each group). 2) Contusive SCI was induced at C5 level and rhHGF or PBS was infused intrathecally from C7 level from right after SCI for 4 weeks in adult marmosets. To examine efficacy of intrathecal rhHGF in clinically-relevant severe cervical SCI model as preclinical trial, marmosets without any recovery of forelimbs until 3 days after SCI were included (n = 5 in HGF group, n = 3 in PBS group). Motor function was evaluated by our original scoring scale which focuses on primate-specific upper limb function (flexion and extension of fingers, wrists, elbows and shoulders and pronation of forearms) in walking and grasp performance.
Results: 1) Significant motor recovery of hindlimbs was observed when intrathecal rhHGF started from right after or 4 days after SCI, whereas no effects were observed when intrathecal rhHGF started from 2 or 6 weeks after SCI.
2) Original scoring scale revealed that more than one key muscle of forelimbs became useful in marmosets with intrathecal rhHGF infusion, whereas all key muscles remained useless thereafter in control marmosets.

Conclusions: Since we reported dynamism of endogenous HGF expression before and after SCI and therapeutic efficacy of introduction of HGF into spinal cord during acute phase of SCI, we have developed the current therapeutic strategy for people with SCI using rhHGF based on experiments using viral vector and rhHGF in rodent SCI models. Present study suggests evidence of therapeutic time window of intrathecal rhHGF and its efficacy in clinically-relevant severe cervical SCI in primates. Based on results of these consecutive studies, we have recently launched phase I/II clinical trial (randomized, double-blinded, placebo-controlled) for people with cervical SCI who show modified-Frankel A/B1/B2 at 72 hours after onset. rhHGF is injected intrathecally at lumbar level once a week for 5 weeks, with primary injection within 6 hours after final registration at 72 hours after onset.