

Neuroprotective therapy using granulocyte-colony stimulating factor for patients with rapidly aggravating compression myelopathy: phase I and IIa clinical trial

Spine Section, Department of Orthopaedic Surgery, Chiba University Graduate School of Medicine

Sakuma Tsuyoshi, MD, Takahashi Hiroshi, MD, Hayashi Koichi, MD, Hashimoto Masayuki, MD, PhD, Hashimoto Mitsuhiro, MD, Koda Masao, MD, PhD, Okawa Akihiko, MD PhD, Yamazaki Masashi, MD, PhD

Introduction

- For most patients, myelopathy progresses like a slow stepwise. However, in some patients, motor paresis and paresthesia rapidly progress with mild or no trauma.
- Rapidly aggravating compressive myelopathy results in severe neurological deficit, and its functional recovery is quite poor. To date, there has been no effective therapy except for early surgical treatment.

Granulocyte-Colony Stimulating factor : G-CSF

- A 19.6 kDa cytokine
- Survival, proliferation and differentiation of cells of neutrophil lineage
- Clinical use in Japan
 - Leukocytopenia
 - Donors of peripheral blood-derived hematopoietic stem cells for transplantation
- Clinical trial of acute ischemic stroke

G-CSF promotes the restoration of damaged spinal cord tissue

- G-CSF mobilizes bone marrow-derived cells into injured spinal cord (Koda, 2007)
- G-CSF attenuates neuronal death (Nishio, 2007)



Phase I and IIa clinical trial of neuroprotective therapy using G-CSF for patients with rapidly aggravating compression myelopathy.

- Safety
- Efficacy (no institutional control group)

Patients and methods

- 20-75 years of age
- Japanese Orthopaedic Association (JOA) score for cervical myelopathy decreased 2 points or more during a recent one-month period
- No severe complication



G-CSF (5 μ g/kg/day) was intravenously administered for 5 consecutive days

Evaluation

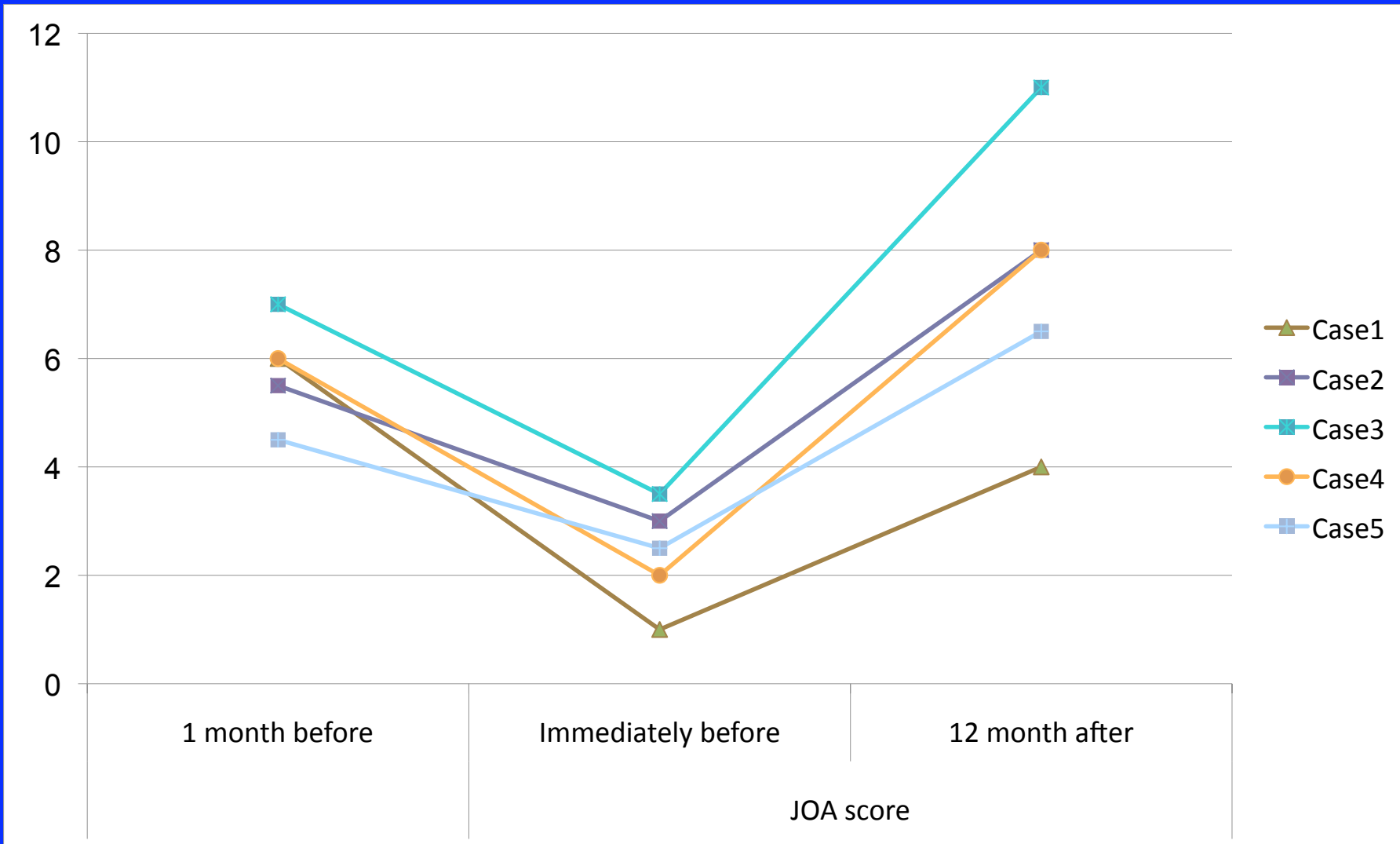
- Motor and sensory functions
 - American spinal injury association (ASIA) score
 - Japanese orthopaedic association (JOA) score for cervical myelopathy
- Blood date
 - White blood cell (WBC)
 - Neutrophil lineage
 - C-reactive protein (CRP)

Data of patients who underwent G-CSF therapy

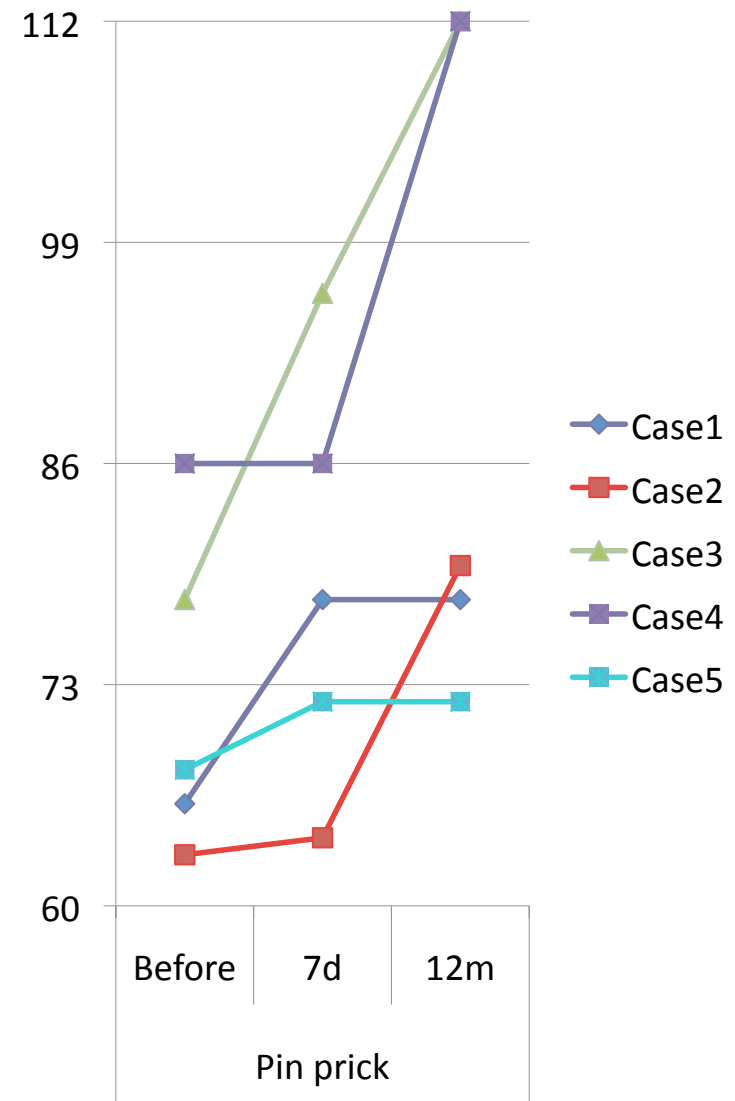
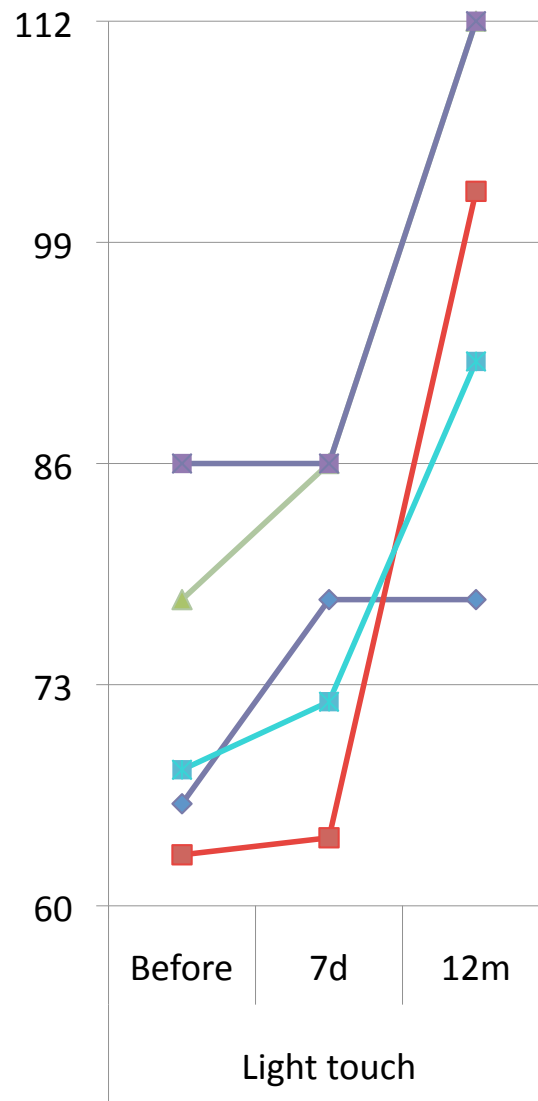
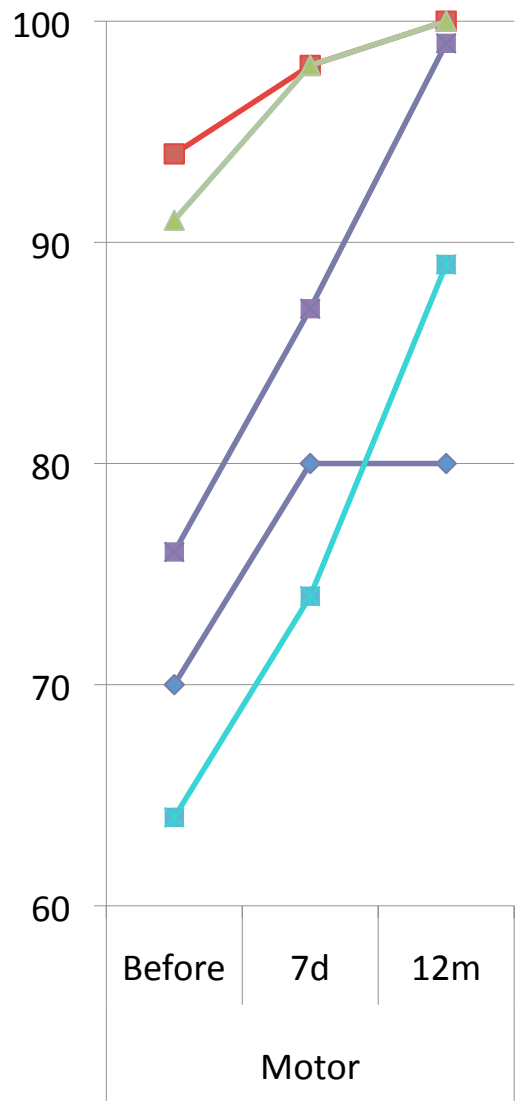
Case No.	Age (yrs)	Gender	Diagnosis	Most Stenotic level	Height (cm)	Weight (kg)	Follow-up
1	62	Male	T-OLF	Th10/11	168	85.5	12 mths
2	68	Male	T-OPLL	Th4/5	166	60.8	12 mths
3	52	Male	T-OPLL	Th1/2	161	86	12 mths
4	38	Male	T-OPLL	Th3/4	195	150	12 mths
5	35	Male	C&T-OPLL	C6/7	173	110	12 mths

T: thoracic, OLF: ossification of ligamentum flavum, OPLL: ossification of the posterior longitudinal ligament, C: cervical

JOA score before and after G-CSF administration



ASIA score before and after G-CSF administration



- ◆ Case1
- Case2
- ▲ Case3
- Case4
- Case5

Blood data before and after G-CSF administration

	Baseline	After G-CSF administration											
		1d	2d	3d	4d	5d	6d	7d	14d	1m	3m	6m	12m
WBC													
($\times 10^3/$	7.2	26.7*	25.0*	24.9*	23.3*	20.8*	10.4	8.2	8.2	7.3	6.6	7.2	7.3
mm ³)	± 1.6	± 10.7	± 5.5	± 6.6	± 9.3	± 9.6	± 3.2	± 2.4	± 2.4	± 2.8	± 0.9	± 0.4	± 0.6
Neutro													
phils													
($\times 10^3/$	4.5	22.1*	20.9*	20.6*	19.0*	15.9*	6.8	5.1	5.9	4.7	3.8	4.1	4.4
mm ³)	± 1.5	± 9.2	± 5.8	± 6.1	± 7.7	± 7.7	± 2.8	± 2.0	± 2.4	± 2.3	± 1.2	± 0.1	± 0.5
CRP	0.7	0.8	0.8	0.8	0.8	0.7	0.7	0.8	4.6*†	2.9*†	1.2	0.2	0.2
(mg/dl)	± 1.2	± 1.3	± 1.3	± 1.1	± 1.0	± 1.0	± 1.0	± 0.9	± 6.9	± 6.1	± 2.2	± 0.2	± 0.2

*: p<0.05 compared to the base line level

†: increase due to the surgical site infection of case 4

Conclusions

- We performed a neuroprotective therapy with granulocyte-colony stimulating factor for 5 patients with rapidly aggravating compression myelopathy.
- In all the patients, neurological recovery was obtained, and no adverse event occurred.

Future clinical trials

Phase I and IIa (2nd stage)

10 µg/kg/day for 5 days in 5 cases

Phase IIb

Double-blind randomized controlled trial

Control group: saline administration

G-CSF group: 10 µg/kg/day for 5 days

Financial Disclosure: I (or a member of my immediate family) do not have a financial interest or other relationship with a commercial company or institution