Spine

SPINE Volume 37, Number 17, pp 1475–1478

CLINICAL CASE SERIES

Neuroprotective Therapy Using Granulocyte Colony–Stimulating Factor for Patients With Worsening Symptoms of Thoracic Myelopathy

A Multicenter Prospective Controlled Trial

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Study Design. An open-labeled multicenter prospective controlled clinical trial.

Objective. To confirm the feasibility of granulocyte colony–stimulating factor (G-CSF) administration for patients with thoracic myelopathy.

Summary of Background Data. Although G-CSF is best known as an important cytokine commonly used to treat neutropenia, it also has nonhematopoietic functions. Previous experimental studies have shown that G-CSF can enhance tissue regeneration of several organs, such as the heart and the brain. We previously reported that G-CSF promotes functional recovery after spinal cord injury in rodents. On the basis of those findings, we started a clinical trial of neuroprotective therapy, using G-CSF for patients with worsening symptoms of thoracic myelopathy.

Methods. Patients whose Japanese Orthopaedic Association (JOA) score for thoracic myelopathy had decreased 2 points or more during a recent 1-month period were eligible for entry. After giving informed consent, patients were assigned to G-CSF and control groups. The G-CSF group (n = 10) received G-CSF 10 μg/kg per day intravenously for 5 consecutive days. The control group (n = 14) received similar treatments as the G-CSF group except for G-CSF administration. The primary outcome was JOA recovery rate at 1 month after G-CSF administration or initial treatment.

Results. There was greater improvement in neurological functioning between baseline and 1-month follow-up in the G-CSF group (JOA recovery rate: 29.1 ± 20.5%) than in the control group (JOA recovery rate: 1.1 ± 4.2%) ($P < 0.01$). No serious adverse events occurred during or after the G-CSF administration.

Conclusion. The results provide evidence that G-CSF administration caused neurological recovery in patients with worsening symptoms of thoracic compression myelopathy.

Key words: neuroprotective therapy, granulocyte colony–stimulating factor, thoracic myelopathy, clinical trial. **Spine 2012;37:1475–1478**

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Acknowledgment date: September 6, 2011. Revision date: January 13, 2012. Acceptance date: January 30, 2012.

The device(s)/drug(s) that is/are the subject of this manuscript is/are not FDA approved for this indication and is/are not commercially available in the United States.

Health Labour Science Research Grant of Japan funds were received to support this work.

No benefits in any form have been or will be received from a commercial party related directly or indirectly to the subject of this manuscript.

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DOI: 10.1097/BRS.0b013e318260cc71

Granulocyte colony–stimulating factor (G-CSF) is a 19.6 kDa glycoprotein. It is best known as a growth factor for hematopoietic progenitor cells and is commonly used to treat neutropenia and to mobilize peripheral blood-derived hematopoietic stem cells for transplantation.[1] Several experimental studies have indicated that G-CSF also has nonhematopoietic functions and can enhance the tissue regeneration of several organs such as the heart and the brain.[2,3] We previously reported that G-CSF promotes functional recovery after spinal cord injury in rodents.[4–6]

On the basis of the experimental results described earlier, we hypothesized that administration of G-CSF can effect neurological recovery in patients with progressive compression

myelopathy and started a phase I/IIa clinical trial of G-CSF neuroprotective therapy.[7] In this study, we conducted a multicenter prospective controlled clinical trial (phase IIb) to assess the feasibility of the G-CSF therapy for patients with worsening symptoms of thoracic compression myelopathy.

MATERIALS AND METHODS

This clinical trial was designed as an open-labeled multicenter prospective controlled study and was performed with the approval of the institutional review board of each participating institute. Since April 2010, we recruited patients 20 to 85 years of age, in whom the Japanese Orthopaedic Association (JOA) score (full score = 11 points) decreased 2 points or more during a recent 1-month period.[7]

We assigned patients to a G-CSF group and a control group. Patients in the G-CSF group were given G-CSF 10 μg/kg per day intravenously for 5 consecutive days. Patients in the control group were enrolled in similar treatments as the G-CSF group except for the G-CSF administration. To evaluate neurological improvement resulting from neuroprotective therapy with G-CSF, we planned to follow patients in both groups without surgical treatment for 1 month after G-CSF administration or initial treatment and to provide them with equivalent conservative treatment, such as bed rest. When patients were given informed consent documents, we explained our plans regarding the time of surgery, and we administered G-CSF only to those patients who agreed with the protocol.[7] The G-CSF therapy was performed only in the institute to which the corresponding author (MY) belonged. At the other institutes, patients were treated without G-CSF administration.

The primary outcome was the JOA recovery rate at 1 month after G-CSF administration or initial treatment. We evaluated the patients' severity of myelopathy using the JOA score.[7] Then, we evaluated their motor and sensory functions by determining scores for muscle power and pain sensation according to the American Spinal Injury Association score.[7] In this study, 2 orthopedic spine surgeons specializing in thoracic spine surgery evaluated patients' neurological status independently after G-CSF administration and then mean data were calculated. In addition, we analyzed hematological data from the treated patients.

Statistical analyses were performed using a Mann-Whitney *U* test and a Fisher exact probability test. A *P* value less than 0.05 was considered statistically significant. Results are presented as means ± standard deviation of the mean.

RESULTS

Patient Data

Between April 2010 and October 2010, 24 patients (10 patients in the G-CSF group and 14 patients in the control group) were enrolled and examined for 1 month. Patient data for both groups are summarized in Table 1. In the control group, many patients had the most stenotic level at the lower thoracic spine (T9–T12), although no statistical difference was observed in the distribution of the most stenotic level between the G-CSF and control groups. No statistical difference was observed between groups regarding the spinal canal occupation ratio by heterotopic ossification or vertebral spurs at the most stenotic level.

TABLE 1. G-CSF and Control Group Patient Data

	G-CSF	Control
No. of patients	10	14
Sex		
Male	9	11
Female	1	3
Age, *M* ± SD (range), yr	49.7 ± 8.9 (32–74)	53.1 ± 10.6 (22–72)
Diagnosis		
Thoracic OPLL	5	4
Thoracic OLF	2	6
Thoracic spondylotic myelopathy	3	4
Most stenotic level		
Upper thoracic (T1–T4)	4	4
Middle thoracic (T5–T8)	4	2
Lower thoracic (T9–T12)	2	8
Surgical procedure		
Posterior decompression	5	10
Posterior decompression with instrumented fusion	5	4

G-CSF indicates granulocyte colony–stimulating factor; OPLL, ossification of posterior longitudinal ligament; OLF, ossification of ligamentum flavum.

Neurological Recovery

The JOA score immediately before G-CSF administration or initial treatment was 3.8 ± 1.3 in the G-CSF group and 4.1 ± 1.4 in the control group, showing no statistical difference between groups (Table 2). There was greater improvement in neurological functioning between baseline and 1-month follow-up in the G-CSF group (JOA recovery rate: 29.1 ± 20.5%) than in the control group (JOA recovery rate: 1.1 ± 4.2%) ($P < 0.01$) (Table 2).

Regarding the muscle power score, greater improvement between baseline and 1-month follow-up was observed in the G-CSF group (improvement of muscle power score: 2.8 ± 2.8) than in the control group (improvement of muscle power score: 1.6 ± 5.3) ($P < 0.05$) (Table 2).

There was also greater improvement in the pain sensation score between baseline and 1-month follow-up in the G-CSF

TABLE 2. Neurological Recovery

	G-CSF *M* ± SD (range)	Control *M* ± SD (range)	*P*
JOA score			
Immediately before treatment	3.8 ± 1.3 (1–5.5)	4.1 ± 1.4 (1.5–6.0)	0.501
One month after treatment	5.7 ± 2.4 (1.0–9.0)	4.3 ± 1.3 (2.5–6.0)	0.061
Recovery rate	29.1 ± 20.5 (0.0–63.6)	1.1 ± 4.2 (0.0–15.8)	<0.01
Muscle power score			
Immediately before treatment	41.9 ± 7.8 (22–50)	37.0 ± 15.5 (0–50)	0.884
One month after treatment	44.7 ± 7.6 (25–50)	38.6 ± 12.6 (20–50)	0.241
Increase of muscle power score	2.8 ± 2.8 (0–9)	1.6 ± 5.3 (0–20)	<0.05
Pain sensation score			
Immediately before treatment	68.3 ± 9. 7 (59–78)	74.1 ± 9.8 (60–92)	0.364
One month after treatment	74. 7 ± 10.4 (62–88)	74.9 ± 8.9 (64–92)	0.578
Increase of pain sensation score	6.4 ± 5.5 (1–17)	1.0 ± 3.2 (0–12)	<0.01

Recovery rate = (postoperative score − preoperative score/full score − preoperative score) × 100 (%).

Muscle power score (motor: 0–50 points) and pain sensation (pin prick: 0–98 points) score were defined according to the American Spinal Injury Association score.

G-CSF indicates granulocyte colony–stimulating factor; JOA score, Japan Orthopaedic Association score (thoracic myelopathy: 0–11 points).

group (improvement of the pain sensation score: 6.4 ± 5.5) than in the control group (improvement of the pain sensation score: 1.0 ± 3.2) ($P < 0.01$) (Table 2).

Blood Data and Adverse Events

In the G-CSF group, white blood cell count immediately before G-CSF administration was 7.3 ± 1.6 (× 10^3/mm^3). During the administration, it increased up to 36.7 ± 9.4 (× 10^3/mm^3), ranging from 19.2 to 50.3 (× 10^3/mm^3) (Table 3). G-CSF mobilized cells of the neutrophil lineage, but lymphocytes were not affected (Table 3). G-CSF also caused an increase of monocytes. There was no significant change in inflammation during G-CSF administration, as indicated by C-reactive protein levels (Table 3).

In this series, there was no patient who showed bone pain or hepatic dysfunction after the G-CSF administration. No other severe adverse event occurred during or after the administration.

DISCUSSION

To date, 3 clinical trials of G-CSF administration for neurological disorders have been reported; 2 for amyotrophic lateral sclerosis[8,9] and 1 for cerebral infarction.[10] Zhang *et al*[8] reported that the progression of amyotrophic lateral sclerosis symptoms was inhibited by G-CSF administration, although they did not use controls. Neffussy *et al*[9] performed a controlled study, but they showed no significant difference in the progression of amyotrophic lateral sclerosis symptoms between their G-CSF-treated group and controls. A single clinical trial with G-CSF administration for cerebral infarction has been reported by Shyu *et al*.[10] They reported that neurological symptoms were significantly improved by G-CSF administration.

In this study, we conducted the first clinical trial using G-CSF for patients with worsening symptoms of thoracic

TABLE 3. Hematological Data Before and After G-CSF Administration

	Baseline *M* ± SD (range)	Peak Value After G-CSF Administration *M* ± SD (range)*	*P*
WBC, ×10^3/mm^3	7.3 ± 1.6 (5.0–10.3)	36.7 ± 9.4 (19.2–50.3)	<0.01
Neutrophils, ×10^3/mm^3	4.6 ± 1.4 (2.1–6.9)	30.6 ± 6.7 (16.6–40.5)	<0.01
Lymphocytes, ×10^3/mm^3	2.1 ± 0.4 (1.5–2.5)	2.4 ± 0.7 (1.5–3.2)	0.29
Monocytes, ×10^3/mm^3	0.4 ± 0.2 (0.2–0.8)	1.9 ± 0.9 (0.7–2.8)	<0.01
CRP, mg/dL	0.1 ± 0.1 (0.0–0.3)	0.3 ± 0.2 (0.1–0.6)	0.08

**Highest level between the first and seventh day after G-CSF administration.*

G-CSF indicates granulocyte colony–stimulating factor; WBC, white blood cell; CRP, C-reactive protein.

compression myelopathy. One month after G-CSF administration, mean recovery rate of JOA score was 29.1%. In contrast, it was 1.1% in the control group at 1 month after initial treatment. In addition, we observed that both motor power and pain sensation scores significantly increased in the G-CSF group compared with the control group at 1 month after treatment. No surgical treatment was performed in patients of either group during the month after G-CSF administration or initial treatment, and they were equally provided conservative treatment such as bed rest. Thus, the present results strongly suggest that G-CSF administration exhibited a neuroprotective effect for the injured spinal cord in patients with worsening symptoms of thoracic myelopathy and improved the myelopathy.

To the best of our knowledge, there has been no other medical treatment that has provided reliable evidence for improvement of thoracic myelopathy. This study provides evidence that G-CSF neuroprotective therapy may be useful as a medical treatment of patients with worsening symptoms of thoracic compression myelopathy. The G-CSF therapy may be especially useful for patients in whom the treatment of complications other than myelopathy needs to be given priority and thus requires a long waiting period before surgery.

In our present trial, no severe side effects occurred. Thus, we suggest that the dose (10 μg/kg per d), duration (5 consecutive days), and route (intravenous administration) of G-CSF administration used in this study are principally safe for the treatment of patients with thoracic myelopathy.

The biggest limitation of this study was that the trial was performed as an open-labeled study and the selection of patients to the G-CSF group and the control group was not randomized. We cannot deny the possibility that a placebo effect of injection may participate in the improvement of neurological symptoms. To increase the level of evidence, in the next stage the study design should be a randomized, double-blind placebo-controlled study. By conducting a phase IIb clinical trial in a large number of patients with the study design described earlier, we will be able to reach a better conclusion regarding the effectiveness of G-CSF neuroprotective therapy for patients with worsening symptoms of thoracic compression myelopathy.

➢ Key Points

- ❑ A multicenter prospective controlled clinical trial was performed to confirm the feasibility of G-CSF administration for patients with worsening symptoms of thoracic myelopathy.
- ❑ For 10 patients with progressive myelopathy, G-CSF (10 μg/kg per day) was intravenously administered for 5 consecutive days.
- ❑ The administration of G-CSF caused neurological recovery in the patients.

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