Intravenous infusion of auto serum-expanded autologous mesenchymal stem cells in spinal cord injury patients: 13 case series

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**ABSTRACT**

**Background:** Although spinal cord injury (SCI) is a major cause of disability, current therapeutic options remain limited. Recent progress in cellular therapy with mesenchymal stem cells (MSCs) has provided improved function in animal models of SCI. We investigated the safety and feasibility of intravenous infusion of MSCs for SCI patients and assessed functional status after MSC infusion.

**Methods:** In this phase 2 study of intravenous infusion of autologous MSCs cultured in auto-serum, a single infusion of MSCs under Good Manufacturing Practice (GMP) production was delivered in 13 SCI patients. In addition to assessing feasibility and safety, neurological function was assessed using the American Spinal Injury Association Impairment Scale (ASIA), International Standards for Neurological and Functional Classification of Spinal Cord Injury (ISCSCI-92), Ability of daily living was assessed using Spinal Cord Independence Measure (SCIM-III).

**Results:** The study protocol was based on advice provided by the Pharmaceuticals and Medical Devices Agency in Japan. No serious adverse events were associated with MSC injection. There was neurologic improvement based on ASIA grade in 12 of the 13 patients at six months post-MSC infusion. Five of six patients classified as ASIA A prior to MSC infusion improved to ASIA B (3/6) or ASIA C (2/6), two ASIA B patients improved to ASIA C (1/2) or ASIA D (1/2), five ASIA C patients improved and reached a functional status of ASIA D (5/5). Notably, improvement from ASIA C to ASIA D was observed one day following MSC infusion for all five patients. Assessment of both ISCSCI-92, SCIM-III also demonstrated functional improvements at six months after MSC infusion, compared to the scores prior to MSC infusion in all patients.

**Conclusion:** While we emphasize that this study was unblinded, and does not exclude placebo effects or a contribution of endogenous recovery or observer bias, our observations provide evidence supporting the feasibility, safety and functional improvements of infused MSCs into patients with SCI.
1. Introduction

Traumatic spinal cord injury (SCI) is a major cause of disability in developed countries [1]. The financial burden is significant in terms of direct health care costs as well as loss of economic productivity. Even small improvements in mobility and/or manual dexterity may substantially reduce these costs and improve quality of life [2]. However, current therapeutic options remain limited, and there is a need for more effective treatments to restore function in SCI patients [3].

Cellular therapy with intravenous infusion of mesenchymal stem cells (MSCs) derived from bone marrow improves functional outcome in experimental models of SCI [4–12]. While the mechanisms underlying these beneficial effects have not been fully elucidated, potential mechanisms include neuroprotection and immunomodulation [5,10,12], induction of axonal sprouting [4], remyelination [4], restoration of blood-brain/spinal cord barrier [4,6,11], and enhancement of remote gene expression responses in brain [7].

Several clinical trials for SCI using autologous cultured MSCs derived from bone marrow have been reported. However, the MSCs in these previous studies were delivered via intramedullary injection [13–15] or intrathecally [16–18] rather than intravenously as in the present study. The medium used to culture the autologous bone marrow MSCs in most prior studies was FBS [13,15,18], or pooled human platelet lysate containing medium [16]. In the present case series we used autologous human serum to culture the MSCs. The use of autologous human serum supports relatively rapid expansion of human MSCs and results in stable gene expression of less highly differentiated and transcriptionally stable cells [19]. Importantly, intravenously infused MSCs may affect not only the injury site, but other parts of the central nervous system including brain and blood vessels [20]. In a previous study we demonstrated feasibility and safety of intravenous administration of autologous MSCs cultured in autologous human serum in stroke patients [19].

Auto serum-expanded autologous bone marrow-derived mesenchymal stem cells (Stemirac® for I.V. injection) for acute SCI patients has been given conditional, time-limited approval for clinical use as human-derived somatic stem cell product in Japan. The rationale for the safety, efficacy and quality of the product, and for the ethics of its approval, are presented in the evaluation report by Japan’s Pharmaceuticals and Medical Devices Agency (PMDA) which made the decision to grant this approval;

(English version: http://www.pmda.go.jp/files/000231946.pdf).

Here, we report our observations on individual clinical records beyond the Good Clinical Practice (GCP) data available in the Report on the Deliberation Results of Medical Device Evaluation Division, Pharmaceutical Safety and Environmental Health Bureau Ministry of Health, Labour and Welfare of Japanese government. We describe in detail the 13-case histories in terms of safety and scoring on neurological scales including AIS Grade, AIS motor score, AIS sensory score, and SCIM-III score.

2. Methods

2.1. Study design

The clinical protocol is shown in Fig. 1. Ethics, Trial registration, Patients, Study procedures, Assessments and Statistical analysis are provided in detail in the Supplementary document. Observations in this initial cohort were not blinded, and there were no placebo controls.

3. Results

Case histories for the 13 patients are presented (Table 1). We present case number (in order), age, sex, level, AIS grade just prior MSC infusion, improved AIS class (days from MSC infusion to improving higher ASIA level), AIS 6 months post-MSC infusion and major adverse effects.

We also show in the each figure of patients the AIS grade, ISCSCI-92 (motor and sensory scores), SCIM-III score during the 6-month observation period post-MSC infusion. In some cases, we report data collected during and after the six-month period which extends the GCP data collection.

3.1. Case presentations

3.1.1. Case 1 (Fig. 2)

A 34-year old male fell from a 1.5 m height, resulting in a C5 SCI (AIS A). MRI demonstrated distractive extension injury at C3-C4 and high

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Fig. 1. Clinical protocol.
intensity area in the spinal cord (arrows). No acute surgical treatment was performed. The patient’s scores plateaued prior to MSC infusion and AIS score was still A with the patient being bedridden. He received an intravenous infusion of $1.0 \times 10^8$ autologous MSCs 47 days after SCI. Rapid but small improvements in motor and sensory (pin prick) function were observed after MSC infusion. Eight days after MSC infusion, AIS score improved to AIS B due to appearance of anal sensation. Two weeks post-MSC infusion, voluntary movement in lower extremities appeared and the AIS was C. On final examination (184 days post-MSC infusion), the patient could eat with upper extremity orthosis, drive a wheelchair for approximately 100 m and walk supported by a walker device with seat.

### 3.1.2. Case 2 (Fig. 3)
A 56-year-old female hit her forehead on a wall and hyperextended her neck after loss of consciousness when she stood up, resulting in a C5 SCI (AIS A). MRI demonstrated spinal cord compression due to a mixed type of ossification of the posterior longitudinal ligament (OPLL) and signal intensity changes at C2-7 (arrows). Laminoplasty (C2-C7) was performed 2 days post SCI. After surgery he remained tetraplegic and required a tracheotomy and ventilator. His scores plateaued prior to MSC infusion and AIS was still A with the patient being bedridden. Autologous human MSCs ($1.38 \times 10^8$) were injected 49 days after SCI. Motor function rapidly improved at day 1, and his AIS score became AIS D. SCIM-III score was increased to 79 because of improved ability of self-care, sphincter management and mobility.

### 3.1.3. Case 3 (Fig. 4)
A 47-year-old male sustained a C5 SCI (AIS A) in a diving accident (AIS A). MRI demonstrated compressive flexion injury at C5 and high intensity area in the spinal cord (arrows). Posterior spinal fusion (C4-C6) was performed 2 days post-SCI. After surgery he remained tetraplegic and required a tracheotomy and ventilator. His scores plateaued prior to MSC infusion at AIS B and he remained bedridden on a ventilator. He received autologous human MSCs ($1.38 \times 10^8$) 54 days after SCI. Rapid improvements in motor function were observed at 1 week after MSC infusion. SCIM-III improved after removal of his tracheotomy tube and incision closure ten days post-MSC. At four weeks, his AIS score improved to AIS C. At 169 days post-MSC infusion, he could drive a wheelchair at day one post- MSC infusion. SCIM-III continued to improve and the patient acquired the ability to walk, stair climb at 2 weeks, eat independently at eight weeks and self-catheterize at 12 weeks post-MSC infusion. On final examination (167 days post-MSC infusion), the patient was able to perform multiple independent living tasks including dressing and grooming.

### 3.1.4. Case 4 (Fig. 5)
A 57-year-old male fell from a 2 m height and hyperextended his neck, resulting in a C4 SCI (AIS B). MRI demonstrated cervical canal stenosis and signal intensity changes at C3-C4 without bone injury (arrows). No acute surgical treatment was performed. Pre-MSC scores plateaued at AIS C and he remained bedridden. Autologous human MSCs ($1.44 \times 10^8$) were injected 49 days after SCI. Motor function rapidly improved at day 1, and his AIS score became AIS D. SCIM-III gradually improved and he was able to use a wheelchair to participate in standing training. He could eat with upper extremity orthosis at two weeks and trained walking supported by a gait trainer (Meywalk® 2000, Meyland-smith A/S, Denmark) at three weeks. At 170 days post-MSC infusion, he could walk with a single-tip cane. At 209 days post-MSC infusion the SCIM-III score was increased to 79 because of improved ability of self-care, sphincter management and mobility.

### 3.1.5. Case 5 (Fig. 6)
A 23-year-old male sustained a C5 SCI (AIS A) due to a diving accident. MRI demonstrated compressive flexion injury at C5 and high intensity area in the spinal cord (arrows). Posterior spinal fusion (C4-C6) was performed 2 days post-SCI. After surgery he remained tetraplegic and required a tracheotomy and ventilator. His scores plateaued prior to MSC infusion at AIS C and he remained bedridden on a ventilator. He received autologous human MSCs ($1.38 \times 10^8$) 54 days after SCI. Rapid improvements in motor function were observed at 1 week after MSC infusion. SCIM-III improved after removal of his tracheotomy tube and incision closure ten days post-MSC. At four weeks, his AIS score improved to AIS C. At 169 days post-MSC infusion, he could drive a wheelchair at 526 days post-MSC infusion (extended data) the SCIM-III score was increased to 66 points, with improved self-care ability, sphincter management and mobility.
Fig. 2. Case 1.
Fig. 3. Case 2.
*Fig. 4. Case 3.*
Case 4: C → D

Fig. 5. Case 4.
Fig. 6. Case 5.
3.1.6. Case 6 (Fig.7)
A 36-year-old male hit his forehead on the ground and hyperextended his neck after falling off a bicycle, resulting in a C4 SCI (AIS B). MRI demonstrated high intensity area in the spinal cord without bone injury (arrows). Expansive laminoplasty (C3-C6) was performed 13 days after SCI. His scores plateaued prior to MSC infusion at AIS C and he remained bedridden. He received $0.84 \times 10^8$ autologous MSCs 53 days after SCI. One day later rapid improvement in motor function was observed and AIS score improved to AIS D. SCIM-III gradually improved and he was able to walk supported by a gait trainer (Meywalk® 2000) at two weeks and self-catheterization at 12 weeks after MSC infusion. At 169 days post-MSC infusion, he could walk with a single-tip cane and no orthotic devices. On final examination at 379 days post-MSC infusion (extended data), the SCIM-III score increased to 89 points with improved self-care ability, sphincter management and mobility.

3.1.7. Case 7 (Fig. 8)
A 52-year-old male collided with another player and hyperextended his neck at a baseball game, resulting in a C5 SCI (AIS B). MRI demonstrated high intensity areas without bone injury (arrows). Laminoplasty (C3-C6) was performed two days after SCI. His scores plateaued prior to MSC infusion (AIS C) and he remained bedridden. At 46 days post-SCI he received $1.44 \times 10^8$ autologous MSCs. One day later, rapid improvements in motor and sensory function were observed and his AIS was D. SCIM-III gradually improved and he acquired the ability to walk supported by a gait trainer (Meywalk® 2000) (3 weeks) and for self-catheterization (12 weeks) post-MSC infusion. At 184 days post-MSC infusion, he could walk with a single-tip cane and no orthotic devices. On final examination at 363 days post-MSC infusion (extended data), the SCIM-III score increased to 84 points and his self-care ability, sphincter management and mobility were slightly improved.

3.1.8. Case 8 (Fig. 9)
A 55-year-old male fell from a 2 m height and hyperextended his neck, resulting in a C5 SCI (AIS C). MRI demonstrated high intensity area in the spinal cord without bone injury (arrows). No acute surgical treatment was performed. His scores plateaued prior to MSC infusion and AIS was C with the patient still remaining bedridden. He received an intravenous infusion of $1.04 \times 10^8$ autologous MSCs 52 days after SCI. One day after MSC infusion, rapid improvement in motor function was observed and his AIS score improved to AIS D. SCIM-III gradually improved with acquisition of the ability to walk supported by a gait trainer (Meywalk® 2000) at three weeks and self-catheterization at 12 weeks after MSC infusion. At 169 days post-MSC infusion, the patient could walk with a single-tip cane and no orthotic devices.

3.1.9. Case 9 (Fig. 10)
A 43-year-old male fell and hyperextended his neck while skiing, resulting in a C5 SCI (AIS B). MRI demonstrated cervical canal stenosis and high intensity area in the spinal cord without bone injury (arrows). Expansive laminoplasty (C3-C6) was performed one day after SCI. The patient’s scores plateaued prior to MSC infusion and AIS score was B and he was bedridden. He received $1.06 \times 10^8$ autologous MSCs 51 days after SCI. One day after MSC infusion, rapid improvements in motor and sensory function were observed; his AIS B score moved to C. Improvements in motor function continued and his AIS scale became D at 18 weeks. On final examination at 189 days post-MSC infusion, he was training for walking supported by a gait trainer (Meywalk® 2000).

3.1.10. Case 10 (Fig. 11)
A 65-year-old male fell from a ladder and hyperextended his neck at home, resulting in a C4 SCI (AIS A). MRI demonstrated spinal cord compression due to a mixed type of OPLL and signal intensity changes at C2-C4 (arrows). Laminoplasty (C2-C6) was performed immediately after SCI, but his tetraplegia did not improve. A tracheotomy and ventilator support were required. His scores did not change, and he was AIS A prior to MSC infusion; he remained bedridden on a ventilator. He received an intravenous infusion of $1.3 \times 10^8$ autologous MSCs 43 days after SCI. One day after MSC infusion, rapid improvement in sensory function was observed; his AIS score became AIS B, although there was little improvement in motor score. SCIM-III subsequently improved due to improvement of respiratory function; use of the tracheotomy tube was terminated and the incision closed three weeks after MSC infusion. On final examination at 497 days post-MSC infusion (extended data), his AIS score was AIS C, with improvements of motor function (increase of motor score from zero to eight). The SCIM-III score was also increased to 17 points because he became to breathe independently without a device and perform two activities without assistance, such as repositioning his upper body and decompression of buttoks.

3.1.11. Case 11 (Fig. 12)
A 66-year-old male fell from the seat of an excavator, resulting in a C4 SCI (AIS A). MRI demonstrated compressive extension injury at C4 and high intensity area in the spinal cord (arrows). No acute surgical treatment was performed. SCIM-III dropped 3 weeks after onset (1 M prior to MSC infusion) because respiration required oxygen with tracheal tube management. His plateau AIS score prior to MSC infusion was A with the patient being bedridden. He received an intravenous infusion of $1.3 \times 10^8$ autologous MSCs 54 days after SCI. Rapid improvements in motor and sensory function were observed after MSC infusion. One month after MSC infusion, his AIS A score improved to AIS B. SCIM-III improved to 4 points because of improvement of respiratory function 20 weeks after MSC infusion. On final examination at 476 days post-MSC infusion (extended data point) improvement in motor function was observed and the SCIM-III score was increased to 14 as respiratory status improved, the tracheotomy tube was removed, and the incision closed. He could breathe independently without assistance or device.

3.1.12. Case 12 (Fig. 13)
A 55-year-old male was injured in a car accident that resulted in a C3 SCI (AIS A) due to unilateral fractures of an articulating process at C4-C5 caused by compressive extension injury. MRI demonstrated high intensity area in the spinal cord (arrows). He also suffered thoracic fractures (T4-T6), not followed by compression of spinal cord. Posterior decompression (C4-C5) and fusion (C3-C6) and posterior spinal fusion (T3-T7) were performed 16 days after SCI. The patient’s scores plateaued prior to MSC infusion and AIS was still A with the patient being bedridden. He received an intravenous infusion of $1.54 \times 10^8$ autologous MSCs 51 days after SCI. Improvements were observed in motor at 1 week and sensory (light touch at 3 days; pin prick at 2 weeks) functions post-infusion. Ten weeks after MSC infusion, his AIS A score improved to AIS B. SCIM-III improved with improvement of his respiratory function at 3 weeks after MSC infusion and development of ability to operate manual wheelchair with assistance at 18 weeks after MSC infusion. On final examination at 168 days post-MSC infusion, he was able to drive a wheelchair and use an iPad®.

3.1.13. Case 13 (Fig. 14)
A 21-year-old male was injured in a car accident that resulted in a C4 SCI (AIS A) due to bilateral facet dislocation at C4-C5 caused by distractive flexion injury. Respiratory support was required and a tracheotomy was performed on the next day. Two days later, he underwent reduction and posterior decompression with fusion, but his tetraplegia did not improve, and sensory score dropped due spinal edema. He was
Fig. 7. Case 6.
Fig. 8. Case 7.
Fig. 9. Case 8.
Fig. 10. Case 9.
Case 10: A → B

Fig. 11. Case 10.
Case 11: A → B

Fig. 12. Case 11.
Case 12: A → B

Fig. 13. Case 12.
Fig. 14. Case 13, “days” in MRI images are from the day of MSC infusion.
transferred to our hospital. MRI demonstrated extensive high intensity
from medulla to lumber spinal cord. The patient’s scores plateaued prior
to MSC infusion; AIS was still A and the patient remained bedridden and
ventilator-dependent. He received an intravenous infusion of $1.6 \times 10^8$
autologous MSCs 43 days after SCI. Improvements were observed in
sensory function after MSC infusion beginning at 3 days. His respiratory
function gradually improved and required a lower level of pressure-
support (ps) ventilation (green line). On final examination at 170 days
post-MSC infusion, he remained AIS A, however, his sensory scores
slightly improved.

3.2. Clinical data

The flowchart of this study is shown in Supplementary Fig. 1. Thir-
teen patients (Table 1) ranging from 21 to 66 (average: 46.9 ± 14.7,
median: 52) years and of both genders were studied, from an initial
group of 17 patients enrolled, who were referred as candidates for this
study. All 17 patients fulfilled the primary inclusion criteria; however,

| AIS impairment class between prior to infusion and 6 months. | A**  | B**  | C**  | D**  |
|------------------------------------------------------------|------|------|------|------|
| A*                                                        | 16.7 % (1/6) | 50 % (3/6) | 33.3 % (2/6) | 0 %   |
| B*                                                        | 0 %   | 0 %   | 50 % (1/2) | 50 % (1/2) |
| C*                                                        | 0 %   | 0 %   | 0 %   | 100 % (5/5) |

* AIS prior to MSC infusion.
** AIS at 6 month post-MSC infusion.

four patients were excluded and did not receive autologous MSCs
because they met exclusion criteria (1 patient each: hepatitis B, chro-
mosomal abnormality, severe pneumonia, possible myelodysplastic
syndrome). No patients refused to participate and no patients withdrew
from the study after MSC infusion. The autologous MSCs were intrave-
nously infused between 43–54 days post-SCI. No serious adverse events
were associated with cell injection. Anemia after peripheral blood
collection (2 cases) and local pain at the bone marrow aspiration site
immediately after bone marrow collection (1 case) were recorded as
protocol-related adverse events (AE). However, all protocol-related AEs
occurred before MSC infusion. Thus, there were no MSC-related AEs in
this study.

Time point of assessment at 6 months post-MSC infusion was
approximately 220 days after SCI onset (median: 219, min: 210, max:
231). Neurologic improvement based on AIS grade occurred in 12 (92.3
%) of the 13 patients, comparing status prior to MSC infusion to status 6
months (± 14 days) after MSC infusion. Five of six patients classified as
AIS A prior to MSC improved to AIS B (50 %: 3/6) or AIS C (33.3 %: 2/6)
at 6 months post-MSC infusion. Two patients classified as AIS B prior to
MSC infusion improved to AIS C (50 %: 1/2) or AIS D (50 %: 1/2). Five
patients classified as AIS C prior to MSC infusion reached a functional
status of AIS D (100 %: AIS D) at six months post-MSC infusion; notably,
 improvement to AIS D was observed one day following MSC infusion for
all five AIS C patients (Table 2). The relationship between AIS impair-
ment prior to MSC infusion and at six months post-MSC infusion is
shown in Table 2. Fig. 15 shows the representative values of ISSCI-92
and SCIM-III scores prior to MSC infusion, and 7, 14, 28, 90 and 180 days

![Outcome measure scores according to AIS class (A: motor, B: light touch, C: pin prick, D: SCIM-III).](image-url)
Fig. 16. Comparison of outcome measure scores prior to infusion and 6 months post-MSC infusion according to AIS class (A: motor, B: light touch, C: pin prick, D: SCIM-III).

Fig. 17. Difference of ISCSCI-92 (A) and SCIM-III (B) scores according to AIS class.
post-MSC infusion, respectively. After MSC infusion, the patients displayed increases in all scores in motor (Fig. 15A) and sensory examinations including light touch (Fig. 15B), pin prick testing (Fig. 15C) and SCIM-III (Fig. 15D). Fig. 16 shows the individual changes of ISCSCI-92 and SCIM-III scores prior to MSC infusion, and 180 days post-MSC infusion, respectively. Motor (Fig. 16A) and sensory scores evaluated with light touch (Fig. 16B) and pin prick tests (Fig. 16C) at six months ($\pm$ 14 days) showed equal or higher points compared to scores prior to MSC infusion in all patients in all groups. In SCIM-III, the total scores at six months ($\pm$ 14 days) are also equal or higher compared to the scores prior to MSC infusion in all patients in all groups (Fig. 16D). No deteriorated scores were observed for either ISCSCI-92 or SCIM-III status at six months post-MSC infusion. The increased magnitude of both ISCSCI-92 (total) and SCIM-III scores, compared prior to MSC infusion and 6 months ($\pm$ 14 days) post-MSC infusion, are shown in Fig. 17. There was no difference in the increased magnitude in ISCSCI-92 between the three AIS groups (Fig. 17A). The increased magnitude of the SCIM-III score was statistically larger for the AIS C group compared to the AIS A and B groups (Fig. 17B).

4. Discussion

This case series provides information that intravenous infusion of autologous bone marrow derived MSCs, expanded in auto-serum into 13 SCI patients was safe and feasible. None of the patients showed CNS tumors, abnormal cell growth or neurological deterioration. Detailed...
individual clinical records beyond the GCP data are in the Report on the Deliberation Results: (https://www.pmda.go.jp/files/000229851.pdf) presented in this paper.

Although this initial case study was unblinded and uncontrolled, the SCI patients appeared to demonstrate a tendency of relatively rapid improvement of neurological function that was often apparent within a few days following infusion of MSCs. We would emphasize that this case series describes an early study on a small number of patients. In addition to being unblinded and uncontrolled, this study has a number of limitations. We cannot rule out observer bias nor a contribution of surgical intervention to recovery in cases where this intervention occurred, or spontaneous recovery.

The mechanism for this early apparent improvement in neurological status is not clear, but studies in animal models suggest that secreted neurotrophic factors from MSCs including brain derived neurotrophic factor (BDNF) [5] might be associated with the rapid improvement. First, BDNF attenuates edema in the injured tissue [19,21] via restoration of blood spinal cord barrier and reduction of microvascular leakage [4,6,22]. Second, BDNF has a major impact on efficiency of the synthesis of adenosine triphosphate [23] resulting in normalization of resting membrane potential. Third, BDNF can affect neuronal excitability and synaptic transmission [19] and the kinetics of potassium channels [24–26] to normalize action potential firing rates [27].

Recent studies have also shown that intravenous infusion of MSCs after acute SCI may induce transient gene expression changes in the brain within days, and it is possible that these changes might trigger additional downstream gene expression to provoke early functional improvements in SCI [7]. Consistent with the present findings, we observed a rapid improvement in both NIHSS scores and lesion volume within the first week in stroke patients who received autologous MSCs [19]. Additional potential mechanisms by which infused MSCs might contribute to gradual functional recovery after initial rapid improvements include remyelination, immunomodulation [28], augmenting the recovery of injured axons [29], replacement of injured cells [30,31], and/or enhancement of neural plasticity [7,32].

Scivoletto et al. (2014) reported that the percentage of subsequent improvement is low if the first (baseline) examination is performed at 30 days post-injury [33]. In that study, comparison of one-year follow-up results of ASIA scores 30 days after injury revealed that only 5% of the ASIA A, 47% of ASIA B and 54% of ASIA C patients converted to higher ASIA grades. In our study MSCs were infused between 43–54 days post-SCI and examinations were performed at six months after MSC infusion, yet the conversion rate to improvement of ASIA scores was greater. Comparative results that juxtapose our observations with those of Scivoletto et al. (2014) are shown in Fig. 18. These data are suggestive that intravenous infusion of autologous MSCs expanded in autologous human serum may provide functional improvements in human SCI, but future studies designed to look for efficacy are necessary.

5. Conclusions

We report the detailed clinical record of infused autologous, autoserum expanded MSCs in SCI patients. Our observations support safety, feasibility and provide initial data that suggests rapid functional improvements following MSC infusion. This case series underscores the importance of a future large-scaled controlled clinical study in SCI patients to determine efficacy.

Trial registration

JMACCT: JMA-IIA00154

Consent for publication

Written informed consent from patients and legal representative (legal representative alone if the patient did not have ability to write) was obtained for each patient before enrollment.

Availability of data and materials

Deidentified individual participant data and relevant supporting clinical study documents are available upon formal request from qualified scientific and medical researchers. Supporting information includes the study protocol, statistical analysis plan, and informed consent form.

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CRediT authorship contribution statement

Osamu Honmou: Conceptualization, Methodology, Investigation, Project administration, Funding acquisition, Project administration, Writing - original draft, Writing - review & editing. Toshihiko Yamashita: Conceptualization, Methodology, Investigation, Project administration, Funding acquisition. Tomonori Morita: Investigation. Tsutomu Oshigiri: Investigation. RyoSuKe Hirota: Investigation. Satoshi Iyama: Investigation. Junji Kato: Investigation. Yuichi Sasaki: Investigation. Sumio Ishiai: Investigation. Yoichi M. Ito: Methodology, Formal analysis. Ai Kamioka: Investigation. Takahiro Kamioka: Investigation. Masahito Nakazaki: Investigation. Yuko Kataoka-Sasaki: Investigation, Data curation. Rie Onodera: Methodology. Shinichi Oka: Investigation, Data curation, Visualization. Masanori Sasaki: Conceptualization, Investigation, Project administration, Funding acquisition, Visualization, Writing - original draft, Writing - review & editing. Stephen G. Waxman: Supervision, Writing - original draft, Writing - review & editing. Jeffery D. Kocsis: Supervision, Writing - original draft, Writing - review & editing.

Declaration of Competing Interest

The Department of Advanced Regenerative Therapeutics at Sapporo Medical University has been endowed by the NIPRO Corporation since 1st February 2014. Sapporo Medical University and NIPRO Corporation have entered into a joint research and development agreement since 1st February 2014. Sapporo Medical University and NIPRO Corporation entered into a joint research and development agreement since 1st April 2014, which provides research support to the Department including work carried out by some of the co-authors (HO, TY, TM, TO, RH, YS, AN, TN, MN, YKS, RO, SO and MS). A joint patent license agreement on MSCs for repair of the nervous system between Sapporo Medical University and NIPRO Corporation was established since 21st April 2014. HO is listed as an inventor on the patent and may receive royalties or other compensation. NIPRO Corporation obtained conditional, time-limited approval for commercialization of the therapy to use autologous MSCs cultured in auto-serum (called Stemirac®) for acute SCI patients under the “sakigake” designation scheme by an expert panel at the Ministry of Health, Labor and Welfare in Japan on 28th December 2018. JDK receives research support through Yale University from NIPRO Corporation for post-doctoral fellow support and associated research on pre-clinical studies of rodent MSCs in animal spinal cord injury models. HO, TY and MS received honoraria from NIPRO.
Corporation for lectures. SI, JK, SI, YMI, SGW report no competing interests.

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Appendix A. Supplementary data

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