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CELLTOP Clinical Trial: First Report From a Phase 1 Trial of Autologous Adipose Tissue–Derived Mesenchymal Stem Cells in the Treatment of Paralysis Due to Traumatic Spinal Cord Injury

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Abstract

Spinal cord injury (SCI) is a devastating condition with limited pharmacological treatment options to restore function. Regenerative approaches have recently attracted interest as an adjuvant to current standard of care. Adipose tissue–derived (AD) mesenchymal stem cells (MSCs) represent a readily accessible cell source with high proliferative capacity. The CELLTOP study, an ongoing multidisciplinary phase 1 clinical trial conducted at Mayo Clinic (ClinicalTrials.gov Identifier: NCT03308565), is investigating the safety and efficacy of intrathecal autologous AD-MSCs in patients with blunt, traumatic SCI. In this initial report, we describe the outcome of the first treated patient, a 53-year-old survivor of a surfing accident who sustained a high cervical American Spinal Injury Association Impairment Scale grade A SCI with subsequent neurologic improvement that plateaued within 6 months following injury. Although he improved to an American Spinal Injury Association grade C impairement classification, the individual continued to be wheelchair bound and severely debilitated. After study enrollment, an adipose tissue biopsy was performed and MSCs were isolated, expanded, and cryopreserved. Per protocol, the patient received an intrathecal injection of 100 million autologous AD-MSCs infused after a standard lumbar puncture at the L3-4 level 11 months after the injury. The patient tolerated the procedure well and did not experience any severe adverse events. Clinical signs of efficacy were observed at 3, 6, 12, and 18 months following the injection in both motor and sensory scores based on International Standards for Neurological Classification of Spinal Cord Injury. Thus, in this treated individual with SCI, intrathecal administration of AD-MSCs was feasible and safe and suggested meaningful signs of improved, rather than stabilized, neurologic status warranting further clinical evaluation.

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Affiliations are at the end of this article.

More than 17,000 people in the United States sustain a spinal cord injury (SCI) each year with over 291,000 affected, translating into major personal and overall socioeconomic burden.[1] The cost to the health care system exceeds $40 billion with a cumulative compromise to the productive workforce.[2] Clinical trials striving to improve neurologic outcomes following SCI have yet to identify an intervention that would enhance the reach of current best practices, improving neurologic outcomes beyond initial surgical stabilization and comprehensive rehabilitation.[3–8]

Novel treatment strategies, including regenerative approaches, have generated interest as potentially transformative in restoring form and function.[9] The safety of these novel treatment strategies for patients with SCI in the acute and subacute phase has been investigated recently in early-stage clinical trials. These trials have focused primarily on change in motor function, with the aim to rigorously establish their clinical relevance.[9] In this context, the use of mesenchymal stem cells (MSCs) has steadily evolved.[10] In particular, adipose tissue represents a readily accessible and viable source of MSCs. Available evidence has shown that adipose tissue–derived (AD) MSCs can regulate inflammatory responses and provide a regeneration-permissive environment in animal models of SCI.[9] However, there is a paucity of trials investigating the role of AD-MSCs in patients with advanced SCI. We present initial results for the first patient enrolled in the clinical multidisciplinary trial CELLTOP (Clinical Trial of Autologous Adipose Derived Mesenchymal Stem Cells in the Treatment of Paralysis Due to Traumatic Spinal Cord Injury; ClinicalTrials.gov Identifier: NCT03308565), a phase 1 clinical trial of autologous AD-MSCs in the treatment of paralysis due to traumatic SCI.

REPORT OF CASE

Study Patient

The patient is a 53-year-old male who suffered a surfing accident resulting in a C3-4 SCI. Neurologic examination at the time of the accident revealed complete loss of motor and sensory function below the level of injury along with loss of bowel and bladder sensation. Accordingly, the individual was diagnosed with an American Spinal Injury Association (ASIA) grade A SCI, and underwent a C2-6 posterior cervical decompression and fusion. Postoperatively, improvement in motor and sensory function and bowel and bladder sensation were demonstrable. However, 6 months after the injury, gains in neurologic function plateaued, and he did not experience additional amelioration.

Following informed consent, the patient was enrolled into the multidisciplinary CELLTOP clinical trial 9 months after the injury (Supplemental Material, available online at http://www.mayoclinicproceedings.org). At the time of enrollment, his neurologic status was found to be ASIA grade C. Imaging revealed bilateral myelomalacia at the C3 level as well as the C2-6 decompression and fusion.

An open biopsy of abdominal wall adipose tissue was performed 8 weeks before the injection. Mesenchymal stem cells were isolated from the adipose tissue biopsy specimen and were expanded and cryopreserved internally in the Mayo Clinic Immune, Progenitor, and Cell Therapeutics Laboratory. Per protocol, the patient received an intrathecal injection of 100 million AD-MSCs suspended in lactated Ringer solution and infused after a standard lumbar puncture at the L3-4 level, 11 months after the injury and 5 months after plateau of improvement. His neurologic status was assessed according to the International Standards for Neurological Classification of Spinal Cord Injury at the baseline visit, at days 2 and 3, and weeks 1, 2, 4, 12, 24, 48, and 72. The Capabilities of Upper Extremity questionnaire and Global Health Score questionnaire were also administered at the same time points.

RESULTS

Safety and Adverse Events

The patient tolerated the procedure well and did not experience any severe adverse events related to the injection. He reported a mild to moderate headache on day 2, which resolved with acetaminophen. Throughout the 18-month follow-up, no other safety issues or adverse events were reported.

ASIA Motor Score

The total upper extremity motor score progressively improved from 35 at baseline to 44 at 18 months, with more marked improvement on the right (19 at baseline to 25 at 18 months) compared with the left side (16 at baseline to 19 at 18 months) (Figure 1A and Table 1). Also, considerable improvement was observed in total lower extremity motor scores, from 36 at baseline to 49 at 18 months following injection. Similar

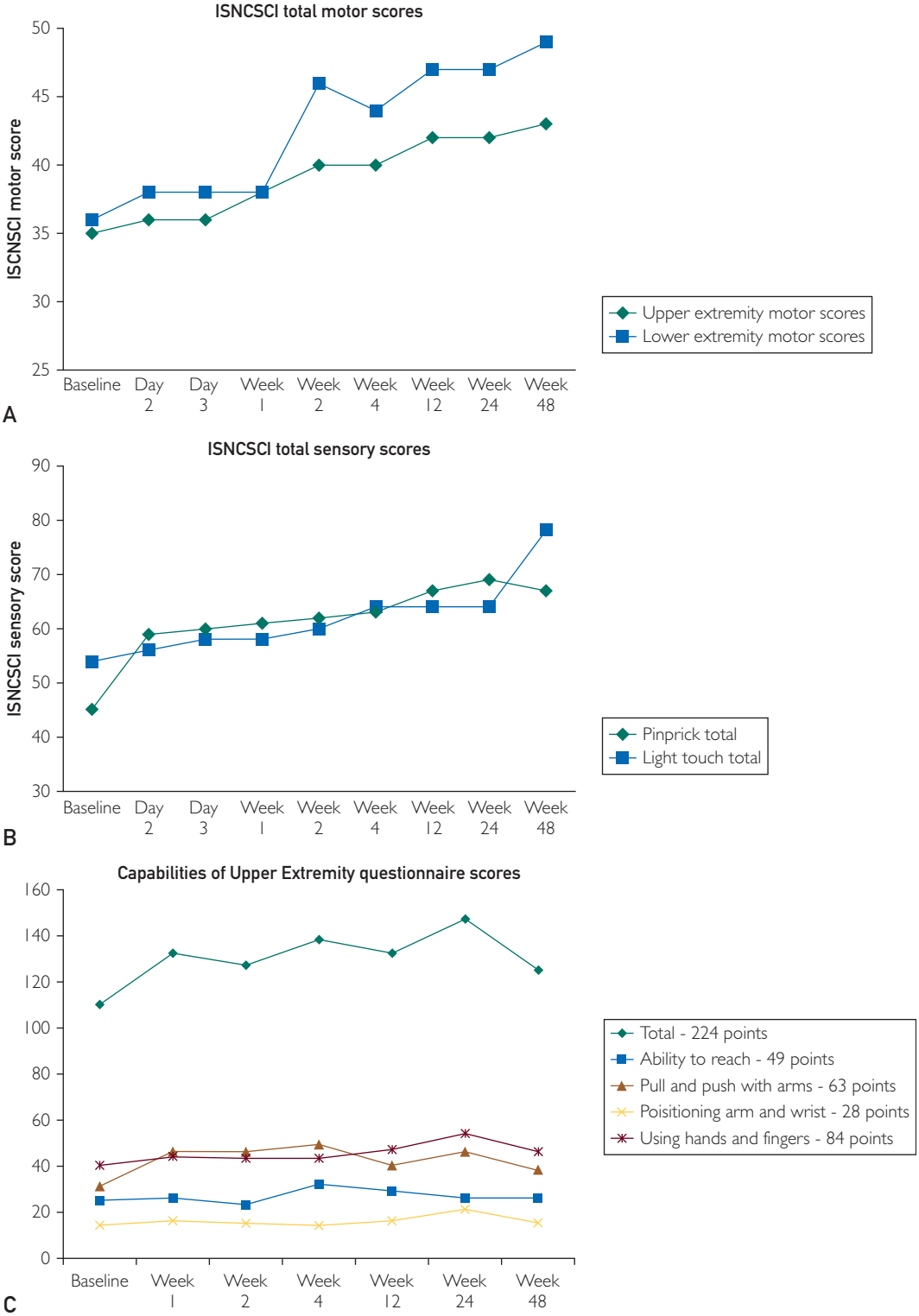

FIGURE 1. A, Total upper and lower extremity motor score at all time points. B, Total pinprick and light touch sensory score at all time points. C, Capabilities of Upper Extremity questionnaire scores at all time points. ISNCSCI = International Standards for Neurological Classification of Spinal Cord Injury.

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TABLE 1. Motor and Sensory Scores at All Time Points According to the International Standards for Neurological Classification of Spinal Cord Injury

Variable	Baseline	Day 2	Day 3	Week 1	Week 2	Week 4	Week 12	Week 24	Week 48	Week 72
Motor scores										
Upper right extremity	19	19	19	20	21	21	23	23	24	25
Upper left extremity	16	17	17	18	19	19	19	19	19	19
Total upper extremity score	35	36	36	38	40	40	42	42	43	44
Lower right extremity	19	19	19	19	24	23	24	24	25	25
Lower left extremity	17	19	19	19	22	21	23	23	24	24
Total lower extremity score	36	38	38	38	46	44	47	47	49	49
Sensory scores										
Right pinprick	25	28	29	30	29	32	33	34	32	46
Left pinprick	20	31	31	31	33	31	34	35	35	49
Total pinprick	45	59	60	61	62	63	67	69	67	95
Right light touch	27	28	29	29	30	32	32	32	39	46
Left light touch	27	28	29	29	30	32	32	32	39	50
Total light touch	54	56	58	58	60	64	64	64	78	96

improvement was noted bilaterally in the lower extremities (right, 19 at baseline to 25 at 18 months; left, 17 at baseline to 24 at 18 months) (Figure 1A and Table 1).

ASIA Sensory Score

The total pinprick score improved consistently at each time point from 45 at baseline to 95 at 18 months of follow-up. The improvement was similar on both sides, improving from 25 at baseline to 46 at 18 months on the right side and 20 at baseline to 49 at 18 months on the left side. Similarly, total light touch score also improved from 54 at baseline to 96 at 18 months of follow-up. Similar improvement was observed bilaterally: 27 at baseline to 46 at 18 months on the right side and 27 at baseline to 50 at 18 months on the left side (Figure 1B and Table 1).

We also examined the improvement in each dermatomal region. In the upper extremity, the improvement was substantially pronounced in the C5 region bilaterally. Additionally, on the left side the patient also experienced marked improvement in the C2-4, C6, and T1-3 region. In the lower extremity, the patient experienced improvement in the L4, L5, and S1-4 region (Figure 2A and B; 3A-D).

Capabilities of Upper Extremity Questionnaire

The Capabilities of Upper Extremity score improved from 110 at baseline to 144 at 18 months. The most notable improvement was in the "pull and push with arms" component, which improved from 31 at baseline to 46 at 18 months, and the "using hands and fingers" component, which improved from 40 at baseline to 51 at 18 months (Figure 1C).

Global Health Score

Substantial improvement in quality of life was observed, as assessed using the Global Health Score or PROMIS (Patient-Reported Outcomes Measurement Information System) 10 questionnaire. The global physical health raw/T score improved from 8/29.6 at baseline to 10/34.9 at 18 months, while the global mental health score improved from 7/11 at baseline to 11/41.1 at 18 months.

Physical Therapy and Occupational Therapy

We also observed considerable improvement in physical therapy and occupational therapy measures at follow-up. The patient's time and speed for the 10-meter walk test improved from 57.72 seconds, 0.17 m/s at baseline to 23.00 seconds, 0.43 m/s at 15 months. His ambulation also improved substantially; at

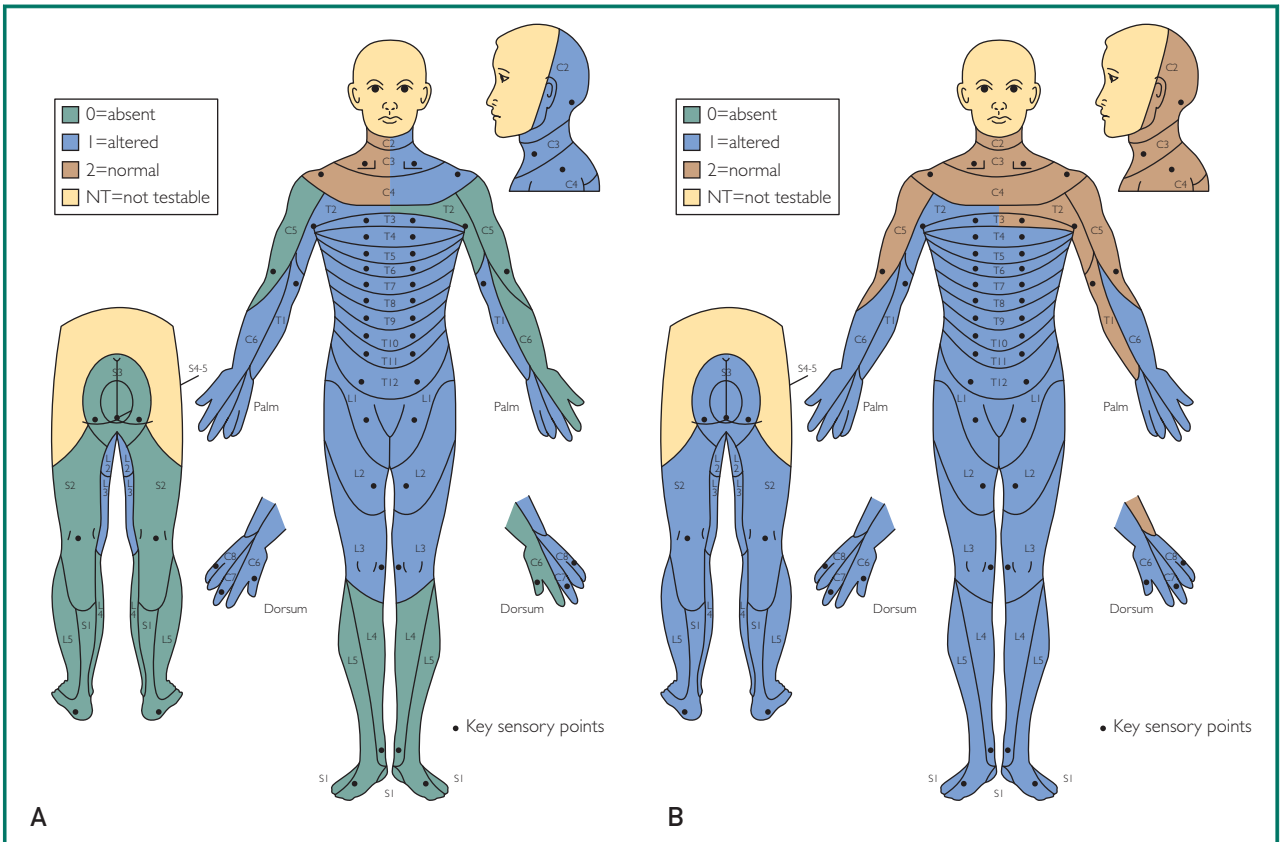

FIGURE 2. Dermatomal sensory scores according to the International Standards for Neurological Classification of Spinal Cord Injury form at baseline (A) and at 18 months of follow-up (B).

baseline, he was able to walk 635 ft for 12.8 minutes at a pace of 0.25 m/s, which improved to 2200 ft for 34 minutes at a pace of 0.33 m/s at 15 months. Moreover, his range of motion also improved considerably, most notably for shoulder flexion (left, 60° at baseline to 100° at 12 months; right, 105° at baseline to 130° at 12 months) and shoulder abduction (left, 60° at baseline to 140° at 12 months; right, 100° at baseline to 140° at 12 months) bilaterally. These and other measures of physical therapy and occupational therapy are summarized in Table 2.

DISCUSSION

Spinal cord injury has a complex pathophysiology. One of the more challenging aspects of this life altering pathophysiology is the onset of secondary mechanisms of tissue insult in the subacute and chronic phase following the primary injury. Glial scarring limits axonal regeneration as a complex physicochemical barrier by secreting growth inhibitor molecules. These microenvironmental changes cause the chronically injured spinal cord to be in a refractory state.[11] In addition to bridging the tissue gap that prevents regeneration in such a state, creating a permissive restorative environment also poses an important challenge. However, current knowledge about the intrinsic ability of the injured nervous system to regenerate, when in a supportive environment, has shortened the gap toward developing new strategies to treat SCI.[12] Regenerative medicine is an emerging field of medicine and surgery that may be a promising source of novel interventions to foster spinal cord regeneration, even in the setting of chronic SCI. Advances made have identified new translatable approaches, such as implantable

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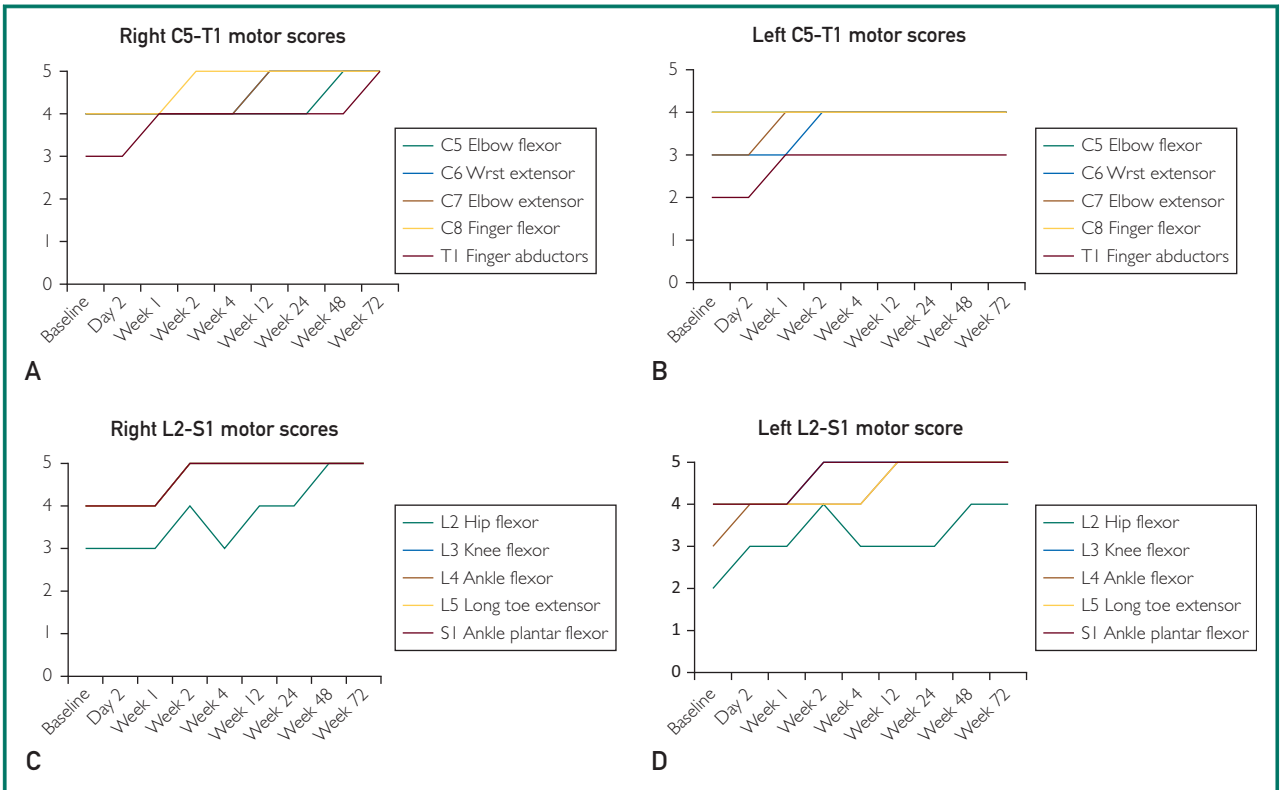

FIGURE 3. International Standards for Neurological Classification of Spinal Cord Injury motor scores for the subject at all time points. A, right upper extremity motor scores. B, Left upper extremity motor scores. C, Right lower extremity motor scores. D, Left lower extremity motor scores.

biomaterials (polymer scaffolds) and stem cell transplant, as promising therapies.[13]

Given the multidimensional complexity of SCI, cell-based therapies have offered substantial promise as a therapeutic strategy because of the multifactorial roles stem cells can potentially provide. One of these roles is providing trophic support to the injured spinal cord microenvironment by modulating the inflammatory response, increasing vascularization, and suppressing cystic change.[12,14]

Adipose Tissue–Derived Mesenchymal Stem Cells in SCI

Mesenchymal stem cells are one of the most frequently tested agents because of the broad range of sources (eg, umbilical cord, bone marrow, adipose tissue) and fewer ethical concerns including the opportunity to secure an autologous approach.[15,16] Preclinical evidence has suggested that human AD-MSCs exhibit considerable proliferative capacity, growth factor production, and performance in improving functional outcomes in SCI.[16] Postulated mechanisms of action in SCI include reduction of glial scarring,[17] promotion of axonal regeneration via secretion of growth factors,[16,18] and putative differentiation into neural elements.[19] The relative ease of tissue harvest, subsequent cell culture under standard conditions, and potency to differentiate into various cell lineages underscore the potential for AD-MSCs as a therapeutic option.

Intrathecal Transplant of AD-MSCs

The safety of autologous AD-MSC delivery via intrathecal injection has been determined previously. Intrathecal injection of up to 100 million cells was found to be safe in a dose-escalation phase 1 clinical trial for 21 patients with amyotrophic lateral

TABLE 2. Physical Therapy and Occupational Therapy Scores at Available Time Points

Variable	Baseline	1 Month	3 Months	6 Months	9 Months	12 Months	15 Months
Physical therapy							
10-Meter walk							
Time (s)	57.72	36.21	33.52	30.02	29.82	25.19	23.00
Speed (m/s^2)	0.17	0.28	0.30	0.33	0.35	0.40	0.43
Ambulation							
Distance (m)	193.5	223.1	298.7	350.5	470	565.7	670.6
Time (min)	12.80	13.80	16.00	17.65	23.95	27.12	34.00
Time (sec)	768	828	960	1059	1437	1627	2040
m/s	0.25	0.27	0.31	0.33	0.33	0.35	0.33
Occupational therapy							
Hand strength (kg)							
Gross grip							
Right	17.1	21.2	22.5	22.5	NA	24.8	NA
Left	15.8	15.8	15.8	15.8	NA	18.0	NA
Lateral pinch							
Right	5.4	8.1	8.1	8.1	NA	5.4	NA
Left	5.0	5.4	5.4	5.4	NA	5.4	NA
3-Point pinch							
Right	5.0	5.8	5.4	5.4	NA	3.6	NA
Left	3.2	4.5	3.6	3.6	NA	2.7	NA
Manual dexterity—9-hole peg test (s)							
Right hand	1.05	0.95	0.96	0.65	NA	0.62	NA
Left hand	1.90	1.33	1.13	1.10	NA	0.93	NA
Active range, sitting (°)							
Right shoulder							
Flexion	105	110	125	120	NA	130	NA
Abduction	100	120	135	110	NA	140	NA
External rotation	65	65	65	65	NA	80	NA
Extension	60	65	65	65	NA	70	NA
Left shoulder							
Flexion	60	60	80	95	NA	100	NA
Abduction	60	80	80	95	NA	95	NA
External rotation	40	40	40	45	NA	45	NA
Extension	50	50	55	55	NA	65	NA

NA = not available.

sclerosis.[20] Hur et al[21] reported the first human trial of intrathecal autologous AD-MSCs (dose, 90 million cells) in 14 patients with SCI, 12 of whom were reported to have ASIA grade A neurologic impairment at baseline. The authors reported improvement in motor function in 5 patients. Additionally, Thakkar et al[22] reported variable and sustained improvement in ASIA score in 10 patients receiving intrathecal coinfusion of autologous AD-MSCs and bone marrow–derived hematopoietic stem cells (average dose, 45 million cells). With the exception of some minor adverse events such as transitory fever, headache, and urinary tract infection, serious adverse effects were not reported in either trial. Combined, these studies suggest a favorable risk to benefit profile for intrathecal AD-MSC administration in SCI.

It is important in such cases to distinguish gains attributable to therapy from spontaneous recovery following the injury. In the current report, we have presented both subjective (physical therapy and occupational therapy reports) and objective (International Standards for Neurological Classification of Spinal Cord Injury scores)

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measures to demonstrate that the patient, after reaching a plateau of spontaneous improvement at 6 to 7 months postinjury, experienced improvement in neurologic status.

Overall, intrathecal AD-MSC administration may be a relatively noninvasive and safe therapeutic option for patients with SCI to improve their neurologic status after they have reached a ceiling effect in terms of spontaneous recovery. It is important to demonstrate the successful translation of novel therapeutics using a multimodal approach at a time when such therapeutic options are attracting scrutiny by the US Food and Drug Administration.[23]

CONCLUSION

Intrathecal AD-MSC administration may have the potential to improve neurologic function in patients with plateaued clinical improvement following SCI. Further clinical translation of this therapeutic strategy would require demonstration of treatment safety and efficacy in a sufficiently powered randomized controlled trial and identification of prognostic factors predictive of response to intervention.

SUPPLEMENTAL ONLINE MATERIAL

Supplemental material can be found online at http://www.mayoclinicproceedings.org. Supplemental material attached to journal articles has not been edited, and the authors take responsibility for the accuracy of all data.

Abbreviations and Acronyms: **AD** = adipose tissue–derived; **ASIA** = American Spinal Injury Association; **MSC** = mesenchymal stem cell; **SCI** = spinal cord injury

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