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Autologous bone marrow-derived stem cells in amyotrophic lateral sclerosis: A pilot study

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» Abstract

Background: Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder with no effective treatment. Stem cell therapy may be one of the promising treatment options for such patients. **Aim:** To assess the feasibility, efficacy and safety of autologous bone marrow-derived stem cells in patients of ALS. Settings and Design: We conducted an open-label pilot study of autologous bone marrow-derived stem cells in patients with ALS attending the Neurology Clinic of a tertiary care referral centre.

Materials and Methods: Ten patients with ALS with mean revised ALS Functional Rating Scale (ALSFRS-R) score of 30.2 (± 10.58) at baseline received intrathecal autologous bone marrow-derived stem cells. Primary end point was improvement in the ALSFRS-R score at 90, 180, 270 and 365 days post therapy. Secondary endpoints included ALSFRS-R subscores, time to 4-point deterioration, median survival and reported adverse events. Paired t-test was used to compare changes in ALSFRS-R from baseline and Kaplan-Meier analysis was used for survival calculations. **Results:** There was no significant deterioration in ALSFRS-R composite score from baseline at one-year follow-up (P=0.090). The median survival post procedure was 18.0 months and median time to 4-point deterioration was 16.7 months. No significant adverse events were reported. **Conclusion:** Autologous bone marrow-derived stem cell therapy is safe and feasible in patients of ALS. Short-term follow-up of ALSFRS-R scores suggests a trend towards stabilization of disease. However, the benefit needs to be confirmed in the long-term follow-up period.

* Registration required (free)

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Keywords: *ALSFRS, amyotrophic lateral sclerosis, autologous bone marrow-derived stem cells, stem cell therapy*

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» Introduction

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disorder characterized by involvement of motor neurons in the cerebral cortex, brainstem and spinal cord. Typically a disease of relentless progression, 50% of patients survive for less than three years after diagnosis, about 20% may survive longer. [1] The pathogenesis of ALS remained an enigma till recent times when a toxic gain-of-function mutation in superoxide dismutase 1 (SOD1) was demonstrated in familial ALS. [2] Subsequent to this, various transgenic mice models have corroborated the pathogenic role of SOD1 and other mutations. [3] However, advances in the pathogenic mechanisms have not been translated into effective therapeutic strategies for ALS. Riluzole is the only agent which has been shown to conclusively slow down the disease progression. Non-invasive ventilation and percutaneous endoscopic gastrostomy are the only known procedures that increase survival in these patients. [4] Among the various experimental therapeutic options, stem cell therapy holds much promise. The observation that SOD1 chimeric mice motor neurons survived longer when surrounded by a wild type environment, suggests the role of glia and other supporting cells in the progression of motor neuron disease. [5] Stem cells which can differentiate into neural as well as glial cells play a multifaceted role in neuroregeneration. [6] Proposed mechanisms include

neurotrophic growth factor release, transdifferentiation, cell fusion and endogenous stem cell proliferation. Systemic as well as intrathecal instillation of mesenchymal stem cells has been shown to be efficacious in rodent models. [7] Human studies have also validated this approach. [8],[9],[10] We conducted an open-label pilot study to assess the feasibility, safety and efficacy of autologous bone marrow-derived stem cells in patients with ALS.

» Materials and Methods

Patients with ALS attending the Neurology Clinic, Postgraduate Institute of Medical Education and Research (PGIMER), Chandigarh, Indian between September 2009 and September 2010 were assessed for eligibility. The study was approved by the Institutional Ethics Committee and written informed consent was taken from all the patients. ALS was diagnosed using the revised El Escorial criteria. [11] Patients above the age of 18 years with a diagnosis of clinically definite, probable or probable lab-supported ALS were included in the study. Patients with comorbidities like hyperthyroidism, diabetes mellitus, chronic liver or renal disease, human immunodeficiency virus (HIV) infection, respiratory insufficiency requiring ventilator support at baseline, pregnant or lactating women and those with local lesions or pressure sores precluding lumbar puncture were excluded. All patients underwent relevant investigations to arrive at a diagnosis of ALS as per institutional protocol including nerve conduction, electromyography and magnetic resonance imaging (MRI) of cervical spinal cord. Baseline hemogram, liver and renal functions were done in all the patients. Revised ALS Functional Rating Scale (ALSFRS-R) score was obtained at baseline and during follow-up. [12] The procedure was performed on in-patient basis and patients monitored for at least 48 h prior to discharge.

Bone marrow aspiration (30-100 ml) from iliac crest was done using disposable bone marrow aspiration needle under all aseptic precautions. Aspirate was collected in heparinized syringes. Mononuclear cells were separated by Ficoll density separation method. The diluted cells were layered over warmed Ficoll medium (specific gravity 1.077) in 50 ml tubes and centrifuged at 700 g for 25 min. After centrifugation, interface cells which formed a whitish ring were aspirated into a separate tube. The cell suspension was washed in sterile Phosphate-Buffered Saline to remove traces of Ficoll and centrifuged twice at 400 g for 5 min at a temperature of 25 ^{o} C. Supernatant of each wash was kept in a sterile container till the final product was released. An aliquot of the harvested mononuclear cells was evaluated for viability by the Trypan blue exclusion test. Cell viability of more than 70% was considered acceptable. Cell morphology was assessed by Giemsa stain under light microscope. Total cell count was assessed by counting in automated cell counter (Hematology Analyzer Orion 30, Pacific Diagnostics, India) **.** Bone marrow mononuclear cells were characterized using CD-34, CD-45 antibodies by flow cytometry (FACSAria, Becton Dickinson, USA). Temperature below 25 ^{o} C was maintained during transportation of bone marrow cells from the site of collection to stem cell facility and back. Intrathecal instillation of stem cells was done within four hours of bone marrow aspiration in all patients. Cells were injected into the subarachnoid space through lumbar puncture at L2-3 or L3-4 levels, using 22G disposable lumbar puncture needles observing all aseptic precautions.

The primary outcome variable was composite ALSFRS-R score at 90, 180, 270 and 365 days post stem cell transplantation. Patients were followed up in the outpatient department on Days 90 (-7 to +14 days), 180 (-7 to +14 days), 270 (-7 to +28 days) and 365 (-7 to +28 days). ALSFRS-R was determined via telephone in patients unable

to come for follow-up within the prescribed time period. Patients alive at the end of one year were further followed-up at six-monthly intervals. Secondary outcome measures included ALSFRS-R bulbar, fine motor and gross motor sub-scores at three months, time to 4-point worsening in composite ALSFRS-R score and median survival. All patients were monitored for self-reported adverse reactions during the follow-up period.

Statistical analysis

Paired T-test was used to compare changes in ALSFRS-R score from baseline at various follow-up periods. Kaplan-Meier analysis was used to estimate median survival and time to 4-point deterioration. *P* values <0.05 were considered statistically significant.

» Results

Ten patients underwent bone marrow harvesting followed by intrathecal instillation of autologous mesenchymal stem cells. Baseline characteristics of the patients are shown in [Table 1]. Six patients had clinically definite ALS as per the El Ecsorial criteria, two had clinically probable ALS and two had clinically probable-lab supported ALS. Symptoms were of bulbar onset in three patients. Mean duration of illness before stem cell therapy was 18.3 (± 13.3) months. Median duration of follow-up was 19.5 months (6.0-24.0 months). Neurological examination, nerve conduction study and electromyography were consistent with a diagnosis of ALS in all the patients. Baseline biochemical and hematological investigations were within normal limits. All patients tolerated the bone marrow aspiration and intrathecal instillation without any significant adverse events. Bone marrow aspirate volumes and cytological parameters are shown in [Table 2].

Variable	
Age (years)	49.1 (± 15.3)
Female (n)	7
Clinically definite ALS (n)	6
Bulbar onset ALS (n)	3
Median duration of illness (months)	16 (range:3- 48)
ALSFRS-R composite score	32.2 (± 10.6)

Table 1: Baseline characteristics of patients receiving intrathecal autologous bone marrow-derived stem cells

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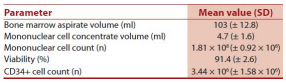

Parameter	Mean value (SD)
Bone marrow aspirate volume (ml)	103 (± 12.8)
Mononuclear cell concentrate volume (ml)	4.7 (± 1.6)
Mononuclear cell count (n)	1.81×10^8 (± 0.92×10^8)
Viability (%)	91.4 (± 2.6)
CD34+ cell count (n)	3.44×10^6 (± 1.58×10^6)

Table 2: Bone marrow volumes and cytological characteristics

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ALSFRS-R composite scores at baseline and during follow-up are shown in [Table 3]. At three months' follow-up, 7 patients maintained their baseline ALSFRS-R score, 1 patient had an early one-point improvement from baseline and 2 patients deteriorated (2 and 4 points each). By six months' follow-up, 2 patients were able to maintain their ALSFRS-R scores, while rest of the 6 patients alive had decrements in ALSFRS-R of -1 to -8 from baseline. This trend continued at Day 270 follow-up, except for 1 patient who showed a delayed improvement of points on the ALSFRS-R score between Day 180 and 270. At one-year follow-up, 1 patient maintained a net improvement of 2 points from baseline ALSFRS-R score and 1 maintained the ALSFRS-R score at baseline. Five others had decrements from baseline score in the range of -2 to -16 points. One patient was lost to follow-up.

Day 0	Day 90	Day 180	Day 270	Day 365
41	39(-2)	38(-3)	38(-3)	37(-4)
26	26(0)	26(0)	28(+2)	28(+2)
32	32(0)	31(-1)	28(-4)	32(0)
12	12(0)	-	-	-
43	43(0)	38(-5)	34(-9)	30(-13)
40	36(-4)	32(-8)	30(-10)	-
36	36(0)	35(-1)	26(-10)	20(-16)
39	40(+1)	-	-	-
36	36(0)	36(0)	36(0)	34(-2)
17	17(0)	16(-1)	14(-3)	14(-3)

Table 3: Revised ALSFRS composite scores and change from baseline during follow-up

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At Day 90, there was no significant difference in the bulbar, fine motor and gross motor sub-scores of ALSFRS-R from baseline. In addition, composite ALSFRS-R scores were also significantly unchanged from baseline at Day 90. There was a statistically significant decline in total ALSFRS-R scores at Day 180 and 270. However, at one-year follow-up, those patients who were alive did not show a statistically significant decline in total ALSFRS-R scores from baseline [Table 4]. Overall, 4 patients had 4 or more point decline in total ALSFRS-R scores during follow-up. The mean time to 4-point decline was 16.74 months (± 2.78 months).

Follow-up duration	Number of patients	Mean difference from baseline	95% Confidence Interval	*P* value
Day 90	10	0.50	-0.53-1.53	0.299
Day 180	8	2.38	0.01-4.74	0.049
Day 270	8	4.62	0.78-8.46	0.025
Day 365	7	5.14	-1.09-11.38	0.090

Table 4: Composite ALSFRS-R scores at follow-up compared to baseline

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At the end of one-year follow-up, 8 patients were alive. Cause of death was respiratory failure in both the patients who died. On extended follow-up, 2 more patients died of respiratory failure and 2 others due to massive aspiration. The estimated median survival of these patients from onset of disease was 33.0 months (95% CI 23.4-42.6 months) and median survival post procedure was 18.0 months (95% CI 8.7- 27.3 months)[Figure 1]. There was no significant difference in the baseline ALSFRS-R scores between the survivors and the non-survivors (*P*=0.468). No significant adverse events were reported by patients during the follow-up period.

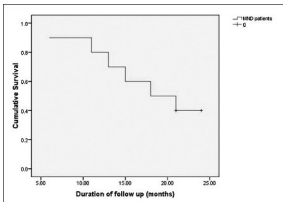

Figure 1: Estimated post-procedure cumulative survival of ALS patients receiving bone marrow-derived stem cells

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» Discussion

The data in this study show that patients receiving stem cells tended to maintain their functional status at three months' follow-up. Deterioration in global functional status was noted during Day 180 and 270 follow-up. One patient showed delayed sustained improvement in FRS starting at six months. Finally, patients who were alive at one year did not significantly deteriorate from their baseline functional status.

Bone marrow-derived stem cells contain both hematopoietic as well as mesenchymal progenitors. Both these cells lines have been shown to ameliorate ALS disease progression in rodent models. [13] Heterologous peripheral blood progenitor cells have been shown to home to spinal cord and engraft successfully at sites of motor neuron distress. [14] Mesenchymal stem cells have the ability to differentiate into astrocytic as well as neuronal lineages. [15] Human mesenchymal stem cells have been shown to engraft and survive in the spinal cord of SOD1-deficient mice, improving motor

performance, extending survival and decreasing neuroinflammation. [16] When infused intravenously, mesenchymal stem cells showed poor homing capabilities and long-term engraftment. In spite of this, significant reduction in markers of oxidative stress and endogenous glutamate release were shown in SOD1-deficient mice. [17] Intrathecal instillation has also been shown to be an effective method of stem cell delivery, with dose-dependent migration of mesenchymal stem cells into the brain and spinal cord. [18] We utilized the intrathecal instillation procedure in our patients as it is safer, less invasive and easier to perform than intraspinal implantation.

Various putative mechanisms have been proposed to explain the observed disease-modifying capability of stem cells. Stem cells bring about cell replacement, increase cell populations and provide a better microenvironment for motor neuron survival. [19] However, data regarding direct neural regeneration is scarce. Moreover, implanted stem cells have been shown to have short life spans at the site of engraftment. [17] Current evidence supports renewal of glial tissue and release of nerve trophic growth factors by stem cells that lead to neuroprotection. Insulin-like Growth Factor-1, Vascular Endothelial Growth Factor, brain-derived neurotrophic factor and glial-derived neurotrophic factor are some of the growth factors considered to play a role. [19] In addition, mesenchymal stem cells also have immunomodulatory effects. [20]

Early human studies confirmed the safety and feasibility of intraspinal stem cell implantation. [8] An open-label Phase I clinical trial reported minor adverse events related to the intraspinal injection procedure causing reversible sensory disturbances and pain. [21] Long-term follow-up of these patients up to nine years failed to detect significant adverse events. [10] Studies designed to assess efficacy showed that intraspinal stem cell delivery delayed the rate of worsening of ALSFRS-R score and forced vital capacity in four of the nine patients at two years. [22] These findings are similar to our observations. However, data from long-term follow-up have failed to demonstrate a sustained benefit. [10] Intrathecal as well as intravenous mesenchymal stem cell transplants are safe and efficacious. [23] A study involving 19 patients with ALS reported stabilization of ALSFRS-R scores for six months post transplant. This study also demonstrated the dissemination of ferumoxide-tagged stem cells in the nervous system on MRI. [23] Hematopoeitic stem cell transplantation also holds promise. In a study involving 13 ALS patients with severe disease, 9 patients showed electromyographic evidence of improvement at six months post intraspinal hematopoietic cell transplantation. [9] Direct implantation of autologous stem cells into the frontal motor cortex is another approach shown to be safe and effective in prolonging survival in a group of 10 ALS patients. [24]

The revised ALSFRS score is well validated as a predictor of survival in ALS patients. [25] In a clinic-based population, patients with ALSFRS-R score less than 38 at baseline had a median survival of 14.0 months and those with score less than 33 had an even shorter survival (Hazard Ratio 27.78 for death at one year). [26] The mean baseline ALSFRS-R score in our patients was below these limits and median survival from baseline visit was 18.0 months. These findings may be early indicators of a short-term survival benefit.

Limitations of our study include a small sample size and relatively short duration of follow-up. Lack of controls makes it difficult to assess conclusively whether the observed stabilization is due to the effect of treatment or natural slow disease progression in these individuals. However, in studies such as the present study involving invasive procedures, it is ethically as well as practically not feasible to have blinded controls. Future trial designs incorporating pre-treatment disease progression,

electrophysiological and objective functional assessments are required to definitely establish efficacy. Addition of radiological, immunological or histological investigations for evidence of cell engraftment will also help to establish the utility of this procedure.

Data from stem cell therapy studies seem to explore a new horizon in the field of treatment of ALS. Newer studies look at stem cells as drug delivery vehicles for various growth factors and immunomodulatory molecules. [27] Induced pleuripotent stem cells from adult somatic tissues with capability to transdifferentiate into neural tissue are being evaluated for feasibility. Optimal strategies for cell-based therapy are yet in evolution.

Bone marrow-derived mononuclear stem cell transplantation appears to be safe and feasible in patients with ALS. Follow-up showed trend towards disease stabilization in this study group. No significant adverse events were noted. However, the experimental nature of this therapy must be emphasized. Larger trials powered to assess efficacy in the long-term are required before this therapeutic option can be put to wider use.

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Figures

[Figure 1]

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