Original Contribution

Clinical Outcomes of Transplanted Modified Bone Marrow–Derived Mesenchymal Stem Cells in Stroke: A Phase 1/2a Study

AQ1

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AQ3

Background and Purpose—Preclinical data suggest that cell-based therapies have the potential to improve stroke outcomes.

Methods—Eighteen patients with stable, chronic stroke were enrolled in a 2-year, open-label, single-arm study to evaluate the safety and clinical outcomes of surgical transplantation of modified bone marrow–derived mesenchymal stem cells (SB623).

Results—All patients in the safety population (N=18) experienced at least 1 treatment-emergent adverse event. Six patients experienced 6 serious treatment-emergent adverse events; 2 were probably or definitely related to surgical procedure; none were related to cell treatment. All serious treatment-emergent adverse events resolved without sequelae. There were no dose-limiting toxicities or deaths. Sixteen patients completed 12 months of follow-up at the time of this analysis. Significant improvement from baseline (mean) was reported for: (1) European Stroke Scale: mean increase 6.88 (95% confidence interval, 3.5–10.3; $P<0.001$), (2) National Institutes of Health Stroke Scale: mean decrease 2.00 (95% confidence interval, −2.7 to −1.3; $P<0.001$), (3) Fugl-Meyer total score: mean increase 19.20 (95% confidence interval, 11.4–27.0; $P<0.001$), and (4) Fugl-Meyer motor function total score: mean increase 11.40 (95% confidence interval, 4.6–18.2; $P<0.001$). No changes were observed in modified Rankin Scale. The area of magnetic resonance T2 fluid-attenuated inversion recovery signal change in the ipsilateral cortex 1 week after implantation significantly correlated with clinical improvement at 12 months ($P<0.001$ for European Stroke Scale).

Conclusions—In this interim report, SB623 cells were safe and associated with improvement in clinical outcome end points at 12 months.

Clinical Trial Registration—URL: https://www.clinicaltrials.gov. Unique identifier: NCT01287936.

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Key Words: allogeneic transplantation ■ mesenchymal stromal cells ■ Notch 1 ■ phase 1 clinical trial ■ stereotactic techniques ■ stroke ■ stem cells

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Stroke is a leading cause of long-term disability.[1] Although an estimated 80% of patients survive for 1 year after stroke, >70% have enduring disabilities.[2] There are no proven medical or surgical neurorestorative treatments for chronic stroke; however, the regenerative effects of different cell types and various routes of delivery are being investigated as potential treatment.[3,4] To date, pilot clinical trials have reported an acceptable safety profile with some functional benefits to patients with stroke using transplanted neuronal cells differentiated from a teratocarcinoma cell line,[5] human immature neural and hematopoietic cells,[6] autologous human bone marrow–derived mononuclear cells, and mesenchymal stem cells.[3,7] The cells used in these pilot clinical trials were administered to patients by intracerebral, intra-arterial, intravenous, or intracerebroventricular routes during the period of days to years after stroke.[3,7]

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Interim data from the PISCES Phase 1 trial for chronic stroke showed that intracerebral implantation of modified human neural stem cells was safe and seemed to be associated with improvements of neurological function in some of the stroke scales; these data were considered sufficient to warrant initiating a Phase 2 trial (PISCES II).[8] In addition, a Phase 2 trial for subacute stroke reported that intravenous infusion of bone marrow–derived mononuclear cells was safe but had no effect on measures of neurological function.[9]

A recent meta-analysis of preclinical studies showed that mesenchymal stem cells used to treat ischemic stroke were associated with improvements of neurological function and that the intracerebral route was associated with the greatest improvement.[10] A Cochrane Database review of the safety and efficacy of transplanted stem cells in patients with ischemic stroke identified a single small randomized clinical trial which reported no cell-related adverse events (AEs) associated with nonstatistically significant improvements in patients after longer follow-up.[11]

The stereotactic implantation of modified bone marrow–derived mesenchymal stem cells (SB623) transiently transfected with the human *Notch-1* intracellular domain is an additional option.[12] Preclinical studies using a model of chronic ischemic stroke in which rodent and human SB623 cells were stereotactically implanted into the striatum of the rat showed improvements in locomotor and neurological function that were associated with a reduction in peri-infarct cell loss.[13] Other preclinical studies have reported that SB623 cells are associated with the promotion of neuronal stem cell migration and differentiation and production of extracellular matrix factors that provide trophic support for damaged cells.[14,15]

This report presents preliminary 12-month interim data from a 2-year, open-label, single-arm study (NCT01287936) that was designed to evaluate the safety and clinical outcomes of the stereotactic placement of SB623 cells at the margin of the stroke in patients with chronic motor deficits >6 months after their initial stroke.

Methods

Patients

We screened 379 patients and enrolled 18 patients (mean age of 61 years; 61% female; Table 1) with chronic motor deficits between 6 and 60 months after sustaining a nonhemorrhagic stroke. Patients had stable chronic stroke at baseline as assessed by 2 evaluations conducted within 3 weeks before enrollment in which there was no change in National Institutes of Health Stroke Scale (NIHSS) score of greater than ±1 point (inclusion criteria listed in Table I in the online-only Data Supplement).[5,16] Patients did not receive poststroke rehabilitation services during the study. This study was conducted at 2 sites in the United States (Stanford University School of Medicine/Stanford Healthcare and University of Pittsburgh Medical Center), with patients being enrolled between September 2011 and August 2013. Clinical study protocols were reviewed and approved by institutional review boards, and patients provided written informed consent. Study inclusion and exclusion criteria are listed in Table I in the online-only Data Supplement.

The intent-to-treat population (n=18) that was used for the clinical evaluation included all patients enrolled in the study; at the time of this interim analysis, 16 subjects had 12-month data (2 patients had withdrawn, both were lost to follow-up [last contact with patients being at the month 3 and month 6 visits, respectively, with the second patient declining her year 1 and year 2 visits because she had moved to Taiwan]). The safety population consisted of 18 patients who enrolled in the study, received cell treatment, and had postbaseline data. Patients enrolled in the study were assessed for acute and long-term outcomes using the following measures: (1) European Stroke Scale (ESS, the primary outcome end point was ESS at 6 months),[17] (2) NIHSS,[18,19] (3) modified Rankin Scale (mRS),[20,21] and (4) Fugl-Meyer (F-M) score.[22–24] ESS, NIHSS, and mRS evaluations were conducted by neurologists, whereas F-M scores were evaluated by physical therapists at the 2 sites. The neurologists were not blinded to SB623 cell dose (they had access to all records) but stated that they were not aware of the dose delivered when conducting evaluations. The study visit schedule is listed in the Methods section in the online-only Data Supplement.

SB623 Cells

SB623 cells are modified bone marrow–derived mesenchymal stem cells that were developed as an allogeneic cell therapy for chronic motor deficit because of stable stroke. SB623 cells are generated under good manufacturing practices by transient transfection with a plasmid containing the human *Notch-1* intracellular domain.[12] The transfection is considered to be transient because expansion and passaging of the cells result in the rapid loss of the transfected plasmid. Using an intracerebral xenograft in stroke and nonstroke rodent models, the SB623 cells only survive 1 month post implantation.[13,25]

Study Design, Dosing, and Administration

Patients were divided into 3 cohorts of 6 patients. The 3 cohorts received single doses of 2.5×10^6, 5.0×10^6, or 10×10^6 SB623 cells. The SB623 cells were implanted using magnetic resonance imaging stereotactic technique to define the target sites surrounding the residual stroke volume. At baseline, the mean poststroke interval was 22 months and mean stroke volume was 42 cm^3. Using a single burr-hole craniostomy and 3 cannula tracks, five 20 µL cell deposits were made at 5 to 6 mm intervals along each track in the peri-infarct area. The concentration of cells ranged from 8000 to 33 000 SB623 cells per microliter. Cells were deposited at a rate not exceeding 10 µL per minute, equating to ≈15 minutes for each needle track. A 0.9-mm outer diameter stereotactic cannula was used for cell injection.[5,16]

Safety

A treatment-emergent AE (TEAE) was defined as any event not present before the initiation of treatment or any event already present that worsened in either intensity or frequency after exposure to study treatment. All AEs were reported according to standard procedures and were classified by investigators as being: (1) mild, (2) moderate, (3) severe, or (4) life threatening. The parameters used by investigators to evaluate the relationship of the AE to the cell treatment or study procedure are listed in Table II in the online-only Data Supplement.

Statistics

Descriptive statistics were calculated for continuous variables that included patient number, mean, SD, SEM (95% confidence interval [CI]=±1.96×SEM), median, minimum, maximum, and 95% CIs. Descriptive statistics were calculated for categorical variables, which included the number and percentage of patients in each category. For prospectively specified end points, Wilcoxon signed-rank test was used to evaluate significance of change versus baseline for clinical outcomes, with $P<0.05$ considered to be statistically significant. In post hoc analyses, Pearson correlations were used to evaluate the associations between: (1) area of transient postimplantation magnetic resonance (MR) fluid-attenuated inversion recovery (FLAIR) signal intensity changes and clinical outcomes and (2) number of contrast-enhancing areas and changes in clinical outcomes. $P<0.05$ was considered to be statistically significant. Data analyses were performed using Statistical Analysis System (SAS) version 9.2 (Cary, NC).

Table 1. Baseline Demographics (Intent to Treat Population)

Characteristics	n=18
Age, y	
Mean (SD)	61.3 (10.29)
Median	64.0
Range: min–max	33–75
Sex, n (%)	
Male	7 (38.9)
Female	11 (61.1)
Race, n (%)	
White	12 (66.7)
Black	1 (5.6)
Asian	5 (27.8)
Native Hawaiian or other Pacific Islander	0 (0.0)
American Indian or Alaska native	0 (0.0)
Other	0 (0.0)
Ethnicity, n (%)	
Hispanic or Latino	0 (0.0)
Not Hispanic or Latino	18 (100.0)
Mean time (range) post stroke (months)	22.0 (7–36)
Mean size (range) of infarct (cm^3)	42.3 (1.0–87.0)
Baseline measures of clinical outcome end points (SD; 95% CI)	
ESS	58.44 (6.27; 55.3–61.6)
NIHSS	9.44 (1.89; 8.5–10.4)
mRS	3.22 (0.43; 3.0–3.4)
F-M total score	133.61 (20.90; 123.2–144.0)
F-M motor function total score	30.44 (15.14; 22.9–38.0)

CI indicates confidence interval; ESS, European Stroke Scale; F-M, Fugl-Meyer; mRS, modified Rankin Scale; and NIHSS, National Institutes of Health Stroke Scale. AQ6

Results

Safety Evaluations

In this analysis, all patients experienced at least 1 TEAE in the 12 months after implantation of SB623 cells (Table 2). The most frequently reported TEAEs (percent of patients) in the pooled dose assessment of SB623 cells were headache related to surgical procedure (77.8%), nausea (33.3%), vomiting (22.2%), depression (22.2%), muscle spasticity (22.2%), fatigue (16.7%), blood glucose increase (16.7%), and C-reactive protein increase (16.7%; Table 2). There was no relation between cell dose levels and frequency of TEAEs. T2

In the safety population (N=18), patients experienced a total of 28 treatment-related TEAEs during 12 months of follow-up. In total, 88.9% of patients (16 TEAEs in 18 patients) experienced a TEAE that investigators evaluated as being unrelated to cell treatment (Table III in the online-only Data Supplement). In comparison, 44.4% (8 TEAEs in 18 patients) experienced a TEAE that was unlikely to be related to the cells and 22.2% (4 TEAEs in 18 patients) experienced a TEAE that was possibly related (Table III in the online-only Data Supplement). No patients experienced a TEAE that was probably or definitely related to cell treatment. The 4 TEAEs (22.2%) that were possibly related to the cells were muscle spasticity (2), gait disturbance (1), and procedural headache (1).

More patients possibly, probably, or definitely experienced TEAEs related to the surgical procedure than to the cells (Table III in the online-only Data Supplement). Postsurgery headache was the most common TEAE that was probably or definitely related to the procedure, experienced by 77.8% (14 in 18 patients) of patients (Table III in the online-only Data Supplement).

There were 6 serious TEAEs experienced by 6 patients, with no clear trends regarding serious TEAEs and cell dosage (Table 3). Serious TEAEs were unrelated or unlikely to be related to cell treatment; however, a single patient developed an asymptomatic subdural fluid collection that was definitely related to the procedure and was managed by burr-hole drainage. An additional patient had a seizure on study day 70, which the investigator evaluated as life threatening and probably related to the surgical procedure. A patient underwent stenting for an asymptomatic cervical carotid artery stenosis on study day 291; the investigator evaluated the event as being unrelated to both cell treatment and surgical procedure. A patient experienced a transient ischemic attack on study day 334 that was associated with worsening facial droop and slurred speech. Although the transient ischemic attack was assessed as being in the same brain area as the original stroke and SB623 cell delivery, it occurred 11 months after surgery and was evaluated by the investigator as being unrelated to both cell treatment and surgical procedure. All serious TEAEs received supportive therapy and were evaluated as being recovered or resolved without sequelae (Table 3). T3

We found no clinically meaningful changes in hematology parameters, biochemistry parameters, lipids, cytokines (tumor necrosis factor-α, interleukin-6, and interferon-γ), or vital signs during this 12-month analysis. In addition, no antibody-related sensitization to SB623 cells was observed.

Clinical Outcome Evaluations

Clinical outcome analyses were conducted on 16 patients who had completed 12 months of treatment in the intent-to-treat population (n=18). The baseline mean (SD) ESS total score was 58.44 (6.27). The mean ESS total score increased significantly from baseline by 6.50 (95% CI, 2.6–10.4; $P<0.01$) at 6 months (the primary outcome) and 6.88 (95% CI, 3.5–10.3; $P<0.001$) at 12 months and was increased significantly from baseline at all other time points, starting at 1 month (Figure 1A). F1

Significant improvements from baseline of the NIHSS total score was also observed at all time points starting with 1 month. The baseline mean (SD) NIHSS total score was 9.44 (1.89). The mean NIHSS total score decreased from baseline by 2.00 (95% CI, −2.7 to −1.3; $P<0.001$) at 12 months, representing a measurable improvement (Figure 1B).

The F-M total score and F-M motor function total score of the baseline means (SDs) were 133.61 (20.90) and 30.44

Table 2. Treatment-Emergent Adverse Events (Safety Population)

System Organ Class Preferred Term, n (%)	2.5×10^6 Cells, n=6	5.0×10^6 Cells, n=6	10×10^6 Cells, n=6	Pooled Cells, N=18
Any TEAE*	6 (100.0)	6 (100.0)	6 (100.0)	18 (100.0)
Headache/procedural headache†	6 (100.0)	4 (66.7)	4 (66.7)	14 (77.8)
Nausea	0 (0.0)	3 (50.0)	3 (50.0)	6 (33.3)
Vomiting	0 (0.0)	2 (33.3)	2 (33.3)	4 (22.2)
Depression	0 (0.0)	2 (33.3)	2 (33.3)	4 (22.2)
Muscle spasticity	2 (33.3)	1 (16.7)	1 (16.7)	4 (22.2)
Fatigue	0 (0.0)	1 (16.7)	2 (33.3)	3 (16.7)
Blood glucose increased	2 (33.3)	1 (16.7)	0 (0.0)	3 (16.7)
C-reactive protein increased	1 (16.7)	1 (16.7)	1 (16.7)	3 (16.7)
Convulsion	1 (16.7)	1 (16.7)	0 (0.0)	2 (11.1)
Dizziness	1 (16.7)	1 (16.7)	0 (0.0)	2 (11.1)
Pneumocephalus	0 (0.0)	2 (33.3)	0 (0.0)	2 (11.1)
Subdural hematoma	0 (0.0)	2 (33.3)	0 (0.0)	2 (11.1)
Constipation	0 (0.0)	1 (16.7)	1 (16.7)	2 (11.1)
Diarrhea	0 (0.0)	1 (16.7)	1 (16.7)	2 (11.1)
Arthralgia	2 (33.3)	0 (0.0)	0 (0.0)	2 (11.1)
Musculoskeletal pain	1 (16.7)	1 (16.7)	0 (0.0)	2 (11.1)
Pain in extremity	1 (16.7)	1 (16.7)	0 (0.0)	2 (11.1)
Pneumonia	0 (0.0)	0 (0.0)	2 (33.3)	2 (11.1)
Urinary tract infection	1 (16.7)	0 (0.0)	1 (16.7)	2 (11.1)
Decreased appetite	0 (0.0)	2 (33.3)	0 (0.0)	2 (11.1)

TEAE indicates treatment-emergent adverse event.

*A TEAE is defined as any event not present before the initiation of treatment or any event already present that worsened in either intensity or frequency after exposure to study treatment.

†Headache/procedural headache: because of reporting verbatim differences, headaches were coded into 2 terms.

(15.14), respectively. The mean F-M total score increased significantly from baseline by 19.20 (95% CI, 11.4–27.0; $P<0.001$) at 12 months (Figure 1C), and the mean F-M motor function total score increased significantly from baseline by 11.40 (95% CI, 4.6–18.2; $P<0.001$) at 12 months (Figure 1D). Both F-M total score and F-M motor function total score were significantly increased from baseline at all time points (Figure 1C and 1D). From a baseline mean (SD) score of 3.22 (0.43), no change was seen in mRS at 12 months (0.00; 95% CI, −0.2 to 0.2; $P=1.0000$). Correlation of improvements of clinical outcome end points with cell dose levels did not show any clear dose–response relationships. There was no association between improvement in clinical outcome measures and either baseline stroke severity or baseline patient age.

Table 3. Serious Treatment-Emergent Adverse Events (All Patients)

Cell Dose	Serious Adverse Event	Relationship to Cell Treatment	Relationship to Procedure	Outcome
2.5×10^6	Seizure	Unrelated	Probably	Recovered/resolved
2.5×10^6	Stenting of asymptomatic carotid artery stenosis	Unrelated	Unrelated	Recovered/resolved
5.0×10^6	Asymptomatic subdural hematoma/hygroma	Unrelated	Definitely	Recovered/resolved
5.0×10^6	Transient ischemic attack	Unrelated	Unrelated	Recovered/resolved
10×10^6	Urinary tract infection/sepsis	Unrelated	Unrelated	Recovered/resolved
10×10^6	Pneumonia	Unlikely	Possibly	Recovered/resolved

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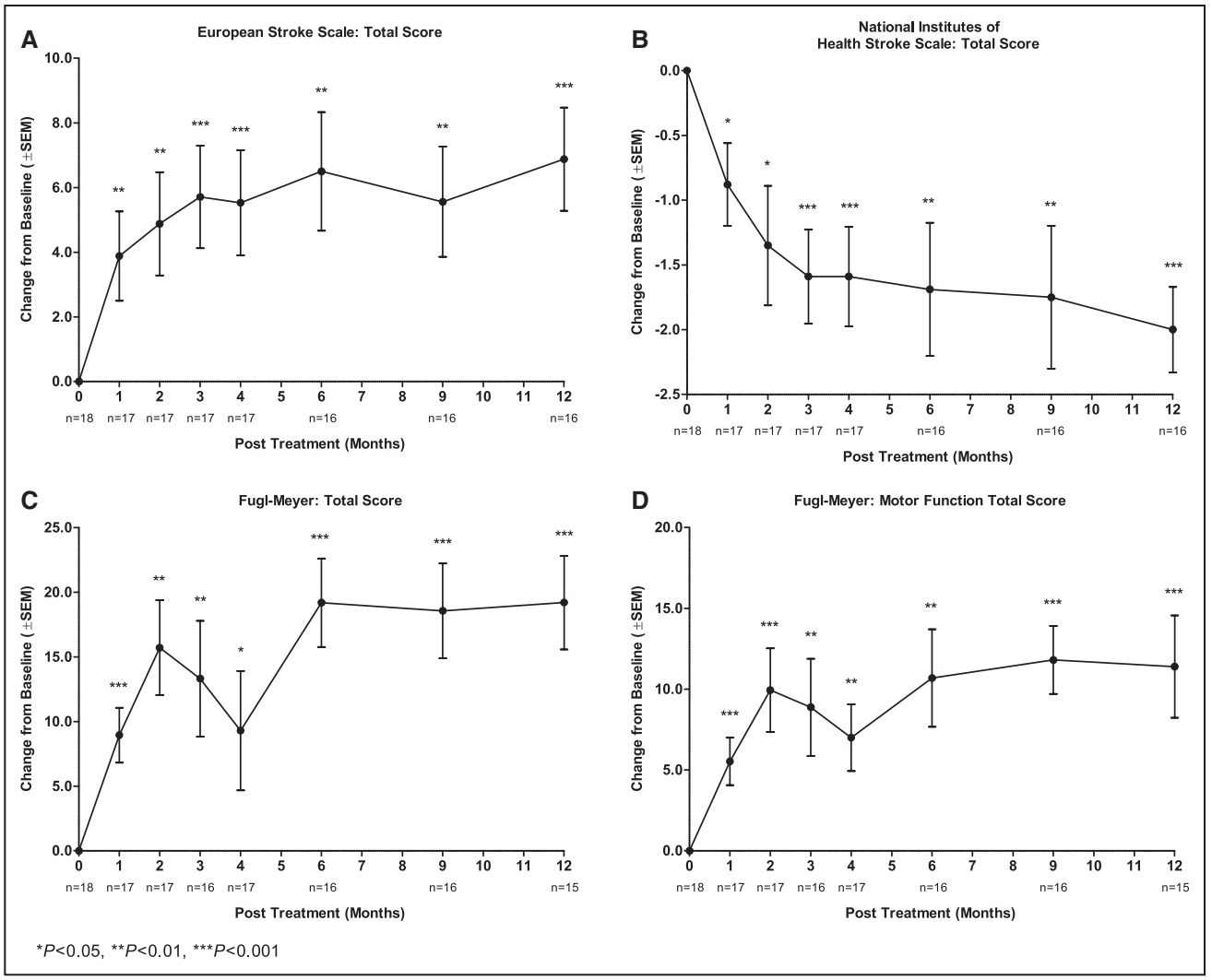

Figure 1. A–D, Change of clinical outcome end points from baseline for pooled SB623 cells at 12 months (intent-to-treat population, n=18). (**A**) European Stroke Scale. (**B**) National Institutes of Health Stroke Scale. (**C**) Fugl-Meyer (F-M) total score. (**D**) F-M motor function total score. Error bars represent SEM. *P* values represent significance of change vs baseline using the Wilcoxon signed-rank test ($P<0.05$), which were not corrected for multiplicity.

MR Findings

Thirteen of the 18 patients in the trial demonstrated new signal changes on MR T2 FLAIR imaging (0.5–9.2 cm^2; 0.6–3.5 cm maximum diameter) primarily in or adjacent to the premotor cortex along the cannula track at 1 week post-transplantation (except 1 patient without a week 1 MR who showed a new FLAIR signal at 2 weeks). These FLAIR signal changes were diffusion-weighted image negative, were not present on the day 1 post-transplant MR scan, and were found to have resolved on the month 1 or 2 post-transplant MR scan (Figure 2). There were significant Pearson correlations between the size of the initial post-transplant FLAIR signal changes and neurological recovery as measured by change from baseline in clinical outcomes at 12 months (ESS total score: 0.818, $P<0.001$; NIHSS total score: −0.688, $P<0.01$; F-M total score: 0.708, $P<0.01$; F-M motor function total score: 0.668, $P<0.01$).

We also examined the relationship between FLAIR signal changes and ≥10% change in the F-M motor function total score, a change that is accepted as a clinically meaningful improvement in chronic stroke.[26–29] At 12 months, the positive predictive value of whether a FLAIR signal change would determine a clinically meaningful improvement was seen in 6 of 12 cases, whereas the negative predictive value (ie, the absence of a FLAIR signal change) of predicting a nonclinically meaningful improvement was seen in 3 of 4 cases.

Contrast-enhancing areas in the cannula tract were observed at 1 week post-transplant in 15 patients (except 1 patient without a week 1 MR who showed contrast enhancement at 2 weeks), 12 of whom had FLAIR signal changes. Such changes resolved with the same time course as the FLAIR signal abnormalities. There were significant Pearson correlations between the number of contrast-enhancing areas and change from baseline in measures of neurological recovery at 12 months (ESS total score: 0.904, $P<0.001$; NIHSS total score: −0.643, $P<0.05$; F-M total score: 0.798, $P<0.01$; F-M motor function total score: 0.728, $P<0.01$).

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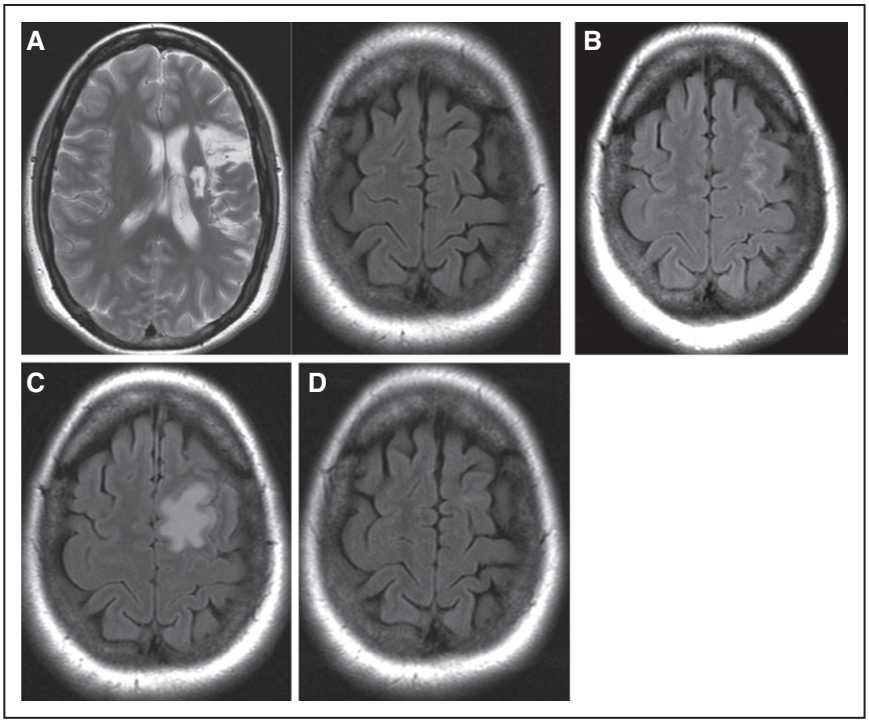

Figure 2. A–D, MR brain scans from a 39-year-old female patient, transplanted with SB623 cells 2 years after a left middle cerebral artery stroke. (**A left**) Axial T2 FSE pretransplant showing the subcortical and cortical infarct. (**A right**) Pretransplant at higher axial level. (**B**) Day 1 post-transplant at higher axial level demonstrating small amount of blood in left frontal sulci. (**C**) Day 7 post-transplant at higher axial level showing new T2 FLAIR signal abnormality in left superior frontal gyrus adjacent to premotor gyrus. (**D**) Month 2 post-transplant at higher axial level showing resolution of T2 FLAIR signal abnormality. FLAIR indicates fluid-attenuated inversion recovery; FSE, fast spin echo; and MR, magnetic resonance. AQ8 AQ10

Discussion

Despite stroke representing a major cause of mortality and severe disability, the only proven therapies for ischemic stroke are intravenous tissue-type plasminogen activator and intra-arterial thrombectomy, both of which must be administered within a few hours of stroke onset.[3,4,30,31] Currently, there are no proven medical or surgical neurorestorative treatments available for subacute or chronic stroke. However, stem cell and cultured cell therapy for chronic stroke is moving quickly into the clinical arena.[3,6] For example, the stereotactic implantation of cultured human neuronal cells into the brains of patients with stroke was investigated in Phase 1 and 2 studies which showed that although the surgical procedure and cell treatment were safe, there was no significant improvement in motor function, despite measureable improvements in some patients.[5,16]

Assessment of Potential Benefit

This is the first reported intracerebral stem cell transplant study for stroke in North America, in which stereotactic implantation of SB623 cells was generally safe and well tolerated by patients with most TEAEs being of moderate intensity. No TEAEs were evaluated as being probably or definitely related to cell treatment; however, consistent with an earlier study that also used stereotactic intracranial administration of cells, many TEAEs were probably or definitely related to the surgical procedure.[5] Of 6 serious AEs (all of which resolved without sequelae), 2 were probably or definitely related to the surgical procedure. Overall in this study, there were no clear dose responses to measures of safety.

The neurological deficits of patients with chronic stroke were assessed using standard impairment scales, specifically the ESS, NIHSS, and F-M scale. Despite these patients having chronic stroke and stable neurological function scores at baseline, there were significant improvements in the mean scale scores of ESS, NIHSS, F-M total score, and F-M motor function total score at 12 months after treatment. The primary clinical outcome measure (significant improvement in ESS at 6 months) was also positive.

The F-M motor function total score is well established as a reliable and valid method of assessing recovery from chronic stroke.[24,32,33] A ≥10-point improvement (ie, ≥10% of the 100-point scale range) in the F-M motor function total score is accepted as a clinically meaningful change in chronic stroke.[26–29] In this study, the mean F-M motor function total score increased from baseline by 11.4 points, representing a clinically meaningful improvement at 12 months. Furthermore, a total of 7 patients experienced a ≥10-point change from baseline of the F-M motor function total score. For patients in the study, this represented a clinical improvement in the power of upper and lower limbs, ranging from an improvement in the ability to stand to the disappearance of tremor.

The mRS has typically been applied to measure long-term outcomes in global neurological function after acute stroke[34]; however, the value of the mRS to measure outcomes in patients with chronic stroke has not been established.[35] In this study, patients did not experience a significant improvement in mRS at 12 months or at any time point after treatment. Considering these factors, it is not surprising that we were unable to detect significant change in the mRS during 12 months. The most dramatic recovery in motor function after stroke is reported to occur in the first 30 days after stroke, with improvements in motor function reaching a plateau at 6 months regardless of stroke severity.[36–38] In addition, patients treated with cultured human neuronal cells in earlier clinical trials were also considered to have stable chronic stroke after 6 months.[5,16] It is significant that patients enrolled in this study

had a minimum poststroke time of 6 months at baseline (mean poststroke time of 22 months) and were therefore already in a chronic stroke setting.

Survival of SB623 Cells

The transfection with *Notch-1* in SB623 cells is temporary but results in altered patterns of DNA methylation and protein expression.[12] In preclinical studies, SB623 cells: (1) secrete factors that protect cells from hypoxic injury, (2) secrete trophic factors that support damaged cells, (3) secrete extracellular matrix proteins that support neural cell growth, (4) have anti-inflammatory effects, (5) have immunosuppressive effects, (6) promote angiogenesis, (7) promote neuronal stem cell migration and differentiation, and (8) provide a biobridge of extracellular matrix metalloproteinases.[14,15,25,39,40] Because transplanted human SB623 cells only survive for 1 month in preclinical stroke and nonstroke models,[13,25] persistent neurological recovery may be achieved by the secretion of supportive molecules rather than by the integration of transplanted stem cells.

Potential Relevance of Postimplant Imaging Changes

The positive correlation between the area of post-transplant MR T2 FLAIR signal changes, which appeared at 1 week and resolved by 1 to 2 months, and measures of neurological recovery at 12 months is interesting. The pathogenesis of the FLAIR signal changes is unknown, but diffusion-weighted image negative and therefore not representative of cytotoxic edema (ie, an acute infarct). Despite resolution of FLAIR signal changes by 1 to 2 months, the neurological recovery documented on several outcome scales was sustained for at least 12 months. The observation that the transplanted cells likely do not persist for >1 month in preclinical models suggests that the acute cell transplantation stimulates a sustained recovery process. Several patients without post-transplant FLAIR signal changes showed some neurological recovery, although only 1 of the FLAIR-negative patients demonstrated a clinically meaningful improvement at 12 months. The significance of the MR findings is uncertain considering the small number of patients, but given the association with clinical improvement, it deserves further examination in subsequent studies.

Study Limitations

This study is a small-scale, open-label, dose-escalation, Phase 1/2a trial and is therefore limited by its nonrandomized, uncontrolled design and small number of patients. In addition, the patient screening process was highly selective, with only 4.7% of all screened patients enrolled in the trial. Therefore, the application of conclusions from this early phase trial to the general chronic stroke population should be performed with caution. The definition of stable chronic stroke used at baseline in this trial (ie, 2 NIHSS evaluations conducted within 3 weeks of enrollment with no score change of greater than ±1 point) has also been used in previous trials. However, other studies have defined chronic stable stroke by use of minimum changes in several stroke scales during 6 weeks. Therefore, differences in the definition of chronic stable stroke should be considered while interpreting conclusions from this trial.

The positive measures of safety and clinical outcomes reported here highlight the need for large-scale Phase 2b and 3 clinical trials to further evaluate the use of SB623 cells for the treatment of chronic stroke.

Conclusions

In this interim analysis of the first intracerebral stem cell transplant study for stroke in North America, treatment with SB623 cells was generally safe and well tolerated and demonstrated a significant improvement in neurological function after 12 months.

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Disclosures

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