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HOKKAIDO UNIVERSITY HOSPITAL

Healios

Allogeneic stem cell therapy for acute ischemic stroke:

The phase 2/3 TREASURE randomized clinical trial

【Important points】

- The world's first phase 2/3 trial of allogeneic stem cell therapy for stroke.
- The intravenous administration of MultiStem® within 18–36 h of ischemic stroke onset was safe. However, no improvement in 90-day outcomes was noted compared to placebo.
- No grade 3 or 4 allergic reactions were observed in the subjects, including many elderly individuals.

【Overview】

Cell therapy shows promise as a therapeutic approach for managing stroke and other diseases. This clinical study evaluated the efficacy and safety of MultiStem®, a bone marrow–derived allogeneic multipotent adult progenitor cell preparation, when administered within 18–36 h after ischemic stroke onset.

The TREASURE study was a multicenter, randomized, double-blind, parallel-group, placebo-controlled phase 2/3 trial conducted at 44 sites in Japan from November 15, 2017 to March 29, 2022. All 206 patients with acute ischemic stroke and National Institutes of Health Stroke Scale (NIHSS) scores of 8–20 were intravenously administered MultiStem® (1.2 billion units) or placebo.

The primary endpoints were safety and an excellent outcome, defined as a modified Rankin Scale (mRS) score of ≤1, an NIHSS score of ≤1, and a Barthel index of ≥95, all measured at 90 days. Secondary endpoints included an excellent outcome at 365 days, mRS distribution at 90 and 365 days, and mRS scores of 1 or 2 at 90 days.

There were no significant differences in the primary endpoint or any secondary endpoints between the MultiStem® and placebo groups. The frequency of adverse events was similar between groups. An exploratory analysis showed a tendency towards a benefit of MultiStem® in patients ≤ 64 years of age and with stroke volume ≥ 50 mL.

These study results indicate that the intravenous administration of allogeneic cell therapy within 18–36 h after ischemic stroke onset is safe but does not improve short-term outcomes. The post-hoc analysis suggested that further studies are necessary to validate these findings.

【Background】

Stroke is the second leading cause of death worldwide and the primary cause of disability. In 2019, 6.6 million people died of stroke. Evidence-based reperfusion therapies, such as intravenous thrombolysis and mechanical thrombectomy, are commonly used to treat stroke. However, approximately 50% of patients remain disabled 3 months after a stroke, highlighting the need for new treatment options.

Stem cell therapy is promising for stroke. The therapeutic effects of various cell types, such as mesenchymal stem cells, bone marrow mononuclear cells, neural stem cells, and induced

pluripotent stem cells, are being investigated. MultiStem® is a mass-produced stem cell product that is believed to provide benefits through various mechanisms, such as suppressing inflammation, modulating immune abnormalities, protecting damaged cells, promoting angiogenesis, repairing tissue, and promoting healing.

Here we report the results of the TREASURE (Treatment Evaluation of Acute Stroke Using Regenerative Cells) study, a phase 2/3 randomized clinical trial investigating the safety and efficacy of MultiStem® in patients within 18–36 h of ischemic stroke onset. Healios K.K. (https://www.healios.co.jp/en/) participated as a sponsor of this TREASURE study.

【Methods】

This study enrolled patients aged ≥ 20 years who had persistent neurological impairment equivalent to an NIHSS score of 8–20 at initial screening. The patients underwent diffusion-weighted magnetic resonance imaging that revealed an acute stroke involving the cerebral cortex with a long axis of at least 2 cm and a modified Rankin scale (mRS) of 0 or 1 before stroke onset. The subjects were randomly assigned to the MultiStem® or placebo group at a 1:1 ratio in a double-blind manner.

Patients were administered either MultiStem® or placebo as a single intravenous infusion lasting 30–60 min given once at 18–36 h of ischemic stroke onset. The primary endpoint was the percentage of patients who achieved an excellent outcome at 90 days defined as meeting the composite score criteria of an mRS score ≤ 1 (range, 0–6), NIHSS score ≤ 1 (range, 0–42), and Barthel index (BI) ≥ 95 (range, 0–100).

The study evaluated MultiStem® treatment safety by monitoring cardiovascular and respiratory dysfunction, severe allergic reactions, serious adverse events, worsening neurologic symptoms, death, life-threatening adverse events, and secondary infections. The evaluation period was within 24 h of the infusion for cardiovascular and respiratory dysfunction or severe allergic reactions and within 7 days of administration for serious adverse events and worsening neurological symptoms. Death or life-threatening adverse events and secondary infections were monitored through day 90.

【Results】

Between November 15, 2017 and March 30, 2021, a total of 229 patients were recruited and followed for 365 days until March 29, 2022.

A total of 207 patients were randomized (105 in MultiStem® group, 102 in placebo group). Of them, 206 received intravenous MultiStem® (n = 104) or placebo (n = 102).

The study involved a significant number of elderly patients (median age, 79 and 78 years in MultiStem® and placebo groups, respectively). The proportion of patients who received reperfusion therapy, the mean NIHSS, and the mean infarct volume were comparable between groups.

The study found no significant difference in the primary efficacy endpoint between the MultiStem® and placebo groups (12 [11.5%] vs. 10 [9.8%], respectively; P = 0.90; adjusted risk difference between groups, 0.5% [95% confidence interval (CI), -7.3% to 8.3%]).

An exploratory analysis was conducted of age and ischemic core volume subgroups to determine the incidence of an mRS ≤ 2 at day 90. Patients with an ischemic core volume ≥ 50 mL had significantly better outcomes in the MultiStem® versus placebo group (8/27 [29.6%] vs. 3/37 [8.1%], respectively; P = 0.04; adjusted risk difference between groups, 20.4% [95% CI, 1.0–39.9%]).

Patients aged ≤ 64 years also exhibited a trend toward a better outcome in the MultiStem® group, although the difference was not significant (8/10 [80.0%] vs. 5/12 [41.7%]; P = 0.08; adjusted risk difference between groups, 37.2% [95% CI, -0.4% to 74.8%]).

There were no significant intergroup differences in the primary safety endpoints, including grade 3 or 4 allergic reactions.

【Future expectations】

The effectiveness of MultiStem® for treating acute stroke was demonstrated in a specific patient group. A comprehensive analysis of the results of this study, along with the ongoing phase 3 studies in the United States and Europe, is expected to further confirm the efficacy of MultiStem®.

【Research paper information】

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【Terminology】

※ 1 mRS: Severity of a patient's neurological condition on a 7-point scale of 0–6, where 0 is asymptomatic and 6 is dead.

※ 2 NIHSS: Severity of neurological symptoms of stroke using a total of 11 scoring items.

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