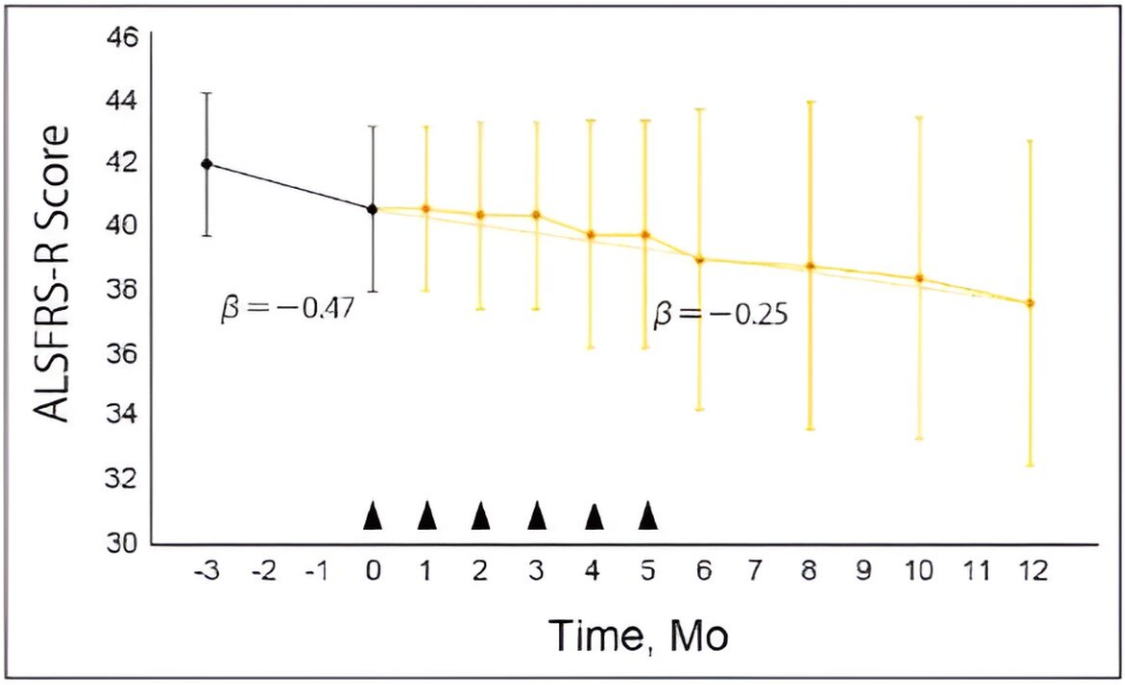
Findings indicate favorable safety profile for CL2020 Muse cell-based therapeutic for amyotrophic lateral sclerosis

February 1 2024



The image above describes the changes in the mean scores for the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) for ALS patients treated with CL2020. The arrowheads indicate the intravenous administration of CL2020 across six months. It was found that the change in ALSFRS-R scores trended upward over 12 months post-CL2020 treatment compared with three months pre-administration. This indicates that repeated CL2020 therapy is safe for ALS patients and has some positive therapeutic effect on certain ALS symptoms. Credit: Toru Yamashita / Okayama University

Amyotrophic lateral sclerosis (ALS) is a neurodegenerative disease characterized by progressive loss of motor functions, which eventually leads to death within five years of its onset. This disease causes weakness and atrophy of limbs and other muscles, which affect mobility speech, eating, and even breathing in patients.

Some drugs, including riluzole, edaravone, and sodium phenylbutyrate/taurursodiol are used for treating ALS, but with limited therapeutic benefits. Therefore, novel, effective ALS treatments are the need of the hour.

Multilineage-differentiating stress-enduring (Muse) cells are pluripotent stem cells derived from the bone marrow, which can be intravenously administered into damaged tissues.

Recent studies have found that regular administration of Muse cells causes tissue repair and functional recovery in mouse models of hepatitis, muscle degeneration, and heart attack. Moreover, it leads to significant improvement in limb muscle weakness, inhibits the activation of inflammation and regulates immune functions.

Keeping this in view, a Muse cell-based product called CL2020 was developed to utilize the therapeutic potential of Muse cells for treating ALS patients.

Recently, scientists in Japan conducted a single-center, open Phase II clinical trial to evaluate the safety and treatment efficacy of repeated intravenous injections of CL2020 in patients with ALS.

The results of this study were published in *Cell Transplantation* . The trial was led by Associate Professor Toru Yamashita from Okayama University Graduate School of Medicine, Dentistry and Pharmaceutical Sciences and Dr. Koji Abe from National Center of Neurology and Psychiatry, Japan.

"Since ALS is a progressive disease, we used multiple regular doses of CL2020, with one monthly dose administered intravenously for six doses. The dosage was set at 15×10^6 cells/dose, proven safe in trials for other illnesses. We only recruited five ALS patients, as this is the first clinical trial for confirming the safety of multiple CL2020 doses," explains Dr. Yamashita.

The primary focus of the trial team was determining the safety and tolerability of CL2020 for up to 12 months after the first administration. In addition, the team assessed disease progression by evaluating the rate of change in the Revised Amyotrophic Lateral Sclerosis Functional Rating Scale (ALSFRS-R) scores over 12 months.

ALSFRS-R uses different criteria, including speaking, eating, swallowing, motor functions, and respiratory failure, among others to reflect ALS progression in patients. The team also analyzed the levels of serum tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and sphingosine-1-phosphate (S1P), along with cerebrospinal fluid chitotriosidase-1 (CHIT-1) and neurofilament light chain (NfL), at the beginning of the trial and regularly for 12 months after the first dose.

TNF-α, IL-6, and S1P are biomarkers associated with inflammatory response and pathogenesis of ALS. Whereas CHIT-1 and NfL are associated with ALS progression and patient survival, which can indicate treatment prognosis and efficacy.

The trial found CL2020 to be highly tolerated by all patients without

severe side effects, like pulmonary embolism and anaphylactic shock. However, one patient had a bone fracture a year after the initial dose but with no significant causal relationship to the CL2020 treatment.

Furthermore, the rate of change in the ALSFRS-R scores improved at 12 months post-treatment, as compared to at three months pre-treatment, and the scores did not worsen until six months post-treatment for three patients. This indicates that multiple CL2020 doses can prevent or delay the symptoms of ALS from worsening.

However, the serum IL-6, TNF-α, CHIT-1, and NfL levels increased over six months post-treatment, suggesting that CL2020 may not suppress the secretion of inflammatory cytokines in ALS patients—which only tends to increase with disease progression.

In contrast, serum S1P levels continuously decreased over 12 months, indicating that CL2020 might functionally neutralize S1P and thus reduce related signaling in ALS patients.

These findings show that multiple CL2020 doses are safe for use in ALS patients. But while this treatment can potentially abate the worsening of some ALS symptoms, it alone may be inadequate to completely halt disease progression. Therefore, a combination therapy of CL2020 with other drugs currently used for ALS should be considered for future treatments.

"Given the promising results of this trial, we now need a double-blind study to be conducted, which includes a larger number of ALS patients with a longer observation period to confirm CL2020's efficacy. Thereafter, we can propose this treatment for ALS patients," concludes Dr. Yamashita.

More information: Toru Yamashita et al, Safety and Clinical Effects

of a Muse Cell-Based Product in Patients With Amyotrophic Lateral Sclerosis: Results of a Phase 2 Clinical Trial, *Cell Transplantation* (2023). DOI: 10.1177/09636897231214370