

News Release

Title

Therapeutic angiogenesis for patients with No-Option Critical limb ischemia by Adipose-derived Regenerative Cells: TACT-ADRC multicenter trial

Key Points

- Critical Limb Ischemia (CLI) is a refractory disease that often requires limb amputation even though multidisciplinary treatment including lifestyle modification, drug therapy, and revascularization is covered.
- Patients with CLI who are often forced to undergo limb amputation not only have a significantly reduced quality of life (QOL), but also have a higher mortality rate due to cardiovascular complications.
- Therapeutic angiogenesis is a treatment to promote blood vessel regeneration at the capillary level in ischemic tissue and is expected worldwide as a novel treatment for patients whose limbs cannot be saved by conventional treatments.
- The results of this multicenter study showed that therapeutic angiogenesis by adipose-derived regenerative cell transplantation is safe and effective for patients with severe ischemic limbs for whom no treatment options are available.

Summary

A research group led by Professor Toyooki Murohara, Assistant Professor Yuuki Shimizu of the Department of Cardiology, and Specially Appointed Professor Rei Shibata of the Department of Advanced Cardiovascular Therapeutics, Nagoya University Graduate School of Medicine, in collaboration with a multicenter research group, has verified the safety and efficacy of therapeutic angiogenesis using adipose-derived regenerative cells (ADRCs) for the treatment of critical limb ischemia.

With the aging of the population and the increase in lifestyle-related diseases in Japan, the number of patients suffering from ischemic diseases based on arteriosclerosis (ischemic heart disease, cerebrovascular disease, peripheral arterial disease, etc.) is on the rise and is the second leading cause of death after malignant neoplasms. Among peripheral arterial diseases (PAD), severe cases with treatment-refractory rest pain and refractory ischemic skin ulcers that cannot be treated, including conventional revascularization procedures, will require amputation of the affected limb if left untreated, resulting in a significant decrease in the quality of daily life. In addition, such patients with severe ischemic limbs are known to have a poor prognosis for life. Therapeutic angiogenesis, which we are actively working to develop and promote, is a treatment that artificially promotes blood vessel regeneration at the capillary level in ischemic tissue and is expected to be a new treatment for patients worldwide whose limbs cannot be saved with conventional therapies. Since it was reported that human subcutaneous adipose tissue contains mesenchymal stem/progenitor cells with multipotent

differentiation ability, these stem/progenitor cells (termed adipose-derived regenerative cells; ADRCs) have attracted attention as one of the cell therapy sources in regenerative medicine. Subsequently, clinical applications with ADRCs in various regenerative medicine fields have begun. We have now conducted the world's first multicenter clinical trial of therapeutic angiogenesis by ADRCs, demonstrating its safety and feasibility in 29 patients (34 limbs) with severe ischemic limbs who have no other conventional options. Furthermore, the trial revealed that it could lead to limb salvage in CLI patients. The results of this study were published in the international scientific journal *Angiogenesis* (electronic edition in 2022).

Research Background

Critical limb ischemia (CLI) is the most severe form of ischemic limb (PAD) (Fontaine Classification III/IV). Although multidisciplinary treatment for CLI, including lifestyle modification, pharmacotherapy, and revascularization, is indicated, it is still an intractable disease that often results in limb amputation. Patients who have to undergo major limb amputation not only have a significantly reduced quality of life (QOL), but also have a high mortality rate due to cardiovascular complications.

Ever since the first TACT [Therapeutic Angiogenesis by Cell Transplantation with Bone Marrow Mononuclear Cells] trial (TACT-BM) was reported in 2002, therapeutic angiogenesis by cell transplantation has proven to be effective in various ischemic diseases around the world. However, the subsequent report of long-term analyses revealed the presence of a specific non-responder group. In addition, the clinical challenge is that the protocol of harvesting approximately 1,000 mL of autologous bone marrow is an invasive procedure for these patients.

Mesenchymal stem cells (MSCs) exist in human subcutaneous adipose tissue and can differentiate into multiple lineages, which have been proven to contribute to tissue regeneration in various pathological models through animal studies. We have focused on these adipose-derived stem/regenerative cells (ADSCs or ADRCs) for therapeutic development as a new cell source for therapeutic angiogenesis in patients with critical limb ischemia. The ADRCs can be obtained in large quantities as primary cells. Furthermore, a collection of subcutaneous adipose tissue can be performed under local anesthesia with established techniques such as liposuction and is considered a less invasive procedure than bone-marrow harvesting.

Previous pilot studies, including the report from our group (published in *Scientific Reports* 2020), have reported that therapeutic angiogenesis with ADRC for CLI may be safe under the limited conditions of small sample sizes and single-center trials. However, no trials have clinically validated whether autologous freshly isolated ADRC implantation is safe, feasible, and effective for patients with CLI in a multicenter setting.

Therefore, a nationwide trial was conducted at eight institutions in different regions of Japan (Nagoya University, Kurume University, Dokkyo Medical University, Kanazawa University, St. Marianna Medical University, Fukuoka Tokushukai Hospital, Shinshu University, and Chiba University), was conducted as the TACT-ADRC multicenter study to verify the safety,

feasibility, and efficacy of therapeutic angiogenesis by freshly isolated autologous ADRCs in patients with CLI.

Research Results

The treatment was performed on 29 patients (34 target limbs) at 6 centers nationwide and completed in all cases. As the primary endpoint for safety evaluation, neither death nor cell transplant-related adverse events were not observed in the perioperative period and during the 6-month observation period.

As the primary endpoint for efficacy evaluation, the current study showed 0% total mortality (0 deaths out of 29 patients for 6 months follow-up period) and a major amputation-free survival rate was 94.1% (32 out of 34 limbs salvaged) at 6 months. In addition, the secondary endpoints of QOL score in terms of numerical rating scale changed from 6 to 1 after treatment, ulcer size was improved from 317 mm² to 109 mm², and 6-minute walking distance in lower limb cases was prolonged from 255 m to 369 m, whose responders were in 90.6%, 83.3%, and 72.2% of patients, respectively.

These results indicate that implantation of autologous ADRC can safely and effectively achieve angiogenesis in a multicenter study, maintaining good survival rates without significant adverse events.

Research Summary and Future Perspective

This study indicates that therapeutic angiogenesis by ADRCs could be one of the therapeutic options for patients with CLI. We aim to expand the indication to include patients with mild disease (Fontaine classification IIb) by clarifying the efficacy from the early stage of the disease. Furthermore, we aim to expand the range of treatment by verifying the efficacy in combination with other conventional methods (e.g. angioplasty, bypass surgery). In the future, we intend to proceed with procedures for insurance coverage, including advanced medical treatment.

Publication

Yuuki Shimizu; Kazuhisa Kondo; Ryo Hayashida; Ken-ichiro Sasaki; Masanori Ohtsuka; Yoshihiro Fukumoto; Shin-Ichiro Takashima; Oto Inoue; Soichiro Usui; Masayuki Takamura; Masashi Sakuma; Teruo Inoue; Tokuichiro Nagata; Yoshihiro J. Akashi; Yoshihiro Yamada; Tamon Kato; Koichiro Kuwahara; Kaoru Tateno; Yoshio Kobayashi; Rei Shibata; Toyoaki Murohara; on behalf of the TACT-ADRC multicenter trial Group, Therapeutic angiogenesis for patients with No-Option Critical limb ischemia by Adipose-derived Regenerative Cells: TACT-ADRC multicenter trial. *Angiogenesis* 2022

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