Therapeutic angiogenesis has emerged as a new treatment strategy for patients with critical limb ischemia (CLI), including thromboangiitis obliterans (TAO), also known as Buerger disease. Gene therapy research focusing on therapeutic angiogenesis using vascular endothelial growth factor and other angiogenic factors started in the 1990s and provided insight into the roles and origins of endothelial progenitor cells (EPCs). In particular, the discovery that EPCs are mobilized from the bone marrow led to successful autologous bone marrow mononuclear cell (BM-MNC) transplantation for inducing vascular regeneration in ischemic tissues. As the first translational approach using cell transplantation in the cardiovascular field in Japan, therapeutic angiogenesis through BM-MNC transplantation was developed to treat patients with CLI who would conventionally require lower limb amputation, and the effectiveness and safety of the technique were reported in 2002. This research was well received by many researchers both within and outside of Japan, and similar clinical studies were subsequently conducted worldwide.

Today, more than 10 years after the development of this approach, the long-term safety of BM-MNC transplantation for therapeutic angiogenesis has been confirmed. The therapeutic outcomes of this approach have been generally favorable, despite there being some non-responders. In particular, the therapeutic effects of BM-MNC transplantation are much greater in patients with CLI associated with TAO than in patients with peripheral arterial disease.

In this issue of the Journal, Mohamad Yusoff et al present Therapeutic Angiogenesis Using Bone Marrow Mononuclear Cell Transplantation — A New Standard Treatment for Thromboangiitis Obliterans —
the results of a long-term study (mean [±s.d.] follow-up period 12.0±8.6 years) that assessed the effects of autologous BM-MNC implantation focusing only on patients with TAO. During the study period, none of the patients treated with BM-MNCs required amputation, and their overall amputation-free survival rates were significantly higher than those of the internal controls and historical controls. Thus, Mohamad Yusoff et al concluded that BM-MNC transplantation prevented the need for major limb amputation in patients with severe TAO over the long term (i.e., >10 years). These results indicate that therapeutic angiogenesis by BM-MNC transplantation is particularly effective in patients with CLI associated with TAO.

Based on the abovementioned findings of Mohamad Yusoff et al, a multicenter clinical study in Japan entitled Therapeutic Angiogenesis Using Autologous Bone Marrow Mononuclear Cells Implantation for Buerger Disease (UMIN000027383) in TAO patients has been ongoing since 2017. The purpose of this study is to improve the availability of therapeutic angiogenesis by BM-MNC transplantation as part of Advanced Medical Care B under the National Health Insurance (NHI). The primary endpoint of the study is the magnitude of the change in skin perfusion pressure values from enrollment to 6 months after cell transplantation. Depending on the results of this study, the therapy is expected to be added to the NHI price list in Japan.

Nevertheless, ethical concerns have been raised about the use of therapeutic angiogenesis via BM-MNC transplantation for patients with CLI owing to the invasiveness of the cell collection process. In addition, non-responders have been identified among patients with underlying diseases or risk factors, including diabetes mellitus, renal failure (dialysis), and a smoking history. Therefore, to meet the current challenges for therapeutic angiogenesis, it is still essential to develop methods that have improved treatment efficiency and are minimally invasive. Thus, cells other than BM-MNCs are currently being explored for use in transplantation. In recent years, attempts have been made within Asia to investigate the use of other cells, such as adipose tissue-derived mesenchymal stem cells and peripheral blood mononuclear cells, for therapeutic angiogenesis in patients with TAO in addition to BM-MNCs, which have shown a certain degree of effectiveness (see Table). Despite promising results from clinical trials, there are still many questions surrounding therapeutic angiogenesis, such as which stem cell types are most effective or efficient and whether hybrid treatment is desirable. Through further clinical studies, we hope that therapeutic angiogenesis through less invasive and more reliable cell transplantation procedures will become possible in the near future as the global standard therapy for CLI, including Buerger disease.

Conflicts of Interest
R. Shibata belongs to a department endowed by Medtronic Japan Co., Ltd. T. Murohara is a member of *Circulation Journal* Editorial Team.

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