

Summary

Background Preclinical studies have established that implantation of bone marrow-mononuclear cells, including endothelial progenitor cells, into ischaemic limbs increases collateral vessel formation. We investigated efficacy and safety of autologous implantation of bone marrow-mononuclear cells in patients with ischaemic limbs because of peripheral arterial disease.

Methods We first did a pilot study, in which 25 patients (group A) with unilateral ischaemia of the leg were injected with bone marrow-mononuclear cells into the gastrocnemius of the ischaemic limb and with saline into the less ischaemic limb. We then recruited 22 patients (group B) with bilateral leg ischaemia, who were randomly injected with bone marrow-mononuclear cells in one leg and peripheral blood-mononuclear cells in the other as a control. Primary outcomes were safety and feasibility of treatment, based on ankle-brachial index (ABI) and rest pain, and analysis was per protocol.

Findings Two patients were excluded from group B after randomisation. At 4 weeks in group B patients, ABI was significantly improved in legs injected with bone marrow-mononuclear cells compared with those injected with peripheral blood-mononuclear cells (difference 0.09 [95% CI 0.06–0.11]; $p < 0.0001$). Similar improvements were seen for transcutaneous oxygen pressure (13 [9–17]; $p < 0.0001$), rest pain (–0.85 [–1.6 to –0.12]; $p = 0.025$), and pain-free walking time (1.2 [0.7–1.7]; $p = 0.0001$). These improvements were sustained at 24 weeks. Similar improvements were seen in group A patients. Two patients in group A died after myocardial infarction unrelated to treatment.

Interpretation Autologous implantation of bone marrow-mononuclear cells could be safe and effective for achievement of therapeutic angiogenesis, because of the natural ability of marrow cells to supply endothelial progenitor cells and to secrete various angiogenic factors or cytokines.

Lancet 2002; **360**: 427–35

*Co-investigators listed at end of report

Department of Medicine II and Cardiovascular Centre

(E Tateishi-Yuyama MD, H Matsubara MD, H Masaki MD, K Amano MD, T Iwasaka MD), and Department of Medicine I and Blood Transfusion

Unit (Y Kishimoto MD), Kansai Medical University, Osaka, Japan;

Cardiovascular Research Institute and Department of Medicine III

(T Murohara MD, S Shintani MD, T Imaizumi MD), Department of

Medicine II (K Yoshimoto MD), and Department of Surgery

(H Akashi MD), Kurume University School of Medicine, Kurume; and

Department of Cardiology, Jichi Medical School, Tochigi (U Ikeda MD, K Shimada MD)

Correspondence to: Hiroaki Matsubara, Kansai Medical University, Osaka 570-8507, Japan

(e-mail: matsubah@takii.kmu.ac.jp)