Letter to the Editor

Letter by Akar et al Regarding Article, "Effect of Autologous Bone-Marrow Cell Transplantation on Ischemic Ulcer in Patients With Buerger's Disease"

To the Editor:

We read with great interest the article by Saito et al[1] concerning the efficacy of autologous bone marrow mononuclear cell (ABM-MNC) transplantation in patients with Fontaine III and IV thromboangiitis obliterans (TAO) as a last treatment option, which appeared in the August 2007 issue of the Journal. In this unblinded pilot study, 14 patients were treated by ABM-MNC therapy! Symptomatic improvement was observed for at least 24 weeks without complications! The investigators are to be commended for their careful follow-up and for using laser Doppler blood flow analysis in their series. Nevertheless, we feel that certain issues must be addressed.

Over the past decade, tremendous excitement and controversy in the field of regenerative medicine and cellular therapeutic strategies for angiogenesis have taken place[2] Contrary to the authors' suggestion about publishing the first report of ABM-MNC therapy for patients with TAO that was uncontrolled with optimal treatment, our study consisting of 28 TAO patients with critical limb ischemia who underwent ABM-MNC implantation between April 2003 and August 2005 and a comparison of the results with saline-infused control limbs appeared in the October 2006 issue of the *Journal of Vascular Surgery*[3] One of our inclusion criteria was unresponsive clinical condition to smoking cessation 6 months before ABM-MNC implantation whereas 2–3 weeks were sufficient for Saito and colleagues. Two weeks of smoking cessation may not be adequate to evaluate clinical unresponsiveness; clinical improvement throughout the study duration can be related to smoking cessation rather than to the effect of cell therapy. The diagnosis of TAO in their series was based on the criteria proposed by the Committee for Buerger's disease of the Japanese Ministry of Health and Welfare. However, the duration between diagnosis and ABM-MNC implantation it is not clear nor whether Saito et al performed C-reactive protein, antinuclear, anticentromere and antiphospholipid antibodies, rheumatoid factor, Scl-70, fibrinogen, complement measurements, serum homocysteine, hypercoagulability screen, Holter monitoring, and transthoracic echocardiography at the baseline evaluation. Moreover, it is essential that the investigators demonstrate treatment variables after diagnosis and whether they considered parenteral administration of PGE-1 or iloprost for 7–28 days to reduce ischemic pain and facilitate ulcer healing prior to cell therapy, which was recommended in the ACC/AHA 2005 Practice Guidelines[4] We also believe that representative digital subtraction angiograms (baseline vs follow-up) would have been useful to demonstrate new collateral formation.

Mean follow-up in our series after ABM-MNC implantation was 16.6±7.8 months (range 7.6–33.8 months), and follow-up was 100% complete, whereas 3 patients in their series rejected re-evaluation at 24 weeks. Furthermore, our findings suggested that self-reported smoking status did not correlate with cotinine-indicated smoking status. Overall, the results of our study suggested that ABM-MNC implantation in ischemic limbs of patients with TAO was associated with improved exercise performance, quality of life, ankle–brachial pressure index, pain control, and augmentation of collateral formation at 24 weeks in 78% of patients. More importantly, no patient in our series experienced periprocedural complications and remained free of a major amputation, malignant ventricular arrhythmias, arteriovenous shunt or teratoma formation, retinopathy observed in funduscopic examinations, or sudden death. The investigators' patient selection, endpoints and the safety profile results were somewhat similar to those of our study.

In conclusion, cell therapy could be useful as a novel strategy for therapeutic angiogenesis in patients with end-stage peripheral vascular disease. Indeed, careful long-term monitoring is essential after cell-based therapies and both clinical improvement and adverse events should be cautiously interpreted. The researchers should make every effort to maintain dialogue that will help to reach a definitive consensus on patient selection criteria, clinical endpoints and how to monitor adverse events after cell-based therapies.

References

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