Letter by Dregelid Regarding Article, “Intra-Arterial Administration of Bone Marrow Mononuclear Cells in Patients With Critical Limb Ischemia: A Randomized-Start, Placebo-Controlled Pilot Trial (PROVASA)”

To the Editor:

During the randomized start phase of the study by Walter et al., there was 1 death and 3 major amputations among the 19 patients who got cell injections and 1 major amputation among the 21 patients in the placebo group. The 3-month combined mortality and major amputation rate for the 3 cell injection groups was 10 of 51 versus 1 of 21 in the placebo group. The differences would have been significant if the same rates had been observed in only twice as many patients.

Because previous intracoronary cell injection studies had not shown consistently positive effects, there was no reason to presume a positive effect of the cell injections. To comply with the Declaration of Helsinki, patients might have been informed about the possible excess rate of major amputations and deaths in the cell injection groups so that they and not the treating physician could have decided whether to enter the extended protocol phase of the study.

It has not been reported how the patients were blinded and whether persons who treated the patients were blinded to the treatment in the randomized start phase of the study. It may have been possible to see the difference between the cell suspension and the control solution. Visual analog pain scores could have been biased by a placebo effect in patients eager to improve after receiving a new and promising but invasive treatment.

Ulcers in patients with critical limb ischemia who do not undergo a major amputation often improve with time, even in patients with a lower ankle-brachial index than the patients in this study. Spontaneous healing therefore may explain the reduction in ulcer area in the open-label phase. Because more patients in the cell injection groups underwent amputation than those in the placebo group, remaining ulcers in the cell injection groups would be a selection of the best in those groups and therefore more prone to heal than those remaining in the placebo group. Ischemic ulcers are affected by the attention given to pressure ulcer prevention and hydration of the patients. Persons treating the patients and enthusiastic about cell treatment might unconsciously have given more attention to such details in patients in the cell injection groups. The rate of previous PTAs or surgeries that may interfere with collateral development as the result of side branch occlusion during PTA and scar tissue after surgical incisions was higher in the placebo group. For these reasons and because of the lack of a placebo group in the open-label phase, the results do not support the conclusion that successful ulcer healing associated with improved limb salvage requires repeated bone marrow mononuclear cell administration.

In Figure 3B of the article, the number of patients in the placebo group should be 11, not 12, because 3 of the initial 15 ulcers had healed and 1 patient with an ulcer had an amputation.

Invoking an unpublished study does not add credence to the idea that cell injections can reduce amputation rates in patients with critical limb ischemia.

Disclosures

None.

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References

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