From the Society for Vascular Surgery

Ethnic minorities with critical limb ischemia derive equal amputation risk reduction from autologous cell therapy compared with whites

S. Keisin Wang, MD,[a] Linden A. Green, PhD,[a] Ashley R. Gutwein, MD,[a] Natalie A. Drucker, MD,[a] Clifford M. Babbey, BS,[a] Alok K. Gupta, MD,[a] Andres Fajardo, MD,[a] Raghu L. Motaganahalli, MD,[a] Michael G. Wilson, PhD,[b] *and* Michael P. Murphy, MD,[a] *Indianapolis, Ind*

ABSTRACT

Objective: Ethnic minorities (nonwhites) with critical limb ischemia (CLI) have historically performed worse compared with whites with regard to major amputation risk reduction and amputation-free survival (AFS) after peripheral vascular intervention. This post hoc analysis was completed to determine whether this precedent also extended to treatment of CLI without a suitable revascularization option with intramuscular injections of concentrated bone marrow aspirate (cBMA).

Methods: The treatment arm of the randomized, double-blind, multicenter MarrowStim PAD Kit for the Treatment of Critical Limb Ischemia in Subjects with Severe Peripheral Arterial Disease (MOBILE) trial was stratified by ethnicity and evaluated for demographics, comorbidities, and outcomes. The primary and therapeutic end point was 1-year AFS and major amputation, respectively. Noninferiority analysis was performed with the margin set at historically reported hazard ratios.

Results: Thirty-seven minority (African American, Hispanic, other) CLI patients (9 placebo, 28 cBMA) with no suitable revascularization option were randomized to cBMA or placebo at a 3:1 ratio during the MOBILE trial. At 1-year follow-up for the treatment group, overall AFS was 80%. Of the 28 minority patients randomized to cBMA intervention, an 89% AFS rate was observed compared with 77% in whites. Specifically, 22 of 24 (92%) African Americans survived amputation free at 1-year follow-up. Noninferiority testing confirmed no difference between whites and the ethnic minority treated with cBMA with respect to major amputation reduction; however, noninferiority could not be confirmed with regard to AFS. No significant differences favoring whites treated with cBMA were noted in the secondary end points of vascular quality of life, limb pain, ankle-brachial index, toe-brachial index, transcutaneous oximetry, and 6-minute walk testing.

Conclusions: This post hoc analysis of the MOBILE trial demonstrates noninferiority of cBMA intervention in minorities with no-option CLI for the therapeutic end point of major amputation prevention. cBMA represents a novel treatment paradigm and should be explored for minorities with poor revascularization options who face impending amputation secondary to progressive CLI. (J Vasc Surg 2018;■:1-7.)

Critical limb ischemia (CLI) is most often a result of progressive atherosclerosis of the extremities leading to insufficient blood flow to maintain tissue viability.[1] The patient may experience ischemic rest pain or tissue loss in the form of chronic ulceration or dry gangrene. If blood flow cannot be restored by surgical revascularization, the only treatment option is major amputation (above the ankle) when pain becomes uncontrollable or infection of the limb occurs. Consequently, up to 500 amputations are performed per million individuals annually, leading to significant costs in hospitalization, rehabilitation, and loss of workforce productivity.[2,3]

The MarrowStim PAD Kit for the Treatment of Critical Limb Ischemia in Subjects with Severe Peripheral Arterial Disease (MOBILE) trial is a recently concluded phase 3, randomized, placebo-controlled, double-blind, multicenter study designed to evaluate the effectiveness of concentrated bone marrow aspirate (cBMA) in preventing major

From the Division of Vascular Surgery,[a] and Division of Clinical Pharmacology,[b] Indiana University School of Medicine.

MOBILE is an industry-sponsored trial (Zimmer Biomet, Warsaw, Ind). Zimmer Biomet was not involved in the trial design, data collection, or interpretation of data. In addition, the industry sponsor was not a factor in the decision to write or to submit this manuscript.

Clinical Trial registration: NCT02474121.

Author conflict of interest: none.

Presented in the Interactive Poster Session of the 2017 Vascular Annual Meeting of the Society for Vascular Surgery, San Diego, Calif, May 31-June 3, 2017.

Correspondence: Michael P. Murphy, MD, Associate Professor, Division of Vascular Surgery, Department of Surgery, Indiana University School of Medicine, 1801 Senate Blvd MPC# 2-3500, Indianapolis, IN 46202 (e-mail: mipmurph@iupui.edu).

The editors and reviewers of this article have no relevant financial relationships to disclose per the JVS policy that requires reviewers to decline review of any manuscript for which they may have a conflict of interest.

0741-5214

Copyright © 2018 by the Society for Vascular Surgery. Published by Elsevier Inc.

https://doi.org/10.1016/j.jvs.2017.11.088

amputations and all-cause mortality in CLI patients without surgical options. In this trial, an 11% (80% vs 69%) absolute risk reduction trend was noted in major amputations in all patients treated with cBMA vs placebo. This therapeutic benefit was statistically significant in the prespecified Rutherford 4 and nondiabetic Rutherford 5 CLI patients.[4]

Up to a third of those with CLI in the United States are an ethnic minority or nonwhite.[5] Of these, African Americans make up the largest subcohort.[6] Historically, recruitment of minorities for randomized controlled trials (RCTs) has been met with significant challenges. Adequate representation of this group is of particular importance as Hispanics and African Americans have a higher prevalence of cardiovascular risk factors and more severe peripheral arterial disease.[7] Not surprisingly, previous outcomes studies have indicated that African Americans with CLI perform worse in terms of primary graft patency and amputation-free survival (AFS) after revascularization.[8] Therefore, the objective of this post hoc analysis was to establish the noninferiority of cBMA as a treatment paradigm for ethnic minority CLI patients of the MOBILE RCT.

ARTICLE HIGHLIGHTS

- **Type of Research:** Post hoc analysis of phase 3 of the MarrowStim PAD Kit for the Treatment of Critical Limb Ischemia in Subjects with Severe Peripheral Arterial Disease (MOBILE) randomized controlled trial
- **Take Home Message:** There was noninferiority in outcome of using concentrated bone marrow aspirate for treatment of unreconstructible critical limb ischemia in 28 African American patients compared with white patients.
- **Recommendation:** The authors suggest that in considering concentrated bone marrow aspirate therapy for unreconstructible critical limb ischemia, race should not exclude patients.

METHODS

Overall trial design. MarrowStim (Zimmer Biomet, Warsaw, Ind), a disposable, modified cylinder used with a tabletop centrifuge, significantly increases efficiency of mononuclear cell harvest from bone marrow aspirate at the point of care by facilitating the harvest, concentration, and treatment of the patient, all within a single encounter.[9] The MOBILE trial is a multicenter, randomized, double-blind, placebo-controlled, phase 3 clinical trial designed to evaluate the safety and efficacy of the MarrowStim cBMA product in the treatment of no-option CLI. Trial design was approved by the respective Institutional Review Boards of the participating institutions; after informed consent was obtained, treatment and follow-up were performed in accordance with the latest iteration of the Declaration of Helsinki.[10]

The rationale and design of MOBILE are described in detail elsewhere.[11] In short, patients who met criteria were randomized at a 3:1 ratio in favor of intramuscular injection of cBMA vs saline placebo. The treatment group underwent general anesthesia, iliac crest bone marrow aspiration, and intramuscular injection of the cBMA treatment product along the longitudinal axis of the tibialis anterior muscle bed.

Postprocedural follow-up consisted of regimented clinic visits and phone calls for 52 weeks before a transition to annual clinic visits for the 2- and 3-year marks. Regardless of randomization, all subjects received the established best medical therapy (BMT).[12] The primary end point was regulatory, chosen by the Food and Drug Administration, and consisted of a composite of all-cause mortality and major amputation (AFS). The therapeutic end point consisted of major amputation alone. Secondary end points were ischemic rest pain severity, ankle-brachial index, toe-brachial index, transcutaneous oximetry, 6-minute walk test, and vascular quality of life.

Ethnicity. Ethnicity was self-reported by patients enrolled in MOBILE as African American, white (Hispanic), white (non-Hispanic), or other. For purposes of this study, all nonwhite patients were classified as ethnic minorities and grouped together as a cohort.

Statistical analysis. Product-limit estimates (Kaplan-Meier) were calculated and plotted to summarize AFS. The hazard ratios (HRs) for the racial groups were model-based estimates from the proportional hazards model, which included terms for treatment, ethnicity, treatment by ethnicity, Rutherford score, diabetes status, and combined site. The detailed rationale for the statistical modeling is provided in the statistical appendix of the MOBILE rationale and design manuscript.[11] The same model was used for both the primary and therapeutic end points. Only if the interaction term between treatment and ethnicity was not statistically significant was further testing of noninferiority conducted. Variance for the log hazards was estimated using the profile likelihoods. The HRs were determined using the standard method for noninferiority hypothesis; specifically, the HR was calculated by subtracting the margin from the difference between racial groups in the estimated log hazard. That difference was exponentiated using the natural logarithm. The margins used were 1.297 for AFS and 2.000 for major amputation as reported by Nguyen et al.[13] Secondary efficacy was examined by fitting the data to a repeated-measures mixed model by ethnicity.

RESULTS

Demographics, comorbidities, and treatment product. In the MOBILE trial, 155 (119 treatment, 36 placebo) patients were enrolled and randomized at a 3:1 ratio

Download English Version:

https://daneshyari.com/en/article/8671430

Download Persian Version:

https://daneshyari.com/article/8671430

Daneshyari.com