Critical limb ischemia (CLI) is the most severe form of peripheral arterial disease and is associated with an excessively high risk for death and amputation of the affected extremity. The clinical hallmarks of CLI are rest pain and tissue loss because of progressive occlusion of the arteries in the leg as a result of atherosclerosis and, less frequently, autoimmune and inflammatory disorders. The estimated annual incidence of CLI in Western society is 500 to 1000 new cases, which is expected to increase as the population ages and obesity and diabetes mellitus become more prevalent. Treatment strategies for CLI have traditionally focused on surgical bypass or endovascular interventions that improve limb perfusion to prevent amputation of the affected leg. Unfortunately, 40% of patients with CLI will not have options for these procedures, and as a result, over 53,000 amputations are performed annually in the United States. Patients with diabetes mellitus, Rutherford class 5 or 6 disease (tissue loss), and renal dysfunction are at highest risk for limb loss.

Over the past decade, there has been an avid interest in cell-based therapies to promote neovascularization and enhance limb perfusion as a strategy to prevent amputation in this no option CLI population. Multiple studies have suggested that autologous cells derived from both bone marrow and peripheral blood may decrease amputation rates; however, these studies had small sample sizes, lacked control groups, and end points were ill defined. To decipher these varied results, the current report in Circulation Research by Rigato et al provides a meta-analysis of all published trials in the last decade using autologous cell therapy to treat CLI. Within, the authors describe analysis of 19 randomized controlled trials (837 patients), 7 nonrandomized trials (338 patients), and 41 noncontrolled studies (1177 patients). Although heterogeneity was high and publication bias could not be excluded, an improvement of 18% was found in amputation-free survival, a composite measure of all-cause mortality and major amputation (defined as above the ankle), compared with controls. Additional improvements were noted in amputation risk reduction (37%), wound healing (59%), ankle brachial index, TcPO2, walking capacity, and rest pain index.

As with any meta-analysis, accumulation of homogeneous data can be a significant challenge. In this article, the authors report 67 total accumulated clinical studies of various designs. The majority of the studies were noncontrolled trials (61%), which spanned 50% of the total number of patients included. Further compromising the ability of this analysis to assess efficacy of autologous cell therapy is that the studies included in the review represented a wide clinical spectrum of patients ranging from claudication to severe CLI. The treatment vehicles also consisted of a combination of bone marrow and peripherally derived stem cells administered intravenously, intramuscularly, or both. The final observations reached by the authors that little to no difference in preventing amputation is observed between placebo and cell therapy in the high-quality, placebo-controlled randomized controlled trials demonstrate that a strong inverse relationship is observed between quality of evidence and therapeutic effect, revealing the ambiguity and confusion that poorly designed trials create, specifically in CLI. Further limitations in this analysis is the inability to compare results based on critical variables that determine limb loss in CLI, diabetes mellitus, renal function, and Rutherford class. Thus, there is an imperative need for well designed, randomized, placebo-controlled trials to provide pivotal data regarding the efficacy of autologous cell therapy in CLI.

Since this report by Rigato et al, we have completed the Phase III multicenter randomized, placebo-controlled MOBILE Trial (Marrowstim Treatment of Limb Ischemia in Subjects With Severe Peripheral Arterial Disease; NCT01049919). From May 2010 to May 2015, 152 patients (male, 88 and female, 64) were enrolled at 24 centers in the United States and randomized in a 3:1 fashion to autologous concentrated bone marrow cells or placebo (sham procedure), respectively. Although patients with renal failure or significant dysfunction were excluded, randomization was stratified to each study group based on the 2 second most important predictors of amputation in CLI, diabetes mellitus and Rutherford class. The primary clinical end point was amputation-free survival at 52 weeks. We found that there was a numeric improvement in amputation-free survival in the concentrated bone marrow cell group at 52 weeks; however, this was not significant (79.8% versus 69.5%; hazard ratio [95% confidence interval], 0.64 [0.31–1.31]; P=0.22; unpublished data). However, on post hoc analyses when Rutherford 5 (tissue loss) diabetics were excluded, amputation-free survival was significantly greater in the concentrated bone marrow cell group compared with placebo at 52 weeks (86.2% versus 66.7%; hazard ratio [confidence interval], 0.37 [0.16–0.85]; P=0.018). These initial results coupled with the findings of Rigato et al critically highlight the importance of randomized placebo controlled trials in CLI.
In conclusion, there is accumulating evidence that autologous cell therapy provides benefit in preventing amputation in select patients with CLI. Future studies need to be stratified based on key variables that determine outcomes in this heterogeneous patient population and should focus on potentially more potent cell sources.

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References


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