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Getting A "Leg Up" on Cell Therapy for Critical Limb Ischemia

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Critical limb ischemia (CLI) is the most severe form of peripheral arterial disease (PAD) and is associated with an excessively high risk for death and amputation of the affected extremity.[1] The clinical hallmarks of CLI are rest pain and tissue loss due to progressive occlusion of the arteries in the leg as a result of atherosclerosis and less frequently, autoimmune and inflammatory disorders.[2] The estimated annual incidence of CLI in Western society is 500 to 1,000 new cases which is expected to increase as the population ages and obesity and diabetes become more prevalent.[3] 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 U.S. and patients with diabetes, Rutherford class 5 or 6 disease (tissue loss), and renal dysfunction at highest risk for limb loss.[3,4]

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[5] provides a meta-analysis of all published trials in the last decade using autologous cell therapy treat CLI. Within, the authors describe analysis of 19 randomized controlled trials (RCTs; 837 patients), 7 non-randomized trials (338 patients), and 41 non-controlled studies (1177 patients). Although heterogeneity was high and publication bias could not be excluded, an improvement of 18% was found in amputation free survival (AFS), a composite measure of all cause mortality and major amputation (defined as above the ankle), compared to controls. Additional improvements were noted in amputation risk reduction (37%), wound healing (59%), ABI, TcPO2, walking capacity, and rest pain index.

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Disclosures. None.

As with any meta-analysis, accumulation of homogeneous data can be a significant challenge. In this paper, the authors report 67 total accumulated reports of various designs. The majority of the reports were non-controlled studies (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 mild claudicants 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 RCTs demonstrate a very 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, renal function, and Rutherford class.[4] 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 and colleagues we have completed the Phase III multi-center randomized, placebo-controlled Marrowstim Treatment of Limb IschemIa in Subjects With Severe Peripheral ArteriaL DiseasE (MOBILE) Trial (NCT01049919). From May 2010 to May 2015, 152 patients (M 88, F 64) were enrolled at 24 centers in the U.S. and randomized in a 3:1 fashion to autologous concentrated bone marrow cells (cBMA) 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 two second most important predictors of amputation in CLI, diabetes and Rutherford class(4- rest pain; 5-minor tissue loss). The primary clinical endpoint was amputation free survival at 52 weeks. We found that there was a numerical improvement in AFS in the cBMA group at 52 weeks however this was not significant (79.8 vs 69.5%), HR (95% CI) = 0.64 (0.31-1.31), P= 0.22 (unpublished data). However on post-hoc analyses when Rutherford 5 (tissue loss) diabetics were excluded AFS was significantly greater in the cBMA group compared to placebo at 52 weeks (86.2 vs. 66.7%, HR(CI)=0.37 (0.16-0.85), P=0.018. These initial results coupled with the findings of Rigato[5] et al critically highlight the importance of randomized placebo controlled trials in CLI.

In conclusion, there is accumulating evidence the 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 heterogenous patient population and should focus on potentially more potent cell sources.

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