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Quality of Life After Treatment with Autologous Bone Marrow Derived Cells in No Option Severe Limb Ischemia

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WHAT THIS PAPER ADDS

The present study investigated quality of life (QoL) at a median of 35 months follow up after bone marrow derived cell therapy for severe limb ischemia. QoL is becoming a more important outcome measure, as amputation rates drop globally. Studies investigating cell therapy in limb ischemia do not usually have long-term follow up results. In the present study, QoL is still increased after almost 3 years, both in the cell treated and placebo arms. The information in the current manuscript is valuable for future trials, since it shows that QoL improvement persists even after long-term follow up, in both the treatment and placebo groups. This also underlines the importance of placebo controlled studies in (cell therapy) trials in limb ischemia.

Objective: Quality of life (QoL) is an important outcome in evaluating treatment effect in severe limb ischemia. The randomized, double blind, placebo controlled JUVENTAS trial, investigating the effect of bone marrow derived mononuclear cell (BMMNC) administration in no option severe limb ischemia, showed an improved QoL at 6 months compared with baseline in both the treatment and placebo groups. The aim of the present study was to evaluate whether the improved QoL persisted beyond 6 months' follow up, whether this differed in both trial arms, and if major amputation influenced QoL.

Methods: Short form 36 (SF-36) and EuroQol 5D (EQ5D), including the EQ Visual Analogue Scale (EQ-VAS), questionnaires were sent to JUVENTAS trial participants. In the JUVENTAS trial, a norm based scoring method was applied to report the results of the SF-36. The results of the long-term follow up were compared with baseline and 6 month follow up and the results of both trial arms were compared, as were the results of patients with and without amputation.

Results: One hundred and nine patients (86.5% of surviving patients) responded to the questionnaires. Median follow up after inclusion was 33 months (interquartile range [IQR] 21.2–50.6) for the BMMNC and 36 months (IQR 21.4–50.9) for the placebo group. The improvement in QoL at 6 months persisted in both arms at a median follow up of 35 months. The long-term QoL did not differ between the BMMNC and placebo group in any of the SF-36 or EQ5D domains. Patients with and without a major amputation had similar QoL scores.

Conclusions: The increased QoL in patients with no option severe limb ischemia persisted until 3 years after inclusion, but did not differ between the BMMNC and placebo arms or between patients with and without a major amputation.

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INTRODUCTION

Severe limb ischemia is an important health care issue with an increasing incidence, and is associated with a poor prognosis for both life and limb, low quality of life (QoL), and high treatment costs.[1,2] A considerable proportion of these patients will reach a stage where revascularization is not an option, and effective pharmacological therapies for severe limb ischemia are lacking. Hence, major amputation is often inevitable.[3] Therefore, novel treatment options are needed, and regenerative medicine strategies, for instance cell based therapies seem promising.[4]

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Besides amputation rates or amputation free survival, QoL is increasingly appreciated as an important outcome to evaluate treatment success in severe limb ischemia, and improving QoL has become an important treatment goal in this patient population.[3,5] Several validated instruments are available to assess health related QoL. One of these is the Medical Outcomes Study Short Form 36 (SF-36) Health Survey, a QoL questionnaire that is widely accepted, validated, and commonly used for the assessment of QoL in various diseases, such as peripheral arterial disease (PAD).[6] Patients with no option severe limb ischemia, participating in the JUVENTAS (reJUVenating ENdothelial progenitor cells via Transcutaneous intra-Arterial Supplementation) trial had worse outcomes in almost every domain of the SF-36 questionnaire than patients with less severe PAD and patients with cardiovascular risk factors only.[1] The results of the JUVENTAS trial showed relatively low amputation and mortality rates in both the bone marrow derived mononuclear cell (BMMNC) and placebo groups, with no significant differences between the groups.[7] The study also reported improved QoL after 6 months compared with baseline in both the BMMNC and the placebo group, without significant differences between the groups. Since there was an improvement in QoL in both groups, the question of whether this may be a result of trial participation itself was raised. The authors have investigated whether this increase in QoL compared with baseline persists in the long-term after finishing the study, when the extra attention and care would be ended. In addition it was assessed whether long-term QoL was influenced by major amputation.

METHODS

The JUVENTAS study was a randomized, placebo controlled, double blind clinical trial that aimed to investigate whether repeated intra-arterial infusion of BMMNCs reduces major amputation rates compared with placebo in a large cohort of no option severe limb ischemia patients. Patients were included from September 2006 through June 2012 if they had severely limiting intermittent claudication or limb ischemia and were not suitable for surgical or endovascular revascularization. A flow chart of the study design is displayed in Fig. 1.

The study rationale and design have been published previously.[8] QoL was assessed at inclusion and 2 and 6 months follow up in the JUVENTAS trial. The study showed no differences in amputation and mortality rates between the BMMNC and placebo group of the trial, and QoL, rest pain, ankle brachial index (ABI), and transcutaneous oxygen (tcO_2) pressure improved in both the BMMNC and placebo group, without differences between them.[7] The main findings of the trial are summarized in Box 1.

Validated Dutch versions of the short form 36[9] and EuroQol 5D-3 level version[10] (EQ5D-3L) questionnaires were

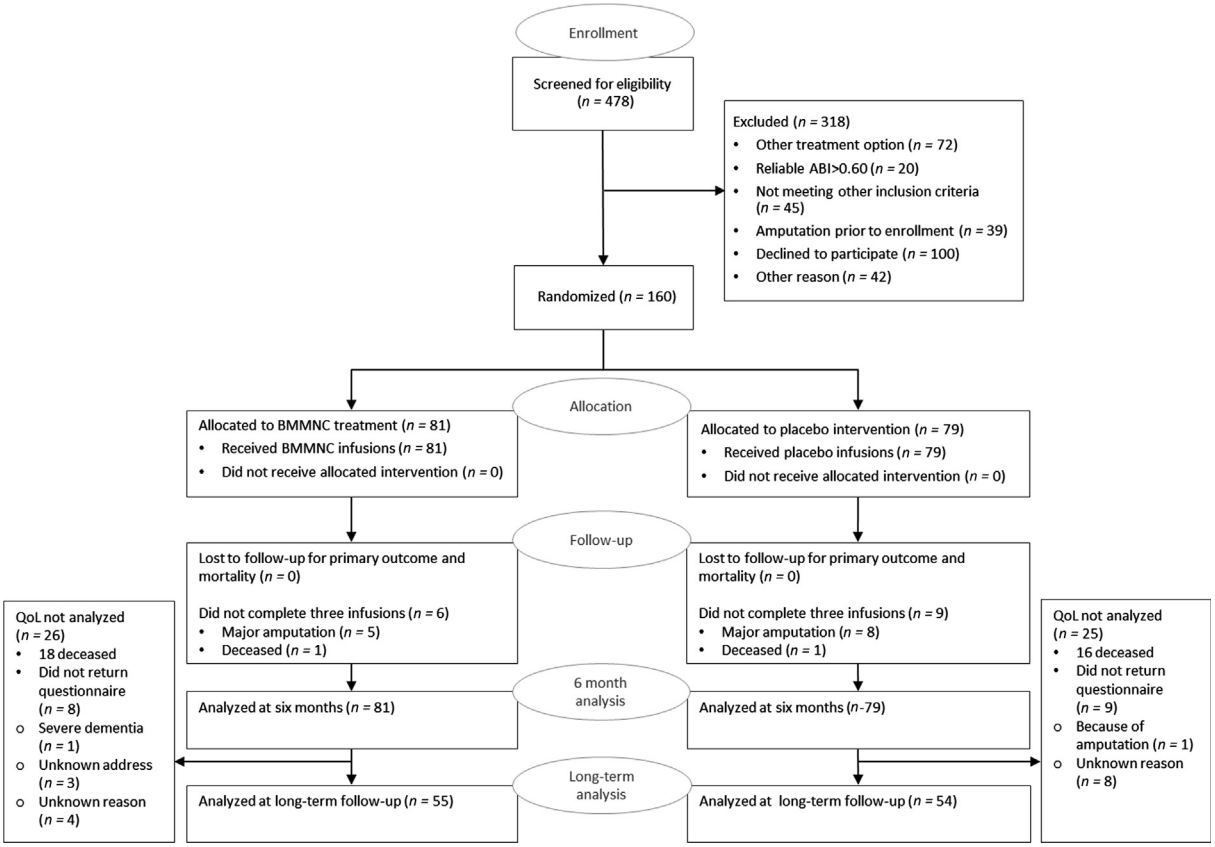

Figure 1. Patient recruitment and trial flow showing the patient flow during the initial JUVENTAS study and long-term follow up. ABI = indicates ankle brachial index; BMMNC = bone marrow mononuclear cell.