Rationale and Design of Randomized Clinical Trial for the Assessment of Macitentan Efficiency as Coadjuvant Treatment to Open and Endovascular Revascularization in Critical Limb Ischemia

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ABSTRACT

INTRODUCTION: Critical limb ischemia (CLI) is defined by ischemic rest pain, tissue loss, or both, secondary to arterial insufficiency, and its prevalence is increasing mainly as a result of the worldwide high prevalence of diabetes. Currently, there are no available conclusive data on the efficacy of any coadjuvant therapy after revascularization procedure benefiting amputation and patency rates. Macitentan is an orally active dual endothelin (ET) receptor antagonist that may contribute to reduce the amputation rate and improve revascularization patency in CLI.

METHODS/DESIGN: REVASC is a proposed pilot, open-label, controlled, randomized, single-center clinical double-blind trial to be conducted in Spain on a study population of European patients with CLI, which will compare the clinical outcomes and cost-effectiveness of macitentan coadjuvant treatment after limb revascularization with the standard antiplatelet treatment strategy for severe limb ischemia. Patients are randomized 1:1 to receive macitentan or placebo for 12 weeks. The primary clinical end point will be amputation-free survival rate at 12 months, defined as the time to major (above the ankle) amputation for the index (trial) limb or death from any cause, whichever comes first. Secondary outcomes include overall survival, quality of life, in-hospital mortality and morbidity, repeat interventions, healing of tissue loss, and hemodynamic changes following revascularization. Sample size is estimated as 120 patients. The economic analysis will consist of two components: a "within-study" analysis, which will be based on study end points; and a "model-based" analysis, which will extrapolate and compare costs and effects likely to accrue beyond the study follow-up period.

DISCUSSION: The REVASC trial is designed to be pragmatic and represents current practice of the real-world population management after limb revascularization for CLI due to atherosclerosis. Current evidence does not support any coadjuvant treatment. A new pathway of treatment may be opened with the use of ET receptor antagonists in these patients.

KEYWORDS: macicenctan, critical limb ischemia, revascularization, randomized clinical trial, coadjuvant treatment, protocol

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Introduction

Atherosclerosis is the underlying cause of lower-extremity peripheral arterial disease (PAD), causing intermittent claudication, leg ulceration, gangrene, and eventually limb amputation.[1] Patients with this condition have a threefold increase in rates of myocardial infarction, stroke, and cardiovascular (CV) death.[2,3]

The final stage of PAD, known as critical limb ischemia (CLI), is a significant cause of death and disability. The worldwide estimated annual incidence of CLI ranges between 500 and 1000 cases per million and carries high rates of one-year mortality, ranging from 10% to 40%.[4] Without revascularization, up to 40% patients affected by CLI will suffer limb loss within six months. Rates of major amputation in Western countries range from 120 to 500 per million inhabitants per year.[5] The global epidemic of diabetes, coupled with smoking, diet, and lifestyle trends, ensures that the burden of PAD will continue to grow.

Patients with CLI are at an exceptionally high risk for major amputation if the blood supply is not restored by revascularization. In addition to medical treatment (which includes treatment with antiplatelet and lipid-modifying agents as well as optimal diabetic control), CLI may be treated either by surgical or endovascular lower limb revascularization (depending on the patient characteristics and the surgeon's experience) or by primary amputation, when the limb is beyond salvage and/or the patient is unfit to undergo revascularization.[6]

Patients who have undergone lower-extremity revascularization, by either open or endovascular procedures, have a nonnegligible risk of restenosis, graft occlusion, and complications linked to atherosclerosis disease, which may eventually lead to major limb amputation. Current practice guidelines suggest that patency rates of lower-extremity revascularization are improved by the long-term administration of aspirin therapy.[5,7] Coadjuvant anticoagulant treatment with warfarin added to aspirin after revascularization is used only in a few settings in order to improve patency and to prevent other ischemic complications as it carries an increased risk of morbidity and mortality.[8]

To date, some meta-analyses have demonstrated benefit for PAD patients in terms of survival and amputation rate,[9,10] but level Ia evidence from clinical trials supporting any coadjuvant treatment after limb revascularization procedures other than antiplatelet therapy in order to improve patency and limb salvage rates is still limited.

Endothelin (ET) is a potent vasoconstrictor peptide that exerts its action by targeting two transmembrane receptors (ET_A and ET_B). Recent studies have suggested that ET may play an important role in the alteration of the endothelial function at the onset of PAD. Likewise, a significant correlation has been shown between plasma ET levels and the number of obstructive arterial atherosclerotic lesions, clinical severity, and impairment of endothelial function in such patients. Accordingly, the ET pathway may represent an important target for PAD treatment and prevention through pharmacological interventions.[11]

Macitentan is an orally active dual (ET_A and ET_B) ET receptor antagonist and prostacyclin agonist that possesses antifibrotic, vasodilatation, and antiproliferative activities.[12] The effects of macitentan on vascular function have not been well established yet, but a recently published study has suggested that even while atherosclerotic processes are already under way, macitentan can reduce its progression in animal models.[13]

Previous experiences with ET dual receptor antagonist, such as bosentan, have already shown beneficial effects in PAD.[11] Although bosentan has a similar mode of action (ET_A and ET_B blockade), macitentan shows an increased ability to block the ET receptors due to its increased tissue distribution and better receptor-binding properties. This improved efficacy may explain the unique efficacy of macitentan in reducing disease progression in patients with pulmonary arterial hypertension (PAH), demonstrated in the SERAPHIN trial. Increasing evidence suggests that macitentan is more efficacious than bosentan in PAH preclinical models.[14,15]

The effects of the ET dual receptor antagonist macitentan have not been analyzed in patients presenting CLI, but previous experience with ET receptor antagonists has found them to be safe and effective in PAD. The REVASC trial is a Spanish single-center, randomized controlled clinical trial that aims to assess the benefits of concomitant administration of macitentan following limb revascularization. Current data on this issue are extremely scarce, with very few randomized clinical trials,[16,17] and no systematic reviews or meta-analyses are available. The effects of the ET receptor antagonist macitentan, such as the antifibrotic, vasodilator, and antiproliferative activities, may contribute to improvement of limb salvage rates in CLI.

This article presents the REVASC trial study protocol.

Methods

Design. REVASC is a pilot single-center, open-label controlled randomized double-blind clinical trial to be conducted in Spain on a population of European patients with CLI, which will compare the clinical outcomes and cost-effectiveness of concomitant treatment with macitentan following limb revascularization with current antiplatelet treatment strategy. The study is being designed according to the recommendations of the Society for Vascular Surgery Ad Hoc Committee on Clinical Research. The trial protocol will be conducted according to the most recent amendments to the Declaration of Helsinki and in adherence to Good Clinical Practice guidelines. Patients are required to give written informed consent before enrollment. The present study consists of a clinical trial protocol, so doesn't require ethics approval at this stage.

Patients. In order to be included in the study, the patients must have been diagnosed with CLI (defined as an ankle pressure [AP] <50 mmHg or toe pressure [TP]/transcutaneous oxygen pressure [$TcPO_2$] <30 mmHg in the presence of rest pain, and AP <70 mmHg or TP/$TcPO_2$ <50 mmHg in the presence of tissue necrosis) and must have been revascularized recently, within the past week before being included.

Subjects must meet all the following inclusion criteria to be eligible for the study: age older than 18 years, capacity to consent, symptomatic PAD (including Rutherford–Baker stages 4–6/Fontaine stages III–IV), pain at rest or presence of nonhealing ulcers for at least 2 weeks, life expectancy longer than 12 months, recent open (autogenous venous bypass) or endovascular revascularization, as well as optimal medical care compliance (OMC). OMC includes smoking cessation, antiplatelet therapy, statin therapy, angiotensin-converting enzyme (ACE) inhibitor therapy, advice on diet, and exercise tips (Table 1).

Potential subjects who meet any of the following criteria will be excluded from participating in the study: moderate-to-severe hepatic impairment (ie, Child–Pugh class B or C), anemia, pregnancy or breastfeeding, known thromboangeitis obliterans, estimated creatinine clearance <30 mL/minute, or any medical or psychological condition that prevents compliance with the protocol or adherence to therapy.

Patients with other causes or forms of peripheral vasculopathy, such as popliteal entrapment syndrome, cystic adventitial disease, collagenopathy, and hypercoagulability, will also be excluded from the study (Table 1).

Table 1. Inclusion and exclusion criteria.

INCLUSION CRITERIA	EXCLUSION CRITERIA
Patients older than 18	Contraindication for macitentan treatment such as patients with liver failure or liver disease, anaemia, or pregnant women
Capacity to consent	
Symptomatic patients (including Rutherford-Baker 4–6/Fontaine III–IV), pain at rest or nonhealing ulcers for at least two weeks	Other medical or psychological condition, which may represent in the investigator's opinion a contraindication to either macitentan treatment or to adequately performing the treatment and procedures of the study
Life expectance higher than 12 months	
Recent open (autogenous venous bypass) or endovascular revascularisation	
No evidence of improvement in response to conventional medical treatment	Patients with other causes or forms of peripheral vasculopathy such as popliteal entrapment syndrome, cystic adventitial disease, colagenopathy, thromboangeitis obliterans (TAO)

End points. The primary clinical end point will be amputation-free survival rate at 12 months, defined as the time to major (above the ankle) amputation for the index (trial) limb or death from any cause, whichever comes first.

Secondary end points include primary assisted patency and secondary long-term revascularization patency, overall survival, in-hospital and 30-day postprocedure morbidity and mortality, major adverse limb event/amputation (transtibial and above) or any major vascular reintervention (thrombectomy, thrombolysis, balloon angioplasty, stenting, or surgery), major adverse CV events (severe limb ischemia and amputation affecting the contralateral limb, acute coronary syndrome, or stroke), relief of ischemic pain (visual analog scale and medication usage), quality of life using generic tools (European Quality of Life Five Levels questionnaire [EuroQol EQ-5L], 12-Item Short Form Health Survey [Short Form-12]), healing of tissue loss (ulcers, gangrene) of presumed arterial etiology as assessed by the Wound/Ischemia/Foot Infection scoring and classification system,[18] healing of minor (toe and forefoot) amputations, hemodynamic changes such as ankle brachial pressure index and toe brachial pressure index, and flow-mediated arterial vasodilation (FMAD) changes.

Stratification and randomization. Eligible patients with revascularized CLI with patent bypass or angioplasty are initially stratified by open or endovascular revascularization. After stratification, patients are randomized 1:1 to receive either macitentan for 12 weeks or placebo, along with OMC, respectively. The experimental group will receive macitentan orally at a dose of 10 mg once daily during the first 4 weeks in order to closely control safety issues and 10 mg in the next 8 weeks.

The OMC, according to the American Heart Association (AHA)/American Stroke Association guidelines for the management of patients with PAD[19] and Trans-Atlantic Inter-Society Consensus Document and Management of Peripheral Arterial Disease (TASC) II recommendations,[5] consisted of antiplatelet therapy (100 mg/day aspirin or 75 mg/day clopidogrel), statin therapy, and antihypertensive treatment (ACE inhibitors, angiotensin II receptor blockers, and/or calcium channel blockers and/or beta-blockers).

Patients are randomly assigned by computer generation (http://ww.randomisation.com) to treatment groups, matched on age and type of revascularization procedure. Research staff recruiting or treating patients are not involved in data collection or analysis processes. Treatment allocation is fully concealed from all other researchers and participants. Unblinding will occur after statistical analyses.

Trial intervention. Macitentan therapy consists of a one-month treatment with 10 mg once daily administered orally. The initial dose is maintained after the first month if significant adverse events attributable to macitentan are ruled out. This full dose (10 mg/24 hours) is maintained for the following 2 months if liver function tests and blood cell count remain within the normal range. Patients are given analgesic treatment, if necessary. Ischemic lesions and necrotic ulcers are treated with standard daily care and antibiotic therapy as necessary. No special methods of treatment are used nor is absolute bed rest prescribed during the study.

Patient assessments and follow-up. At baseline, demographic information, medical history, vascular risk factors, complete medical examination, indication for surgery, hemodynamic test including ankle and toe blood pressures, site of revascularization, status of arterial outflow vessels, foot assessment using the Wound/Ischemia/Foot Infection scoring and classification system,[18] Quality of Life score using the European Quality of Life Five Level questionnaire and Short Form-12, FMAD changes, and laboratory assessments will be recorded.

FMAD change is used as a surrogate measure of endothelial function and performed according to the American College of Cardiology/AHA guidelines. Briefly, FMAD is determined after visualization of the brachial artery using high-resolution Doppler ultrasound (12 MHz linear array transducer; Philips, Eindhoven, the Netherlands) over the fold of the elbow in a longitudinal section, 60° transducer angle, with three measurements of the diameter between the intima–media interfaces. A pressure cuff above the transducer is inflated to 250 mmHg for 5 minutes, and the brachial artery diameter is measured again at 60 seconds after its release. FMAD (%) is calculated by subtracting the mean of the baseline diameter from the mean of the postischemia diameter, divided by the mean baseline diameter, and is expressed as percentage. The coefficient of variation for FMAD in our laboratory is 7.3% ± 5.1%, as described previously, meeting the standardized method and variability measurement values recommended by AHA/American College of Cardiology. FMAD is assessed according to a previously described technique,[20] in each patient before and after treatment with macitentan and at six months and one year after the end of treatment.

After randomization, treatment compliance, adverse events, concomitant medications, hepatic function, and hematology values will be monitored through the study. Patients will be assessed at the 1st, 3rd, 6th, and 12th month after revascularization procedure to record any symptoms or signs of limb ischemia. Revascularization patency is assessed by clinical examination and Doppler or duplex scanning, as well as by arteriography if indicated. Information is collected and will include the following data: limb salvage, clinical improvement, major and minor amputations, hemodynamic changes, FMAD changes, short- and long-term revascularization patency, the composite rate of major adverse CV event, quality of life, and adherence to trial medication.

Statistical analysis. Superiority tests will be conducted comparing macitentan with control groups in terms of primary and secondary end points. The null hypothesis is that the mean change in each variable from baseline to weeks 28 and 52 in the macitentan group equals that in the control group. Hypothesis testing of the treatment effect of macitentan on each study end point is based on two-sided 95% confidence intervals (CIs) using Student's *t*-distribution. Demographics/baseline data and end points/outcomes are presented as mean ± SD. Comparisons between groups are made using the Mann–Whitney test for independent variables.

Differences in the primary clinical outcome (amputation-free survival rate) will be assessed by comparing time from randomization to major (above ankle) limb amputation or death from any cause (whichever occurs first) between the two arms. Primary analysis will use Kaplan–Meier plots and test the difference between two arms using the log-rank test. Data will be censored when individuals reach the end of follow-up or are lost to follow-up before incurring the primary outcome.

Further analysis of the primary outcome will involve the fitting of flexible parametric survival models to estimate both relative and absolute differences in hazard of the primary outcome, to model the underlying differences in hazard and to allow for nonproportional hazards. The addition of covariates to the model, derived from the minimization variables (age, sex, and the presence or absence of chronic kidney disease, diabetes, and tissue loss) will allow baseline adjustments and the ability to test for further subgroup effects. The primary analysis will be performed on an intention-to-treat basis.

Secondary outcome measures that are based on continuous scales will be examined using a repeated-measures multilevel model to examine the effects over time. Treatment effects will be reported from these measures at 1 and 12 months from randomization and at the end of the study. Other outcomes will be measured using standard statistical methods, such as Fisher's exact test for categorical data and log-rank test for time-to-event data. All of these analyses will be performed using the intention-to-treat principle, with 95% CIs with associated *P*-values.

Sample size. Sample size allocation was calculated based on a time-to-event analysis, undertaken at the first year postrandomization. Recruitment is aiming to take place over one year. Allowing for a conservative estimate of 10% dropout rate for the primary outcome, a trial of 120 patients will have 90% power to detect a one-third reduction in amputation-free survival (hazard ratio [HR] 0.66) at a 5% significance level.

Pilot phase. Recruitment will be reviewed at the end of a six-month pilot phase. The following criteria are proposed to arrive at a decision to discontinue the trial at that stage:

Less than 20 patients randomized in total; and

Less than 90% of patients have received their allocated treatment.

At the end of the pilot phase, the completeness of the quality-of-life data will also be assessed.

Economic evaluation. The economic analysis will consist of two components: a "within-study" analysis, which will be based on study end points, and a "model-based" analysis, which will extrapolate and compare costs and effects likely to accrue beyond the study follow-up period. The analysis will be presented in terms of cost per additional quality-adjusted life year gained and cost per year of amputation-free survival. In line with existing recommendations, the base-case analysis will adopt a health care system (payer's) perspective.

Costs will be calculated on the basis of patient-level data related to (a) the treatment under assessment, (b) hospital stay and readmissions, and (c) postdischarge use of social services. Procedure-related costs will be estimated in a separate microcosting study. If plausible, additional analyses will be undertaken from a wider societal perspective. Quality of life will be derived from patients' responses to the EuroQol EQ-5D-5L[10] instrument. In addition to the trial-based evaluation, a model-based analysis will be conducted to consider the costs and benefits likely to accrue over a lifetime time horizon. Both deterministic and probabilistic sensitivity analyses will be undertaken to explore the robustness of the obtained results to sample variability and the plausible variations in key assumptions and used analytic methods.

Discussion

Current evidence on coadjuvant treatment for limb revascularization is scarce with very limited level Ia evidence from dedicated multicenter clinical trials.

Data from previous trials have shown that ET receptor antagonists such as bosentan are well tolerated and improve endothelial function, claudication distance, as well as inflammatory and hemodynamic parameters in patients with PAD.

The trial aims to be pragmatic and representative for real-world population management following limb revascularization in CLI secondary to atherosclerosis.

Even though some meta-analyses have demonstrated benefit for PAD patients in survival and in amputation, the level Ia evidence from clinical trials supporting any coadjuvant treatment after limb revascularization procedures other than antiplatelet therapy in order to improve patency and limb salvage rates is limited. However, theoretically there is room for

improvement in this field. A new pathway of treatment might have been opened with the use of ET receptor antagonists in these patients.

Author Contributions

Conceived and designed the experiments: IM, JDH, SB. Analyzed the data: IM, JDH, SB, IVL, JU, FA. Wrote the first draft of the manuscript: IM, JDH, SB. Contributed to the writing of the manuscript: IM, JDH, SB, IVL, JU, FA. Agree with manuscript results and conclusions: IM, JDH, SB, IVL, JU, FA. Jointly developed the structure and arguments for the paper: IM, JDH, SB, IVL, JU, FA. Made critical revisions and approved final version: IM, JDH, SB, IVL, JU, FA. All authors reviewed and approved of the final manuscript.

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