AUTOLOGOUS STEM CELL TREATMENT FOR CLI PATIENTS WITH NO REVASCULARIZATION OPTIONS: AN UPDATE OF THE HEMOSTEMIX ACP-01 TRIAL WITH 4.5 YEAR FOLLOWUP

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Introduction

- Patients with critical limb ischemia (CLI) face a high risk of amputation when revascularization options are exhausted.
- ACP-01 are autologous angiogenic stem cells derived from the patient's peripheral blood
  - Proprietary technology allows for the harvesting of peripheral blood only and then grown under specific conditions that promotes differentiation to angiogenic precursor cells
  - *In vitro* and *In vivo* models have demonstrated these cells can migrate through peripheral tissues and contribute to neovascularization and angiogenesis in ischemic tissues
- The Hemostemix Phase II trial is an ongoing international multicentre randomized double-blind placebo-controlled clinical study to assess the safety and efficacy of ACP-01 injected into the lower extremity of 95 CLI patients who have no revascularization options.
- We present the blinded long-term follow up of all concurrent patients enrolled at the first two clinical sites

Methods

- Blinded review of all patients entered in the Hemostemix Phase II trial with follow-up of at least 1 year. Study subjects were randomized 2:1 to direct injection into predefined areas in the lower extremity (Fig. 1) with autologous angiogenic precursor cells or placebo.
- Major trial inclusion criteria include:

  1) Subject is diagnosed with critical limb ischemia with one or more of the following hemodynamic indicators of severe peripheral arterial occlusive disease:
  a) Systolic ankle pressure less than 70 mmHg
  b) Toe systolic pressure 50 mmHg (or absent palpable pedal pulse)

  2) The subject is not a candidate for revascularization due to anatomical or physiological limitations
- Major exclusion criteria include uncorrected aortoiliac occlusive disease, very large or extensive wounds (>10cm^2), and wounds felt by the assessing surgeon to be more likely than not to require a major above ankle amputation within 4 weeks of enrollment
- Primary endpoints included: 1) Time to major amputation/mortality; 2) Primary safety endpoint
- Secondary endpoints included change in the following parameters during follow- up: 1) ABI/TBI; 2) Wound size; 3) Analgesia requirements; 4) Quality of life; 5) Ischemia-related hospitalizations

Methods

- All enrolled patients had 250 cc's of peripheral blood drawn and sent to the core laboratory for processing
- Central lab processes the cells of patients randomized to the treatment arm to produce >5 million ACPs and are sent back to participating centers for treatment
- The ACP are injected directly into the designated leg (see Fig. 1) and patients are followed up on post-treatment days 1, 2, 30, 90, 180, 270, 365 and annually thereafter

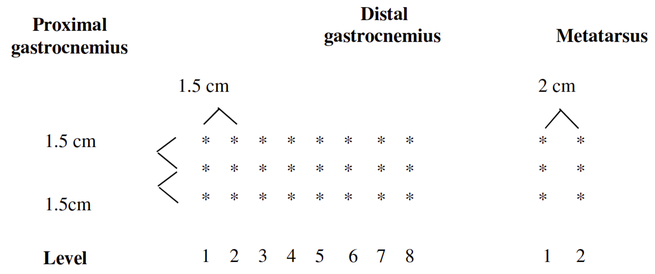
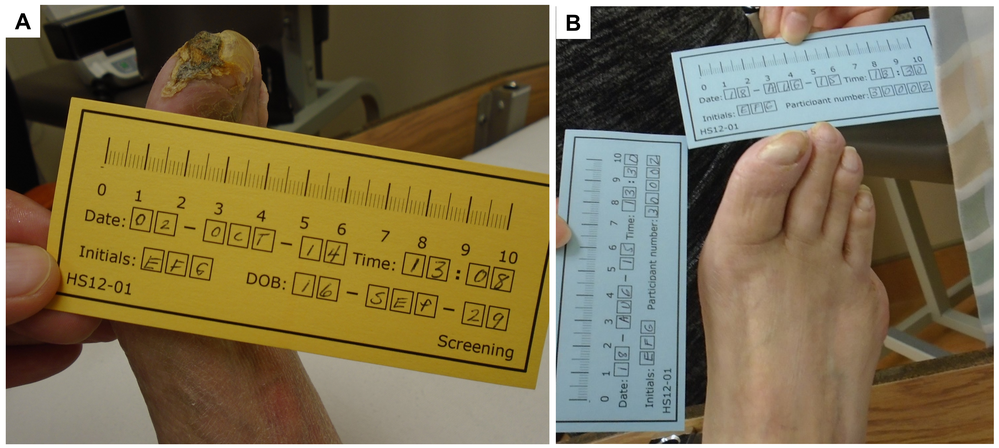


Fig. 1: Official schematic of injection sites for patients enrolled into both treatment and control arms. The patients have approximately 1 cc of cellular suspension or placebo saline injected directly into each of the labelled sites, with 24 in the leg and 6 in the foot. The injections on the gastrocnemius were performed with the patient in the lateral position directly into posterior leg, through the fascia into the belly of the gastrocnemius muscle. Injections were placed deep into the dorsum of the foot.

Results



- **Fig. 2:** Patient with ischemic ulceration to the right toe. The patient had intact circulation to the midcalf with no direct flow to the foot and occlusion of both the dorsalis pedis and posterior tibial arteries. They were deemed to have no revascularization options. **A)** Demonstrates dry wound involving the distal tip of D1 immediately prior to enrollment. **B)** The wound had successfully healed 4 weeks after treatment with no evidence of recurrence.

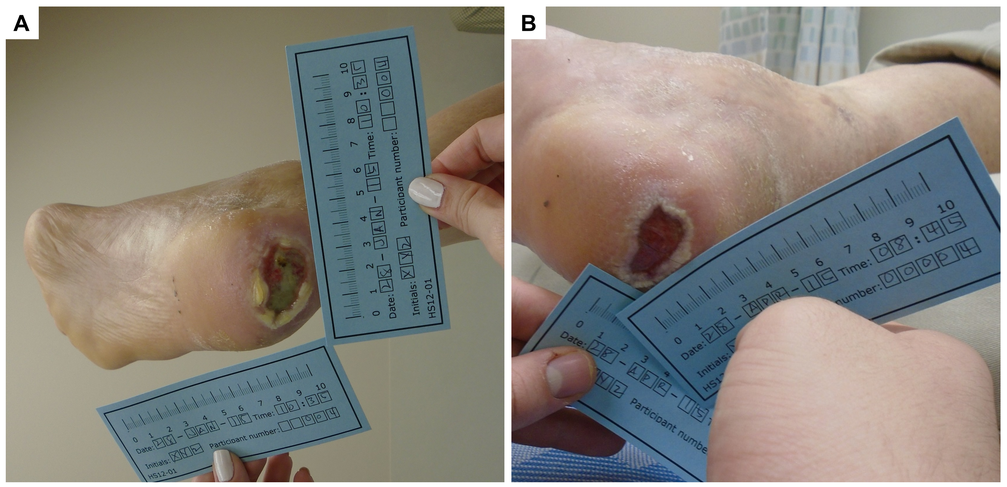


Fig. 3: Patient with large, nonhealing decubitus ulceration to heel of right foot. The patient had a history of 2 prior interventions including a failed femorotibial bypass graft with prosthetic. **A)** Demonstrates the ulcer at the time of enrollment with a large, mostly nonviable base. The patient had been offered below knee amputation for symptom palliation; **B)** 4 months post-treatment showing significant improvement. Concurrent treatment wearing an offloading orthotic and regular dressing changes

Results

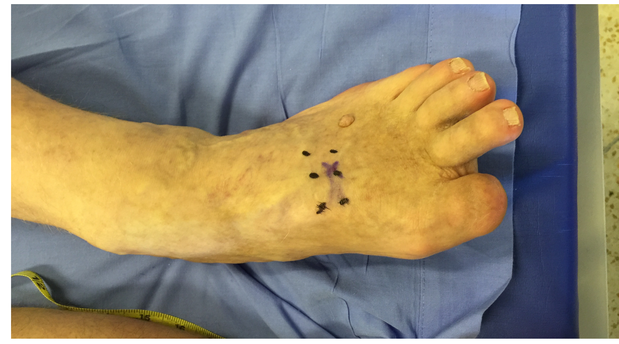


Fig. 4: Patient enrolled following a failure of a second femorotibial bypass. An initial vein bypass hat had remained patent for several years failed, with a redo composite vein graft failing soon after. The patient had no good outflow target and was deemed to have exhausted autogenous options. Ankle pressure was 22 mm Hg at enrollment and the patient had significant rest pain with no wounds. At follow-up at 90 days the rest pain had resolved.

- Twelve patients at 2 treatment centers with CLI and no interventional options were enrolled (10 male, 2 female, mean age 76 years).
- Prior to treatment with ACP-01 or placebo, 3 patients had ischemic rest pain, 8 patients had ulceration, and one patient had gangrene.
- Post treatment, one patient with unremitting rest pain and toe gangrene required a below knee amputation, and one patient with gangrene of the first to third toes required a forefoot amputation.
- Healing of ulcers and resolution of ischemic rest pain occurred in the other 10 (83%) patients.
- There were no clinically significant safety issues. Outcomes have been maintained for up to 4.5 years (3.5 years for 2 patients, 3 years for 1 and 1 patient died after ulcer healing secondary to congestive heart failure at 6 months).

Conclusion

- Preliminary results are promising with an acceptable safety profile and no ACP- related adverse events
- Early data indicate that many ischemic wounds can improve or even heal completely with diligent wound care, close follow-up and appropriate support
- Further investigation and prospective study is critical to better delineate accurate prognostication, to identify new treatment modalities and provide improved care to patients with ischemic wounds and exhausted or no conventional revascularization options