Spray-Applied Cell Therapy With Human Allogeneic Fibroblasts and Keratinocytes for the Treatment of Chronic Venous Leg ulcers: A Phase 2, Multicentre, Double-Blind, Randomised, Placebo-Controlled Trial

Kisner RS, Marston WA, Snyder RJ, et al. Lancet 2012;380:977-85.

Conclusion: Venous ulcers can be healed with a spray formulation of allogeneic neonatal keratinocytes and fibroblasts without the need for tissue engineering.

Summary: Venous insufficiency results from venous valve dysfunction or venous obstruction, or both, of the superficial or deep veins. Subsequent venous hypertension results in edema, tissue inflammation, and microcirculatory destruction. The end result can be a venous ulcer that can be notoriously difficult to heal, with many not responding to standard compression therapy. Surgery can result in reduced recurrence of venous ulceration, but no interventions on veins themselves have been shown to speed healing of chronic venous ulcers (Barwell JR, et al, Lancet 2004;363:1854-9). Nonsurgical therapies for venous ulceration have used tissue constructs of allogeneic adult keratinocytes. Such tissue constructs are fragile and have required incorporation of one or more dermis-like substitutes for delivery of the keratinocytes to the wound. In a large randomized controlled trial, repeated application of a tissue construct demonstrated an improvement in venous ulcer healing compared with standard compression therapy (Falanga V, Arch Dermatol 1998;134;293-300). However, allogeneic cells do not engraft. It is therefore unclear if an elaborate tissue construct is actually needed. HP802-247 is composed of cryopreserved allogeneic growth-arrested fibroblasts and keratinocytes derived from neonatal foreskin (Goedkoop R, Dermatol 2010;220:114-20). Success of foreskin-derived allogeneic keratinocytes in a two-component fibrin glue suggest that these cells can deliver essential growth factors to a nonhealing wound without the need for an elaborate tissue construct. In this study, the authors delivered growth-arrested allogeneic neonatal keratinocytes and fibroblasts to nonhealing venous ulcers using a spray, without an elaborate tissue construct. Outpatients from 28 centers in the United States and Canada with up to three ulcers, venous reflux confirmed by duplex ultrasound imaging and sufficient arterial flow for healing were randomized in a phase 2, double-blind, placebo-controlled trial. The study required that one ulcer measure between 2 and 12 cm in area and had persisted for 6 to 104 weeks. Randomization was by computer-generated block method in a 1:1:1:1:1 ratio to 5.0×10^5 cells/mL every 7 days or every 14 days, or 0.5×10^5 cells/mL every 7 days or every 14 days, or to vehicle alone every 7 days. All experimental groups received four-layer compression bandages. Trial monitors, trial sponsors, investigators, center personal, and patients were all masked to treatment allocation. The primary end point was the mean percentage change in wound area at the end of 12 weeks. Analysis was by intention to treat. There were 45 patients assigned to 5.0×10^5 cells/mL every 7 days, 44 patients to 5.0×10^5 cells/ mL every 14 days, 43 patients to 0.5×10^5 cells/mL every 7 days, 46 patients to 0.5×10^5 cells/mL every 14 days, and 50 patients to vehicle alone. There were 205 patients who completed all required study visits. Primary outcome analysis demonstrated greater mean reduction in wound area associated with active treatment compared with vehicle ($P = .0446$), with the dose of 0.5×10^5 cells/mL every 14 days showing the largest improvement compared with vehicle (15.98%, 95% confidence interval, 5.56-26.41; $P = .0028$). Adverse events were the same in all groups, with new skin ulcers and cellulitis occurring in >5% of patients.

Comment: This was a large well-conducted randomized trial suggesting benefit in healing of venous leg ulcers with a spray application of allogeneic cells. This study, combined with previous work, suggests allogeneic cell therapy for venous leg ulcers is likely to be effective. A larger study of the optimum dose of HP802-247 compared with standard therapy for venous leg ulcers seems indicated.

Systematic Review and Meta-Analysis of Vein Cuffs for Below-Knee Synthetic Bypass

Twine CP, Williams IM, Figelstone LJ. Br J Surg 2012;99:1195-202.

Conclusion: There is a small but significant benefit for vein cuffs in conjunction with synthetic grafts used for femoral to below-knee popliteal anastomoses. There is little benefit for more distal anastomoses.

Summary: The TransAtlantic Inter-Society Consensus (TASC) for the Management of Peripheral Arterial Disease guidelines advocate use of vein cuffs for bypass grafts of synthetic material to infrageniculate arteries. Evidence favoring use of vein cuffs for polytetrafluroethylene (PTFE) infrainguinal grafts comes primarily from case series. One randomized trial from the Joint Vascular Research Group did show a significant benefit in the favor of vein cuffs for below-knee bypasses (Stonebridge PA, et al, Vasc Surg 1997;26:543-50). However, a more contemporary randomized study, the Scandinavian Miller Cuff Study (SCAMICOS) showed no benefit for vein cuffs as adjuncts to below-knee synthetic grafts (SCAMICOS, Eur J Vasc Endovasc Surg 2010;39:747-54). There has also been a Cochrane Review on the use on vein cuffs, but it was performed without the SCAMICOS data (Cochrane Database Syst Rev 2010;CD001487). The authors note that a meta-analysis of all available data has not been performed on the use of vein cuffs to enhance patency of synthetic below-knee bypass grafts. They sought to combine the results of the two major randomized trials with pertinent cohort studies to provide the most complete estimate on the use of vein cuffs as adjuncts to synthetic grafts to below-knee arteries. The authors identified three cohort and two randomized studies for inclusion in their meta-analysis. This involved an analysis of data from 885 patients. That analysis was preformed according to recommendations of the Cochrane Collaboration, and the PRISMA guidelines (Liberati A, et al, PLoS Med 2009;6:e1000100; and Higgins JPT et al, Cochrane handbook for systematic reviews of interventions, version 5.0.2., Chicester: John Wiley & Sons; 2010). Non-randomized studies were included in the review if they had sufficient quality as assessed by the Newcastle-Ottawa scale. In this study, analysis was ultimately carried out on 483 patients with cuff grafts and 402 with no cuff. Analysis was divided into below-knee popliteal (377 cuffed, 279 uncuffed) and distal (106 cuffed, 123 uncuffed) grafts. Graft material was PTFE in all cases. Follow-up was limited to 3 years. Analysis for below-knee popliteal bypasses showed a significant improvement in primary patency for cuffed grafts at 2 years, but not at 1 or 3 years (odds ratio at 2 years, 0.46; 95% confidence interval, 0.22-0.97; $P = .04$). Limb salvage was significantly improved in cuffed grafts up to 2 years. For more distal grafts, cuffs did not provide any improvement in primary patency at any time interval. However, it did appear that limb salvage was improved for cuffed distal grafts at 2 years (odds ratio, 0.29; 95% confidence interval, 0.11-0.75; $P = .01$). There was no significant difference at any other time interval.

Comment: A reasonable conclusion from this study is that there is a small benefit for using vein cuffs as adjuncts to PTFE grafts to the below-knee popliteal artery. There is minimal to no benefit to the use of a vein cuff as an adjunct to a PTFE graft to a tibial vessel. However, it does not appear that a vein cuff, under any circumstances, worsens outcomes. Vein cuffs can be safely used at the discretion of the operating surgeon even for synthetic bypasses to tibial vessels.