Rationale and Trial Design of MesEnchymal Stem Cell Trial in Preventing Venous Stenosis of Hemodialysis Vascular Access Arteriovenous Fistula (MEST AVF Trial)

Ameet K. Piryani,1 Sreenivasulu Kilari,1 Edwin Takahashi,1 Randall R. DeMartino,2 Jay Mandrekar,3 Allan B. Dietz,4 and Sanjay Misra1,5

Key Points
- At 1 year after placement, 60% of hemodialysis arteriovenous fistulas (AVF) will develop venous neointimal hyperplasia (VNH) and subsequent venous stenosis (VS).
- Autologous adipose-derived mesenchymal stem cells may help reduce VS formation associated with hemodialysis AVF.
- There are no therapies available to prevent VS formation associated with hemodialysis AVF.

Abstract
Background Hemodialysis arteriovenous fistulas (AVFs) are the preferred vascular access for patients on hemodialysis. In the Hemodialysis Fistula Maturation Study, 44% of the patients achieved unassisted maturation of their fistula without needing an intervention. Venous neointimal hyperplasia (VNH) and subsequent venous stenosis are responsible for lack of maturation. There are no therapies that can prevent VNH/VS formation. The goal of this paper is to present the background, rationale, and trial design of an innovative phase 1/2 clinical study that is investigating the safety of autologous adipose-derived mesenchymal stem cells delivered locally to the adventitia of newly created upper extremity radiocephalic (RCF) or brachiocephalic fistula (BCF).

Methods The rationale and preclinical studies used to obtain a physician-sponsored investigational new drug trial are discussed. The trial design and end points are discussed.

Results This is an ongoing trial that will complete this year.

Conclusion This is a phase 1/2 single-center, randomized trial that will investigate the safety and efficacy of autologous AMSCs in promoting maturation in new upper-extremity AVFs.

Clinical Trial registration number: NCT02808208

Introduction There are >4 million patients worldwide who have ESKD, and the majority require hemodialysis for RRT (1). The National Kidney Foundation Kidney Dialysis Outcomes Dialysis Initiative guidelines recommend an autogenous arteriovenous fistula (AVF) be placed in patients as the preferred vascular access (2). Despite the better patency of AVF when compared with polytetrafluorethylene grafts, approximately 60% of AVFs fail to mature due to development of a venous stenosis (VS) because of neointimal hyperplasia (VNH) of the outflow vein (3). It is postulated that abnormal shear stress, hypoxic injury, inflammatory cytokines, matrix deposition, and other factors cause a cascade of events that result in VNH/VS formation (3). Multiple studies have focused on developing local therapies, such as gene therapies, recombinant elastase (PRT-201), biologic small molecule inhibitors, and stem cells to prevent VNH/VS formation (4–12). However, there are no therapies that can prevent AVF stenosis and reduce the need for costly invasive procedures, such as angioplasty, stents, and other therapies.

Previous work from our laboratory and others utilizing experimental animal models of pigs, rats, and mice has demonstrated a significant increase in the expression of proinflammatory cytokines, such as monocyte...
chemoattractant protein-1, C-X3-C motif chemokine receptor 1, TNF-α, and others, in the outflow veins of AVFs result in VNH/VS formation (13–19). The inflammatory process is thought to be one of the principle causes of VNH formation leading to access failure. However, biologic therapies, such as adipose-derived mesenchymal stem cells (MSCs), have not been tested clinically. MSCs have generated interest for their potential application of treating vascular injury (10,12).

Our laboratory has shown in a preclinical study using immunodeficient mice that topical administration of human adipose-derived MSCs to the adventitial surface of the outflow vein at the time of AVF creation attenuates the formation of VNH/VS, thereby improving AVF patency (12). We used these preclinical data to obtain approval from the Food and Drug Administration and Mayo Clinic Institutional Review Board to perform a phase 1 randomized clinical trial in patients with ESKD undergoing the placement of a newly created upper-extremity radiocephalic fistula (RCF) or brachiocephalic fistula (BCF).

The goal of this paper is to describe the trial design and discuss the rationale for the clinical trial. The primary objective of this phase 1/2 clinical trial was to assess the safety of autologous adipose derived MSCs for use in patients with ESKD undergoing the creation of a new upper-extremity hemodialysis AVF. The secondary objectives were to assess the treatment effect of adipose-derived MSCs on outflow vein remodeling, maturation, blood flow as assessed using serial ultrasound evaluation, patency, and reduction in the number of procedures needed to maintain vascular access patency.

Methods
We obtained funding from the Mayo Clinic Center for Regenerative Medicine and National Institutes of Health grants HL098967 and DK107870 to support the research and creation of this paper.

Institutional Review Board and Investigational New Drug Approval with clinicaltrials.gov Registration
We obtained approval to perform a phase 1/2 randomized clinical trial from the Food and Drug Administration in the form of an Investigational Drug Approval (IND16884) and Mayo Clinic Institutional Review Board approval (15–009053) in patients with ESKD undergoing the placement of a new upper-extremity RCF or BCF.

Trial Overview and Aim
This was a randomized phase 1/2 clinical trial in which patients were randomized to either autologous adipose-derived MSC treatment or no treatment at the time of surgical assessment for placement of an AVF. Figure 1 shows the overall study design.

Preoperative Vein Mapping
All patients underwent preoperative vein mapping before evaluation for surgical placement of hemodialysis AVF. The ultrasound was performed using a Sequoia ultrasound in the outpatient center in the Gonda building. The ultrasound department has been certified by the Intersocietal Commission for the Accreditation of Vascular Laboratories.

Ultrasound of the upper extremity was performed to assess for suitability of veins (cephalic and basilic) and arteries (radial and brachial) for surgical creation of an upper-extremity RCF or BCF (20). In general, by ultrasound vein mapping for the placement of an RCF, a diameter of the radial artery ≥2.5 mm and a cephalic vein diameter of ≥2.0 mm was required. For BCF placement, a brachial artery diameter of ≥3.0 mm was required with a cephalic vein diameter of >3.0 mm. After vein mapping, patients underwent assessment by a vascular or transplant surgeon for suitability of creation of an upper extremity surgical fistula. We had eight different transplant and vascular surgeons who place RCF or BCF participate in the trial.

Outcome Analysis
Patients returned for follow-up ultrasound after AVF creation at 1, 2, 3, 6, and 12 months. We assessed for the development of stenosis at the anastomosis, where cells were delivered compared with controls including outflow vein remodeling and blood flow. The primary and secondary end points of the trial are listed in Table 1.

Primary End Point
The primary end point was safety at 4-week follow-up on the basis of on infection, thrombosis, and patency of the

**Figure 1.** Trial design. AVF, arteriovenous fistulas; AMSC, adipose-derived mesenchymal stem cell.
Table 1. Inclusion and exclusion criteria

| Criteria |
|----------|
| **Inclusion criteria** |
| Patients who are predialysis or on dialysis |
| Age 18–85 years old |
| New planned BCF or RCF |
| Two stage fistulas not allowed |
| Life expectancy of ≥2 years |
| **Exclusion criteria** |
| Active infection |
| Central venous stenosis in the arm where the access is being planned |
| History of cancer with ongoing treatment |
| Participation in another study |
| BCF, brachiocephalic fistula; RCF, radiocephalic fistula. |

AVF. This was on the basis of clinical exam, complete metabolic panel test, and ultrasound evaluation.

Secondary End Points

The secondary end points for each group included assessment of primary and secondary patency of the AVF, number of interventions performed to maintain patency, time to maturation as assessed by ultrasound, and ultrasound assessment of diameter of outflow vein with blood flow.

Enrollment of Patients

**Inclusion Criteria**

The inclusion criteria for the study included patients aged 18–85 years, who were predialysis or dialysis dependent, requiring placement of a new upper-extremity brachiocephalic or RCF. We did not enroll patients requiring a brachiobasilic fistula. Patients in other investigational trials were not included (Table 2).

**Exclusion Criteria**

Patients were excluded if they had active infection or were being treated for cancer. In addition, we excluded patients who had central VS in the extremity where the access was being planned (Table 1).

Table 2. Primary and secondary end points

| End Points |
|-----------|
| **Primary** |
| Safety: Assessed on the basis of infection, thrombosis, patency at 30 days |
| **Secondary** |
| Kaplan–Meier estimate of primary patency, secondary patency |
| Number of interventions performed per group |
| Time to maturation as assessed by ultrasound |
| Ultrasound assessment of diameter of outflow vein and blood flow |

Informed Consent

Patients eligible for the study were asked to enroll. Informed written consent was received, and the risk and benefits of the trial were explained to them.

Randomization of Patients

Patients were randomized using block randomization with size of two to either autologous adipose-derived MSC or placebo with anatomic location of AVF (RCF or BCF), age (<65 years versus ≥65 years) and sex as stratification factors.

MSC Isolation from Fat

Patients in the adipose-derived MSC group underwent a subcutaneous procedure to obtain adipose tissue to isolate and culture MSC cells. The samples were taken from the right lower quadrant. Briefly, the procedure was performed steriley, and the skin was anesthetized with 1% lidocaine, followed by a small incision (approximately 1–2 inches) made to remove approximately 1–5 g of subcutaneous fat. The fat was used to isolate the MSCs. The incision was sutured.

Adipose MSC Isolation and Characterization

The fat-derived MSCs from patients were isolated and cultured by the Immune, Progenitor, and Cell Therapeutics Lab at the Mayo Clinic, as described previously (21). The MSCs are CD73 (+), CD90 (+), CD105 (+), CD44 (+), and HLA-ABC (+).

Surgical Creation of RCF or BCF AVF

The surgical fistula was created as described previously (2).

Surgical Creation of RCF or BCF AVF

After creating the fistula, the diameter of the outflow vein was measured (Figure 2). The dose of stem cells that was delivered was on the basis of the surface area of outflow vein using the formula: \( \pi \text{(diameter in cm)}^2 \times 500,000 \text{ cells per cm}^2 \). Stem cells in Lactated Ringer’s solution were dripped on the outside of the distal radial or brachial artery 1 cm proximal to the anastomosis. Table 3 shows the total amount of stem cells delivered on the basis of the different diameters of the cephalic vein. These data will be entered into a redcap database.

Follow-up

All patients will return for follow-up after their surgery. The schedule of events with the different evaluations are described at 7, 28 days, with ultrasound and laboratory values, with clinical examination at 1, 2, 3, 6, and 12 months (Table 4).

Ultrasound Assessment of AVF Maturation

For BCF, maturation was assessed by ultrasound (ultrasound) and defined as matured when the cephalic vein diameter ≥6 mm with the cephalic vein within 6 mm of the skin surface, and a blood flow ≥600 ml/min².

For RCFs, we defined matured by ultrasound of the cephalic vein diameter ≥4 mm of the cephalic vein within 4 mm of the skin surface, and a blood flow ≥500 ml/min (22).
Safety and Adverse Events

Patients will be evaluated for adverse events for 1 year after enrollment. The descriptions and grading scales are found in the revised National Cancer Institute Common Terminology Criteria for Adverse Events (CTCAE) version 4.0 and will be utilized for adverse event reporting. Each CTCAE term in the current version is a unique representation of a specific event used for medical documentation and scientific analysis and is a single MedDRA Lowest Level Term. Grade is an essential element of the guidelines and, in general, relates to severity for the purposes of regulatory reporting to National Cancer Institute. A copy of the CTCAE version 4.0 can be downloaded from the website: (https://evs.nci.nih.gov/ftp1/CTCAE/CTCAE_4.03/CTCAE_4.03_2010-06-14_QuickReference_8.5x11.pdf).

Statistical Analysis

Descriptive summaries will be reported as median (minimum, maximum). Comparisons between the groups (stem cell versus placebo) will be performed using Wilcoxon rank-sum tests for continuous variables and using Fisher’s exact test for categorical variables. Nonparametric tests will be used due to smaller sample size and non-normally distributed data. No adjustment for multiple comparisons will be done. Patency and maturation as time to event end points will be analyzed using Kaplan–Meier survival curve analysis approach and median time to event and interquartile range will be presented. All tests will be two sided and P values <0.05 will be considered statistically significant. Analysis will be performed using SAS software version 9.4 (SAS Inc., Cary, NC, USA).

Discussion

In 2017, there were approximately 750,000 US patients with ESKD who required chronic hemodialysis (23). The ESKD population will double in the next decade due to the increase in obesity and diabetes (23). Optimal hemodialysis and clearance of uremic toxins requires vascular access through an AVF. Approximately 40,000 AVFs are placed for hemodialysis in the United States annually (23). Approximately 60% of AVFs will fail due to VNH/VS. More than US$4 billion are spent annually to maintain the optimal function of AVFs (24). Unfortunately, there are no therapies that can prevent stenosis formation in hemodialysis AVFs.

Several factors have been hypothesized to cause VNH, including shear stress, inflammation, oxidative stress, hypoxic injury to the vessel wall, and mechanical injury after AVF placement (3,13,15,17,25–35). An ideal cellular therapy will be one that can be obtained in large numbers with anti-inflammatory and antiproliferative properties that can be used with manufactured with good manufacturing process for use in clinical trials. MSCs have been used to abrogate vascular injury. They have been isolated and expanded from several different sources, including bone marrow, adipose tissue (adipose-derived MSC), and cord blood (36). These cells have anti-inflammatory properties that can result in homeostasis, repair, and aid in regeneration in pathologic responses caused by vascular injury (37).

| Diameter of Cephalic Vein, cm | Total Number of Adipose-Derived Mesenchymal Stem Cells Delivered |
|-----------------------------|---------------------------------------------------------------|
| 0.3                         | 2,355,000                                                     |
| 0.4                         | 3,140,000                                                     |
| 0.5                         | 3,925,000                                                     |
| 0.6                         | 4,710,000                                                     |
| 0.7                         | 5,495,000                                                     |
| 0.8                         | 6,280,000                                                     |
| 0.9                         | 7,065,000                                                     |
| 1                           | 7,850,000                                                     |
other studies, investigators have demonstrated that MSC transplantation can reduce fibrosis in the heart, lung, liver, and kidney in experimental animal models (38–43). Along with having anti-inflammatory properties, MSCs can inhibit the proliferative effects of monocytes, tumor cells, and cardiac fibroblasts (44–47). Finally, MSCs have been shown to reduce hypoxic injury after myocardial infarction because they home to regions of hypoxia (48,49).

Previous studies have shown stem cells and progenitor cells can have beneficial effects on blood vessel remodeling and endothelial regeneration (50–52). Our laboratory reported that autologous late outgrowth endothelial cells delivered to the anastomosis after placement of a hemodialysis polytetrafluoroethylene grafts could reduce VS in a porcine model (9). We showed in cell culture that endothelial progenitor cells cocultured with fibroblasts reduced phenotypic conversion of fibroblasts to myofibroblasts under hypoxic injury (53). In a rat model, MSCs were shown to reduce carotid artery stenosis after arteriotomy (54). Furthermore, the luminal area in MSC-treated carotid arteries was 36% greater than in control arteries. Optimizing vascular healing and remodeling around the arteriovenous anastomosis after AVF creation is crucial to minimize stenosis formation, as justified by the fact that the juxta anastomotic is the most common location for AVF stenosis to occur (55). In addition, reduced late remodeling at the anastomosis due to changes in vessel wall shear stress may be influenced by MSCs (56,57).

Our laboratory has investigated the role of periadventitial xenotransplantation of 250,000 human adipose tissue-derived MSCs in an immunodeficient male mouse with carotid artery to jugular vein AVF has been shown to reduce expression of the Mcp-1 gene. This gene is involved in monocyte migration and lowering infiltration of CD68 (+) cells in the vessel wall (12). In addition, the mean lumen vessel area increased by 176% at day 7 and 415% by day 21, with a reduction in proliferation and smooth muscle cells. Moreover, 89Zr-labeled MSCs were tracked using positron emission tomography imaging and we observed that there was 89Zr activity for <3 weeks after delivery.

There are limited available data regarding the cell transplant in human AVFs. However, a prior study by Conte et al. investigated the use of allogeneic (human) endothelial cell implantation after dialysis access creation. Vascular intimal hyperplasia: Extending arterial and venous patency, limiting vascular trauma, and inhibiting hyperplasia while re-establishing vascular health (V-HEALTH) was a multicenter phase 1/2 trial assessing the safety of allogeneic endothelial cell implants (Vascugel) after the creation of arteriovenous access for hemodialysis use (58). In phase 2, 57 patients (30 AVG and 27 AVF) were enrolled and randomized in a 2:1 fashion to receive either Vascugel or control matrices (placebo) at surgery. The study met its primary end point of safety because there was no difference in early complication rates between the Vascugel and placebo groups at 4 weeks (11% versus 21% respectively). The adverse events observed were typical vascular access-related complications or comorbidities associated with the ESKD population. The secondary end point was efficacy and there were no statistically significant differences in patency between the intent to treat groups at 24 weeks; however, the trial may not have been adequately powered to demonstrate a statistical difference. The authors found no significant difference in unassisted or

| Table 4. Schedule of events |
|-----------------------------|
| **Study Activity** | **Screening (Visit 1)** | **Surgery (Visit 2)** | **7 Days (±2 Days)** | **4 Weeks (±5 Days)** | **8 Weeks (±7 Days)** | **3 Months (±14 Days)** | **6 Months (±14 Days)** | **12 Months (±14 Days)** | **Off Study** |
| Written informed consent | x | | | | | | | | |
| History: detailed or brief | x | x | x | x | x | x | | | |
| Physical exam (Ht, Wt, BSA, VS) | x | | | | | | | | |
| Blood collection for CBC/ CMP | x | | | | | | | | |
| Blood collection for inflammatory cytokines<sup>b</sup> | x | x | | | | | | | |
| Ultrasound: vessel measurements and flow | x | x | x | x | x | x | x | | |
| Outflow vein samples | | | | | | | | | x |
| Brief exam, vitals, and adverse event evaluation | | | | | | | | | |

Ht, height; Wt, weight; VS, venous stenosis; CBC, complete blood count; CMP, complete metabolic panel.

<sup>a</sup>Off-study evaluation/every dialysis visit.

<sup>b</sup>Inflammatory cytokines: Pro TNF-α, MCP-1, IL-1β; Anti IL-10.
assisted primary patency among AVFs or arteriovenous grafts when compared with a placebo cohort. This indicates that MSCs may have a more robust role in prolonging dialysis AVF durability compared with other cell therapies. This study will investigate the role of autologous adipose–derived MSCs in preventing venous neointimal hyperplasia and stenosis in porcine arteriovenous fistulas. *J Am Soc Nephrol* 32: 866–885, 2021

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