NEW INSIGNTS OF REGENERATIVE MEDICINES: HUMAN ACELLULAR VESSELS

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RECENT ADVANCES: HAV FOR HEMODIALYSIS

In this section we will give a short introduction to the recent advances in regenerative medicines, specifically the use of Human Acellular Vessels (HAV) as a bioengineered vascular conduit for kidney failure and chronic kidney disease (CKD) patients that need long-term dialysis. Also, we will give a brief overview of why HAV is a potential alternative over native AVF and synthetic AVG. Finally, presenting a new cohort study that supported the long-term use of HAVs for hemodialysis.

PROMISING RESULTS FOR VASCULAR INJURY AND CORONARY ARTERY BYPASS GRAFT

In this section, we will highlight HAV utilization in traumatic vascular injuries and coronary artery bypass graft (CABG), and explain the capability of HAV as a conduit for restoring vascular injuries. Finally, we will present an actual case scenario that showed the efficacy of using HAV for soldiers who suffered war injuries.

ADVANCED RENAL EDUCATION PROGRAM
Asia Pacific

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FRESENIUS MEDICAL CARE

RECENT ADVANCES: HAV FOR HEMODIALYSIS

Native arteriovenous fistula (AVF) is the favorite access for hemodialysis but may develop complications such as chronic venous hypertension, hemorrhage and long-waiting time while AVF is healing and maturing. Patients with kidney failure who are not candidates for AVF or whose fistulas have failed, rely on synthetic arteriovenous grafts (AVG) created from materials such as enlarged polytetrafluoroethylene (ePTFE). Primary unassisted patency in ePTFE grafts is lost in up to 75% of patients after one year, and long-term patency rates are around 27% after five years. Graft failure can force patients to rely on central venous catheters, which are associated with greater rates of infection, all-cause mortality, and cardiovascular events (1).

HAV may be a promising alternative for AVF and AVG. The recent cohort study of 11 patients reveals that its durability and low risk of infection has further supported the long-term use of HAVs for hemodialysis. Results have shown one patient maintained primary patency, and 10 maintained secondary patency at month 60. No HAV conduit infections were reported during the follow-up period from month 24 to month 60 (1).

Another significant observation from imaging of explants taken during this follow-up is that host cells continue to integrate over time during dialysis use. Not only did cells repopulate the HAV, but they also rebuilt it into vascularized adventitial and medial tissue layers. This suggests that the HAV evolves after implantation, taking on properties comparable to the patients' native blood arteries (Table 1) (1).

RESULTS	LOW INFECTION	DURABILITY	INTEGRATION OF HOST CELLS
HEMATOXYLIN AND EOSIN STAINING			Progressive re-population of the HAV with host cells after implantation
QUARTERLY SURVEYS	-No serious safety signals -No conduit infections during follow up, from 24 to 60 months		
IMAGING		Maintained structural integrity	Integration of host cells over time and re-populated HAV
EXPLANTED SAMPLES		-No vessel wall thinning, degradation, lymphocytic infiltration associated with immunological recognition -No multinucleated foreign body giant cells associated with a chronic host inflammatory response	
HISTOLOGICAL ANALYSIS			Remodeled the implant into vascularized adventitial and medial tissue layers.

Table 1: Evidence supporting the durability, low infection rate and the indication of integration of host cells in patients with implanted HAV. Adapted from EJVES vascular forum 2022; 54: 58–63.

PROMISING RESULTS FOR VASCULAR INJURY AND CABG

With the promising results of HAV in dialysis. Humacyte has conducted clinical trials for vascular injury and coronary artery bypass graft (CABG). Currently, HAV is being evaluated in two Phase 3 trials in arteriovenous access for hemodialysis, and HAV is also evaluated for vascular trauma in one Phase 2/3 trial (2).

TRAUMATIC VASCULAR INJURY

At the American Heart Association Scientific Sessions 2022 Meeting congress, Dr. Rasmussen reported that the incidence of vascular trauma increased by 5-fold over the past several decades due to wars, and surgeons are increasingly confronted with end-stage critical limb ischemia (CLI) with limited revascularization choices. A graft with long-term durability is essential for the younger generation of active-duty soldiers (2,3). The HAV has the potential to be used in the setting of trauma, a scenario associated with contaminated wounds, injury to autologous veins, and the need for quick reconstructive options (4).

HAV can be refrigerated and has an 18-month shelf life, allowing it to be used for definitive vascular repair within hours following injury and has shown utility across different anatomic regions with simple installation and infection resistance (3). Additionally, it eliminates the need for harvesting a vessel from a patient, and clinical evidence suggests that it is non-immunogenic and can become durable living tissue (5). Therefore, HAV may be a more permanent choice for limb salvage in both military and civilian vascular diseases. A case series study has further confirmed the benefits of HAV as resistance to infection, reliable patency, and provides surgeons with a rapid option when faced with complicated revascularization procedures (3).

THE SUCCESS OF HAV IN UKRAINE

Humacyte supported surgeons in areas of conflict in Ukraine and reported the effective use of HAV for treating soldiers with blast injuries successfully implanted HAV and have shown no sign of post-surgery complications (5).

At the 36th European Society for Vascular Surgery (ESVS) annual meeting, Dr. Shaprynskyi stated that “Access to the HAV, a biologic conduit, has improved our ability to perform vascular reconstructions by eliminating the need to harvest a venous conduit and saving time required to look for useable vein, assisting greatly in limb salvation.”

He continued, “Partnerships with groups like Humacyte allow us to overcome many limitations in wartime medical care that we previously experienced, such as lack of readily available conduits that are resistant to infection, particularly important in the contaminated battlefield setting.” (5).

CORONARY ARTERY BYPASS GRAFT (CABG)

CABG commonly use saphenous vein which has 10-25% failure rate at one year and a 40-50% failure rate at 10 years. Also, during the procedure it can be painful alongside other complications including persistent surgical site numbness, infection, swelling, and poor graft longevity requiring re-grafting procedures. Therefore, HAV can be used as an alternative to CABG (6).

At the American Heart Association Scientific Sessions 2022 Meeting, Dr. Kypson presented the Humacyte CABG program which is undergoing non-human primate trials which aim to assess HAV safety and advantages to support the first-in-human clinical study in the future (6). The pre-clinical study on baboons showed promising results such as maintenance of patency for up to 6 months with no evidence of dilatation. In addition, the HAVs were thoroughly recellularized and remodeled by host cells eventually resembling native blood vessel (7).

References:
1) Jakimowicz T. et al, *EJVES vascular forum* 2022; 54, 58–63; (2) Rasmussen, T.E. Humacyte 2022; https://investors.humacyte.com/news-releases/news-release-details/humacyte-announces-presentation-investigational-human-acellular ; [Accessed 12 January 2023]; (3) Lauria A. et al, *Annals of vascular surgery* 2022; 87, 100–112; (4) Lauria A. L. et al, *JAMA surgery* 2022; 157(8), 731–732; (5) https://evtoday.com/news/ukrainian-surgeons-present-experience-with-humacytes-human-acellular-vessel-to-treat-wartime-vascular-trauma; (6) Kypson A. P. Humacyte, Inc. 2022; https://humacyte.gcs-web.com/news-releases/news-release-details/humacyte-presents-six-month-human-acellular-vesseltm-havtm; [Accessed 12 January 2023]; (7) Williams A. R. et al, *Circulation Research* 2022; 146(Suppl_1), A10957-A10957.