American Journal of Transplantation 2011; 11: 13–17
Wiley Periodicals Inc.

Special article

doi: 10.1111/j.1600-6143.2010.03374.x

Implementation of Vascularized Composite Allografts in the United States: Recommendations From the ASTS VCA *Ad Hoc* Committee and the Executive Committee

L. Cendales[a], D. Granger[b], M. Henry[c], J. Jones[d], A. Langnas[e], D. Levi[f], J. Magee[g], R. Merion[h], K. Olthoff[i], T. Pruett[j], J. Roberts[k] and M. Abecassis[l]

[a] *Emory Transplant Center, Emory University, Atlanta, GA*
[b] *Transplant Surgery, St John Hospital and Medical Center, Detroit, MI*
[c] *Division of Transplantation, The Ohio State University Medical Center, Columbus, OH*
[d] *Transplant Surgery, Blue Ridge Surgical Associates, Johnson City, TN*
[e] *Section of Transplantation, University of Nebraska, Omaha, NE*
[f] *Miami Transplant Institute, University of Miami, Miami, FL*
[g] *Department of Surgery and* [h] *Division of Transplantation, University of Michigan, Ann Arbor, MI*
[i] *Department of Surgery, University of Pennsylvania Hospital, Philadelphia, PA*
[j] *Division of Transplantation, University of Minnesota, MN*
[k] *Division of Transplantation, University of California-San Francisco, San Francisco, CA*
[l] *Division of Transplantation, Northwestern University, Chicago, IL*
Corresponding author: Linda C. Cendales, lcendal@emory.edu

Like all other areas of transplantation, vascularized composite allografts (VCA) has the capacity to transform the lives of patients, for the better or for the worse. It is this duality that mandates VCA be performed in centers prepared for the intricacies accompanying other transplant procedures. Similarly, the complexities of VCA require that the procedures be driven by surgeons and physicians with experience in the multidisciplinary management of immunocompromised postsurgical patients. Furthermore, the grafts should be considered as organs rather than tissues from a regulatory and a biological standpoint. The ASTS supports the field of VCA and has demonstrated its support and leadership by actively formulating a strategy for its systematic development. The goal of this document is to provide a framework for the prospective, thoughtful realization of VCA in the United States from the American Society of Transplant Surgeons (ASTS) perspective.

Key words: Composite allograft, composite tissue, composite tissue program, donor, oversight, reconstructive transplantation, regulations

Abbreviations: ABO, Blood types A, B and O; ASTS: American Society of Transplant Surgeons; CMS, Centers for Medicare and Medicaid Services; FDA, Food and Drug Administration; HLA, Human Leukocyte Antigen; HRSA, Health Resources and Services Administration; NOTA, National Organ Transplant Act; OPO, Organ Procurement Organization; OPTN, Organ Procurement and Transplantation Network; SRTR, Scientific Registry of Transplant Recipients; VCA, Vascularized Composite Allotransplantation.

Received 29 June 2010, revised 12 October 2010 and accepted for publication 06 November 2010

Introduction

Vascularized composite allografts (VCA) (a.k.a. composite tissue allotransplantation) has been introduced as an option for limb replacement and reconstruction of major tissue defects. VCA refers to the transplantation of nonautologous tissues (i.e. skin, muscle, tendon, nerve and bone) as a functional unit to reconstruct defects that cannot be reconstructed with autologous tissues. To date, over 70 patients have received a VCA worldwide (1). At the time of this submission 10 patients have received hand(s) and 2 have received face transplants in the United States. To the best of our knowledge, US programs have performed VCA under the infrastructure delineated in this document (2,3).

Like other transplants, VCA has the capacity to transform the lives of patients, for the better and for the worse. It is this duality that mandates that VCA be performed at centers capable of appropriately responding to the inevitable contingencies that have been described in organ transplantation. Centers moving forward with VCA should demonstrate the same depth and breadth of services currently mandated by the Transplant Final Rule for solid organ

transplantation (4). The ASTS believes that creating standards for VCA under the definition of Organs under the Final Rule and under the definition of Human Organs under Section 301 of NOTA will provide the necessary framework to promote the highest quality practice with consistency, safety and professionalism. Additionally, it would provide assurance that all centers performing these transplants follow similar governs. The ASTS recognizes the need of outlining considerations for the wide and safe implementation of VCA. As such, the goal of this document is to propose a structured framework for the development of a prospective thoughtful realization of VCA in the United States.

Background

On May 1, 2008 the ASTS responded to the Request for Information put forward by the Health Resources and Services Administration on the March 3, 2008 Federal Register regarding VCAs (5). The ASTS supported the inclusion of VCAs within the definition of organs recovered by regulations governing the Organ Procurement and Transplantation Network (OPTN) and supported adding VCA to the definition of human organs recovered by the National Organ Transplant Act. Due to the fact that recovery of VCAs from deceased donors entail direct interaction with Organ Procurement Organizations (OPOs) in connection with recovery of solid organs, the ASTS strongly believes it is appropriate that the OPTN's regulatory oversight be extended to VCAs. This stems from the recognition that as VCA transplantation expands, it will be necessary to have a standard assessment of the safety and quality of the graft. Additionally, an acceptable algorithm for determining the process of recovery of VCAs from deceased donors must be coordinated with teams obtaining other organs for transplantation. The ASTS also identifies other advantages; it would provide assurance that all centers performing these transplants follow similar governs. Additionally, the relationships with the OPO's would be facilitated, donors could be considered over a wide geographic area, it would be helpful when questions in the government or the public arise, and it would facilitate acceptance from the public for donation of VCAs. VCAs share characteristics and present differences compared to conventional organ transplants. Similarities include that all (1) involve vascularized allografts, (2) are recovered from a human donor as an anatomical/structural unit, (3) are transplanted into a human recipient as an anatomical/functional unit, (4) are minimally manipulated, as defined by the FDA in Title 21 CFR 1271.3, (5) are not combined with another article such as a device, (6) are used fresh and not cryopreserved, (7) are susceptible to ischemia and therefore not stored temporarily or for a long term—for example, not more than 36 h and (8) are susceptible to allograft rejection thus requiring the recipient to take immunosuppression. VCA differs from most conventional organ transplants in that the grafts, (i) are transplanted to enhance quality of life, (ii) are external and visible, and have the potential of being identifiable after donation, (iii) require nerve function and (iv) include tissues from three germ layers.

Program Organization

Since its beginning, clinical transplantation has grown in close association with research. Today, transplantation continues being a unique setting to study immunology, and transplant-related applications to improve patient care. As with other transplants, VCA has its unique challenges and considerations. Thus, the following draft provides a proposal for a VCA program in the United States with special reference to the research nature of the field at this time.

General Program Organization

A VCA program from its inception should target an interdisciplinary approach conducted within a UNOS/OPTN approved Transplant Center with laboratory, clinical and human resources dedicated to this effort both physically and administratively. Integration between clinical care and research is ideal. The interdisciplinary team should include surgical and medical physicians (reconstructive surgeon, transplant surgeon and medical transplant physician), nurse coordinator, pathologist, pharmacologist, mental health provider, rehabilitation medicine, tissue typing specialists, data entry personnel, infectious disease specialist, social worker and basic laboratory personnel. Regular meetings should include planning and budgetary matters. In addition, patient selection, posttransplant follow-up, morbidity and mortality and scientific studies should be conducted such that the team is integrated into patient care and program development. A computer database should be used for patient and protocol data management.

Screening and Consenting Procedures

Given the investigational nature of the field, all VCA programs should be subject to institutional regulations for the conduct of human research and all patients should be enrolled in Institutional Review Board approved protocols. As such, every patient should undergo a research consenting process. Due to the innovative nature of the procedure, candidates may demonstrate enthusiasm to take the risk of receiving a VCA to improve their quality of life but would not be suitable candidates for the procedure. Alternatively, candidates may be medically appropriate but lack evidence of compliance, social support or a thorough follow-up commitment. Thus, the importance of patient selection and a multidisciplinary evaluation process cannot be overemphasized. Patient recruitment should be initiated with education about research and standard of care/nonresearch options, research patient responsibilities and an information package should be provided to the candidates.

Information in the package should include up to date national and international outcomes and statistics in VCA, standard of care options such as prosthesis, reconstruction with autologous-tissue, rehabilitation, immunosuppressive medications and their complications and an overview of the transplant process. All patients should be made aware of the concept of nonobligating participation and be given sufficient time to think about their research participation.

Organ Procurement Organization

A required and invaluable component for the success of VCA both in terms of development and clinical results is the participation and expertise of the OPO community. With the assistance of the VCA transplant center, the OPO should develop standardized policies and procedures for the evaluation of the potential VCA donor, informed consent for VCA donation, donor management and graft procurement. Procurement procedures for VCA grafts should be integrated into the multiorgan procurement process without jeopardizing other organs potentially being procured for transplant. In addition to the knowledge that their involvement will help the development of VCA and potentially improve the lives of our patients, participating OPO's should be rewarded for their service. The VCA should be considered an additional organ procured and thus count toward the OPO's yield (organs per donor). Also, graft-specific acquisition costs should be determined and the OPO should be fully reimbursed for their expenses and efforts.

Evaluation and Listing

All patients should undergo an extensive and thorough medical, social and psychological evaluation process. These include one-on-one teaching sessions to cover specific terminology and general transplant information. In addition to the medical evaluation, all patients should undergo psychosocial appraisals after the informed consent has been signed. The purpose is multidimensional with specific focus on the candidate's suitability for the protocol. Special consideration to the receipt and potentially loss of a visible transplant should be carefully examined. Essentially all recipients have experienced rejection episodes and the current rejection rate of 85% within the first year should be addressed (6). Psychological support should be available at all times and alternatives to failure such as returning to a prosthetic device after hand transplantation or death after a face transplant should be well outlined.

Funding is mainly from federal sponsors. As a research field, of importance is to examine financial susceptibilities and assure resources to warranty quality of care. A well-delineated plan should be in place for protocol-related expenses and the patient's responsibilities for the other costs. The candidate must be aware about the need of medication and regular medical care for as long as he/she has the transplant. Social work assessment and involvement in ongoing bases is an essential aspect of the process.

After the evaluation is completed, each case should be reviewed in a multidisciplinary format. The requirements for listing a patient should be similar to those for other transplant candidates. This includes documentation of an evaluation by a transplant physician and surgeon, a reconstructive surgeon, a social worker, financial clearance, two separate blood-type determinations, approval for listing by the transplant team's multidisciplinary 'listing committee', and completion of all Centers for Medicare and Medicaid Services (CMS) documentation requirements. If the candidate is approved to move forward with the transplant, the OPO should be notified. Thereafter, the transplant coordinator should maintain the listing requirements on site. Periodic reevaluations should be required to maintain medical fitness and to keep the candidates aware of the field and protocol/outcomes development.

Criteria for VCA Transplant Members

Each program should be under the leadership of a Program Director. Given the diverse surgical requirements for VCA, the Program Director need not be the primary operating surgeon, but rather should have expertise in the aggregate application of VCAs. In addition, the VCA program should identify a qualified primary surgeon with expertise in microsurgical reconstruction, prior experience in VCA, or in lieu of actual VCA experience, extensive experience in the applicable reconstructive procedure as required (e.g. hand replantation and facial reconstruction).

The Surgical Director and the Primary and Recovery Surgeon should have a current US medical license and be credentialed to practice at the OPTN member transplant center hospital.

An immunosuppression team should support the surgical team, both of who should perform posttransplant follow-up. Transplant immunology and immunosuppression expertise should reside in at least one team member, ideally the Program Director. This will be evidenced by completion of an approved transplant fellowship in a medical or surgical specialty and current qualifications as a transplant physician or surgeon by UNOS criteria. Evidence of cooperative planning and posttransplant care for the patients from the team members cannot be overemphasized.

Policies need to be in place at the transplant hospital to incorporate the new program into the existing safety policies. The specific policies dealing with donor and recipient blood types A, B and O, HLA, cross-match identification and compatibility, the organ/tissue chain of custody, identification and subsequent disposal also need to be covered

as does the identification and disposition of the vessels that may accompany the VCA.

Procurement

Each program should work closely with the respective OPO. Planning meetings with members of the organization should be scheduled to coordinate the logistical and administrative aspects of the process.

Given the unique and novel components of VCA, OPOs should have a trained designated requestor for VCA. Policies should be in place for vascularized tissue recovery and transport along with a confirmation of the qualifications of the recovery surgeon. At this point, a memorandum of understanding describing the bilateral agreement between the transplant center and the OPO or some similar explicit document should be in force to provide the necessary framework to establish a common line of action with respect to VCA. In-services should be developed by the VCA team to provide information about donor and recipient screenings, selection criteria, order of the VCA procurement and the consenting process. The OPO should have an identified person for communication of donor cultures or pathology results. All appropriate behavioral and safety policies for organ recovery shall apply to VCA recovery. The use of anatomically appropriate prosthetics for use on the deceased postprocurement should be available and offered to the consenting family member. Periodic reevaluation of the process is recommended.

Donor Selection Criteria

OPTN/UNOS approved criteria should be developed for all VCA donors and the screening guidelines should include parameters developed for other organ transplants (7). Donor criteria and donor–recipient matching parameters should include ABO type, and size compatibility with the recipient. Pending the addition of the specifics for the different tissue risks infections, matching of infectious risks should follow those established for organ transplantation (7). Traumatic injuries will be critical information for VCA donor acceptance and allocation. Consideration regarding distance between the donor hospital and the transplant center are important as this related to ischemic time. At this time, exclusion of children—defined by radiographic evidence of growth plate nonfusion—as VCA donors is recommended due to limited systematic data in VCA. However, as the field develops the inclusion of children will require following established considerations for pediatric donors in other organs with additional VCA-specific factors.

Listing criteria should also comprise amount and type of tissue to be included. It is anticipated that organ offers will follow the similar processes as other organ allocation.

Expanded donor criteria remain undefined. Arthritis, prior musculoskeletal surgeries, skin cancer excision and prior facial procedures should be considered.

Due to the uniqueness of VCA, involvement of the transplant team is necessary from the early planning stages. These include, but are not be limited to, dry runs of the procurement in a laboratory, pretransplant strategy sessions to deal with public relations matters such as protection of donor confidentiality, society and public education and participation of prosthetists for deceased donor reconstruction.

Consent for Donation

The informed consent process should reflect the research nature of the field. As for other organs procured for transplantation, consent should be obtained from the appropriate family member or designated surrogate by qualified OPO personnel. As with other organs, there should be neither financial benefit nor added expense for the donor family. The process should be organ specific and purpose specific; general consent for donation of everything that can utilize is insufficient. It should be clearly presented that VCA grafts are considered 'organs' for clinical transplantation under a research protocol.

Proper informed consent requires a discussion of the procurement procedure, the potential benefits, risks and alternatives for the recipient and the impact on the deceased donor. Specifically, the person providing consent should understand how the appearance of the donor will be altered by the procurement procedure and if, how, and to what degree that appearance will be restored.

Theoretical Donor Allocation

In solid organ transplantation, the relative shortage of donors compared to candidates has led to the need to develop allocation policies. While the numbers of potential candidates for VCA is small initially, we believe specific allocation policies should be developed prospectively. Such policies are necessary to operationalize VCA nationally given the number for OPO's and centers. Additionally, established allocation policies promote transparency of processes for all involved, including the public. Common frameworks for organ allocation are based on principles including Equity, Utility, Urgency and Benefit. Given the nature of VCA, it is unlikely that measures of urgency and benefit will provide a sufficiently robust framework for allocation. Consequently, components of equity (e.g. waiting time) and utility (e.g. matching for form and function) are likely to predominate any VCA allocation system. Consistent with the previous recommendations, we believe any allocation system should be developed within the preexisting structure provided within the OPTN.

Transplantation

The technical aspects involved to transplant different tissues have rapidly evolved and are standard. Close monitoring of both the reconstructive and immunological aspects are required. During the postoperative phase, rounds should be conducted by the interdisciplinary team and a thorough review of the condition of the transplant and medication and doses should be recorded. Priority should be placed on the patient's education, identification of visible changes in the skin, therapy and postoperative recovery. A staff member should be available for the instruction of the patients regarding the follow-up appointment, timing and dosing of medications. Each patient should undergo education by a pharmacist.

Rehabilitation medicine should work in close communication with the primary surgeon before and after surgery. Therapy should be performed according to the VCA needs. The therapists should participate in the preoperative evaluation and continue functional progress, needs and modify/advance therapy following each patient's progress according to the reconstruction.

Evidence-Based Evaluation of VCA

Organ transplantation has benefited from the systematic collection of data and rigorous analysis. The NOTA specifically mandated such a process. In context of VCA, a similar registry should be developed to collect specific data so that the state of the art can be shared within those working or approaching VCA. VCA should be included in the US national database of statistics related to solid organ transplantation. The Scientific Registry of Transplant Recipients (SRTR) 'covers the full range of transplant activity, from organ donation and waiting list candidates to transplant recipients and survival statistics' (8). As such, VCA should be included within the scope of work of the SRTR.

Conclusion

It is acknowledged that VCA is in its initial experimental stages. Nonetheless, VCA has reached a phase where clinical development is clearly appropriate and cost effectiveness analyses are taking place. ASTS would like VCA to develop in a scholarly, evidence-based fashion. Most importantly, the field should advance focused on the care for donors, donor families and recipients, and in doing so insure the best outcomes for VCA recipients both present and future.

Acknowledgments

The authors are appreciative to Dr. David Reich for his insightful comments. The authors are thankful to the thoughtful discussions with the ASTS Council. The authors are grateful of Katrina Crist, MBA, ASTS Executive Director, Chantay Parks, ASTS Communications Director and the ASTS staff for the invaluable support and leadership. The members of the ASTS VCA *Ad Hoc* Committee are Linda Cendales, Darla Granger, Jon Jones, John Magee, Timothy Pruett, Douglas Tadaki, David Levi and Suzanne Ildstad.

Disclosure

The authors of this manuscript have no conflicts of interest to disclose as described by the *American Journal of Transplantation*.

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