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REVIEW

Regulatory oversight in the United States of vascularized composite allografts

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SUMMARY

Vascularized composite allograft (VCA) transplantation is a medically acceptable treatment for the reconstruction of major tissue loss. The advent of VCA transplantation has spurred regulatory and policy development in the United States to address the multiple clinical, ethical and legal issues that must be considered for the practice of VCA donation and transplantation to develop within the existing framework of public trust and transparency vital to the success of donation and transplantation.

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Introduction

Vascularized composite allograft (VCA) transplantation has become a recognized treatment option for the reconstruction of major tissue loss. VCA transplantation refers to a nonautologous transplant of tissues that may include skin, muscle, nerve, bone, cartilage and vessels as a functional unit to replace anatomical defects that cannot be reconstructed with autologous tissue [1]. Through the end of 2013, more than 150 patients worldwide had received VCA transplants including face, hand, laryngeal and uterine and abdominal wall [2]. Although what constitutes medical success in the context of VCA transplants is not yet well defined, the initial clinical achievement of VCA transplantation surgery led to the expansion of potential indications for VCA and significantly more widespread application within the United States. There are many distinct differences between types of VCAs some of which are constructive such as double hand or arm transplants and others restore function but are nonreconstructive such as uterus transplantation. Although each type of VCA presents unique clinical aspects including anticipated risks and benefits to potential transplant recipients, they share a common definition: transplantation of a vascularized multitissue graft.

Regulatory implications of VCA transplantation initially unclear

While the demand for VCA transplantation and the number of VCA programs began to increase, there was growing recognition that the lack of regulatory clarity in the United States created challenges and uncertainty for the emerging field [3]. VCAs combine elements of both organ and tissue donation and transplantation, each of which is separately regulated in the United States. As a result, VCAs did not fit squarely under the existing U.S. regulatory frameworks. VCAs were not included in the definition of "organs" as defined and regulated under the National Organ Transplant Act (NOTA) [4] and the Organ Procurement and Transplant Network (OPTN) Final Rule [5]. Prior to 2013, the legal definition of "organs" under NOTA for purposes of regulatory purview under the OPTN included heart, lungs, liver, kidneys, pancreas, small intestine, and islet cells. The donation and transplantation of VCAs without clear regulatory

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oversight inevitably led to variable clinical practices with potential impact on patient safety (e.g., lack of requirements for verifying ABO blood type compatibility). There was also concern that the lack of regulatory oversight could eventually lead to inconsistent allocation that could undermine public trust [3].

Recognizing the risks of this uncertainty, the U.S. Department of Health and Human Services/Health Resources and Services Administration (DHHS/HRSA) issued a Request for Information in the Federal Register in March 2008 soliciting stakeholders of their opinion as to whether VCAs should be included within the definition of organs covered by the OPTN final rule [6]. A public hearing was held shortly thereafter, and written comments were accepted through July 2, 2008. The American Society of Transplant Surgeons strongly supported oversight of VCAs through the OPTN and subsequently published its recommendations [7].

During the interim period, in the absence of national standards, VCA transplant programs within the United States began working with their local Organ Procurement Organization (OPO) to coordinate the identification of VCA donors and the actual recovery process. In general, OPOs and transplant centers followed the OPTN standards when possible even though they did not technically apply. The three VCA transplant programs in Boston, for example, collaborated with the local OPO, New England Organ Bank to establish protocols regarding: (i) appropriate VCA deceased donor and recipient consent; (ii) the medical suitability of potential VCA donors; (iii) maintenance of a VCA candidate waitlist; (iv) donor recipient matching by biological compatibility (HLA and ABO blood type) and other criteria such as gender and skin tone; and (v) the oversight of the donor recovery procedures necessary for the transplantation to be performed almost immediately after recovery of a VCA graft.

In December 2011, DHHS published a Notice of Proposed Rulemaking [8] to designate VCAs as "organs" and subsequently in July 2013, DHHS took final action to establish OPTN oversight of the donation and transplantation of VCAs to go into effect a year later on July 3, 2014 [9]. Defining VCAs required significant work given the variation between specific types and the need from a policy perspective to avoid triggering other types of transplanted devices or biologics already highly regulated by the FDA. Ultimately, the regulatory definition includes the following nine factor criteria [9]:

1. Vascularized and requires blood flow by surgical connection of blood vessels to function after transplantation;
2. Containing multiple tissue types;
3. Recovered from a human donor as an anatomical/structural unit;
4. Transplanted into a human recipient as an anatomical/structural unit;
5. Minimally manipulated (i.e., processing that does not alter the original relevant characteristics of the organ relating to the organ's utility for reconstruction, repair, or replacement);
6. For homologous use (the replacement or supplementation of a recipient's organ with an organ that performs the same basic function or functions in the recipient as in the donor);
7. Not combined with another article such as a device;
8. Susceptible to ischemia and, therefore, only stored temporarily and not cryopreserved; and
9. Susceptible to allograft rejection, generally requiring immunosuppression that may increase infectious disease risk to the recipient.

This regulatory action led to a series of steps for implementation including creation of a VCA Committee within the OPTN oversight structure, development of guidance documents, and interim policy requirements.

Current regulation of VCA donation and transplantation in the United States

To meet the effective implementation date of designating VCAs as organs, the OPTN quickly established a VCA Committee to begin the process of policy development. The initial priority was to establish basic requirements that could serve as interim rules pending the full policy development process that would require more time given public comment periods and other requirements. In June 2014, the OPTN/UNOS Board of Directors unanimously approved the first set of national policies and standards for VCA transplantation in the Unites States. These interim policies went into effect for 15 months to provide for public comment and further refinement. Most recently at the June 2015 OPTN/UNOS Board of Directors meeting, final bylaw provisions and policies on VCA were finalized and approved [10]. Because the federal regulations and OPTN/UNOS policies have been in place for such a short period of time, it is premature to determine the benefits and challenges, but there are several aspects including program requirements, donor authorization, allocation, and living donation of critical importance to the future development of VCA transplantation.

VCA program requirements

One key component to the new regulatory framework in the Unites States was to establish the requirements for VCA programs. Recognizing that the surgeons developing VCA programs were not necessarily from the discipline of organ transplantation but also from the field of reconstructive microsurgery, there was a recognized need to define basic program requirements and team expertise (including reconstructive surgeon as well as transplant surgeon or physician). The decision to require UNOS/OPTN membership was critical to effective oversight because by requiring membership, VCA transplant programs are subject to continuous outcome review, audit, and possible discipline for OPTN/UNOS policy violations. The current policy provides that a VCA program must specify and be approved for the type of VCAs it will transplant. Other programmatic requirements were also established [10]. As of July 3, 2015, 49 specific VCA transplantation programs had been approved (at 22 different transplant centers); nine candidates were waiting for VCA transplants, and seven VCAs had been allocated through the OPTN [11].

Donor authorization

While transplantation is regulated at a federal level in the United States, the laws governing deceased organ donation exist at the state level codified through the Uniform Anatomical Gift Act (UAGA) [12]. The UAGA sets the legal requirements for the donation and use of any gifted "anatomical part" which could include the donation of VCAs from a decedent [3]. The question that required policy attention was not therefore the legal mechanics of how donor authorization of how VCA donation could proceed. Rather, the issue for consideration was whether registering as a donor—which under U.S. law is legally valid authorization for deceased donation that next of kin cannot override—should as a matter of policy be considered to include VCA donation. The opinion of the professionals in the field at the time the interim policies were under development recognized that the U.S. public does not reasonably expect to become a VCA donor when registering as an "organ donor" as part of the driving licensure process. With over 125 million registered organ donors in the United States [13], there was consensus that the priority must be to maintain the public trust in the donor registries and therefore require specific permission for VCA donation [14]. The UNOS policy requires that permission be granted specifically for VCA donation rather than the general statement authorizing "organ donation." The expectation (and experience to date) is that the requirement of specific authorization for VCA donation is obtained from next of kin at the time of VCA donation. Importantly, however, this policy leaves open the future possibility that a potential donor specifically authorized VCA donation prior to death (by specifying the gift of a VCA in an advanced directive, donor registry, or other document of gift).

Allocation

There are two primary ethical principles of allocation under the U.S. statutory and regulatory scheme—utility and justice [15]. For all organ transplants, utility refers to the maximization of transplant benefit by optimizing outcomes such as increased quality-adjusted life years (QALYs). Justice refers to the fair distribution of the transplantation benefit—an equality of opportunity for wait-listed candidates to undergo transplantation. In the context of VCA, these ethical principles must be balanced recognizing some unique factors such as the desire for skin tone and age range matching. Unlike other organs where scarcity requires rationing, it is likely that the demand for VCA transplantation at least initially can be met. As a result, at this time VCA allocation in the United States may be more a matter of matching and distribution than prioritization of one candidate over another. Under the new OPTN policy, VCAs must be allocated by waiting time to candidates with compatible blood type and "similar physical characteristics to the donor" waiting within the OPOs service area first and then outside of the OPO's service area [16].

Living VCA donation

As is often the case with nascent fields, the policy development lags behind scientific innovation. Although the policy-makers strive to regulate in a manner that is based on established principles rather than exceptionalism of new frontiers, this is easier said than done. With VCA, although some unique issues were immediately identified, the possibility of potential living VCA donors (such as uterine donation) had largely not been considered at the time of the interim guidance. Public comment in 2014 identified this potential and the need to address the unique attendant considerations [17]. Specifically, it was quickly recognized that there are some types of VCAs (such as face) that should never be from living donors

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because "unacceptably serious physical disfigurement, and/or psychosocial disability resulting from the donation are inherent results of the procedure itself [18]." Furthermore, the goals of VCA transplantation are restorative and not lifesaving changing the risk-benefit calculation for living donors and, unlike other lifesaving transplants where the demand significantly outpaces the supply of deceased donor organs, deceased donor VCAs are likely to meet the demand for VCA transplantation at least in foreseeable future. As a result, the OPTN VCA Committee with input from the Ethics Committee and the Living Donor Committee put together a guidance document for Living VCA Donation that was passed by the OPTN/UNOS Board on June 1, 2015 [17]. The guidance document, recognizing the lack of "minimum requirements for the protection of the living VCA donor, including criteria for living donor recovery programs, recommendations for the informed consent, and the donor's medical and psychosocial evaluation... covers some general aspects regarding VCA types that may be suitable to consider from living donors, given the likely risk-benefit profile for these donors [18]." It is anticipated that the living VCA donor guidance will require future policy development as experience with VCA transplantation from living donors increases.

Conclusion

The regulation of VCA donation and transplantation in the United States is emerging within the existing framework established for other organs under the OPTN. As with other innovations at the cutting edge of transplantation, unique factors have required policy-makers to consider how to appropriately support the rapid development of VCA transplantation as a promising and important therapy while ensuring that the safety and public trust in the U.S. system of organ donation and transplantation is preserved. It is likely that the advent of new types of VCA transplantation will raise questions not yet considered and necessitate revision and refinement to the newly minted OPTN policies regulating VCA in the United States.

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