

Facial transplantation: a review of ethics, progress, and future targets

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Abstract: The surgical history of transplantation in the modern era begins in 1956 with the successful transplantation of a kidney between identical twins. Since then the field of transplantation has seen remarkable advancements in both surgical techniques and our understanding and ability to manipulate the immune response. Composite tissue allotransplantation involves the transplantation of any combination of vascularized skin, subcutaneous tissue, blood vessels, nerves, muscle, and bone. Orthotopic hand transplantation is considered the first clinical example of CTA and has seen success at many different centers worldwide. Facial allotransplantation is a recent development in the field of CTA and the first successful case was performed as recently as November 2005. Since then there have been a number of successful facial transplants. The purpose of this paper is to examine some of the issues surrounding facial transplantation including the complex ethical issues, the surgical and clinical issues, cost and administrative issues, and future directions for this new, exciting, and controversial field.

Keywords: composite tissue allograft, facial transplantation

Introduction

In 1954 Dr Joseph Murray, a plastic and reconstructive surgeon at Brigham and Women's hospital in Boston, performed the first successful renal transplantation between identical twins.¹ Since then, the field of transplantation has evolved to include the successful transplantation of heart, lungs, liver, pancreas, and small bowel. Extrapolation of the concepts and techniques involved in solid and hollow visceral transplantation has led to the development of the field of reconstructive transplantation. A composite tissue allograft (CTA) can comprise any combination of vascularized skin, subcutaneous tissue, blood vessels, nerves, muscle, and bone. The field of facial CTA has received significant attention in the last several years since the first reported case of a successful partial face transplant in November 2005 in Amiens, France.²

Facial allotransplantation truly allows for the axiomatic replacement of "like with like." It permits the reconstructive surgeon to replace exactly the tissues that are missing, without incurring the donor deficit that accompanies traditional techniques. Indeed, there are critical specialized structures in the face (eg, eyelids, lips, nose) whose exact functions cannot be replicated via current autologous surgical techniques. The risks entailed in facial CTA are complex and multifaceted and include the risk of rejection of the transplanted tissue, the risks associated with requisite immunosuppressive medications, the risks of the surgery itself, the social and emotional toll on the patients, and the financial burden that can accompany the procedure and all its perioperative details. The benefits derived from these transplants appear to be both psychosocial as well as functional. Patients with

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severe facial deformities are often reclusive and feel socially inhibited (although the degree of adjustment to the deformities does not always correlate with severity of disfigurement). Thus, in addition to the restoration of function after facial CTA transplant the patient can note improved self-image and be more open to increased social interaction.

Since November 2005 there has been a total of 13 partial or complete facial transplant cases with several more centers having been approved for facial transplantation.^{3,4} This manuscript summarizes the ethical, surgical, clinical, and administrative issues surrounding facial CTA and outlines directions for the future of the field.

Ethical considerations

In the current discussion of facial allotransplantation perhaps no topic is more controversial than the ethical considerations and impact. The scientific literature is replete with discussions on the ethical implications of CTA and while there is some consensus on specific issues, there remains a great deal of controversy. Presented herein are a few of the major ethical issues concerning facial CTA.

“Experimental” surgery?

At the heart of the ethical debate lies the fact that facial CTA is still regarded as an experimental procedure. No long-term studies have demonstrated improved quality of life for facial transplant recipients. Nor has it conclusively been shown that current immunosuppressive regimens will maintain long-term viability of the transplant. Thus far, evaluation of outcomes is limited to the small number of patients transplanted with the longest transplant only 5 years postoperative.⁵ In addition, unlike solid organ transplantation (liver, heart, and lung), facial CTA is not a life-saving transplant. While there may be substantial psychosocial and functional benefits to the patient, the transplant will not extend life. Meanwhile, the risks to the patient who chooses to undergo this procedure are significant. The surgery is extremely complex from a technical standpoint, requiring long operative times and the potential of significant postoperative complications. Finally the requisite use of immunosuppressive medications expose the patient to the risk of opportunistic infection, malignancy, and toxic end-organ side effects.

Codification of the standards and ethical requirements used in experimental surgery can be found in documents such as the Nuremberg code, the Declaration of Helsinki, and the Belmont Report.^{6–8} Thus, the patient must understand the significant uncertainty that is associated with any experimental procedure.

Patient selection

One of the most important decisions that can be made in the facial transplantation process is who is a candidate for surgery. A number of issues must be taken into account before someone should be considered eligible.

The initial step is to determine which types of facial disfigurement would be amenable to reconstruction via CTA. Thus far, patients have received facial transplants for trauma, burns, and benign facial tumors (neurofibromatosis).⁴ Each type of patient has unique considerations. Patients with severe maxillofacial trauma or burn injury have typically had their outward identity suddenly changed and have been forced to cope with a new way of life due to their injuries.⁹ Patients with congenital problems such as neurofibromatosis have probably had progressive disfigurement over the course of their lives. In either case, unique psychological adaptation must be taken into account during the evaluation process. While the degree of facial disfigurement does not predict the severity of psychological stress, it is important to factor in each patient’s situation and the manner and the degree to which they are able to cope with their disfigurement.^{10,11} The ideal patient is extremely motivated and has realistic preoperative expectations of the goals of surgery.

Psychological evaluation is necessary throughout the entire reconstructive process, from initial assessment to postoperative monitoring. It is important that a team of mental health professionals (such as clinical psychologists, psychiatrists) works closely with the transplant team, and regular communication between these teams is essential.¹² The ideal, if possible, is staff who are dedicated to mental health. Patients should undergo a rigorous preoperative assessment to determine suitability. Counseling should then be done at each phase of the process, including the preoperative period while the patient is waiting for a transplant, immediately following the transplant while the patient is still in the hospital, and after the patient returns home. There are many recognized issues as the patient tries to assimilate back into their home environment and has their first interactions in a social or public setting. It is important to note if the patient has previously undergone psychosocial therapy and how effective that therapy was. It has been clearly shown in solid organ transplantation that patients with poor psychological coping mechanisms have worse outcomes.¹³

Cognitive evaluation is another tool that aids in the initial evaluation process. If there is an inability to understand the reconstructive process and comply with the treatment plan as well as to provide informed consent, patients with significant cognitive impairment (related to age, injury, or learning dis-

ability) should not be considered for facial transplantation. Patients must be able to take in and assimilate enough information to enable them to understand the nature of the procedure they are consenting to, and the outlined risks and benefits. Patients should be able to weigh the proposed improvement in quality of life against the potential morbidity and mortality of lifelong immunosuppression and the possibility of rejection of the transplant. Because people filter information about potential risks and benefits in different ways,¹⁴ and because unrealistic optimism about risk and outcome in surgical patients is common,^{15,16} comprehension of all relevant risk/benefit information must be assured before proceeding with the procedure.

The issue of compliance is crucial to the success of facial transplantation. Adherence to complex postoperative medication regimens and lifestyle modifications depends on several factors which include: the age and educational level of the recipient, satisfaction with the outcome of the transplantation, beliefs about the consequences of nonadherence, side effects of the regimen, psychosocial status, and levels of practical and emotional support from family and friends.¹⁷ There is also an issue of unintentional noncompliance, seen in both young children and older adults. Even in motivated patients who have undergone successful solid organ transplants, the incidence of noncompliance can be over 40%.¹⁷ A thorough assessment should be done to determine the prospective patient's history of compliance to medication regimens or other forms of treatment.

The patient's relatives and/or friends form a social support network, which is crucial to a successful recovery and reintegration into society. Evaluation of the patient's support network should be done preoperatively and routine evaluation should be done in the perioperative and postoperative periods.^{14,18,19} Having key members of the patient's social support network participate in the evaluation process (such as attend clinic appointments, read any relevant documentation) and learn about the specifics of the reconstructive process helps to ease the patient's transition from the preoperative phase. A strong social support network will help the patient deal with stressors at each stage of the reconstructive process.

Informed consent

The issue of informed consent is perhaps the most challenging ethical concern surrounding facial CTA. In order for informed consent to be professionally and legally acceptable, several requisite areas must be addressed including: medical literacy, competence, disclosure, voluntariness/noncoercion, and consent.

Medical literacy has recently become identified by the Institute of Medicine as an important, yet insufficiently examined, patient characteristic that can affect health outcomes. Medical literacy, as defined by the Institute of Medicine, is "the degree to which individuals have the capacity to obtain, process, and understand basic health information and services needed to make appropriate health decisions." This multifaceted concept draws on cultural and conceptual knowledge, and requires skills in reading, writing, numeracy, listening, and speaking. Numeracy entails "the ability to use and understand numbers in daily life," and includes basic calculations, measurement, and logic.²⁰ People with limited medical literacy skills have difficulty reading and understanding patient education materials, medication labels, discharge instructions, and health surveys.¹⁹ Limited medical literacy has been linked to poorer understanding of one's medical condition and treatment, worse adherence to medical instructions, inadequate self-care skills, poorer physical and mental health, poorer health outcomes, increased mortality risk, and increased healthcare costs. One-third of men and women in the US are at the lowest levels of health literacy. An estimated 93 million of the US adult population (43%) possess limited health literacy skills, and may have trouble understanding and acting on health materials. Adults without a high school diploma or GED, who are socioeconomically disadvantaged, belong to ethnic minority groups, the elderly, or immigrants have disproportionately low health literacy skills.²¹

Little is known about the medical literacy levels of facial transplantation candidates or its relationship to their health status and well-being. However, the limited research on kidney transplant recipients suggests that 10% to 30% have inadequate or marginal literacy levels, and that medical literacy is related to serum creatinine levels. Individuals with limited medical literacy are especially vulnerable in their ability to grant informed consent since lower literacy is an important determinant of understanding information presented in consent forms.³ Although patient education materials should be written at the fifth to eighth grade reading levels, most materials are written above the eighth grade level, including consent forms.²² Thus, individuals with limited literacy are at a disadvantage in providing informed consent. In particular, facial CTA candidates with limited literacy and numeracy skills may have difficulty understanding the risks involved in the transplant. These risks are typically expressed in terms of percentages or frequencies and may not be easily interpretable by patients during the consent process.²²

The issue of competence is reflected in the patient's ability to communicate and maintain choices about their treatment.

The issue of competence is related to cognitive function, and should be rigorously evaluated during the screening phase of the reconstructive process. These choices must be maintained long enough for their implementation. Assessing the patient's ability to make his or her own decisions is difficult and we tend to assume that the patient has the capacity unless there is evidence suggesting otherwise. Certain guidelines have been established that examine a patient's ability to make rational decisions.¹⁷ Included in these guidelines are the patient's ability to intake, retain, and manipulate information in a rational fashion and to comprehend the situation and its possible consequences. Certain conditions may affect patient competency: thought or personality disorders, long/short-term memory impairment, issues with attention-span or even severe ambivalence. These conditions may lead to changes in the health decisions that are made and can even result in the inability to make a decision or decisions that are subject to change based on the fluctuating cognitive function of the patient.²³

Disclosure represents another facet of informed consent that must be given careful attention. The physician is obligated to disclose all relevant information to the patient as well as any significant risks.^{23,24} The quality and amount of information must be enough for the patient to make an informed decision about whether or not to proceed. There should be an exhaustive discussion of the benefits as well as all known risks. Discussion of specific risks should happen regardless of the severity or expected frequency. In addition to risks, potential side effects with severe or fatal consequences should also be discussed exhaustively.

Not all patients wish to have complete disclosure however. Some patients will try to actively avoid learning about their disease process and the risks and benefits of the proposed treatment in order to lessen the emotional impact of their situation. This is termed "cognitive avoidance." It is crucial to determine how much information a patient wants to receive before proceeding with the consent process. There are physicians who caution that providing more detailed information to patients who do not want it and imposing choice on those who prefer their physician to assume decision-making responsibility is anxiety provoking and potentially harmful.²⁵ It is also important to be aware that patients who perceive that there is a lack of information presented to them, or who perceive that they are being asked to participate in more decision-making than they are comfortable with can also have heightened levels of anxiety.²⁶

When it comes to facial transplantation, it is compulsory from an ethical standpoint not only to have the patient

understand all relevant information, but also to become an active part of their own treatment team by assuming a working partnership with the transplant team and all related providers. To that end, all presented information must be understandable by the patient. It should represent the technical and anatomic details of the procedure in simple terminology, free from complex medical jargon. As mentioned above, the postoperative care must be detailed to the patient, including the immediate postoperative period and the period after the patient returns home. Information about the complex postoperative medication regimen, including all immunomodulating medications should be given and should include understandable explanations of the relative risks and benefits. To achieve full disclosure it is also imperative that the patient have all forms of alternative therapy explained to them. This would include no surgical treatment, essentially leaving them as they are, as well as detailing conventional reconstructive techniques and their expected outcomes.²⁵

It must also be explained to the patient that complete disclosure in regards to this experimental procedure is impossible. We are learning more about facial transplantation from those few patients who have undergone this novel surgery, but much remains unknown about outcomes. It is clear that consent to facial transplantation assumes an unknown amount of risk. While the majority of risks and benefits are calculable, it is imperative that the patient understands the potential for unanticipated complications and the uncertainty regarding long term outcomes.

Another central principle of informed consent is noncoercion. The decision to pursue facial transplantation should be related to the patient's independent level of motivation to seek treatment after all details have been disclosed and it is assured that the patient understands the process and all the inherent risks and benefits (as well as the possibility of unknown risks). The surgical team runs the risk of influencing patients through conscious or subconscious assertion of their own value system.^{13,27} The family and social support network of the patient can also unduly influence the decision to pursue facial transplantation. For the physician, withholding information about viable treatment alternatives, downplaying potential risks, and overstating the potential benefits are considered coercion. Family and friends have often witnessed the psychological toll extracted on the patient with severe facial deformity and may view facial transplantation as the panacea for this problem. While the coverage of facial transplantation in the lay press has highlighted our early successes, the general public is not likely to understand the complexities

involved in the procedure and may be more apt to push their loved one to proceed with surgery. It is crucial then that there be no coercion on the part of the surgical team or any affiliated researchers. Having at least one close member of the patient's social support network present during the consent process may also serve as an effective buffer against undue pressure from friends and family. For consent to be properly given, the decision to proceed with surgery must be based on the patient's own volition and the strict adherence to the principle of noncoercion.

Identity issues

The face is central to our conceptualization of self and serves as a major portion of our external identity. In addition, the face serves as our major tool of communication with the outside world, be it through direct speech or the conveyance of subtle nonverbal expressions. The face is our direct link to our family and culture, providing phenotypic expression of our parentage, ancestry, and racial identity. It has also been shown that our facial expressions influence our mood.²⁸ Thus facial disfigurement can result in a profound change in personal identity and body image. Depending on the etiology of the facial disfigurement, patients will have likely have been living with this condition for a significant amount of time and will have developed coping strategies for interacting with the outside world and generally adapted to their altered appearance. The next important question is how CTA would further alter their identity.

One important consideration is whether the recipient of a facial transplant resembles the donor in any significant way. It is potentially disturbing for the family of the recipient to think that their loved one's countenance and likeness is being exhibited by someone else. Based on work done by Pomahac et al, observers presented with a computer simulation that digitally "transplanted" the midface of one person onto another had negligible residual appearance of the "donor" and significant persistence of the appearance of the recipient.²⁹ It stands to reason that facial appearance is the composite result of the facial soft tissues in relation to the underlying facial skeleton. Appearance is further dictated by resting motor tone of the mimetic muscles, which varies from person to person.³⁰ While certain facial transplants may involve a portion of the facial skeleton, the majority so far have not.⁴ Transplanting the facial soft tissue envelope from one person to another is likely to produce a markedly different appearance given that the underlying bony framework is different. There is no evidence in the literature that comments on residual donor appearance are a significant problem.

Treatment of the donor

Due consideration must necessarily be paid to the donor and the donor's family. Standard protocols for organ procurement should be followed and potential donors would be initially screened by the local organ procurement organization (OPO). A member of the OPO would first approach the family of a potential donor. Also, discussions with the family of a prospective donor should be conducted by a leading member of the transplant team and preferably someone who will be directly involved in the proposed surgery. In addition, a member of the mental health arm of the transplant team should be involved in preconsent counseling of the donor family. Families in this instance are making a decision about donation while faced with the stress accompanying the death of a loved one. The complexity of this decision is higher than in standard organ transplantation because the face, as mentioned above, is so closely related to recognition and identity. Families should be counseled that the final result of the surgery is not going to produce someone who looks exactly like their loved one. Also, given the media exposure of facial transplantation so far, families should be counseled that they might inadvertently be made aware of the recipient of their loved one's facial donor tissues. This may be potentially distressing for the family and may extend or intensify the bereavement process. Psychological counseling should be offered at the time of the original discussion and consideration should be given to counseling related to any issues that may arise after the transplantation. This stands in contrast to solid organ and even other types of CTA. Normally, members of the transplant team do not communicate directly with members of the donor family. However, given the sensitive nature of facial transplantation and the complex issues involved along with the potential for further stress on the donor family, it is not uncommon practice for a member of the transplant team to meet with the family before surgery.

In respect to the donor and the donor's family, the visage of the donor should be restored as closely as possible to his/her natural state. While several techniques have been written about, the one that has been used most successfully is a silicone facial prosthesis.³¹ Typically, a preoperative mold is made of the donor's face and a moulage is constructed and used after the facial harvest has taken place to construct a multilayer silicone facial prosthesis.

Surgical issues

General reconstructive principles

The face can be divided into specific aesthetic and functional subunits. Loss of any subunit is typically amenable to

reconstruction via traditional techniques whereby autologous tissues are used to resurface and recreate, as closely as possible, the appearance and function of the subunit. In so far as traditional reconstructive techniques are concerned, it is much easier to provide for coverage of a facial subunit than to mimic its function. The critical specialized functional structures in the face (the eyelids, lips, nose, and ears) are near impossible to reconstruct from a functional standpoint. Beginning with basic principles, if a portion of the face were removed or damaged due to trauma, burns, or oncologic resection, a simple skin graft, with no intrinsic blood supply, could be used to cover the area. This too often results in a suboptimal aesthetic result and is not typically the first choice for reconstruction unless urgent or emergent coverage is needed. Using autologous tissue, either through local flap, distant flap, or free tissue transfer often results in a superior result compared with skin grafting because you are using vascularized tissue or similar thickness and pliability for the reconstruction. Until the advent of CTA however, fulfillment of the axiom “to replace like with like” has not been possible. Composite tissue allotransplantation allows for replacement of specialized functional tissues. Facial CTA is a complex endeavor with little long-term outcome data; it remains as the only reconstructive alternative with the potential to restore a patient to their premorbid functional status.

Facial allotransplantation

The typical patient considered for facial allotransplantation usually has severe disfigurement from either burns, massive facial trauma, or due to resection of facial tumor (ie, neurofibromatosis). By definition, a composite tissue allograft is made up of multiple tissue types consisting of any combination of skin, subcutaneous tissue, blood vessels, muscle, nerve, tendon, and bone. Once a suitable recipient was found, a suitable donor would be sought out. Issues to consider are age, sex, skin type, and color of the donor tissues.

Once a properly identified donor was found, harvest would consist of careful removal of those facial tissues needed to reconstruct the recipient defect. It is prudent initially to take more tissue than needed in order to have extra tissue to work with and to be able to tailor the facial allograft exactly to the donor deficit. Ideally, two teams would be working concurrently, one team harvesting the face from the donor and one team preparing the recipient, similar to visceral transplantation. One issue specific to facial allotransplantation pertains to the amount of donor tissue that should be resected in order to properly prepare the donor to receive the allograft. It has previously been shown that an optimal aesthetic outcome

is achieved when whole subunits are replaced as opposed to partial subunit reconstruction.⁷ The area of disfigurement in patients who are eligible for facial transplantation often spans several (if not all) facial subunits. Another aspect of this question also relates to the depth of resection. To what depth should the donor facial tissues be resected to prepare for the allograft? If the donor mimetic muscles are nonfunctional, and reconstruction is to include reconstruction with the recipient's facial muscles, should the donor muscles be removed? The answers to these questions lie outside the scope of this paper but the questions presented here illustrate the complexity of the procedure and the individual consideration that must be given to each and every patient.

While the anatomic details of each transplant thus far have been different, certain specific principles apply to nearly every case. For arterial input to the facial construct, the facial artery would be used. In rare situations where the facial artery is absent or diminutive, the transverse facial artery could be used. In cases of transplantation of the upper third of the face or for transplantation of a functional subunit eyelid flap, the superficial temporal artery may be able to be used.³² The venous outflow would be via the corresponding facial, transverse facial, or superficial temporal veins. While a single arterial and venous anastomosis would likely be sufficient, more than one may be done depending on the size of the facial allograft and the observed flow and perfusion via a single set of vessels.

Cutaneous sensation would be gained via anastomosis of one of the branches of the trigeminal nerve. In the upper third of the face, anastomosis between the supraorbital, supratrochlear, and/or zygomaticofrontal nerve would provide sensation. In the middle third of the face, sensation would be supplied by anastomosis of the infraorbital nerve. In the lower third, sensation would be restored via anastomosis of the mental nerve. Sensory recovery does seem possible, as it has been documented that the first transplant patient (from November 2005 in Amiens, France) has had significant recovery of facial sensation, in addition to some motor recovery.³³

For restoration of function of transplanted mimetic muscles, branches of the facial nerve will have to be coapted to each other. Where the nerves are coapted depends somewhat on how the facial nerve and mimetic muscles have been damaged and at what level there are viable donor facial nerve ends available.

Certain anatomic and surgical issues lie outside the scope of this manuscript. Repair and reconstruction of the periorbital, perinasal, and perioral structures require special attention because of their complex three-dimensional

relationships and functional attributes. For instance, replacement of the central midfacial region would require establishing a new relationship between the internal component of the perioral region (ie, the mucosal surfaces and gingival) of the allograft and whatever donor perioral tissues remain. It would also involve recreation of the nasal vestibules and repair of the mucosal surface of the allograft to the remaining donor nasal mucosa in addition to septal repair/reconstruction.

The question then becomes, “What happens if the facial allograft completely fails?” While cases of acute rejection may be the standard and not the exception, to date none of the allografts have completely failed and episodes of rejection have been successfully managed with corticosteroids and an increase in other immunosuppressive medications.³ If rejection were not treated promptly or effectively, the graft may fail. Also, should the allograft become compromised from a vascular standpoint (ie, thrombosis) and microvascular salvage is impossible, the allograft would have to be removed in its entirety. It has been suggested that if the allograft were removed, the patient would then be starting over completely on the reconstructive ladder and skin grafts or other traditional reconstructive techniques could be used to cover the area.³⁴ There may be a problem, however, if the patient has had previous reconstruction. The first patient to have a facial transplant in the US (in December 2008 at the Cleveland Clinic) had several reconstructions prior to her facial transplant, including a temporoparietal muscle transposition, radial forearm free flap, free fibula flap, calvarial bone grafting, and multiple autologous skin grafts.³⁵ While there are still certainly reconstructive options available were this patient’s facial allograft to fail, the decrease in the number of available options as well as the possibility that donor facial tissue had been resected in order to achieve a more aesthetic outcome may lead to an even worse appearance than that before the transplant.

While accomplishing the facial transplantation is an achievement to be lauded on its own, it is by no means the final surgery in the reconstructive progression. As expected, nearly every patient who has undergone facial transplantation has had some form of revision surgery. For some, this has been an anticipated part of the process, such as the Cleveland Clinic patient whose surgery was planned as a multistage process where craniofacial reconstruction and rehabilitation was the initial goal followed by removal of soft tissue excess and graft contouring at a later date.³⁶ So far, the few patients who have had reconstruction of the periorbital subunits with a facial allograft have gone on to need smaller procedures such as ectropion repair.

Clinical issues

Immunologic aspects

In 1954, when Joseph Murray successfully transplanted a kidney from one person to another, he was able to accomplish this because the donor and recipient were identical twins.¹ Transplantation is much more complex when unrelated individuals are considered. Transplantation of any organ or tissue will provoke an immune response in the host directed against the donor tissues. The magnitude of this response is influenced by the type and amount of tissue transplanted and any prior sensitization the recipient may have had to host histocompatibility antigens. Composite tissue allografts that contain skin as a component may evoke a stronger immune response, given the fact that the skin is recognized as one of the most antigenic tissues in the body.³⁷

Immunologic compatibility

As a first step, it is necessary to ensure that there is ABO blood group antigen compatibility between the donor and the recipient. It is also necessary to run a crossmatch between recipient and donor to ensure that the donor has no antibodies to the recipient’s (human leucocyte antigen) HLA antigens. A panel reactive antibody test (PRA) should also be done to measure baseline immune system activity. This practice is routinely performed in solid organ transplants as part of the pretransplant work-up. In addition to the immunologic testing, standard pretransplant evaluations should be done including donor and recipient viral serology (Epstein–Barr virus [EBV], cytomegalovirus [CMV], HIV) and blood chemistries.

Risk of rejection

The Royal College of Surgeons, in their 2003 working party report, estimate the risk of graft loss to be around 10% from acute rejection, with chronic rejection accounting for loss of graft function in 30% to 50% at 2 to 5 years.³⁸ These figures are derived from studies of solid-organ transplant recipient populations. Acute rejection of the skin was reported in the first patients to undergo hand transplants and has been a common occurrence in most subsequent transplants. Acute rejection episodes have occurred in 70% of hand transplants, but no grafts have been reported lost as a direct result.³⁹ The well-documented first hand transplant recipient underwent episodes of acute rejection but became noncompliant with medication and subsequently had the graft removed.⁴⁰ Acute rejection has also been shown to occur in abdominal wall transplants as well.⁴¹ Facial transplantation has shown some form of acute cellular rejection in almost all cases. These

have been successfully treated and there has been no loss of any of the grafts to date (with the exception of those two patients that have died after receiving their transplants). For the first French face transplant, there were noted episodes of acute rejection on postoperative days 18 and 214. This was treated by increases in tacrolimus, mycophenolate mofetil (MMF), and prednisone as well as prednisone mouthwashes, clobetasol topical ointment and three 1000 mg doses of iv methylprednisolone. Rejection of the skin is usually easily recognized and confirmed by biopsy. Treatment then typically consists of increased corticosteroid therapy, or if resistant to steroids, antilymphocyte therapy (such as antithymocyte globulin) is used.

Chronic rejection has not been reported in facial transplantation to date, because the period of follow up is not yet long enough for sufficient evaluation. The closest analogous clinical situation would be hand transplantation where the incidence of acute rejection is high. The suggestion of chronic rejection in hand transplantation in the literature is surprising, but very few studies in the medical literature formally document chronic rejection. There has been some preliminary presentation of data at scientific meetings suggesting that the incidence of chronic rejection among hand transplant recipients as evidenced by regular serial biopsies may be much higher than originally thought. Direct comparison of hand to facial transplants may not be accurate as the hand transplants typically include muscle and bone (while facial transplants may or may not) and this may modulate the immune response resulting in differing patterns of rejection. Comparison of chronic rejection rates to renal transplantation may also not be appropriate, as some long-term renal graft failure is due to drug parenchymal damage and is not immunologically mediated. Therefore, although long-term immunological reactivity of skin and subcutaneous tissue is not yet fully known, the incidence of chronic rejection in hand and renal transplants may not predict the incidence of rejection in facial transplants, although there is no reason to expect that it will be worse.

The consequences of immunosuppression

Immunosuppression and its adverse reactions and complications represent both a major clinical and ethical hurdle in CTA. As mentioned above, patients must be allowed to make an informed decision considering the possibility that they may suffer from one or more of the negative effects of these medications. Over-immunosuppression can lead to dose-dependent drug toxicities such as hypertension, renal parenchymal damage, diabetes mellitus, gastrointestinal issues,

osteopenia via increased bone resorption, and dyslipidemia. In addition, immunosuppression confers the risk of serious opportunistic infection and malignancy.^{42,43}

In terms of nonimmunologic risk, immunosuppressive agents increase cardiovascular risk by altering cholesterol levels, increasing triglycerides, increasing blood pressure, causing steroid related diabetes, and causing renal dysfunction via direct parenchymal damage. Tacrolimus can exacerbate hypertension by induction of vasoconstriction. It also contributes to nephrotoxicity by the reduction of glomerular filtration rate via preglomerular arteriolar vasoconstriction. Long term tacrolimus nephrotoxicity can result in interstitial fibrosis and tubular atrophy. Steroids cause diabetes by increasing insulin resistance and induce hyperlipidemia by interacting with key enzymes in the hepatic lipid synthesis cycle.⁴⁴

Interestingly, in human hand transplant recipients, there was an increase in creatinine in 11% of patients and postoperative transient hyperglycemia in 50% of patients.⁴⁵

Transplant recipients are also at increased risk for infection. They are particularly susceptible to viral infections such as CMV, EBV, and herpes simplex infections. Risk for other opportunistic infections include *Pneumocystis carinii* pneumonia and various fungal infections.⁴⁶ Bacterial infections typically happen early in the postoperative period and are thought to be related to surgery rather than immunosuppression.⁴⁷ While most bacterial infections are easily recognized and treated, transplant patients are at increased risk for life threatening sepsis.

Long-term immunosuppression also carries the increased risk of cancer. There is a two- to four-fold increased risk of colorectal and lung cancer. In addition, malignancies whose etiology is thought to be viral (non-Hodgkin's lymphoma, squamous cell cancer, Kaposi's sarcoma, and cervical cancer) show a 50-fold increase in incidence. Post-transplant lymphoproliferative disorder is observed mostly in solid organ transplant recipients and has not been observed in any hand or face transplant recipients.

Cost and administrative issues

The price of facial transplantation

Very little in the medical literature describes the monetary cost of facial transplantation. In the early stages of this experimental procedure the question has been if we *could* perform facial transplantation successfully and reproducibly. We are still in the very steep learning phase of this procedure and as with any new and exciting technology, persons and organizations are willing to fund the *initial* efforts. In addition to the groups in the US, France, Spain, and China, multiple other groups within these countries and other countries are

trying to establish CTA programs and are eager to perform their first facial transplant. In the US, some of the funding for these initial efforts has come from direct institutional sources as well as research grants and endowments.⁴⁷ The US military has taken a keen interest as well and the recently formed Armed Forces Institute of Regenerative Medicine, dedicated to helping soldiers with burn and blast injuries regrow tissues, has contributed funding to some of the early US facial transplantation efforts.⁴⁸ All the press and media coverage surrounding the few cases so far has also led to a relative windfall for some institutions, with investors contributing money and a broad range of public and private organizations donating money.

With the continuing success of facial transplantation, the question will eventually become, will we be *allowed* to perform this surgery. Once the initial fervor over facial transplantation subsides, where will funding come from? Will insurance companies and third-party payors cover the costs of CTA? In a recent study of unilateral and bilateral hand transplant recipients, which again is the closest analogous situation to facial transplantation, the lifetime costs of single hand transplantation averaged \$528,293 and \$529,315 for double hand transplantation. This contrasts to the costs of adoption of unilateral and bilateral hand prostheses, which averaged at \$20,653 and \$41,305 respectively. If you index these costs against quality-adjusted life-years (QALYs), the cost-utility ratio of double-hand transplantation was \$381,961/QALY, which exceeds the accepted cost-effectiveness threshold of \$50,000/QALY.⁴⁹ While it is impossible to directly extrapolate these data to facial transplantation, it is not expected that the initial hospital and surgical fees would be any lower and the life-long costs of immunosuppression would be similar. One source documents the possible total costs of facial transplantation to be between \$250,000 and \$1,500,500.⁵⁰ In addition, the cost (in QALY) of complications (major, minor) and complete graft loss would be similar or increased compared with facial transplantation.

While initial examination of cost-effectiveness may argue for or against facial transplantation, the final determinant of whether this procedure is funded will be how society views the benefits of the procedure. When renal transplantation is examined, the relative monetary cost versus alternative therapy (outpatient dialysis) is initially high but the improvement in quality of life is significant and has been deemed “worthy” by society. In addition, after approximately 2 to 3 years, the cost of renal transplantation compared with conventional or intensive renal dialysis is much lower, owing to the fact that most of the cost for transplantation is incurred “up front”

in the form of surgical costs and related perioperative expenses.⁵¹ For facial transplantation, economic analysis would have to focus on the direct benefits to the patient, such as their improved sense of self and reintegration back into society. The benefits to society have to be taken into account, as patients may be able to rejoin the workforce and participate socially rather than being reclusive and isolating themselves. The first French facial transplant patient, Isabelle Dinoire, has been reported to have gone back to work and is considered to have had successful reintegration into society.

Forming a facial transplant program

The complexity surrounding facial transplantation is not strictly limited to the surgery itself. As evidenced above, a number of issues must be considered before potential patients are screened. An initial consideration is that any CTA program should be established in the university hospital setting, where all components of the program (including personnel, research facilities, and the physical sites where therapy will occur) are centrally located.

The initial goal should be establishment of a facial transplant team. A team leader should first be chosen. This person coordinates oversight and development in all phases of construction of a CTA program. Ideally this person should have specific knowledge of the clinical portion of transplantation (including the pre-, peri-, and postoperative phases) and the research goals of the program. The team leader should expect a significant weekly time commitment and will need to be able to communicate with the IRB during all phases of formation of the program.⁵²

The team leader should oversee formation of the remainder of the CTA team. All recruited individuals should understand that the program is not a temporary or transient entity but should be approached as if it is a long-term process that requires a significant time commitment by all members. The team itself will consist of:

Surgical transplant team – five + surgeons with expertise in microsurgery/craniofacial surgery

Medical transplant team members – Physicians with expertise in infectious disease and management of immunosuppressive medications in all phases of transplantation as well as intensivists who will participate in the immediate postoperative critical care period.

Facial transplant coordinator – represents a person who is knowledgeable about the medical and surgical issues involved in facial CTA as well as the administrative issues. This person helps coordinate screening of potential patients as well as arranging clinic visits for patients.

Research members – Should include 1 or more lead researchers who coordinate the basic science and clinical research projects and oversee research personnel.

Psychology/psychiatry – Personnel involved in preoperative evaluation of patients, counseling during the period awaiting transplantation, perioperative counseling and postoperative follow-up. There must be enough personnel to counsel the patient and those in the patient's social support network. Clinicians should also be available to counsel the donor patient's family during the perioperative phase.

Ancillary personnel – Should include social workers, patient advocate, ethicist, physical and speech rehabilitation staff, institutional media liaison/public relations personnel, and security (for the immediate perioperative period).

This list is by no means all-inclusive but represents the minimum number of clinicians and ancillary personnel necessary to establish a facial CTA team.

Another critical component of establishing a CTA program is involvement of the locally designated OPO. In 1984 the National Organ Transplant Act was approved and provided for the initial funding for establishment of OPOs and also established the formation of the Organ Procurement and Transplantation Network (OPTN) and the Scientific Registry of Transplant Recipients. The OPO is designated for a specific area and each hospital is assigned to a specific OPO. OPOs are nonprofit organizations that are involved in the evaluation, procurement, and allocation of organs within their designated service area and are overseen by the OPTN.⁵³ There was some initial question about which agency would oversee procurement and allocation of facial allografts because they are incorrectly labeled as “grafts,” when they are actually vascularized tissues with an intact blood supply at harvest and after they are used for reconstruction. For the transplants done in the US, the OPOs, under the direction of the OPTN have been the agency responsible for allocation of facial allografts. The local OPO should be involved in the formation of a CTA program from very early on in the process, during the formation of the CTA team and during the IRB approval process.

Future directions

The current strategy for the post-transplant management of composite tissue allograft is to treat them with well-established regimens of immunosuppression used in solid organ transplantation. Most CTA transplant patients have been treated with an induction agent (such as antihymocyte globulin [ATG]) and then maintained with up to three immunosuppressive (tacrolimus, MMF, and steroids) medications. This has led to a high level of success in terms of initial graft survival.

However, in order for the field of reconstructive transplantation to expand its indications beyond the experimental arena, techniques need to be designed to either significantly reduce or eliminate the need for chronic immunosuppression. The future direction of this field is heavily dependent on the development of innovative approaches to the use of immunosuppressive agents and tolerance induction protocols.

T-cell depleting therapies have been effective at promoting graft acceptance and tolerance in several animal models.^{54,55} However, clinical translation of these protocols had been unsuccessful until the development of the anti-CD52, Campath-1H (alemtuzumab; Genzyme), antibody. CD52 is expressed on most T and B lymphocytes, natural killer cells and monocytes, and Campath-1H rapidly depletes these cells with varying kinetics of repopulation. Initial clinical reports by Calne et al suggested that the use of Campath-1H in combination with low-dose cyclosporine in kidney transplantation could achieve a state of “prope” tolerance (graft acceptance with reduced immunosuppression).⁵⁶ However, the use of Campath-1H alone or in combination with deoxyspergualin led to 100% acute rejection,^{57,58} showing that Campath-1H was not tolerogenic in itself. Campath-1H has recently been demonstrated to reduce significantly the episodes of biopsy-proven acute rejection (14% versus 26%), compared with thymoglobulin. However, there was no difference in survival, initial length of stay, and maintenance immunosuppression (including early steroid elimination).⁵⁹

Attempts to use T-cell depletion agents such as Campath-1H or ATG in CTA have yielded similar results and highlight the need for additional strategies to allow for the reduction of immunosuppression. Recently, a group from the University of Pittsburgh has introduced a strategy that takes advantage of the cellular depletion provided by Campath-1H combining it with a donor bone marrow infusion. This technique has had some initial success with living-related kidney transplants. Thus far, they have provided early reports on three hand transplants performed under the protocols currently maintained on tacrolimus alone. Despite the combination of Campath and the donor bone marrow all of the transplants have experienced acute rejection that required additional treatment. This technique may lead to a reduction of initial acute rejection but does not appear to allow for the future withdraw of all immunosuppression.

It appears that T-cell depletion alone (with or without bone marrow) is not likely to provide sufficient preconditioning to lead to tolerance to organ allografts. Regimens that lead to the induction of mixed hematopoietic chimerism have been shown to lead to tolerance to organ allografts in multiple

preclinical studies.^{60–63} In addition, case reports have shown tolerance to a kidney allograft in patients who received a bone marrow transplant from the same donor, sometimes years apart.^{64–66} However, the combination of most conditioning regimens combined with the infusion of bone marrow often results in graft versus host disease (GVHD). The greater the genetic disparity between the bone marrow recipient and the donor the more likely the recipient will develop GVHD. These findings lead to a clinical trial to use this approach to attempt to induce tolerance in patient with end-stage renal disease and advanced multiple myeloma using HLA-identical sibling donors.⁶⁷ Six patients received cyclophosphamide, antithymocyte globulin, thymic irradiation as well as cyclosporin (which was tapered off after 2 months) and subsequently followed by donor leukocytes infusions to improve graft-versus-tumor effects.^{68,69} All patients demonstrated initial engraftment of the donor marrow but the donor cell chimerism was lost in all of the patients except two. These two patients converted to full donor chimerism and had to be treated for GVHD. The other four patients maintained long-term renal function (up to >9 years) in the absence of immunosuppression. One of the four patients did have a single rejection episode that was controlled by the transient use of immunosuppression.

The have recently modified the protocol to address the induction of tolerance in recipient kidneys from HLA-mismatched living donors. To reduce the risk of GVHD they now use an anti-CD2 mAbs (siplizumab or MEDI-507) for their T cell depletion rather than antithymocyte globulin. Five patients received cyclophosphamide, MEDI-507, thymic irradiation and cyclosporin.⁷⁰ Occurrences of humoral rejection and engraftment syndrome led to addition of rituximab and corticosteroids for the last two patients.⁷¹ Mixed chimerism was transiently achieved in all patients but donor cells could not be detected after day 21 and GVHD did not develop. One patient lost his kidney graft as a result of an early and irreversible antibody-mediated rejection. In the other four patients, immunosuppression was successfully withdrawn during the first year posttransplant and normal renal function has been sustained for more than 3 to 6 years to date. The mechanisms underlying this operational tolerance are not fully elucidated. This model is also designed for living related transplants and in its current form would not be possible for use in for CTA transplants.

Conclusion

The emerging field of reconstructive transplantation offers a chance to significantly alter the current paradigm for the

reconstruction of complex defects. The development of protocols and the medical infrastructure are constantly being refined as we learn from the transplants performed thus far. While the current guidelines and ethical considerations are based on data from solid organ transplantation, new data from those patents who have undergone CTA continues to lead to refinements and alterations in strategy. While CTA is successful with current immunosuppressive therapies, the widespread application and acceptance of this emerging field will likely depend on future scientific discoveries that will allow for the reduction or elimination of chronic immunosuppression.

Disclosure

The authors declare no conflicts of interest in relation to this paper.

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