

The World's Experience With Facial Transplantation

What Have We Learned Thus Far?

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Abstract: The objective of this review article is to summarize the published details and media citations for all seven face transplants performed to date to point out deficiencies in those reports so as to provide the basis for examining where the field of face transplantation stands, and to act as a stimulus to enhance the quality of future reports and functional outcomes. Overall long-term function of facial alloflaps has been reported satisfactorily in all seven cases. Sensory recovery ranges between 3 and 6 months, and acceptable motor recovery ranges between 9 and 12 months. The risks and benefits of facial composite tissue allotransplantation, which involves mandatory lifelong immunosuppression analogous to kidney transplants, should be deliberated by each institution's multidisciplinary face transplant team. Face transplantation has been shown thus far to be a viable option in some patients suffering severe facial deficits which are not amenable to modern-day reconstructive technique.

Key Words: facial composite tissue allograft, composite tissue transplant, candidate selection, systematic review, immunosuppression, functional outcomes

(*Ann Plast Surg* 2009;63: 572–578)

Facial transplantation is a new, complex procedure entailing uncertain outcomes, including short- and long-term risk for recipients. To date, 7 reported facial transplantations have been performed from France, China, and the United States. To ensure that outcomes from this innovative procedure are maximized and risks, minimized, it is important for the facial transplant community to share their approaches, results, and missteps. This review article will discuss the details contained in the published reports of these transplantations, pointing out the deficiencies in those reports so as to both provide the basis for examining where this field stands and to act as a stimulus to enhance the quality of future reports and outcomes. Outcomes for only the first 4 patients are available in published reports.^{1–4} Details for patients 5 through 7 (March/April 2009) are still not reported and were based on media releases. The following descriptions of the first 7 cases are outlined in chronological sequence.

Received July 29, 2009, and accepted for publication, after revision, August 1, 2009.

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ISSN: 0148-7043/09/6305-0572

DOI: 10.1097/SAP.0b013e3181ba5245

OVERVIEW

The first successful face transplant was performed on November 27, 2005 in Amiens, France.¹ Since 2005, there have been 6 additional reports of successful facial composite tissue transplantation (CTA) (Table 1).^{5–7} Of total 5 (71%) recipients are male and 2 (29%) female. Traumatic facial injury was the indication for transplantation in 6/7 (86%) patients, 2/7 (29%) had suffered a close-range shotgun blast injury, 2/7 (29%) an animal attack, 1/7 (14%) injuries from a fall, and 1/7 (14%) severe burns. The only nontraumatic indication was for neurofibromatosis. Of 7, 3 (43%) of the CTAs have been osteomyocutaneous containing maxillary components. All donors were gender matched.

As of July 2009, 5/7 (71%) of the recipients are alive. There have been 2 face transplant-related mortalities (2/7, 29%). The first occurred in China nearly 2 years postoperative, after the patient became noncompliant with his immunosuppression regimen.⁸ The other death involved a concomitant face and hand transplant recipient who underwent a triple transplantation to treat extensive burn after effects. At almost 2 months posttransplant, the patient developed overwhelming infection, requiring surgical revisions, and subsequent cardiac arrest leading to death.⁹

REVIEW OF FACIAL CTA RECIPIENT CASES

Patient 1

Date: November 2005

Place: France

Team Leader: Dubernard

Recipient: 38-year-old woman

Donor: Brain-dead 46-year-old woman

Indication: Dog bite

Elapsed time to transplant: 4 months

Transplant type: Myocutaneous

Allotransplant design: Nose, lips, chin, partial cheeks, mucosa

Nerves: Left facial nerve, bilateral mandibular, and maxillary branches

Accessory donor transplant for biopsies: Concomitant forearm flap

Previous reconstruction: none

Human leukocyte antigen (HLA) Compatibility: 5/6 match

Panel reactive antibodies (PRAs): unknown

Cytomegalovirus (CMV) status: unknown

Time of operation: 15 hours

Status: Alive

Immunosuppression

Immunosuppression was induced with antithymocyte globulin for 10 days and a prednisone taper (250 mg: day 1, 100 mg: day 2, 60 mg: days 3–12, and so forth). The patient received tacrolimus for 14 months (target level of 10–15 ng/mL). Approximately 1.7 L (unknown cell count) of donor bone marrow was harvested from the iliac crest and stored in 2 parts nitrogen. Approximately 50% of the

TABLE 1. A Recent Timeline of Facial Transplantation

Date	Location	Team Leader	Indication
November 2005	France	Dubernard	Dog bite
April 2006	China	Zhang	Bear attack
January 2007	France	Lantieri	Neurofibromatosis
December 2008	Cleveland, Ohio	Siemionow	Shotgun injury
March 2009	France	Lantieri	Shotgun injury
April 2009	France	Lantieri	Burn
April 2009	Boston, Massachusetts	Pomahac	Fall injury

bone marrow cells were injected on days 4 and 11 posttransplant, similarly to the Miami protocol.^{10,11} Microchimerism was assessed at interval time points utilizing a PCR assay with a lower limit of 0.1%. There was only one early instance of detectable microchimerism at 2 months in the recipient's peripheral blood, which demonstrated 0.1% of CD34+ donor cells. Standard cytomegalovirus (CMV) and *Pneumocystis carinii* (PCP) prophylaxis was given. A decrease in posttransplant renal function led to a change from tacrolimus to sirolimus at 14 months. The current maintenance regimen includes Sirolimus (8–12 ng/mL), mycophenolate mofetil (MMF) (2 g/d), and prednisone (10 mg/d). Extracorporeal photochemotherapy was introduced at 10 months for additional immunomodulation.¹²

Graft Rejection

Biopsies of both the transplanted skin/oral mucosa and the sentinel transplant were taken every week for the first month, then every month for 4 months, and every 6 months thereafter to monitor for rejection. Rejection episodes occurred on postoperative days 18 and 214 and both were successfully reversed. These episodes presented with edema and erythema of the mucosa and skin of both the face and the sentinel transplant. The first episode was reversed by increasing the doses of oral prednisone, tacrolimus, and MMF in conjunction with clobetasol topical ointment, prednisone mouthwashes, and three 1000 mg doses of intravenous methylprednisolone. The second acute rejection episode was treated with 3 doses of 750 mg IV methylprednisolone every other day, prednisone mouthwash, topical clobetasol and tacrolimus ointments, and 50 mg oral prednisone daily with an 8-week tapered dose schedule.

Complications

At day 185, the patient had a perioral Herpes simplex exacerbation, which was treated with valacyclovir and topical acyclovir cream. At day 220, she had molluscum contagiosum outbreak of both the facial graft and her native cheeks, which was effectively treated by curettage. She developed moderate thrombotic microangiopathy with thrombocytopenia, hemolytic anemia, acute renal failure, and hypertension, which was treated by reducing the Sirolimus and infusing fresh frozen plasma and IV immunoglobulins for 4 days. These adverse events resolved in 8 days and Sirolimus was restarted 1 week later after achieving a stable creatinine of 1.2 (similar range to preoperative level). Reoperation was required for parotid duct stenosis.

Aesthetic/Functional Outcome

Sensitivity to light touch (as assessed with Semmes monofilaments) and to hot and cold returned to normal levels 6 months posttransplant. At 10 months, the patient regained labial contact allowing complete mouth closure. At 3 months, the patient was reintroduced into society without difficulty. At 18 months, she was

“satisfied” with her aesthetic result and reported that she felt more comfortable in public.

Patient 2

Date: April 2006

Place: China

Team Leader: Zhang

Recipient: 30-year-old man

Donor: Brain-dead 25-year-old man

Indication: Bear bite

Elapsed time-to-transplant: 18 months

Transplant type: Osteomyocutaneous

Allotransplant design: Skin, soft tissue, upper lip, nose (cartilage/soft tissue), the right anterior maxillary sinus wall, right zygoma with lateral orbital wall, right parotid gland, and partial masseter with intraoral mucosa

Nerves: Bilateral facial nerve (right facial nerve repair reported as “suboptimal”)

Vascular design: bilateral facial arteries and anterior facial veins

Previous reconstruction: left radial forearm transplant

HLA Compatibility: 3/6 match

PRAs: unknown

Donor/Recipient CMV status: unknown

Time of operation: 18 hours

Status: Died around 2 years posttransplant

Immunosuppression

In an effort to decrease the risk of acute graft rejection since the PRA was significantly elevated, the recipient was treated with protein A immunoadsorption to a PRA level of <5%. The donor transplant was also preradiated with a dose of 4 cGy. Induction therapy included a humanized IL-2 receptor antibody. Immunosuppression after transplantation consisted of tacrolimus 5 mg IV (target trough level 25 ng/mL), MMF 500 mg (BID), and methylprednisone (0.5 g IV for 2 days followed by 0.25 g for the next 3 days). Maintenance therapy included tacrolimus (5–9 mg BID at 2 weeks, 1 mg BID at 6 months, and 2 mg BID at 2 years), MMF (1.5 g BID initially, 1 g BID at 6 months, and 250 mg BID at 2 years), and prednisone, 25 mg daily for 3 months, 20 mg daily for the next 3 months, 10 mg daily for 9 months, and complete cessation of prednisone therapy was accomplished at 22 months. Of note, a 50 mg dose of hIL-2 antibody was given twice on days 14 and 28 as additional antirejection therapy. Infection prophylaxis included ceftazidime, vancomycin, flagyl, acyclovir, and allicin. Medilac was used to maintain the normal homeostatic levels of gastrointestinal flora. In addition, glucuronolactone was administered for liver function protection.

Graft Rejection

Episodes of acute cellular graft rejections occurred in months 3, 5, and 17 after transplantation, all of which were successfully controlled with tacrolimus dose adjustment (increased serum trough levels to 15–25 ng/mL) and methylprednisone pulse therapy for 5 days followed by a taper schedule from 80 to 10 mg.

Complications

The patient developed hyperglycemia on postoperative day 3 requiring 21 months of insulin therapy after which he was transitioned to repaglinide and metformin. Although the details have not yet been published, this patient died during his third-year posttransplant. The patient became noncompliant with his immunosuppressive regimen possibly at the advice of a “witch doctor” (nonmedical tribe doctor) and had a very limited social support system in place. He resided in a remote village at a far distance from the hospital.

This suboptimal situation eventually culminated in the patient developing multisystem organ failure, irreversible organ dysfunction, and subsequent death.

Aesthetic/Functional Outcome

This face transplant patient required multiple surgical revisions including scar revision, redundant tissue excision, local transplant transposition to the oral commissure, and an autologous cartilage graft to the right orbital floor. The patient also had persistently poor right facial nerve function posttransplant, including significant right eyelid lagophthalmos presumably from poor intraoperative nerve adaptation. His facial muscles, including the levator labii superioris and levator angular oris, never improved function resulting in suboptimal posttransplant smiling. However, normal skin and oral mucosa sensation, as measured by Semmes-Weinstein filament testing, was documented at 3 months. Thermal sensation returned by 5 months posttransplant.

Patient 3

Date: January 2007

Place: France

Team Leader: Lantieri

Recipient: 29-year-old man

Donor: Brain-dead male

Indication: Neurofibromatosis Type 1

Elapsed time to transplant: Immediate reconstruction following excision

Transplant type: Myocutaneous

Allotransplant design: Lower two-thirds of face including skin, soft tissue, lips, cheeks, nose (cartilage/soft tissue), bilateral parotid glands, parotid ducts, and intraoral mucosa

Nerves: Bilateral facial and trigeminal (V2 and V3) nerves

Vascular: bilateral external carotid arteries, facial veins

Previous reconstruction: 14 tumor resections (lifting-suspensions and modeling resections)

HLA Compatibility: 3/6 match

PRAs: unknown

CMV status: unknown

Time of operation: 15 hours

Blood loss: 35 units

Status: Alive

Surgical Technique

Prior to undergoing facial transplantation, the patient underwent 14 various surgical procedures (1993–2006) for plexiform neurofibroma removal on the face before inclusion in this protocol. Bilateral blepharoptosis was corrected and the function of the left eyelid was fully restored but poor aesthetics and function remained persistent. Plexiform neurofibroma excision included removal of all the soft tissues below the zygomatic arch.³ The left facial nerve was dissected down to the level of the stylomastoid foramen. Of note, this extensive plexiform neurofibroma removal resulted in massive surgical bleeding, when compared with the second part of the procedure (transplant inset). The allotransplant included the donor's skin, oral mucosa (including parotid duct), parotid glands, facial, infraorbital (V2), and mental (V3) nerves. However, the mental nerves were unable to be repaired to the recipient side destroyed by the tumor at level of the mental foramen. The external carotid arteries and the facial veins of the donor were anastomosed in an end-to-end fashion to the external carotid arteries and the thyrolinguofacial veins respectively of the recipient.¹³

Immunosuppression

The induction protocol included 1.25 mg/kg of thymoglobulin for 10 days, oral tacrolimus to achieve a target level of 10 to 13

ng/mL, MMF 2 g/d (target = 40–60 ng/mL), and prednisone. Initially, methylprednisone was administered at a dose of 500 mg on day 1, 1250 mg on day 2, 120 mg on day 3, and followed by prednisolone, 60 mg for 7 days, and then tapered to a dose 10 mg/d. The maintenance protocol included tacrolimus (8–10 ng/mL), MMF (2 g/d), and oral prednisone (10 mg/d). Twice-weekly immunomodulatory therapy by extracorporeal photopheresis was initiated 3 months after surgery and then reduced to 1 course every 2 weeks for the next 3 months, to control persistent subclinical rejection.¹²

The donor was CMV and *T. pallidum* positive, whereas the recipient was negative for both. He therefore required CMV and syphilis prophylaxis including valacyclovir 900 mg for 6 months and methylpenicillin 3,000,000 IU for 15 days. In addition, the patient received PCP prophylaxis in the form of Bactrim 400 mg/d for 6 months. Of note, the main adverse event was a valganciclovir-resistant viremia that coincided with the second acute rejection episode. Treatment included Foscarnet IV 6 g/d for 8 weeks, and the MMF was withheld from days 120 to 165 posttransplant. At 1 year, the maintenance protocol consisted of tacrolimus (10 mg/d), MMF (500 mg/d), and prednisone (7.5 mg/kg/d). Microchimerism was also assessed at 1 year using PCR with a detectable lower limit of 0.1%. There was no evidence of microchimerism, as defined as >1% donor cells in the peripheral blood.

Graft Rejection

Two episodes of clinical rejection occurred on days 28 and 64. The first rejection episode presented with mild cervical edema and a skin biopsy demonstrating grade 1 rejection (mild dermal CD3+ lymphocytic infiltrate and absent epidermal inflammation). In response, prednisone was increased to 60 mg for 3 days with 3 daily 500 mg IV boluses. The rejection episode resolved 100% clinically, but subsequent biopsies still demonstrated a grade 1 rejection. The second rejection episode also presented with mild skin erythema and rejection grade 1 and 2 on skin and mucosal biopsies, respectively. This rejection episode was again successfully treated with 3 daily IV prednisone boluses. However, the mucosal rejection still persisted and therefore antilymphocyte serum was given at 1 mg/kg/d for 7 days. Coincidentally, this second rejection episode was associated with a cytomegalovirus infection. Both episodes eventually resolved with no further clinical signs of rejection.

Complications

The patient had a transient episode of steroid-induced delirium postoperatively, which resolved following the administration (25–50 mg) of chlorpromazine for 5 days. In addition, revisional surgery included correction of right eyelid ectropion and titanium discus dental implants.

Aesthetic/Functional Outcome

The patient saw his face for the first time on day 10, without any adverse psychologic sequelae. At 6 months the patient was able to voluntarily contract the left orbicularis oculi and orbicularis oris. The patient achieved spontaneous mimicry at 9 months, and at 12 months demonstrated EMG-documented bilateral trigeminal and facial motor function. The facial motor nerve function recovered better on the left side. Sensation of the transplant was noted at 3 months and continued to improve over the next year. The transplant surgery ultimately reduced the patient's appearance-related concerns, and he was able to obtain a full-time job at 13 months. Psychologic recovery was reported as "excellent," with complete social reintegration.

Patient 4

Date: December 2008
 Place: Cleveland, Ohio
 Team Leader: Siemionow
 Recipient: 45-year-old woman
 Donor: Brain-dead 44-year-old woman
 Indication: Shotgun injury
 Elapsed time to transplant: 4 years
 Transplant type: Osteomyocutaneous
 Allotransplant design: Composite LeFort III midfacial skeleton transplant including overlying skin, soft tissue, total nose, lower eyelids, upper lip, total infraorbital floor, bilateral zygomas, bilateral parotid glands, anterior maxilla with central maxillary incisors, total alveolus, anterior hard palate, and intraoral mucosa
 Nerves: Bilateral facial nerves
 Vascular: bilateral external carotid arteries, external jugular veins, posterior facial vein
 Previous reconstruction: temporoparietal muscle transposition, radial forearm free flap, free fibula flap, calvarial split-thickness grafts, multiple autologous skin grafts
 HLA Compatibility: 2/6 match
 PRAs: none
 CMV status: D+/R-
 Time of operation: 22 hours
 Blood loss: 500 mL
 Status: Alive

Immunosuppression

Induction included rabbit antithymocyte globulin (dosing ratio of 1.2 mg/kg IV daily) for 9 days in combination with high-dose (1000 mg) IV methylprednisolone. The maintenance immunosuppressive regimen employed tacrolimus, MMF, and prednisone (5–10 mg/d). There have been no reports of microchimerism thus far (defined as >1% donor cells in the peripheral blood).

Prophylaxis for cytomegalovirus (CMV) and *Pneumocystis jiroveci* included ganciclovir for 8 weeks followed by valganciclovir 900 mg twice daily for 5 months, and trimethoprim-sulfamethoxazole 400 mg 3 times per week indefinitely. The patient was evaluated with weekly mucosa and skin biopsy for the first 10 weeks, bimonthly for 2 months, and then monthly thereafter. Given the patient's high-risk CMV donor+/recipient- (D+/R-) status, maintenance of a high level of ganciclovir was a priority. Subsequently, ganciclovir was switched to valganciclovir, and no CMV viremia has been reported.

Graft Rejection

On day 47, a routine biopsy showed subclinical rejection of the graft mucosa (Banff III/IV), but without any clinical evidence of skin rejection (Banff 0/IV). A single dose of IV corticosteroids reversed rejection, confirmed by normal biopsy on day 50. There has been no use of donor bone marrow infusion, phototherapy (REF), or irradiation since transplantation.

Complications

No major complications have been reported thus far. Two minor additional surgeries included bilateral ectropion repair and surgical closure of her PEG tube. Of note, a palatal obturator was needed postoperatively for a small 2 cm palatal defect between the native and transplanted palates. There has been no CMV viremia reported, nor have there been signs of opportunistic infection, new-onset diabetes, or renal insufficiency.

Aesthetic/Functional Outcome

Rehabilitation physical speech/swallow therapy, initiated on POD 3, was performed daily for the first 6 weeks and then 3 times/wk for the entire follow-up period, and included static and dynamic exercises. Quantitative neurosensory testing at 3 months showed sensory reinnervation of the transplanted skin progressing bilaterally from the graft's lateral boundaries toward the nose. At 5 months posttransplant, normal sensation returned including under the lower eyelids, upper lip, and the tip of the nose.

Motor recovery including facial mimetics progressed at a slower, steady rate, as demonstrated by improved facial mimetics with symmetric smiling and upper lip occlusion. The patient's upper lip and lower eyelid movements remain imperfect. Physiotherapy and speech therapy have consisted of supervised controlled passive and active motion exercises, gentle massage, sensory reeducation, and reeducation in facial acceptance.

At 6 months posttransplant, the functional outcome of her facial composite tissue allograft has been reported as "well-above expectation."⁵ The patient reported normal sensation to both pain and temperature at 5 months posttransplant. In great contrast to her pretransplant status, she can now breathe through her new nasal cavity with a reestablished sense of smell, her taste has dramatically improved, she eats solid foods and drinks from a cup, and she now speaks more clearly and intelligibly.

From an aesthetic standpoint, this patient's transplant was planned as a multistage procedure, with successful craniofacial reconstruction and rehabilitation set as the first goal. A later surgical procedure scheduled at around 1 year posttransplant will address soft-tissue redundancy and graft contouring. Coincidentally, excised midfacial scarred tissue removed in preparation for facial transplantation may explain why the patient reports reduction of pain from a chronic pain level of "8/10" before transplantation to "1/10" after transplantation.

Patient 5

Date: March 2009
 Place: France
 Team leader: Lantieri
 Recipient: 28-year-old man
 Indication: Shotgun injury
 Transplant type: Osteomyocutaneous
 Allotransplant design: Premaxilla (anterior maxillary osteotomy), chin, nose (cartilage/soft tissue), and overlying lower two-third of face including skin, soft tissue, lips, cheeks, bilateral parotid glands, parotid ducts, and intraoral mucosa
 Nerves: Bilateral facial and trigeminal (V2 and V3) nerves
 Vascular: bilateral external carotid arteries, facial veins
 Time of operation: 15 hours
 Status: Alive

Patient 6

Date: April 2009
 Place: France
 Team leader: Lantieri
 Recipient: 30-year-old man
 Indication: Extensive burn sequelae
 Transplant type: Facial myocutaneous transplantation with concomitant bilateral below-elbow upper limb transplantation
 Allotransplants designs (face): Upper two-third of face including nose (cartilage/soft tissue) skin, soft tissue, lips, cheeks, bilateral parotid glands, and scalp
 Nerves (face): Bilateral facial and trigeminal (V2 and V3) nerves
 Vascular (face): bilateral external carotid arteries, facial veins
 Time of operation: 30 hours (face and both hands)
 Status: Expired nearly 2 months posttransplant

Patient 7

Date: April 2009
 Place: Boston, Massachusetts
 Team Leader: Pohomac
 Recipient: 59-year-old man
 Indication: Fall/electrical injury
 Transplant type: Facial osteomyocutaneous transplant
 Time of operation: 17 hours
 Status: Alive

DISCUSSION

Plastic and reconstructive surgeons, along with their multidisciplinary colleagues, have recently embarked on a novel method of restoring facial defects using principles such as "replacing like with like," unimaginable to our surgical forefathers.¹⁴ Multiple centuries have passed with surgeons attempting complex facial reconstruction by way of numerous autologous flaps, each and every one of them falling short of aesthetic "perfection." It was not until the 1980s when cyclosporine was introduced did the field of CTA turn from a dream to reality, and in less than 3 decades, that transplantation of facial composite allotransplants entered the clinical arena.¹⁵

When comparing the facial organ to other solid organs, it is without question, unmatched in dominance in relation to our daily social interaction and self-being.¹⁶ Consequently, many patients may well consider this surgery nothing short of "life-saving." Offering these individuals a surgical option eradicating the detrimental "stigmata" of being different, is underappreciated by many of its critics. It is naive to call this "cosmetic surgery" requiring lifelong immunosuppression. This surgery is not "immoral" simply because it both restores critical facial organ function and indisputably restores human appearance.¹⁷ To those unfortunate patients missing multiple facial subunits preventing normal social interaction and vital daily functions such as smiling, smelling, laughing, kissing, drinking, eating, and speaking, face transplantation may evolve to become the "gold-standard."¹⁸

However, most reconstructive transplant surgeons would consider transplanting a functional and restorative facial allotransplant the most challenging CTA subset. This translated into a recently proposed classification system, which assigns face and hand allotransplants into a class all to themselves (ie, Gordon Type III), based on their unmatched level of relative surgical complexity and accompanying psychologic/rehabilitative challenges.¹⁹ In fact, we may in the future need to assign separate clinical grading systems to various CTA skin-containing subtypes. With currently over 13 different types of CTA encompassing varying combinations of tissue composition, skin amounts, and antigenicity,²⁰ modifying the currently accepted Banff CTA classification in the near future seems unavoidable.²¹

Besides the surgery itself, preoperative face transplant candidate selection is another important characteristic separating this transplant from its solid organ counterparts such as a kidney for example. A kidney transplant, for the sake of comparison, is an "internal" transplant. The recipient receives an organ whose function and perioperative recovery is self-driven and hidden from society, meaning that as long as its vascular/ureteral anastomoses are sufficient and its antigenicity is controlled, it will ultimately provide renal function eliminating dialysis dependence. For this kidney patient, walking down the street in public remains constant, and everyday social confrontations and physical rehabilitation of his/her organ are nonexistent.

In great contrast, a candidate wishing to receive a face transplant (ie, "external" transplant), in this particular example, is one who undoubtedly suffers both from a psychosocial standpoint causing varying social withdrawal, and from a facial deficit standpoint where everyday facial function and expression is complicated. Recovery of the face allotransplant is often much more challenging

than that of a kidney. Analogous to a chronic renal failure patient, life may continue in these unfortunate patients with severe facial deficit and absent facial function, but they are making an informed decision to pursue facial transplantation. They must not only maintain immunosuppression compliance, but they must actively engage in aggressive rehabilitation to recover intricate allograft function via cortical reorganization.²² By the nature of this operation, they are forced to engage new social interaction by externally displaying their new organ transplant; thereby encountering unpreventable postoperative psychosocial conflict.

Therefore, with these unique obstacles separating face transplantation from solid organ transplantation, we as pioneering reconstructive surgeons, must be extremely selective and diligent in candidate selection and work in collaboration with our transplant psychiatry and bioethics colleagues.²³ One must recognize that all potential face transplant candidates should be treated as a solid organ transplant candidate and be rigorously screened for compliance and social/familial support. We must all realize that the best aesthetic face transplant performed in a noncompliant patient is undoubtedly a pending failure, both from a rehabilitation and immunosuppression standpoint. More importantly, early face transplant-related complications will not only jeopardize patient safety, they will make it more and more difficult for other institutions to obtain Institutional Review Board approvals.²⁴

Many CTA surgeons envision an algorithm transformation for facial transplantation. Instead of selecting patients who have undergone years of torment with dozens of autologous reconstructive attempts and now scarred, stenotic target vessels, perhaps the future will allow first-line composite tissue alloconstruction at a time when the patient has acquired complete informed consent thereby understanding all associated risks, potential complications, and alternatives.

CONCLUSIONS

A total of 7 face transplants have been performed since 2005 (Fig. 1). All have all been revolutionary in their own right, providing varying combinations of skin, muscle, and/or bone. Indications include severe trauma, congenital disease (ie, neurofibromatosis), and severe burn. All 7 patients have encountered at least 1 episode of acute graft rejection. Of total, 5 patients have been reversed successfully, with 2 mortalities that may have been rejection-related. Limited details as to exact causes of death have been reported (patient 2 and 6).

Overall function has been reported satisfactory in all long-term reports thus far, with sensory function recovery ranging between 3 and 6 months and acceptable motor function recovery being between 9 and 12 months. Aesthetic outcomes have been variable, but delaying secondary cosmetic procedures (ie, lid tightening procedure, excision of soft tissue redundancy, etc) in the setting of complex face transplantation is an advisable option. The risks and benefits of face transplantation, which involves mandatory lifelong immunosuppression at levels analogous to kidney transplants, should be deliberated by a multidisciplinary face transplant team at each institution supported by a group of experienced transplant psychiatrists and bioethicists.

In conclusion, face transplantation has been shown thus far to be a viable option in some patients suffering severe facial deficits which are not amenable to modern-day reconstructive technique. As newer immunosuppression options become available, indications for face transplantation, along with its parent specialty known as CTA, will be greatly expanded.^{25,26} Future research in regards to the ethical and psychologic challenges complicating the identification of the optimal face transplant candidate, establishing effective face transplant rehabilitation protocols, and expanding large animal immunologic basic science investigation, is undoubtedly warranted.

General	Dubendorf	Zhang	Larrier	Somaiwong	Larrier	Larrier	Polonsky
Date	Nov-05	Apr-06	Jan-07	Dec-08	Mar-09	Apr-09	Apr-09
Operative Time	18 months	18 hours	15 hours	22 hours	15 hours	30	17
Follow-up		2 years	1 year	180 days			
Recipient							
Etiology of Defect	Dog attack	Bear attack	Pharyngeal Neurofibroma	Shedgun blast	Shedgun blast	Burn	Electrical injury
Age	38	30	29	45	28	30	59
Gender	F	M	M	F	M	M	M
Donor							
Age	46	25	M	44	-	-	-
Gender	F	M	M	F	-	-	-
Status	Brain dead, alive	Cardiac arrest	Brain dead, alive	Brain dead, alive	Brain dead, alive	Brain dead, alive	Brain dead, alive
Compatibility							
ABO	Both O+	Both A	Both O+	Donor A Recipient AB	-	-	-
HLA	5/6	3/6	3/6	2/6	-	-	-
PHA	95-99%				-	-	-
Anatomical							
Neural	Bilateral maxillary (V2) and marginal (V3) branches, left facial motor segment of the splanchnic foramen	Bilateral facial nerve at the level of the splanchnic foramen	Facial, infraorbital (V2) and mental (V3) trigeminal branches	Bilateral facial nerve	Facial, infraorbital (V2) and mental (V3) trigeminal branches	Facial, supra (V1) and infraorbital (V2) trigeminal branches	
Vascular	Bilateral facial artery and vein anastomoses	Bilateral maxillary arteries and anterior facial veins	Bilateral external carotid arteries and facial veins	Bilateral donor external carotid artery to recipient common facial artery, two external carotid veins and one posterior facial vein	External carotid artery, external jugular vein and thyrovascular trunk (includes concomitant bilateral hand transplants)	External carotid artery, external jugular vein and thyrovascular trunk (includes concomitant bilateral hand transplants)	
Bone/Carilage		Nasal cartilage, right anterior maxillary sinus wall, right zygoma including lateral orbital wall	Nasal cartilage	Infraorbital foramen, bilateral zygomatic, anterior maxilla with central maxillary incisors, total alveolus, and anterior hard palate	Infraorbital foramen, bilateral zygomatic, anterior maxilla with central maxillary incisors, total alveolus, and anterior hard palate	Infraorbital foramen, bilateral zygomatic, anterior maxilla with central maxillary incisors, total alveolus, and anterior hard palate	Osteomyelitis
Soft Tissue/Muscle	Levator palpebrae superioris and zygomatic muscles connected	Nasal soft tissue, right parotid gland, parotid masseter, intra-oral mucosa, upper lip	One mucosa	53% square cm of skin surface area, nasal soft tissue, lower eyelids, upper lip, bilateral parotid glands	53% square cm of skin surface area, nasal soft tissue, lower eyelids, upper lip, bilateral parotid glands	Lower 2/3 of the face, parotid glands, masseter, oral mucosa, upper and lower lips	Scalp, ears, upper 2/3 of the face, parotid glands, masseter, oral mucosa, upper and lower lips
Therapies							
Immunosuppressive Regimen	Induction - ATG/Maintenance - Tacrolimus, MMF, steroids Adjunct - phototherapy and BM1*	Induction - IL-2 receptor mAb, Tacrolimus, MMF, and Prednisone/Maintenance - Tacrolimus, MMF, and Prednisone	Induction - ATG, Tacrolimus, MMF, and Prednisone. Maintenance - Tacrolimus, MMF, and Prednisone	Induction - ATG and Methylprednisolone Maintenance - Tacrolimus, MMF, and Prednisone	Induction - ATG and Methylprednisolone Maintenance - Tacrolimus, MMF, and Prednisone	Induction - ATG and Methylprednisolone Maintenance - Tacrolimus, MMF, and Prednisone	Induction - ATG and Methylprednisolone Maintenance - Tacrolimus, MMF, and Prednisone
Medical Prophylaxis	CMV, PCP	Cefazolin, Vancomycin, Flagyl, Acyclovir, Atelvia, Metformin, and Gabapentin	Cefazolin, Vancomycin, Flagyl, Acyclovir, Atelvia, Metformin, and Gabapentin	CMV (ganciclovir and valganciclovir), PCP (Bactrim)	CMV (ganciclovir and valganciclovir), PCP (Bactrim)	CMV (ganciclovir and valganciclovir), PCP (Bactrim)	CMV (ganciclovir and valganciclovir), PCP (Bactrim)
Complications							
Rejection Episodes	2	None	2	1	NTD	-	-
Infection	HSV flare of the lips (no vacuum contamination)		Gancyclovir resistant CMV				
Non-infection	Thrombotic microangiopathy with thrombocytopenia, hemolytic anemia, ARS, and HTN		Blood loss requiring transfusions, blood transfused (all units returned), ectropion (corrected)	Partial defect and ectropion (impaired)			
Functional Recovery							
Status	Alive	Expired	Alive	Alive	Alive	Alive	Alive
Sensation	LT Temperature (6 months)	LT (3 months), Temperature (6 months)	LT (3 months)	Bowel (POD 2), QST documented sensation (12 months), complete LT and Temperature (12 months)	Bowel (POD 2), QST documented sensation (12 months), complete LT and Temperature (12 months)	Expedit	
Motor	mouth closure (10 months)	Right Laryngopharynx, Levator palpebrae superioris and Levator Anguli Oculi poor (unable to contract), levator palpebrae superioris (unable to contract), secondary to inadequate coaptation	Alive to speak and eat on day 10, voluntarily contract the orbicularis oculi and orbicularis oris (unable to contract), levator palpebrae superioris (unable to contract), and EMG-documented bilateral trigeminal and facial motor function (12 months)	Upper lip occlusion, facial mimicry (premature), soft food and drinks (premature), levator palpebrae superioris (unable to contract), and EMG-documented bilateral trigeminal and facial motor function (12 months)	Upper lip occlusion, facial mimicry (premature), soft food and drinks (premature), levator palpebrae superioris (unable to contract), and EMG-documented bilateral trigeminal and facial motor function (12 months)		

*Patient is thought to have discontinued immunosuppressive treatment resulting in multi-organ system failure and eventual death
 *1/24 ml of donor bone marrow was harvested from the iliac crest and stored in two parts aliquots. One half of the bone marrow was then injected on days 4 and 11 post transplant

Abbreviations: ARS - Acute Renal Failure; ATG - Anti-Thymocyte Globulin; BM1 - Bone Marrow Transplant; HTN - Hypertension; LT - Left Tissue; MMF - Mycophenolate Mofetil; NTD - New To Donor; QST - Quantitative Sensory Testing

FIGURE 1. Relevant details pertaining to all 7 face transplants.

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