First Human Face Transplantation: 5 Years Outcomes

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Background. The first human facial allotransplantation, a 38-year-old woman, was performed on November 27, 2005. The aesthetic aspect and functional recovery and the risk-to-benefit ratio are evaluated 5 years later.
Materials and Methods. The facial transplantation included nose, chin, part of cheeks, and lips. The immunosuppressive protocol included tacrolimus, mycophenolate mofetil, prednisone, and antithymocyte globulins. In addition, donor bone marrow cells were infused on days 4 and 11 after transplantation.
Results. The aesthetic aspect is satisfying. The patient has normal protective and discriminative sensibility. She showed a rapid motion recovery, which has remained stable for 3 years posttransplantation. She can smile, chew, swallow, and blow normally whereas pouting and kissing is still difficult. Phonation recovery was impressive therefore the patient can talk normally. Two episodes of acute rejection developed during the first year. Donor-specific anti-human leukocyte antigen antibodies were never detected. Five-year mucosal biopsy showed a slight perivascular inflammatory infiltrate while skin biopsy was normal. The main side effect of the immunosuppressive treatment was a progressive decrease in renal function, which improved after switching from tacrolimus to sirolimus. Moreover, she developed arterial hypertension, an increase in lipid levels, and in situ cervix carcinoma treated by conization. Since 2008, she showed mild cholangitis possibly caused by sirolimus. In September 2010, bilateral pneumopathy occurred and was successfully treated with antibiotics.
Conclusion. Despite some long-term complications, which are similar to those reported after solid organ transplantation, the patient is satisfied of her new face and has normal social interaction.

Keywords: Face allotransplantation, Composite tissue allotransplantation, Functional recovery, Immunosuppression side-effects, Rejection.

(*Transplantation* 2012;93: 236–240)

Facial transplantation has been performed in disfigured patients to restore the aesthetic appearance and function when all the other conventional reconstructive techniques had failed or were expected to fail. It is important to remind that of all the physical handicaps, none is so socially devastating as facial disfigurement, which may lead to depression, social isolation, alcohol abuse, and increased risk of suicide in the majority of cases. Indeed, facially disfigured patients experience many psychologic and social problems, such as lowered self-confidence, negative self-image, social anxiety, and marital problems (*1*). For all these reasons, we decided to perform the first face allotransplantation on November 27, 2005. Not only did the recipient, a young woman disfigured after an accident that resulted in the loss of part of the face, including nose and mouth, experience the disfigurement but also the impossibility to eat, drink, and speak normally. Thus, social interaction became problematic, resulting in tremendous psychologic and social difficulties. The patient accepted the risks of facial allotransplantation to gain functional, aesthetic, and social benefits. The early outcome confirmed the technical feasibility of this new procedure and the immunosuppressive regimen, which was the same used in hand transplantation with the addition of two infusions of donor bone marrow, assured graft survival (*2*). The evolution of the graft was favorable with a notable recovery of sensibility and mo-

The authors declare no funding or conflicts of interest.

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All the authors have collaborated, read, and approved the manuscript. B.L., S.T., and B.D. performed the surgical procedure. J.P.G. and H.P. evaluated sensibility and motion recovery in the follow-up. J.K. performed the biopsies and the histologic studies. The remaining authors managed the patient during the 5 years of follow-up. P.P. collected the data. P.P., J.K., and E.M. wrote the manuscript. J.M.D. and B.D. both have to be considered as "last author" being the coordinator of the transplantation team and the maxilla-facial surgery team, respectively.
Received 26 May 2011. Revision requested 17 June 2011.
Accepted 14 October 2011.

ISSN 0041-1337/12/9302-236
DOI: 10.1097/TP.0b013e31823d4af6

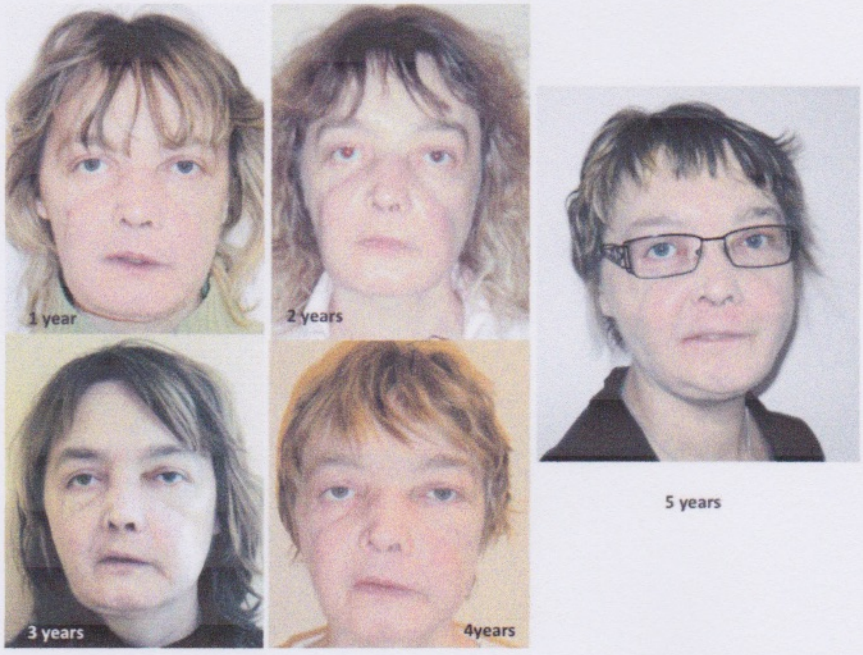

FIGURE 1. Macroscopic aspect of the graft during the follow-up.

tility, although two reversible episodes of acute rejection occurred (*3*).

This first face allotransplantation showed the feasibility of this new composite tissue allotransplantation; subsequently, additional facial allotransplantations have been successfully performed all over the world (*4–7*).

Five years after the first human allograft, herein, we report the present aesthetic aspect and functional recovery of the graft and discuss the risk-to-benefit-ratio of this composite tissue allotransplantation.

RESULTS

Aesthetic and Functional Results

The aesthetic results (Fig. 1) have been satisfactory since the first days after transplantation till now. The patient was kept without bandages and since the first days she had the opportunity to look at her grafted face in the mirror to become familiar with her new appearance and integrate it into her "body image."

At present, the patient has normal pain and cold sensation without dysesthesia and normal discriminative sensibility. The analysis of motion recovery showed a rapid and continuous improvement of muscle function, starting 4 months after transplantation (*3*), and this has remained stable from the third year posttransplantation. The patient has achieved normal mouth opening (36 mm), and she can smile although there is a slight synkinesis on the left side and a mild contracture of some skin muscles. Orbicularis muscle recovery is incomplete but blowing is normal, chewing and swallowing is possible, whereas pouting and kissing are still difficult. Phonation recovery was impressive, and the patient can talk easily and intelligibly.

From the beginning, the patient was satisfied of her new face, she took care of herself and had normal social interaction with healthcare staff and relatives. The fact that the graft gained quickly sensibility and motor function helped the patient "to use" her face. The patient's new facial appearance is identical neither to that of the donor nor to her own face before the accident. The patient accepted easily her new facial appearance and has been satisfied since the first days. She gained not only a "new" face but also a "new" life as she started to interact again socially and experienced the absence of reactions of others when going out to the restaurant, shopping, applying for jobs, meeting new people, and traveling abroad.

Histology and Magnetic Resonance Imaging Results

The recipient developed two episodes of acute rejection during the first postgraft year (on days 18 and 214 after transplantation), which were successfully treated (*2*). Face skin appeared normal at all the other time points of the follow-up.

Histologic examination was performed on a skin biopsy taken from the submammary sentinel skin graft at the third, fourth, and fifth transplant anniversary. At the third anniversary, factor XIIIa+ dermal dendrocytes, the epidermis looked normal. The dermis contained a sparse perivascular infiltrate mostly made of CD3+ T cells, with rare TIA1+ cytotoxic T cells. Human leukocyte antigen (HLA)-DR antigens were expressed on capillary endothelial cells. Dendritic cells were present in normal numbers and distribution, both in the form of intraepidermal CD1+ Langerhans cells and of factor XIIIa+ perivascular dermal dendrocytes. The epidermis contained Ki67+ cycling basal keratinocytes, EGF-R+ keratinocytes in the basal and suprabasal layers, and Melan-A+ basal melanocytes. These findings were consistent with rejection grade 0, according to the Banff score (*8*).

At the fourth anniversary, pathologic findings from the sentinel skin graft included a rather thin epidermis contain-

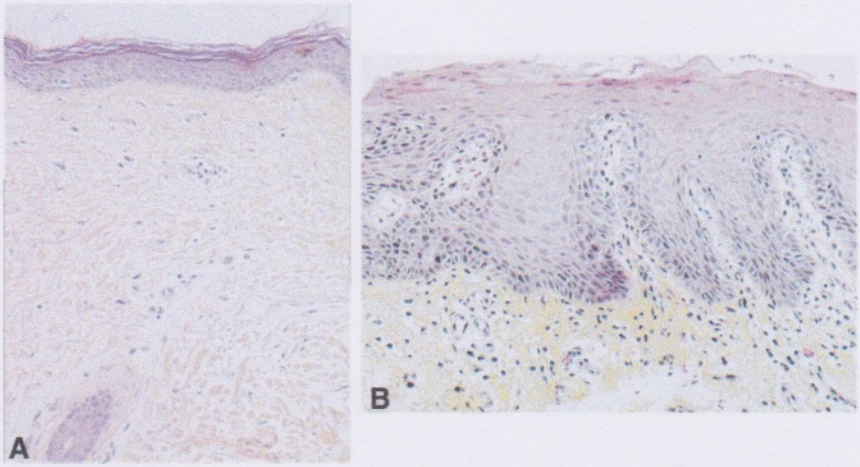

FIGURE 2. (A) Histologic aspect of the sentinel skin graft. The epidermis and dermis look normal (hematoxylin-eosin-saffron stain). (B) Histologic aspect of the oral mucosa. The epithelium looks normal. A mild lymphocytic infiltrate is seen in the corium (hematoxylin-eosin-saffron stain).

ing occasional vacuolated basal keratinocytes and an exocytosis of lymphocytes. The upper dermis contained a rather dense lymphocytic infiltrate made of CD3+ T-cells with several TIA1+ cytotoxic and occasional FoxP3+ T-reg cells. Similar findings were observed in the biopsy taken from the oral mucosa. These findings were suggestive of rejection grade II. At the fifth transplant anniversary, the epidermis was still rather thin, but looked otherwise normal (Fig. 2A). The underlying dermis looked normal, containing collagen fibers of normal density, sweat glands, hair follicles, nerves, and blood capillary vessels surrounded by occasional lymphocytes and mast cells. The subcutaneous adipose tissue looked also normal. CD3+ lymphocytes were seen as small perivascular cuffs; a small percentage of them corresponded to FoxP3+ Treg or to TIA1+ cytotoxic cells. A biopsy taken from the buccal mucosa showed an epithelium of normal thickness, overlaying a corium containing occasional lymphocytes and mast cells (Fig. 2B). The aspect seen on both the sentinel skin graft and the oral mucosa was consistent with grade 0 rejection according to the Banff score (*8*).

The magnetic resonance imaging and ultrasonography examinations of the various tissues composing the graft, particularly vessels, connective, and adipose tissues showed no modifications, namely vasculopathy or fibrosis (*9*).

Immunosuppression and Immunologic Results

Starting from 12 months after transplantation, the immunosuppressive regimen consisted of sirolimus (targeted trough level: 6–12 ng/mL), mycophenolate mofetil (1500 mg/day), and prednisone (5 mg/day). Sirolimus was introduced 11 months after transplantation to slowly reduce tacrolimus; however, when the drugs were combined, the patient developed mild thrombotic microangiopathy; consequently, both drugs were stopped for 15 days and then only sirolimus was reintroduced. Extracorporeal photochemotherapy was performed from August 2006 to December 2008 to prevent acute rejection.

The patient did not develop graft-versus-host disease or chimerism in the peripheral blood, except for an episode of microchimerism that occurred 2 months after transplantation, when real-time quantitative polymerase chain reaction study showed 0.1% of donor cells among the CD34+ enriched bone marrow cell population. Anti-HLA antibodies were never detected. After thymoglobulin induction, T and NK lymphocyte subsets were rapidly and profoundly depleted and remained at low levels over time (Fig. 3A). Immune reconstitution was characterized by a large expansion of memory CD4 and CD8 T-cell subsets (Fig. 3B). Treg cells that were initially increased decreased to stable normal values, whereas activated $CD4^+DR^+$ and $CD8^+DR^+$T cell subsets were preferentially increased during the follow-up (Fig. 3C).

Complications

The main side effect of the immunosuppressive treatment was a progressive decrease in renal function. Indeed, measured creatinine clearance was 90 mL/min/1.73 m^2 before transplantation and dropped to 59 and 43 mL/min/1.73 m^2 at 6 and 12 months posttransplant, respectively. Renal function improved slowly after tacrolimus withdrawal: 4 years after transplantation with the new immunosuppressive regimen creatinine serum value was 71 μmol/L, measured creatinine clearance was 71 mL/min/1.73 m^2, and inuline clearance was 59 mL/min/1.73 m^2; whereas, at 5 years, serum creatinine was 69 μmol/L, measured creatinine clearance was 59 mL/min/1.73 m^2, and inuline clearance was 43 mL/min/1.73 m^2. This further decrease in renal function was correlated to the uncontrolled arterial hypertension. Proteinuria never occurred. Triglyceride levels increased after conversion to sirolimus but could be easily controlled by statins.

Five years after transplantation, no signs of osteoporosis was detected. Infectious complications included an HSV1 infection of the lips and poxvirus infection (*Molluscum contagiosum*) of the cheeks (recipient and graft), which occurred 5 months after transplantation and were successfully treated as previously reported.

Fifty months after transplantation, the patient developed cervical in situ carcinoma due to papilloma virus that was treated by conization. Because of an increase in gamma-glutamyl transpeptidase (GGT) values in 2008 and in 2009 (583 UI/L and 474 UI/L, respectively), a hepatic biopsy was performed showing focal mild biliary lesions and a slight periportal inflammatory infiltrate. In March 2010, liver mag-

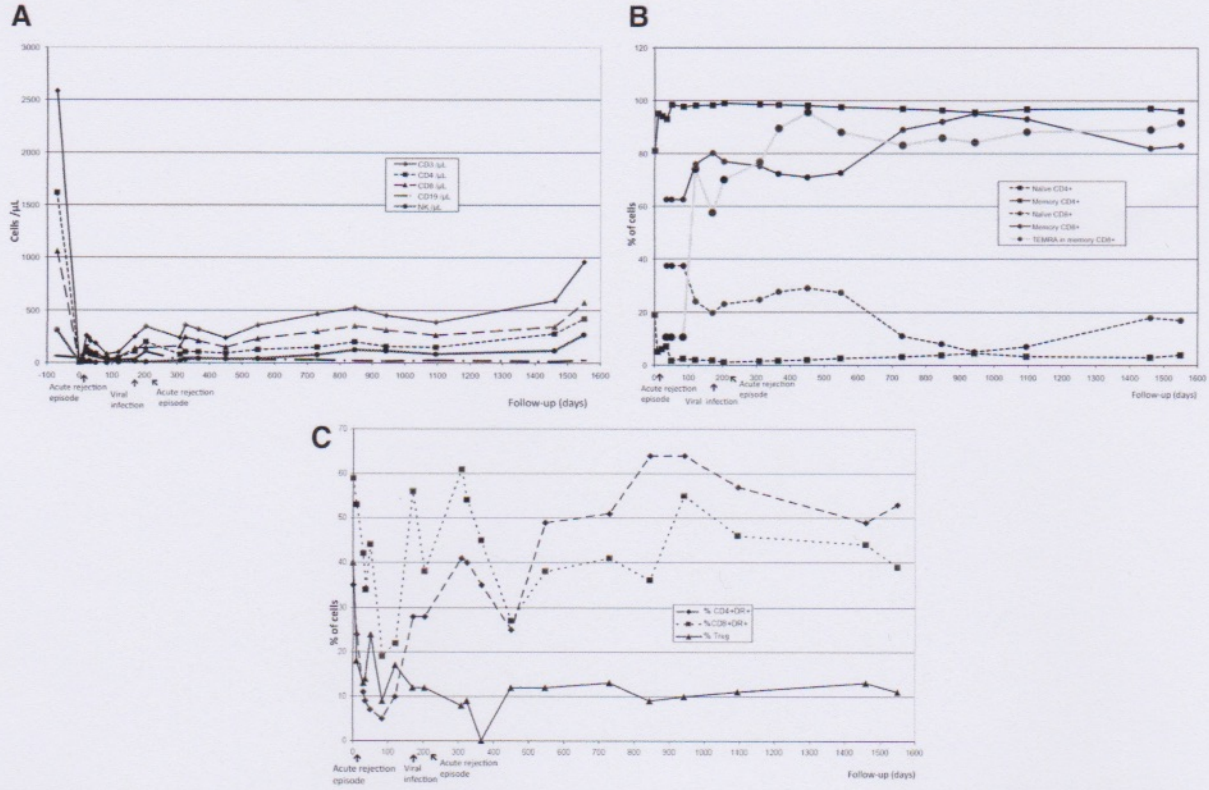

FIGURE 3. (A) T, B, and NK peripheral blood lymphocyte subsets. After depleting induction therapy CD3+, CD4+, CD8+, and NK lymphocyte subsets were profoundly depleted with a slight recovery at the last time point of follow-up. CD4+ to CD8+ T-cells ratio was persistently low. CD4 and CD8 cells showed a large expansion of memory phenotype cell subsets. B-lymphocyte count showed only a limited depletion and remained at a low level. (B) Naive-memory CD4 and CD8 peripheral blood lymphocyte subsets. Proportion of CD4+ and CD8+ memory cells increased during T-lymphocyte immune reconstitution and remained at a high level over time. CD8+ cells developed a large population of terminal differentiated memory phenotype CD27-CD45RA+CD8+ cells at month 5 posttransplantation when viral infection occurred. This population increased progressively from month 5 to month 15 posttransplantation and then remained stable. (C) Activated CD4+DR+, CD8+DR+, and Treg peripheral blood lymphocyte subsets. The mean percentage of Treg cells increased (19%±10%) during the first 4 months after transplantation, then they decreased significantly to stable normal values (11%±3%, P=0.01). Activated CD4+DR+ and CD8+DR+ T-cell subsets preferentially increased during the whole follow-up, remaining at abnormally high levels after the second episode of acute rejection.

netic resonance imaging showed no alterations of biliary tree although GGT value was 489 UI/L.

In September 2010, the patient presented a bacterial bilateral pneumopathy (without germ identification), which was successfully treated with antibiotics.

DISCUSSION

Face transplantation elicited many debates on identity change, social re-acceptance, adverse effects of immunosuppressants in patients who are disfigured but still otherwise healthy, quality and quantity of life after transplantation.

Five years after the first face transplantation, the results are encouraging, indeed the patient shows an almost complete recovery of sensitivity and motion, which allows her to chew, swallow, eat, drink, and speak normally. The oral commissure is a difficult area to reconstruct and to this aim good vascularization and innervation are essential. The goals are not only restoration of oral competence for speech and food retention but also contralateral symmetry. In this patient, the first two goals were achieved, whereas a slight asymmetry of the mouth persists correlated to slight synkinesis and mild muscular contracture as reported in facial palsy.

At present, the patient has a face that can adequately express her feelings and this capacity is important because it plays a key role in how people are seen and perceived by others. Even though facial allotransplantation has provided results that drastically improved the patient's quality of life, she has also encountered some difficulties and complications correlated to the transplantation. First, the patient had to take immunosuppressive drugs daily and underwent ECP as a supportive therapy for 14 months after the second episode of acute rejection. She experienced the psychologic trauma of acute rejection episodes in the first posttransplant year and she is conscious of the possibility of chronic rejection. For this reason, the patient underwent physical examination and biopsy of skin and oral mucosa at least at each anniversary of the graft.

Although at the fourth anniversary pathologic findings from the sentinel skin graft were suggestive of rejection grade II, the patient did not receive additional treatment because both the face and the submammary skin graft looked normal. Indeed at present, there is no compelling evidence that subclinical rejection, defined by skin infiltration without any clinical sign of rejection, should be treated to reduce the risk of long-term chronic rejection.

So far, the patient has shown no signs of chronic rejection although her peripheral blood immunologic phenotype profile is that of an immunosuppressed patient with an "active" profile, which does not seem to have been influenced by the infusion of bone marrow cells performed to facilitate a tolerance process (*10*). The ratio between regulatory T cells (Treg) and activated cytotoxic T cells remains low, despite the infusion of bone marrow and the introduction of sirolimus, which is known to expand regulatory T cells (*11*). Circulating anti-HLA antibodies and C4d deposits in her skin and oral mucosa were never detected, suggesting that B cells do not play a significant role in the allogenic immune response. Despite bone marrow infusion at days 4 and 11, the patient did not develop graft-versus-host disease. The absence of a durable donor chimerism can be explained by an insufficient hematopoietic engraftment due to poor hematopoietic stem cells quality or insufficient conditioning regimen (*12*).

Regarding side-effects of the immunosuppressive treatment, the most severe complication experienced by the patient was a progressive decrease in renal function due to the nephrotoxicity of calcineurin inhibitors with consequent switch to sirolimus and amelioration of the renal function, which worsened again in these last months because of high blood pressure. The conversion did not induce signs of rejection.

The decision to switch to sirolimus was taken because of the decreased renal function. Indeed, the immunosuppressive protocol, including low dose of steroid, mycophenolate mofetil, tacrolimus, apparently is able to assure graft survival, the acute rejection episodes were easily reversed and until now we did not detect any sign of chronic rejection. For all these reasons, we are going to use the same maintenance regimen and to switch to sirolimus only the patients who will develop or side-effects or signs of graft vasculopathy.

The cause of the cholangitis remains unclear, although everolimus was reported to cause cholestasis (*13*); however, GGT values were not influenced by sirolimus dose and trough blood levels.

In conclusion, despite these complications and all the other potential risks correlated to the immunosuppressive therapy, which she will have to take for life, facial allotransplantation offered new opportunities to the patient, who is satisfied of her transplantation.

MATERIALS AND METHODS

Transplantation

The first facial allotransplantation included nose, chin, part of cheeks, and lips. The recipient was a 38-year-old woman, who had been severely bitten by her dog on May 28, 2005. The donor was a brain-dead 46-year-old woman; they shared the same blood group (O+) and five HLA antigens.

The harvesting and surgical procedures have been previously described in detail (*2*). The immunosuppressive protocol included tacrolimus, mycophenolate mofetil, and prednisone, and antithymocyte globulins as induction.

In addition, before surgery, bone marrow was collected from the donor's iliac crests. Half of the bone marrow cells were infused into the recipient on days 4 and 11 after face allotransplantation.

Rehabilitation therapy started 48 hr after surgery, twice a day for the first 4 months then once daily. The rehabilitation program included supervised controlled–motion passive and active facial exercises, mainly focused on the restoration of lip suspension and mouth occlusion.

Evaluation Procedures

The patient's general condition and functional results were evaluated at each anniversary of transplantation. Each year the recipient underwent an accurate evaluation to detect possible complications due to the immunosuppressive treatment, such as metabolic complications, infections, and neoplasia.

Anti-HLA antibodies were monitored by LUMINEX and microchimerism by real-time quantitative polymerase chain reaction (Taqman) analysis of DNA from blood, purified CD3+ cells, bone marrow, and purified CD34+ bone marrow cells. Blood lymphocyte subsets were monitored by FACS analysis at each time point of the follow-up.

Oral mucosa and skin biopsies (from the chin and the sentinel skin graft) were taken at various time points of the regular follow-up or during suspected rejection episodes. Tissue specimens for histology were formalin fixed and paraffin embedded. Five-micrometer-thick sections were stained with hematoxylin-eosin-saffron or labeled immunohistochemically with antibodies detecting various lymphocyte subsets and cells present in normal skin.

At 3 and 5 years after transplantation, ultrasound and magnetic resonance imaging of the face were performed to study the tissues composing the graft. Thermal and Semmes-Weinstein tests were performed at the different time points of the follow-up. Motor recovery was evaluated by using motion images, which were periodically captured by a video camera, and by recording the phonetic exercises.

ACKNOWLEDGMENTS

The authors thank Barbara Trudu for her careful English proofreading and Mrs. Celine Dagot for her invaluable organizational assistance.

The patient has provided signed consent to publish her pictures.

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