Human facial allotransplantation: a 2-year follow-up study

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Summary

Background Progress in composite tissue allotransplantation could provide a new treatment for patients with severe facial disfigurements. We did a partial facial allotransplantation in 2006, and report here the 2 year follow-up of the patient.

Methods The recipient, a 30-year-old man from China, had his face severely injured by a bear in October, 2004. Allograft composite tissue transplantation was done in April, 2006, after careful systemic preparation. The surgery included anastomosis of the right mandibular artery and anterior facial vein, whole repair of total nose, upper lip, parotid gland, front wall of the maxillary sinus, part of the infraorbital wall, and zygomatic bone. Facial nerve anastomosis was done during the surgery. Quadruple immunomodulatory therapy was used, containing tacrolimus, mycophenolate mofetil, corticosteroids, and humanised IL-2 receptor monoclonal antibody. Follow-up included anastomosis of the right mandibular artery and anterior facial vein, whole repair of total nose, upper lip, contracture deformity, upper lip, total nose, the front wall of the right maxillary sinus, the lateral right orbital wall and infraorbital wall, the right zygomatic bone, and a large portion of the right parotid gland (figure 1). Panel reactive antibody (PRA) was detected using a complement-dependent microlymphocytotoxicity test. Two reports of the UK's Royal College of Surgeons outlined the difficulties associated with face transplantation—ie, technical failure, acute rejection, chronic rejection, side-effects of immunosuppressive therapy, non-compliance with immunosuppressive medication, and psychological, societal, and ethical issues.

In November, 2005, the first successful partial facial transplantation was done in Amiens, France. We did a partial facial transplantation on April 13, 2006. Here we report the 2 year follow-up of the recipient after transplantation.

Methods

Patient The face of the patient, a 30-year-old man from a remote village of Yunnan province, China, was severely damaged by a bear in October, 2004. Shortly after the attack, he was treated by debridement and the wound was repaired with a left forearm pedicle flap. But the effectiveness of these conventional techniques was unsatisfactory and the facial wounds did not heal. The patient came to our hospital for further examinations and treatment on March 11, 2006.

The major injury was extensive skin and soft tissue in the right buccal division combined with severe cicatricial contracture deformity, upper lip, total nose, the front wall of the right maxillary sinus, the lateral right orbital wall and infraorbital wall, the right zygomatic bone, and a large portion of the right parotid gland (figure 1). Panel reactive antibody (PRA) was detected using a complement-dependent microlymphocytotoxicity test. Two examinations showed that PRA was very high (99% and 98%), which implied that the recipient was highly sensitive. Patients with high PRA values often present with acute rejections. To decrease PRA and surgical risks, a protein A immunoabsorption therapy was used.
Re-examinations showed that two separate PRA measurements were below 5% before transplantation. Other medical examinations indicated that there were no surgical contraindications.

For this patient, the usual reconstructive procedures, such as free skin graft, application of local flaps, tissue prefabrication, tissue expansion, and free tissue transfer, could only cover the wound. Without the facial bone framework, reconstruction of the nose and upper lip would not be possible. Allotransplantation was therefore chosen as the first therapeutic option to reconstruct the face of the recipient.

We had a great deal of communication with the recipient and his family about the risk versus benefit of surgery, and possible complications. The patient strongly wanted surgery, and he and his family gave written consent. We had our hospital’s ethics committee approval. According to the guidelines of the Chinese medical ethical committee, we asked the donor’s family’s for consent to obtain and transplant part of the face from a man aged 25 years who had died from a traffic accident, which the family gave. Final approvals certified that the protocol fulfilled all ethical, medical, and scientific rules obtained from the health department of Shaanxi Province, China.

Procedure
The transplantation took place on April 13, 2006. The donor and recipient had the same blood type (A). Three sites were matched within six HLA sites (donor: A-11,9; B-38,7; DR-10,15; recipient: A-11,2; B-38,52; DR-4,14; of which 14, 10, and 15 were in the same group). Mixed lymphocyte reaction was below 5%. After the composite tissue flap was obtained, it was cold-compressed in ice, and exposed to X-ray irradiation (4 Gy). 1000 mL 4°C perfusate (University of Wisconsin) was infused into each side of common carotid arteries of the donor cadaver. The composite tissue flap was then obtained after clinical examinations and three-dimensional CT (figure 2). The bilateral mandibular arteries and the anterior facial veins in the neck and lower mandible were dissected at the pedicle. Facial nerves were cut from the root in the mastoid region. The composite tissue flap contained the whole parotid gland, partial buccal mucosa, partial masseter, partial zygomatic arch, the lateral orbital wall and infraorbital wall, the front wall of the maxillary sinus, total upper lip, total nose, nasal septal cartilage, and nasal bone.

Under general anaesthesia, the wound of the recipient’s face was extensively debrided. Scar tissue was removed to reset the soft tissue stretched by the scar. The wound was found to be severely avulsed. Only a small part of the caudal lobe of the parotid gland was preserved. The infraorbital nerve at the infraorbital foramen was also absent. Curettage was done for maxillary sinus mucosa. Nerves and arteries in the left side were not separated, and were to be treated after the arteriovenous anastomosis in the right side was finished (figure 3).

First the right anterior facial vein and then the right external maxillary artery were anastomosed end-to-end. Because the grafted tissue was obtained from the donor at the time of cardiac death, no measures were taken for haemostasis. Blood circulation was affected, and 5000 mL blood was lost from acute bleeding around the wound. About 2 h were spent on haemostasis, and 6260 mL plasma and erythrocytes were used after anastomosis.

The left anterior facial vein was occluded and blood circulation of the composite tissue flap was good. Therefore the left external maxillary artery and the anterior facial vein were not anastomosed, and the
pedicle of the donor in the left side of the face was preserved and embedded for use if needed. 2 h after the arteries were connected, no hyperacute rejection changes such as erythema or blood stasis had occurred.

The bones were then fixed. The orbital bone of the donor was smaller than that of the recipient and the nose was 0·5 cm shorter when the middle line was fixed; the floor of orbit was higher and was 1 cm short from the lateral orbital margin to the corresponding site of the recipient. The nasal bone and the floor of orbit were trimmed and the lateral orbital margin of the donor was cut to fit the skeleton structure of the recipient. The nasal bone, zygomatic arch, and the lateral orbital margin were fixed with a titanium microplate. Partial masseter with pedicle of the donor was filled into the maxillary sinus of the recipient for prevention of postoperative infection. Tissues surrounding the nasal septal cartilage of the donor and the apertura piriformis of the recipient were sutured to stabilise the nose. Bilateral nasal cavities were packed with iodoform gauze to prevent infection and to fix the nose.

The stylomastoid foramen was avulsed and scarred, and only the neural stem of the facial nerve remained and was difficult to dissect. The remaining neural stem was trimmed and deep, so the quality of the facial nerve anastomosis was not satisfactory. Finally, the soft tissue of the wound was sutured in layers. The overall operation lasted 18 h.

**Medication**

To effectively control acute rejection, we adopted quadruple chemotherapy with tacrolimus, mycophenolate mofetil, corticosteroids, and humanised IL-2 receptor monoclonal antibody. At the same time, we used various adjuvants to ensure the stability of the patient’s physiological status to avoid infection and to protect the function of gastrointestinal tract, liver, and kidney. Immunosuppressants consisted of 25 mg prednisone and 500 mg mycophenolate mofetil, which were given orally both at 1200 h and in the evening the day before transplantation and at 0000 h on the day of transplantation.

At the beginning of the operation, intravenous tacrolimus was used (5 mg diluted with glucose, 14 µg/min). During transplantation, blood concentration of tacrolimus was regularly checked and controlled at 25 ng/mL. Before the circulation to the facial allograft was opened, 1 g methylprednisolone was infused over 10 min and 50 mg humanised IL-2 receptor monoclonal antibody administered. To improve patency of the wound was sutured in layers. The overall operation lasted 18 h.

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Immunosuppressive treatment after transplantation is summarised in figure 4. Tacrolimus was orally administered in a dose of 5–9 mg, twice a day, and blood concentration monitored daily to maintain 20–25 ng/L.

For 2 weeks. The dose was then changed to 6 mg, twice daily. The dose was reduced at 3 months, and blood concentration was maintained at about 20 ng/L. The dose was then reduced gradually to 1 mg, twice a day, at 15 months, And increased to 3 mg at 17 months. After 2 years, the dose of tacrolimus was 2 mg, twice a day to maintain blood concentration between 10 ng/L and 15 ng/L. Mycophenolate mofetil was given as 1·5 g twice a day. At 6 months, the dose was reduced to 1 g, twice a day. At 17 months, the dose was 0·25 g and 0·5 g a day, twice daily. From 21 months after transplantation to 24 months, the dose was 0·25 g, twice a day.

Glucocorticoids were given as follows: methylprednisolone was administered at the dose of 0·5 g for 2 days and 0·25 g for 3 days after transplantation. Prednisone tablets were used from the 6th day postoperatively, which replaced methylprednisolone. Prednisone was started at 80 mg, once daily, and then reduced gradually to a maintenance dose of 25 mg a day for 3 months, 20 mg a day for another 3 months, and 10 mg a day for a further 3 months. Prednisone was stopped 22 months after transplantation. 2 weeks after
transplantation, 50 mg humanised IL-2 receptor monoclonal antibody was given and the same dose 2 weeks later. To prevent infection, various anti-infection treatments were used in the intraoperative immunosuppression-induction period. Cultures from the pharynx, nose, and other parts were taken for bacteria and fungi. The type and dose of drugs were adjusted according to the results of these cultures. Ceftriaxone was used as prophylactic antibiotic at a dose of 2 g, three times daily, for 2 weeks. When enterobacter, Enterococcus faecalis, and Staphylococcus epidermidis were identified from sputum and oropharyngeal swabs, vancomycin (1 g, twice daily) was used for 4 days. In the perioperative period, prophylactic medication included metronidazole, acyclovir, and allicin.

After administration of vancomycin, intestinal bacteria examination showed dysbiosis of intestinal flora II. After the administration of medilac-s (Streptococcus faecium 2·225×10⁸, Bacillus subtilis 0·25×10⁸/g per 500 g bottle, Hanmi Pharmaceuticals, Beijing, China) and MIYA-BMP (clostridium butyricum MIYAIRI588 stain preparation, Miyarisan Pharmaceuticals, Japan), no abnormalities were recorded in stool or bacterial cultures. Liver and kidney functions and red blood cell morphology were monitored to detect possible drug side-effects, and glucuronolactone was used to protect liver function. To avoid stimulation of the gastrointestinal tract, omeprazole, and famotidine were used. Human immunoglobulin (10 g, Institute of Biological Products, Lanzhou, China) was used once every other day, within the first month after transplantation.

Role of the funding source
The sponsors supplied the funding, and inspected the procedure and results of the studies. The authors of this manuscript had responsibility for the design, implementation, data collection, data analysis, data interpretation, and writing of the report. The corresponding author had full access to all the data in the study and had final responsibility for the decision to submit for publication.

Results
After surgery, the recipient had a good appetite and normal micturition and bowel function. Blood supply of the transplanted tissue was good, with normal wound healing. About a week after transplantation, swelling of the composite flap began to subside and had disappeared at 1 month. The patient was then discharged from the isolation ward. 2 months after transplantation, the graft showed no signs of acute rejection. On day 3, blood glucose concentration rose to 15·9 mmol/L. Glucose tolerance testing showed that after 75 g glucose had been taken, blood glucose was 20·1 mmol/L after 30 min, 18·9 mmol/L after 1 h, and 13·7 mmol/L after 2 h. After being controlled with insulin for 2 weeks, blood glucose returned to normal, and insulin was stopped.
At 3, 5, and 17 months after transplantation, the flap showed signs of acute rejection. Early manifestations included flap swelling, skin congestion, visible erythema, and small inflammatory mass. During the first acute rejection, we increased the dose of tacrolimus, such that blood concentration of tacrolimus increased from 15 ng/mL to 25 ng/mL, and signs remitted. The second rejection was successfully treated with methylprednisolone pulse therapy (1 g, 0·5 g, 0·5 g, 0·25 g, and 0·125 g) for the first 5 days. Prednisone was then given once a day in decreasing doses of 80 mg, 70 mg, 60 mg, 50 mg, 40 mg, 30 mg, and 20 mg, and finally 15 mg as the long-term maintenance dose.

14 months after surgery the transplanted facial tissue had normal colour, skin temperature, and texture. The patient was healthy. He then returned home to his remote village. At 16 months after surgery, he stopped taking immunosuppressants and began to take herbs for 3 weeks. The third acute rejection was at 17 months after transplantation (figure 5). We increased the dose of tacrolimus until the signs were abated, but slight flap swelling and skin congestion remain (figure 6).

3 months after transplantation, blood glucose concentration rose again, with a peak of 25–30 mmol/L, but was controlled with insulin of 70 units per day. With decreasing doses of immunosuppressants, insulin was also decreased. Insulin dependency for hyperglycaemia after transplantation defines new-onset diabetes mellitus, and was the main complication in this case. At 21 months, insulin was stopped. Repaglinide tablets and metformin hydrochloride enteric-coated tablets were then used to control blood glucose. Insulin blood glucose remained normal. Insulin function test showed that the insulin-secretion peak was delayed by 2 h after a meal, suggesting that pancreatic islet function was impaired. Bone-scan of the hip joint and thoracic vertebrae 1 year after transplantation indicated there was no osteoporosis or femur head necrosis. Renal function remained normal after transplantation. The table shows serum creatinine and creatinine clearance throughout follow-up.

1 month after transplantation, histological examination of the edge of the flap showed that the cuticular layer of the skin was thinner than normal skin and the papillary layer of dermis was smooth. Beneath the epidermis hair follicles, sweat glands, arterioles, and venules were visible, and there were a few mononuclear cells infiltrating the glands and vessels. The lesions were graded 0 and I according to the classification established for composite tissue acute rejection. At 5 months after transplantation, we noted moderately dense mononuclear cells, infiltrating around the vascular, sebaceous and sweat glands in the dermis; lesions were graded 1–II (figure 7).

Within a month after transplantation, helper T lymphocytes (Th, CD3+CD4+) and cytotoxic lymphocytes (CD3+CD8+) in the plasma were tested by flow cytometry. During the first acute rejection, the ratio of CD3+CD4+T cells increased gradually, and returned to normal after it was under control. In the second rejection, the prednisone pulse therapy led to a substantial decrease in CD3+CD4+T cells’ proportion, which represented only 41%, a
The dominant causes of renal failure include hypertension and diabetes. However, promising results could mean that this term, but the procedure was not without complications. Facial transplantation could be successful in the short term, but the procedure was not without complications. Therefore, in preparation of the graft tissue from the donor, we retained the bilateral facial arteries and anterior facial veins. However, during transplantation, we found that unilateral facial arterial anastomosis was enough to guarantee survival of the transplanted tissue. The survival of the opposite side tissue was probably due to an extensive anastomotic branch of the facial artery. We also found that the facial nerve was severely damaged and was difficult to distinguish, and anastomosis was difficult because the site was deep. Although the facial nerve stem was found and anastomosed, recovery was poor.

Highly sensitised patients with positive PRA often present with acute rejection. The dominant causes of sensitisation were rejection of a previous transplant, pretransplant blood transfusions, sex of the patient, and a history of pregnancy. Sensitised individuals have been defined as moderate or high on the basis of their pre-transplant PRA values in sensitised patients –19 –20,21. We did some preliminary cadaver studies, after which we concluded that anastomosis of the bilateral facial arteries would be necessary to guarantee survival of the transplant. Therefore, in preparation of the graft tissue from the donor, we retained the bilateral facial arteries and anterior facial veins. However, during transplantation, we found that unilateral facial arterial anastomosis was enough to guarantee survival of the transplanted tissue. The survival of the opposite side tissue was probably due to an extensive anastomotic branch of the facial artery. We also found that the facial nerve was severely damaged and was difficult to distinguish, and anastomosis was difficult because the site was deep. Although the facial nerve stem was found and anastomosed, recovery was poor.

Highly sensitised patients with positive PRA often present with acute rejection. The dominant causes of sensitisation were rejection of a previous transplant, pretransplant blood transfusions, sex of the patient, and a history of pregnancy. Sensitised individuals have been defined as moderate or high on the basis of their peak PRA values (1–50%, moderate; >50%, high). Additionally, PRA test results are useful for donor-recipient selection. PRA testing should be done routinely in patients awaiting transplantation. Singh and colleagues tested the assertion that patients with high PRA would have improved graft survival if their current PRA had fallen substantially and spontaneously compared with those who continued to have high PRA. Ishida and colleagues reported that reduction of the pre-transplant PRA values in sensitised patients immediately before transplantation seemed to greatly contribute to improved function of the kidney graft soon after transplantation. Peak PRA of our patient was very high, possibly because of an edible fungi diet, chronic infection, or pretransplant blood transfusions. After immunoabsorption, PRA fell to below 5% before transplantation. After transplantation, episodes of acute rejections were easily controlled by medication.
Reduction of the pre-transplant PRA could be useful to reduce the likelihood of rejection.

The mixed lymphocyte reaction is widely used to assess immune response to alloantigens in both experimental and clinical transplantation. The mixed lymphocyte reaction assay was initially used to determine the proliferation of host (responder) T cells in response to antigens expressed on leucocytes obtained from the donor. Later, host cytotoxic T cells against antigens of the donor could be generated in mixed lymphocyte reaction. Mixed lymphocyte reaction of this case was below 5%. After the composite tissue flap was obtained, it underwent radiography (4 Gy), since such treatment has proved effective in human and animal transplant studies.

Clinical application of immunosuppressive treatment for allograft facial transplantation is still in its infancy. However, in recent years new immunosuppressants such as tacrolimus and mycophenolate mofetil have shown good prospects for visceral organ allograft. Humanised IL-2 receptor monoclonal antibody is useful to reduce acute rejection reaction in visceral transplantation without increasing drug side-effects. In our patient, increasing blood concentration of tacrolimus or methylprednisolone pulse therapy proved useful for controlling the rejections.

Because these immunosuppressants can cause side-effects, drug treatment should be timely. In our case a transient high blood inosine happened after transplantation, which was well controlled after symptomatic treatment. 1 month later, hepatic, renal, and gastrointestinal tract functions were normal. As for tacrolimus, the effect on blood glucose is a major complication, which is shown as dose-dependent hyperglycaemia. The rate of renal transplantation is reported to be up to 15–20%. 3 months after transplantation, our patient presented with sustaining new-onset diabetes mellitus, which was controlled with insulin. From this observation, we acknowledge that the heavy immunosuppressive protocol that was used could have directly induced the new-onset diabetes mellitus. With decreasing dose of tacrolimus, blood glucose could be controlled with a reduced insulin dose. Whether the high blood glucose can recur with decreasing of tacrolimus needs further study.

Another adverse reaction of immunosuppressants is the decrease in immunity, which can induce opportunistic infections, cancers, and other diseases. Therefore, we had to constantly adjust the maintenance dose of immunosuppressants to prevent rejection, while paying attention to the fact that excessive inhibition immunity could induce infection, malignant tumours, and other side-effects. Perioperatively, the patient received a surgery accompanied with high doses of immunosuppressants, and showed low immunity. We should therefore take active measures (such as an isolated ward or sterile food) to prevent infection. Moreover, we undertook frequent microbial cultures. Once an abnormality was identified, we used effective antibiotics to control infection as early as possible. When we identified *E. faecalis*, *S. epidermidis*, and *Enterobacter cloacae* from sputum and oropharyngeal swab cultures 2 weeks after transplantation, we applied vancomycin in time, and no clinical signs of infection were detected. During 2 years' follow-up, we noted that opportunistic infections caused by immunosuppressants were not of concern to the recipient.

There were some important differences between our study and that of the first partial facial transplantation in France by Devauchelle and colleagues in 2005. For example, the condition of the wound was different in our patient, and part of the bone structure of the face was damaged. Furthermore, the damage to the facial nerve was severe, which was the main reason for its poor functional recovery. The immunosuppressive regimen and medication were also different. X-ray irradiation, but not infusions of donor bone-marrow cells, was used. Our patient had three acute rejections and developed hyperglycaemia, whereas in Devauchelle's study the recipient had two acute rejections, acute renal failure, and hypertension. The difference between these outcomes might partly be attributable to the different immunosuppressive regimens used. The procedures of two cases also differed, since the donor tissue in our case was obtained at the time of cardiac death and in the French case was obtained at the time of brain death.

Before transplantation, our recipient was living in a remote rural area without access to proper medical care. His facial wounds did not heal for 18 months, which seriously affected his appearance and function. After transplantation, the recipient had a good mental status and accepted his new face easily. At present, the general result is good, although there were some complications after surgery. However, this case suggests that facial transplantation might be an option for restoring a severely disfigured face, and could enable patients to readily reintegrate themselves back into society.

**Contributors**

The recipient's operation and postoperative treatments were done under the supervision of SG. The donor's operation was done under the supervision of YH. The whole operation was done by SG, YH, KL, BL, XM, LY, HZ, DW, and XZ. The postoperative immunosuppressive regimen and nursing care were under the supervision of SG, XZ, CY, YL, and XF. All authors contributed to the final version of the manuscript.

**Conflict of interest statement**

We declare that we have no conflict of interest.
Acknowledgments
This study was completely funded by the New Clinical Technique Foundation of Xijing Hospital (grant number XJCX06005M02). The animal studies were funded by the National Nature Science Foundation of China (number 30672189). We thank the following specialists or teams for their close cooperation in this facial transplantation:
Zhang Yongsheng, Zhang Yingbi, Li Xiangdong, Li Xiaokang, Guo Minghua, and Fan Daiming; Xiong Liru, Chen Shaoyang, and their team; Wang He, Dou Kefeng, Yi Dinghua, Zhao Qingquan, Tao Kaishan, and their team; Wen Aiding, and his team; Ji Quhe and his team; Liu Baolin; Lin Manchang; Hao Xiaoke, Ding Zhengnuo, and their team; Shi Mei and her team; Fu Jufang, Bian Dongmei, and their teams; Xu Fuming, and we especially thank the people who have worked on this study, but are not mentioned here.

References
Repair of the lower and middle parts of the face by composite tissue allotransplantation in a patient with massive plexiform neurofibroma: a 1-year follow-up study

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Summary
Background The risk to benefit ratio of face transplantation with a composite tissue allograft remains debatable, although this procedure is technically feasible. We report here a 1-year follow-up of a patient who underwent face transplantation with a composite tissue allograft.

Methods On Jan 21, 2007, a 29-year-old man with neurofibromatosis type 1 underwent resection of a massive plexiform neurofibroma diffusely infiltrating the middle and lower part of his face. The main goal was to restore both the cutaneous appearance and function of the face, including, in particular, control of orbicularis oculi and oris muscle contraction. The issues of immunosuppressive therapy, psychological outcome, and social reintegration were addressed, together with the monitoring of graft rejection by biopsies of the skin and mucosa.

Findings The initial postoperative course was uncomplicated. Two episodes of clinical rejection occurred on days 28 and 64. The second episode was associated with cytomegalovirus infection. Both episodes resolved favourably, with no further clinical signs of rejection, making the reduction of immunosuppressive treatment possible. A year after surgery, the functional outcome was very good, with successful sensory and motor reinnervation in the transplanted territory. Psychological recovery was excellent, with complete social reintegration.

Interpretation This case demonstrates the feasibility of surgically removing a large part of the face and replacing it with a composite tissue allograft. This facial repair procedure, which seems to have a satisfactory risk to benefit ratio, could be offered in rare and selected cases.

Funding Programme Hospitalier de Recherche Clinique.

Introduction The risk to benefit ratio of face transplantation using a composite tissue allograft (CTA) remains debatable, although the procedure seems to be technically feasible. However, reports of cases that have assessed the risk to benefit ratio of the procedure are rare. The need for large doses of immunosuppressive drugs to ensure CTA survival and the need for intense psychological support to prevent distress has raised ethical concerns, preventing many teams from attempting this type of transplant.

Most facial defects can be reconstructed using autologous tissues and standard plastic surgery techniques. However, in some cases, conventional plastic and reconstructive surgery cannot provide satisfactory results to severely disfigured patients. The patients concerned have generally been disfigured by burns, ballistic trauma, tumours, or congenital deformities. Congenital deformities can have a genetic origin, as in the case of neurofibromatosis type 1 (NF1), which is an autosomal dominant genetic disease with an incidence of 1 in 2500–3300. Plexiform neurofibromas associated with NF1 occur in about 10% of cases, can be disfiguring, and have a major effect on quality of life. Conventional surgery often has little to offer patients with these conditions, and face transplantation has been identified as a possible alternative treatment. We report here a 1-year follow-up of a patient with deforming plexiform neurofibroma associated with NF1 who underwent face transplantation with a CTA. We focus on the management of post-transplantation immunosuppression and on functional and psychosocial outcomes.

Methods In 2002, we asked the French National Ethics Advisory Committee for Life Sciences and Health to give advice about facial repair using a CTA. The committee’s response was delivered in 2004: this kind of transplant could be proposed for severely disfigured patients—cases of total destruction of the mouth and the nose for example—and should be presented to the patient as highly experimental. Preclinical anatomical studies had already been done to optimise the surgical technique. A clinical research protocol was thus designed to assess not only the feasibility of the procedure, but also immunological, psychological, and functional aspects of transplantation, and to estimate the risk to benefit ratio. The main goal was to restore both the cutaneous appearance and function of the face, including, in particular, control of orbicularis oculi and oris muscle contraction. In addition, a technique based on the use of a resin mask was...
developed to restore the face of the donor. The issue of immunosuppressive therapy was addressed, together with the monitoring of graft rejection by biopsies of the skin and mucosa. Psychological and psychiatric evaluation was also done to assess acceptance of the procedure and its possible psychological benefit. The protocol was designed as an open study of five patients, with an intermediate analysis of the first patient to be done before proceeding with the subsequent cases. This design was approved in 2005 by the French Agency for the Sanitary Safety of Health Products, which guarantees the efficacy, quality, and appropriate use of all human health products, including organs of human origin in France. The final research protocol was approved by the Ile de France IX (CPP) ethics committee. Each indication of composite tissue allotransplantation required validation by an independent committee of experts.

Patient
A 29-year-old French Caribbean man presented with a massive plexiform neurofibroma diffusely infiltrating and disfiguring the middle and lower parts of his face (figure 1A). At baseline, complete facial paralysis of the right side of the face and partial paralysis of the left side were observed, probably due to distal facial nerve infiltration by the massive neurofibroma. The patient gave informed consent to transplantation and was placed on the French national transplantation agency (Agence de Biomédecine) waiting list on Aug 26, 2006. The patient underwent various surgical interventions before inclusion in this protocol. Bilateral blepharoptosis was corrected. The function of the left eyelid was fully restored after initial surgery, with good vision achieved for this eye. Functional restoration was incomplete for the right eyelid, but the patient had lost vision in this eye several years earlier, due to glaucoma. No sphenoid dysplasia was observed in this case, classified as type 1 according to the Jackson classification. MRI and three-dimensional CT scans confirmed that the intracranial portion of the facial nerve was normal. An independent expert committee confirmed that a transplant of the middle and lower parts of the face would probably be functional, cosmetically acceptable, and would improve the patient’s quality of life.

We then evaluated coping strategies with the patient and the members of his family (sister and mother). We focused in particular on the way in which the patient had coped with previous harmful and stressful situations and, more specifically, on the way in which the patient had reacted to and coped with his facial disfigurement. Lifetime history of adaptive disorders was assessed during interviews with the patient and his family. Depression and anxiety were assessed, using a semi-structured diagnostic interview (Mini International Neuropsychiatric Interview 5.0.0 DSM IV, French version). Triggering factors were also investigated. The patient had no personal history of axis I psychiatric disorders. With respect to the progression of facial disfigurement and the associated handicap in professional and affective domains, the patient did not fulfil any DSM IV criteria for an adaptive disorder with anxiety or depressive mood.

The inclusion criteria applied (normal IQ, absence of personal history of schizophrenia and non-schizophrenic psychotic disorders, normothymia) ensured that the patient clearly understood the risk to benefit ratio. Full explanations (oral and written) were delivered to the patient and his family (with the patient’s agreement) about the risks and constraints of the medical, psychological, and surgical procedures, both before and after surgery. Quality of life was assessed in a non-standardised way, including assessment of social integration and professional activities.

Figure 1: Photographs of the patient with massive facial plexiform neurofibroma taken before and 1 year after face transplantation

Figure 2: Diagram of the transplant, showing the margin of the resection and the site of anastomosis
Procedure

The face transplant took place on Jan 21, 2007. Two surgical teams worked simultaneously, one to remove the patient’s tumour and the other to harvest the facial CTA (figure 2).

Plexiform neurofibroma excision included removal of all the soft tissues below the zygomatic arch. The facial nerve was identified at the point at which it left the stylomastoid foramen. The two eyelids and forehead, innervated on the left side only, were the only facial tissues remaining. The tumour was debulked using bipolar coagulation scissors (Powerstar, Ethicon, Somerset, NJ, USA). Despite massive infiltration of the tumour with a saline-adrenaline solution, substantial blood loss occurred requiring the perioperative transfusion of 35 units of packed red blood cells.

A CTA from the face was the first tissue obtained from a brain-dead patient with a beating heart. First on the right side, then on the left, the facial nerve was approached via the access route used for parotidectomy and transsected at its origin. The upper skin incision ran along the zygomatic arch, following the infraorbital margin and ended in the nasofrontal suture. A composite tissue flap was raised, along the masseter plane to the oral mucosa. This tissue flap included the overlying skin, facial, mental and infraorbital nerves, both parotid glands, and the nose. The trunks of both external carotid arteries and thyrolinguofacial veins were isolated to be used as donor vessels for the face CTA.

The graft was washed with a saline solution containing heparin and transported in SCOT preservation solution (MacoPharma, Mouraux, France) in a standard ice box. The body was returned to the family with a painted resin mask prepared during the operation.

The CTA was inset. Although an end-to-end arterial anastomosis to the left external carotid perfused the entire CTA, the right external carotid system was also Anastomosed. Venous end-to-end anastomoses were performed to the thyrolinguofacial trunks. The facial and infraorbital nerves were sutured and glued with fibrin glue (Tisseel, Baxter, Maurepas, France). The submental nerves could not be sutured because they were transected at the submental foramen. However, the graft was positioned so that the recipient nerve could be placed in front of the foramen. The entire procedure lasted 15 h and involved two senior surgeons, three fellows, and four residents.

The donor and recipient were of the same blood group (0+) and had three human leucocyte antigen (HLA) mismatches (recipient: HLA A23A26, B7B51, DR11DR13; donor: HLA A2A24, B7B72, DR11DR18). HLA A23 and A24 have identical sequences. The patient had no anti-HLA panel-reactive antibodies and retrospective cross-match was negative. The induction immunosuppressive regimen included 1-25 mg/kg per day antilymphocyte serum (thymoglobulin, Genzyme, Lyon, France) for 10 days, oral tacrolimus, the dose of which was adjusted to maintain a concentration in the plasma of 10 to 13 ng/mL for the first 3 months, mycophenolate mofetil, administered at a dose of 2 g per day to maintain the area under the curve within the range of 40 to 60 ng/mL, and prednisone (500 mg on day 1, 250 mg on day 2, 120 mg on day 3 followed by 60 mg per day for 7 days, with the dose progressively reduced to 10 mg per day thereafter). Maintenance immunosuppression was achieved with tacrolimus, administered at a dose adjusted so as to maintain its plasma concentration within the target range of 8 to 10 ng/mL, mycophenolate mofetil (2 g per day), and prednisone (10 mg per day). The donor was cytomegalovirus-positive, whereas the recipient was cytomegalovirus-negative. The recipient therefore received prophylaxis for cytomegalovirus infection, in the form of valganciclovir (900 mg a day for 6 months). The patient also received trimetoprim-sulfamethoxazole (400 mg a day for 6 months) for the prevention of *Pneumocystis carinii* pneumonia. Biopsies of mucosa and skin were done on day 2 and were repeated once a week for the first 2 months, twice a month for the next 2 months, and then once a month between months 4 and 6. They were analysed by determining skin pathological score for acute CTA rejection.3 The donor tested positive for syphilis, whereas the recipient was negative. The recipient therefore received 300000 IU penicillin twice a day for 15 days, for prophylaxis.

10 months after transplantation, the patient underwent further surgery for correction of the right eyelid and dental restoration with surgical titanium implants. Postoperative swelling was managed with one intravenous bolus of 500 mg of prednisone.

Results

The only postoperative complication seen was transient steroid-induced confusion, which was treated with 25–50 mg of chlorpromazine for 5 days. The swelling resolved within 1 week. The tracheotomy cannula was

![Figure 3: Immunosuppressive treatment follow-up](image-url)
removed on day 8 and the patient was able to speak and eat by day 10.

The follow-up immunosuppressive regimen is described in figure 3. Early biopsies of skin and mucosa (days 2, 7, 14, and 21) showed no lymphocyte infiltration, corresponding to grade 0 on the acute rejection scale. Mild erythema of the lower cervical part of the allograft was seen on day 28. Skin biopsies showed grade-1 rejection, characterised by mild dermal CD3+ lymphocyte infiltrate in the absence of epidermal inflammation or interface dermatitis. On day 35, the dose of prednisone was increased to 60 mg a day, followed by an intravenous bolus of 500 mg of prednisone on 3 consecutive days due to persistent grade 1 acute rejection. This treatment led to the complete disappearance of skin erythema. However, subsequent skin biopsies showed persistent grade 1 acute rejection. On day 64, mild skin erythema developed on the graft. Skin biopsy showed grade 1 and mucosal biopsy showed grade 2 acute rejection. The patient was treated with a daily intravenous bolus of 500 mg of prednisone for 3 consecutive days. On clinical examination, the skin lesions were found to have faded, but control mucosal biopsies showed persistent grade 2 acute rejection leading to treatment with antilymphocyte serum, at a dose of 1 mg/kg per day, for 7 consecutive days. Concurrent twice-weekly immunomodulatory therapy by extracorporeal photopheresis (ECP) was initiated 3 months after surgery and then reduced to one course every 2 weeks for the next 3 months, to control persistent subclinical rejection. Biopsies up until 10 months after surgery showed grade 0 rejection for skin, but persistent grade 1 rejection for oral mucosa. The main clinical adverse event related to the immunosuppressive regimen was valganciclovir-resistant cytomegalovirus viraemia coinciding with the second episode of clinical acute rejection (day 64) and treated with intravenous foscarnet; 6 g per day for 8 weeks. Immunosuppressive treatment had to be decreased because of persistent cytomegalovirus viraemia, with the total withdrawal of mycophenolate mofetil from day 120 to day 165. It was reintroduced on day 165, at a dose of 500 mg a day. 12 months after surgery, the immunosuppressive regimen included tacrolimus (10 mg a day), mycophenolate mofetil (500 mg a day), and prednisone (7.5 mg a day; figure 3).

Peripheral blood microchimerism was investigated by analyses of whole blood from our recipient 12 months after surgery. We used a real-time quantitative polymerase chain reaction (RQ-PCR) with TaqMan technology and an ABI 7700 Sequence Detector (Applera, Courteboeuf, France). The lower limit of detection of the assay was 0.1%. Microchimerism was defined as the presence of 1% donor cells. No microchimerism was observed.

The patient saw his new face for the first time on day 10 and gradually came to accept it (figure 1B). He has presented no psychiatric events or compliance problems to date. He is able to carry out activities of daily living unassisted and the transplant has reduced his concern about his appearance, which has made having a social life easier for him. He began a full-time job 13 months after transplantation.

3 months after surgery, an electroneuromyographic examination showed no evidence of reinnervation, with the exception of a minor motor response to facial nerve stimulation in the left orbicularis oculi muscle. 6 months after surgery, electromyographic activity was detected during voluntary contraction, in the left orbicularis oculi muscle and in both orbicularis oris muscles. 9 months after surgery, the patient began to display spontaneous mimicry. 12 months after surgery, electroneuromyography showed signs of motor reinnervation of both trigeminal and facial territories (figure 4). In addition to direct motor responses to ipsilateral facial nerve stimulation, the patient also recovered involuntary reflex contraction of facial muscles in response to stimulation of the supraorbital branches of the trigeminal nerves (blink reflex). The motor reinnervation has predominantly concerned the left side of the face. Quantitative sensory testing showed clear sensory reinnervation of the grafted skin, for both thermal and mechanical sensations, from the first examination, 3 months after surgery. The patient required local anaesthesia for biopsies 4 months after surgery, 12 months after surgery, further improvements in sensory thresholds were observed in the grafted zone.

Discussion

Our case confirms that face transplantation is surgically feasible and effective for the correction of specific disfigurement, due in this case to a genetic disorder. The procedure involved three technical challenges: the removal of a disfiguring tumour, plexiform neurofibroma, which is difficult to debulk due to its vascularity,10 the...
Blood loss is a known, life-threatening complication of surgery for plexiform neurofibromas. This complication has been linked to the increase in vascular fragility caused by NF1-associated arterial dysplasia and venous neurofibromatous invasion. Technically, the surgical approach to facial plexiform neurofibroma should result in conservation of the cosmetic units of the face, although the tumour is not removed in its entirety. Plexiform neurofibroma should be treated more as a malformation than as a tumour. Indeed, the neurofibroma infiltrates neighbouring tissues, which makes the definition of clear margins between normal and pathological areas difficult, if not impossible. Complex haemostatic surgery, involving infiltration with saline-adrenaline solution and the use of coagulation scissors (Powerstar, Ethicon, Somerset, NJ, USA) or an ultrasound knife (Ultrascision, Ethicon), is required, but these techniques do not completely prevent bleeding and massive transfusion is therefore needed.

French law assumes the consent of the deceased for organ donation including composite tissue. However, we nonetheless specifically sought the consent of the donor’s family for the procurement of this graft. The family understood perfectly that the face has a critical function for communication and that the transplant could potentially restore this function in the recipient, without transferring the donor’s physical appearance. The knowledge that the face of the donor would be reconstructed with a moulded resin mask helped the family to accept this donation. French law requires the restoration of the body after organ procurement, but the care taken to ensure restoration of the donor’s face was particularly important to demonstrate the seriousness of our work and our respect for the donor to the donor’s family, the organ procurement organisation, and other transplant surgeons. The entire procedure was protected from media intrusion and therefore had little mass media effect on either the donor’s family or our patient.

In addition to technical aspects of the transplantation, we also assessed functional and psychological benefits to the patient and the risks associated with the systemic immunosuppression required by this procedure, a year after surgery.

12 months after surgery, there was evidence of motor and sensory reinnervation in the transplanted zone, as would be expected for repair with autologous nerves. The recovery of involuntary reflex contraction of facial muscles in response to stimulation of the supraorbital branches of the trigeminal nerves (blink reflex) was more surprising. This result was unexpected because it required the connection in the brainstem of sensory afferents from the host (supraorbital nerves) and motor efferents from donor tissues (facial nerves and muscles). In terms of sensory function, only the suborbital branches of the trigeminal nerves were sutured. The mental nerve branches transected directly from the submentum foramen were not sutured. Nonetheless, quantitative sensory testing clearly showed sensory reinnervation of the grafted skin for both thermal and mechanical sensations, by the time of the first examination, 3 months after surgery. This might have been due to regrowth into the recipient nerve or direct sprouting of the nerve into the face.

Immunological outcome included two episodes of clinical acute rejection, both confirmed by skin biopsy. A high incidence of acute rejection in the early post-transplantation period was also described in the first reported case of face CTA transplant. These results confirmed the high immunogenicity of CTA transplants and retrospectively justified the use of antilymphocyte serum induction with maintenance tritherapy. Clinical outcome was uneventful, whereas repeated biopsies of mucosa, but not of skin, showed persistent subclinical rejection. In solid organ transplantation, subclinical rejection has been identified as an important cause of progressive deterioration of graft function, but the relative benefits of treating or not treating this rejection remain unclear. Since our patient had previously received an intensive immunosuppressive regimen, we decided not to treat subclinical rejection. The therapeutic strategies for subclinical rejection in the CTA and solid organ transplant contexts can be different. In CTA transplants, acute rejection is usually diagnosed and treated immediately and concerns the epithelium, which has regenerative properties. The tissues implicated in later functions of CTA transplants (eg, muscles and nerves) are not the primary targets of the immune response. Further analysis of the long-term clinical and functional outcome of this patient will establish whether our conservative management was justified.

We introduced ECP on day 65 to decrease alloreactivity without increasing immunosuppression to maximal levels. ECP is an apheresis-based immunomodulatory therapy initially used to treat cutaneous T-cell lymphoma. The indications for ECP are expanding and include both prophylactic treatment and the treatment of recurrent rejection after transplantation. This procedure has an immunomodulatory rather than an immunosuppressive effect. It can thus be used to minimise chemical immunosuppression in recipients at high risk of or displaying refractory rejection. Our patient presented valganciclovir-resistant cytomegalovirus viremia at the time of a second episode of clinical acute rejection, justifying the use of ECP, which overcame the need for maximal immunosuppression. Routine repeat biopsies showed persistent grade 1 acute rejection in oral mucosa, so ECP treatment was continued until day 160 to ensure that this subclinical rejection was controlled.

The use of skin and mucosal biopsies for monitoring raised problems in the correlation of clinical and pathological rejection episodes. Other authors have tried to avoid additional scaring by using skin grafts or skin...
flaps (particularly the radial forearm flap) for monitoring. However, although the constitutive elements of the skin are similar all over the body, the thickness of the skin and the number of Langerhans cells differ. As other specific elements, such as muscle and mucosa, were also present in the face transplant, we decided to do direct facial biopsies (of skin and mucosa). These biopsies did not impair cosmetic appearance.

The second episode of clinical rejection was accompanied by cytomegalovirus viraemia, in this positive donor–negative recipient situation. A high incidence of cytomegalovirus infection in cases of CTA transplantation has been reported before. This high incidence might be related to the larger viral load with respect to the endothelial mass than for kidney, liver, or heart allografts, and to the high level of immunosuppression. The close correlation of cytomegalovirus infection with acute rejection is also well documented in both solid organ and CTA transplantation. Thus, the virus might trigger the immune response against the graft. Our case confirms previous reports and strongly suggests that cytomegalovirus-mismatch should be avoided in CTA transplantation.

In addition to systemic toxicity, immunosuppression might also potentially promote malignant transformation of nerve sheath tumours in this patient with NF1. Indeed, the NF1 gene is a tumour suppressor gene associated with a 10% lifelong risk of malignant peripheral nerve sheath tumours (MPNST). In the context of solid organ transplantation, two cases of MPNST have been reported in patients with NF1. However, MPNSTs are not immunodependent tumours and debulking of the plexiform neurofibroma in our patient might have reduced the risk of such tumours. After a year of follow-up, immunosuppressive treatment had no effect on NF1 expression in our patient. Indeed, the rest of the patient’s body was mildly affected by NF1, with café-au-lait spots, freckles, and a few cutaneous neurofibromas. These lesions remained stable. The immunosuppressive regimen was substantially reduced 9 months after transplantation to reduce the oncogenic risk: mycophenolate mofetil was reduced from 2 to 1 g a day and tacrolimus dose was reduced from 10 to 6 mg a day. This approach also justifies the early use of ECP, which has an immunomodulatory, but not immunosuppressive effect. Clinical screening for the early detection of skin and mucosal cancers is done monthly in this patient and PCR analyses of HHV8 and Epstein-Barr virus replication are done every 6 months. The 12-month assessment also included radiological screening for the early detection of lymphoproliferative diseases and kidney, lung, and liver cancers.

Immunosuppressive tritherapy is a standard therapeutic strategy in CTA transplantation. Studies in animals have shown that immunological tolerance can be achieved by combining organ and haematopoietic stem cell transplantation. However, these data cannot be confirmed in humans without the use of whole-body irradiation. The low level of immunosuppression needed after 1 year in our patient suggests that organ engraftment could have occurred, as previously described in liver and kidney transplantation, although we were unable to show microchimerism.

The procedure had an excellent, positive psychological effect on the patient, with the early, rapid, and full integration of the new face into the patient’s self-image, even before nerve regrowth. The choice of the recipient might have had a key role in this success. Patients with deforming plexiform neurofibroma often undergo repetitive major surgery, the functional and cosmetic results of which are often poor. Our patient had a comprehensive understanding of the procedure, was psychologically stable and received strong support from his family and close friends. A year after surgery, we assessed the patient’s social integration. Before surgery the patient felt he was considered a “monster”, whereas he now feels like “an anonymous person in the crowd”. Daily social activities are easier. For example, the patient can now go shopping in peace, without provoking aggressive reactions. He is now employed as an accounting agent. There was thus a clear improvement in the patient’s quality of life, but no scale was used, since 60–80% of quality of life variance is accounted for by depression and anxiety, which were assessed before and during follow-up.

The French National Ethics Committee regards face transplants to be highly experimental and in the domain of clinical research. Strict evaluation of each case is required to assess the risk to benefit ratio of the procedure. Each case should be assessed by an independent committee of experts, including surgeons aware of all the possibilities of reconstruction and taking into account the indication. This classification of the procedure as clinical research might not guarantee its use for the best indications, but it does guarantee the scientific evaluation of cases. The procedure can be proposed to the patient only after validation by the expert committee. Immunological, anatomical, and psychological assessments are then required and evaluation criteria must be defined in advance. The main objective of this procedure was to allow the patient to have a normal social life. The procedure can therefore be considered successful in terms of this criterion. Indications for face transplantation are rare and only a meta-analysis of all the cases reported from single-centre series would make it possible to assess the overall risk to benefit ratio.

Face CTA transplantation has moved from ethical debate to surgical reality. Potential indications are not restricted to trauma, and include other types of disfigurement due to genetic disorders, such as NF1. The functional and psychological results obtained in this case exceeded our initial expectations and clearly outweighed the risks in the first year of follow-up. Nevertheless, face transplantation should still be regarded as experimental.
Long-term follow-up is needed to assess the risks linked to the immunogenicity of allogenic composite tissues, particularly as regards life expectancy. Following this initial success, other patients are currently being assessed.

Conflict of interest statement
We declare that we have no conflict of interest.

Acknowledgments
We thank Laurence Allanore and Marion Gabillet, Department of Dermatology, Henri Mondor Hospital, Mehdi Karaoui Department of General Surgery, Henri Mondor Hospital, Marie Hélène Grivell, psychologist, for her precious help in the psychological follow up, Frédéric Martin, orthophonist, for his remarkable facial rehabilitation work, and Michael Yaremchuk, Clinical Professor of Surgery, Harvard Medical School, Boston, Massachusetts for his help in reviewing our manuscript. We also wish to thank all the team at Henri Mondor Hospital involved in the management of the patient, including in particular the doctors and nurses of the Departments of Plastic Surgery, Dermatology, Anaesthesiology (especially Alain Gilton), Nephrology, and Pathology. We also extend our gratitude to the family of the donor.

References
**Face transplantation**

Composite tissue allografts have opened up a new era in transplantation. Most are visible, replacing non-vital parts of the body, and as described by one of our first hand-transplant recipients are not only life-saving but also life-giving. The two recipients of face transplants presented in today’s *Lancet* and the first patient who received a face transplant would probably share this view. Important contributions of the teams from Xi’an and Paris in addressing the issues of face transplantations have shown the need for progress in three directions: surgery, immunology, and psychology.

For surgery, several key questions remain. Which type of donor is most suitable? Although the French donors were beating-heart, the Chinese donor was not, with the risk of making harvesting more difficult and imprecise. What are the effects of ischaemia and its duration on the technical and functional results? The recipient sites in each patient were prepared immediately before transplantation. Although the Paris group reported substantial blood loss, this risk can be reduced by doing a tumour resection as a separate step. However, delays and difficulties in finding suitable donors might be an obstacle. What kind of vascular support is needed if the initial lesion does or does not include bones and other tissues? What are the roles of direct nerve sutures (motor and sensitive branches) and intramuscular reinnervation related to muscular sutures?

With regards to immunology, the recurrent episodes of acute rejection seen in both patients during the first year despite potent immunosuppression (induction therapy with antilymphocyte polyclonal antibodies or monoclonal antibodies against the interleukin-2 receptor, with triple immunosuppressive therapy) show the high immunogenicity of a composite tissue allograft of the face. Surprisingly, in both patients, skin rejection was easily reversed by high doses of corticosteroids, perhaps because of early clinical diagnosis. Skin biopsies to confirm a diagnosis are nevertheless needed, but these lead to scars that are not aesthetic. Rejection in the oral mucosa cannot be used as a surrogate marker for the diagnosis of skin rejection on the basis of an observed parallelism in only three patients. Inflammation tends to be more intense in mucosa than in skin. In human hands, a good surrogate diagnostic marker is a vascularised sentinel skin graft, because the sentinel skin and facial skin have similar clinical features and evolve concomitantly during rejection. The sentinel flap in the vascularised skin was used for systematic biopsy tests and to monitor skin rejection.

The number of recipients with composite tissue allografts is too few for randomised trials of immunosuppressive therapy. According to the results of kidney transplantation trials, antithymocyte polyclonal antibodies are more efficient than monoclonal antibodies against interleukin-2 receptor in the prevention of rejection in recipients at high immunological risk. A potent induction protocol with thymoglobulins was effective in the first face-transplant recipient when haemopoietic stem cells from the donor were infused postoperatively.

Transplantation of haemopoietic stem cells might thus be a way to improve long-term allograft survival. The absence of chronic rejections in patients who have had hand transplants so far and the presence of immunoregulatory CD4+CD25+Foxp3+ cells in their skin suggest that donor haemopoietic stem cells from the vascularised bone transplant are immunoregulatory, as already described in animals. Psychological acceptance seems easier for the face than for hand allografts. Further psychological studies are, however, needed to offer the best preparation and follow-up for patients, because personality...
and motivation are key factors. Shuzhong Guo and colleagues\(^1\) reported the short 1-month interval between initial admission to hospital and transplantation, which might explain difficulties with compliance. Resemblance between the transplanted face and the patient’s previous face also needs to be discussed, even if we know that the shape of the face depends on deep bone structure and on restoration of facial function and expressivity. The surgeon aims to aid social acceptance and not just to restore a facial expression; clearly, these factors will limit the generalisation of face transplantation.

Cooperation between the three pioneering teams is essential to answer the many technical, functional, immunological, and psychological questions raised by face transplantation. The definition of the best indications (trauma, malformations, benign tumours, burns) will also greatly benefit from this cooperation. The International Registry on Hand and Composite Tissue Transplantation\(^2\) would be an ideal forum to help solve these challenges and define new indications. Our main objective is to give back a normal life to disfigured patients.

*Jean-Michel Dubernard, Bernard Devauchelle

**A king in the CASTLE? Optimum initial HIV protease inhibitor**

In today’s *Lancet*, Jean-Michel Molina and colleagues describe the 48-week results of the CASTLE study,\(^1\) a 96-week, phase III, open-label randomised comparison of ritonavir-boosted atazanavir versus fixed-dose lopinavir-ritonavir, each in combination with the fixed-dose nucleoside reverse-transcriptase inhibitor (NRTI) pairing of tenofovir and emtricitabine. During the past decade, potent antiretroviral therapy has substantially decreased morbidity and improved survival in patients infected with HIV, and the goal of HIV infection as a chronic manageable disease seems achievable. Antiretroviral therapy guidelines delineate preferred options for patients starting therapy, including a combination of two NRTI plus either a non-NRTI (NNRTI) or a ritonavir-boosted protease inhibitor.\(^1\) Although endorsed as a preferred agent by the treatment guidelines, until now there have been few data to support the use of atazanavir-ritonavir in treatment-naive patients.

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We declare that we have no conflict of interest.


