Composite tissue allograft (CTA) is defined as heterologous transplantation of a complex comprising skin and subcutaneous, neurovascular and mesenchymal tissue, including bone, cartilage, muscle and/or fascia [1,2]. Such transplantsations may in future be of great interest for repair of loss of substance of traumatic or oncologic origin and for the treatment of congenital differences. They enable complex reconstruction using vascularized grafts of equivalent but normal tissue harvested from organ donors; donor site morbidity is avoided, as there is no donor site [1,3—5]. The transplanted tissue is supple and well vascularized — an advantage in irradiated or scleros terrain [6]. In children, epiphyseal growth cartilage conserves its growth potential [7—11]. Vascularized composite allografts thus enable the reconstruction surgery principles defined by Harold Gillies — “Replace the lost part like with like” — to be perfectly met for the first time: a moment’s reflection will show that no current reconstruction technique using allografts or flaps can achieve such a result. For example, in a young 20-year-old police officer presenting with an elbow destroyed by ballistic trauma, it would be possible to perform a vascularized graft of the joint, including the capsuloligamentary structures and muscle insertions; and the result would be durable, unlike with present-day non-vascularized massive allografts. Or again, in a little girl presenting with bilateral lower limb amputation secondary to meningococemia, bilateral vascularized allografts could be performed, although with a risk of insufficient reinnervation and consequent neuropathic ulceration.

At the present time, however, medical immunosuppression remains mandatory (the skin in particular being highly antigenic), entailing risks that are not acceptable in purely functional surgery, except in very particular indications. The main hope for the future lies in induction of graft-specific tolerance.
functional surgery, whereas classical reconstruction using grafts, flaps or endo- or exoprosthesis provides acceptable results in a large majority of cases. Once immunosuppression can be circumvented or its risks significantly reduced, indications for CTA in orthopedics-traumatology will greatly exceed the frequency of the present indications of heart, lung, liver, kidney and pancreas.

Background

Legend has it that the martyred brothers Cosmas and Damian, the patron saints of surgery, during the reign of Diocletian in the 3rd century AD, attempted taking a leg from a black slave to transplant it onto the sacristan of the Church of Saint Cosmas and Saint Damian in Rome, who was suffering from gaseous gangrene. Several famous paintings illustrate this legend. Alexis Carrel, the French father of vascular surgery (who notably developed the techniques of arterial anastomosis and venous graft) and winner of the Nobel prize for physiology and medicine in 1912, performed the first experimental grafts, including a paw graft on a dog in 1912. Schwind, in 1936, described the phenomenon of "parabiosis": he performed a pediculated graft between two rats, of different races but both very young (and hence immunologically immature); a period of 10 or so days' 'coupling' between the animals via the graft allowed blood cells to be exchanged; after separation, the transplanted extremity survived, in ortho- or heterotopic position, with no signs of rejection [12–14]. The first attempted hand transplantation was performed in Ecuador in 1964 but, lacking modern immunosuppressants, was quickly rejected [3]. The literature testifies to more than 100 models of experimental limb transplant in animals, with varying degrees of success [1,4–9,15–48]. Lachinsky et al. succeeded in inducing graft tolerance in newborn dogs [49]. The discovery of immunosuppressant agents during the 1960s and of cyclosporine in particular in 1976, combined with the relatively recent notion of associating them to enhance efficacy and reduce side-effects, then revolutionized transplant surgery. The first "modern" unilateral hand transplant was performed in Lyon (France) in 1998 [50,51], and was rapidly followed by the first bilateral hand transplant, once again performed in Lyon [52].

Hand transplantation

Since May 2002, the various teams (with the exception of certain Chinese surgeons) involved in hand transplantation have established the International Registry on Hand and Composite Tissue Transplantation (IRHCCT). In September 2007, the registry contained 38 hand transplants (18 unilateral and 10 bilateral), and two thumb transplants, in 30 patients, with follow-up ranging from 6 months to 9 years. No deaths or early failures were observed. Patients were administered immunosuppressants, as in kidney transplantation. Except in the case of the Chinese patients, allograft survivorship was better than 95%, with failure exclusively associated with defective compliance to medication. Acute rejection was observed in 85% of patients, mainly during the first year, but was always able to be brought under control. All patients at least developed protection sensitivity, and 72% developed discrimination sensitivity. All patients recovered useful and indeed sometimes excellent hand function. Immunosuppression complications were moderate, although one American patient, with preoperative glucose intolerance, developed insulin-dependent diabetes linked to the use of Tacrolimus, followed by osteonecrosis of the femoral head requiring total hip arthroplasty (THA). Several patients contracted severe Cytomegalovirus infections, complicated by episodes of rejection. No fatal complications were reported [53]. As well as these well-documented cases, there has been a series of transplantations performed in China, not included in the international registry. In most of these Chinese cases, it appears that immunosuppression and physiotherapy were discontinued after about 1 year, resulting in chronic rejection with atrophy and progressive loss of function in the transplanted hand; several patients had to be reamputated [54]. This rather questionable experience on the one hand highlights the importance of pursuing immunosuppression beyond the first year, and also presents a surprising rarity of acute rejection at 1 year despite termination of medication (role of bone marrow).

In Brussels, in June 2002, we performed a unilateral hand transplant, reporting excellent functional results [55], but also very particular problems of rejection when at one point in time the rather non-compliant patient took the initiative of reducing his immunosuppression regime for a period of 6 months [56,57]. This clinical experience, currently limited to a single case, underlies an ongoing original research program on tolerance induction, being run at the Gosselies Medical Immunology Institute [58,59].

In conclusion, worldwide experience has demonstrated the feasibility, both surgical and immunological, of hand transplantation, with recovery of useful function and good sensibility, which are as yet beyond the capacity of even the most state-of-the-art myoelectric prostheses. Function is indeed probably better than that obtained by replanting the actual amputated hand, partly as the graft is composed of non-traumatized tissue, and also probably thanks to a beneficial impact of Tacrolimus on axon regeneration. The psychological benefit, moreover, is enormous [57]: unlike in replantation of an amputated hand, transplant patients have had and suffered from the experience of being without a hand or hands, and lived in hope of one day recovering it (or them).

Indications and contra-indications

The prime indication for hand transplantation would be amputation in a patient already under immunosuppressants for other reasons — although, to our knowledge, this dream ticket has never actually turned up. The most widely agreed indication at present is bilateral mid-forearm amputation with good stumps, in a highly motivated patient. Unilateral amputation of the dominant hand is a more controversial indication [57]. Indications that are presently not accepted include partial hand amputation (immunosuppression risks, and existence of alternative reconstruction techniques), conserved hands, however stiff and desensitized (principle of reversibility), and congenital amputation (ethical problem of lack of informed consent, possible problem of cerebral plasticity, and uncertainty as to long-term outcome).
Contra-indications are general (diabetes and significant cardiovascular, renal, oncologic or infectious history), age-linked (50-year threshold?), and lastly and above all lack of patient motivation. The frequency of serious psychological problems associated with hand injuries is to be borne in mind here [60—65]. Preoperative psychological assessment is essential, as is postoperative psychological support. Nor should the financial aspect be overlooked: apart from direct transplantation costs, the immunosuppression regime costs about €25,000 per annum, and insurance cover, or the equivalent depending on the country, needs to be checked before surgery is considered.

In our opinion, a hand transplant program requires an adequate hospital environment, with on-site presence not only of a team experienced in microsurgical repair of the hand, backed up by specialized rehabilitation physicians, anatomopathologists, neurologists and specialized psychologists, but also a donor harvesting organization; we further consider it essential to associate fundamental research in composite transplantation to clinical experience.

Other vascularized composite allografts in orthopedics-traumatology

In 1992, Guimberteau presented two cases of vascularized flexor tendon allograft, including the glide system, performed under limited immunosuppression that was stopped at 6 months, with good functional results [66]. The same team in Bordeaux is currently focusing research on cryopreserved tissue transplantation, potentially a very interesting attitude, conserving segments of tissue for subsequent revitalization after thawing and microsurgical revascularization [67]. In 1996, Doi et al. reported a vascularized peroneal allograft [68]. As of 1998, Hofmann and Kirschnner reported a long experience of knee and femur transplantation [69—70]. Finally, in 2006, Zuker performed a lower limb transplantation between siamese twins [11].

Hofmann and Kirschnner’s experience is of particular interest. They consider extensive loss of knee and/or femoral substance to remain a severe therapeutic challenge. Reconstruction by TKA is difficult in case of concomitant destruction of the extensor apparatus. Classic non-vascularized cryopreserved allografts show rapid joint deterioration and a very high rate of complications. Arthrodesis consolidation is also difficult in case of extensive loss of substance. Morbidity is high secondary to progressive bone lengthening using the ilizarov technique, with a high rate of failure. Many cases end in mid-thigh amputation. Given all this, Hofmann and Kirschnner recommend a novel approach: reconstruction by vascularized knee and/or femoral allograft after “carcinologic” exeresis of all the infected bone. They performed three such allografts of the femoral diaphysis (one case of chondrosarcoma, two of posttraumatic infection) with respectively 12, 14 and 33 cm defects. They also performed five knee allografts for posttraumatic defect involving the joint and extensor apparatus (femur: 10 to 15 cm; tibia: 5 to 10 cm). After femoral allograft, immunosuppression was stopped when bone consolidation was achieved. In one case, the allograft needed to be removed for recurrent infection. In all cases, healing was finally achieved. In four of the five knee allografts, bone consolidation was achieved with recovery of good joint function (complete extension, mean 120° flexion). All patients required subsequent total knee arthroplasty (TKA) for resurfacing, after termination of immunosuppression. There was one failure due to recurrence of infection. The authors reported difficulty in following up rejection, and recommend iterative arthroscopy with synovial biopsy [69,70]. Diefenbeck et al. reported a recent case with non-controlled late rejection [71], and reviewed long-term results for the Hofmann and Kirschnner series, disclosing several ultimate failures [71]. It may be wondered why the success rate in these vascularized composite allografts was so low.

Alongside these interesting clinical experiences, the literature contains many fundamental research protocols in vascularized bone allograft. Rejection signs include neighboring soft tissue swelling, and reduced marker take-up on bone scan. Early termination of immunosuppression leads to rejection and delayed consolidation [72]. Prolonged immunosuppression, on the other hand, appears to be harmful, inducing osteoporosis in the long term [73]. Cessation of immunosuppression after bone consolidation is followed by rapid bone necrosis, but without bone resorption or fracture. In fact, the heterologous bone seems to be progressively replaced by new host bone (“creeping substitution”), as found with classic allografts [73,74].

Other vascularized composite allografts in general and plastic surgery

In 1998, Jones et al. reported a case of muscular flap allograft for scalp reconstruction in a renal transplant patient [75]. Clinical experience with vascularized composite allografts has been burgeoning in recent years, particularly as concerns laryngeal transplantation [76], with great success and low-dose immunosuppression [77], and the famous cases of face transplantation [78,79]. There have also been transplantations of the tongue, abdominal wall after intestinal transplantation [80] and uterus, with varying degrees of success.

Discussion

Worldwide experience clearly shows that vascularized composite allografts are feasible and offer interesting clinical results. Immunosuppression (at renal transplantation doses) currently remains indispensable. Rejection episodes are found, but can be treated. The ethical debate remains open: do we have the right, in seeking to restore lost function, to expose young healthy patients to the complications and risks inherent to immunosuppression? And another issue is how allotransplants will evolve over time.

In the medical community, as in the public at large, there are supporters and opponents, and the arguments are not always fully rational. We consider that the decision to resort to vascularized composite allotransplantation is the patient’s, to be made in the light of his or her own perception of the trade-off between quality and quantity of life. To make such a decision, the patient needs to have full information as to possible results and the risks entailed. The data we have on these points, however, remain sketchy. Pace, the
received wisdom, kidney or pancreas transplantation does not save the patient’s life but basically improves its quality; yet these procedures are not seen as burning ethical issues. A parallel may be drawn with THA: the patient is exposed to immediate risks (surgical, infectious, embolic, dislocation, etc.) and to medium and long-term risks (loosening, chronic infection, etc.). The patient decides freely, after full information, to run these risks in order to improve quality of life, which hip arthritis obviously impair. The question probably needs turning around: what right do we have to deprive a bilateral hand amputation victim of the option of transplantation?

The risks incurred for a candidate for vascularized composite allograft are threefold: accelerated senescence, risks inherent to chronic immunosuppression, and the risk of graft-versus-host disease (GVHD).

Accelerated senescence

Some 50% of cadaveric renal grafts dysfunction after 10 years (chronic transplant dysfunction) [81—84]. Histologically, chronic rejection is characterized by myo-intimal proliferation within the graft arteries and by organ-specific lesions [82]. The risk of chronic rejection is exacerbated by human lymphocyte antigen (HLA) incompatibility and by iterative acute rejection [81,82,85,86]. In hand transplantation, onchomadesis and tendinous adherence have been reported, which may be early signs of chronic rejection [56].

Risks incurred by chronic immunosuppression

Immunosuppressants have numerous side-effects, but which can be reduced by associations, which moreover enhance their effect [2,6,16,37,87—94]. Risks are mainly cardiovascular. Tacrolimus may induce diabetes and, at high dose, is neurotoxic and nephrotoxic. Corticosteroids induce osteoporosis and osteonecrosis.

The transplantation literature shows that 80% of kidney transplant patients develop at least one opportunistic infection, which tends to be benign; 40% of deaths, however, involve infectious complication. The risk of opportunistic infection is especially high during the first 6 months [6,85,92,95—97]. Certain viral infections are especially severe, particularly those caused by *Cytomegalovirus*, and also induce episodic rejection [29,98,99].

The risk of neoplasia is not elevated in the more frequent cancers (bronchial, prostate, breast or colon) [100—102]. On the other hand, immunosuppression does increase the risk of cancer involving oncogenic agents (sun, virus): i.e., especially skin cancer and lymphoma; the risk is estimated at 3% [103], one-third being skin cancers, which are relatively easy to prevent (UV protection when exposed to sunlight), detect and treat [85,92,100,101,103—106]. The risk of lymphoma is mainly during the first year, in Epstein-Barr negative patients grafted from a positive donor [107,108]. The risk of non-Hodgkin lymphoma is between 0.3 and 0.4% during the first year, falling to 0.06—0.09% thereafter [103,109,110]. Certain lymphomas resolve with reduction or cessation of immunosuppression, probably entailing amputation of the grafted member. Kaposi sarcoma can be resolved by changing immunosuppressants: replacing Tacrolimus by Sirolimus [111].

About 30% of kidney transplant patients (especially teens) fail to comply with immunosuppression, leading to frequent graft rejection and loss [29,82,93,112]. Our own hand transplant patient was a case in point.

Graft-versus-host disease

The risk of GVHD is probably very small in hand transplantation, except in case of associated lymphopenia. It might be higher for macrotransplantation of a limb, involving a large volume of bone marrow [18,26,30,88,94,97,113—115].

Future strategies

If immunosuppression could be circumvented or reduced, indications for vascularized composite allotransplantation would be very numerous, especially in orthopedic traumatology [19,29,30,114,116—124]. There are in principle three prospects: improved HLA compatibility, which seems unrealistic; minimal immunosuppression protocols, to reduce toxicity — maintenance monotherapy based on low-dose Tacrolimus has been developed in pediatric kidney transplantation [125]; or tolerance induction, defined by definitive allograft acceptance, conserving normal immunity without any immunosuppression. The potential risk of this third option is obviously GVHD, although this has been observed neither clinically nor in animal studies. There are a variety of tolerance induction strategies, none of which are clinically applicable at present in orthopedic transplantation. Tolerance induction could be relatively straightforward in neonates, whose immune system is immature, and this holds out hope for the treatment of congenital differences [2,6,13,14,122,126,127]. Apart from the obvious technical problems and dangers of such surgery in babies, the ethical issue remains. In Malaysia, Pathmanathian transplanted an upper limb between homoyzous twins, with major operative difficulties but an excellent functional result, and without, of course, any immunosuppression. In adults, depending on the animal species and especially on acquired immune history, it has proved difficult to induce robust tolerance [2,5,21,25,29—31,58,59,98,114,121,128—132]. The current best hope lies in the presence of stem cells in the graft bone marrow, which migrate to the host, inducing central tolerance. Siemionow thus obtained indefinite tolerance of limb transplant in rat, after short immunosuppression associating cyclosporine A to anti-TCR antibodies [2,5]. With a slightly different protocol, our own research team managed to induce robust tolerance in mouse. We observed microchimerism with presence of T lymphocytes from the graft throughout the host, and especially in the thymus [58,59]. Such a strategy could be more effective than the intravenous donor stem-cell injection attempted in face transplantation.

Conclusion

Vascularized composite allotransplantation is feasible, both surgically and immunologically. The technique raises ethi-
cal issues. The optimal, but exceptional, indication would be extensive bone and/or soft tissue defect in a patient already under immunosuppression. The prime hope lies in tolerance induction, which probably requires vascularized bone marrow within the allograft, a short immunosuppression protocol, and careful follow-up.

Conflict of interest

None.

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