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REVIEW

Achievements and challenges in composite tissue allotransplantation

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Summary

Overall, more than 60 hand/forearm/arm transplantations and 16 face transplantations have been performed in the past 12 years. In the European experience summarized here, three grafts have been lost in response to a vascular thrombosis ($n = 1$), rejection and incompliance with immunosuppression ($n = 1$) and death ($n = 1$). The overall functional and esthetic outcome is very satisfactory, but serious side effects and complications related to immunosuppression are challenges hindering progress in this field. The high levels of immunosuppression, skin rejection, nerve regeneration, donor legislation and the acceptance level need to be addressed to promote growth of this promising new field in transplantation and reconstructive surgery.

Introduction

Over 60 hand and 16 face transplantations have been performed over the last decade and composite tissue allotransplantation (CTA) has become a new clinical entity (see also Table 1). To foster communication and information exchange for advancement of the field, the ESOT CTA Working Group (WG) has been established in November 2009. We aimed to institute information exchange between CTA centers and ESOT and to augment the scientific and clinical development of CTA in Europe.

Surgical realization of human hand transplantation was first attempted in Ecuador in 1964 [1]. Progressive rejection under azathioprin and steroid treatment, however, required reamputation and over three decades passed until the second attempt was carried out in Lyon, France [2]. A significant increase in graft survival following solid organ transplantation (SOT) and a series of rodent and large animal studies investigating the efficacy of novel immunosuppressant in CTA indicated that hand loss could now be prevented [3–5]. While the first transplant of this new era failed at 2½ years after transplantation over a dozen hands transplanted at this point provided ample proof that graft survival can be achieved [6]. It became obvious, however, that hand transplantation not only required diligent surgery and well-adjusted immuno-

Table 1. Summary of data on hand and face transplantation in Europe.

	Lyon	Innsbruck	Milan	Brussels	Trzebnica	Valencia	Creteil	Seville	Barcelona
No. cases	7	4	3	1	3	4	4	1	1
Gender	M (6)/F (1)	M (4)	M (3)	M	M	M (3)/F (1)	M	M	M
Allograft (s)	Unilateral hand (1) Bilateral hand (4) Face (2)	Unilateral hand (1) Bileteral hand (3)	Unilateral hand (3)	Unilateral hand	Unilateral hand	Bilateral hand (3) Face (1)	Face (4) Bilateral hand (1)	Face	Face
Induction regimen	ATG + MPred	ATG + MPred (2) Alemtuzumab + MPRED (2)	Basiliximab + Mpred	ATG + MPred	Basiliximab + Mpred	Alemtuzumab + MPred (3) Basiliximab + Mpred (1)	ATG + MPred	Basiliximab + Mpred	ATG + MPred
Maintenance regimen	Tac + MMF + Pred	Tac + MMF ± Pred	Tac + MMF + Pred	Tac + MMF + Pred	Tac + MMF + Pred	SRL + MMF + Pred	Tac + MMF + Pred	Tac + MMF + Pred	Tac + MMF + Pred
Longest graft survival (days)	3650	3102	2920	1710	1460	1460	750	450	307
No. graft lost	1	0	0	0	1	0	0	0	0
Functional result	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent	Excellent
Metabolic complications	Hyperglycemia Increased SCr	Hyperglycemia Increased SCr	–	–	No	Hyperglycemia Increased SCr	Hyperglycemia	–	Increased SCr
Infectious complications	HSV, EBV	CMV, HPV, Fungal	CMV	–	–	VZV, Fungal	CMV	–	–
Death	No	No	No	No	No	No	Yes (1)	No	No

Follow-up and outcomes as published.

ATG, antithymocyte globulin; MPRED, methyl-prednisolone; SRL, sirolimus; Eve, everolimus; Tac, tacrolimus; MMF, mycophenolate mofetil; SCr, serum creatinine; Pred, prednisone; HSV, herpes simplex virus; EBV, Epstein–Barr virus; HPV, human papilloma virus; CMV, cytomegalovirus; VZV, varicella zoster virus.

suppressive treatment, but also a high degree of compliance and close follow up with the patient.

The convincing results encouraged investigators to proceed with forearm, arm and face transplantations. Risks and side effects associated with high dose multi-drug immunosuppression represent the most prominent obstacle to further advancement in this field. In this review, we summarize the outcomes and challenges in CTA and discuss innovative techniques for reduction of immunosuppression.

Indications for CTA

The amputation of the upper extremity is a devastating injury affecting function in addition to the loss of physical integrity. When replantation is not possible or fails, upper limb prostheses are available as a substitute but have shown poorer function [7]. Both unilateral and bilateral upper extremity transplantation have been performed at different levels between wrist and shoulder [8–11]. Traumatic amputations of the upper limb usually present with near-normal anatomy at the stumps and transplantation can be considered if the brachial plexus is not injured. While the challenges in bilateral hand transplantation are more related to the logistics and complexity of the surgical procedure as well as the intense rehabilitation and patient dependence on support early after transplantation, challenges in unilateral hand transplantation are more related to patient selection and compliance. Inclusion and exclusion criteria in unilateral hand transplantation therefore differ from bilateral cases in the sense that the patients desire to undergo transplantation and his expectations need to be more carefully reviewed to identify suitable candidates.

Reconstruction of abdominal wall defects in recipients of multivisceral or intestinal allografts can be difficult or impossible in some cases [12–14]. Abdominal wall allograft transplantation can be considered a valuable therapeutic modality in these recipients.

Complex facial defects (CFD) are a major surgical challenge. They compromise several esthetic facial units (EFU) and result in different degrees of functional impairment. Such defects are difficult to manage using conventional techniques with limited cosmetic and functional results [15,16]. Availability of color-matched skin grafts is limited to areas above the clavicles and local flaps are confined to reconstruction of superficial defects [17–19]. The major drawbacks of microsurgical reconstruction of the head and neck are absence of function, need for multiple-stage procedures, skin color mismatch and suboptimal cosmetic results [20–23]. By contrast, face transplantation is a single stage procedure using ideally matched tissue for reconstruction of both sensitivity and motion as required for normal facial appearance. *A priori* the indication for allotransplantation would include cases were conventional reconstruction has been exhausted. Such an algorithm of ''conventional reconstruction first'', however, results in a high number of surgical procedures and a prolonged period of treatment until a satisfactory reconstruction is achieved. A ''face transplantation first'' concept is a single step surgical procedure. This concept seems appealing but relies on criteria to define the likelihood of an unsatisfactory result for the individual patient. It is important to point out, however, that the life-boat procedure for face allograft loss remains undefined and that loss of a face transplant may be life threatening. Furthermore, donor body integrity represents and important challenge. Alginate prostheses seem to be a suitable technique for reconstruction after donation [24]. Both donor and recipient families should be advised on the different appearance of the recipient after transplantation [25]. In addition, exposure to the media should be discussed with the recipient but with the donor family. A specific consent form designed for the donor family should include these two issues before donation.

Outcome after hand transplantation

Loss of a hand has a devastating impact on the victim's functional abilities and psyche [26]. At this point, a relatively small group of otherwise healthy patients suffering from poor functional or psychological adaptation, unsatisfied with the function provided by prostheses and/or a serious disturbance of body integrity have undergone transplantation [8].

Hand recovery is performed at a level just proximal to the level of the actual amputation or proximal to the elbow. A cold flush with HTK or UW preservation solution is performed. Upper limb prostheses are fitted on the donor stumps to maintain the integrity of the corpus. Transplantation commences with bone synthesis using rigid plates and screw fixation. Next, the graft is revascularized by anastomosis of arteries and veins prior to repair of tendons and nerves and skin closure [8]. While most centers follow this algorithm, variations have been applied [28–30]. Cold ischemia time was kept below 13 h as the consequences of prolonged ischemia include muscle injury and fibrosis [29].

For immunosuppression (IS) basiliximab, antithymocyte globulin (ATG) or alemtuzumab together with gradually reduced methylprednisolone was used in all cases. For maintenance, tacrolimus (serum concentrations between 6 and 15 ng/ml), mycophenolic acid (2×1 g) and steroids (5 mg/day) were applied and adjusted as per the individual protocol and requirements [8,27–32].

The rehabilitation program is based on principles developed for rehabilitation after replantation and focused

on early protective joint motion and continued for 1 year. Forearm splints such as a dynamic crane outrigger splint and various types of positioning, functional night and daytime splints were used early after surgery.

The postoperative courses of hand allograft recipients in Europe have been mostly uneventful [8–10,27–32]. The unification of bones was completed at 12 weeks. Nerve regeneration was progressing rapidly, reaching fingertips at 8–9 months. All patients developed protective sensibility and 90% developed tactile sensibility [8]. Discriminative sensation returned in 82.3% of all patients and they were able to distinguish between different thermal stimuli [8]. The return of intrinsic hand muscle function was observed at 9–15 months but varied depending on the level of amputation/transplantation. All patients are able to perform grasp and pinch grip. The patients have fully incorporated the transplanted limb into their body image and regained self-confidence. Patients are able to drive a car, ride a bicycle, hold small objects, turn pages, turn door knobs, write, and work [8].

Rejection episodes have been observed in 85% of the patients within the first year [8]. One patient died as a consequence of sepsis on day 65 after simultaneous bilateral hand transplantation and face transplantation [8]. Two patients transplanted in the US and Europe have lost their grafts: one patient as a consequence of intimal hyperplasia in the arteries of the graft on day 275 and one patient as a result of progressive rejection of the skin after stopping immunosuppression at 29 months [33,34]. This case also illustrated the importance of patient selection and compliance as lack thereof resulted in hand loss in this case. Both patient selection and adherence to immunosuppression and physical therapy are critical challenges especially in unilateral hand transplantation. While logistics, surgical procedure and rehabilitation are less demanding in unilateral hand transplantation, difficulties with patient selection and compliance have only been observed in this group of patients.

Transient hyperglycemia, hypertension, increased creatinine values, and hypertension were frequent but reversed with proper medical treatment [8]. A basal cell carcinoma of the nose was detected and successfully treated by surgical excision [35]. The thrombosis of an ulnar artery required thrombectomy [29]; a case of venous thrombosis was treated by microsurgical revision [28]. There was one case where arterio–venous fistulas which resolved after ligation [36]. Small skin necroses appeared in four cases and were treated successfully with a skin graft [8]. In one case, wound margins separated on day 15 because of a large hematoma [37]. In one patient, flexor tendon adhesions required tenolysis at 14 months [27]. Cytomegalovirus (CMV) infection was reported in the majority of cases. Other infections included human papilloma virus infection, herpes simplex infection, fungal infections affecting skin and mucosa and a *Clostridium difficile* enteritis [8]. In one case ulnar osteitis caused by *Staphylococcus aureus* was encountered and treated with antibiotics [8]. Patients may experience psychiatric disorders like depression, fear or denial of the transplanted hand, especially during the early postoperative course [27]. In some cases, the disorders resolved after sensitivity was achieved and the allografts integrated in cerebral cortex and body image. A suicide attempt was reported in one patient [27].

Outcome after forearm transplantation

The functional outcome after transplantation at the upper extremity is highly dependent on the anatomical level of amputation/transplantation. While hand function after transplantation at the wrist level results in very good function early after the surgery, the outcome after transplantations at more proximal levels is less consistent and only evident after prolonged follow up [37,38]. The term ''forearm transplantation'' has been used inconsistently, but is only suitable in cases were the entire forearm muscles are of donor origin while biceps, triceps and brachialis muscles are from recipient origin with intact innervation. Hand motor function in these cases is entirely dependent on re-innervation and reactivation of (grafted) forearm muscles. As a consequence, major differences to hand transplantation arise: (i) hand function is absent early after transplantation and only recovers slowly in the subsequent years, (ii) completion of functional recovery is approximately 2 years, (iii) hand function will be inferior when compared with hand transplantation, (iv) re-innervation and reactivation of intrinsic hand muscles cannot be expected, (v) protective but not discriminative sensation can be expected, (vi) ischemia time and preservation of forearm muscle tissue until reactivation requires attention, (vii) patients require more physical and psychological support in the months and years after transplantation, and (viii) secondary surgeries have been carried out more frequently when compared with hand transplantation.

Despite the postoperative course being significantly more challenging when compared with hand transplantation, forearm transplantation has resulted in good patient satisfaction [1,2]. In addition to restoration of body integrity, better motor function, better movement control and less everyday challenge when compared with myoelectrical prostheses justify continuation of forearm transplantation. Thorough and cautious patient selection, however, is critical as the challenging rehabilitation can overburden patients easily and result in frustration and impact on compliance.

With regard to the immune response and the levels of immunosuppression, the number of cases remains to small to draw meaningful conclusions. While the postoperative immunological course was particularly challenging in one case [37–39], other cases have not confirmed an impact of the larger amount of tissue on rejection/immunosuppression [11].

Outcome after arm transplantation

Amputees who suffer from a bilateral above elbow amputation adapt poorly to prostheses and are usually dependent on others for care and personal hygiene [40]. Arm transplantation was first carried out after forearm transplantation had shown good functional results with reinnervation and reactivation of forearm muscles [38].

While the surgery is arguably easier than in more distal transplants, anatomical adjustment of bone length and rigid fixation are of utmost importance. The major challenge in arm transplantation is the long distance between the nerve stump and their end organs. Rehabilitation can be started soon and may be intensified after reinnervation of forearm muscles. Tendon transfers to gain intrinsic function of the hand and joint arthrodeses are considerations for the improvement of the function [11].

The first arm transplantation was performed in Munich in July 2008 in a 53-year-old farmer who had lost both arms in an accident with a corn cracker 6 years earlier. Both upper arms had been amputated just below the shoulder. The function and sense of body integrity provided by myoelectric prostheses was considered insufficient by the patient. Two arms were transplanted and a portion of the subclavian vein was replaced using saphenous vein grafts because of thrombosis. After induction therapy with ATG, tacrolimus, mycophenolate mofetil (MMF) and methylprednisolone (later prednisolone) were used for maintenance therapy. The postoperative course was complicated by three rejection episodes (BANFF grade II) within the first 6 months. After 2 years of extensive physiotherapy, the patient is able to perform full elbow flexion and extension as well as wrist and finger movements. He uses both hands during daily activities. Arm and especially hand function is still improving at this point and it is too early to determine the final functional outcome. Motor and sensory nerves regenerated approximately 1 mm/day as expected. Elbow flexion begun after about 6 months. From experience in forearm transplantation, it can be estimated that motor function might continue to improve during 5 or more years after transplantation.

The second bilateral arm transplant was performed in Valencia; the recipient was a 29-year-old man who had lost both forearms as a result of an electrical burn injury [11]. A latissimus dorsi transfer was required to allow flexion of the elbow prior to waitlisting on one arm. Myotendorrhaphies were performed to connect triceps, brachialis, and biceps brachii muscles on the right side, and triceps and transferred latissimus dorsi muscles on the left side. Saphenous vein grafts were required for reconstruction of both arteries and veins. Fasciotomies on forearms and hands were performed to prevent compartment syndrome [11].

Unilateral arm transplantations were since performed in Wroclaw and Pittsburgh with good early results. While elbow function has been satisfactory in all cases, more patients and a longer time follow-up is needed to determine hand function after arm transplantation.

Outcome after face transplantation

Five years after the first case has been carried out in Amiens, 16 patients have received facial allografts in France, USA, Spain, and China. Face transplantation aims to re-establish motion required to speak, swallow and express feelings and to offer esthetic improvements allowing patients to lead a normal social life. While a systematic analysis of all cases has not been performed, the results of the first transplantations are convincing. The immunosuppressive regimen used for face transplantations is equivalent to that used in hand transplantation [42–46].

Two patients have died after face transplantation. The first death was attributed to cardiac arrest during surgical revision 2 months following transplantation [47]. The second patient died 27 months post-transplant under unclear circumstances [48]. Hot and cold sensation and discriminative sensitivity returned to normal at 6–9 months [42–46]. Recovery of passive and active lip movements was obtained between month 6 and 12 but differed between full or partial face transplantation [42–46]. Patients are able to breath through the nose, to smell, masticate, swallow, eat and recover phonation allowing them to speak. Recovery of facial movements allows them to express feelings and gives these patients a facial expression. The esthetic outcomes are satisfactory and patients are able to go about their daily lives without the need to wear a mask and without attracting unwanted attention. Recently, the psychological outcomes after face transplantation were reviewed and demonstrated that face transplantation decreases the rate of depression and verbal abuse but may not alter anxiety levels or self-esteem [49]. Overall, however, patients experience an acceptable quality of life with social re-integration [42–46,50]. Of all CTA recipients, 70% report a significant improvement in their quality of life by having regained their body image and a new ''sense of self'' [8]. Careful patient selection and a thorough psychological and psychiatric screening

prior to the transplant are considered critical. More and detailed studies are required to assess the psychological consequences of face transplantations such as change in body image, mood changes and self-esteem in greater depth. Rating scales and questioners need to be specifically adapted to be applicable for psychiatric assessment of face transplant recipients.

The main surgical complications reported were cutaneous necrosis and mucosal leakage [47]. In some cases, secondary surgical interventions were required to improve the esthetic outcome with scar revision, removal of redundant tissue and the sentinel flaps [44,45,47]. Metabolic and cardiovascular complications included post-transplantation diabetes [42], transient leucopenia, hypertension and renal failure in one case reversed by switching tacrolimus to sirolimus [43,45]. One CMV infection [46] as well as two type 1 human herpes simplex virus (HSV-1) infections was reported. In both cases, HSV-1 infections were followed by episodes of acute rejection, suggesting that the inflammatory response may trigger acute rejection [43]. An Epstein–Barr virus (EBV)-related post-transplant lymphoma occurred at 5 months post-transplant in one case. MMF was stopped and four courses of Rituximab administered resulting in full remission. Antiviral treatment to prevent CMV and HSV-1 for at least 3 months post-transplantation seems mandatory.

Three patients transplanted in Lyon and Boston also received a vascularized sentinel skin flap, which was used to perform systematic cutaneous biopsies without interfering with the integrity of the facial graft. The sentinel flap could also help to differentiate rejection form infection [51,52]. Acute rejection is diagnosed by erythema of the skin and mucosa with infiltration of mononuclear cells in the dermis and/or epidermis [43,46,51]. Early observations suggest that the oral mucosa is more susceptible to rejection than the skin [51,52]. Rejection was reversible in all cases using corticosteroids [42,43,45] or thymoglobulin [46]. Five years after the first transplant, there is no evidence for chronic rejection or deterioration of graft function/appearance. Patients who received a hemopoietic stem cell injection developed only transient micro-chimerism [53].

Cortex reorganization

One of the main hurdles after hand loss is the cortical organization shift that occurs after sensory and motor deprivation in amputees: face and forearm motor areas surround the representation of the missing hand expand into the de-efferented cortex [54]. Studies in bilateral hand-transplanted patients have demonstrated, however, that amputation-induced cortical reorganization was reversed following bilateral hand transplantation [55]. In addition, newly transplanted intrinsic muscles can be recognized and integrated into the patient's motor cortex [56], facilitating the fine and skillful hand movements after the graft. Such brain plasticity is believed to contribute to the favorable outcome after hand transplantation and is believed to also occur in face transplantation.

Conventional immunosuppression versus IS minimization versus tolerance induction protocols in CTA

One of the unique features of a composite tissue allograft is that these grafts unlike solid organ transplants consist of various different tissue components including muscle, tendon, nerve, blood vessels, bone, and skin. Historically, CTAs have been considered an immunological challenge – in particular because the skin is highly antigeneic/immunogeneic [57].

Immunosuppressive protocols applied in CTA are extrapolated from regimens used in SOT and allograft survival can be achieved on conventional triple-drug immunosuppressive regimens [8]. Of note, two mortalities related to hand or face transplantation have been reported to date [8]. In for example hand transplantation, this has resulted in an >95% patient and graft survival at 1 year after transplantation [8]. The majority of hand and face transplant patients received either polyclonal (ATG) or monoclonal (alemtuzumab and basiliximab) antibody preparations as an induction agent followed by a high-dose triple drug combination for maintenance therapy including tacrolimus, MMF and steroids [8]. Such regimens have proven sufficient to prevent early immunological graft loss but were not able to prevent acute akin rejection in 85–90% of all CTA recipients. All acute skin rejections after face or hand transplantation were reversible with either an increase in oral steroid treatment, a course of high-dose intravenous steroids or ATG, basiliximab or alemtuzumab in the case of steroid-resistance. Both topical tacrolimus and steroid ointments were administered in 95% of all cases displaying signs of acute rejection [8]. The small number of patients and the multitude of different treatment protocols do limit the ability to perform meaningful statistical analysis at this time. The need to balance the serious risks of chronic immunosuppressive medication against the benefits of function and body integrity remains. More recently, steroid sparing/avoidance, conversion from tacrolimus to the mTOR inhibitor sirolimus for long-term therapy and the use of topical steroid and tacrolimus ointments have been applied [41].

Small and large animal studies demonstrated that a whole limb allograft elicited a less intense alloimmune

response than allografts of each of its individual components thereby indicating a scale of tissue antigenicity [58,59]. While the diverse immune response toward different tissues of a CTA remains to be fully understood, this phenomenon indicates that application of immunomodulating strategies might be particularly interesting in such transplants. CTA offers some unique advantages such as continuous monitoring and adequate biopsy sampling of the graft by simple visual inspection of the skin allowing for a timely intervention, treatment and precise adjustments of immunosuppression on an individualized basis. In addition, some CTAs contain varying amounts of donor bone marrow (BM) together with a vascularized BM niche, which could serve as a continuous source of donor cells, including BM-derived stem cells. This has been demonstrated in experimental models to favorably modulate the host immune response [60,61]. Hence, novel cell-based strategies to minimize immunosuppression or induce immune tolerance are particularly appealing in CTA. Along these lines, cell-based protocols including donor BM and/or stem cells have resulted in reduction or elimination of long-term immunosuppression in SOT and CTA [62–67]. While the mechanisms of BM-cell induced tolerance or prope tolerance are not entirely understood, the induction of macro-, micro- or mixed chimerism seems to be an important factor [66–73]. BM cell infusion in the absence of recipient myeloablation has not resulted in an increased incidence of graft-versus-host disease (GvHD) [74,75]. Nevertheless, the use different types and volumes of cells from different resources – manipulated, fractionated or not – in combination with established as well as novel immunosuppressants and biologicals, GvHD remains a concern. The implementation of cell-based therapies including as T regulatory cells and tolerogenic dendritic cells could further help to induce immunomodulation subsequent to CTA and thus optimize the outcomes [76–80].

Legislation and regulations

Composite tissue allotransplantation will predictably suffer if not carried out it in a research setting as the initial cardiac experience attested [81]. This setting should provide standardized protocols and documented outcome analysis. Like all emerging fields it would be best served by development of a strong and unified evidence base. Other composite tissue transplants such as face, larynx and other tissues would benefit likewise.

Composite tissue transplantation and its regulation are dealt with under the European Union Tissue and Cells Directives (EUTCD) 2004 [82]. This directive was initiated to regulate the use of tissues and cells across the European Union. The EUTCD is made up of three Directives, the parent Directive (2004/23/EC), this provides the framework legislation and two technical directives (2006/17/EC and 2006/86/EC), which provide the detailed requirements of the EUTCD.

The directive replaced existing legislation in member states such as the Human Tissue Act 1961, the Anatomy Act 1984 and the Human Organ Transplants Act 1989 in the UK. Each member state of the European Union appointed a competent authority to oversee the directive implementation.

In a number of member states, there was significant debate as to whether composite tissue transplantation should be classified as a tissue or an organ [83]. Competent authorities classified composite tissue transplantation as a tissue and not an organ because composite tissues 'are not defined as organs as they fulfill no physiological life-saving function'. This was disputed by one of the authors of this review (PB) and others as an impractical way to discriminate between an organ and tissue. A more practical definition that took into consideration issues such as ischemic period was suggested. The EUTCD is now under revision and following input it has been determined that composite tissue transplantation will be considered as an organ in the revised legislation [84] (D. Fehily, personal communication, National Transplant Centre, Rome, Italy). It is still unclear whether it will considered under an exemption under tissue legislation or be more sensibly included under organ legislation.

Other issues that limit CTA donation is public and professional attitudes [85]. This is mainly related to CTA being an external organ donation and is associated with fear of disfigurement. It has been reported by many centers that asking for CTA donation has no impact on the likelihood of donating other organs such as kidney, heart or liver [86]. This was predicted by donor surveys and focus groups before CTA programs became established.

Summary and discussion

Over the past decade, transplantation of composite tissue allografts has become a clinical reality and vivid treatment option for selected patients. In patients compliant with immunosuppressive medication and rehabilitation, early and intermediate functional return after hand, forearm and face transplantation are highly encouraging. However, the functional outcome is dependent on intensive, continuous and individualized rehabilitation and this requires a high degree of patient motivation and compliance. Unlike solid organ transplants, which provide metabolic function soon following revascularization, a CTA is viable after reperfusion but activity of intrinsic muscles and sensation are absent. Hence, neuroregeneration represents a unique challenge as muscle degeneration occurs if not reactivated

timely and plasticity and rerouting in the central nervous system is required when reintegrating the graft in sensory and motor cortex.

The risks associated with surgery and long-term immunosuppression imply that patient selection must be rigorous, that clear information must be provided and that patients must be managed by multi-disciplinary teams with experience in organ transplant follow-up. Evidence from the pioneering initial transplants over the past 10 years has reinforced that the two main challenges need to be addressed: the immunogenicity of the skin and peripheral nerve regeneration.

Several exciting novel therapeutic strategies such as the implementation of cellular therapies including donor BM or stem cells that integrate the concepts of immune regulation with those of nerve regeneration are on the horizon. Reduction or elimination of long-term immunosuppression will ultimately enable wider application of such treatment options for patients in need of complex reconstructive surgery for congenital deformities or devastating injuries that are not amenable to standard methods of repair.

As more and more centers are embarking on CTA and implementing hand and face transplant programs, it will be important that new centers ally with experienced teams, which could provide help and guidance during the process. Clearly, further studies and larger patient numbers are required to assess the benefits before firm conclusion can be drawn regarding the overall relevance of face transplantation in reconstructive surgery. Ultimately, data and information should be shared between institutions and organizations such as the ESOT CTA WG might serve as exchange platforms to foster scientific and clinical development of CTA in Europe thereby ushering in a new era in CTA by improving the safety, efficacy and applicability of these promising reconstructive modalities.

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