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REVIEW

Face transplantation—current status and future developments

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SUMMARY

More than thirty-five facial allograft transplantations (FAT) have been reported worldwide since the pioneering case performed in France in the year 2005. FAT has received tremendous interest by the medical field and the general public while gaining strong support from multiple disciplines as a solution for reconstructing complex facial defects not amenable/responsive to conventional methods. FAT has expanded the frontiers of reconstructive microsurgery, immunology and transplantation, and established its place in the cross section of multiple disciplines. The procedure introduces complex scientific, ethical, and societal issues. Patients and physicians are called to deal with a variety of—sometimes everlasting—challenges, such as immunosuppression management and psychosocial hurdles. This review reflects on the surgical and scientific advancements in FAT and milestones reached in the last 12 years. It aims to encourage active discussion regarding the current practices and techniques used in FAT and suggest future directions that may allow transitioning into the next phase of FAT, which we describe as safe, reliable, and accessible standard operation for selected patients.

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Introduction

Devastating facial injuries distort the anatomy of the face, leading to severe functional and esthetic impairments. Most patients presenting for face transplant consultations are missing major components of the face such as nose, mandible, maxilla, ears, lips, and/or parts of the oral cavity. Motor function of the face requires an intricate interplay of these unique three-dimensional anatomical structures [1]. Thus, defects impair not only appearance, but also functions such as mastication, speech, vision, and breathing [2–5]. Furthermore, the face provides information about the identity, age, gender, and ethnicity of an individual and thus affects social interactions, integration, and perception of body image. Impairment in these social functions impacts quality of life that can result in discrimination and depressive symptoms [2,6–9].

Conventional reconstructive techniques for treatment of extensive facial defects include skin grafts, local/regional flaps, or free tissue transfer. These approaches yield mostly suboptimal esthetic and functional results as they cannot replace the anatomically refined structure of tissues, function of missing muscles, and concerted interplay of sensation, proprioception, and movement. Recent advancements in microsurgery, transplantation,

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and immunology enabled the transition of Face Allograft Transplantation (FAT) into clinical reality. The first clinical case of FAT was performed in 2005 in France [10]. Thus far, thirty-five procedures have been reported worldwide [11,12]. To the best of our knowledge, five FAT recipients have died (three deaths were not reported [11]) resulting into a 86% patient survival rate [13]. Many publications list all FAT procedures conducted to date; analysis of each case is out of the scope of this review [4,11,12,14]. Overall, the literature on FAT suggests a "smooth" progression from the first partial to the most extensive FAT which included scalp, ears and ear canals, elements of bone and oral tissues [15]. FAT is a quality of life improving rather than a life-saving intervention; therefore, risks and benefits must be weighed carefully in light of post-transplant complications brought on by lifelong immunosuppression including infections, malignancies, metabolic imbalances, and wound healing challenges.

As detailed reporting in the field has been somewhat scarce and of limited scope, we review outline principles of FAT and portray future directions in the field.

Patient selection/inclusion–exclusion criteria

Selection of individuals eligible for FAT is a crucial determinant for success. At this time, there is no general consensus on inclusion–exclusion criteria. The American Society of Plastic Surgeons (ASPS) and the American Society of Reconstructive Microsurgery (ASRM) recommend FAT only in patients with severe facial disfigurement, only after conventional autologous reconstruction techniques have been exhausted with unsatisfactory results [16]. We define "severe facial disfigurement" as loss of more than 25% of the total face and/or including central facial units [17]. Ballistic trauma and burn victims make up 2/3 of the current FAT recipients worldwide [12]. Other indications include gunshot wounds, neurofibromatosis 1, animal attacks, and cancer defect. The potential pool of FAT recipients is expected to continue expanding with increased publication of favorable outcomes, and advancements in immunosuppression [18].

Face allograft transplantation should be considered the first reconstructive option for severely disfigured patients that fulfill indication criteria as approved by ASRT [19], and not as a last resort after conventional reconstruction has yielded suboptimal results. In the early stages post-trauma, patients should have acute wounds closed using the simplest options and then get engaged in discussions regarding facial allotransplantation versus conventional reconstruction. The simplest wound closure option may be a skin graft, local flap(s), but even free tissue transfer. Management of facial allograft loss remains challenging. It is our opinion that in such cases, the recipient should be considered for another FAT. Should the patient or the treating team disagree on re-listing the patient for transplant, conventional reconstruction has to take place, stressing the importance of maintaining salvage options, and preserving functional tissues [3,20].

Brigham and Women's Hospital team in Boston first reported a set of inclusion and exclusion criteria for FAT [17]. Siemionow and colleagues developed an assessment tool to identify optimal FAT candidates called "The Cleveland Clinic FACES Score," which may help predict outcomes and prognosis of the procedure by measuring comorbidities, psychosocial status, medication adherence, etc. [21]. Psychosocial history and previous immunological status are particularly important [22]. Recent outcome studies report that the post-transplantation period of FAT recipients with pre-existing mental disorders was challenged by suboptimal adherence, difficulties in social reintegration and higher incidence of rejection episodes, albeit overall enhancement of quality of life [23].

There have been many discussions on whether burn survivors with high Human Leukocyte Antigen (HLA) sensitization should be considered for FAT. The initial management of severe burns often involves potentially sensitizing events including allogenic blood products transfusion and cadaveric skin grafts [24,25]. Positive T-cell CDC crossmatches are usually considered a contraindication for solid organ transplantation [26,27]. Some, but not all have excluded sensitized patients with a positive crossmatch for FAT because of increased risk for rejection and high immunosuppression requirements [28–31]. Chandraker *et al.* [32] reported antibody-mediated rejection (ABMR) in a highly sensitized FAT recipient with a calculated panel reactive antibody of 98%. ABMR was successfully treated with a combination of plasmapheresis, eculizumab, bortezomib, and alemtuzumab [33]. We recently reported the immunological characteristics of this patient up to 4 years following transplantation; the patient was controlled by an all-encompassing immunosuppressive regimen that also included B-cell-targeted therapies and after the ABMR episode had three episodes of T-cell-mediated AR [33]. The patient has not presented with any clinical or pathologic signs indicative of chronic vascular rejection and has a functioning graft. Notably, none of the numerous reports of acute rejection in FAT recipients

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has been shown to correlate with HLA mismatch [34]. Nonetheless, Chandraker's single case report of manageable ABMR rejection does not constitute sufficient evidence to reduce the current cautionary approach in sensitized FAT recipients.

Face allograft transplantation candidates are often partially or completely linked to the original trauma. Inclusion of blind patients in FAT protocols remains open to debate. There is no comparative study on FAT outcomes in recipients with normal vision versus blind recipients. Blindness introduces additional challenges to the postoperative period related to physical therapy, graft surveillance, and personal appreciation of the overall result [35].

Finally, emergency FAT remains widely discussed and motivated by the surgical challenges introduced by patients with extensive conventional reconstruction histories that introduce scarring, fibrosis and others. While emergency FAT introduces concerns about access to the donor pool, organ donation issues, and adequate presurgical planning [36], one team has successfully performed such a procedure [10].

Operative details and challenges

Face allograft transplantation relies on recent advances in reconstructive microsurgery techniques [1]. Many studies describe the surgical stages of FAT in detail including graft procurement, preservation, and transplantation [1,34,37]. This review is limited to a brief overview of some of the most important surgical steps. FAT can be considered as a complex functional (osteo)myocutaneous-free tissue transfer. Extensive surgical planning involving multiple disciplines is crucial. Radiologic assessment of the recipient with computer tomography (CT) and/or magnetic resonance imaging (MRI) helps to determine the amount of missing tissues allowing a patient-specific design of the allograft. Our team prefers a more conservative approach that preserves recipient's tissues and functional units in order to maintain salvage options in cases of graft failure.

Computer tomography/magnetic resonance imaging angiography is essential for planning vascular anastomoses [38]. Branches of the external carotid artery can support the entire splanchnocranium [39]; however, fullface transplants can also be sufficiently supported by the facial artery [40]. Furthermore, a single unilateral facial artery can perfuse allografts comprising the lower two-thirds of the face while maintaining bilateral venous outflow [41–43]. Nonetheless, to maximize graft survival, we recommend a bilateral arterial and venous anastomosis whenever possible.

Nerve repair is central to the functional outcomes of FAT. Motor and sensory function is a critical part for the success of the procedure. Coaptations of the facial nerve, at either the level of the facial nerve trunk or more distally have been reported [28,44]. Our team prefers distal coaptations as they enable targeted muscle regeneration with decreased risks of synkinesia.

Craniofacial alignment, dental occlusion, and orthognathic planning also play important roles determining facial width, position, and function in FAT [45].

The optimal extent of FAT remains controversial, and there is no general accepted categorization of FAT per size and composition. Different groups use different definitions for "partial," "near-total," "total," "complex," "soft-tissue only," "scalp-including" FAT. We favor the conservation of vascular territories within the head and neck and original size of the facial defects in order to facilitate back-up solutions in case of allograft failure that would not result into disfigurement worse than the pretransplant state [1].

Face allograft transplantation is an extensive surgery, and the time that the allograft spends in ischemic conditions must be as short as possible, ideally within less than 4 h. Indeed, brief ischemic times may prevent harmful immune activation and inferior functional outcomes, although direct evidence linking ischemia/reperfusion injury (IRI) and alloimmunity are missing. In hand transplantation, some have suggested poorer graft function because of prolonged ischemia [46,47]. However, we have not identified a relationship between facial allografts' prolonged ischemia, and frequency of acute rejection episodes [48]. Extracorporeal preservation of the facial allografts shows promise toward mitigation of IRI, enhancement of functional outcomes FAT, and expansion of facial donor pools, based on kidney transplantation experience [49]. Early promising research results on novel preservation methods relevant for Vascularized Composite Allotransplantation (VCA) have been reported [50,51].

Functional outcomes

Motor

Defining success and measuring outcomes are critical for progress in the field. Facial functional outcomes are difficult to quantify uniformly, because of the complexity of facial functions, wide range of extent of injuries across FAT recipients, and variations in protocols

among providers of FAT. However, there is consensus that motor recovery is detectable 6–8 months after transplant [4]. Various techniques used in general Speech and Swallow therapy may improve motor recovery, and functional motoric outcomes. These include facial muscle reeducation, speech therapy, chewing, and swallowing therapy, starting virtually immediately following the transplantation [52]. To date, motor recovery outcomes of FAT have been characterized as somewhat below the original expectations and as average for sensory recovery outcomes [12,52–56].

We believe that restoration of breathing, eating, tasting, smelling, speaking, facial expressions, and sensation largely determines the success or failure of FAT. In our center, all seven FAT recipients showed improved functionality when compared to pretransplantation impairment [52]. We observed 100% improvement in the abilities to smell and eat, and in facial sensation. All gastrostomies were removed, and ten patients were decannulated after FAT. There was overall 93%, 76%, and 71% improvement in breathing, facial expressions, and intelligible speech, respectively [52]. Similar results are reported by other institutions. Functional outcomes of FAT are reported in only approximately 50% of all FAT cases worldwide. Strikingly, 25% of outcome data are by groups not directly involved in the patients' treatment [52], raising concern about accuracy of data.

Sensory

Sensation in the allograft returns as early as 3 months postoperatively [40,57], with satisfactory results around 8–12 months [28,40,57,58]. Tests such as Semmes-Weinstein, 2-point discrimination, and temperature differentiation are used to evaluate sensory function of the facial allograft [59]. Importantly, the immunosuppressant tacrolimus, often used after FAT, has been linked to accelerating axonal regeneration [60–64].

Different surgical techniques have been reported to enhance sensory recovery; these include all direct end-to-end neurorraphies of trigeminal nerve branches [10,58], simple placement of bilateral donor mental nerves near the mental foramen without neurorrhaphy [57], and strikingly, even no nerve repair at all [28,65]. Our team suggests primary end-to-end neurorraphies with nerve grafting or nerve transfer if necessary.

Psychosocial implications/quality of life

Despite encouraging motor and sensory function after FAT, quality of life outcomes varies widely across patients. This may be because of the implications of the surgery on the patients' psychological status. Most recipients accept their transplanted faces shortly after the surgery without any issues related to facial identity [10,28,57,58,66–68]. This is not unexpected, as the return of human appearance following transplant is vastly better than prior major deformity [1]. Perhaps another consideration is that one does not observe its own face on a regular basis during the day. The identification with one's face is therefore mediated by gradual improvement of its function over time. Reports on quality of life-related challenges after FAT may include drug or alcohol abuse, behavioral changes, social disintegration issues, family issues, depression, and even suicidal attempts [23,53,69–71]. Quantitative scales (validated in separate individual psychological diseases) [23,28,35,52,72–76] or qualitative methods (descriptive, provider- or self-reported) have been introduced to measure postoperative quality of life in FAT recipients [10,57,58,65–67,77–81]. When assessing post-FAT quality of life, pre-existing mental disorders and risk factors should be carefully considered. Eventful pre-FAT psychological history can portend long-term follow-up risks such as poor medication adherence, quality of life issues, and increased incidence of rejection episodes.

Lastly, although return to work appears to be an ultimate goal secondary to improvements in quality of life after FAT, its fulfillment realistically depends on the severity of the initial injury, other comorbidities, and social factors. Although most FAT recipients have reintegrated into their family and social environments, there are few available data on return to work.

Immunological aspects

Immunosuppressive regimens have been largely adapted from solid organ transplantation with good results thus far. In most cases, immunosuppression induction treatment for VCA typically includes anti-thymocyte globulin (ATG), a potent T-cell depleting agent [82]. In addition, several other drugs including humanized IL-2 receptor antibody [67,83], alemtuzumab [15], and rituximab [84] have been reported for induction in FAT recipients. Following transplantation, maintenance immunosuppression usually consists of triple therapy with tacrolimus (TAC), mycophenolic acid (MMF), and prednisone taper [5,82,85]. Among VCA teams, TAC target blood levels in FAT patients varied anywhere between 3 ng/ml [74] and 24 ng/ml [67] and MMF was administered from 0.18 g twice daily [74] to 3 g daily [10]. Attempts to withdraw MMF [86] or prednisone

[87] were also reported. In some patients, calcineurin inhibitors-related complications have led to conversion of TAC to sirolimus [58,88]. Additionally, one FAT recipient was also converted to belatacept; however, after an episode of belatacept-resistant AR, low dose TAC (target level 4–5 ng/ml) needed to be reintroduced to the immunosuppression regimen [89].

Many innovative avenues of research have been attempted to overcome the serious complications of immunosuppression, and thus enable widespread practice of FAT. Approaches that include minimization/progressive weaning of immunosuppression lack long-term follow-up reports [40]. Other immunosuppression minimizing or tolerance approaches include microchimerism induction through simultaneous bone marrow transplantation [90,91], development of anti T-cell antibodies, or stem cell therapies [90,92–95]. Currently, recipients of FAT will need lifelong immunosuppression; however, all efforts should be made to minimize dosages safely while monitoring adverse side effects. Immune tolerance may not be possible to achieve in a near future for FAT recipients, because of tissue immunogenicity, and in particular its skin component [1]. At the same time, excessive immunosuppression reducing protocols introduces a high risk of allograft damage and/or loss [88,96].

Complications

Face allograft transplantation is not exempt to the complications inherent to any surgical procedure, including blood loss, wound healing challenges, graft misalignment, bone nonunion, eyelid asymmetry and ptosis, ectropion, and functional issues such as obstruction of nasal passages and salivary glands, and necrosis of the hard palate [5,10,52,57,67,86,97,98].

Infectious complications are not uncommon after FAT, although tailored antibiotic prophylaxis is standard peri- and postoperative practice. In solid organ transplantation, opportunistic cytomegalovirus (CMV) infection plays a significant role in development of allograft dysfunction and patients' mortality and morbidity [99]. The impact of CMV infection in FAT recipients is not well-understood, because of the relatively small number of FAT performed to date. More than a third of FAT recipients presented with active CMV infections during the postoperative follow-up. All CMV infection episodes occurred in donor seropositive/recipient seronegative combinations did not correlate with acute rejection and were successfully treated with antiviral therapy [100]. In rare cases when CMV infections did not respond to conventional therapies, extracorporeal photopheresis and vaccines had been sucessful [23]. More recently, multidrug-resistant CMV infections in spite of 6 months of valganciclovir prophylaxis have been reported after FAT and led to a rare complication involving Guillain–Barré syndrome [101]. Complete recovery of the neuropathy was achieved after administration of intravenous immunoglobulin.

Metabolic complications after FAT are mainly attributed to immunosuppression, and entail diabetes mellitus, hypertension, and hypercholesterolemia. Lantieri *et al.* [23] showed that diabetes mellitus, hypercholesterolemia, and hypertension occurred in one, four, and three of seven patients, respectively. At our center, one patient had been borderline diabetic prior to transplantation, developed diabetes mellitus 8 months postoperatively and is currently successfully managed with insulin therapy and lifestyle modifications [74]. Another team reported earlier onset of hyperglycemia on postoperative day 3 and insulin-dependent diabetes mellitus 3 months after FAT [67]. Cumulative world experience in FAT suggest that metabolic complications are common and patients should be closely monitored, and whenever appropriate, treated for diabetes mellitus, hypercholesterinemia, or hypertension.

Chronic deterioration of recipients' kidney function has been reported and appears to present a growing issue with FAT recipients approaching 10 years after transplant. Lantieri *et al.* [23] reported on four of seven FAT recipients that presented with reduced eGFR. FAT providers have started minimizing immunosuppression, or substituting calcineurin inhibitors with alternative medications to prevent chronic kidney disease [40,58,74].

There are numerous reports on secondary revisions after FAT for esthetic and functional improvements [55,102]. Bone and dental realignment, soft-tissue resuspension and contouring, full-thickness skin grafting, fat injection and dermabrasion are examples [15,103–105], as are Le Fort I rotation, Le Fort III advancement, coronal eyebrow lift, submental lipectomy, bilateral blepharoplasty, revision rhinoplasty, removal of excess glandular tissue, and chin augmentation [57,106–108]. The benefits of these secondary interventions must outweigh the risks in this population of immunocompromised patients.

Malignancies after FAT have been reported with Epstein-Barr virus (EBV)- and HIV-related lymphoma, cervical dysplasia, and lung cancer [5,13,23,71,96,109]. A patient has developed primary asymptomatic EBV infection, followed by EBV+ B-cell lymphoma, which

could be successfully treated with rituximab and chemotherapy [88]. Malignant peripheral nerve sheath tumors can potentially occur and introduce the question of inclusion of neurofibromatosis 1 patients in FAT protocols [110].

Acute rejection (AR) is frequent in FAT. Early studies predicted a 10% risk of AR within the first year after FAT and 30–50% by the second to fifth year [111]. More recent assessments showed that the majority of patients (approximately 80%) have at least one episode of AR within the first year, with skin biopsies ranging from BANFF grade 1 to BANFF grade 3. The vast majority of rejections have been steroid-sensitive with a few exceptions requiring antilymphocytic agents including thymoglobulin or campath [4,112]. We also reported one case of acute ABMR [32]. Treatment protocols for acute rejection in FAT are established. Management of rejection with BANFF grades 1–2 is usually treated with a bolus steroid treatment, increasing TAC trough levels and sometimes introducing topical steroid or TAC treatment alone. ABMR may require the addition of plasmapheresis, eculizumab, bortezomib in addition to lymphocytic antibodies and/or other regimen changes [10,66,67,80,86]. Our management of grade 1 rejections has evolved from aggressive treatment to complete resolution of the rejection episode to a more conservative approach suggesting patients to avoid sun exposure, mechanical trauma, etc. Some groups speculate that aggressive treatment of grade I rejection in the early stages of FAT may help prevent progression to chronic rejection. Chronic rejection (CR) is a well-established complication in solid organ transplantation and has also been reported for FAT. The incidence of CR in FAT was initially predicted as 30–50% within the first 5 years however, the condition appears to occur less frequent with only two reported pathology-proven CR [88,92,109]. The first case was a T-cell-mediated CR after programmed reduction of the immunosuppression therapy because of complications (i.e. EBV-induced lymphoma and hepatic EBV-associated post-transplant smooth muscle tumor) [88]. The other patient developed chronic vascular rejection (described by Morelon *et al.* [109] as chronic antibody-mediated rejection) with partial loss of the face allograft. There are certain allograft changes that may be relevant to potential development of CR, and in our experience include fibrotic changes, telangiectasias, and skin thinning. Lantieri *et al.* [23] comment on a progressive lymphedematous aspect of the skin as a possible manifestation of CR. On histological examination, CR may entail vascular changes associated with vasculopathy in general and neointimal hyperplasia [91].

Mortalities have also been reported. A FAT recipient in China died 3 years after the procedure because of medication nonadherence and lack of access to medical care. Perioperative deaths were recorded in Paris, France after face and bilateral upper extremity transplantation, and in Turkey. Other deaths were attributed to a recurrence of malignancy in HIV+ patient (Spain). Most recently, the very first face transplant patient succumbed to lung cancer.

Adherence

Despite successes in optimizing technical, surgical, and follow-up protocols, FAT is unique in that it requires a rigorous outpatient medical schedule and numerous hospitalizations [56]. There are two cases of FAT allograft loss as a result of noncompliance and thus compliance is an imperative assessment of the transplant evaluation. There are some well-understood pretransplant risk factors that can predict future nonadherence in solid organ transplantation, including previous history of nonadherence, inadequate social support, and educational level that urge for further psychosocial evaluation [113]. FAT providers should stress the importance of adherence and the benefits of compliance, rather than focusing on the harmful consequences of nonadherence, always keeping in mind that positive psychological outcomes will ultimately lead to adherence [114].

Ethical dilemmas

Face allograft transplantation is an intervention intertwined with ethical dilemmas, and controversies. Over- or under-informing FAT candidates prior to face transplantation have both been linked to anxiety and poor outcomes [115]. It remains open to debate whether facially disfigured patients are truly in a position to give informed consent, especially for such a complex procedure and while being in a vulnerable state because of the disfigurement [116–118].

With regard to the VCA practice in children, the literature is fairly divided [119]. The youngest FAT and hand transplant recipients reported were, respectively, 19 and 8 years old [53]. Solid arguments against FAT in children include the lifelong risks of immunosuppression and the disputed informed consent [120,121].

Face allograft transplantation is a complex and resource-demanding process requiring full investment of a multidisciplinary team in the pre- and postoperative periods [1]. FAT may be more costly than conventional reconstruction or than solid organ transplants, with its most expensive components being surgery and nursing followed by anesthesia and immunosuppression [122,123]. In Europe and the USA, it is still considered an experimental procedure and thus not unanimously covered by medical insurance. The majority of VCA programs are currently funded by research grants (most commonly from the U.S. Department of Defense) and through institutional support challenging cost benefit analyses of FAT over conventional reconstructive procedures.

Future directions

Facial allograft procurement processes have been optimized in collaboration with solid organ transplant teams [22]. Limited allograft ischemia time continues to dictate the maximum travel time for allograft recovery and reduces geographical pool of donors. Currently used allograft flush with University of Wisconsin (UW) solution, or ILG-1 [10,66,67] combined with cold storage does not extent the cold ischemia time beyond 4–6 h. Extracorporeal tissue preservation research may provide innovative solutions to this problem. Translational research in this area has currently been performed only for extremity preservation and storage for following replantation and/or transplantation. Extracorporeal perfusion devices have been used to preserve swine limbs for 12–24 h after amputation with superior outcomes in terms of muscle damage, ischemia reperfusion injury, and animal survival following replantation when compared to the current standard of care, which is 4-h storage in ice [51,124,125]. Similar technology has more recently demonstrated feasibility as a promising modality in extremity preservation through near-normothermic *ex situ* perfusion for 24 h in a human limb model [50].

Future innovations in noninvasive monitoring, diagnosis, and prediction of acute rejection and overall graft health assessment in FAT are expected [126]. Although the skin in FAT can be easily monitored and biopsied, there are reports of allograft injury in the absence of visible signs of rejection on the skin [127]. This raises the concern that deeper components of the allograft, such as the vascular endothelium may undergo subclinical rejection. We must therefore develop methods of investigating the entire allograft rather than the skin only when investigating immune rejection [128,129]. Diagnosis of acute rejection in FAT can be challenging with the current available methods [130,131]. It is therefore imperative to implement quick, noninvasive, predictive methods for diagnosis of rejection in FAT recipients in order to avoid over- or under-immunosuppression and subsequent negative implications. Noninvasive markers for assessment of the transplanted allografts are investigated as alternatives to biopsies in the field of solid organ transplantation. These markers include gene-expression profiling [132,133] and proteomic analysis [134,135] as biomarkers for allograft vasculopathy, identification of donor derived cell-free DNA in the recipient's circulation as a marker for prediction of AR [136–140] and B-cell repertoire sequencing [141] analyzed from samples acquired mainly through blood draws. Urine samples and breath tests have also showed feasibility as modalities in noninvasive diagnosis of rejection [142,143]. Further studies evaluating these diagnostic markers in VCA still need to be performed to assess the accuracy of these methods in diagnosing AR.

Many authors find interpretation of rejection by BANFF classification inadequate for FAT. It is important to note that this classification is derived from hand transplant patient experience and does not address rejection of oral mucosa [144]. Additional concerns include biopsy site selection bias, and inadequate sampling size.

Noninvasive monitoring for CR and specifically for chronic graft vasculopathy could constitute another major challenge that necessitates improvement. It is known from reported studies on hand transplantation that intimal hyperplasia is associated with CR [127]. Assessing the individual-specific donor facial to recipient sentinel flap artery (e.g. radial artery) intima ratio through ultrasound biomicroscopy monitoring (a high-resolution ultrasound technique measuring the arterial wall of smaller arteries) has proven feasibility and reproducibility as a method and could potentially serve as a sensitive measure to detect early changes during chronic rejection [126].

Nerve regeneration is a vital component of functional success of FAT and contributes to the motor and sensory return of the recovery phase. However, nerve regeneration and thus clinical outcomes differ between centers because of the different pretransplant defects among patients and the multiple coaptation methods (e.g. direct nerve repair, nerve graft) tailored to each patient [11]. There is a great interest in novel translational research strategies to enhance nerve regeneration

and thus improve the functional outcomes of FAT but also for VCA in general. The usage of TAC has been demonstrated to accelerate nerve regeneration, decrease muscle denervation time, and improve Schwann cell migration, proving its neuroprotective and neurotrophic effects [145,146]. A study from Labroo *et al.* [147] showed that systematic administration of FK506 for 2 months following anastomosis of transected facial nerve resulted in an increase in axonal diameter, myelin thickness, and number of myelinated axons. It has also been shown that the use of glial cell-derived neurotrophic factor following facial nerve injury in a rat model led to increased survival of injured axons and improved functional outcomes [148]. Subcutaneous administration of growth hormone [149], and chondroitinase [150–152] have also been reported to accelerate axonal regeneration and enhance muscle reinnervation in peripheral nerve rat models following crush injuries, raising the question if these approaches could be applied to facial nerve models. Finally, stem cell-induced nerve regeneration is of increased research interest. Cooney *et al.* [153] showed that local and systematic administration of bone marrow derived mesenchymal stem cells improved nerve regeneration in a hindlimb transplantation rat model, by increasing the number of nerve fibers distal to the repair site.

Outcomes reporting after FAT have not been universal to date. Sosin *et al.* [11] observed a marked discrepancy between the number of FAT performed versus the ones reported worldwide. Documentation and reporting in the International Registry on Hand and Composite Tissue Transplantation is voluntary, and therefore, information and follow-up data are incomplete. We firmly believe that consistent reporting would empower the entire VCA research community by enriching the knowledge available to all. Delayed, partial, and varying disclosure creates a selection bias where groups report only on positive results [11,53]. We encourage all face transplant teams to publish their results in order to avoid speculation and unjustified criticism. Ultimately, this would help to enhance scientific knowledge, safety, and availability of FAT.

This publication is meant to promote "analysis and not paralysis" to aid further advancement of the field of FAT. As with other developing fields in early stages, FAT will continue to run into many challenges [129]. Expertise should be maintained in dedicated centers, collection, and critical analysis of outcomes must continue, supported by research grants [53].

Conclusion

Facial allograft transplantation improves quality of life of our most disabled patients. Providers must work together, and agree on outcomes measures that should be strictly adhered to, and reported. Standardization of care and outcomes analysis among different centers will continue to advance our field forward.

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