Hand Allotransplantation

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ABSTRACT

In the past decade, more than 100 different composite tissue allotransplantation (CTA) procedures have been performed around the world including more than 50 hand and 8 facial transplants with encouraging graft survival and excellent functional outcomes. Broader clinical application of CTA, however, continues to be hampered by requirement for long-term, high-dose, multidrug maintenance immunosuppression to prevent graft rejection mediated particularly by composite tissue allograft's highly immunogenic skin component. Medication toxicity could result in severe adverse events including metabolic and infectious complications or malignancy. Notably, unlike in solid organs, clinical success is dictated not only by graft acceptance and survival but also by nerve regeneration, which determines ultimate functional outcomes. Novel strategies such as cellular and biologic therapies that integrate the concepts of immune regulation with those of nerve regeneration have shown promising results in small and large animal models. Clinical translation of these insights to reconstructive transplantation and CTA could further minimize the need of immunosuppression and optimize functional outcomes. This will 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.

KEYWORDS: Transplantation, composite tissue, hand, immunosuppression, nerve regeneration

Millions of individuals each year sustain injuries, have tumors surgically resected, or are born with congenital defects that require complex reconstructive surgeries to repair the resulting large tissue defects. However, limitations of current reconstructive procedures for such major tissue loss include poor functional and aesthetic outcomes, several revision procedures, prolonged rehabilitation, donor-site morbidity resulting from use of autologous tissues, and high costs of multiple surgeries and hospitalization. Transplantation of composite tissue allografts (composite tissue allotransplantation; CTA) offers a new alternative and possibly a potential solution to this great need for native tissue.

The idea of transplanting body parts from one individual to another dates back to the ancient times of human history. One of the most cited reports is the myth of the two Arabian saints Cosmas and Damian who attempted in the early third century to replace the amputated gangrenous leg of a monk with the limb of an Ethiopian Moor.[1] Inspired by the milestones achieved in solid organ transplantation in the late 1950s, the world's first hand transplantation was performed in

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1964 by Roberto Gilbert Elizalde in Ecuador. The procedure performed on a young male bilateral amputee was a technical success, but unfortunately the hand was lost to severe rejection due to the lack of effective immunosuppressive options at that time.[2] The introduction of calcineurin inhibitors (cyclosporin A in the 1980s and tacrolimus in the 1990s) and the purine analogue mycophenolate mofetil into the transplant arena enabled reproducible improvements in long-term graft survival in small and large animal models of CTA including skin.[3,4] The first human hand transplantation in this so-called modern era of immunosuppression was performed in September 1998 in Lyon, France, by a team led by Jean-Michel Dubernard.[5] Shortly thereafter, groups from Louisville, Kentucky, Innsbruck, Austria, and again Lyon, France, followed and successfully performed several other cases of single as well as bilateral hand and forearm transplants and thereby led the groundwork for multiple teams all over the globe to initiate hand transplantation and CTA programs.[6,7]

WORLD EXPERIENCE

Today, hand transplantation has become a clinical reality. In addition, more than one hundred different composite tissue allografts have been performed over the past decade including transplantation of hand and forearm, partial face, abdominal wall, larynx/trachea, uterus and penis, as well as individual tissue components like vascularized bone, joint, cartilage, tendon, and peripheral nerves. To date, more than 50 hand transplants in more than 37 recipients have been performed in centers in Europe, the United States, and in China, and all were technically successful.[8]

FUNCTIONAL OUTCOME AFTER HAND TRANSPLANTATION

Experience from these initial transplants has reinforced that the two main challenges to successful outcomes are the immunogenicity of the skin and the degree of nerve regeneration. No hand grafts were lost to acute rejection when conventional triple-drug immunosuppression was used with overall levels comparable with solid organ transplantation.

In hand transplant recipients compliant with immunosuppressive medication and rehabilitation, early and intermediate functional outcomes are highly encouraging, superior to those secondary to prosthesis and in quite a few cases comparable with what can be achieved after replantation. Such excellent functional results are dependent on intensive and continuous rehabilitation including physiotherapy and occupational therapy, as well as electrostimulation. With regard to recovery of motor function, extrinsic muscle function during the early postoperative phase allows patients to perform grasp and pinch activities. At later stages, on average between 9 and 15 months posttransplantation, intrinsic muscle recovery is observed in the majority of patients.[8] Such return of extrinsic and intrinsic muscle function allows most patients after hand transplantation to perform almost any activity of daily life including eating, writing, brushing teeth, shaving, combing hair, or personal hygiene thereby regaining a high level of independence.

In addition to gross and fine motor function, all patients transplanted to date demonstrated return of protective sensation. Ninety percent of patients regained tactile sensibility, and several recipients reported that discriminative sensory function as assessed by 2-point discrimination or the Semmes-Weinstein monofilament test regained normal values.[8–10] In all patients, hand function and sensitivity continuously improved during the first few postoperative years following which it reached a stable phase thereafter with minor improvement. Most strikingly, in some hand transplant recipients, both motor as well as sensory action potentials still increased at more than 5 years after transplantation, suggesting that nerve regeneration also occurs late after CTA.[10] Reorganization of the somatosensory cortex and reintegration of the transplanted hand into the central nervous system has been extensively studied in patients after CTA. Such studies revealed that the transplanted hand is represented at the physiologic cortical site as it is in normal control subjects, independent of the time passed between amputation and transplantation.[11] The majority of patients after hand transplantation judge the procedure as a significant improvement in their quality of life and consider their daily life "as almost completely normal." However, a high degree of functional recovery is paramount to warrant the potential side effects of immunosuppressive therapy and to justify or favor the risk-benefit ratio for such a non-lifesaving procedure as hand transplantation.

IMMUNOSUPPRESSION IN CTA

Because composite tissue allografts are derived from genetically disparate cadaveric donors, recipients need to be immunosuppressed for life to prevent rejection of the transplant. A unique feature of CTA is that such grafts unlike solid organ transplants are composed of various different tissue components such as muscle, tendon, nerve, blood vessels, bone, and skin. In particular, due to the fact that the skin is thought to be highly antigeneic, historically composite tissue allografts have been considered an immunologic challenge.[12] Thus, broader clinical application of hand allotransplantation has been hampered by particularly strong rejection of the skin component, necessitating long-term, high-dose, multidrug maintenance immunosuppression. This led to considerable concern for adverse effects of those

immunosuppressive drugs that are required to sustain the graft. Such risks include but are not limited to infection, diabetes, hyperlipidemia, nephrotoxicity, or malignancy.

The current immunosuppressive protocols applied to hand transplantation are extrapolated from regimens used in solid organ transplantation. The overall amount of immunosuppression required to ensure graft survival is comparable with or even slightly higher than it is for kidney transplantation. However, as mentioned earlier, the use of maintenance immunosuppression in hand transplantation has resulted in a 100% patient and graft survival at 1 year after transplantation, an outcome that has not been achieved in any other field of transplantation.[13] Such immunosuppressive strategies rely, for the most part, on agents that halt the robust immunologic attack on the graft in a nonspecific manner. According to the International Registry on Hand and Composite Tissue Transplantation, the majority of hand transplant patients received either polyclonal (antithymocyte globulins; ATGs) or monoclonal (alemtuzumab, basiliximab) antibody preparations as an induction agent followed by a high-dose triple-drug combination for maintenance therapy including tacrolimus, mycophenolate mofetil (MMF), and steroids.[8] Such regimens have proved sufficient to prevent early immunologic graft loss but were not able to prevent acute rejection so that 85 to 90% of all hand transplant recipients experienced at least one acute rejection episode within the first year after transplantation. Episodes of acute rejection were always macroscopically characterized by erythematous, maculopapular, heterogeneously scattered cutaneous lesions that correlated well with the histomorphologic findings of mononuclear cellular infiltrates.[14]

The other components of a hand allograft like muscle, nerves, tendon, and bone do not seem to be subject to significant damage when episodes of skin rejection occur. However, available information on the involvement of these components is still very limited, and more data are needed before a final conclusion can be made that the skin is the sole and prime target of rejection in CTA. Recently, various modifications have been applied to the immunosuppressive protocols used in hand transplantation such as steroid sparing/avoidance attempts, conversion from tacrolimus to the mammalian target of rapamycin (mTOR) inhibitor sirolimus for long-term therapy, or the use of topical steroid and tacrolimus ointments to reduce the overall amount of systemic immunosuppression. Although great strides in these regimens have been made, the side effects and complications related to chronic multidrug immunosuppression after hand transplantation are considerable. Side effects observed and reported to the International Registry on Hand and Composite Tissue Transplantation after hand transplantation included opportunistic cytomegalovirus infections, *Clostridium difficile* enteritis, herpes simplex infections, cutaneous mucosis, and *Staphylococcus aureus*–mediated ulnar osteitis. Recipients also developed metabolic complications such as hyperglycemia, hyperlipidemia, impaired renal function, arterial hypertension, and aseptic hip necrosis requiring bilateral hip replacement. Of note, no life-threatening complications or malignancies have been observed in the world experience thus far.[8,13]

In addition, chronic multidrug immunosuppression is expensive and causes substantial long-term costs. Furthermore, due to the amount of daily oral medication required and its resulting high patient burden, such regimens frequently lead to noncompliance. However, considering these obvious downsides of multidrug immunosuppression and its various, sometimes severe side effects, there is an evident need for novel concepts of systemic immunosuppression in CTA. In this regard, hand transplantation might offer some unique advantages because continuous monitoring of the graft in contrast with solid organ transplants can be performed by simple visual inspection of the skin being the main target of rejection. This allows for directed biopsies and unbiased pathologic confirmation of the earliest stages of acute rejection and subsequent timely intervention, treatment, and precise adjustments of immunosuppression on an individualized basis. When treated adequately and effectively, acute rejection does not seem to impair graft function or long-term survival. Therefore, novel strategies to minimize immunosuppression or even to achieve the ultimate attainable clinical goal of transplantation to induce immune tolerance are particularly appealing in hand transplantation and CTA. Studies from our own group demonstrated that a whole-limb allograft elicited a less intense alloimmune response than did allografts of each of its individual components thereby challenging the relative scale of tissue antigenicity.[15] In addition, composite tissue allografts contain immunocompetent elements such as bone marrow and lymph nodes that may hasten the rejection processes or result in graft-versus-host disease (GvHD). These factors not only govern the immune reactivity of these allogeneic tissues but also define potential immunomodulating strategies that are different from those currently used in solid organ transplantation.[16,17]

NOVEL CELL-BASED APPROACHES FOR IMMUNOMODULATION IN HAND TRANSPLANTATION

When considering development of novel therapeutic strategies for minimization or avoidance of maintenance immunosuppression after hand transplantation, cell-based protocols including donor bone marrow (BM) or stem cells are promising candidates due to the unique nature of CTA. This trend is further fueled by recent innovative advancements in solid organ transplantation,

where both cell-based therapies and non–cell-based protocols have resulted in reduction or elimination of long-term immunosuppression.[18–20] Some composite tissue allografts, in particular limb transplants, include BM and might thereby function as a vascularized bone marrow transplant by itself.[21,22] Such a graft could be a continuous source of donor cells, including BM-derived dendritic cells, which have been demonstrated in animal models to favorably modulate the host immune response.[22] In experimental models, induction of donor-specific tolerance was attributed to this BM component and to specific immunomodulatory protocols permissive for BM engraftment.[23] This recently led to an intense search of optimal BM-based protocols to prolong composite tissue allograft survival and reduce maintenance immunosuppression. Why does just donor BM show great promise for novel immunosuppressive strategies in CTA? (1) Donor BM cell infusion has been successfully used as part of induction regimens for both solid organ transplants and CTA; (2) BM promotes the opportunity to reduce/avoid maintenance immunosuppression required for graft survival[24]; (3) BM is critical to establish macrochimerism, microchimerism, or mixed chimerism after organ transplantation, which is known as a prerequisite for potential donor-antigen specific tolerance induction[25,26]; (4) BM or hematopoietic Schwann cells have been identified to possess tolerogenic properties and have become the backbone of several protocols aiming for tolerance induction in transplantation.[27,28]

BM-based therapeutic principles have thus been intensively investigated in animal models and preclinical trials. Such protocols have consistently shown a beneficial effect of supportive cellular therapy on organ as well as composite tissue allograft survival.[29–31] Underlying mechanisms that have been studied include, for example, effects such as macrochimerism and microchimerism, and exhaustion and deletion of the recipient's T-cell clones. These insights now help to refine treatment protocols aiming to support long-term graft survival on minimal maintenance immunosuppression.[32] One potential disadvantage of transplanting a graft with functional immune effector cells is the potential for these mature allogeneic T cells to attack the host, resulting in the serious and clinically most feared reaction, GvHD.[33] Most importantly, it is now widely accepted that high doses of BM cells infused in the absence of recipient conditioning with irradiation do not induce GvHD, and although an obstacle in CTA, GvHD has not been observed in any human clinical hand transplant performed to date.[34]

Thus, the idea of donor BM cell infusion either to induce chimerism or for the intensification of clonal exhaustion and deletion of alloreactive T cells is appealing. Nevertheless, the combination of such a concept with high-dose multidrug immunosuppression might be counterproductive because such regulatory mechanisms require the persistence of a certain degree of immune response to be successful in a clinical setting.[14,35] However, the implementation of cell-based therapies in CTA that integrate and unify the concepts of immunoregulation and tolerance induction with those of tissue/nerve regeneration could fine-tune current immunomodulatory approaches and further optimize the outcomes of these reconstructive modalities.

NERVE REGENERATION AFTER HAND TRANSPLANTATION

In addition, overcoming the immunogenicity and optimizing nerve regeneration is key to success in CTA. Unlike solid organ transplants such as the kidney, liver, or heart that are immediately functioning after revascularization, a composite tissue allograft is viable after revascularization of the graft but not functional. The recipient nerves/axons have to regrow and replace the donor nerves, which serve as temporary scaffold, and finally reinnervate the muscles and sensory end organs within the graft. Thereby, the nerve undergoes a chimeric state, which is progressively replaced by host tissue. Although peripheral nerve regeneration is essential for the function of transplanted composite tissue allograft, there is very limited data on nerve regeneration in this context. Neuroregeneration after CTA represents a unique challenge as in addition to functional loss caused by lack of innervation, changes occur along the entire route of the nerve from the target end organ to the central nervous system, which might have important implications in recovery and outcome.[36]

As outlined above, the backbone of immunosuppressive protocols applied to CTA are still calcineurin inhibitors of which tacrolimus can be considered the "gold standard" used for immunosuppression in hand transplantation. Tacrolimus apart from potent T-cell inhibitory effects has also been demonstrated to have neuroregenerative capacity. Thereby, pathways and mediators independent of calcineurin inhibition such as FK binding protein 52 (FKBP52), growth associated protein 43 (GAP43), or heat shock proteins have been shown to be responsible for the neuroregenerative properties of tacrolimus.[37] Studies evaluating the enhanced neural regenerative effects of tacrolimus in isolated nerve allograft transplantation have also established that timing, dosing, and combinations of immunosuppressive therapies affect nerve regeneration.[38]

CELL-BASED THERAPIES TO ENHANCE NERVE REGENERATION

Schwann cells (SCs) surround axons and are key players during the process of axonal regeneration. SCs are on one hand vulnerable to immune rejection while on the other hand stimulated to migrate during limited bouts of

rejection leading to enhanced nerve regeneration. In this regard, both recipient and donor SC migration and viability are critical. In isolated nerve allotransplantation, allograft survival depends on proximal and distal SC migration. However, in CTA, critical distal host SCs are lacking.[38] Therefore, it is essential that sufficient immunosuppression is given to prevent loss of donor SCs and subsequent demyelinization, which might result in permanent or irreversible functional impairment.[39]

Several therapeutic agents have been added to the immunosuppressive protocols used in CTA and are currently studied in cadaveric peripheral nerve allografts for their ability to enhance neuroregeneration. In particular, studies in small and large animal models have suggested the use of autologous SCs in conjunction with nerve allotransplantation as a potential means to enhance nerve regeneration.[40,41]

SCs are known to support and promote nerve regeneration in vivo by myelinating regenerating axons, producing neutrotrophic factors, and increasing synthesis of cellular adhesion molecules such as N-cadherin.[42] In addition, autologous cultured SCs were shown to be viable after injection and to permit axonal regeneration without causing SC-derived tumors or iatrogenic nerve injury in rodent models.[40] These studies all confirm the integral role of SCs in neuronal regeneration. As a therapeutic agent, SCs can be successfully and safely harvested, cultured, and reintroduced into peripheral nerves to promote neuroregeneration.[40] However, the exact mechanisms by which SCs enhance nerve regeneration as well as their feasibility and potential to improve functional outcome in clinical CTA are yet to be elucidated.

STEM CELLS TO COMBINE IMMUNOREGULATION AND NEUROREGENERATION

In the recent past, more and more emphasis has been placed on exploring various other cell sources, in particular stem cells or progenitor cells that are easily accessible, rapidly expandable in vitro, and capable of survival and integration within the host tissue to be added to the armamentarium of treatment protocols used in CTA.

In particular, mesenchymal stem cells (MSCs) have been identified as a promising tool to further enhance not only the beneficial immunoregulatory effect of BM-cell infusion but also to improve neuroregeneration. This most interesting concept has been investigated in large animal trials for solid organ as well as composite tissue allografts survival.[43,44]

MSCs are pluripotent cells that are present in multiple tissues, including bone marrow, adipose tissue, skin, heart, and placenta and can be isolated and expanded ex vivo.[45] MSCs are characterized by their expression of a panel of cell-surface markers including CD29, CD44, CD90 (THY1), CD71, CD105 (SH2), CD106 (VCAM-1), and HLA class I. However, they do not express hematopoietic or endothelial lineage markers such as CD14, CD34, CD45, the costimulatory molecules CD80, CD86, and CD40, or HLA class II.[46] MSCs are capable of differentiation along multiple mesenchymal lineages into osteocytes, chondrocytes, myocytes, adipocytes, and SCs thereby emerging as a promising tool for tissue engineering and cell therapy.[47] MSCs have been reported to have significant potential for improving the neurologic outcomes after stroke and traumatic brain injury. In addition, MSCs have shown phenotypic, biochemical, and functional properties similar to SCs and promote functional recovery of peripheral nerves when introduced at the site of nerve injury.[48] The mechanisms of MSC-induced nerve regeneration include in vivo transdifferentiation into neural phenotypes as well as paracrine effects on SCs via released cytokines and growth factors.[49] Although potent MSC-enhanced nerve regeneration has been demonstrated in vitro and by local administration in vivo, systemic application as would be required for immunomodulation has not been tested. Such ongoing studies will yield important insights toward minimizing immunosuppression and improving functional outcomes after CTA.

Recently, BM-derived MSCs, apart from their capacity for multilineage differentiation and neuroprotection, have also been identified to have potent immunosuppressive properties to inhibit the activation and proliferation of immune cells. Numerous in vitro studies have reported that MSCs are immunoregulatory and can alter differentiation, maturation, and cytokine secretion profiles of dendritic cells (DCs), B cells, natural killer (NK) cells, as well as T cells.[50] It has also been shown that autologous and allogeneic MSCs have comparable immunosuppressive capacity and most importantly that MSCs are considered to be immunoprivileged by their low immunophenotype.[51] MSCs offer some potential advantages over conventional immunosuppressive agents by specifically targeting immunoinhibitory effects that could prevent rejection and minimize the systemic complications of nonspecific immunosuppressants in the setting of CTA.[43,52] The addition of MSCs to a particular immunosuppressive regimen might also allow reducing or minimizing the dose of conventional immunosuppressive drugs without affecting the overall efficacy of the therapy. Studies have shown that injection of allogeneic MSCs prolonged skin-graft survival in primates.[53] In addition to the immunomodulatory effects of MSCs, these cells have also demonstrated the ability to prevent and treat GvHD, one of the most serious complications after transplantation, and a particular concern in composite tissue allografts containing BM.[54] The use of MSCs for clinical purposes in CTA takes advantage of their described poor immunogenicity in vitro as well as in

preclinical and human studies, which supports the possible use of MSCs obtained from allogeneic donors. The ideal cellular immune treatment for hand transplantation should be able to provide both systemic and local therapeutic effects. Transplant experiments in non-human primates have shown that MSCs are able to spread to many tissues after intravenous administration but seem to preferentially home to the site of injury, where they support functional recovery.[55] Furthermore, the application of MSCs in combination with BM transplants has revealed that simultaneous or subsequent administration of MSCs significantly increased BM engraftment. The exact mechanism by which MSCs exert their beneficial effects on BM cell engraftment are still poorly described but may relate to their role as supportive cells within the hematopoietic stem cell niche.[56] However, there are several factors that need to be carefully considered when regarding MSCs for cellular immune therapy in organ and composite tissue transplantation or in combination with BM cell infusions. One of the most critical questions concerning the clinical application of MSCs is the source of these cells whether using MSCs of autologous or allogeneic origin. Other factors that need to be taken into consideration are the route of administration and migration of MSCs as well as optimal dose and timing in relation to the transplant. Overall, available current data indicate that although MSCs were first proposed for purposes in regenerative medicine, their therapeutic effect can result from the immunosuppressive activity of MSCs. This may provide a novel promising tool for minimizing immunosuppression or tolerance induction after systemic injection. The underlying effect seems to depend on the capacity of MSCs to inhibit proliferation of immunocompetent, alloreactive cells after antigenic stimulation and maintaining them in a quiescent state. In addition, MSCs may enhance and improve nerve regeneration and promote engraftment of BM cells as supportive cells within the stem cell niche, which makes them particularly attractive for novel treatment regimes in CTA.

CONCLUSION

Despite initial skepticism and debate, hand transplantation is a clinical reality. However, there is still concern and hesitation toward broader application due to the requirement for long-term, high-dose, multidrug maintenance immunosuppression. Today, several exciting novel therapeutic strategies such as the implementation of cellular therapies including BM or stem cells that integrate the concepts of immune regulation with those of nerve regeneration are on the horizon. Such protocols might further optimize functional outcomes and minimize/avoid the need for chronic immunosuppression. This could usher in a new era in CTA by improving the safety, efficacy, and applicability of these promising reconstructive modalities.

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