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REVIEW

Immunosuppression in an emerging field of plastic reconstructive surgery: composite tissue allotransplantation

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Summary Composite tissue transplantation (CTA) refers to the transplantation of an allograft consisting of heterogeneous cadaveric tissues. It provides a means of restoring structural, functional and aesthetic form in severely injured patients. Recent progress in facial transplantation has highlighted the immense strides made in this field of reconstructive surgery. However the potential for improvements in quality of life must be offset by the need for life-long immunosuppression in adults with nonlife-threatening injuries.

The benefits and difficulties of immunosuppressive drugs have been established in solid organ transplantation. Regimens derived from renal transplantation have been successfully applied to CTA. However the published incidence of complications seen in organ transplant recipients may not be easily extrapolated to potential CTA candidates and may be overstated. Accepted views that high dose immunosuppression would be needed to overcome highly antigenic tissues such as skin have not been borne out by clinical experience. It is therefore important to assess the current state of affairs, attempt to quantify the perceived risks and explore novel research methods being investigated. In doing so one can make a well-informed judgment of the potential benefit of this surgical modality as an integral part of the reconstructive ladder.

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The world's first partial facial transplant highlighted the significant strides made in the field of composite tissue allotransplantation (CTA).[1–3]

CTA refers to the transplantation of an allograft consisting of heterogeneous cadaveric tissues as a means of

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restoring structural, functional and aesthetic form in patients with severe injuries and thereby improve their quality of life.

To date successful transplantation of partial face, hands, abdominal wall, larynx, tongue, knees, flexor tendon apparatus and nerves has been achieved with encouraging outcomes and in some cases results beyond expectations.[4,5]

However, the potential for improvements in quality of life must be offset by the need for life-long immunosuppression in adults with nonlife-threatening injuries. Progress in this field has facilitated the transition of CTA from research models to clinical reality,[6,7] yet controversy still exists over the risk-benefit balance of this surgical modality.[8,9]

Doubts are understandable if one accepts the traditional view that higher doses and complication rates must be required to overcome one of the most immunogenic organs in the body, namely skin.[10] If CTA techniques are to be widely accepted it is essential that opinion is based on sound clinical evidence. It is therefore crucial to assess current immunosuppressive options, quantify their perceived risks and explore novel research methods attempting to shift the balance in favour of CTA.

Current immunosuppression practices and their risks

In the clinical transplant setting immunosuppression involves the use of a preliminary combination of potent induction regimens followed by lower dose maintenance regimens. This may be interspersed later by short courses of intensive therapy to overcome any episodes of acute rejection.[11]

During induction a combination of agents is used, including calcineurin inhibitors, e.g. cyclosporine (CsA) or tacrolimus (TRL) and anti-proliferative agents, e.g. mycophenolate mofetil (MMF). These are supplemented with corticosteroids, e.g. prednisolone and antibody immunosuppression, including polyclonal anti-thymocyte globulins (ATG), anti-interleukin-2 (IL-2) receptor antibodies such as daclizumad and basiliximab and anti-CD3 monoclonal antibodies such as OKT3. Maintenance therapy involves exploiting synergistic effects of drugs to reduce dosages and minimise individual side effects. To date TRL, MMF and prednisolone have been favoured in CTA, with the protocols extrapolated from solid organ renal transplantation regimens.[4]

Renal transplantation success has demonstrated the effectiveness of these agents, but the experience has also highlighted their unique complications. These can include infection, organ toxicity and malignancy.[12]

Eighty per cent of solid organ transplant recipients develop some form of infection and 40% of post-transplant deaths are due to infective causes.[13] Of all infections, 55% are bacterial, 30% viral and 15% fungal.[4] In addition, up to 10% of transplant patients develop a chronic viral infection (hepatitis B or C), which can lead to liver failure or hepatocellular carcinoma.[14]

Tacrolimus is neuro- and nephrotoxic and can also induce diabetes. Though the incidence of the complications varies, nephrotoxicity of some form has been reported in up to 70% of patients in the literature.[15] Mycophenolate mofetil (MMF) causes gastrointestinal upset in up to 35—60% of patients and leucopenia in 20—40%.[16]

In a recent review Gander et al.[17] noted that the primary complication associated with immunosuppressive therapy in the hand transplant population so far has been infection. To date, complications such as malignancies, cardiovascular-related disease, nephrotoxicity, gastrointestinal adverse effects and diabetes have not been reported.

Unlike organ transplant data, bacterial infection occurred at a lower rate of 12% (two infections: *Clostridium difficile enteritis* and *Staphylococcus aureus osteitis*), while fungal infections occurred in 28% (all cutaneous mycoses without invasive disease) and viral infection in 34% of cases. Only 6% of patients experienced cutaneous herpes simplex infections. None of these infections resulted in graft or patient loss.[17]

Post-transplantation bone disease was reported in a single case of avascular necrosis of the hip. Post transplant diabetes mellitus has not been reported in hand transplant recipients; however, transient hyperglycaemia occurs in 50% of patients, primarily while receiving high corticosteroid doses early after transplantation.

The chronic use of high dose corticosteroids can be associated with potentially significant morbidity from well known side effects. Effects on normal metabolic physiology produce hypernatraemia, water retention, hypertension, fat redistribution, glucose intolerance, hyperlipidaemia and adrenal suppression. In addition, chronic use can affect tissue morphology by causing cataracts, peptic ulcerations, osteoporosis, aseptic necrosis of the femoral and humeral heads and dermal atrophy.[18]

Based on a systematic review of published literature, Veenstra et al.[19] estimated the incidence of steroid-related complications in renal transplant recipients. These included 15% hypertension, 10% post-transplantation diabetes mellitus, 2% per year peripheral fractures, 8% avascular necrosis of the hip, and 22% cataracts. Concerns about these significant adverse effects were the driving force behind the increasing use of combination therapy and research into steroid-free immunosuppression.[20]

The most serious complication from immunosuppression is the occurrence of malignancies. In transplant patients as a whole this has been reported as 4—20%, depending on the immunosuppressive regimen used.[21] For renal transplant patients, the risk of developing post-transplant lymphoproliferative disease has been stated to be between 2 and 10%.[4] Other Australian-based studies have reported the probability of developing any type of cancer, 20 years after cadaveral renal transplantation, to be as high as 63%, with skin cancer being 54% and non-skin cancer 21%.[22]

However, other studies have not drawn the same conclusions. In a retrospective study Baumeister et al.[23] found the published data used to predict risk values was either based on small patient populations or contained information on outdated immunosuppressive regimens. The Australian studies, for example, were based on azathioprine and cyclosporine and the increased level of sun exposure in this region could have also caused an increase in the incidence and risk of skin cancer.[24] Several studies also used data from non-renal organ transplantations (liver, heart, gastrointestinal, or pancreas), which require greater

immunosuppression and therefore have a predictably higher incidence of side effects.[24,25]

Pre-existing medical co-morbidities in renal patients would be expected to result in a higher risk of post transplant morbidity and mortality compared to an otherwise healthy younger CTA population. Potential CTA candidates are not considered similar to kidney transplantation recipients with all the same overall risks.[23]

When considering the risk of malignancy, Baumeister et al.[23] point out that the incidence of de novo malignancies was actually lower than previously reported in the literature. Three per cent of patients were projected to develop a malignant tumour within 5 years, one-third of these originating in the skin. Less than 1% were expected to develop a malignant lymphoproliferative disease such as non-Hodgkin's lymphoma. While acknowledging the limitations of the work, Baumeister et al. concluded that the data available should be considered as a rough estimate and upper limit of the potential risks faced. The incidence of side effects and immunosuppression-associated mortality within the CTA population is likely to be lower than renal transplant patients.[23]

Based on these findings it is probable that CTA recipients will have less morbidity related to immunosuppression than a kidney transplant patient.[23] It should be pointed out that the average CTA patients will be younger and will have a longer life span than the average renal transplant patient. Thus the cumulative immunosuppressive risks need to be considered in calculating the risk-benefit ratio for CTA. A longer life span will also increase the possibility of chronic rejection and of the graft.

Chronic rejection

Chronic rejection is the most prevalent cause of long-term failure in organ transplantation and has remained stubbornly unchanged despite major developments in immunotherapy and postoperative care. It is a poorly understood phenomenon with multi-factorial aetiology, including ischaemic damage and immune reactivity.[4] In renal transplantation this process leads to gradual loss of function so that after 7–8 years loss of allografts can be seen in up to 50% of cases.[26]

The frequency and timing of acute rejection can be a predictor of future chronic episodes,[27] a concern in CTA development, as there have been instances of acute rejection in many of the transplants performed to date. Although these cases were easily controlled, previous solid organ transplantation experience suggests a potential risk of chronic rejection. Many CTAs will be preformed on patients requiring good outcome longer than 7–8 years and this must be considered when reviewing the best course of action. Encouragingly however, some of the next generation of immunosuppressive agents have shown promise in reducing the incidence of chronic rejection in a renal transplant setting.[28]

New immunosuppressive agents and combination strategies

Current research seeks to identify novel agents that effectively suppress rejection while causing minimal toxic side effects. New drugs such as sirolimus, everolimus, leflunomide, active metabolites FK778 and FK779, anti-T cell antibodies, e.g. deoxyspergualine with anti-CD3 immunotoxin and campath-1-H, have all shown promise and are in various stages of development.[29] FTY720 for example, has been shown to prolong skin allografts in small and large animal models.[30]

Other strategies include the use of novel combinations, which eliminate the need for corticosteroids altogether, thereby significantly reducing their toxicity profiles. Despite being the mainstay of immunosuppression for decades, steroids produce the greatest long-term morbidity in transplant patients. Sirolimus and cyclosporine (CsA) combinations or tacrolimus (TRL) and rapamune hold the promise of this greater efficacy. In several phase III trials sirolimus has allowed the reduction of CsA dosages and even total withdrawal of corticosteroids.[30,31] TRL has also permitted the reduction of adjunctive immunotherapy for rejection episodes and the reduction or removal of corticosteroid doses.[32,33]

Application of topical routes

Another approach aimed at reducing possible systemic complications that is particularly relevant to CTA is that of local topical immunosuppression. Tacrolimus, for example, acts on antigen-presenting epidermal dendritic cells, limiting the initiation and promotion of the rejection process of skin components. TRL ointments have been shown to have efficient penetration and prolong skin allograft survival in small animal models without systemic effects.[34] To date topical therapy has been used in two cases of hand CTA recipients, to successfully assist in reversing rejection episodes.[30]

Ultraviolet A and B at low doses have also been shown to modify local immune systems by altering cell interaction, antigen expression and cytokine production. Research groups are currently investigating the use of this form of phototherapy as a potential modality in CTA.[35]

Novel research strategies: tolerance induction

Tolerance describes a state in transplantation where the recipient does not mount an immune response to the donor tissue but still retains the ability to respond to all other stimuli. If successfully achieved, it holds the promise to negate the need for immunosuppression altogether and overcome current limitations.[4]

The integration of donor cells and the subsequent reprogramming of the recipient's antigenic response has been shown to successfully induce tolerance to many antigenic tissues in rodents, swine and primates using a variety of approaches in foetal, neonatal and adult animals.[36–41] Mixed haematopoietic chimerism, peripheral tolerance using co-stimulatory blockage using monoclonal antibodies and novel tolerance-inducing protocols have all been reported across major histocompatibility complex (MHC) barriers.[42–44] More recently, Siemionow et al.[45] illustrated how allogeneic stem cell transplantation could be used to extend the survival of transplanted limbs in animal studies. Intraosseous allotransplantation of donor-derived

haematopoietic bone marrow stem and progenitor cells (CD90+) were successfully used on chimerism induction. Bartholomew et al.[46] also showed that administration of mesenchymal stems cells (MSC) could prolong skin graft survival. A subset of non-haematopoietic cells, MSCs give bone marrow cells the capability to differentiate into different tissue types including tendon, muscle, cartilage and bone, making MSCs a potential tool in tissue engineering research.[47] Unfortunately skin still remains a significant obstacle and further studies are required to allow these procedures to be applied in the CTA setting.

Antigenicity of skin: experimental predictions verses clinical experience

Skin is thought to be one of the most antigenic tissues and the principle target of rejection.[10,48] The antigenic nature has been attributed to its complex immunological structure, with an abundance of dendritic cells in the dermis and epidermis.[49] Early experimental studies in primates showed the need for a higher level of immunosuppression to prevent skin rejection, leading to the prediction that higher doses would also be required in humans.[50,51]

Clinical experience has questioned these conclusions and has shown that routine renal immunosuppressive regimens allow skin to survive.[4,52,53] Experience with hand CTA has produced the most encouraging results. Since the first successful transplant in 1998, only two of the 24 cases performed to date have been rejected, one due to a period of non-compliance.[4] In some cases the regimens used in hand CTA were in fact lower than renal allografts.[54] In studies of combined allogenic human small intestine and abdominal wall, it was the intestine that was rejected while the abdominal wall, inclusive of skin, was preserved.[55] Lanzetta et al. attributed these findings to a number of probable factors. Antigen competition, induction of antibodies and activation of regulatory T cells were sited as possible reasons for the observed slower rejection rate of the skin component of CTA, compared to skin alone.[49] Consumption phenomenon, where the immune system is challenged to deal with different antigen loads was also considered. The use of synergistic combinations of drugs described above was probably a significant contributory factor.[49] The antigenicity of skin and its antigenicity in comparison to other tissues is not as straightforward as previously assumed. The real position of human skin antigenicity will become apparant as more human CTA is performed and more manipulation of immunosuppression regimens occurs.

In conclusion, new experimental procedures or techniques have always generated debate in the medical community. CTA and specifically facial transplantation are no exceptions. The well accepted view that high dose immunosuppression would be needed to overcome highly antigenic tissues such as skin has not been borne out by clinical experience. To date routine regimens extrapolated from renal transplant protocols have been successfully used to maintain CTAs. Although immunosuppressive therapy can have many potential complications, the published incidence of adverse events seen as a result of immunosuppression in renal transplant recipients may not be easily extrapolated to potential CTA candidates. Renal patients have a higher pre-existing morbidity, due to renal insufficiency and their risks of post transplant morbidity and mortality would be expected to be greater than in an otherwise healthy younger CTA population.

The next generation of immunosuppressive agents may provide the opportunity to lower cortocosteroid doses and even facilitate their removal from the regimens completely. Concurrent research into alternative options, such as tolerance induction and topical therapies, may further potentiate a reduction in complication rates. It is likely that in the near future the benefits of CTA as a therapeutic option, for appropriate carefully selected patients, will be measured against the potential immunogenic drawbacks. What part chronic rejection or transplant tolerance induction will play in the long-term success of CTA is still open to debate and requires further research.

Ultimately the choice of applying a CTA technique must be decided on an individual basis with an up to date and well-balanced view of the current position and in conjunction with the informed wishes of the patient.

References

1. Butler PE, Clarke A, Hettiaratchy S. Facial transplantation. A new option in reconstruction of severe facial injury. *BMJ* 2005;**331**:1349–50.
2. Devauchelle B, Badet L, Lengele B, et al. First human face allograft: early report. *Lancet* 2006;**368**:203–9.
3. Macartney J. Face transplant for bear attack victim. *Times (Lond)*, http://www.timesonline.co.uk/article/0, 25689–2135297, 00.html; April 15, 2006 (accessed Sept 21, 2006).
4. Hettiaratchy S, Butler PE. Extending the boundaries of transplantation. *BMJ* 2003;**326**:1226–7.
5. Hettiaratchy S, Randolph MA, Petite F, et al. Composite tissue allotransplantation: a new era in plastic surgery? *Br J Plast Surg* 2004;**57**:381–91.
6. Clarke A, Butler PE. Facial transplantation: adding to the reconstructive options after severe facial injury and disease. *Expert Opin Biol Ther* 2005;**5**:1539–46.
7. Hettiaratchy S, Butler PE. Facial transplantation – fantasy or the future? *Lancet* 2002;**360**:5–6.
8. Butler PE, Hettiaratchy S, Clarke A. Managing the risks of facial transplantation. *Lancet* 2006;**368**:561–3.
9. Brouha P, Naidu D, Cunningham M, et al. Risk acceptance in composite-tissue allotransplantation reconstructive procedures. *Microsurgery* 2006;**26**:144–9. discussion 149–50.
10. Lee WPA, Yaremchuk MJ, Pan YC, et al. Relative antigenicity of components of a vascularized limb allograft. *Plast Reconstr Surg* 1991;**87**:401–11.
11. Gorantla VS, Barker JH, Jones JW, et al. Immunosuppressive agents in transplantation: mechanisms of action and current anti-rejection strategies. *Microsurgery* 2000;**20**:420–9.
12. Cendales L, Hardy MA. Immunological considerations in composite tissue transplantation: overview. *Microsurgery* 2002; **20**:412–9.
13. Rubin RH, Young LS, editors. *Clinical Approach to Infection in the Immunocompromised Host*. 3rd ed. New York: Plenum Press; 1994.
14. Fishman JA, Rubin RH. Infection in organ-transplant recipients. *N Engl J Med* 1998;**338**:1741–51.
15. Shapiro R, Fung JJ, Jain AB, et al. The side effects of FK 506 in humans. *Transplant Proc* 1990;**264**:63–7.
16. Sratta RJ, for the FK/MMF Multi-Center Study Group. Simultaneous use of tacrolimus and mycophenolate mofetil in

combined pancreas—kidney transplant recipients: a multicenter report. *Transplant Proc* 1997;**29**:654–5.
17. Gander B, Brown CS, Vasilic D. Composite tissue allotransplantation of the hand and face: a new frontier in transplant and reconstructive surgery. *Transpl Int* 2006;**19**:868–80.
18. Schulak JA. Steroid immunosuppression in kidney transplantation: a passing era. *J Surg Reas* 2004;**117**:154–62.
19. Veenstra DL, Best JH, Hornberger J. Incidence and long-term cost of steroid-related side effects after renal transplantation. *Am J Kidney Dis* 1999;**33**:829–39.
20. Clavijo-Alvarez JA, Hamad GG, Taieb A, et al. Pharmacologic approaches to composite tissue allograft. *J Hand Surg* 2007; **32**:104–18.
21. First MR, Peddi VR. Malignancies complicating organ transplantation. *Transplant Proc* 1998;**30**:2768–70.
22. Sheil AGR, Disney APS, Mathew TH, et al. Cancer development in cadaveric donor renal allograft recipients treated with azathioprine (AZA) or cyclosporine (CsA) or AZA/CsA. *Transplant Proc* 1991;**23**:1111–2.
23. Baumeister S, Kleist C, Dohler B, et al. Risks of allogeneic hand transplantation. *Microsurgery* 2004;**24**:98–103.
24. Jones NF. Concerns about human hand transplantation in the 21st century. *J Hand Surg [Am]* 2002;**27**:771–87.
25. Brenner MJ, Tung TH, Jensen JN, et al. The spectrum of complications of immunosuppression: is the time right for hand transplantation? *J Bone Joint Surg Am* 2002;**84**:1861–70.
26. Cecka JM, Terasaki PI. The UNOS Scientific Renal Transplant Registry. In: Terasaki PI, Cecka JM, editors. *Clinical Transplants 1994*. Los Angeles: UCLA Tissue Typing Laboratory; 1994. p. 1–18.
27. Tejani A, Sullivan EK. The impact of acute rejection on chronic rejection: a report of the North American Paediatric Renal Transplant Cooperative Study. *Paediatr Transplant* 2000;**4**: 107–11.
28. Kahan BD. Potential therapeutic interventions to avoid or treat chronic allograft dysfunction. *Transplantation* 2001;**71**:S52–7.
29. Krieger NR, Emre S. Novel immunosuppressants. *Paediatr Transplant* 2004;**8**:594–9.
30. Lima RS, Nogueira-Martins MF, Silva Jr HT, et al. FTY720 treatment prolongs skin graft survival in a completely incompatible strain combination. *Transplant Proc* 2004;**36**:1015–7.
31. Kahan BD. Sirolimus: a ten-year perspective. *Transplant Proc* 2004;**36**:71–5.
32. Ayrout C, Lanzetta M, Chunasuwankul R, et al. Experimental limb transplantation, part I: identification of an effective tapered triple combination immunosuppressive regime. *Transplant Proc* 2004;**36**:669–74.
33. Ringe B, Braun F, Lorf T, et al. Tacrolimus and mycophenolate mofetil in clinical liver transplantation: experience with a steroid-sparing concept. *Transplant Proc* 1998;**30**:1415–6.
34. Fujita T, Takahashi S, Yagihashi A, et al. Prolonged survival of rat skin allograft by treatment with FK506 ointment. *Transplantation* 1997;**64**:922–5.
35. Gruber SA, Shirbacheh MV, Jones JW, et al. Local drug delivery to composite tissue allografts. *Microsurgery* 2000;**20**:407–11.
36. Kawai T, Cosimi AB, Colvin RB, et al. Mixed allogeneic chimerism and renal allograft tolerance in cynomolgus monkeys. *Transplantation* 1995;**59**:256–62.
37. Schwarze ML, Menard MT, Fuchimoto Y, et al. Mixed hematopoietic chimerism induces long-term tolerance to cardiac allografts in miniature swine. *Ann Thorac Surg* 2000;**70**:131–9.
38. Huang C, Fuchimoto Y, Scheier-Dolberg R, et al. Stable mixed-chimerism and tolerance using a nonmyeloablative preparative regimen in a large-animal model. *J Clin Invest* 2000;**105**: 173–81.
39. Lee WP, Rubin JP, Bourget JL, et al. Tolerance to limb tissue allografts between swine matched for major histocompatibility complex antigens. *Plast Reconstr Surg* 2001;**107**:1482–90. discussion 1491–2.
40. Butler PE, Lee WP, van de Water AP, et al. Neonatal induction of tolerance to skeletal tissue allografts without immunosuppression. *Plast Reconstr Surg* 2000;**105**:2424–30. discussion 2431–2.
41. Cober SR, Randolph MA, Lee WP. Skin allograft survival following intrathymic injection of donor bone marrow. *J Surg Res* 1999;**85**:204–8.
42. Tai C, Goldenberg M, Schuster KM, et al. Composite tissue allotransplantation. *J Inv Surg* 2003;**16**:193–201.
43. Hettiaratchy S, Melendy E, Randolph MA, et al. Tolerance to composite tissue allografts across a major histocompatibility barrier in miniature swine. *Transplantation* 2004;**77**:514–21.
44. Seimionow M, Ortak T, Izycki D, et al. Induction of tolerance in composite-tissue allografts. *Transplantation* 2002;**74**:1211–7.
45. Siemionow M, Zieliniski M, Ozmen S, et al. Intraosseus transplantation of donor-derived hematopoietic stem and progenitor cells induces donor-specific chimerism and extends composite tissue allograft survival. *Transplantation Proc* 2005;**37**:2303–8.
46. Bartholomew A, Sturgeon C, Siatskas M, et al. Mesenchymal stem cells suppress lymphocyte proliferation in vitro and prolong skin graft survival in vivo. *Exp Hematol* 2002;**30**:42–8.
47. Siemionow M, Agaoglu G. Tissue transplantation in plastic surgery. *Clin Plastic Surg* 2007;**34**:251–69.
48. Kanitakis J, Jullien D, Petruzzo P, et al. Clinicopathologic features of graft rejection of the first human hand allograft. *Transplantation* 2003;**76**:688–93.
49. Lanzetta M, Petruzzo P, Vitale G, et al. Human hand transplantation: what have we learned? *Transplant Proc* 2004; **36**:664–8.
50. Stark GB, Swartz WM, Narayanan K, et al. Hand transplantation in baboons. *Transplant Proc* 1987;**19**:3968–71.
51. Hovius SER, Stevens HPJD, Van Nierop PWM. Allogenic transplantation of the radial side of the hand in the rhesus monkey. *Plast Reconstr Surg* 1992;**89**:700–9.
52. Petit F, Minns AB, Dubernard JM, et al. Composite tissue allotransplantation and reconstructive surgery: first clinical applications. *Ann Surg* 2003;**11**:1–6.
53. Dubernard JM, Burloux G, Giraux P, et al. Three lessons learned from the first double hand transplantation. *Bull Acad Natl Med* 2002;**186**:1051–62.
54. Dubernard JM, Owen E, Herzberg G, et al. Human hand allograft: report on first 6 months. *Lancet* 1999;**353**:1315–20.
55. Selvaggi G, Levi DM, Kato T, et al. Expanded use of transplantation techniques: abdominal wall transplantation and intestinal autotransplantation. *Transplant Proc* 2004;**36**: 1561–3.