Chapter 12
Locoregional Immunosuppression in Composite Tissue Allografting

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12.1 Introduction

Unlike visceral solid-organ transplants, composite tissue allografts (CTAs) are modules composed of various tissues, each with differing antigenicity, and therefore differing potential for rejection. Skin and muscle (and perhaps synovium) are the most antigenic and appear to be most susceptible to rejection, while bone, tendon, cartilage, and neurovascular tissue appear to be less immunogenic and evoke rejection responses of lower magnitude. Although CTAs have tremendous potential clinical application for functional and structural reconstruction of major congenital and acquired peripheral tissue defects, these transplants have remained one of the last frontiers in clinical organ transplantation because of concerns expressed beginning 15–20 years ago regarding their risk/benefit ratio. Even now, with the performance of unilateral hand, bilateral hand, or digit transplantation in a total of 18 patients from 1998 to 2004, there still remains much concern with regard to the risks of long-term immunosuppression and the potential for development of chronic rejection. The following two questions address the key issues involved. (1) Can rejection of these highly antigenic tissues be prevented using currently available immunosuppressive regimens with acceptable drug-specific and generalized toxicity? (2) Will function be restored to a significant degree so as to justify the surgical and immunosuppressive risks involved?

Information recently provided on 18 CTA recipients followed for 17–70 months in the aforementioned inaugural report of the International Registry on Hand and Composite Tissue Transplantation has begun to shed some light on the answers to these questions. Virtually all patients received a form of antilymphocyte antibody for induction (Thymoglobulin [ATG] and/or Basiliximab), and tacrolimus (TCL), mycophenolate mofetil, and prednisone therapy for maintenance immunosuppression. Despite this clinically acceptable but nonetheless intensive immunosuppressive regimen, akin to that currently utilized for rejection-prone, nonuremic, insulin-dependent diabetics who receive a pancreas transplant, two of the three patients experienced at least one episode of acute rejection and 50% of patients experienced multiple episodes. In most cases, the episodes were reversed following combination intravenous and/or oral “pulse” steroid and topical TCL-clobetasol cream treatment,
but in eight instances, ATG \((n=2)\), Basiliximab \((n=5)\), or Campath 1-H \((n=1)\) was required, further significantly increasing the already-elevated immunosuppressive burden in these patients. Along these lines, five recipients developed CMV infection or disease, with the majority of these cases requiring second-line agents more toxic than ganciclovir or valganciclovir to achieve long-term control of viral infection. Metabolic complications from the immunosuppressants included transient hyperglycemia \((n=9)\), increased serum creatinine \((n=2)\), Cushing’s syndrome \((n=1)\), and avascular necrosis of the hip \((n=1)\). Overall, patient and graft survival were 100% and 89%, respectively, with one of the two graft losses due to noncompliance. All patients achieved protective sensation with 17 achieving discriminative sensation, and extrinsic and intrinsic muscle recovery enabled patients to perform most daily activities. These intermediate-term results suggest that clinical application of CTAs is more likely to gain widespread acceptance if the systemic immunosuppressive burden and its attendant long-term risks of infection, drug-specific side-effects, and although not yet encountered, malignancy, could be reduced while simultaneously preventing rejection and maintaining function.

### 12.2 Local Immunosuppression

One approach toward reducing the drug-specific and general adverse consequences of systemic immunosuppression in CTA recipients, and thereby improving the clinical feasibility of the procedure, is the utilization of local drug administration systems to establish a more selective presence of currently available nonspecific immunosuppressive agents in the transplanted limb or limb component, with a concomitant reduction in systemic drug exposure. Interestingly, the first report illustrating this concept appeared as early as 1951, in which Billingham et al. found that topical application of cortisone acetate at a dosage that was ineffective when administered systemically prolonged skin allograft survival in a rabbit model. This work was followed by conflicting reports regarding the effectiveness of local treatment of canine and human renal allografts with a variety of antimetabolites and corticosteroids administered via indwelling arterial catheters in the late 1960s. With the exception of experimental and clinical studies demonstrating the efficacy of local graft irradiation, further examination of local immunosuppression was abandoned for 15 years, awaiting technological advances in drug-delivery systems and a better understanding of both the cellular events within the rejecting allograft and the pharmacokinetics of target-aimed drug delivery.

In 1986, Ruers et al. demonstrated that continuous intra-arterial (IA) infusion of prednisolone in rat renal allograft recipients produced a significant increase in graft survival when compared with same-dose systemic administration. This work was rapidly followed by multiple reports of favorable experiences with local immunosuppressive therapy utilizing a variety of different agents in rat heterotopic cardiac, renal, pancreatic islet cell, and liver allograft models and in canine renal and