New Minimal Immunosuppression Strategies for Composite Tissue Allograft Transplantation: The Cleveland Clinic Experience

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Abstract

Clinical application of composite tissue allografts requires the introduction of new minimal immunosuppressive or tolerance-inducing protocols. We have established a protocol for tolerance induction under α/β selective blocking antibody T-cell receptor combined with interleukin-2 blocker cyclosporin A therapy. Application of this therapy resulted in induction of tolerance in fully allogenic and semiallogenic limb allograft transplants. Based on this experience we have found that the bone marrow component of the allograft is essential for tolerance induction and have confirmed that injection of bone marrow of donor origin directly into the bone marrow compartment of allograft recipients resulted in higher chimerism levels. In addition, we have developed a system for isolation of chimeric cells, which are specific for both the donor and recipient, by using magnetic activated cell sorting technique and flow cytometry. These new, experimental approaches confirm that introducing minimal suppression to patients undergoing hand or face transplantation will likely be achieved in the near future.

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Clinical application of composite tissue allografts, such as hand, face, larynx, and abdominal wall transplants, requires the introduction of new minimal immunosuppressive or tolerance-inducing protocols to reduce the significant side effects of currently available immunosuppressive therapies. Working for the past 20 years on strategies for tolerance induction in composite tissue allografts by using a standard 7-day limb transplantation model across major histocompatibility barrier, we have established a protocol for tolerance induction under α/β selective blocking antibody T-cell receptor (TCR) combined with interleukin-2 blocker cyclosporin A (CsA) therapy.[1-7]

Application of this combined α/β TCR–CsA therapy for 7 days resulted in induction of tolerance in fully allogenic and semiallogenic limb allograft transplants. Tolerance was maintained for >720 days without need for lifelong immunosuppression. Induction and maintenance of tolerance correlated with the induction of donor-specific chimerism and maintenance of chimerism over the time of allograft survival.[2,3] Based on this experience, as well as on experience with vascularized skin allograft transplants, we have found that the bone marrow component of the allograft is essential for tolerance induction.[1-9]

To test this hyopothesis, we used a model of vascularized bone allograft

transplantation and compared this model with a composite vascularized skin/vascularized bone and face transplantation model for chimerism and tolerance induction. To make these studies clinically applicable, we tested the injection of crude and processed bone marrow directly into the bone of the recipients of the skin allografts and compared injection with the conventional intravenous transplantation of the bone marrow. We confirmed that injection of bone marrow of donor origin directly into the bone marrow compartment of allograft recipients resulted in higher chimerism levels. Donor chimerism was characterized by T-cell (CD4, CD8) and B-cell (CD45RA) populations. Following intraosseous injection, the maintenance of stable chimerism was supported by a B-cell population at long-term follow-up. These studies have confirmed that the route of bone marrow delivery plays an essential role in allograft engraftment and also supports long-term survival.[5]

Finally, based on promising results with induction of donor-specific chimerism following peritransplant bone marrow injection, we have developed a system for isolation of chimeric cells, which are specific for both the donor and recipient, by using magnetic activated cell sorting technique and flow cytometry. Once the chimeric cells were isolated, we established a protocol for cellular therapy based on created donor/recipient chimeric cells. Injection of chimeric cells on the day of transplantation, in combination with our established 7-day minimal suppression therapy of α/β TCR and CsA, resulted in good engraftment and survival of vascularized skin allografts supported by maintenance of donor chimerism. These results are specifically encouraging because, with further development, chimeric cells likely will lead in the long term to cell banking for peritransplant application as well as to boosting therapy in case of graft rejection.

These new, experimental approaches are encouraging. They confirm that our goal of introducing minimal suppression to patients undergoing hand or face transplantation will likely be achieved in the near future. Specifically, the introduction of shorter acting and selective antibodies, such as our α/β TCR protocol, is promising because, under this therapy, a specific population of gamma-delta T cells, known for its tolerogenic properties, is preserved, as are a B-cell population, macrophages, and natural killer cell population, thereby protecting the transplant recipient from the development of severe infections and the long-lasting effect of immunodepletion.[2,3]

Potential clinical application of these novel, minimal suppression protocols for hand and face transplantation seems to be feasible within the next 2 to 5 years. Once these new tolerance-inducing therapies are applied, proved to be efficacious for engraftment, and found to be safer for the recipients of face and hand allograft transplants, they will expedite the development of composite tissue transplantation in the fields of plastic, reconstructive, and orthopaedic surgery.

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