ADVANCES IN IBD

Current Developments in the Treatment of Inflammatory Bowel Disease

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Small Bowel Transplantation for the Treatment of Crohn's Disease

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G&H What is the current status of small bowel transplantation for the treatment of Crohn's disease?

SS Despite advances in pharmacologic therapies for Crohn's disease (CD), nearly 50% of patients will require surgery within the first 10 years following diagnosis. While a variety of bowel-sparing surgical techniques have evolved, repeat resections may eventuate in short gut in a subset of patients. These individuals are typically patients with extensive small bowel disease or a penetrating CD phenotype. CD is currently the second leading indication for intestinal transplantation worldwide; within this group, small bowel transplantation is most often performed in CD patients with short bowel syndrome and intestinal failure in whom total parenteral nutrition (TPN) is beginning to fail. TPN failure can manifest as loss of venous access due to catheter-associated thromboses or as liver dysfunction, both of which can compromise the adequate provision of nutrients.

While our collective experience with small bowel transplantation in patients with inflammatory bowel disease (IBD) is limited, outcomes for intestinal transplantation in general have improved because of increased surgical and technical successes and the advent of tacrolimus-based immunosuppression protocols. However, outcomes for small bowel transplantation remain generally poor, with only 50% survival at 5 years. The major issues that arise in bowel transplant recipients are acute cellular rejection and infection due to potent immunosuppression.

G&H How many small bowel transplantations have been performed in patients with CD?

SS Over the last few decades, just over 50 patients with CD have undergone small bowel transplantation. As a comparison, the number of patients who receive intestinal transplants for any indication is approximately 100 patients per year worldwide.

G&H How successful is small bowel transplantation in patients with CD?

SS Currently, we have little data on outcomes in these patients. The reported literature on small bowel transplantation in CD patients is comprised mostly of a few case series and case reports, as well as some anecdotal experience. However, CD patients who have undergone transplantation are being followed longitudinally in an international registry, so more data may be available in the future.

The largest series that has been reported is comprised of 6 adult patients. Two of these patients developed early, persistent histologic changes that were consistent with CD, but none of the patients developed endoscopically or clinically measurable disease up to 2 years post-transplantation. Also, all of these patients experienced episodes of mild rejection that were responsive to conventional therapies (such as pulsed steroid therapy), and none of these patients were on CD-specific immunosuppressive therapy after transplantation.

Two patients in this series received combined liver-and-intestine transplants and died of severe sepsis post-operatively. Transplantation of the liver is thought to offer an immunologic advantage by enabling a truce between

the donor organ and the recipient; however, patients who require a liver due to advanced liver disease tend to be sicker going into transplantation.

G&H When should gastroenterologists consider small bowel transplantation for patients with CD?

SS Patients with short bowel syndrome who are failing TPN due to complications should be referred to a transplantation center so that small bowel transplantation can be considered. One clue that should alert physicians to the possibility that patients may be failing TPN is the presence of liver abnormalities, which can range from cholestasis to advanced cirrhosis. In these patients, early recognition of liver dysfunction is important so that patients can be referred for small bowel transplantation before advanced liver disease develops. Patients who experience frequent episodes of catheter-related sepsis, such as catheter-associated venous thrombosis with loss of venous access, should undergo evaluation.

Another area of interest is combined transplantation of bowel plus abdominal wall tissue in individuals with penetrating CD who have developed enterocutaneous fistulae refractory to conventional medical and surgical therapies. This procedure will require a better understanding of the immunologic mechanisms underlying tolerance for transplanted skin and/or fascia. The skin, like the gut, is immunologically poised to handle exogenous antigens and is similarly immunogenic. Rejection can occur independent of the intestine.

G&H When is small bowel transplantation contraindicated?

SS The contraindications for small bowel transplantation parallel the contraindications that have been identified for transplantation of other organs. Specifically, the 2 contraindications that are most significant in this population are active systemic infection and malignancy. Infection is likely a bigger issue in patients with IBD because they may have already been exposed to potent immunosuppressive therapy and/or they may have deficits in their intrinsic immune surveillance mechanisms. Preexisting active Crohn's enteritis should be medically optimized, when possible.

G&H What challenges do clinicians face during the postoperative period?

SS Acute cellular rejection and infection are the 2 prevailing obstacles to success in the postoperative period. Acute cellular rejection is a major cause of graft failure both in patients with CD and in patients with other indications for bowel transplantation. Episodes of severe rejection compromise the integrity of the intestinal barrier and can enable bacterial translocation from the gut to the systemic circulation and to remote locations. Infection is a major cause of morbidity and mortality following small bowel transplantation. The potent immunosuppression required to prevent rejection coupled with preexisting malnutrition and its attendant immune deficiencies increase the overall infectious risk.

Cytomegalovirus (CMV) infection can be a significant cause of morbidity in the post-transplantation period. CMV exhibits a well-described tropism to enterocytes and has been associated with rejection. Although CMV can be an innocent bystander in the bowel of patients with IBD, it may have an inciting role in intestinal allograft rejection. One reason CMV is difficult to treat in bowel transplant recipients is because CMV viremia and allograft disease may not parallel one another, and intestinal involvement therefore may evade early detection. Moreover, treatment and eradication of CMV disease can be more challenging in transplant recipients in part because of the alteration in vascular anatomy and disruption of lymphatics that occur during intestinal transplantation.

Finally, a temporary chimney ileostomy is created in intestinal transplant recipients to allow surveillance of the allograft. This can impart significant fluid and electrolyte derangements that require close monitoring and intervention. Drug-specific metabolic and organ toxicities are frequently encountered due to the requirement for heavy immunosuppression.

G&H How can clinicians address some of the obstacles that arise following small bowel transplantation?

SS It is critical to have a multidisciplinary team comprised of a surgeon, a gastroenterologist, transplant infectious disease experts, dieticians, and pharmacists dedicated to the care of these patients. Clinicians should have expertise in both intestinal transplantation and CD. The appropriate screening and selection of patients for transplantation is critical for post-transplantation successes.

In addition, better technological modalities for detection of recurrent CD and early subclinical allograft rejection would be particularly helpful in this population. Biomarkers such as fecal calprotectin have been separately investigated in IBD and intestinal transplantation with some successes, but biomarkers are unlikely to be discerning in a dysfunctional allograft. The presence of disease in the allograft can be patchy, and the length of bowel to be surveilled introduces a potential diagnostic challenge. The symptoms of rejection are protean and commonly include fever and altered ostomy output, which mandate frequent and prompt endoscopic monitoring.

G&H What is the typical postoperative medication regimen for small bowel transplant recipients?

SS Most transplant centers use tacrolimus-based immunosuppression protocols. Immunosuppression includes a

T-cell–depleting induction agent (such as antithymocyte globulin) in the perioperative period, corticosteroids, and tacrolimus. Post-transplantation patients also receive prophylaxis for opportunistic infections, including CMV infection. Finally, TPN is often resumed in the short term after transplantation as a bridge to enteral autonomy.

G&H How long do patients continue these medications?

SS There is a greater collective density of antibody-producing cells in the small intestine than in the spleen and lymph nodes combined, and the immunologic load associated with an intestinal allograft is a unique challenge. Thus, small bowel transplant recipients remain on postoperative immunosuppression longer than other organ transplant recipients. In addition, therapeutic drug levels are maintained at much higher trough levels in bowel transplant recipients compared to other transplant recipients. Approximately 20% of patients are on monotherapy with tacrolimus at 1 year. Our center strives to achieve steroid-free immunosuppression by 6 months after transplantation. The ultimate goal would be to achieve an immunologic truce between the transplanted organ and the recipient so that immune suppression could be withdrawn altogether.

G&H How frequently does CD recur following small bowel transplantation?

SS Histologic recurrence has been reported in the limited number of patients who have undergone bowel transplantation to date. As with CD in native bowel, however, this histologic recurrence might not be of clinical importance.

G&H How might clinicians prevent recurrence of CD following small bowel transplantation?

SS Post-transplantation immunosuppression protocols include both tacrolimus and steroids; while tacrolimus is not thought to impact the immune pathways that are mechanistically important in CD, steroids act globally on all arms of the immune system and therefore should have some impact on the patient's native disease. Biologic agents such as infliximab (Remicade, Janssen Biotech) have only been used in a limited fashion to address acute cellular rejection that is refractory to conventional therapies. Currently, there is limited clinical experience with the use of CD-specific therapies in CD patients who have undergone small bowel transplantation.

G&H Do you think that small bowel transplantation will become more common as a treatment for CD?

SS Small bowel transplantation may be a life-saving procedure in a small number of patients with CD, and I think it will become more common as surgical and technical successes continue to improve. However, growth of this procedure will hinge on significant improvement in our understanding of the immunology of the bowel, T-cell homing patterns, and the influence of the enteric microbiota on rejection. Clinicians should proceed very cautiously, with measured concern regarding the risks and benefits of this procedure and attention to proper patient selection. Intestinal transplantation combined with transplantation of the abdominal wall or abdominal fascia for patients with penetrating CD and an enterocutaneous fistula may become viable in the future.

G&H What additional studies are needed in this area?

SS Innumerable deficits remain in our understanding of small bowel transplantation and its application as a treatment for CD. Specifically, we need to have a better understanding of the immunology of tissue tolerance—not only of the intestine but also of the skin and fascia. We also need better bench-to-bedside understanding of immunosuppression in general and of the immune-mediated pathways involved in CD and intestinal transplantation. Research surrounding the role of the commensal flora in epithelial barrier integrity and modulation of the immune system at the epithelial interface will add insight and may allow us to shift conditions favorably. Advances in understanding of the bidirectional migration of donor and recipient lymphocytes and emphasis on tissue tolerance induction rather than chronic immunosuppression will be a departure from the current standard of care, but these changes likely underpin long-term allograft success.

Suggested Reading

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