

## Successful living donor intestinal transplantation in cross-match positive recipients: Initial experience

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### Abstract

Sensitized patients tend to have longer waiting times on the deceased donor list and are at increased risk of graft loss from acute or chronic rejection compared to non-sensitized candidates. Desensitization protocols are utilized to decrease the levels of alloantibodies and to convert an initial positive cross-match to prospective donors into a negative crossmatch. These procedures are mostly available in the setting of living donation. Due to the elective nature of the procedure, desensitization protocols can be extended until the desired result is obtained prior to transplantation. We present two cases of successful desensitization protocol applied to living donor intestinal transplant candidates that converted to negative cross-match to their donors. We present two cases of intestinal transplant candidates with a potential living donor to whom they are sensitized. Both cases underwent successful transplantation after desensitization protocol. No evidence of humoral rejection has occurred in either recipient. Living donor intestinal transplantation in sensitized recipients against the prospective donors provides the ability to implement a desensitization protocol to convert to negative cross-match.

**Key words:** Living donor; Positive crossmatch; Intestinal

transplant; Desensitization protocol; Donor specific antibody; Plasmapheresis

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**Core tip:** Intestinal transplant candidates are frequently sensitized and waiting longer on the list. Living donation of intestine has been successful and allows for time to immunologically prepare sensitized recipient prior to transplant to achieve higher degree of success.

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## INTRODUCTION

Allosensitization represents a common problem for patients awaiting small bowel transplantation. In this patient population, allosensitization occurs often consequent to multiple blood transfusions administered during complex abdominal procedure, eventually leading to short bowel syndrome.

The presence of donor specific antibodies to the human leukocyte antigens (HLA) antibodies augments the risk of either acute or chronic immune mediated graft loss<sup>[1]</sup>. In kidney transplantation, removing anti-HLA antibodies by a combination of plasmapheresis, immunoglobulins (IVIG) and immunosuppression have been successfully applied to prevent antibody-mediated rejection (AMR). However, this approach can logistically only be applied in the context of elective living donor transplantation.

Outcomes after living donor small bowel transplantation in experienced centers are comparable to those obtained with cadaver grafts<sup>[2]</sup>. The elective nature of living donor intestinal transplantation offers the opportunity for the use of desensitization protocols in highly sensitized patients. Herein, we present the first report of two successful small bowel transplants after desensitization protocol in recipients with a positive cross-match (CM) to their prospective living donors.

## CASE REPORT

### Case one

A 13-year-old Caucasian male was diagnosed of pseudo-papillary tumor of the head of the pancreas with vascular encasing of portal vein and superior mesenteric artery. He underwent a Whipple procedure with vascular resection and reconstruction. Twelve months later, the patient presented with acute bowel ischemia secondary to superior mesenteric artery thrombosis and underwent

nearly total enterectomy and extended right colectomy. The patient was placed on total parenteral nutrition (TPN) as he was left with less than 5 cm of intestine. Given the young age of the patient and the high sensitization we suggested living donor small bowel transplant.

The other of the patient, 36-year-old in perfect health without previous abdominal surgeries, volunteered as a potential donor for intestinal transplantation. The donor evaluation process was carried out according to our standard protocol previously reported<sup>[3]</sup>.

Due to the multiple blood transfusions required during the events leading to transplantation, his Panel Reactive Antibodies (PRA) was 67% for class I and 100% for class II. He had strong donor specific antibodies (DSA) at locus A × 11:01 (MFI = 7359). The initial CM was positive by flow cytometry technique with pronase treatment at + 55 channel shifts for T cell and + 40 for B cell (negative CM less than + 17 channel shift); the standard cytotoxic CM was negative. The patient underwent seven plasma exchange treatments before the planned transplant procedure, each followed by IVIG at the dose of 100 mg/kg. The final flow cytometry CM remained weakly positive, with + 19 channel shifts for T cell and + 23 channel shift for B cell; the standard CM stayed negative. At the time of transplant our recipient was 36.7 kg (the 10<sup>th</sup> percentile in the growth chart) and fully dependent on total parenteral nutrition. The transplant event was successful; the 180 cm ileal graft was revascularized through anastomosis to the aorta and the vena cava. Proximally, the bowel graft was anastomosed to the stomach and distally to the residual colon; a loop ileostomy was created for graft monitoring.

Induction immunosuppression consisted of methylprednisolone taper along with of five doses of thymoglobulin (100 mg/kg) and 5 plasmapheresis treatments every other day followed by IVIG (125 mg/kg based on ideal body weight) on alternative days. He was closely monitored with ileoscopy and graft biopsy for surveillance of rejection weekly for a month, biweekly for another 2 mo and monthly thereafter. There was no evidence of rejection in any of the biopsies over two years follow-up.

Two months post-transplant, his course was complicated by an Epstein barr virus positive post-transplant lymphoproliferative disorder (PTLD) involving lymph nodes in both sides of the diaphragm. He was successfully treated with reduction of immunosuppression, antiviral therapy, Rituximab (375 mg/m<sup>2</sup>) weekly for total of 6 doses and Cytosan (600 mg/m<sup>2</sup>) every 21 d for a total of 6 doses.

Nine months after transplant, he had successful ileostomy reversal and his TPN was completely discontinued. He is currently fully supported by unrestricted oral diet and his most recent weight is 51.7 kg (the 18<sup>th</sup> percentile of his peers) at 2 years follow up; he remains in remission from PTLD. His maintenance immunosuppression consists of prednisone 5 mg daily and low dose Tacrolimus with target levels of 4-6 ng/mL.

## Case two

A 56-year-old Caucasian female with history of scleroderma complicated by intestinal pseudo-obstruction, underwent several intestinal resections and diverting ileostomy. Unfortunately, an injury to the superior mesenteric vessels occurred during one of the surgical procedures, resulting in near total enterectomy and extended right colectomy. At the time of presentation to our center, she was TPN-dependent for 6 mo, with high output tube duodenostomy; she was underweight at 42.2 kg with a body mass index (BMI) of 17 kg/m<sup>2</sup>.

Her daughter, a healthy 36-year-old female ABO compatible, with a BMI of 24 kg/m<sup>2</sup>, volunteered as a potential donor. The recipient was sensitized with a PRA class I 80% and class II 26%; no DSAs were identified. While the standard cytotoxic CM was negative, the flow cytometry CM was negative for T cell but positive for B cell with + 69 channel shifts. Desensitization was conducted by three plasma exchange treatments prior to transplant followed by IVIG, obtaining a completely negative flow cytometry and standard CM at the time of transplant.

A donor ileal graft of 190 cm was transplanted successfully in the recipient with our standard technique. Thymoglobulin (3 mg/kg) was given intraoperative and followed by three more doses (1.5 mg/kg) on alternate days to plasmapheresis; Tacrolimus was initiated the day prior to procedure with rapid taper of steroids to 10 mg daily by post-operative day 5. Endoscopic surveillance at previously described intervals during the initial 6 mo follow up revealed no evidence of rejection. The patient has had successful ileostomy reversal at 6 mo and is tolerating oral intake; she is no longer on supplemental TPN.

## DISCUSSION

Small bowel transplantation is an accepted treatment for patient with irreversible intestinal failure with life-threatening complications of TPN. At the end of 2014, there were approximately 250 patients listed for bowel transplantation in the United States. For candidates wait-listed in 2010, the median time to transplant was 14.9 mo for those younger than 18 years and only 2.8 mo for those aged 18 years or older<sup>[4]</sup>. The United Network of Organ Sharing does not report separately the waiting time on sensitized candidates for bowel transplantation, but experience in kidney recipients suggests potentially longer waiting times<sup>[5]</sup>. Importantly, transplant outcomes performed on recipients receiving total parenteral nutrition for less than one year are significantly better than those on TPN of a year or longer<sup>[6]</sup>.

In the current literature there are limited publications concerning small bowel transplantation in CM positive recipients. While intestinal transplantation has a higher rejection rate than most other solid organs (42% in the first year)<sup>[4]</sup>, antibody mediated rejection (AMR) is not well characterized and understood in this set of patients.

In other solid organs, the presence of C4d staining in the biopsies is indicative of AMR but this may not apply to intestinal transplants<sup>[7]</sup>.

Recently, virtual crossmatch has been successfully used to facilitate allocation of intestinal grafts specifically in the subgroup of sensitized candidates<sup>[8]</sup>. With this strategy, the group at Georgetown University has achieved 80% successful allocation with negative cross-match in sensitized recipients compared to 86.7% in non-sensitized, minimizing the discard rates of suitable organs originating out of state. However, sensitized patients with elevated PRA achieving a negative CM showed a survival disadvantage. The 1-year graft survival was lower in the sensitized group at 66.7% compared to 85.2% in the group with low PRA<sup>[8]</sup>. Although the authors did not observe a statistically significant difference between the two groups, likely due to a small sample size, the discrepancy is clinically concerning. The study also did not comment on specific therapy to reduce the levels of alloantibodies.

Experience in other solid organ transplantation such as kidney or heart indicates that outcomes in sensitized recipients are inferior to those observed in non-sensitized patients. Sensitized patients exhibit higher rejection rates, lower graft and patient survival<sup>[9]</sup>. Similarly, in intestinal transplantation, the risk of AMR has been reported to be higher in sensitized recipients and in those developing *de-novo* DSA. Diagnosis of AMR should be based on clinical suspicion in the presence of DSA or increased PRA since intestinal biopsy may not be conclusive<sup>[10,11]</sup>. Independent risk factors for worse outcomes in intestinal transplantation are: recipient PRA more than 20%, liver-sparing grafts and absence of recipient splenectomy<sup>[12]</sup>. Persistence of DSA after transplantation or *de-novo* formation of DSA result in increased risk of graft loss due to rejection (58% and 47% respectively). The risk of graft loss in patients without DSA was 8% and 13% in those clearing DSAs after transplant. Liver containing grafts are immunoprotective, effectively clearing pre-formed antibodies and reducing the risk of *de-novo* formation, but the recipients with persistent DSA after transplantation correlated with lower graft survival despite the presence of the liver<sup>[13]</sup>. Additionally, the rates and aggressiveness of rejection are worse in isolated intestine vs transplant containing liver graft<sup>[14]</sup>.

Contrary to these results, Kubal *et al.*<sup>[15]</sup> recently reported similar 3-year survival rates in small bowel transplantation (67% in positive CM vs 65% in negative CM). The also did not found a significant difference in the incidence of acute rejection between liver sparing and liver containing grafts (30% vs 29%). Additionally, the use of anti-interleukin-2 antibody as part of the induction therapy was noted to significantly reduce the rate of rejection overall.

Protocols to desensitize recipients continue to evolve and emerging therapeutic strategies allow successful positive CM transplantation<sup>[16]</sup>. The application in small bowel transplantation is not widely reported but the use of Bortezomib during induction in sensitized candidates has been suggested<sup>[13]</sup>. Performing surveillance DSA

to identify patients at risk, especially those without a concomitant liver, and rapidly initiate treatment with a combination of plasmapheresis, IVIG may optimize outcomes<sup>[17,18]</sup>. The use of Bortezomib to treat resistant rejection was successful in one case report<sup>[19]</sup>.

The only Desensitization protocol reported in wait list candidates to intestinal transplantation used escalating doses of IVIG according to the level of response in reducing the PRA level and included plasmapheresis or mycophenolate mofetil as the final step. The rate of rejection was found to be similar to non-sensitized recipients and the waiting time was also reduced on patients responding to the protocol<sup>[20]</sup>.

Our center is experienced in living donor small bowel transplantation and the elective nature of the procedure offers several advantages, especially in the sensitized candidates. We can optimize the immunological condition prior to transplantation with current desensitization protocols existing in other solid organs, mostly in kidney transplantation. As noted before, the risk antibody mediated rejection is increased in patients with elevated PRA, *de-novo* DSA formation and those with positive B cell CM. We realize that the CM was weak prior to desensitization, especially in the second case, and resulted in easier conversion to a negative CN. The one-year follow-up on both patients without rejection episodes are encouraging and suggest that pretransplant plasmapheresis may effectively prevent humoral rejection in sensitized intestinal transplant recipients. We acknowledge this is a very short follow and follow up DSA surveillance studies may be necessary to confirm the success of this protocol.

In conclusion, living donation offers the possibility to initiate therapy to optimize the immunological condition at the time of transplant, converting to a negative CM sensitized intestinal transplant recipients to their prospective donors.

## COMMENTS

### Case characteristics

Two patients with short bowel syndrome treated with living donor intestine transplantation.

### Clinical diagnosis

Both cases present highly sensitized making their chances for a deceased donor transplant unlikely.

### Differential diagnosis

Sensitization can be from autoantibodies or atypical antibodies and not identified in by donor specific antibodies (DSA) studies.

### Laboratory diagnosis

Cross-match and DSA studies performed.

### Pathological diagnosis

Biopsies taken from the intestinal mucosa were normal.

### Treatment

They underwent desensitization protocol and elective intestine transplant.

## Related reports

Intestinal transplant candidates are frequently sensitized and tend to wait for an organ longer than non-sensitized patients. Living donation is a scheduled procedure allowing for desensitization protocol to be completed prior to transplantation. This is not available when a deceased organ is offered. Desensitization protocols are applied frequently for sensitized patients before receiving a kidney transplant from live donors. The application to prospective recipient of intestine is novel.

## Term explanation

Desensitization protocols can turn positive crossmatch into negative and allow for successful transplantation.

## Experiences and lessons

This is a two cases report with limited follow up, but successful so far in both recipients. Post-transplant lymphoproliferative disorder is a risk in patients receiving high immunosuppression as the desensitization protocol.

## Peer-review

This is a manuscript that presents a valuable potential solution to the shortage of small bowel grafts, particularly in the setting of patients who are sensitized. The authors provide an interesting hypothesis for larger studies.

## REFERENCES

- 1 **Iyer HS**, Jackson AM, Zachary AA, Montgomery RA. Transplanting the highly sensitized patient: trials and tribulations. *Curr Opin Nephrol Hypertens* 2013; **22**: 681-688 [PMID: 24076558 DOI: 10.1097/MNH.0b013e328365b3b9]
- 2 **Tzvetanov IG**, Oberholzer J, Benedetti E. Current status of living donor small bowel transplantation. *Curr Opin Organ Transplant* 2010; **15**: 346-348 [PMID: 20445448 DOI: 10.1097/MOT.0b013e3283398fa4]
- 3 **Testa G**, Panaro F, Schena S, Holterman M, Abcarian H, Benedetti E. Living related small bowel transplantation: donor surgical technique. *Ann Surg* 2004; **240**: 779-784 [PMID: 15492558 DOI: 10.1097/01.sla.0000143266.59408.d7]
- 4 2011 OPTN & SRTR Annual report: intestine 2011. [Cited 2014]. Available from: URL: [http://srrt.transplant.hrsa.gov/annual\\_reports/2011/pdf/04\\_intestine\\_12.pdf](http://srrt.transplant.hrsa.gov/annual_reports/2011/pdf/04_intestine_12.pdf)
- 5 **Bostock IC**, Alberù J, Arvizu A, Hernández-Mendez EA, De-Santiago A, González-Tableros N, López M, Castelán N, Contreras AG, Morales-Buenrostro LE, Gabilondo B, Vilatobá M. Probability of deceased donor kidney transplantation based on % PRA. *Transpl Immunol* 2013; **28**: 154-158 [PMID: 23684945 DOI: 10.1016/j.trim.2013.05.002]
- 6 **Abu-Elmagd KM**, Costa G, Bond GJ, Soltys K, Sindhi R, Wu T, Koritsky DA, Schuster B, Martin L, Cruz RJ, Murase N, Zeevi A, Irish W, Ayyash MO, Matarese L, Humar A, Mazariegos G. Five hundred intestinal and multivisceral transplantations at a single center: major advances with new challenges. *Ann Surg* 2009; **250**: 567-581 [PMID: 19730240 DOI: 10.1097/sla.0b013e3181b67725]
- 7 **Troxell ML**, Higgins JP, Kambham N. Evaluation of C4d staining in liver and small intestine allografts. *Arch Pathol Lab Med* 2006; **130**: 1489-1496 [PMID: 17090190]
- 8 **Hawthornthwaite JS**, Rosen-Bronson S, Island E, Girlanda R, Guerra JF, Valdiconza C, Kishiyama K, Christensen KD, Kozlowski S, Kaufman S, Little C, Shetty K, Laurin J, Satoskar R, Kallakury B, Fishbein TM, Matsumoto CS. Successful isolated intestinal transplantation in sensitized recipients with the use of virtual crossmatching. *Am J Transplant* 2012; **12** Suppl 4: S33-S42 [PMID: 22947089 DOI: 10.1111/j.1600-6143.2012.04238.x]
- 9 **Lim WH**, Chapman JR, Wong G. Peak panel reactive antibody, cancer, graft, and patient outcomes in kidney transplant recipients. *Transplantation* 2015; **99**: 1043-1050 [PMID: 25539466 DOI: 10.1097/TP.0000000000000469]
- 10 **de Serre NP**, Canioni D, Lacaille F, Talbot C, Dion D, Brousse N, Goulet O. Evaluation of c4d deposition and circulating antibody in small bowel transplantation. *Am J Transplant* 2008; **8**: 1290-1296

- [PMID: 18444932 DOI: 10.1111/j.1600-6143.2008.02221.x]
- 11 **Dick AA**, Horslen S. Antibody-mediated rejection after intestinal transplantation. *Curr Opin Organ Transplant* 2012; **17**: 250-257 [PMID: 22476220 DOI: 10.1097/MOT.0b013e3283533847]
  - 12 **Farmer DG**, Venick RS, Colangelo J, Esmailian Y, Yersiz H, Duffy JP, Cortina GR, Artavia K, Ngo K, McDiarmid SV, Busuttil RW. Pretransplant predictors of survival after intestinal transplantation: analysis of a single-center experience of more than 100 transplants. *Transplantation* 2010; **90**: 1574-1580 [PMID: 21107306 DOI: 10.1097/TP.0b013e31820000a1]
  - 13 **Abu-Elmagd KM**, Wu G, Costa G, Lunz J, Martin L, Koritsky DA, Murase N, Irish W, Zeevi A. Preformed and de novo donor specific antibodies in visceral transplantation: long-term outcome with special reference to the liver. *Am J Transplant* 2012; **12**: 3047-3060 [PMID: 22947059 DOI: 10.1111/j.1600-6143.2012.04237.x]
  - 14 **Bond G**, Reyes J, Mazariegos G, Wu T, Schaefer N, Demetris J, Fung JJ, Starzl TE, Abu-Elmagd K. The impact of positive T-cell lymphocytotoxic crossmatch on intestinal allograft rejection and survival. *Transplant Proc* 2000; **32**: 1197-1198 [PMID: 10995904 DOI: 10.1016/S0041-1345(00)01181-7]
  - 15 **Kubal CA**, Mangus RS, Vianna RM, Lobashevsky A, Mujtaba MA, Higgins N, Beduschi T, Fridell JA, Tector AJ. Impact of positive flow cytometry crossmatch on outcomes of intestinal/multivisceral transplantation: role anti-IL-2 receptor antibody. *Transplantation* 2013; **95**: 1160-1166 [PMID: 23435456 DOI: 10.1097/TP.0b013e3182888df0]
  - 16 **Hardinger KL**, Brennan DC. Novel immunosuppressive agents in kidney transplantation. *World J Transplant* 2013; **3**: 68-77 [PMID: 24392311 DOI: 10.5500/wjt.v3.i4.68]
  - 17 **Tsai HL**, Island ER, Chang JW, Gonzalez-Pinto I, Tryphonopoulos P, Nishida S, Selvaggi G, Tekin A, Moon J, Levi D, Woodle ES, Ruiz P, Weppeler D, Lee OK, Tzakis AG. Association between donor-specific antibodies and acute rejection and resolution in small bowel and multivisceral transplantation. *Transplantation* 2011; **92**: 709-715 [PMID: 21804443 DOI: 10.1097/TP.0b013e318229f752]
  - 18 **Gerlach UA**, Lachmann N, Sawitzki B, Arsenic R, Neuhaus P, Schoenemann C, Pascher A. Clinical relevance of the de novo production of anti-HLA antibodies following intestinal and multivisceral transplantation. *Transpl Int* 2014; **27**: 280-289 [PMID: 24279605 DOI: 10.1111/tri.12250]
  - 19 **Island ER**, Gonzalez-Pinto IM, Tsai HL, Ruiz P, Tryphonopoulos P, Gonzalez ML, Solano JP, Rossique M, Selvaggi G, Tekin A, Smith LJ, Tzakis AG. Successful treatment with bortezomib of a refractory humoral rejection of the intestine after multivisceral transplantation. *Clin Transpl* 2009; 465-469 [PMID: 20524316]
  - 20 **Gondolesi G**, Blondeau B, Maurette R, Hoppenhauer L, Rodriguez-Laiz G, Schiano T, Boros P, Bromberg J, Akalin E, Sauter B. Pretransplant immunomodulation of highly sensitized small bowel transplant candidates with intravenous immune globulin. *Transplantation* 2006; **81**: 1743-1746 [PMID: 16794543 DOI: 10.1097/01.tp.0000226078.94635.76]

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