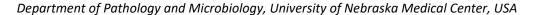# International Journal of
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ORIGINAL ARTICLE

Therapeutic Plasma Exchange in Small-Bowel Transplant Recipients

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Abstract

Introduction: Therapeutic plasma exchange (TPE) is an important adjunct therapy to reduce levels of donor-specific antibodies (DSAs) associated with antibody mediated rejection (AMR) in solid organ transplant recipients, especially kidney recipients. The purpose of this study was to examine the effect of TPE on DSAs and clinical/pathologic evidence of rejection in small bowel transplant recipients.

Methods: Six small bowel transplant recipients with elevated serum DSA levels were treated with at least 5 TPE procedures in addition to usual immunosuppressive regiments. Patients were evaluated with surveillance ileoscopies, allograft biopsies, and DSA levels. DSA presence and strength, histopathologic rejection, and clinical response are reported.

Results: All six patients in this study had class I and/or class II DSAs following small bowel transplant. After TPE, four of six patients had reductions in class I DSA levels, and five of six patients had reductions in class II DSA levels. Three of the six patients developed new DSAs during the course of treatment despite undergoing TPE. Four patients (4/6) had histopathologic evidence of acute cellular rejection (ACR) prior to TPE initiation. In two of the patients the ACR resolved prior to TPE start. The remaining patient's ACR improved during TPE, and one patient developed ACR in post TPE period.

Conclusion: In this study, TPE in small bowel transplant recipients with elevated DSAs was safe to perform. While existing DSAs tended to decrease with TPE, new DSAs also emerged.

Keywords

Antibody mediated rejection, Donor specific antibodies, Solid organ transplantation

Introduction

Over the past two decades, small bowel transplantation has become increasingly more common for the treatment of irreversible intestinal failure, with nearly 200 transplants performed annually in the United States [1]. Intestinal failure can be caused by a multitude of disease processes such as short gut syndrome or a chronic functional disease (e.g., Crohn's, refractory sprue, radiation enteritis, etc.), which renders the intestine unable to digest and absorb the nutrients necessary for survival [2].

Despite continued improvements to the medical management of small bowel transplant patients, acute cellular rejection complicates up to 50% of small bowel transplants [2]. Consequently, patients undergo routine surveillance endoscopy with allograft biopsies to evaluate for the histologic features associated with acute cellular rejection, such as increased mononuclear cell infiltrate, epithelial injury, and increased apoptosis within the intestinal crypts [3]. Oftentimes, these histologic features appear prior to the development of any clinical symptoms such as increased watery ileostomy output, abdominal pain, nausea, vomiting, diarrhea, or fever. Early recognition of acute cellular rejection allows clinicians to intervene in the rejection process before clinical manifestation by increasing the activity of anti-rejection medications.

Traditionally, the pathophysiology of acute rejection of small bowel transplants has been ascribed to

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the function and activity of T-cells within the mucosa of the transplanted organs. Recently, however, antibody mediated rejection (AMR) has been proposed as a contributing mechanism leading to acute rejection in small bowel transplant patients [4]. AMR is the result of donor-specific antibodies (DSAs) directed against human leukocyte antigen (HLA) molecules located on the surface of nucleated cells, [5] and is a well-known complication of solid organ transplantation, with DSAs developing in up to 50% of heart and kidney transplant recipients [6]. Interestingly, it has recently been shown that the development of HLA antibodies after an intestinal transplant greatly increases the risk of both acute and chronic rejection, leading to a poor prognosis for both the patient and allograft [4]. At the same time AMR, unlike ACR, does not have defined histologic criteria in small bowel transplant.

TPE has been shown by many studies to be beneficial in reducing the burden of circulating antibodies that are known to be the etiologic agent in various disease processes. TPE has been shown to be effective in reducing the number of DSAs in kidney transplant recipients which is reflected in designation of category I indication by American Society for Apheresis (ASFA) - "Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment" [7,8]. At the same time, the use of TPE in treatment of AMR of other solid organs (heart, liver, lungs) is not as effective or well-studied, earning category III indication from ASFA - "Optimum role of apheresis therapy is not established, decision making should be individualized" [8,9].

Because of the growing evidence that DSAs against donor small bowel tissue may play a significant role in rejection, we postulated that TPE may provide benefit to transplant patients by reducing levels of circulating DSAs. Here, we present our clinical experiences with six patients who received small bowel transplants, developed evidence of rejection, and were subsequently treated with TPE.

Materials and Methods

Patients

A total of six patients, (4 males, 2 females) between ages 5-41 were included in our study (Table 1). All patients received isolated small bowel or multi-visceral organ transplants (liver, small bowel, pancreas). All patients received ganciclovir and trimethoprim-sulfamethoxazole (Bactrim) for infection prophylaxis against CMV and *Pneumocystis jiroveci*, respectively. Anti-rejection protocol medications were administered to all patients post-operatively including corticosteroids (methylprednisolone, prednisone, orprednisolone), tacrolimus, and anti-thymocyte globulin. Five out of six (5/6) patients received Mycophenolate mofetil and four out of six (4/6) received Basiliximab. The decision to undergo TPE was made by the transplant surgeons upon emergence of DSAs.

Following transplant, patients were followed with surveillance ileoscopy and allograft biopsies, as well as assessment of serial serum DSA levels to assess for evidence of rejection. Once biopsies revealed histologic evidence of acute rejection and/or donor specific antibodies were identified, doses of the above-mentioned anti-rejection medications were increased, IVIG and Rituximab (5/6 patients) were introduced, and patients were offered TPE by the clinical transplant team.

Apheresis parameters

TPE was initiated between 12-58 days post-transplant and was generally scheduled to occur every other day (Table 2). All patients had vascular access through central venous catheters (3 subclavian, 1 internal jugular, 2 femoral lines). The procedure was conducted using the COBE® Spectra Apheresis System (TerumoBCT, Inc., Lakewood, CO) using standard protocols [10]. Total exchange volumes were calculated using the Nadler equation and all patients had 1 plasma volume exchange.

Table 1: Patient Demographics.

Patient	Sex	Age at transplant	Type of transplant	Indication for Transplant
1	Male	29	Liver, SB, Pancreas	Short-gut syndrome secondary to mesenteric and portal vein thrombosis with subsequent bowel necrosis
2	Male	5	Isolated SB transplant	Short-gut syndrome secondary to gastrochisis and enterocutaneous fistulas and bowel ischemia
3	Male	15	Isolated SB and partial colonic transplant	Short-gut syndrome secondary to jejunal atresia
4	Female	6	Isolated SB, followed by Liver, SB, Pancreas	Short-gut syndrome secondary to intestinal volvulus due to congenital malrotation
5	Male	41	Isolated SB, followed by Liver, SB, Pancreas	Short-gut syndrome secondary to bowel resections following trauma
6	Female	10	Isolated SB, followed by Liver, SB, Pancreas	Short-gut syndrome secondary to midgut volvulus

Table 2: Apheresis data.

Patient	# of Days post-transplant apheresis initiated	Frequency	Replacement fluid	Total # of Apheresis procedures
1	34 days	Every other day	2000 ml 5% albumin and 1500 ml plasma; 3500 ml 5% albumin	7
2*	21 days	Every other day	750 ml plasma after RBC prime	5
3	28 days	Every other day	2000 ml 5% albumin	7
4*	15 days	Variable; Daily or Every other day	500 ml 5% albumin and 500 ml plasma after RBC prime	11
5	12 days	Every other day	1000 ml 5% albumin and 2300 ml of plasma	7
6*	58 days	Every other day	1500 ml 5% albumin and 500 ml plasma	5

*: Pediatric patient.

Table 3: Pre and post apheresis donor specific antibodies.

Patient	DSAs					
	Pre TPE	Post - TPE				DSA Trend
		Days 1-14	Days 14-28	Days 28-55	Days 56-82	
1		Day 8	Day 16	Day 31		Class I -Decreased level of A2 and disappearance of A3, B57.
						Class II - Disappearance of DQA1, new weak DQ6.
	Class I:	**Class I:**	**Class I:**	**Class I:**		
	A2 (M)	A2 (W)	A2 (W)	A2 (W)		
	A3 (W)		B57 (W)			
	B57 (W)					
	Class II: DQA1*01:03 (S)	**Class II:**	**Class II:**	**Class II:**		
	DQA1*01:01 (M)	DQ6 (M)	DQ6 (M)	DQ6 (W)		
	DQA1*01:02 (M)					
	DQA1*02:01 (W)					
2		Day 6	Day 20	Day 28		Class I – Disappearance of A30, new weak CW6 and CW17.
						Class II – Disappearance of DR7, new DQ7 and DQ9.
	Class I:	**Class I:**	**Class I:**	**Class I:**		
	A30 (M)	A30 (W)	A30 (W)	CW6 (W)		
		B57 (W)	B57 (W)	CW17 (W)		
		CW6 (W)	CW6 (W)			
		CW17 (W)	CW17 (W)			
	Class II	**Class II:**	**Class II:**	**Class II:**		
	DR7 (M)	DR7 (W)	DR7 (W)	DQ7 (M)		
		DQ7 (S)	DQ7 (S)	DQ9 (M)		
		DQ9 (M)	DQ9 (M)			

3	**Class I:** B58 (M) **Class II:** DQ2(S) DQA1*05 (S)	**Day 5** **Class I:** B58 (W) **Class II:** DQ2(M) DQA1*05 (M)		**Day 40** **Class I:** No DSA **Class II:** No DSA	**Day 71** **Class I:** No DSA **Class II:** No DSA	Class I – Disappearance of B58. Class II – Disappearance of DQ2 and DQA1*05.
4	**Class I:** A2 (S) A68 (M) B57 (L) CW8 (L) **Class II**: No DSAs	**Day 7** **Class I:** A2 (S) A68 (L) B57 (M) CW8 (L) **Class II:** DR53 (L) DQ2 (VL)	**Day 15** **Class I:** A2 (M) A68 (L) B57 (L) CW8 (L) **Class II:** DQ2 (L)	**Day 30** **Class I:** A2 (M) A68 (L) B57 (VL) **Class II:** DQ2 (L)		Class I – Decreased levels of A2, A68, B57. Disappearance of CW8. Class II - New DQ2 and DR53. DR53 disappeared on follow up.
5	**Class I:** A2 (S) B8 (L) **Class II**: DR53 (S) DQ8 (S) DR4 (S) DQ2 (M)	**Day 1** **Class I:** A2 (S) B8 (L) **Class II:** DR53 (S) DQ8 (S) DR4 (S) DQ2 (M)				Class I – No change. Class II – No change.

6		Day 8	Day 16	Day 42	Day 80	Class I - Not applicable.
	Class I:	**Class I:**	**Class I:**	**Class I:**	**Class I:**	Class II - Decrease in level of DPB1˚04:02. Disappearance of DR52 and DR13.
	No DSAs	No DSAs	No DSAs	No DSAs	No DSAs	
	Class II:	**Class II:**	**Class II:**	**Class II:**	**Class II:**	
	DQ7 (S)	DQ7 (S)	DQ7 (S)	DQ7 (S)	DQ7 (S)	
	DR13 (S)	DR13 (W)	DR13 (W)	DR13 (W)	DPB1˚04:02 (W)	
	DR52 (M)	DPB1˚04:02 (W)		DPB1˚04:02 (W)		
	DPB1˚04:02 (M)					

Green: Pre-apheresis; Day 8 - days post last TPE day; See Materials and Methods for antibody strength abbreviations.

The replacement fluid consisted of either all plasma or a combination of 5% albumin and plasma, except one patient where replacement fluid was all 5% albumin. Patients that had endoscopic biopsies taken within 48 hours of initiation of TPE were provided replacement fluid consisting of 100% plasma as these patients were at increased risk of bleeding. For extracorporeal anticoagulation during the procedure, anticoagulant citrate dextrose solution formula A (ACD-A) was used at an anticoagulant to whole blood ratio of 1:12. All patients received prophylactic IV calcium gluconate (1-2 grams) during the procedure as prophylaxis against citrate toxicity. One unit of cross-matched red cells was used for priming the apheresis machine prior to exchange in two of three pediatric patients, weighing less than 20 kg.

DSAs

Initial donor specific antibody levels were drawn between 1 and 18 days of transplant. The strength of Class I and Class II HLA donor specific antibodies was determined by Luminex® LabScreen® single antigen bead assay (One Lambda, Thermo Fisher Scientific) and categorized according to the mean florescence intensity (MFI) with the following reference ranges: very Low = 500-999 (VL), low = 1,000- 4,999 (L), moderate = 5,000-9,999 (M), and strong = >10,000 (S). During the study, new MFI reference ranges were used to classify DSA strength (weak = 1,000 - 4,999 (W), moderate = 5,000-9,999 (M), and strong >10,000 (S)) as background interference was high in the range below 1,000 MFI. Donor specific antibody levels were compared before and after the initiation of TPE (Table 3). The post TPE results are dated from the last day of TPE and presented in 4 time frames: Days 1-13, 14-27, 28-55 and days 56-82 after the last day of TPE. If multiple results were present in the time frame, the result with the highest number of DSA was selected.

Small Bowel Allograft Biopsies

Biopsies of the proximal and distal small bowel allograft were collected on a weekly or bi-weekly basis, with more frequent ileoscopy and biopsies during times of clinical concern. The biopsies were collected and fixed in 10% buffered formalin prior to embedding in paraffin wax. Slides were prepared using standard techniques. Two hematoxylin and eosin stained slides were prepared from each biopsy with 2-3 serial sections per slide. Biopsies were examined by gastrointestinal/transplant pathologists and evaluated for histologic evidence of acute rejection according to the International Grading Scheme for acute cellular rejection (Table 4) [3,11]. Biopsy results were collated in four time frames after the last day of TPE (days 1-13, 14-27, 28-55 and days 56-82) with most representative/informative result displayed from each timeframe, if multiple biopsies have been performed.

Results

To determine potential benefits of TPE toward mitigating small bowel transplant rejection, we examined three different parameters in the post-apheresis period: 1) DSA presence and strength; 2) Histopathologic findings in allograft biopsies; 3) Clinical response.

All six patients included in this series had Class I and/or Class II donor specific antibodies following transplant. In 5 out of 6 patients, existing DSAs either disappeared or had levels that were reduced following TPE (Table 2). One patient had complete resolution of DSAs. Three of the six patients developed new DSAs despite being treated with TPE. In 2 of the patients with new DSAs, the new antibodies were weak, while in one (#2) they were of strong and moderate strength. Overall, there was a trend in existing DSA strength decrease and disappearance, more pronounced in the third time period after TPE (days 28-55).

Table 4: Post-Transplant small bowel allograft biopsies for assessment of cellular rejection.

	Pre TPE		Post TPE Days 1-13		Post TPE Days 14-27		Post TPE Days 28-55		Post TPE Days 56-82	
	Prox	Distal	Prox	Distal	Prox	Distal	Prox	Distal	Prox	Distal
1	N	MS	N	U	N	U	U	N	N	U
2	Md	Md	N	N	N	N	N	N	n/a	n/a
3	MS	MS	N	U	N	N	N	N	MS	MS
4	MI	I	MI	N	N	N	N	N	N	N
5	N	U	N	MI	I	U	N	N	N	N
6	MI	I	N	N	N	N	N	N	MI	N

Green: Pre-apheresis (most recent evaluable biopsy); n/a: Not applicable (biopsy not taken); N: Negative for ACR; I: Indeterminate for ACR; MI: Mild ACR; Md: Moderate ACR; MS: moderate-severe ACR; U: Unable to evaluate.

Small bowel biopsies were taken during scheduled surveillance endoscopy or when a positive DSA result was obtained (Table 4). All of the patients got a biopsy at least a week after TPE with the majority having follow up biopsies for 4 or more weeks post procedure. The justification for this follow up schedule is based on experience and literature findings that the changes in response to treatment of ACR appear a week after the treatment has started, with complete resolution in 3 weeks if successful [12]. Biopsy results were collated into four time frames post TPE: Days 1-13, 14-27, 28-56 and 57-82 (0-2, 2-4, 4-8 and 8-12 weeks respectively) Five patients (#1, #2, #3, #4, #6) had biopsies that were diagnostic for varying degrees of ACR prior to the start of TPE. One patient (#5) did not develop ACRuntil the post-apheresis period. Four patients (#1, #2,#3,#6) who had histologic evidence of rejection prior to TPE had a histologic resolution of findings during or in the first 2 weeks after TPE. The remaining 2 patients had resolution of histological findings later (including patient #5 with first histologically confirmed rejection signs in post TPE period). Interestingly, some patients did develop recurrence of histologic findings later on between the weeks 8 and 12.

Only 1/6 patients displayed clinical signs and symptoms of acute rejection (increased watery ostomy output, bloating, and abdominal pain) prior to the laboratory diagnosis of acute rejection being made. These symptoms persisted and were present after completion of the scheduled apheresis procedures. While the majority of patients was being examined in the study did not have objective clinical signs of rejection (watery ileostomy output or fever), it was difficult to obtain information regarding possible subjective symptoms such as nausea and pain, as some patients were intubated and sedated.

Discussion

Acute rejection in small bowel transplant patients is likely caused by a combination of both antibody-mediated and T-cell mediated processes. The management of suspected acute rejection in intestinal transplant patients is complex, and a number of factors may contribute to the efficacy of treatment of acute antibody mediated and/or cellular rejection. Currently, small bowel transplant patients are managed using a variety of medical approaches, principally through the use of immuno-modulatory agents (e.g. thymoglobulin, IVIG, rituximab, corticosteroids). While some of the mechanisms mediating small bowel transplant rejection suggest that donor specific antibodies may contribute to clinical symptoms, the role of TPE has not been established within this patient population. The use of plasmapheresis in small bowel transplant rejection has been described in 2 case reports, suggesting that a combination of TPE with bortezomib had variable success (1 patient had induction of tolerance, while other needed additional intervention) [13,14]. Interestingly, plasmapheresis in the setting of small intestine transplant has been tried for management of AIHA due to new red cell autoantibody formation and management of passenger lymphocyte syndrome [15,16]. Two studies coming from Germany and France retrospectively evaluated the significance of DSAs post-intestinal transplantation [17,18]. In the first study, Gerlach UA, et al. found 10 patients among a larger rejection cohort that had evidence of AMR. The investigators used a treatment protocol that included steroids, rituximab, plasmapheresis and IVIG and were successful in eliminating DSA sin 8 of 10 patients with one extra patient having no evidence of impaired graft function despite presence of DSAs. Unfortunately the strength of the antibodies was not discussed in the paper. Despite similarities in immunosuppression protocol and overall outcomes, there are differences in the DSA persistence between our findings and in the study by Gerlach, et al. Despite an overall similar trend in existing DSA reduction with TPE, we completely eliminated DSA only in only 1 out of 6 patients. In the second study by Petit LM, et al., TPE was a part of initial treatment for the AMR alongside with steroids and IVIG, which was followed by rescue treatment including ATG, rituximab, ecolizumab, infliximab and boretezomib. Due to differences in algorithm, it is hard to compare the outcomes

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and assess the impact of TPE. Confounding results is that a cohort of the patients (n = 10) had DSAs, but lacked clinical symptoms. Also, all the patients who had clinical symptoms had evidence of ACR alongside with AMR, which is more reflective to our cohort. The Petit, et al., did not specifically evaluate the effectiveness of the plasmapheresis in this cohort, focusing more on the clinical outcomes.

Our study examined the potential impact of performing TPE in patients that demonstrated both histologic evidence of acute rejection and elevated DSAs. For a majority of TPE procedures, plasma was used as the replacement fluid in majority of the patients out of concern of hemorrhagic complications of acute rejection of the small intestine or from the bleeding risk associated with frequent endoscopic biopsies of the allograft. Overall, there were no TPE-related complications during the 42 procedures and we conclude that performing TPE in small bowel transplant patients is safe.

In 5 out 6 patients we observed the tendency in existing DSAs to disappear or decrease in strength. Patient #5 who did not have change in DSA strength of number, unfortunately, had only 1 measurement of DSA levels immediately after TPE. As highlighted by patients #3 and #4, reductions in DSA levels can take more than 2 weeks to occur, so it is unknown whether patient #5 received any DSA level benefit. Unfortunately, half the patients in this series developed new DSAs during rejection treatment that included TPE. The new DSAs tended to be weak in strength.

Interpretation of histologic evidence of rejection and possible influence of TPE on resolution of histologic factors was examined with TPE. In 5 patients who had histologic evidence of ACR prior TPE, the ACR resolved by week 4 post TPE. In the remaining patient whose biopsy didn't have enough crypts to be evaluated for rejection before TPE, did have a biopsy with mild rejection in the first 2 week post TPE, but ACR in this patient also resolved by day 28 post TPE. This timeline of resolution of ACR post TPE is similar to the previously published experience [12]. At the same time, TPE is only part of the protocol and in the absence of clinical studies it is impossible to evaluate the individual input of TPE on ACR resolution.

Conclusions

The six patients in the series along with the two previous case reports evaluating the role of TPE in the setting of small bowel transplantation are too small to draw clear conclusions. In addition, individualized changes in immunosuppressive regimens in addition to TPE make studying this population difficult. Overall, TPE likely had an effect to reduce existing DSA antibody levels in 5 out of 6 patients. Small bowel transplant recipients undergoing TPE had ACR resolution in all 6 patients 28 days after conclusion of TPE. Due to limitations of this study

and the current case reports, definitive conclusions cannot be made, and performing TPE in small bowel transplant patients with elevated DSAs should be considered as ASFA category III - optimum role for apheresis therapy is not established and decision to perform apheresis should be individualized.

Conflict of Interest

Funding

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