ISSN 2515-8260 Volume 09, Issue 02, 2022

Therapeutic plasmapheresis in kidney transplant patients: 30 years experience

[1]Suhas Bavikar, [2]Ajay Oswal, [3]Swarnalata Gourishankar, [4]Purva Bavikar

[1]Associate Professor, Department of General Medicine, IIMSR Medical College, Badnapur, Jalna, Maharashtra, India
[2]Consultant Urologist, Seth Nandlal Dhoot Hospital, Aurangabad, Maharashtra, India
[3]Professor, Head, Department of Pathology, Apollo Hospital, Hyderabad, Telangana, India
[4]Consultant Nephrologist, Safe Hospital, Hyderabad, Telangana, India

Corresponding Author:
Dr. Suhas Bavikar (drbavikar@yahoo.com)

Abstract

This retrospective observational study illustrates 30 years of experience of Therapeutic Plasma Exchange in 35 cases out of 1210 kidney transplantations performed between 1990 till 2020. Total 11 patients underwent Plex before undergoing kidney transplantation whereas 24 patients underwent Plex post kidney transplantation. Pre-transplant therapeutic plasma exchange was done in 5 Human Leukocyte Antigen incompatible, 5 ABO incompatible kidney transplant prospects and 1 prospective recipient with monoclonal gammopathy of renal significance. Whereas 15 kidney transplant recipients (Kidney Transplant Recipients) with antibody mediated rejection, 6 Kidney Transplant Recipients with thrombotic microangiopathy, 1 with myeloma cast nephropathy, 1 recurrence of Focal Segmental Glomerulosclerosis post transplantation & 1 Anti-Glomerular Basement Membrane antibody positive Kidney Transplant Recipient underwent Plex. The clinical end point after Plex exchange was achieved in 23 patients, 6 patients had a partial response. There was no response after Plex done for Kidney Transplant Recipient with Anti-Glomerular Basement Membrane antibody positive transplant glomerulopathy who subsequently progressed to requiring maintenance dialysis. One patient undergoing Human Leukocyte Antigen incompatible kidney transplant developed hyper acute rejection & had to undergo graft nephrectomy and another case with myeloma light chain cast nephropathy could not be salvaged. Pre-transplant Therapeutic Plasma Exchange used for desensitization of ABO incompatible & Human Leukocyte Antigen incompatible kidney transplants has benefitted 9 out of 10 patients in our study. Patient with end stage renal disease due to monoclonal gammopathy of renal significance was ultimately able to undergo kidney transplantation due to complete response after Therapeutic Plasma Exchange. Notably, we observed partial response for stabilizing chronic Antibody Mediated Rejection and late acute Antibody Mediated Rejection. Pathogenic entities like anti-endothelial cell antibody, thrombotic microangiopathy causing graft dysfunction can be successfully managed by Therapeutic Plasma Exchange. Therapeutic Plasma Exchange for the treatment of recurrence of Focal Segmental Glomerulosclerosis (focal segmental glomerulosclerosis) after kidney transplant has shown a partial response in terms of reduction in proteinuria.

Keywords: Therapeutic plasmapheresis, kidney transplant, human leukocyte antigen, ABO Blood type incompatible kidney transplantation

ISSN 2515-8260 Volume 09, Issue 02, 2022

Introduction

Therapeutic plasma exchange (Therapeutic Plasma Exchange) is an indispensable modality deployed to eliminate high molecular weight substances from plasma. Therapeutic plasma exchange (Therapeutic Plasma Exchange) is an extra-corporeal therapy for removal of a single or allied group of high molecular weight substances, greater than 15,000 Daltons. Therapeutic Plasma Exchange is being successfully deployed in the field of nephrology, since its introduction in 1952 [1]. Therapeutic Plasma Exchange works on the principle of removal of substances based on their relative distribution in extravascular and intravascular compartments, their inter-compartment transfer & regeneration rates, plasma half-life and volume of plasma removed [2]. There is paucity of evidence regarding the efficacy of Therapeutic Plasma Exchange given the varying frequency, dosing, modalities and financial burden. Removal of culprit immunoglobulins, antibodies, immune complexes through plasmapheresis, helps reduce the immunological burden, thus preventing graft dysfunction. Our study focuses on a retrospective analysis of 1210 kidney transplant cases of which 35 patients underwent Therapeutic Plasma Exchange for various indications. It focuses on the following indications for plasma exchange based on 2019 guidelines from ASFA (American Society for Apheresis)

1. Human Leukocyte Antigen incompatible kidney transplant.
2. ABO incompatible kidney transplant.
3. Myeloma light chain cast nephropathy & monoclonal gammopathy of renal significance,
4. Antibody mediated rejection.
5. Anti-Glomerular Basement Membrane antibody disease.
6. Recurrent Focal Segmental Glomerulosclerosis.
7. Thrombotic microangiopathy.

We employed single membrane separation for plasma exchange in all our patients. Along with Therapeutic Plasma Exchange, our patients also received appropriate immunosuppression as indicated. Despite of several advantages of Therapeutic Plasma Exchange like reduction in pathogenic immunological burden, improving endogenous clearance, supporting immune system to alleviate graft dysfunction, the procedure is cumbersome with variable tolerance, clinical response, dosing, frequency, and additional financial burden. Here we describe clinical outcomes and problems faced while providing Therapeutic Plasma Exchange to patients undergoing kidney transplant.

Material & Methods

This is a retrospective observational analysis of 1210 kidney transplants done under the care of single kidney transplantation unit consisting of a nephrologist and urologist at a tertiary care center in Aurangabad, Maharashtra along with the support of a pathologist from Hyderabad, Telangana, India. Of the 1210 kidney transplants performed between 1990 till 2020, 35 patients had undergone therapeutic plasmapheresis. Transplantation was done after completing medico-legal formalities. Pre-transplant donor-recipient work up of all patients was coherent with 2004 Amsterdam Forum guidelines [3] and 2009-KDIGO guidelines for transplantation [4]. After seeking ethical approval, patient data was obtained from hospital records.

Desensitization protocol used for Human Leukocyte Antigen & ABO incompatible kidney transplant, employed at our centre was as follows: Administration of intra-venous (IV) Anti-CD-20 Antibody (1000 mg) 3 weeks prior to kidney transplantation. Administration of 3 doses of IV Inj. Bortezomib (2 mg). 1st dose given 3 weeks prior (along with Anti-CD-20 Antibody) to kidney transplantation, subsequent doses given at an interval of 1 week each. 5

ISSN 2515-8260 Volume 09, Issue 02, 2022

sessions of alternate-day therapeutic plasma exchange started 2 weeks prior to the day of surgery. Lymphocyte cross match by (CDC + DSA) done after 4th session of Therapeutic Plasma Exchange. Alternate-day maintenance hemodialysis sessions were continued and done between 2 Therapeutic Plasma Exchange sessions. Administration of IVIg (100 grams) along with Injection Rituximab (1000mg) were given after the 5th session of Therapeutic Plasma Exchange, done 48 hours prior to kidney transplantation.

This protocol was subject to modification as per patient's clinical status and response to therapy. The cost of all Therapeutic Plasma Exchange sessions was incurred by the patient undergoing kidney transplantation. As of 2022, the approximate cost of undergoing one session of therapeutic plasma-exchange in India, is around 30,000-50,000 Indian Rupees (~$ 350-650 USD), which includes cost of consumables (Plasma filter, blood tubing, syringes, replacement fluid, etc), procedure and hospital fee. Therapeutic Plasma Exchange dosing, frequency used for other indications was variable depending on mainly clinical indication, feasibility and financial burden. Each patient underwent single membrane filtration on Fresenius 4008H hemodialysis machine. A new plasma filter was used for each session. 30-40 ml per kg plasma volume per session was replaced with fresh frozen plasma, Hemaccel, Ringer's lactate, 5% & 20% human albumin along with appropriate immunosuppression.

Primary end points of Therapeutic Plasma Exchange done for above mentioned indication varied before and after transplant and were as follows: Serial monitoring of DSA (donor specific antibodies) was done pre-transplant. Notably, CDC (complement dependent cytotoxicity) cross match was the only test available in Aurangabad until 2010. DSA was introduced in 2010. T & B cell flow-cytometry cross match is available since 2013-14 and single bead antigen assay is available since 2017-18. Thus, with the advances in immunological testing and their availability in Aurangabad, testing modalities differed.

ABO incompatible (ABOi) kidney transplant (KT): Therapeutic Plasma Exchange was done pre-transplant for all ABO blood type incompatible kidney transplantation. Anti-blood type IgG antibody titres were checked. Transplant was done after achieving a Anti-blood type IgG Antibody titre of 1:4.

Patient with end stage renal disease secondary to monoclonal gammopathy of renal significance was eligible for kidney transplant after Therapeutic Plasma Exchange. Serial monitoring of serum free light chains was done before and after Therapeutic Plasma Exchange. While patient diagnosed with myeloma light chain cast nephropathy post kidney transplant underwent Therapeutic Plasma Exchange for hyper-viscosity syndrome. Post-transpant, antibody mediated rejection (Antibody Mediated Rejection) was diagnosed based on allograft biopsy-histopathology, positive C4d staining and positive donor specific antibodies. For the ease of understanding, Antibody Mediated Rejection occurring immediately post-transplant upto 1 month were grouped as early-acute, Antibody Mediated Rejection occurring 1 month to 1 year post-transplant was termed late-acute & Antibody Mediated Rejection after 1 year post transplantation was grouped as chronic Antibody Mediated Rejection.

Reduction in serum creatinine/proteinuria, improvement in graft function were measured after Therapeutic Plasma Exchange, for cases with Anti-Glomerular Basement Membrane antibody disease and recurrence of Focal Segmental Glomerulosclerosis. Anti-Glomerular Basement Membrane antibodies were also monitored for the former entity. Improvement in platelet count and clinical status of patient with TMA was used as primary response to Therapeutic Plasma Exchange. Apart from the above mentioned investigations, patients also underwent timely allograft biopsy, hemogram, urine protein creatinine ratio, ultrasonography, graft vessel Doppler when needed. 1 patient underwent Anti-complement factor H antibody & C3 nephritic factor testing. A case based approach for ordering investigations was mandatory. Allograft biopsy samples were processed namely for light microscopy and immunofluorescence, done at tertiary care centre in Hyderabad, Telangana.

ISSN 2515-8260 Volume 09, Issue 02, 2022

Data was compiled and analysed on MS Office Excel Sheet (v 2019, Microsoft Redmond Campus, Redmond, Washington, United States).

Results

Total 1210 kidney transplants done by our team at Aurangabad, between 1990 till 2020 were screened for need for Therapeutic Plasma Exchange around transplantation period. 2.89% (N=35) of kidney transplant patients underwent Therapeutic Plasma Exchange in our study population. Of these, 29 were male & 6 were female. The mean age of study population was 36 years, youngest being 13 years and eldest patient being 58 years old. Allograft biopsy was done in 29 cases. 11 patients underwent Therapeutic Plasma Exchange prior to kidney transplant as a part of desensitization protocol while the remaining 24 patients underwent Therapeutic Plasma Exchange post kidney transplantation. Our case series of 35 patients included 32 live-donor and 3 deceased-donor kidney transplant recipients who underwent Therapeutic Plasma Exchange. In this study 4 patients were 2nd kidney transplant recipients.

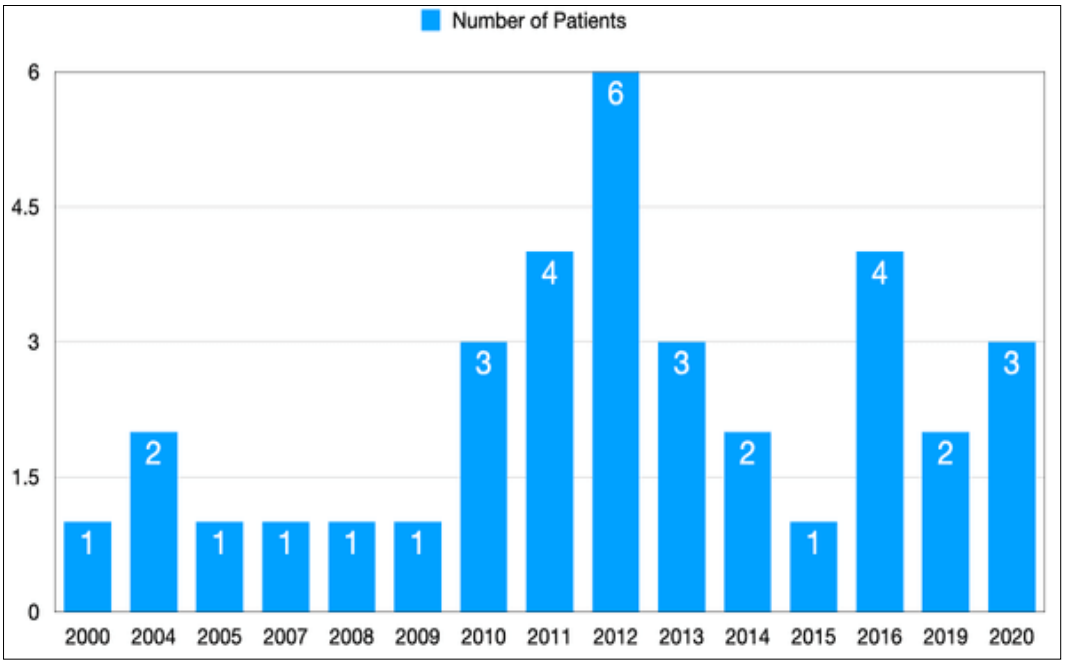

Fig 1: Year-wise distribution of kidney transplants requiring Therapeutic Plasma Exchange

Of the 1210 kidney transplantations done from 1990 until 2020, Therapeutic Plasma Exchange was employed in 35 cases. The above bar diagram illustrates year-wise distribution of these 35 patients. 6 kidney transplants recipients from 2012, 4 each from 2011 and 2016 respectively, 3 each from 2010, 2013, 2020 respectively, followed by 2 each from 2004, 2014, 2019 and 1 Kidney Transplant Recipient each from transplants done in 2000, 2005, 2007-2009 and 2015 respectively underwent Therapeutic Plasma Exchange as seen in Figure 1. On an average 4.88 sessions of plasma exchange were done per patient, 5 patients underwent 3 sessions of Therapeutic Plasma Exchange, another 5 underwent 5 sessions of Therapeutic Plasma Exchange, 1 patient required 9 sessions while 13 patients underwent 6 sessions of Therapeutic Plasma Exchange for respective indications. No patient developed life-threatening complications during or after Therapeutic Plasma Exchange.

ISSN 2515-8260 Volume 09, Issue 02, 2022

Table 1: Clinical outcomes of Therapeutic Plasma Exchange along with their respective indications

Indication of Therapeutic Plasma Exchange	Number of Patients	Desired clinical response post Therapeutic Plasma Exchange achieved in (no.)
Desensitisation for Human Leukocyte Antigen Incompatible Kidney Transplantation	5	4/5
Desensitisation for ABO blood type incompatible kidney transplantation	5	5/5
Hyper-viscosity syndrome in myeloma of renal significance	2	1/2
Antibody mediated rejection (Antibody Mediated Rejection)*	15	8/15 + 5/15 (partial) + 2/15 (no response)
Post-transplant Thrombotic microangiopathy	6	5/6
Post-transplant recurrence of Focal Segmental Glomerulosclerosis	1	Partial response
Anti-Glomerular Basement Membrane Antibody positive transplant glomerulopathy	1	No response

As Table 1 describes various indications of Therapeutic Plasma Exchange in our case series and response to therapy (Therapeutic Plasma Exchange). Clinical response of Therapeutic Plasma Exchange done for patients having antibody mediated rejection is illustrated in figure 2. 11 patients underwent pre-transplant Therapeutic Plasma Exchange, whilst 24 Kidney Transplant Recipients underwent Therapeutic Plasma Exchange post-transplant. However desired clinical response was achieved in 23 cases, 6 Kidney Transplant Recipients showed partial-response whereas 6 cases did not benefit with therapeutic plasma exchange.

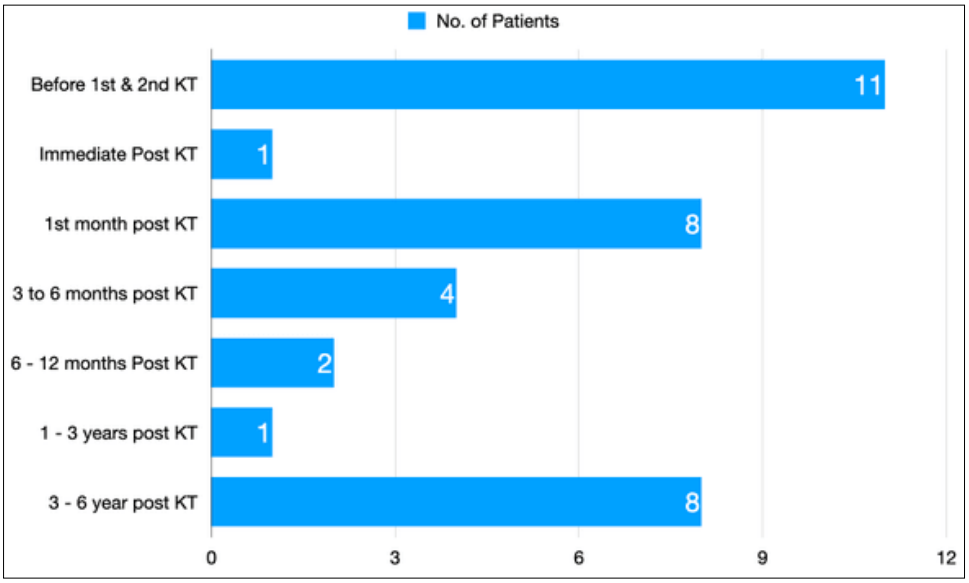

Fig 2: Timeline of Therapeutic Plasma Exchange done in study population

Pre-transplant Therapeutic Plasma Exchange was done in 5 patients each, as a part of desensitization protocol in HLAi & ABO blood type incompatible kidney transplantation, whilst 1 case of hyper viscosity syndrome in MGRS was made eligible for kidney transplantation after Therapeutic Plasma Exchange. Figure 2 describes the timeline of Therapeutic Plasma Exchange done in our study population. Majority of Therapeutic Plasma Exchange (N=8) in the post-transplant period were done in the 1st month and after 3 to 6 years of kidney transplantation. Therapeutic Plasma Exchange benefited 100% (n=5) ABOi kidney transplant prospects as evident by reduction in Anti-blood type antibody titers, whilst it benefited 80% (n=4) of KT prospects undergoing HLAi transplantation.

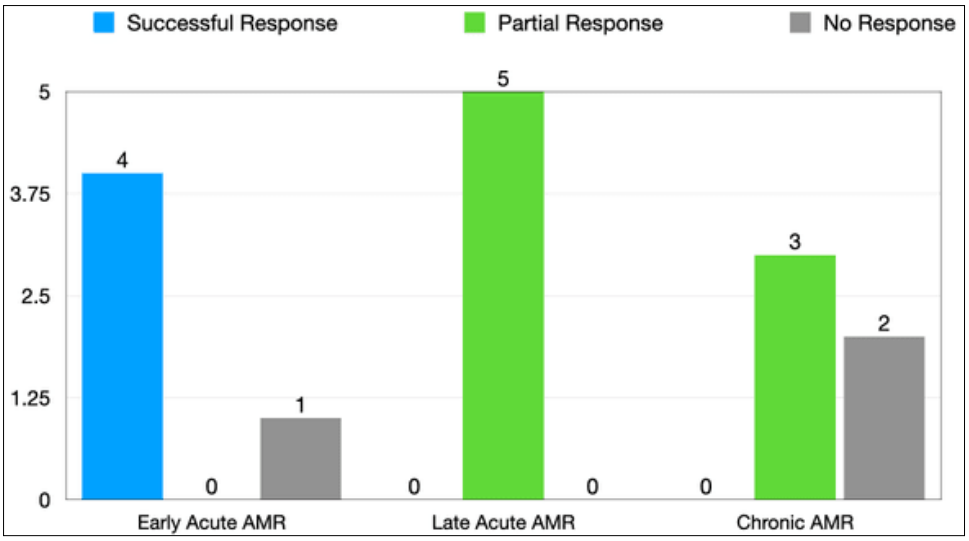

Fig 3: Bar diagram illustrating response to Therapeutic Plasma Exchange in antibody mediated rejection

As Figure 3 describes appropriate immunosuppressive agents along with Therapeutic Plasma Exchange was deployed for 15 Kidney Transplant Recipients with antibody mediated response. Antibody mediated rejection was categorized into early-acute (N=5), late-acute (N=5) and chronic (N=5) based on the timeline of detection, as described in methodology. Desired clinical response was achieved in 4 cases with early acute Antibody Mediated Rejection. Partial response was achieved in late-acute Antibody Mediated Rejection and 3 cases with chronic Antibody Mediated Rejection. However Therapeutic Plasma Exchange was of no benefit to 2 chronic Antibody Mediated Rejection patients & 1 patient categorized as early-acute Antibody Mediated Rejection developed on-table hyper acute rejection and could not be salvaged despite of Therapeutic Plasma Exchange. Therapeutic Plasma Exchange was done in 19 DSA (donor specific antibody) positive and 5 DSA negative kidney transplant patients, the remaining 11 underwent Therapeutic Plasma Exchange for non-DSA related indications. Amongst the 19 DSA positive patients, 4 DSA positive patients were desensitized pre-transplant, while 15 underwent post-transplant Therapeutic Plasma Exchange for DSA positive Antibody Mediated Rejection.

Discussion

Our study is a retrospective observation study in which 1210 kidney transplants done between 1990 till 2020 at a tertiary care center in Aurangabad, Maharashtra, India, were screened for undergoing therapeutic plasma-exchange. 35 cases were found to have undergone Therapeutic Plasma Exchange either as a part of desensitization protocol prior to undergoing kidney transplant or as part of treatment protocol for antibody mediated rejection, thrombotic microangiopathy, post-transplant recurrence of Focal Segmental Glomerulosclerosis, Anti-Glomerular Basement Membrane antibody disease in primary alport's syndrome, hyper-viscosity syndrome in MGRS.

Therapeutic Plasma Exchange was employed when indicated for kidney transplants done in 2000-2020, in our study. Majority of our knowledge regarding the role of Therapeutic Plasma Exchange in respective clinical indications comes from case series. Despite of weak evidence regarding its efficacy, expert consensus at FDA Antibody mediated Rejection workshop in 2017 & KDIGO 2010 regarded Plex & IVIg as a standard of care for Antibody Mediated Rejection [5]. Montogomery, *et al.* studied 7 live-donor kidney transplant recipients who developed acute humoral rejection and were successfully treated with Therapeutic Plasma Exchange/IVIg for removal of antibody specific for donor Human Leukocyte Antigen

ISSN 2515-8260 Volume 09, Issue 02, 2022

antigens [6]. Out of the 15 cases who developed antibody mediated rejection, in our study, 3 were deceased-donor and 12 were live-donor kidney transplant recipients. Hyperacute graft rejection occurred in 1 such deceased-donor Kidney Transplant Recipient requiring graft nephrectomy. The Therapeutic Plasma Exchange/IVIg regimen proved beneficial as it reversed graft dysfunction in 4 of 5 patients with early acute Antibody Mediated Rejection. Partial improvement in graft dysfunction was seen in 5 patients with late acute Antibody Mediated Rejection and 3 chronic Antibody Mediated Rejection after receiving Therapeutic Plasma Exchange/IVIg. Non-responders progressed to graft dysfunction requiring dialysis. Hence our data supports the role of Therapeutic Plasma Exchange/IVIg to treat early antibody mediated rejection vs late and chronic antibody mediated rejection. With the advent of variations in Therapeutic Plasma Exchange like cascade plasmapheresis, immunoadsorption, previous contraindications of kidney transplantation (HLAi, ABOi), are now being performed with ease. We employed single filtration Therapeutic Plasma Exchange to desensitise 5 HLAi and 5 ABOi patients. 100% success rate was achieved when Therapeutic Plasma Exchange was used for reducing anti-blood type antibody titres to desired cut-off levels, in our case 1:4 and 1 year graft survival was 80%.

An end stage renal disease patient with MGRS and a high titre of kappa light chains (> 300 - 2000 ng/ml) could successfully undergo kidney transplantation after receiving therapeutic plasma exchange. Czarnecki PG *et al.* determined the outcome of 12 patients with fibrillary glomerulonephritis who successfully underwent kidney transplantation without any evidence of recurrence [7]. Our experience was similar to Karthikeyan *et al.* [8] supporting Therapeutic Plasma Exchange to be beneficial for post-transplant thrombotic microangiopathy. 3-4 sessions were prescribed for treating these cases. 80% (4/5) patients recovered, however 1 patient underwent graft nephrectomy due to absence of blood-flow to allograft evident on 5th day post-transplant. The role of therapeutic plasma exchange to manage recurrence of Focal Segmental Glomerulosclerosis post-transplant has been extensively studied in children [9-11]. We treated a patient who developed with massive proteinuria 1 month post transplantation. It was a live-related donor kidney transplant recipient who was diagnosed to have Focal Segmental Glomerulosclerosis on allograft biopsy and normal serum creatinine.

This case was treated with 9 sessions of plasma exchange done over 30 days, resulting in partial reduction in proteinuria from 6.2 gm/day to 1.8 gm/day with progression to end stage renal disease over 2 years (Creatinine rose from 1.2 to 10mg/dL).

An unusual case of myeloma cast nephropathy (detected one month post-transplant on allograft biopsy (fractured casts), was treated with Therapeutic Plasma Exchange and bortezomib post-transplant in 2013. Pre-transplant native kidney biopsy was suggestive of chronic interstitial nephritis without any clinical evidence to suspect myeloma. Therapeutic Plasma Exchange proved to be of no role in treating myeloma cast nephropathy. Patient ultimately progressed to ESRD within 3 months. Consensus statement of International Myeloma Working Group (IMWG) in 2010 acknowledged "The role of plasma exchange in patients with suspected light chain cast nephropathy and renal impairment is controversial" [12]. A case of Alport's syndrome who underwent 2nd unrelated-live donor kidney transplant developed anti-glomerular basement membrane antibody disease. Our attempt to manage this case with Therapeutic Plasma Exchange proved unsuccessful with persistence of graft injury. Despite of growing advances in the field of transplantation, therapeutic plasma exchange remains to be a fundamental modality of treatment owing to it's principle of reducing circulating high molecular weight substances.

Limitations

The indications of Therapeutic Plasma Exchange in kidney transplant patients in our study are splayed. A meta-analysis of clinical outcomes of specific indications for Therapeutic

Plasma Exchange in kidney transplant patients would be more useful in devising treatment protocols.

Conclusion

Therapeutic Plasma Exchange along with immunosuppression can be used successfully for pre-transplant conditioning of ABOi and HLAi kidney transplants. It would be premature to conclude therapeutic role of plasma exchange in managing pre-transplant monoclonal gammopathy of renal significance and post-transplant Anti-Glomerular Basement Membrane antibody disease, owing to the paucity of cases included in the study. Therapeutic Plasma Exchange undoubtedly helps in reduction of donor specific antibodies implied in early antibody mediated rejection. However Therapeutic Plasma Exchange when employed to treat late-acute Antibody Mediated Rejection and chronic Antibody Mediated Rejection provided a sub-optimal clinical response in our study. The role of Therapeutic Plasma Exchange to treat post-transplant thrombotic microangiopathy has been pivotal. Nonetheless, Therapeutic Plasma Exchange may be considered as an adjunct to immunosuppression in the management of graft dysfunction, when indicated.

References

1. Tiwari AK, *et al.* Changing trends in therapeutic plasmapheresis: An Indian perspective. Ther Apher Dial. 2017;21:500-06.
2. Reeves HM, Winters JL. The mechanisms of action of plasma exchange. Br J Haematol. 2014;164:342-51.
3. The Ethics Committee of the Transplantation Society the Consensus Statement of the Amsterdam Forum on the Care of the Live Kidney Donor, Transplantation. 2004;78(4):491-92.
4. Kidney Disease: Improving Global Outcomes (KDIGO) Transplant Work Group. KDIGO clinical practice guideline for the care of kidney transplant recipients. American Journal of Transplantation. 2009;9(3):S1-S157.
5. Schinstock, Carrie A, *et al.* Recommended Treatment for Antibody-mediated Rejection after Kidney Transplantation: The 2019 Expert Consensus From the Transplantation Society Working Group, Transplantation. 2020;104(5):911-22.
6. Montgomery RA. Plasmapheresis and intravenous immune globulin provides effective rescue therapy for refractory humoral rejection and allows kidneys to be successfully transplanted into cross-match-positive recipients. Transplantation. 2000;70(6):887-89.
7. Czarnecki PG. Long-term outcome of kidney transplantation in patients with fibrillary glomerulonephritis or monoclonal gammopathy with fibrillary deposit- Kidney Int. 2009;75(4):420-22.
8. Vanji Karthikeyan. Outcome of Plasma Exchange Therapy in Thrombotic Microangiopathy after Renal Transplantation, American Journal of Transplantation. 2013;10:614-17.
9. Kashgary A, *et al.* The role of plasma exchange in treating post-transplant focal segmental glomerulosclerosis: A systematic review & meta-analysis of 77 case reports & series. BMC Nephrol. 2016;17:104-07.
10. Bouts A. Members of the Working Group "Transplantation", "Idiopathic Nephrotic Syndrome" of the European Society of Pediatric Nephrology. European Society of Pediatric Nephrology survey on current practice regarding recurrent focal segmental glomerulosclerosis after pediatric kidney transplantation. Pediatr Transplant. 2019;23(3):e13-385.
11. Uffing A *et al.* Recurrence of Focal Segmental Glomerulosclerosis after Kidney

ISSN 2515-8260 Volume 09, Issue 02, 2022

Transplantation in Adults. Clin. J Am. Soc. Nephrol. 2020;15:247.
12. Dimopoulos MA. Renal impairment in patients with multiple myeloma: a consensus statement on behalf of the International Myeloma Working Group. J Clin Oncol. 2010;28:4976-84.