Chapter

Therapeutic Apheresis in Renal Transplantation: Indications and Strategies

Jean Jeanov Filipov and Emil Paskalev Dimitrov

Abstract

Kidney transplantation (KT) is the best renal replacement therapy in patients with chronic kidney disease (CKD). However, its success is limited due to insufficient number of donors worldwide and graft or patient loss. A major cause for poorer graft survival is donor-specific antibodies (DSAs). Therapeutic apheresis (TA) is a well-recognized option for increasing the donor pool by treating HLA-sensitized patients and making AB0-incompatible KT possible. In addition, its use in patients with DSA has beneficial effect on graft survival. The aim of our review is to demonstrate the current knowledge on the use of TA (plasma exchange and immunoadsorption) in KT. In addition to the current guidelines, new trends in TA use prior to and after KT will be reviewed.

Keywords: therapeutic apheresis, kidney transplantation, desensitization, AB0 incompatible transplantation, plasma exchange, immunoadsorption

1. Introduction

Kidney transplantation is a type of renal replacement therapy (RRT) in patients with end-stage renal disease (ESRD), which is associated with the best patient outcomes. A major breakthrough was detected with the introduction of cyclosporine A in the immunosuppressive regimen. One-year survival improved further more with the use of novel immunosuppression (tacrolimus and mycophenolate), with graft survival rates for the first year after KT surpassing 95%. Despite the amazing results over the years, several problems are still unsolved.

A major obstacle to the success of KT is the shortage of donors worldwide [1]. An additional cause for donor insufficiency is the presence of donor-specific HLA antibodies (DSAs) in ESRD patients. HLA sensitization is caused mainly by blood transfusions, pregnancy, and previous organ transplantation. DSAs are associated with increased risk for acute rejection and poorer graft survival [2].

Another option to increase donor options could be AB0-incompatible transplantation. However, in these cases the innate blood group barrier should be overcome in order to avoid hyperacute rejection.

Finally, long-term graft survival (at the fifth and tenth year after KT) is significantly lower, compared to short-term one. One of explanations for this finding is the development of de novo DSA, which in turn are related to antibody-mediated rejection and poorer graft survival [3].

Therapeutic apheresis (TA) is a method by which pathological elements of the immune system (cells, antibodies, and immune complexes) are being removed via extracorporeal system, thus influencing disease activity. Different TA techniques have been developed over the years. The most important ones in organ transplantation are plasma exchange (PEX) and immunoadsorption (IA).

1.1 Types of TA in kidney transplantation

1.1.1 Plasma exchange (PEX)

PEX is an invasive therapeutic method, separating plasma from blood cells. Thus pathogenic antibodies or other large molecules are removed and plasma is replaced by human albumin and/or fresh frozen plasma (FFP). The blood is pumped out of patient's circulation, and is transferred to a separator (centrifugal bowl or hollow fiber membrane), separating plasma from blood cells. Afterward blood cells are pumped into patient's vein and patient's plasma is substituted by protein solution (human albumin and/or FFP). Generally, central venous catheter is used as vascular access, though arteriovenous fistulas and large peripheral veins can also be used. The mechanism of action of PEX is removal of pathogenic antibodies, substitution of plasma proteins, and modification of cell response. However, the procedure is associated with albumin and fibrinogen loss, the latter being linked to increased bleeding risk. Therefore, more selective techniques for antibody removal were developed. A subset of PEX is the selective PEX, in which a special membrane plasma separator with smaller pores is used. Its use in renal transplantation currently is limited.

1.1.2 Double filtration plasmapheresis (DFPP)

DFPP is a semi-selective separation technique, based on membrane PEX. After initial separation of plasma from blood cells, additional filtration of plasma is performed with different diameter of fiber pores, so that target protein fractions are filtered and the rest are returned into the circulation. This technique showed up to 70% reduction in albumin loss after the procedure lower risk for infections and allergic reactions. The method was used initially for ABo-incompatible transplantation [4].

1.1.3 Cryofiltration

The technique was designed to remove cryoglobulins in several immune diseases. After plasma is initially filtrated, it is cooled to 4°C. This causes precipitation of cryoglobulins and they do not pass the second membrane. Afterward, the cooled plasma is warmed to body temperature again and is returned to the patient. The method was used in AB0-incompatible transplantation and HLA-sensitized patients. However, further studies are needed to incorporate cryofiltration in transplantation practice [5, 6].

1.1.4 Selective adsorption, immunoadsorption

In selective adsorption the plasma is filtered at the first step of the procedure, and at the second stage the initial filtrate runs through pre-arranged immunosorbents. Thus specific antibodies can be selectively removed, whereas albumin and clotting factors are returned to the patient. There are two types of selective adsorption—*immunoadsorbtion (IA)* and *selective plasma adsorption*. In IA either the plasma runs through column bearing antigens directed against certain antibody,

or antibodies against certain plasma constituents. In selective plasma adsorption plasma components are removed by binding to ligands other than antibodies and antigens (e.g., heparin and dextransulfate in LDL adsorption).

Practically only IA is used in transplantology. There are different IA techniques according to IA devices [7]:

1. IA using immobilized antibodies—sheep polyclonal anti-human IgG antibodies are used to remove IgG antibodies from plasma

2. IA using immobilized antigens and synthetic epitopes—the IA columns contain only immobilized antigens/epitopes, thus removing the pathogenic antibodies only. This method is the most specific one.

3. IA using staphylococcal protein A—IA columns containing immobilized Staphylococcal protein A, which effectively clears IgG types 1,2, and 4 by binding their Fc portions

1.1.5 Extracorporeal photopheresis (ECP)

ECP is a method, in which white blood cells are separated from plasma and are being treated extracorporeally with 8-methoxypsoralen (8-MOP) followed by exposure to ultraviolet A (UVA) light. The treated cells are then returned into patient's circulation. Initially used in the treatment of T-cell lymphoma, its indications have expanded in solid organ transplantation (heart, lung, and kidney). In renal transplantation ECP was used in recurrent and refractory rejection, as well as in antibody-mediated chronic rejection with conflicting results [7].

1.2 TA immunosuppression in KT

PEX and IA can remove the already produced antibodies, but they cannot influence the antibody production. However, after TA a rise in antibody formation and increase in B-cell proliferation occurs [8]. Therefore, TA should be coupled with adequate immunosuppression. In TA prior to or after renal transplantation the most widely used immunosuppressive medications are the biological agents—Thymoglobulin (ATG, dose 1–1.5 mg/kg, different protocols exist), Rituximab (standard dose 375 mg/m^2/weekly for 2–4 weeks) and intravenous immunoglobulins (IVIG, 100 mg/kg after each procedure). Eculizumab is also taken into consideration in high-risk patients prior to and after KT. Its effectivity is fully recognized in post-transplant atypical hemolytic uremic syndrome (aHUS). Further trials are needed to evaluate the exact place of this monoclonal drug in transplantation [9]. In addition, as the KT in sensitized patients is regarded as high-risk procedure, anti-CD25 agents can also be applied.

1.3 Classification of TA according to effectivity

The beneficial effect of TA is difficult to assess due to the relatively low number of randomized controlled trials (RCTs). According to the American Society for Apheresis (ASFA) the indications for TA have been classified into four categories, according to the possible beneficial effect of the procedure [10]:

- Category 1—Disorders for which apheresis is accepted as first-line therapy, either as a primary standalone treatment or in conjunction with other modes of treatment, for example, recurrent focal segmental glomerulosclerosis (FSGS).

- Category 2—Disorders for which apheresis is accepted as second-line therapy, either as a standalone treatment or in conjunction with other modes of treatment, for example, antibody-mediated rejection (AMR) in AB0-incompatible KT.

- Category 3—Optimum role of apheresis therapy is not established. Decision-making should be individualized—for example, HLA desensitization in deceased donation in AB0-compatible transplantation.

- Category 4—Disorders in which published evidence demonstrates or suggests apheresis to be ineffective or harmful—for example, lupus nephritis.

2. TA prior to renal transplantation

The presence of antibodies against donor HLA alleles significantly increases the risk for acute rejection and graft survival. Similarly, AB0-incompatible KT is associated with hyperacute rejection due to the presence of antibodies against A-/B-antigens on the surface of vascular endothelial cells. Therapeutic apheresis plays a key role in reducing the titers of pathogenic antibodies, thus significantly improving graft survival, reduces the risk for graft rejection, and increases the chances for successful KT.

2.1 AB0-incompatible (AB0i) KT

The antigens, associated with AB0 blood groups are expressed not only on the red blood cell's membrane, but also on the surface of the endothelial cells, making the A-/B-glycolipids one of the most important antigens, related to transplantation immunology. The naturally circulating antibodies against the above-mentioned AB0 antigens in AB0i renal transplantation lead to hyperacute rejection, severe endothelial damage, and thrombosis, which finally leads to graft loss within minutes after revascularization. Therefore, AB0 incompatibility is a major obstacle to successful KT. It was estimated, that its treatment can effectively increase the numbers of living donors by up to 30%. In addition, the current protocols for AB0i KT demonstrate comparable success to AB0-compatible KT [11].

Different protocols for desensitization in AB0i KT exist, generally most of them aim for target post-procedure isoagglutinin titers ≤1:8 (**Table 1**, [12–14]). In the early stages of AB0i KT splenectomy was performed in addition to PA. However, this practice was abandoned due to the risk for infectious complications and immunosuppressive agents were introduced in everyday practice. In cases, in which PEX was used, substitution with albumin or FFP is needed. FFP should be both donor and recipient AB0 compatible [10]. The number of procedures varies according to baseline isoagglutinin titers. The most widely used TA techniques are PEX and selective IA, though DFPP can also be taken into consideration (**Table 1**). As TA markedly improves prognosis in AB0i KT, it is regarded as first-line therapy in AB0i recipient-donor pairs (ASFA category 1) [10].

2.2 HLA desensitization

The presence of antibodies against the HLA alleles of the donor prior to KT is another obstacle for the success of the procedure. The presence of donor-specific anti-HLA antibodies (DSAs) cause graft loss due to antibody-mediated rejection (AbMR) and is also referred as HLA-incompatible (HLAi) KT. At higher titers DSA

Target antibody level at KT day	TA strategy	Immunosuppression	Results	Reference
1:8 initial phase, later 1:32	PEX 30 ml/kg/ session, alternate days, start 7 days prior to KT	RTX 200 mg on day (−15); IVIG 5 g after each PEX (total 10–25 g), Thymoglobulin—two doses, total 3 mg/kg	1 year graft and patient survival 97.8%	Ray DS et al.
1:8	DFPP start: 7 days prior to KT, alternate days, performed post KT	RTX at day −14 Tac and mycophenolate at day (-7)	Graft survival 87%, patient survival 93%, post-transplant infection rate 13%	Jha PK et al
1:8	Antigen-specific IA Start: day (-6) four sessions, treatment volume: two plasma volumes After KT three more sessions within nine days	RTX 375 mg/m^2—day (-14) Triple immunosuppression (Tac, MMF, Prednisolone) IVIG 0.5 g/kg after final IA	All patients had good graft function during the follow-up	Tydén G et al

TA—therapeutic apheresis, PEX—plasma exchange, DFFP—double filtration plasmapheresis, IA—immunoadsorption, RTX—rituximab, IVIG—intravenous immunoglobulin, Tac—tacrolimus, MMF—mycophenolate mofetil.

Table 1.
Desensitization protocols in ABo incompatible kidney transplantation.

cause hyperacute AbMR, whereas lower titers result in acute or chronic AbMR [7]. The major causes for HLA sensitization are previous transplantation, blood transfusion, or pregnancy.

Due to the increased immunological risk, sensitized candidates remain significantly longer on the waiting list. It was estimated, that approximately 30% of the candidates for KT have detectable anti-HLA antibodies and half of them are highly sensitized, being sensitized to more than 80% of the possible HLA alleles. Desensitization protocols, by which undetectable DSA titers and negative cross-match are achieved, significantly improve graft survival, especially in living donation.

2.2.1 HLA desensitization in AB0-compatible KT, deceased donors

In deceased donor KT (DDKT) there are conflicting data considering the effectivity of TA. In patients on the waiting list, attempts have been made to perform HLA desensitization, with unclear benefit (**Table 2**, [15–21]). However, the prolonged exposure to immunosuppressive agents should be taken into consideration.

More studies have been performed in TA and DDKT in the perioperative setting. Generally, the aim is negative cross-match to be achieved prior to KT. Different protocols were suggested, using PEX/IA, accompanied by immunosuppressive agents (rituximab, IVIG, ATG). Though short-term results were encouraging, long-term ones are still conflicting [21]. AbMR and T-cell rejection had higher incidence in DSA/+/ kidney transplant recipients (KTRs), especially in those with higher mean intensity fluorescence (MFI) [19, 21]. Therefore, higher pre-transplant DSA titers have poorer prognosis, despite current desensitization protocols in deceased donors. Currently, due to the insufficient data on the use of TA in HLA desensitization in DDKT and the conflicting results it falls into category 3 of the latest ASFA guidelines [10].

TA on the waiting list				
Study design	**TA strategy**	**Immunosuppression**	**Results**	**Reference**
IA and immunosuppression in HLA-sensitized ESRD patients	IA	Cyclophosphamide + steroids	Unclear benefit, safe procedure	Hiesse C. et al
PEX and immunosuppression in HLA-sensitized ESRD patients	PEX—12 procedures	Cyclophosphamide + steroids on the first day of PP, tapered till KT	9 out of 23 lost grafts in the first 2 months post KT, 59% graft survival at fifth year post-transplant	Alarabi A. et al.
Peritransplant TA				
PEX in DDKT, positive cross-match, aiming negative one	PEX—1 procedure	RTX	First year graft survival 92.4%, patient survival 95.8%	Morath C et al.
Desensitization IVIG vs. IVIG/RTX/PEX, negative cross-match on KT day *Short-term results*	PEX—9 procedures, alternate days post KT	IVIG 2 g/kg on days 0,2,42, 63; RTX days 2 and 22	Better GFR and greater DSA-MFI decrease in IVIG/RTX/PEX group	Loupy et al.
Desensitization with IVIG/RTX/PEX MFI˃3000 vs. MFI 500–3000, both groups with negative cross-match on KT day *Long-term results*	PEX—9 procedures, alternate days post KT	IVIG 2 g/kg on days; 0,2,42, 63 RTX days 2 and 22	Similar GFR in both groups; lower incidence of T-cell rejection in MFI 500–3000	Amrouche L et al.
Desensitization in DDKT broadly sensitized patients; KT performed after negative cross-match achieved	IA (staphylococcal protein A) initial volume 6 L, later 2–3 plasma volumes; first session—immediately before KT; after KT—IA every 1–3 days, up to 7 weeks	ATG	Similar graft and patient survival compared to DSA/−/ at third year post KT	Bartel G. et al. The Vienna group
Extended previous study of the Vienna group, no change in protocol			Poorer graft survival compared to DSA/−/ at third year post KT, higher incidence of AbMR in DSA/+/, higher MFI was associated with higher risk for rejection	Schwaiger E et al. The Vienna group

TA—therapeutic apheresis, PEX—plasma exchange, IA—immunoadsorption, RTX—rituximab, IVIG—intravenous immunoglobulin, KT—kidney transplantation, DDKT—deceased donor kidney transplantation, MFI—mean intensity fluorescence, ATG—thymoglobulin, DSA—donor-specific antibodies, AbMR—antibody-mediated rejection, GFR—glomerular filtration rate, ESRD—end-stage renal disease.

Table 2.
HLA desensitization protocols in ABo-compatible deceased donors kidney transplantation.

2.2.2 HLA desensitization in AB0-compatible KT, living donors

HLA desensitization is far more important and more effective in living donor kidney transplantation (LDKT). A multicenter study demonstrated that KTRs with HLAi LDKT have better survival than patients on the waiting list without being transplanted or those on the waiting list with deceased donor KT. The benefit was significant in the short and in the long run [22].

The most used TA techniques in LDKT desensitization protocols are PEX and IA. Usually 4–8 sessions of PEX are performed prior to KT on alternate days. In most of the studies low-dose IVIG (10–150 mg/kg) was infused after each PEX, though the IVIG can be applied at the end of the series too [10]. Post-transplant PEX procedures were also performed (5–9 sessions) [22, 23]. In some studies mycophenolate and tacrolimus were added to the protocol 14 days prior to KT [23]. RTX was also used in certain protocols, forming a triple regimen—PEX/low-dose IVIG/RTX. Though an overall AbMR rate between 30 and 40% was detected, graft and patient survival reached up to 93 and 95% respectively at the first year [10, 24].

IA is the other most widely used TA modality in LDKT desensitization. It is coupled with RTX ± IVIG and graft survival rates reach up to 100% at the second year. Pre-transplant oral immunosuppressive agents could be used (tacrolimus + mycophenolate + steroids) and ATG/Basiliximab induction therapy as well [25].

2.3 Desensitization in combined HLAi/ABOi KT

In the rare setting of both HLAi and AB0i KT desensitization using PEX/IA plays a key role. A study using TA (PEX or specific/non-specific IA), combined with IVIG, two doses of RTX (375 mg/m^2) and Tacrolimus (0.2 mg/kg started 10 days prior to KT) demonstrated excellent graft and patient survival [26].

3. TA after renal transplantation

The major indications for TA after successful KT are AbMR and recurrent or de novo glomerular disease.

3.1 TA in AbMR

3.1.1 Acute AbMR

In HLA-desensitized patients AbMR ranges between 30 and 40% post-transplant, despite successful desensitization prior to KT. However, acute AbMR can occur in up to 10% after KT due to de novo DSA. The diagnosis is based on the presence of DSA, C4d deposition in peritubular capillaries, and evidence of tissue injury (typically associated with neutrophil/macrophage infiltration) [27]. However, AbMR without C4d deposition is also possible according to the BANFF criteria [28]. Acute AbMR is categorized into early (within 6 months after KT) and late (more 6 months after KT). Both types are associated with poorer graft survival; however, early acute AbMR is more responsive to the current treatment protocols.

PEX and IA play a key role in acute AbMR treatment and fall into ASFA category 1 [10]. The protocol consists usually of at least five TA procedures, coupled with IVIG infusion (total does 1–2 g/kg, 100–200 mg/kg after each procedure). In addition, RTX was tested as immunosuppressive agent, added to TA + IVIG combination. The results for RTX-based protocols so far are inconsistent, as some studies indicate benefit from the triple combination, whereas others fail to establish positive effect on short-term or long-term graft survival [29, 30].

Other preparations were tested in combination to TA as well: Bortezomib, complement component 1 (C1)—inhibitor and eculizumab (C5a inhibitor) currently with unclear benefit, indicating the need for further research in this field [31].

3.1.2 Hyperacute AbMR

Hyperacute AbMR presents with cyanosis and anuria, occurring minutes after revascularization of the graft, and is caused by pre-formed antibodies against the graft (AB0 incompatibility, HLA-DSA, antibodies against endothelial and monocyte antigens). It is currently a rare finding due to improved pre-transplant immunological evaluation. Histologically small vessel endothelial damage is detected, as well as thrombosis and neutrophil infiltration. There is no treatment, the only option is nephrectomy [32].

3.1.3 Chronic AbMR

Chronic AbMR is diagnosed by the presence of donor-specific antibodies, C4d deposition in peritubular capillaries, and evidence of chronic tissue injury. Chronic tissue injury encompasses duplication of the glomerular basement membrane (GBM), multilamination of the peritubular capillary basement membrane, arterial intimal fibrosis without elastosis, and interstitial fibrosis with tubular atrophy [27]. Though different TA techniques have been tested in chronic AbMR, including ECP, the procedure is generally ineffective due to the chronic histology findings [27].

3.1.4 De novo DSA and subclinical AbMR

The detection of de novo DSA after KT is associated with poorer transplant outcomes due to higher incidence of chronic allograft nephropathy (CAN) [33]. Subclinical AbMR is main cause for CAN in these cases. It presents with the typical histology and serology for AbMR, without significant changes in the laboratory and clinical findings. A recent study failed to demonstrate significant beneficial effect from two sessions of DFPP+RTX in subclinical AbMR. In this paper, patients with de novo DSA without data for rejection, who received no treatment, were also evaluated. In the follow-up period no significant changes in graft function and proteinuria in this subgroup occurred [34]. Therefore more clinical trials are needed to evaluate the importance of TA in subclinical AbMR and in de novo DSA without rejection.

3.1.5 TA in non-DSA post KT

The importance of non-DSA post KT is currently unclear. Though certain studies demonstrate association between non-DSA and acute AbMR, others fail to establish such relationship, even at MFI up to 10,000 [35, 36]. Additional trials are needed to fully evaluate the significance of non-DSA and the possible treatment methods in the future.

3.2 TA in recurrent disease

3.2.1 Recurrent focal segmental glomerulosclerosis (FSGS)

FSGS is a disease, in the pathogenesis of which an unidentified plasma factor plays a key role by increasing glomerular barrier permeability and causing podocyte

injury. The presence of such factor is further supported by the fact, that primary FSGS has high recurrence rate after KT—up to 50% after the first KT and up to 100% in repeated transplantations [10]. Though the molecule has not been definitely identified, a considerable research has been performed in order to evaluate the role of TA in the treatment of FSGS.

TA is regarded in the treatment of primary FSGS only after treatment with steroids and calcineurin inhibitors (CNI) have failed. However, PEX/IA is considered as first-line treatment in recurrent FSGS after KT, as it leads to complete or partial remission in more than 50% of the KTRs [10]. They usually combined with immunosuppression—high-dose steroids, cyclophosphamide, higher doses of CNI and RTX. The needed number of procedures to achieve effective control of the disease by evaluating proteinuria is highly variable.

In recurrent FSGS PEX/IA are performed daily/every other day. The treatment should be started as early as possible in order to avoid progression of the disease. Proteinuria is the only marker that is used to assess the effect from the treatment. Treatment may have longer duration in order to avoid new episodes. Unfortunately, no predictors for TA effectivity in recurrent FSGS exist [10]. In addition, pretransplant treatment failed to prevent recurrence of the disease [37].

Lipoprotein apheresis (LA) was assessed as a third TA modality in the treatment of FSGS. In LA lipoprotein particles are selectively removed from blood. The possible explanation for the benefit of this method is reducing the lipotoxic effect of hypercholesterolemia on podocyte function. Usually it is performed twice per week for 3 up to 6 weeks [10]. Currently LA is approved for primary/recurrent FSGS only in the USA.

3.2.2 Immunoglobulin A (IgA) nephropathy/Henoch-Schönlein Purpura

IgA nephropathy recurrence rate varies between 9 and 53% and is associated with poorer graft survival. Different predictors have been identified: crescentic forms of the disease, earlier onset of the primary disease, serum IgA levels, and steroid withdrawal after KT [38].

PEX did not prove to be effective in the treatment of primary IgA nephropathy [10, 39]. Indeed, predominantly cases with rapidly progressive crescentic IgA were evaluated without significant beneficial effect. The data for PEX treatment after KT are insufficient; therefore TA is generally not prescribed in recurrent IgA nephropathy. Similarly to IgA nephropathy, TA has no significant efficacy in Henoch-Schönlein Purpura.

3.2.3 Recurrent membranous nephropathy (MN)

Primary (idiopathic) membranous nephropathy (IMN) is characterized with the presence of autoantibodies against the podocyte localized phospholipase A2 receptor (anti-PLA2R). Currently, the recognized treatment options are cycling regimen (steroids/alkylating agent), CNI, or RTX. A single study demonstrated significant improvement from the combination of PEX + IVIG + RTX in resistant to conservative treatment (steroids/cyclophosphamide *or* CNI *or* RTX) IMN [40]. In this study, four PEX procedures were performed, coupled with a dose of 20 g IVIG and single dose RTX 375 mg/m^2.

The recurrence rate of IMN reaches 50%. High titers of anti-PLA2R were found to be a risk factor for recurrence after KT. Generally, switching from mTOR inhibitor to CNI is recommended, as well as use of RTX; alkylating agent should be avoided due to the risk for too potent immunosuppression [41]. Unfortunately, the role of TA in recurrent IMN is unclear and further research in this sphere is needed.

3.2.4 Recurrent membranoproliferative glomerulonephritis (MPGN)

Primary MPGN has two major types according to its pathogenesis: immune complex mediated and complement mediated. The new classification enables not only the better understanding of the disease, but also evaluates better the risk for recurrence after KT.

Immune complex-mediated MPGN is characterized by the glomerular deposition of polyclonal or monoclonal immunoglobulins. It is believed that the types and patterns of immunoglobulins may influence post-transplant characteristics of recurrent MPGN. For instance, IgG3k and IgG3λ deposits are linked to earlier recurrence and faster graft loss [41].

In the complex-mediated MPGN there are C3 glomerular deposits without immunoglobulin ones. It is known also as C3 glomerulopathy and consists of two entities—C3 glomerulonephritits and dense deposits disease (DDD). The two diseases have similar pathogenesis and clinical course. A recurrence rate up to 67% was reported for both diseases; DDD tended to recur later after KT and in both types graft failure was 50% [41, 42].

The suggested treatment so far includes PEX and immunosuppression—cyclophosphamide, RTX or eculizumab. However, the published studies are small and the results are inconsistent. Therefore larger trials are needed to evaluate the effectiveness of TA and the concomitant immunosuppressive agents in post-transplant MPGN [41].

3.2.5 Complement-mediated thrombotic microangiopathy (cmTMA, atypical hemolytic uremic syndrome)

Complement-mediated thrombotic microangiopathy (cmTMA), previously known as atypical hemolytic uremic syndrome is a life-threatening condition, which is caused by over-activation of the alternative pathway of the complement system. It presents with thrombocytopenia, microangiopathic hemolytic anemia, acute kidney injury, minimal to absent neurologic involvement, and fever. Over-activation is caused by genetic mutations causing impaired function of the alternative pathway inhibitors (factor H, membrane cofactor protein, and factor I) or overexpression of activators (factor B and complement component C3). Anti-Factor H autoantibodies can also cause cmTMA.

Generally, the disease's recurrence rate peaks up to 75% and is a significant predictor for poorer graft survival—90% of these grafts are lost within the first post-transplant year as the pathogenic serum proteins persist after the operation. However, membrane cofactor protein-associated cmTMA recurs significantly less—up to 20% after KT, with better graft survival due to the normal graft membrane proteins [43].

Initially, cmTMA was treated with daily PEX and immunosuppression. The recommended substitution fluid was FFP or FFP/albumin. However, with the introduction of Eculizumab in the treatment of the disease, the role of PEX is uncertain, as studies failed to demonstrate any advantage of PEX + Eculizumab vs. Eculizumab only [44]. PEX is reserved as first line therapy only in the presence of anti-Factor H autoantibodies, combined with immunosuppression [10].

3.2.6 Thrombotic thrombocytopenic purpura (TTP) after KT

TTP is TMA, characterized by similar clinical and laboratory findings as in cmTMA. However, it is more common in adults, presents with more pronounced thrombocytopenia, usually severe neurological impairment, and varying degree

of renal insufficiency. In the post-transplant setting TTP is associated with CNI/mTOR inhibitors treatment, AbMR, viral infections, and ischemia reperfusion injury [45].

The key point in the treatment is correction of immunosuppressive treatment or treatment of the underlying condition. PEX can be included in the therapy, though the current data fail to demonstrate clear benefit from the procedure. Eculizumab proved to be more effective in these cases [46]. AbMR-associated TMA is usually treated with PEX + IVIG; RTX and Eculizumab can also be added to the treatment, especially in resistant to the standard PEX treatment cases [47, 48].

3.2.7 ANCA-associated vasculitis

The recurrence rate of ANCA-associated vasculitis is relatively low—approx. 10%. In these cases treatment as per general population is recommended.

Usually PEX is used in ANCA vasculitis in the native kidney in cases of rapidly deteriorating kidney function, diffuse alveolar hemorrhage, and serum creatinine above 5.7 mg/dl (504 μmol/L) [10, 39]. In recurrent ANCA vasculitis after KT the indications for TA are similar, usually the procedures are combined with immunosuppressive agents—steroids + cyclophosphamide or steroids + RTX [49]. Generally 7–12 procedures are needed. In alveolar hemorrhage the substitution fluid for PEX is FFP in order to avoid further increase in bleeding [10].

It is recommended in patients with ANCA vasculitis and end-stage renal disease transplantation to be delayed until a complete extrarenal remission for at least 12 months is achieved. However, ANCA-positive patients with extrarenal remission can be transplanted [39].

3.2.8 Recurrent/de novo anti-glomerular basement membrane (GBM) disease

Anti-GBM disease is usually caused by autoantibodies against the α3 chain of type IV collagen. The disease recurs in up to 50% of the cases post-transplant; the presence of detectable auto-antibodies' titer prior to KT is a well-established factor for recurrence. Therefore a period of at least 6 months of undetectable anti-GBM antibodies is recommended prior to KT [39].

De novo anti-GBM disease post-transplant usually develops in cases with Alport syndrome. In this clinical setting, the patients have impaired synthesis of collagen 4, with missing chains from α3 to α5 (usually α5), due to genetic mutations. After successful KT the graft expresses the normal α chains, which can trigger immunological response against these normal structures. De novo anti-GBM disease is detected in approx. 15% of the Alport patients after KT [7].

De novo anti-GBM disease presents with the symptoms of the disease in native kidneys. However, the recurrent form can present with subclinical course [50].

Generally, treatment is performed as per native kidneys' anti-GBM disease. Therapy should be initiated as early as possible. PEX is performed daily or every other day, anti-GBM antibody titers should be monitored and the procedure should be performed until the autoantibodies are undetectable (approx. 10–14 sessions). PEX is combined with steroids and cyclophosphamide; the role of RTX is currently unclear [10, 39].

3.2.9 Catastrophic antiphospholipid syndrome (cAPS)

Catastrophic antiphospholipid syndrome (cAPS) is acute life-threatening condition, associated with multiple thromboses in at least three systems within days or weeks, due to the presence of antiphospholipid antibodies (lupus anticoagulant,

anticardiolipin, and anti-β2-glycoprotein I). The presence of cAPS is an indication for PEX. The procedure should be performed in combination with steroids ± IVIG and anticoagulants. This triple combination proved to be effective in cAPS. However, cyclophosphamide, eculizumab, and RTX were also used in the treatment [51]. PEX in cAPS is performed daily or every other day, substitution fluid is usually FFP or FFP + albumin [10].

The data for cAPS after KT are limited. The presence of antiphospholipid antibodies is a recognized risk factor for cAPS and anti-phospholipid syndrome (APS) recurrence [7]. A paper demonstrated that the use of Eculizumab can prevent post-transplant cAPS [52]. Barbour et al. demonstrated partial graft function improvement in patient with post-transplant cAPS, treated with PEX (28 procedures over 49 days), IVIG, and anticoagulation [53]. Further research in the field is needed, as the number of patients with APS/cAPS is small, especially those after KT.

4. Conclusions

TA has a well-established role in desensitization protocols prior to KT and treatment of AbMR in the post-transplant period. However, its place in the treatment of recurrent/de novo post-transplant glomerular disease is not fully understood due to the relatively small number of patients, insufficient controlled clinical trials, and different immunosuppressive agents used alongside with the procedure. In addition, the different TA modalities further complicate the assessment of TA effectivity. A multicenter approach could give better insight into TA role after renal transplantation and optimize its use in everyday clinical practice.

Author details

Jean Jeanov Filipov[1,2]* and Emil Paskalev Dimitrov[1,2]

1 Department of Nephrology and Transplantation, University Hospital "Alexandrovska", Sofia, Bulgaria

2 Medical University – Sofia, Sofia, Bulgaria

*Address all correspondence to: jeanphillipov@yahoo.com

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