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Annals of Immunology & Immunotherapy
ISSN: 2691-5782

Therapeutic Apheresis in Renal Diseases with Immunologic Origin

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Review Article
Volume 2 Issue 1
Received Date: February 01, 2020
Published Date: March 04, 2020
DOI: 10.23880/aii-16000113

Abstract

Since the mid-1970s, when membrane modules became available, plasma separation techniques have gained in importance especially in the past few years. Systemic autoimmune diseases based on an immune pathogenesis produce autoantibodies and circulating immune complexes, which cause inflammation in the tissues of various organs. In most cases, these diseases have a poor prognosis without treatment. Therapeutic apheresis (TA) in combination with immunosuppressive therapies has led to a steady increase in survival rates over the last 40 years. The different diseases can be treated by various apheresis methods such as therapeutic plasma exchange (TPE) with substitution solution, or with online plasma or blood purification using adsorption columns, which contain biological or non-biological agents. Here, the authors provide an overview of the most important pathogenic aspects indicating that TA can be a supportive therapy in systemic autoimmune diseases such as renal disorders.

Keywords: Therapeutic Apheresis; Immunologic Renal Diseases; Immunopathologic Aspects; Autoantibodies; Immune Complexes

Abbreviations: TA: Therapeutic Apheresis; TPE: Therapeutic Plasma Exchange; IA: Immunoadsorption; ACE: Angiotensin Converting Enzyme Inhibitors; DFPP: Double Filtration Plasma Exchange; IC: Immune Complex; ASFA: American Society for Apheresis; AAC: Apheresis Applications Committee; ANCA: Anti Neutropil Cytoplasm Antibodies; WG: Wegner's Granulomatosis; MPA: Microscopic Polyangiitis; GBM: Glomerular Basement Membrane; GFR: Glomerular Filtration Rate; DAH: Diffuse Alveolar Hemorrhage; ESRD: End-Stage Renal Disease; EUVAS: European Vasculitis Study Group; NS: Nephrotic Syndrome; FSGN: Focal Sclerosing Glomerulosclerosis; MCGN: Minimal Change Glomerulonephritis; HUS: Hemolytic-Uremic Syndrome; AKI: Acute Kidney Injury; TPV: Total Plasma Volume; DSA: Donor Specific Alloantibodies; TMA: Thrombotic Microangiopathic.

Introduction

The introduction of hollow fiber modules in TA shows a complete separation of the corpuscular components from the plasma and due to increased blood flow rate and higher efficacy. Furthermore, cell damage-especially to thrombocytes-occur less using membranes than centrifuges for cell separation [1-3]. There is no advantage that TA using centrifuges has shorter treatment times such as TA using hollow fibers shown by Hafer C, et al. [4]. More important is to keep the blood levels with antibodies, and/or pathogenic substances on a very low level over longer time during the

treatment. In this situation the substances that should be eliminated could invade into the intravascular space and be eliminated by the membrane separators.

The conventional TA equipment's are, however, not perfect, because the filtered plasma fractions have discarded. Substitution solutions supplemented with human albumin, plasma substitutes (e.g., gelatin solutions), or fresh frozen plasma are used to replace the discarded fractions [3]. Immunoadsorption (IA) or other selective plasma adsorption methods are available without the use of a substitution solution. The indications of TA are immunological and non-immunological diseases.

The term of autoimmune or auto-aggression diseases which caused by antibodies acting against the body´s own tissue. The cause of autoimmune reactions is still generally unknown. The spectrum of autoimmune diseases ranges from those diseases in which autoimmunization is solely responsible for the disease condition (e.g., autoimmune hemolytic anemia), to those in which it possibly has a major influence on the further course of the disease (e.g., rheumatoid arthritis), and those in which the autoimmunization phenomena are probably only of diagnostic importance [3]. The autoantibodies (auto-ab), which activate immunological processes that are self-destructive for the organism, have their effects in different ways.

These autoantibodies can also be directed at leukocytes or thrombocytes. If thrombocytes are the target, then opsonization and phagocytosis can lead to idiopathic thrombocytopenic purpura. In the case of other forms of auto aggressive cell and tissue, destruction (e.g., glomerulonephritis) complement-dependent direct lytic cell destruction also plays a role [3]. Thus differentiation must be made between physiological low-titer IgM autoantibodies with low affinity and broad specificity and higher-titer, high affinity IgG and IgA autoantibodies [5].

Autoantibodies are not necessarily primarily auto aggressive or destructive. They only lead to inflammatory tissue reaction when, through their binding to cells and through complement activation, the reaction chain of the serum complement system is triggered [3]. Circulating antibodies bind the offending antigens and participate in several other functions. Together they can trigger tissue inflammation ranging from slight vascular irritation to necrosis. The serum concentration of the individual components varies considerably, so that here the concept of the "limiting factor" applies [3].

Autoantibodies can, however, have a serious effect on a given organ even without the activation of the complement system, namely when either functionally important receptors are blocked by antibodies or else important proteins are rendered inactive through the union with antibodies, such as hormones or enzymes [6]. These principles of receptor blockade have used for several years in medicaments such as, for example, angiotensin converting enzyme inhibitors (ACE) or angiotensin II type receptor blockers [3]. Autoantibodies can also block the physiological decomposition of enzymes, which results in an extreme disorder of the regulatory mechanisms. Thus, for example, membranoproliferative glomerulonephritis, type II, is probably due to autoantibody formation against an enzyme, which breaks down.

Immune complex (IC) is a physiological process and serves to eliminate foreign material, such as bacteria, their components and viruses. If such ICs are formed, they are removed from the blood by the adhesion of the Fc-fragments of the antibodies to the corresponding phagocyte receptors in the liver and spleen. Phagocytosis can even be enhanced if the ICs activate the complement system (immune clearance). However, if not all the ICs are eliminated quickly enough in this way, then they can establish themselves in the intima of the vessels and from there trigger inflammatory lesions through local activation of the complement system [3]. The ICs probably first form in situ; the antigen adheres to the basal membrane and binds circulating antibodies. If this is correct, then IC deposition processes in tissue are not necessarily detectable through serum IC determination, as, on the other hand, circulating ICs (CIC) may not indicate organ damage.

Immune complexes deposit preferentially in certain sites throughout the body, the kidneys, the joints, the lungs and the skin. The kidney accumulates ICs because the blood pressure in the glomerular capillaries is four times higher than in other capillaries and because the glomerulus retains immune ICs by a simple filtering effect. Similarly, ICs may also accumulate in other body filters; the ciliary body eye, where aqueous humor forms, and the choroid plexus in the brain, where cerebrospinal fluid is produced.

Circulating immune complexes are involved in the regulation of various immune phenomena. These ICs interact with the Fc and/or antigen receptors of the T, B, NK cells and macrophages. They correlate to the primary and secondary immune response [7]. The elimination of the CICs plays an important therapeutic role. It is possible to interrupt the pathological process by eliminating antibodies by TA. The methods of TA such as TPE, double filtration plasma exchange (DFPP) or the different semi selective or selective plasma exchange methods available are published elsewhere and discussed in detail by Bambauer R, et al. [3,8,9].

There are only a few prospective controlled trials available that are of adequate statistical power to allow definitive

conclusions to be reached regarding the therapeutic value of TA. This drawback reflects, in part, the relative rarity of most of the disorders under investigation. To compensate, many investigators have understandably grouped heterogeneous diseases together, often retrospectively, and used historical controls. The latter design is potentially hazardous, given that earlier diagnosis, recognition of milder cases, and improved general care over time may be lost as a benefit of TPE.

For those diseases for which the use of TA is discussed, the guidelines on the use of TA from the Apheresis Applications Committee (AAC) of the American Society for Apheresis (ASFA) are cited [1,2]. Since the introduction of hollow fiber modules in TPE, this therapy method is mostly used in nephrology, as many of these membranes can use with the currently available dialysis equipment.

Rapidly Progressive Glomerulonephritis (RPGN)

RPGN is a diffuse glomerulonephritis that frequently begins acutely. RPGN is a histologic diagnosis including a number of etiologies such as anti-basement membrane antibody glomerulonephritis (ABM ab-GN), which is very rare, Anti Neutropil Cytoplasm Antibodies (ANCA), and even IgA nephritis. Its histological characteristics are usually necrosis of the capillary walls and semi-lunar formation, and deposition of IgG and C3 along the glomerular basement membrane. Most cases are simultaneously accompanied by acute kidney injury [9]. More than 90% of patients with RPGN due to Good pasture/anti-GBM RPGN have anti-GBM antibodies in their circulation.

RPGN consists of rapid loss of renal function with the histologic finding of crescent formation in over 50% of glomeruli [3]. A proliferation of cells within Bowman's space of the glomerulus due to the extravasations of proteins into the space is observed histologically. These cells consist of proliferating parietal epithelial cells as well as infiltrating macrophages and monocytes. RPGN is not a single disease entity but is a clinical syndrome with a different number of etiologies. Histologic classification divides RPGN into three subtypes based on the immunofluorescence pattern on renal biopsy [9]:

1. Linear deposition of IgG due to autoantibodies to type IV collagen representing ant glomerular basement GN (15%).
2. Granular deposits of immune-complexes caused by a variety of GNs including post streptococcal GN, Henoch Schonlein purpura, IgA nephropathy, membranoproliferative GN, cryoglobulinemia, and lupus nephritis (24%).
3. Minimal immune deposits in the glomerulus with the presence of anti-neutrophil antibodies in the serum. This pauci-immune RPGN also referred to as ANCA-associated RPGN, is seen in Wegner's Granulomatosis (WG) and Microscopic Polyangiitis (MPA) (60%) [2].

The incidence is 0.85per 100,000/year. Importantly, when discussing RPGN, a number of entities are frequently included in case series and trials, thus confounding results [9]. Therapy consists of administration of high-dose corticosteroids (e.g., methylprednisolone) and cytotoxic immunosuppressive drugs (e.g., cyclophosphamide or azathioprine) [10]. Other drugs used include leflunomide, deoxyspergualin, tumor necrosis factor blockers, calcineurin inhibitors, and antibodies against T cells and rituximab [9,11,12].

Table 1: Therapeutic apheresis in renal diseases with immunologic origin.

	TA modality	Category	Recommendation grade (RG)	Treated volume (TPV)	Replacement solution	Frequency
RPGN (ANCA-associated) dialysis dependent, DAH	TPE	**I** **I** **III**	**1A** **1C** **2B**	1-1.5	Human-albumin-electrolyte Solution, or FFP	Daily or every day
Anti-glomerular basement disease (Goodpasture s.) dialysis dependent no DAH, DAH dialysis dependent	TPE	**III** **I** **I**	**2B** **1C** **1B**			
Immune complex nephritis, dialysis independent		---	---	---	---	---

Focal segmental GN - primary - secondary - recurrent (in transplanted kidney)	TPE	**III** **III** **I**	**---** **---** **1B**	1-1.5	Human-albumin-electrolyte Solution, or FFP	Daily or Every day
Hemolytic uremic syndrome (HUS) -complement gene Mutations -Factor H ab -MCP mutations Children	TPE	**II** **I** **IV** **---**	**2C** **2C** **1C** **---**			
Renal transplantation -ABO compatible, ab mediated rejection, desensitization living donor desensitization -ABO incompatible, desensitization, live donor, humoral rejection group A2/A2B into B decreased donor	TPE	**I** **I** **III** **I** **II** **IV**	**1B** **1B** **2C** **1B** **1B** **1B**			

Category I: accepted for TA as first line therapy;
Category II: accepted for TA as second-line therapy;
Category III: not accepted for TA, decision should be individualized;
Category IV: not accepted for TA, approval is desirable if TA is undertaken [1,2].

The rationale for therapeutic apheresis is that RPGN with dialysis dependence (Cr>6mg/dL) and RPGN with diffuse alveolar hemorrhage has the category I with the recommendation grade (RG) 1A and 1C. RPGN dialysis independent has the category III with the recommendation grade 2C [2] (Table 1). Because of the benefit of TPE in the crescent GN of anti-GBM, TPE was applied to all causes of RPGN. The role of TPE has examined in some trials in pauci-immune and immune complex GNs. Results of other trials indicate that TPE may be beneficial for dialysis-dependent patients presenting with severe renal dysfunction; however, there is no therapeutic benefit over immunosuppression in milder disease. The predominance of pauci-immune GN cases in these series may account for these results [1]. The duration of therapy is not well defined in the literature. Some trials have stopped TA if there was no response after 4weeks of therapy.

Anti-Basal Membrane Antibody Glomerulonephritis (Good pasture Syndrome, ABM-ab-GN)

ABM-ab-GN is a rare but life-threatening autoimmune vasculitis characterized by the development of pathogenic autoantibodies to type IV collagen antigens. In ABM-ab-GN, antibodies appear that are directed against a peptide component of one of the two non-collagen parts of type IV collagen. However, type IV collagen is found not only in the kidney, but also in the vessels of other organs, such as the lung [9]. The mechanisms responsible for the production of antibodies against the antigens are still not clear. A large number of diseases have been associated with ABM-ab-GN based on different cases; however, the most consistently reported associations are with membranous nephropathy and ANCA associated vacuities. Only a small part of ANCA GN has anti-GBM ab, mostly it is thought to be an environmental or infectious exposure that triggers the onset of these diseases. It is reasonable to speculate that for both membranous and ANCA-positive vasculitis, damage to the kidney elicits an immune response against the Glomerular Basement Membrane (GBM) leading to the production of antibodies, which may or may not contribute to disease progression [13]. ANCA GN responds to TPE even when the patient is on dialysis and anti-GBM GN does not.

Good pasture syndrome is a rare autoimmune disease in which antibodies attack the basement membrane in the lungs and kidneys. The frequency of anti-GBM disease vary from 0.5to1 cases per million population [14,15]. The formation

of anti-basement membrane antibodies is frequently limited in duration. The autoantibodies cause severe disturbances in the permeability in the lung with significant deterioration in diffusion capacity and hemoptysis. The renal deposition of this autoantibody frequently leads to rapid deterioration in renal functioning, which expresses itself histologically in a necrotizing glomerulonephritis in part. Linear deposits of IgG can be immunohistologically detected both at the basement membrane of the lung, as well as of the kidney [16]. An antigen with a probable size of 26,000-28,000Daltons is considered responsible for these deposits, its immunogenic epitopes being located on the stable glomerular domain NC1 of collagen IV [17].

Lookwood CM, et al. [18] found in patients with a serum creatinine of <600μmoll/L (<6.8mg/dL creatinine) and plasmapheresis, a significant improvement in renal function. With a serum creatinine of >600μmoll/dL (>6.8mg/dL creatinine) and/or oligo-anuria with less than 400mL urine secretion in 24h, only one patient out of 27 showed a significant improvement in renal function (5%).

The various forms of glomerulonephritis are treated with immunosuppression not only with corticoids, alkylating agents, and cyclosporine A, but also with combinations of almost all of these drugs. Trials with anticoagulants, cyclooxygenase inhibitors, and ACE inhibitors suggest that in addition to an immunological genesis of glomerulonephritis, other factors must also be considered [9]. The combination of corticoids, immunosuppressive, and TPE in varying combinations was the first step in improving the overall prognosis for RPGN. In subsequent years, RPGN has treated with a combination of immunosuppressive drugs and IA with excellent results.

However, Kaplan AA, et al. reported, that several controlled studies have failed to show a generalized benefit of TPE for all patients with RPGN; however, subset analysis of all these studies showed TPE to be beneficial for patients presenting with severe disease or dialysis dependency [19]. A more recent study of Jayne et al. was limited to patients presenting with creatinine levels greater than 5.8mg/dL [20]. In another study based on a TPE trial, Weingarten DLV, et al. observed that chronic and acute tubulointerstitial lesions predict the Glomerular Filtration Rate (GFR) at 12months, yet it was the use of TPE and the number of normal glomeruli on biopsy that remained positive predictors of dialysis independence in the same time interval [21]. This finding is important because it suggests that unaffected glomeruli determine long-term renal outcome at 1year. In a second study, the same group of investigators extended their work in determining the rate of renal recovery [22]. In 69 dialysis-dependent patients who were part of the TPE trial, TPE was superior to pulse methylprednisolone with respect to the change of coming of dialysis. The outcome measure depended on the relative number of normal glomeruli (MEPEX study).

Treatment with TA also provides the possibility of improvement in cases of pulmonary bleeding, which is based on the same immunological process, even when renal function is already irreversibly impaired. A final long-term prognosis for patients whose condition improved after TA cannot be made. As basement membrane antibody formation often ceases during treatment, recovery or at least partial recovery is possible.

Before TPE was available to remove autoantibodies, prognosis was poor and most patients die or was left with permanent renal impairment. In patients with Diffuse Alveolar Hemorrhage (DAH) alone, corticosteroids may be effective. Cytotoxic agents like cyclophosphamide or azathioprine, may occasionally reverse the renal failure, but their main function is to control DAH. The current combination therapy of plasmapheresis and immunosuppressive drugs is successful if applied early, i.e., in patients without oliguria who do not require dialysis.

Some oliguria dialysis-dependent patients also show a significant response to this combination therapy, as a result of which dialysis can discontinue. In contrast, anuria patients do not improve in renal function, and continued dialysis is required; renal transplantation may be considered in these often-young patients. Fortunately, the autoimmune process in Good pasture syndrome seems to be limited, as demonstrated by the small number of reported cases of recurrent disease [23].

After the available results and trials, TA has provided a more rapid decrease in anti-GBM antibodies, lower post-treatment serum creatinine level, and decreased incidence of End-Stage Renal Disease (ESRD). Given these results and the integral role of the anti-GBM antibody, TA as a means of rapidly decreasing anti-GBM titers has become the standard of care (Table 1) [19]. Other authors showed in their findings highlight the safety, efficacy and feasibility of TPE using membrane filtration [24-26].

The treatment strategy could be:

1. Early initiation of TA is essential to avoid ESRD.
2. Initial prescription is 14 daily 3-4 L exchange.
3. Continued apheresis may be required if antibody titers remain increased.
4. Steroids, cyclophosphamide, azathioprine, or rituximab are added to decrease production of anti-GBM antibody and minimize the inflammatory response [11,21,27].

Walsh and the European Vasculitis Study Group (EUVAS) found in 2013 that patients with anti-neutrophil cytoplasmic antibody-associated vasculitis requiring dialysis

at diagnosis are at risk for developing ESRD or dying [27]. Short-term results of a trial comparing TPE to intravenous methylprednisolone suggested TPE improved renal recovery. However, after Walsh and the EUVAS, the long-term follow-up of patients with severe ANCA-associated vasculitis comparing TPE to intravenous methylprednisolone treatment is unclear. TA should be continued until antibodies fall to undetectable levels in patients with active disease and anti-GBM antibodies present [2]. Further research is required to determine the role of TPE in this disease.

Immune Complex Nephritis (ICN)

Many types of glomerulonephritis are initiated by the deposition of immune complexes, which induce tissue injury via either engagement of Fc receptors on effector cells or via complement activation [28]. The generation of antibody and subsequent tissue deposition of ICs is thought to trigger the pathogenic consequences of systemic autoimmune disease. Modulation of the autoantibody response disrupts pathogenesis by preventing the formation of ICs; however, uncoupling IC formation from subsequent inflammatory response seems unlikely because of the apparent complexity of the IC-triggered inflammatory cascade [29].

In view of the devastating pathophysiologic consequences of interaction between circulation immune complexes and the basement membrane, the authors share the opinions of Lockwood et al. that TPE in combination with immunosuppression should be carried out as quickly as possible [30]. Pusey CD, et al. [31]recommended TPE for severe cases of immune complex nephritis (Table 1). Besides TPE, Immunoadsorption, monoclonal human antibodies such as rituximab are used successfully in ICN [32,33].

RPGN with or Without Glomerular Deposition, (ANCA ab) Pauci-Immune RPGN

Approximately 60% of patients with RPGN present with crescentic glomerulonephritis characterized by few or absent immune deposits, the so-called pauci-immune RPGN. Patients with this disease have either Wegner's granulomatosis, ANCA ab associated vasculitis, polyarthritis nodosa, or "renal limited" pauci-immune GN. These diagnoses may represent a spectrum of manifestations of a single disease, because there is marked overlap of clinical and his to pathological features and several patients have ANCA in their blood, which are more common that anti-GBM. The concentration of circulating ANCA correlate with the disease activity in some patients, and ANCA may contribute to the pathophysiology of pauci-immune RPGN through reactivity with neutrophils or endothelial cells, and other inflammatory mechanisms [16,34].

The prognosis of pauci-immune RPGN in general has been poor. Precise therapy therapeutic recommendations are difficult to obtain from the literature, because most series comprise patients with different types of RPGN. However, available data suggest that 80% of such patients progress to ESRD without therapy with high dose immunosuppression or cytotoxic drugs. Some trials have evaluated the efficacy of TA as an adjunct to conventional immunosuppressive in patients with pauci- immune RPGN [20,34,35].

In the above-mentioned MEPEX study, Weingarten DLV, et al. showed that in patients with dialysis-dependent, ANCA-associated vasculitis, the chances of recovery differ depending on the type of adjunctive treatment, the percentage of normal glomeruli and glomerulosclerosis, the extent of tubular atrophy, and the presence of arteriosclerosis. Even with an ominous biopsy at diagnosis in combination with dialysis dependence, the chance of renal recovery exceeds the chance of therapy-related death when the patient is treated with plasma exchange as adjunctive therapy (Table 1) [22]. Further studies are necessary.

The following therapy recommendation is based on the few uncontrolled and controlled studies available [10,19,21,36-40]. TA is indicated in combination with an immunosuppressive therapy with prednisolone (intravenous pulse therapy, or oral therapy), cyclophosphamide (intravenous pulse therapy or oral therapy), or azathioprine in indicated in the following cases:

1. RPGN with serum creatinine under 5.8mg/dL without oliguria in anti-GBM disease.
2. All severe forms of RPGN with or without ANCA ab, like the pauci-immune complexes, (Cr>6 or patient on dialysis).
3. Good pasture syndrome with life-threatening hemoptysis, or diffuse alveolar hemorrhage from ANCA or MPA independent of renal function status.
4. Preparation for kidney transplant with and basement membrane antibodies still detectable in the serum.

The cause of Nephritic Syndrome (NS) of various GN such as Focal Sclerosing Glomerulosclerosis (FSGN) (Table 1), Membranoproliferative GN (MPGN), and Mesangioproliferative GN etc. is most idiopathic [41]. There is evidence pointing to a role of the immune system in pediatric Minimal Change Glomerulonephritis (MCGN). Another hypothesis has described an association between allergy and MCGN in children. Relapses in this syndrome are triggered commonly by minor infections and occasionally by reactions to be stings or poisoning. Abnormalities of both humeral and cellular immunity have described. Finally, the induction of remissions by high doses of immunoglobulin G (IgG, 0.4g/kg BW), corticosteroid, alkylating agents, or cyclosporine therapy provides indirect evidence for an immune etiology.

None of these observations, however, provides direct evidence of immunologically mediated pathogenesis [42]. Other therapeutic measures for NS are anticoagulants, thrombocyte inhibitors, ACE inhibitors, immunosuppressive drugs, lipid reducers, rituximab, and diet [1,43,44]. In high-risk patients, pre-transplant TA appears to prevent or delay recurrence. TPE is started once recurrence is diagnosed. The number of treatments needed to control proteinuria, surrogate marker of FSGN, is quite variable and can reach dozens [2]. The rationale for TPE in FSGN has the category I with the RG 1B (Table 1).

In the case of resistance to medication or severe progression of the disease, additional TA therapy should be considered, as a continuing treatment given once a week, or every 2 weeks, or once a month. Further renal diseases such as light chain nephropathy, dense deposit diseases or others can be in severe cases and if the conservative therapy has failed treated with TA, too [44].

Hemolytic Uremic Syndrome

Hemolytic-Uremic Syndrome (HUS) is a disease that can lead to Acute Kidney Injury (AKI) and often to other serious sequelae, including death. The disease is characterized by microangiopathic hemolytic anemia, thrombocytopenia and AKI. The etiology and pathogenesis of HUS are not completely understood, and the therapy of HUS is complicated. The pathophysiologic aspects of the different pathogenic types of HUS and the therapeutic modalities are discussed by Bambauer R, et al. [45].

The advantage of TA over other therapeutic procedures is that it intervenes at an early stage in the pathogenetic processes by quickly removing immune complexes and toxins. Furthermore, it eliminates fibrinogen, fibrinogen degradation products, and other high molecular complexes, all of which can both support and inhibit coagulation. All other toxins produced by bacteria and viruses like Shigatoxin, the pathogenic pathway which follows the activation of the complement system of the factor HF1 with a partial HF1 deficiency and all other toxic substances can be quickly removed by TA.

Therapeutic apheresis methods that are introduced in HUS as a supportive therapy are TPE, DFPP, and IA with protein-A columns. All methods are described elsewhere [45-48]. The rationale for TA in HUS is discussed controversially because of the limited and or conflicting data available in the literature. The rationale is that TA can effectively remove antibody or mutated circulating complements regulators [2]. TA seems a reasonable option considering the poor prognosis of HUS in adults. The role of TA is uncertain but this treatment may be appropriate as supportive therapy under certain circumstances and with a defined therapeutic endpoint because of the high mortality (Table 1).

A large outbreak of diarrhea and the HUS caused by an unusual serotype of Shiga-toxin-producing Escherichia coli (O104:H4) occurred in Germany in May to July 2011 with 3167 without HUS patients with 16 deaths, and 908 with HUS patients and 34 deaths [49,50]. 241 patients with HUS were treated with TPE and 193 patients with TPE and eculizumab. The treatment strategy was dependent on disease severity [48,49]. TPE and eculizumab in combination seems to be prudent [51-53].

Kidney Transplant Rejection

In chronic renal failure, kidney transplantation is the decisive alternative to permanent dialysis. Rejection of the transplanted kidney is a grave problem. Although various therapeutic interventions to delay or prevent rejection exist, steroids, immunoglobulin's, immunosuppressive, cyclosporine A, OKT3, and other new developed immunosuppressive therapies are used. Infections and rejection reactions are the most frequent complications of modern transplantation [54]. Thus, acute kidney transplant rejection is considered an indication for TA [55]. TA is indicated in the management of rejection crisis due to preformed specific antibodies or a high degree of immunization [56].

Immunological problems like performed donor specific antibodies or a high degree of immunization complicate the outcome of donor transplantation. Postoperatively the antibody-mediated rejection or drug-related side effects of the medication can limit the therapeutic success of transplantation. Acute allograft rejection is one of the important complications after renal transplantation, and it is a deleterious factor for long-term graft survival. Rejection is a complex pathophysiologic process, which has been explained by transcript me and proteome in RNA transcripts and proteins level, respectively [57]. Therefore, therapeutic strategies include a primary avoidance of immunization, careful patient selection, a meticulous immunological workup and a proper follow up and therapeutic apheresis as improved therapy [58,59].

After the blood group barrier had successfully crossed in Japan in the 1980s, different protocols were developed for ABO-incompatible kidney transplantation and the procedure has gained widespread acceptance [60,61]. Immunosuppression consists of tacrolimus, mycophenolate and steroids together with induction therapy with an IL-2-receptor blocking agent. The isoagglutinine antibodies against the donor can be eliminated. Firstly, the CD 19/20-positive pre-B cells with a single infusion of rituximab

4 weeks prior to transplantation and in a second step, the already existing antibodies are depleted by using TA such as TPE, DFPP or IA. Novel sensitization and production of antibodies is thereby efficiently prevented [62,63].

The disadvantage by using TPE is the elimination of physiological proteins, the limitation to 1.0-1.5 Total Plasma Volume (TPV) as treating dose and the potential for infectious complications such as HIV or hepatitis B or C by using plasma as substitution solution. Therefore, various groups use the DFPP or IA with unselective IgG columns. Patients with performed HLA antibodies, i.e., a high percentage of panel reactive antibodies, accumulate on the waiting list for kidney transplantation and can experience a substantially longer waiting time [55,64]. Therefore, center-specific desensitization protocols were developed in order to transplant these highly immunized patients, if transplantation from a living donor with DSA is planned, within a reasonable period (Table 1) [55,65-67].

Anti-HLA alloantibodies that are Donor-Specific Alloantibodies (DSA) also are a contraindication to transplantation unless they can be depleted to the point that the cross match becomes negative. Intravenous Immunoglobulin (IVIG) alone has been successful for this purpose in many patients. However, combinations of TPE, IVIG, and rituximab achieve desensitization in a greater percentage of potential recipients, and with less subsequent rejection [68]. TA in all forms can be applied to remove DSA and multiple HLA antibodies. No selective secondary absorbers exist, and available columns with selectivity for immunoglobulins would be considered the best option. Some treatments are usually needed to deplete the DSA- and/or anti-HLA titer of the recipient.

Acute antibody rejection of organ allografts usually presents as severe dysfunction with a high risk of allografts loss. HLA antibodies are involved in AMR [66,69]. The renal biopsy often cannot rule out one cause or the other with sufficient certainty, leaving the physician with the decision of how to treat vascular rejection that can be caused by antibodies or cellular infiltration [70,71]. TA accompanied by T cell depletion (ATG, ALG, or OKT3) conversion to tacrolimus-based Immuno suppression and pulsed steroids, is used to limit the interstitial and vascular damage [62]. The use of DFPP or IA targeted against IgG has been used successfully. It is not possible, due to conflicting and limited data, to give general recommendations in regard to the treatment of TPE or IA, the number of apheresis sessions and the best immunosuppressive therapy [65]. A screening for donor-specific antibodies should be performed to monitor the antibody titer during treatment, until 10 sessions with daily treatments initially followed by apheresis every other day can be necessary in a patient with vascular rejection (Banff IIb-III or AMR) [55,67].

TA can be attempted to ameliorate the course of the disease and subsequent graft damage, if switching to a different immunosuppressive regimen or the treatment of an underlying infection does not lead to an improvement of the Thrombotic Microangiopathic (TMA) [66]. The treatment regimen is comparable to TMA in non-transplanted patients. The treated volume is usually one TPV with human albumin and/or fresh frozen plasma as substitution fluid and anticoagulation with heparin on a daily basis until platelet count and lactate dehydrogenase have normalized. Up to 50% of patients demonstrate a prompt exacerbation if daily TA is stopped. Continuation of TA on an alternate day strategy for at least two additional treatments can reduce the recurrence rate. Nevertheless, TMA reduces graft survival both in recurring or de novo TMA and treatment might not alter the progression of the disease [55]. Good pasture syndrome or anti-GBM disease can occur de novo in patients following transplantation or as a manifestation of underlying Alport disease, but is rare (e.g., 3% of transplanted male Alport patients) [47,72]. The recipient's immune system is exposed to a collagen component carried by the transplanted organ that is lacking in Alport patients and, consequently, the patient might develop antibodies against this antigen in the glomerular basement membrane. These antibodies may then induce post-transplantation anti-GBM disease.

The treatment of this condition and of de novo disease is identical to the strategy applied to non-transplanted patients. TA is used in order to remove the causative antibody. TPE, DFPP and IA have been shown to deplete the patient effectively of antibodies and halt disease progression [73,74]. The TA should be a rapid removal of the antibodies with daily treatments. Treatment frequency should be tapered later to antibody titer measurements. TA is accompanied by an intensified immunosuppressive regimen to suppress further antibody formation [55,75,76].

Little information is available about long-term results of kidney transplantation in adults with focal segmental glomerulosclerosis. However, primary FSGS recurs with uncertain incidence after kidney transplantation (presumably 20%). A circulating factor is assumed to play a causative role and TA has been successfully applied in patients with recurrent FSGS. In patients treated with a protein-A adsorption column or TPE, a dramatic but usually transient reduction in proteinuria has observed [75]. This effect was larger with the use of IA, but remissions that are more prolonged were reported with the use of TPE with or without combination with cyclophosphamide [55,77].

Therapeutic apheresis in transplantation as an important part of different therapy strategies like for therapy of several

conditions such as AMR or ABOi transplantation is accepted today. TA enables physicians to develop strategies to provide the best organ replacement to patients with high degrees of immunization or performed DSA, thereby expanding the use of living donation. The standard method has been TPE but it is increasingly being replaced by the more selective methods provided by DFPP or IA. Due to the considerable costs of IA, the selection and application of an adsorbed and device for IA should be preceded by a judicious effort to characterize and plan the treatment. The specific characteristics of the clinical problem, the capabilities of the choice available and the current evidence have to be known to avoid high costs or inadequate therapy. TA is an important therapy for several kidney disorders, based on strong evidence from clinical trials, and embodied in well-established guidelines [47,78,79]. A combination of TA and monoclonal human antibodies such as rituximab is successful, too [80].

Conclusion

All mentioned TA methods are still technically complicated and very expensive. The costs of the mentioned TA methods varied widely. The prognosis of immunological diseases has improved considerably in recent years due to very aggressive therapy schemes. These include TA in combination with immunosuppressive therapies and/or biologic agents. In mild forms of autoimmune diseases, immunosuppressive therapies and/or biologic agents seem to be sufficient. TA indicates only in severe cases, such as rapid progression despite immunosuppressive therapy, and/or biologic agents in acute generalized vasculitis, thrombocytopenia and leukopenia, pulmonary, cardial, or cerebral involvement. In these cases, TA must combine with immunosuppressive therapy and/or biologic agents. The use of never technologies, such as Immunoadsorption, possible in combination with recent biologics, might offer some new perspectives for extracorporeal treatment of immunological diseases.

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