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Review

Complications of therapeutic apheresis in pediatric kidney transplantation

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ABSTRACT

In the setting of kidney transplantation, therapeutic apheresis (TA) is employed both for pre-intervention procedures and during the post-transplant period. In pediatric nephrology units, TA is usually performed as a therapeutic plasma exchange (TPE) with dialysis equipment, and using non-plasma replacement fluids. In children undergoing kidney transplantation, complications of TPE are mainly related to its depletive properties combined with the iatrogenic immunodeficiency status of the patient. Moreover, the use of small central venous catheters and the equipment standardized for adults can increase the risk of adverse events. Focusing on these preconditions, TA in kidney-transplanted children should be performed in specialized centers with specific protocols and a trained staff.

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Contents

1. Introduction

Therapeutic apheresis (TA) is a valuable treatment option in kidney transplantation and is most often used as a pre-intervention procedure to remove circulating donor directed alloantibodies (DSA) or in the preconditioning of ABO incompatible donor recipient pairs. In the post-transplant setting, TA has a huge role in eliminating DSA actively injuring the renal graft (antibody-mediated kidney rejection) and/or treating the recurrence of primary diseases, such as focal segmental glomerular sclerosis, thrombotic microangiopathies, complement-mediated and immune complex-mediated glomerulonephritis. In transplantation medicine, TA is available in different technical variants, including therapeutic plasma exchange (TPE), immunoadsorption (IA), and double filtration plasmapheresis (DFPP). Despite the increasing use of fractional and immunoadsorbitive techniques in the treatment of transplantation-associated conditions, the evidence for effective and safe treatment is still largely on the side of TPE, especially in children.

In a published case series of children, the incidence of adverse effects per apheresis procedure ranges from 5 to 50% [1–4]. The frequency and types of complications from TPE depend on the overall condition of the patient, the number of procedures, the replacement fluid, and the venous access device. A review of the reported complications from over 15,000 TPE treatments in adults found

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that the overall incidence of adverse reactions was 9.7%, and events were substantially more common with plasma than with albumin replacement (20 versus 1.4 percent) [5]. Nowadays, when applied to renal transplant patients, TPE is more frequently performed with non-plasma replacement fluids. Use of complement-blockers has, in fact, decreased the use of TPE with fresh frozen plasma (FFP) in preventing and treating the recurrence of thrombotic microangiopathies in renal allograft [6].

Complications of TA in kidney transplantation are mainly related to its depletive properties applied in patients with an iatrogenic (drug-induced) immunodeficiency. In children, the risks are further emphasized, and are often associated with a burden of technical issues deriving from the fact that treatments are performed using small central venous catheters and machines which have been studied and standardized for adult patients.

In this review, we will describe potential complications of TA in pediatric kidney transplantation, focusing mainly on TPE.

2. Immunoglobulin depletion and infections

Repeated sessions of TPE with a non-plasma replacement fluid can cause a remarkable depletion in immunoglobulins (Ig), resulting in low serum IgG levels. IgG clearance follows an exponential curve and with a single TPE of 1.25 plasma volumes, the estimated decrease in intravascular Ig is about 71% [7]. After a complete treatment of apheresis, serum levels of IgG depend not only upon the exchanged plasma volumes, but also on the numbers of sessions performed, the patients' immune status and their ability to produce Ig. Transplanted children have a secondary immunodeficiency. Immunosuppressant drugs such as calcineurin inhibitors, mycophenolatemofetil, and m-TOR inhibitors act mainly against T lymphocytes, but indirectly also impair the proliferation of B-cells and eventually antibody production. Furthermore, several patients with a diagnosis of AMR received anti-CD20 drugs, causing a dramatic reduction in B-cells levels.

In children, the humoral immune system is relatively underdeveloped as compared with adults. The differences are not only quantitative, but also qualitative; in fact, IgG responses to pathogens appear to be weaker during early life [8]. Association of Ig depletion with a qualitative deficiency might increase the risk of infections. Although it is unclear whether TPE alone can lead to a significant increase in the risk of serious infectious diseases [9–11], this seems potentially increased when TPE is performed in iatrogenic immunocompromised patients, especially when concurrent therapy with biological agents (rituximab or bortezomib) is given. Various types of infections are reported, bacterial or viral, including urinary tract infections, tonsillitis, pneumonia, and abscesses with need for surgical intervention, meningits, CMV reactivation, Herpes Zooster and opportunistic infections [12,13]. When not already included in the treatment protocol, for those patients who experience a post-TPE fall of IgG level below 4 g/L, regular infusion of intravenous Ig (IVIg) at a dosage of 200–400 mg/kg should be considered.

3. The donor-specific HLA antibodies rebound

Rebound of immunoglobulin production after TPE in humans is well known since the early 90s [14]. During TPE, the removal of circulating Ig is associated with a remarkable drop in autoregolatory inhibitors of antibody production, with a subsequent intense stimulus to the immune system [14,15]. After an intensive session of TA there is an increase in the percentage of circulating B-cells coupled with an even higher production of Ig per B-cell [15].

TPE still represents a cornerstone in the treatment of AMR. However, the reduction rates of DSA by TPE alone are not consistent, depending on the patient's characteristics, DSA levels and specificity, and eventually the balance between DSA removal and production. TPE modifies the negative feedback between circulating DSA and DSA-producing B-cells. This effect is mitigated by the administration of IVIg after every TPE session, which is mandatory in the protocol of AMR treatment [16].

Several other mechanisms have been proposed in the pathogenesis of DSA rebound after TPE [17]. TPE may activate naïve B-cells with subsequent production of de novo DSA due to sensitization by antigens from the transplanted kidney. Furthermore, TPE can activate memory B-cells with production of DSA peaking 7 to 9 days after a TA procedure [18]. In both cases, the production and/or release of DSA may be further emphasized by the exposition of antigens from graft tissue that is damaged by AMR.

Due to the DSA rebound phenomenon, in treating AMR or in the desensitization protocol for ABO incompatible transplantation, TPE should always be associated with other treatments to reduce the production of antibody including IVIg, oral immunosuppression, and use of rituximab or bortezomib [16,19,20].

4. Removal of immunosuppressant drugs

Since TPE removes large amounts of plasma, it can also eliminate circulating drugs depending on their volume of distribution and/or the rate of protein binding. In particular, medications with a low volume of distribution and/or a high rate of protein binding are associated with increased depletion [21].

The most widely accepted immunosuppressant regimen in pediatric kidney transplanted patients is composed of steroids (prednisone) plus calcineurin inhibitors (cyclosporine or tacrolimus) and a cytostatic agent, including mycophenolatemofetil or everolimus. Only 1% of the total daily dose of prednisone is removed by TPE [21], since it is highly protein bound, with a large volume of distribution. Cyclosporine and tacrolimus present a large volume of distribution but, despite a high rate of protein binding, only a minor fraction of these drugs is removed by TPE [22,23].

Several monoclonal antibodies (infliximab, rituximab, eculizumab, bortezomib, etc.) are used in the standard immunsuppressive protocol and/or AMR treatment of kidney transplantation. All these drugs have a low volume of distribution and a relatively long elimination half-life. Therapeutic PE may thus remove a significant amount of therapeutic antibodies, in particular when the infusion is performed 3 days prior to the TA[24]. To overcome this problem, monoclonal antibodies should be administered after the exchange and/or additional "rescue" doses should be used after a complete TPE session.

5. Hypocalcemia

In a retrospective review of our center's experience, 370 TPE procedures for nephrological indications were performed over 5 years (from January 2008 to December 2012) using exclusively a membrane-based system (personal unpublished data). The median body weight of the patients was 21 kg and the median replacement fluid volume was 1000 ml, consisting of 5% albumin in 84% of procedures and fresh frozen plasma in the remaining treatments. Insufficient blood flow and hypocalcemia were the more frequent complications, both accounting for 6.7% of all procedures. In 2009, the Italian Registry of Pediatric TA reported on 219 TPE procedures in 38 patients [3]. Similar to our results, the authors found that adverse events were registered in 22 procedures (10%), the most frequent being symptomatic hypocalcemia (6.4%) and inadequate blood flow (1.8%). Michon et al. described the type and frequency of adverse events to TA in a large pediatric cohort consisting of 186 children who had

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