Immunoadsorption in nephrology and kidney transplantation

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Immunoadsorption finds incremental implementation in the treatment of several autoimmune disorders as well as for kidney transplant indications (see Table 1). As opposed to plasmapheresis, immunoadsorption allows not only a more specific but also a more effective clearance of circulating immunoglobulins without the side effects associated with the substitution of fresh frozen plasma or albumin. In addition, even multiple plasma volumes may be processed, and a reduction of immunoglobulins of 80% and more is feasible [1]. However, one has to consider that plasmapheresis is not only utilized for removal of immunoglobulins but also for the substitution of different plasma components such as ADAMTS-13 in the case of thrombotic thrombocytopenic purpura [2]. Therefore, plasma infusion itself may have beneficial effects independent of the removal of circulating pathogenic substances. The use of plasmapheresis for the treatment of different kidney diseases remains controversial due to a lack of randomized controlled trials demonstrating the benefit of this procedure. This applies even more to immunoadsorption. However, for some indications especially in the field of kidney transplantation, there is now growing evidence pointing to the large potential of this treatment modality. This editorial comment will focus on the available evidence on immunoadsorption in kidney diseases and kidney transplant indications.

General considerations

Immunoadsorption devices

In general, one has to differentiate single-use versus reusable immunoadsorption devices and antigen-agnostic versus antigen-specific columns. These are dextran sulphate (e.g. Selesorb) and DNA-binding columns, especially for the treatment of systemic lupus erythematosus (SLE). IMPH-350/IMTR-350 are single-use columns with phenylalanine and tryptophan as ligands which bind a broader spectrum of antibodies. The protein A (Immunosorba) immunoadsorption device consists of two parallel, regenerable columns that bind IgG subclasses 1, 2 and 3, IgA and IgM with variable affinity. The synthetic peptide peptide-GAM, which is bound to sepharose (Globaffin), is comparable to the pro-
tein A column. The regenerable Ig-Therasorb column has polyclonal sheep anti-human IgG antibodies bound covalently to sepharose. Ig-Therasorb binds all IgG subclasses with high affinity (>97%); IgM and IgA are bound to a lesser extent (∼30%). The antigen-specific Glycosorb column will be discussed in detail below [3]. During one apheresis session, >80% of IgG may be removed by, e.g. the protein A column. With the treatment of 2.5 plasma volumes, immunoadsorption is capable of removing 87% of IgG [1], whereas albumin or antithrombin III remains almost unaffected [4]. In general, during one session, ~1–2.5 plasma volumes are exchanged, and therapy is performed everyday in severe disease states with high antibody titres or every other day (three times a week), e.g. in less aggressive diseases. For maintenance therapy, e.g. in patients with SLE and stable disease, two treatments on alternate days every 4–6 weeks may be sufficient. In general, immunoadsorption ensures rapid antibody depletion; potent immunosuppression is then needed for the sustained reduction of the pathogenic antibodies, e.g. rituximab in highly sensitized kidney transplantation, or cyclophosphamide in SLE and vasculitides.

**Immunoadsorption for the treatment of glomerulonephritis and vasculitis**

**Focal segmental glomerulosclerosis**

Both plasmapheresis and selective immunoadsorption have been studied in patients with focal segmental glomerulosclerosis (FSGS) because a circulating permeability factor has been suggested in the pathogenesis of this disease. Several studies demonstrated a beneficial effect of

### Table 1. Indications for immunoadsorption in nephrology and kidney transplantation

<table>
<thead>
<tr>
<th>Indication</th>
<th>Pathogenic factor</th>
</tr>
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<tbody>
<tr>
<td>Systemic lupus erythematosus</td>
<td>Anti-ds-DNA antibodies, anti-nuclear antibodies, immune complexes</td>
</tr>
<tr>
<td>Focal segmental glomerulosclerosis</td>
<td>Circulating humoral factor</td>
</tr>
<tr>
<td>ANCA-associated small vessel vasculitis</td>
<td>ANCA</td>
</tr>
<tr>
<td>Goodpasture's disease</td>
<td>Anti-GBM antibodies</td>
</tr>
<tr>
<td>TTP</td>
<td>ADAMTS-13 antibodies</td>
</tr>
<tr>
<td>Cryoglobulinemia</td>
<td>Immune complexes</td>
</tr>
<tr>
<td>Highly sensitized kidney transplant recipient</td>
<td>HLA and non-HLA alloantibodies</td>
</tr>
<tr>
<td>Antibody-mediated allograft rejection</td>
<td>HLA and non-HLA alloantibodies</td>
</tr>
<tr>
<td>ABO-incompatible transplantation</td>
<td>Blood group isoagglutinins</td>
</tr>
</tbody>
</table>

### Table 2. Immunoadsorption in systemic lupus erythematosus (adopted from Stummvoll G, NephroScript 2007; 2:34)

<table>
<thead>
<tr>
<th>Ligand/device</th>
<th>Patient (n)</th>
<th>Investigated parameter</th>
<th>Reference</th>
</tr>
</thead>
<tbody>
<tr>
<td>IgG-Therasorb</td>
<td>16</td>
<td>Proteinuria, disease activity, dsDNA in lupus nephritis [12]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>16</td>
<td>Infection, dsDNA [51]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Outcome of pregnancy in active SLE [13]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>1</td>
<td>Proteinuria, dsDNA in lupus nephritis with active tuberculosis [52]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>2</td>
<td>Infection, dsDNA, IgG in SLE with/without immunoglobulin substitution [53]</td>
<td></td>
</tr>
<tr>
<td>Protein A/Prosurba, Imunosorba</td>
<td>8</td>
<td>dsDNA, IgG [54]</td>
<td></td>
</tr>
<tr>
<td>Dextran sulphate/Selesorb</td>
<td>1</td>
<td>Renal function in class IV lupus nephritis [55]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>19</td>
<td>Clinical improvement in dermal vasculitis [56]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>Proteinuria, disease activity, dsDNA in lupus nephritis [58]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>6</td>
<td>dsDNA, disease activity [59]</td>
<td></td>
</tr>
<tr>
<td>Phenylalanine/Immunosorba</td>
<td>6</td>
<td>dsDNA, proteinuria in lupus nephritis [60]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>50</td>
<td>Disease activity [61]</td>
<td></td>
</tr>
<tr>
<td></td>
<td>10</td>
<td>Disease activity, dsDNA (comparison to the Therasorb device) [11]</td>
<td></td>
</tr>
<tr>
<td>C1q</td>
<td>8</td>
<td>Proteinuria, renal function, arthritis, dermal vasculitis [62]</td>
<td></td>
</tr>
</tbody>
</table>

Results of numerous uncontrolled studies in patients diagnosed, e.g. with SLE (see also Table 2) are difficult to compare and interpret due to multiple variations in protocols and techniques ranging from different exchange volumes, methods of plasma separation (membrane versus centrifuge plasma separation), substitution of substances, anticoagulation and frequency of intervention (daily versus alternate day) to concomitant immunosuppression, etc. In general, during one session, ~1–2.5 plasma volumes are exchanged, and therapy is performed everyday in severe disease states with high antibody titres or every other day (three times a week), e.g. in less aggressive diseases. For maintenance therapy, e.g. in patients with SLE and stable disease, two treatments on alternate days every 4–6 weeks may be sufficient. In general, immunoadsorption is applied in combination with immunosuppressive therapy in the different disease entities. Immunoadsorption ensures rapid antibody depletion; potent immunosuppression is then needed for the sustained reduction of the pathogenic antibodies, e.g. rituximab in highly sensitized kidney transplantation, or cyclophosphamide in SLE and vasculitides.
plasmapheresis in patients with FSGS. Plasmapheresis might, at least in patients with steroid responsiveness, diminish proteinuria and stabilize renal function [5,6]. It was suggested that an in vitro system (GVV-test) for the presence of a factor altering glomerular albumin permeability according to the description by Godfrin [7] may distinguish a favourable response of apheresis in patients with FSGS [8].

Although plasmapheresis cannot be generally recommended in patients with FSGS, plasmapheresis and probably immunoadsorption might be beneficial, at least in those patients who respond to steroid treatment. There are conflicting results on the effectiveness of immunoadsorption in the treatment of FSGS. Haas and co-workers found a reduction of proteinuria by >50% in four out of eight patients; however, after cessation of immunoadsorption, recurrence of the disease was noted in most patients (Immusorba and Ig-Therasorb device; 2.5 plasma volumes; five treatments on alternate days) [8].

Immunoadsorption for the treatment of SLE

Autoantibodies, e.g. anti-double-stranded DNA antibodies, and circulating immune complexes play a pivotal role in the pathogenesis of SLE and may also reflect disease activity [9]. Formation of immune complexes within glomeruli appears to be a central event in the pathophysiology of lupus nephritis. Therefore, depletion of these immune complexes and antibodies by plasmapheresis has been suggested to be beneficial in addition to conventional immunosuppression. However, a large multicentre trial failed to demonstrate superiority of plasmapheresis over conventional immunosuppression with respect to clinical outcome [10]. Nevertheless, a therapeutic benefit of plasmapheresis in a subset of SLE patients, particularly in those with rapidly progressive glomerulonephritis, pulmonary haemorrhage or catastrophic antiphospholipid syndrome, as well as patients who failed to respond to conventional therapy is likely. With respect to immunoadsorption, there exist predominantly case reports or small case series from single centres (see Table 2). Studies in general show efficient reduction of the specific antibodies as well as clinical response in most patients. However, these are uncontrolled data, and cases with negative outcome might have not been reported (‘report bias’). One randomized clinical trial in 20 SLE patients compared the efficacy of two different adsorption columns (Immusorba versus Ig-Therasorb, n = 10 in each group) [11]. Both groups showed an 80% clinical response after 1 month. Stummvoll and colleagues treated 16 patients with severe SLE and renal disease in whom cyclophosphamide was either contraindicated (e.g. in the case of active tuberculosis) or failed to halt disease progression with immunoadsorption (Ig-Therasorb; 6000–8000 mL plasma; mean of 3.2 treatments per week) [12]. Within 3 months, 14 patients responded to therapy, and 11 out of those 14 patients were followed up for additional 9 months. Proteinuria in those patients dropped from 6.7 g/day at baseline to 2.9 g/day at Month 12. Anti-dsDNA antibodies were significantly reduced by immunoadsorption, and clinical improvement was noted in all patients, whereas infections or other adverse events were infrequent. In another case series, immunoadsorption was effective in one out of two pregnant women with SLE and a disastrous course during prior pregnancies [13]. Though no data from randomized controlled trials exist, immunoadsorption has to be considered for the treatment of patients with SLE and life-threatening disease, severe kidney involvement, diffuse pulmonary haemorrhage, neuropsychiatric involvement or catastrophic antiphospholipid syndrome, or in those patients with contraindications to conventional therapy or who failed to respond to conventional therapy [14].

ANCA-associated small vessel vasculitides

Although there are cases with ANCA-negative pauci-immune crescentic glomerulonephritis, there is some evidence that ANCA themselves are pathogenic [15,16]. Early trials in ANCA-associated small vessel vasculitides showed no overall benefit of plasmapheresis in addition to conventional immunosuppression; however, there is now evidence that, at least in those patients with very severe disease, plasmapheresis increases the probability of renal recovery [17–19]. These data are in contrast to other reports demonstrating a lack of efficiency of plasmapheresis [20], probably because they did not include renal function as a primary end point. While one can imagine that immunoadsorption will also have beneficial effects in ANCA-associated small vessel vasculitides, there are no randomized controlled trials but only case reports available [21,22]. Notably, one study by Stegmayr and co-workers compared plasmapheresis with immunoadsorption (protein A column; six treatments) in patients with rapidly progressive crescentic glomerulonephritis; 33 out of 44 patients in this study had ANCA-associated small vessel vasculitides [23]. Most patients had improved renal function after six treatments regardless whether they were assigned to plasmapheresis or immunoadsorption.

Anti-glomerular basement membrane antibody disease (Goodpasture's disease)

Another less frequent pattern of rapidly progressive crescentic glomerulonephritis is anti-glomerular basement membrane antibody (anti-GBM) disease. In anti-GBM disease, disease activity correlates well with the circulating antibody against the 28-kDa non-collagenous C-terminus of the alpha-3 chain of type IV collagen. In addition, the antibody is pathogenic, and the goal of treatment is the rapid reduction of those antibodies. Even though there have been only small controlled trials of plasmapheresis in the treatment of Goodpasture’s disease, it is now an approved therapy for all patients with rapidly progressive glomerulonephritis and/or pulmonary haemorrhage [24–26]. Prior to the introduction of plasmapheresis, mortality and end-stage renal disease from Goodpasture’s disease were extremely high [27]. The beneficial effect of plasmapheresis on the long-term outcome of patients with anti-glomerular basement membrane antibody disease was summarized in a retrospective analysis of 71 patients [25]. As in ANCA-associated small vessel vasculitides, there is
a similar lack of evidence on the use of immunoadsorption in Goodpasture’s disease. There are only a few case reports available, with conflicting results [28,29]. Of note, as with plasmapheresis, immunoadsorption should be administered aggressively, e.g. daily immunoadsorption with 2.5 plasma volumes for 14 days [30].

Immunoadsorption in kidney transplantation

Immunoadsorption is increasingly used in kidney transplantation for either the preparation of the ABO-incompatible or the highly sensitized kidney transplant candidate before transplantation, or the treatment of antibody-mediated rejection after transplantation. Different protocols using different immunoadsorption devices have been published.

ABO-incompatible kidney transplantation

The first attempts to overcome the ABO barrier had been performed in the early 1970s with unsatisfactory results. Today, there are essentially three different protocols available for the transplantation of the ABO-incompatible kidney graft recipient—from Japan, the USA and Europe. The Japanese protocol included plasmapheresis or double-filtration plasmapheresis, immunosuppression with anti-lymphocyte globulin and/or desoxyspergualin and/or cyclophosphamide, splenectomy at the time of engraftment, and anticoagulation therapy. Success rates were below the rates in ABO-compatible transplants, and rejection rates were as high as 58% [31]. The Johns Hopkins (USA) protocol consisted of perioperative plasmapheresis followed by low-dose CMV hyperimmunoglobulin and rituximab (until 2007, then without rituximab). Patient and graft survival rates in ABO-incompatible transplantation were comparable to ABO-compatible kidney transplantation [32]. More recently, the Stockholm protocol has been introduced by Tyden and co-workers [33]. This protocol was aimed to achieve a target ABO isoagglutinin titre of <1:8 at the morning of transplantation. Patients with a starting ABO isoagglutinin titre of <1:256 were considered eligible for ABO-incompatible transplantation and received a single dose of rituximab (375 mg/m²) 10 days before transplantation. Patients routinely received four immunoadsorption treatments on alternate days (1 plasma volume) before kidney transplantation and 3 thereafter using an antigen-specific immunoadsorption column (Glycosorb ABO, Glycorex Transplantation, Lund, Sweden). Other European centres adopted this algorithm with only minor modifications [34,35]. Meanwhile, long-term results with more than 3 years of follow-up are available as well as pooled data from three different centres, indicating that the outcome in ABO-incompatible kidney transplantation is not different from ABO-compatible transplants [36,37].

The Glycosorb ABO column is a single-use column that efficiently reduces donor-specific anti-A and anti-B IgM and IgG at 81% and 56%, respectively, at the first treatment. The median reduction of total IgM and IgG is 34% and 18%, respectively. Of note, antibodies against pneumococcus and haemophilus polysaccharide antigens are significantly reduced, whereas anti-tetanus and anti-diphtheria protein antibodies are not affected [38]. So far, there are no reports on the use of other immunoadsorption devices, and we have no direct comparison on the efficacy of plasmapheresis versus double-filtration plasmapheresis or versus antigen-specific immunoadsorption available in the preparation of the ABO-incompatible kidney transplant candidate. From our own experience, we feel that antigen-unspecific immunoadsorption by, e.g. the Globaffin or Ig-Therasorb device is equivalent to antigen-specific immunoadsorption in terms of efficacy, whereas plasmapheresis seems to be superior to immunoadsorption especially in the removal of IgM isoagglutinins (unpublished data).

Preparation of the highly sensitized patient for transplantation

As in the management of the ABO-incompatible kidney transplant candidate, several protocols exist for the removal of antibodies, e.g. HLA and non-HLA alloantibodies in the highly sensitized kidney graft recipient. In general, these protocols use plasmapheresis and/or intravenous immunoglobulins for rapid antibody depletion before transplantation in combination with potent immunosuppression for sustained reduction of donor-specific antibodies after transplantation [39,40]. Since the early 1990s, there have been single reports on the successful removal of HLA alloantibodies by immunoadsorption [41,42]. In 1996, a first report on the efficacy of immunoadsorption in the removal of HLA alloantibodies in highly sensitized kidney transplant candidates was published by Higgins et al. [43]. In 13 deceased donor kidney recipients, immunoadsorption was capable of rendering a positive pre-transplant crossmatch negative; however, long-term graft loss was inadequately high. More recently, the Vienna group established an algorithm for the transplantation of highly sensitized patients using immunoadsorption with the staphylococcal protein A column in combination with potent immunosuppressive therapy including anti-lymphocyte antibody therapy [44,45]. Between 1999 and 2003, 40 patients were transplanted according to this algorithm, including nine patients with an initially positive CDC crossmatch, which was rendered negative after a single preoperative immunoadsorption session. After transplantation, immunoadsorption was performed every 1–3 days until stabilization of graft function was noted; the median duration of immunoadsorption treatment was 22 days. Though successfully transplanted with satisfactory long-term allograft survival, antibody-mediated rejection was rather high, with 33% and 32% of patients with an initially positive or negative CDC crossmatch, respectively. In contrast to the study by Higgins et al. [43], the approach of repeated post-transplant immunoadsorption treatments may have prevented the deleterious effects of rapid rebound of donor-specific antibodies in the early postoperative period. Of note, in this report, a median of 9.4 and 8 L of plasma were processed.
during the pre-transplant immunoadsorption session in CDC crossmatch-positive and CDC crossmatch-negative kidney recipients, respectively. These numbers may not be achieved with the use of plasmapheresis due to a high likelihood of adverse reactions attributable to the administration of fresh frozen plasma or albumin.

Our own group recently introduced an algorithm for the transplantation for high risk sensitized patients. So far, a total of nine living donor kidney recipients with a positive crossmatch and/or donor-specific HLA alloantibodies have been transplanted using immunoadsorption as the mainstay of therapy with no graft or patient loss during a follow-up of up to 3 years [46].

Treatment of antibody-mediated rejection

Approaches to reduce or eliminate donor-specific alloantibodies in the context of antibody-mediated rejection include the same measures as described above, e.g. plasmapheresis and/or intravenous immunoglobulins together with potent immunosuppressive medication [47,48]. A first report that highlighted the efficacy of immunoadsorption in kidney transplant recipients with acute antibody-mediated rejection was published in 2001 [49]. In 9 out of 10 kidney transplant patients, kidney function recovered after the initiation of anti-humoral therapy. A recently published randomized controlled trial of Böhmig and co-workers confirmed the efficacy of immunoadsorption therapy in the reversal of severe antibody-mediated allograft rejection [50]. Patients with severe graft dysfunction and the demonstration of peritubular capillary C4d deposits were randomized to receive either tacrolimus conversion and immunoadsorption treatment (protein A column; 2.5 plasma volumes; initially daily treatment for 3 days then every 3 days up to 6 weeks), or tacrolimus conversion only. The study was stopped after 10 patients only (five patients in each treatment arm) since all patients with immunoadsorption treatment showed a clinical response, whereas four out of five patients in the tacrolimus conversion arm remained dialysis dependent. With the major limitations of a small sample size as well as the absence of a control group receiving plasmapheresis or intravenous immunoglobulins, this trial clearly suggests the efficacy of immunoadsorption therapy in reversing antibody-mediated allograft rejection.

Conclusions

Immunoadsorption is increasingly used for the treatment of different disease entities in nephrology and kidney transplantation. Due to the lack of data from randomized controlled trials, however, a general recommendation for the widespread use of immunoadsorption cannot be made. In contrast to plasmapheresis, immunoadsorption (i) provides more specific elimination of pathogenic substances, especially the removal of IgG1, IgG2 and IgG4 antibodies, (ii) needs no substitution of fresh frozen plasma or albumin with a lower frequency of side effects, and (iii) allows the treatment of higher plasma volumes with a greater reduction of immunoglobulins (immunoadsorption is capable of removing >85% of IgG during one session). On the other hand, plasmapheresis, as opposed to immunoadsorption, can substitute large volumes of plasma as needed, e.g. in the treatment of the atypical haemolytic ureaemic syndrome or in intoxications. In the future, immunoadsorption may replace plasmapheresis in the treatment of some but not all diseases due to a higher efficacy and a lower rate of side effects; however, the high costs associated with immunoadsorption therapy must be taken into account. Randomized controlled multicentre trials are mandatory to support the therapeutic opportunities offered by immunoadsorption.

Conflict of interest statement. None declared.

References

18. Nakamura T, Matsuoka T, Kawagoe Y et al. Plasmapheresis with immunosuppressive therapy vs immunosuppressive therapy alone for rapidly progressive anti-neutrophil cytoplasmic autoantibody-


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