Plasmapheresis and Intravenous Immunoglobulin in the Treatment and Prevention of Antibody Mediated Rejection

Background: Acute antibody-mediated rejection (AMR) is a rare complication which often results in the loss of kidney graft. The objective of this retrospective monocentric study was to evaluate three different approaches to AMR.

Methods: We retrospectively evaluated data files from 1226 patients who had undergone renal transplantation in 1/2002 – 12/2008. In 2002 - 2003, patients with AMR were treated with 5 plasmaphereses (PP group, n= 13), and in 2004 - 2008 they received 5 PP along with intravenous immunoglobulin (PP+ IVIG, 0.2g/kg, n=21). Third group consisted of patients with persistence of presence of donor specific antibodies who received a single dose of rituximab (PP+ IVIG+ anti-CD20, n= 11). At 12 months follow-up data were analyzed.

Results: First year graft survival was significantly higher in the PP+ IVIG group than in PP group (90.5% vs. 46.2%; p= 0.027), similarly patient survival was higher in the same group (95.2% vs. 76.9%; p= 0.001). The incidence of infectious complications was similar. First year graft survival in rituximab group was 63.5%.

Conclusion: In this retrospective single center study the superiority of plasmapheresis and intravenous immunoglobulin was proven in the treatment of early acute antibody-mediated rejection of renal allograft.

Key words: acute antibody-mediated rejection, plasmapheresis, intravenous immunoglobulin, anti-CD20, graft survival, patient survival

**Ergebnisse:** Das Transplantatüberleben im ersten Jahr war in der PP+ IVIG-Gruppe signifikant höher als in der PP-Gruppe (90.5% vs. 46.2%; p= 0.027), ähnlich war in derselben Gruppe auch das Patientenüberleben besser (95.2% vs. 76.9%; p = 0.001). Komplikationen durch Infektionen traten vergleichbar häufig auf. Das Transplantatüberleben im ersten Jahr lag in der Rituximab-Gruppe bei 63.5%.

**Schlussfolgerung:** In dieser retrospektiven Single-Center-Studie konnte die Überlegenheit von Plasmapherese und intravenösem Immunglobulin zur Behandlung der frühen akuten antikörpervermittelten Abstoßung des Nierentransplantats bewiesen werden.

**Schlüsselwörter:** akute antikörpervermittelte Abstoßung, Plasmapherese, intravenöses Immunglobulin, anti-CD20, Transplantatüberleben, Patientenüberleben

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**Introduction**

Antibody-mediated rejection (AMR) represents the important cause of renal allograft failure. Deposition of the C4d complement, first described by Feucht et al. in 1993 [1], has been shown to have, in peritubular capillaries, 95% sensitivity and specificity for the presence of circulating antibodies against HLA antigens of the recipient. Early AMR accounts for 5-10% of all acute rejections [2, 3]. The risk of renal graft loss is high and the one-year graft survival is reduced [4, 5]. The diagnosis of AMR is supported by histological verification staining including peritubular capillary deposition of the C4d complement fragment and confirmation of positive donor-specific antibodies [6]. Early AMR usually occur within the first 3 weeks after kidney transplantation.

**Patients and Methods**

From the 1st of January 2002 through the 31st of December 2008, there were 1226 kidney transplantations performed in our centre, with AMR diagnosed in 45 patients (3.7%). 44 patients received kidneys from deceased donors and one patient received a kidney from a living donor. For the purposes of this study we analyzed follow-up of 45 patients treated with plasmapheresis (PP), PP along with intravenous immunoglobulin (IVIG), PP+IVIG+rituximab in resistant cases. The patient’s demographic parameters are shown in Table 1. Patients were treated with maintenance immunosuppression based on either tacrolimus (0.2 mg/kg) or cyclosporine A (8 mg/kg), mycophenolate mofetil (2000 mg/day) and corticosteroids. In the case of a higher PRA frequency (> 50%), patients received induction therapy with ATG (antithymocyte globulin) or with OKT3 (anti-CD3 monoclonal antibody). Since 2005 the muronamok OKT3 has not been available in the Czech Republic and patients received ATG. Concomitant acute T-cell mediated rejections were treated with methylprednisolone or ATG as appropriate.

**Histology**

Case biopsies were performed under ultrasound control, using a 14G biopsy guide needle. The diagnosis was based on histological verification according to the Banff classification [7, 8].

**Verification of Donor-specific Antibodies (DSA)**

DSA were detected either by cytotoxic cross-match (CDCXM) or by flow cytometry (FCXM). These tests were carried out at the same time when histology suggested AMR. The advantage of CDCXM is its quick availability while FCXM is an accurate analytical method.

**Treatment of AMR**

The aim of this study was to evaluate the efficacy of treatment of AMR in two periods using different approaches. In 2002-2003, patients were treated in average with 5 cycles of plasmapheresis (PP) while, in 2004-2008, they received a combination of 5 PPs followed by intravenous immunoglobulin (IVIG; 0.5g/kg from 2004-2007 and 0.2g/kg since 2008). The minimum of performed PP was 3, the maximum was 7. Resistant cases were defined by the positivity of cytotoxic (CDC) and flow cytometry cross-matches (FCXM) 10 days of therapy when patients received rituximab in a single dose (375 mg/m²). Plasmapheresis was performed on a Prisma system (HOSPAL, GAMBRO DASCO, Italy) with a high-permeability capillary filter. Polyvalent human lyophilized immunoglobulin produced from plasma (Endobulin, Kiovig, Gammagard, Baxter-Immuuno, Germany) was used as IVIG. Patients with early AMR and acute cellular rejection received methylprednisolone along with PP or PP+ IVIG and, in cases of type Ib and IIc acute vascular rejection (according to the Banff 97 classification system) they received antithymocyte globulin.

**Statistical Analysis**

Basic statistic parameters such as the absolute and relative frequencies, mean, and tendency excursion were calculated for the purpose of descriptive data analysis. Survival curves were estimated using the Kaplan-Meier method. Agreement between the groups was tested using the log-rank test. The difference between groups was analyzed by the Χ² test for discrete values and by the t-test for continuous values. All statistical tests were two-sided and the da-
Results

Early AMR was observed in 45 out of our 1226 patients who had undergone kidney transplantation in 2002-2008. In 2002-2003, AMR was found in 13 (3.7%) out of 350 renal transplant recipients while in 2004-2008, AMR occurred in 21 (2.3%) out of 924 recipients. Patients receiving the PP+IVIG combination had better one-year graft survival than those treated using the earlier regimen. 19 (90.5%) grafts treated for AMR with PP+IVIG were functioning while only 6 (46.2%) grafts were functioning in the group treated with PP at the end of the first year post-transplant (p= 0.027, Fig. 1). 7 grafts in the PP-treated group failed. In the PP+IVIG group, there was a better patient survival than in the PP group (p= 0.001, Fig. 2). 20 patients treated with PP+IVIG survived the first year; one patient died due to fulminant bronchopneumonia, while three patients in the PP group died within the first year, two from fulminant bronchopneumonia and one patient with a functioning graft died at home, most likely of cardiovascular complications. AMR treatment was associated with similar rates of infectious complications (Table 2).

In the rituximab group, the graft survival was 63.6% and patient survival was 100%.

Discussion

The aim of this large single-centre retrospective study was to compare first year graft survival after early AMR that was treated with three approaches. Compared with plasmapheresis alone, PP+IVIG treatment was clearly more...
efficacious. This was reflected in better graft survival and a lower incidence of acute rejection in rebiopsies. It is obvious that the results may have been influenced by the small numbers of individuals in both groups. However, based on our knowledge, this study is the largest published to date. AMR occurs mostly in patients at high immunologic risk. In 20 out of the 45 patients, the PRA frequency was higher than 50% and 26 patients received retransplants. The incidence of AMR in our study was low (3.7%). Lehrich et al. [8] reported an incidence of 4.5% while Rocha et al. [9] 5.6%. Ibernon et al. [10] came to a similar conclusion. In 1999-2004, seven patients with AMR were treated with daily PP and three patients with the combination of PP+ IVIG. In one case, PP+ IVIG therapy was supplemented with rituximab. The one-year patient survival was 100%, graft survival 70% and serum creatinine after the treatment was 201 μmol/l.

These data were similar to ours. White et al. [11] describes AMR treatment with PP+IVIG patients who received tacrolimus, mycophenolate mofetil, steroids, and basiliximab induction therapy.

Based on these results, plasmapheresis and intravenous immunoglobulin (IVIG) has been adopted as a therapy of choice for AMR. The question remains as to how the improved outcomes after IVIG administration can be explained. Studies have shown that IVIG treatment lowers the level of anti-HLA antibodies quickly, effectively and long-term [12]. The mechanism of this effect is complex and involves blocking of Fc receptors and interference with complement activation, cytokine activity, and the effect of anti-idiotype antibodies. The fact that IVIG may detect the complement [1] is also important for the treatment of rejection. Besides the immunosuppressive effect of higher dosage (1-2g/kg), some authors use small dosage of IVIG (0.1g/kg) to improve non-specific body immunity during intensive immunosuppression. Other indications for IVIG treatment in renal transplantation have been shown to be desensitization [13, 14] and induction therapy after renal transplantation in highly sensitized patients [15]. Some centers administer hyper-immune gammaglobulin against CMV instead of IVIG and CMV prophylaxis with ganciclovir [3]. Firstly, we used 0.5 g/kg of IVIG for a mini-

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Tab. 2: Infectious complications after treatment of AMR

<table>
<thead>
<tr>
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<th>PP</th>
<th>PP+IVIG</th>
<th>PP+IVIG+ antiCD20</th>
</tr>
</thead>
<tbody>
<tr>
<td>CMV disease</td>
<td>1</td>
<td>3</td>
<td>2</td>
</tr>
<tr>
<td>N</td>
<td>%</td>
<td>%</td>
<td>%</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>3</td>
<td>5</td>
<td>1</td>
</tr>
<tr>
<td>PN / UTI</td>
<td>3</td>
<td>6</td>
<td>3</td>
</tr>
<tr>
<td>Herpes Zoster</td>
<td>2</td>
<td>0</td>
<td>0</td>
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<tr>
<td>Others</td>
<td>0</td>
<td>1</td>
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CMV - cytomegalovirus; PN - pyelonephritis; UTI - urinary tract infection
In conclusion, the combination of plasmapheresis and intravenous immunoglobulin administration is considered to be a safe and effective treatment of early acute humoral rejection. A rituximab therapy should be better defined.

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References


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