Pediatr Nephrol
DOI 10.1007/s00467-011-1864-3

ORIGINAL ARTICLE

Acute antibody-mediated rejection in paediatric renal transplant recipients

Birgitta Kranz · Reinhard Kelsch · Eberhard Kuwertz-Bröking · Verena Bröcker · Heiner H. Wolters · Martin Konrad

Received: 18 November 2010 / Revised: 12 February 2011 / Accepted: 17 February 2011

Abstract Acute antibody-mediated rejections (aAMR) after renal transplantation are defined by rapidly deteriorating graft function, detection of donor-specific antibodies (DSA) and characteristic histological features. In adults, anti-rejection strategies comprise intravenous immunoglobulin (IVIG), steroid pulses, plasmapheresis and rituximab. Data of children with aAMR are scarce. We report four episodes of aAMR in three children (aged 10, 10 and 11 years respectively) occurring early after renal transplantation. Pre-transplant complement-dependent cytotoxicity cross-matches were negative; in the case of re-transplantation repeated antigens were excluded. Basic immunosuppression comprised cyclosporine A, MMF and steroids. All four rejection episodes were histologically proven and associated with acute renal failure. De novo DSAs were detected in two aAMRs; one patient was additionally tested positive for AT1-receptor antibodies. All aAMRs were treated with steroid pulses, tacrolimus, MMF, IVIG, plasmapheresis and one single dose of rituximab. Despite therapy one graft was lost; in the remaining three cases kidney function re-established within 1–8 weeks. At follow-up, 14, 15 and 22 months' post-rejection their GFRs were 65, 88 and 105 ml/min/1.73 m^2 respectively. A combined therapy of steroid pulses, IVIG, plasmapheresis and rituximab is potentially effective in the treatment of aAMR in children.

Keywords Acute antibody-mediated rejection · Rituximab · Pediatric renal transplantation · Immunoglobulin · Plasmapheresis · AT1-receptor antibodies

Abbreviations

aAMR	Acute antibody-mediated rejection
AT1	Angiotensin 1
CsA	Cyclosporine A
DSA	Donor-specific antibodies
GFR	Glomerular filtration rate
IVIG	Intravenous immunoglobulin therapy
RTx	Renal transplantation
MMF	Mycophenolate mofetil
PE	Plasmapheresis/plasma exchange
TAC	Tacrolimus

Introduction

Acute antibody-mediated rejection (aAMR) after renal transplantation (RTx) is defined as acute deterioration of kidney function combined with development of donor-specific antibodies (DSA) or reactive antibodies (e.g. ABO isoglutinins, anti-endothelial antibodies) and characteristic histological signs, such as capillaritis and glomerulitis and positive staining for C4d [1, 2]. In contrast to acute cellular

B. Kranz (✉) · E. Kuwertz-Bröking · M. Konrad
Department of General Pediatrics, Pediatric Nephrology,
University Children's Hospital Münster,
Waldeyerstrasse 22,
48149 Münster, Germany
e-mail: kranzab@uni-muenster.de

R. Kelsch
Institute for Transfusion Medicine and Transplantation
Immunology, University Hospital,
Münster, Germany

V. Bröcker
Institute of Pathology, Hannover Medical School,
Hannover, Germany

H. H. Wolters
Department of General Surgery, University Hospital,
Münster, Germany

Published online: 01 April 2011

rejections, aAMR is frequently steroid-resistant and does not respond to the established anti-rejection strategies, hence leading to a poor outcome. Over the last decade several therapeutic concepts have been reported to be effective in adult renal transplant recipients with aAMR: anti-lymphocyte therapies, plasmapheresis, immunoadsorption, immunoglobulin (IVIG) and rituximab [3–9]. However, no generally accepted guidelines exist. Published data on treatment of aAMR in children are scarce.

We report the therapeutic management of aAMR after transplantation in paediatric renal transplant recipients.

Materials and methods

Between 2005 and 2009 a total of 38 paediatric renal transplantations were performed in our Unit. Of these, 4 children received a second graft due to a primary graft loss (2 of them are described here in detail—cases 2 and 3—the others had lost their first grafts because of a chronic allograft nephropathy). All 38 grafts are still functioning.

The primary immunosuppressive regimen for first transplants consisted of CsA (trough level 200 ng/ml), MMF and steroids (tapering within 6 weeks to the maintenance dosage of 4 mg/m^2/day). In the case of living related transplantations the immunosuppression with CsA was initiated 1 week prior to transplantation (dosage 150 mg/m^2/day). For second transplants the primary chosen calcineurin inhibitor was CsA if the T-cell CDC and B-/T-cell-separated CDC crossmatches were negative. The detailed data presented are those of the outcome of three children with aAMR after renal transplantation.

Glomerular filtration rate (GFR) was calculated by the conventional Schwartz formula [10]. Creatinine measurement was based on the Jaffe method.

Immunological methods/assays

The screening of sera for HLA-specific antibodies was performed with the complement-dependent cytotoxicity assay (CDC) using a panel of T-lymphocytes from 58 different donors (Lambda Cell Tray™ Class I, One Lambda, Canoga Park, CA, USA). Additionally, HLA-class I and II antibody-specific ELISA tests (QuikScreen™, B-Screen™, Quick-ID™ Class I and Class II, GTI Diagnostics, Waukesha, WI, USA) were used. Retrospectively, the sera were further characterised using the HLA-antibody specific bead-immuno assay (LabScreen™ Single antigen HLA Class I and II, One Lambda), which uses an array of beads coated with single HLA antigens. Pre- and post-transplant crossmatches were performed by the CDC method using immunologically separated T- and B-lymphocytes from the donor. Dithiothreitol was used for the discrimination of IgM and IgG. Serological typing of HLA-Class I was performed by CDC (Lymphotype HLA-AB72 AN with Complement (lyo.); Biotest, Dreieich, Germany).

For molecular HLA typing DNA was isolated from EDTA-anticoagulated blood by a bead-based technique (Genoprop Cartridge B350, GenoM™-6 instrument; Qiagen, Hilden, Germany). Molecular typing of HLA classes I and II was performed with Dynal-Reli™ SSO HLA-A/HLA B/DRB1/DQB1 using an AutoReli48 instrument and a RELIScan system (Dynal/Invitrogen, Karlsruhe, Germany). When necessary, Olerup-SSP Kits for HLA-A, B, DR/DQ were used for HLA high-resolution typing (Olerup-SSP, Oslo, Norway).

Histology

Transplant biopsy samples were performed and reviewed at the Institute of Pathology, Medical School Hannover, Germany. A second biopsy was initiated 4–6 weeks post-rejection to exclude persistent signs of rejection. Histological techniques are described in Fig. 1.

Case reports

Patient 1

A 9-year-old girl with focal segmental glomerulosclerosis (FSGS, heterozygous for the *WT1* mutation p.H397P; Fig. 2a) received a first kidney transplant from her 30-year-old mother (basic immunological characteristics Table 1). FSGS had been diagnosed at the age of 15 months and was treated with CsA for 7 years. Patient 1 commenced haemodialysis 5 months prior to renal transplantation.

Post-transplant she had a good primary graft function (creatinine drop to 0.4 mg/dl) on immunosuppressive therapy with CsA (trough level around 200 ng/ml), MMF and steroids.

Four days post-RTx creatinine increased to 1.7 mg/dl. The renal biopsy revealed an aAMR showing glomerulitis, peritubular capillaritis, and diffuse linear positivity of peritubular capillaries for C4d and diffuse acute tubular injury. No vascular rejection (endothelialitis) or thrombotic microangiopathy was seen (Fig. 1). Initially, aAMR was treated with steroid pulses, IVIG 2 g/kg (once, day 6 post-RTx) followed by a total of 10 sessions of plasmapheresis (PE). On day 10 post-RTx, as kidney function had not improved on IVIG, steroids and five PEs, she was treated with a single dose of rituximab (375 mg/m^2). Cyclosporine A was switched to tacrolimus (TAC, trough level 8–10 ng/ml). Due to an oliguric acute renal failure she received one session of haemodialysis. Serologically, she reacted

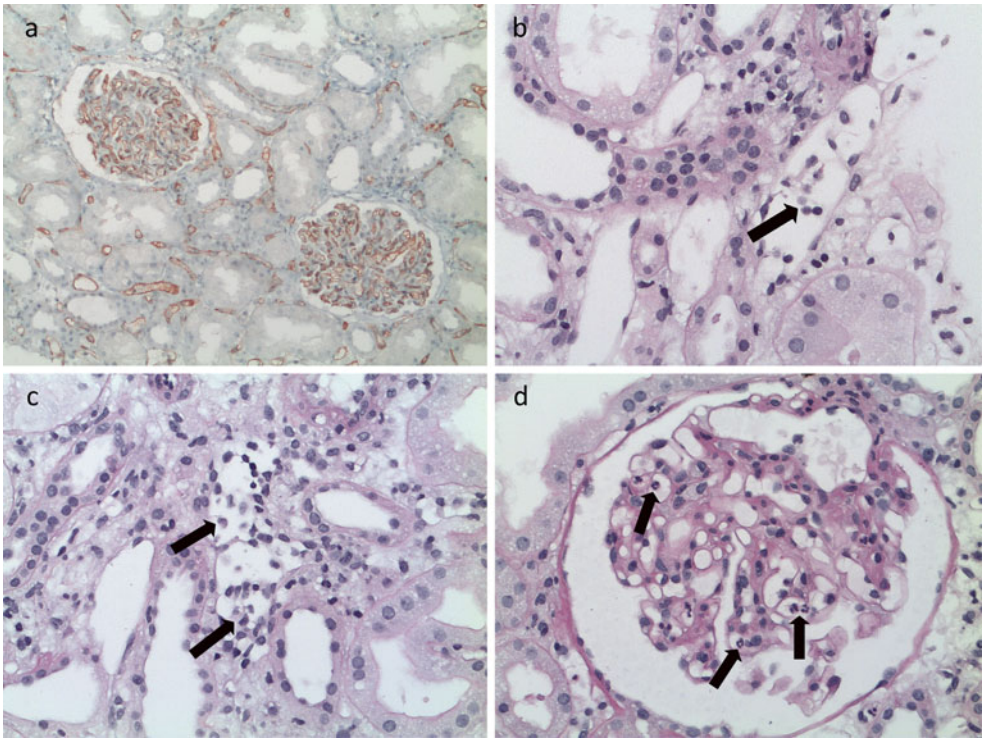

Fig. 1 Histopathological signs of acute humoral rejection. **a** Diffuse and linear endothelial C4d positivity in peritubular and glomerular capillaries (immunohistochemistry for C4d on formalin-fixed, paraffin-embedded material; original magnification, ×100); **b**, **c** Mononuclear cells in peritubular capillaries (PAS-stain, original magnification, ×200); **d** Glomerulitis with granulocytes in glomerular capillaries (PAS-stain, original magnification ×200)

strongly with HLA-DR*2(15,16) antigens and more weakly with HLA-DR*3(17,18).

Clinically, despite extensive antihypertensive therapy (including Na-Nitroprusside), she manifested severe arterial hypertension. High titres of AT1-receptor antibodies were detected (>4 U/dl). The blood pressure could be sufficiently controlled with ramipril and irbesartan.

After 14 days kidney function normalised and the girl was discharged (creatinine 0.6 mg/dl), but was still treated with two antihypertensive drugs. Three weeks post-RTx neither DSA nor AT1-receptor antibodies could be detected any more.

Two years post-RTx the creatinine was 0.9 mg/dl with a GFR of 88 ml/min/1.73 m^2. Complete B-cell depletion lasted for 6 months, B-cells re-increased slowly to 5–6% afterwards. The AT1-receptor antibodies have re-appeared and increased since month 12 (up to 4.2 U/dl), not associated with deterioration of kidney function or increased arterial blood pressure, which has been well controlled under mono-therapy with irbesartan. DSAs were still negative at the 2-year follow-up.

Patient 2

A 7-year-old girl with Joubert syndrome (Fig. 2b) lost a first cadaveric renal transplant after 2 months due to an acute vascular rejection (Table 1). This first RTx (HLA: A*2,–; B*50, *40(61); DRB1*01*07 with a mismatch 0-0-1) had to be removed immediately. Immunological work-up showed anti-HLA-DR1 antibodies. Further refinement revealed that the patient carries the rare DRB1*01:03 allele and sensitisation occurred against DRB1*01:01. As the first renal graft did not carry HLA-DR11, the presence of anti-HLA-DR11 in the ELISA test prior to the second transplantation could not be explained conclusively. As the B-/T-separated and T-cell CDC crossmatches were negative, the father was accepted for living related donation even though he carried HLA-DR11 antigen.

After 4 years on haemodialysis she received the living related second RTx from her 42-year-old father (basic immunological characteristics Table 1) with an excellent primary graft function (creatinine 0.5 mg/dl). The initial immunosuppression comprised CsA (trough level around 200 ng/ml), MMF and steroids. Five days post-RTx creatinine increased to 1.5 mg/dl, a renal biopsy was initiated and showed aAMR with peritubular capillaritis, glomerulitis, diffuse linear positivity of peritubular capillaries for C4d and diffuse acute tubular injury. She immediately received steroid pulses, IVIG (2 g/kg) and a single of dose rituximab (375 mg/m^2) before she started with the first of 10 plasma exchanges. CsA was switched to TAC (day 5 post-RTx) and adjusted to trough levels between 8 and 10 ng/ml. Because of an oliguric acute renal failure she needed haemodialysis sessions for 2 weeks. Within 2 weeks kidney function improved and she was discharged with a creatinine of 0.6 mg/dl. A second kidney biopsy 6 weeks later revealed discrete signs of capillaritis without a positive C4d staining.

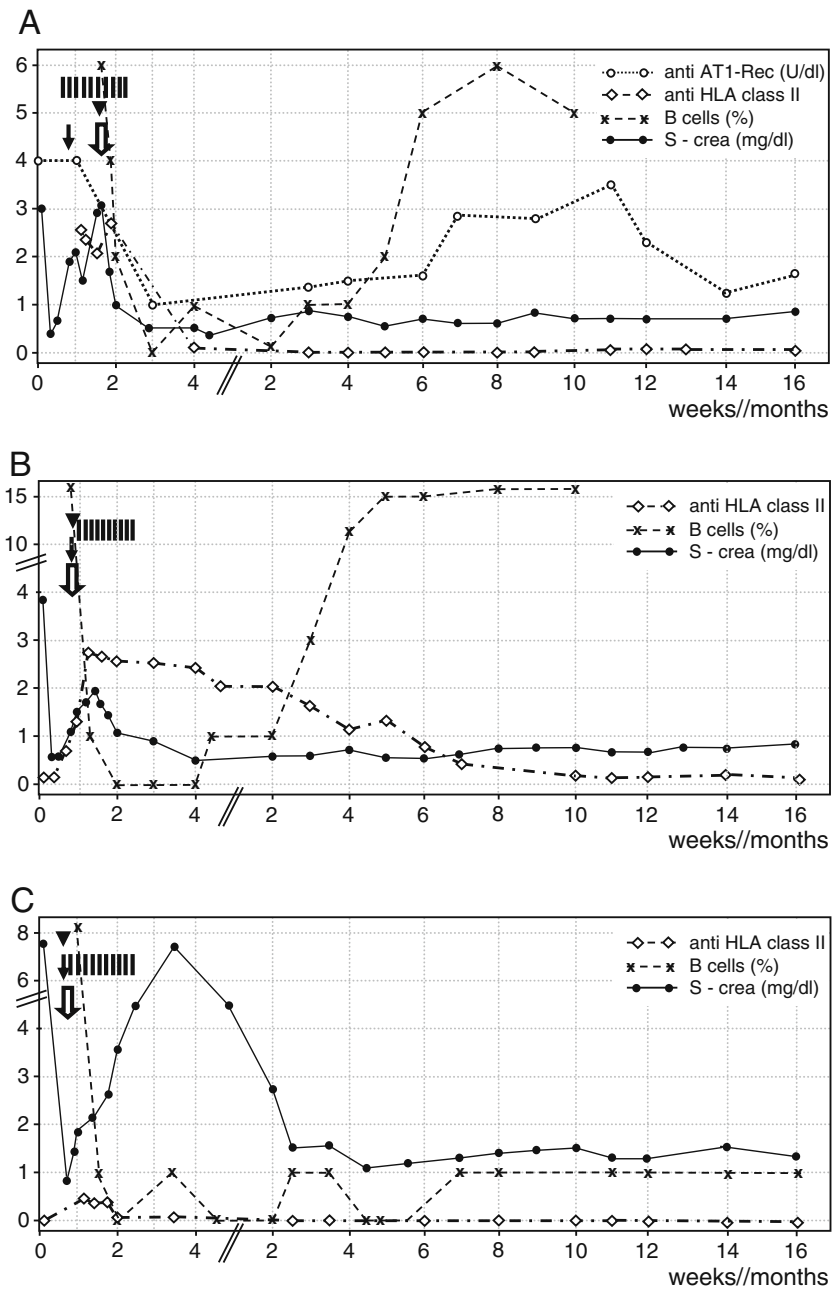

Fig. 2 **a**–**c** Course of creatinine (mg/dl), B-cells (%), HLA antibody ratio and AT1 receptor antibodies (U/dl) in the three patients with acute antibody-mediated rejection: **a** patient 1, **b** patient 2, **c** patient 3 ⇓: application of a single dose of rituximab (375 mg/m^2) **I**: plasmapheresis ↓: IVIG (2 g/kg) ▼: switch from cyclosporine A to tacrolimus

Serologically, anti-HLA-DR1 and DR11 antibodies were detected, whereas AT1-receptor antibodies could be excluded.

Eighteen months post-RTx the patient is well with a creatinine level of 0.8 mg/dl (GFR 105 ml/min/1.73 m^2) despite normalisation of the B-cells.

Patient 3

An 11-year-old boy with renal dysplasia (Fig. 2c) lost a first cadaveric renal transplant because of an aAMR (DSA anti-HLA-DR11, Table 1). Despite intensive therapy with steroids, a switch from CsA to TAC, IVIG, plasma exchanges and rituximab (day 10 of aAMR) the renal transplant had to be removed 4 weeks post-transplant owing to systemic signs of inflammation. One year later he received a living related RTx from his 34-year-old mother (Table 1) with a good primary kidney function (creatinine dropped to 0.8 mg/dl 4 days post-RTx). One day later an increase in creatinine to 1.7 mg/dl justified a kidney biopsy revealing an aAMR with the characteristic signs of glomerulitis, peritubular capillaritis, diffuse linear positivity of peritubular capillaries for C4d and diffuse acute tubular injury. The same day he was started on steroid pulses, was switched to TAC (trough levels 8–10 ng/ml), received IVIG (2 g/kg) and a single dose of rituximab (375 mg/m^2). Ten

Table 1 Donor and recipient HLA-typing and antibodies pre- and post-acute antibody-mediated rejection

	Patient 1 Girl, 10 years	Patient 2 Girl, 10 years	Patient 3 Boy, 12 years
General data			
Underlying disease	FSGS	Joubert syndrome	Renal dysplasia
Number of RTx	1	2	2
Donor/age	Mother/30 years	Father/42 years	Mother/34 years
HLA-typing of recipients and donors			
HLA typing recipient	A *02, *30	A *02:05,*24	A *02,*32
	B *18,*40:01(60)	B *40:01(60), *50	B *07,*44
	DRB1*03:01(17), –	DRB1*01:03,*07	DRB1*13:01,*14
HLA typing of previous transplant	–	A *02, –	A *2,*32(19)
		B *50,*40(61)	B *7,*44(12)
		DRB1*01,*07	DR *11(5), –
Mismatch		0-0-1	0-1-2
HLA typing of actual transplant	A *25,*30	A *02:05,*24	A *02, –
	B *18,*44	B *50,*15(62)	B *07, –
	DRB1*03:01(17),*15	DRB1*07,*11	DRB1*14,*15
			DQB1*05,*06
Mismatch A/B/DR	1-1-1	0-1-1	0-0-1
HLA antibodies and crossmatches before actual RTx			
CDC-PRA pre-RTx (T-cells)	0%	0%	0%
HLA antibodies			
HLA-Class I (ELISA)	Negative	Negative	Negative
HLA-Class II (ELISA)	Negative	Positive	Positive
HLA antibody specificities (ELISA)	–	DR1, DR11	DR11
HLA antibody specificities (retrospectively analysed from pre-transplant sera)	DR15?, DR16? (weak)	A*0201(weak), A*0203 (weak), A*0206 (weak); DR1, DR11, HLA-DP (broad reactivity)	DR11, DQ3
B/T-separated CDC-crossmatch	Negative	Negative	Negative
Antibodies after actual RTx			
Donor-specific HLA antibodies	Anti-HLA-DR 2 (15,16)	Anti-HLA-DR11	No DSA detectable against actual transplant (HLA-A/B/C/DR/DQ/DP)
AT1 antibodies	Positive	Negative	Negative
MICA antibodies (LabScreen-Mix)	n.d.	n.d.	Negative

sessions of plasmapheresis were performed over the following 2 weeks. The clinical course was complicated by an anuric acute renal failure and severe bleeding complications secondary to the renal biopsy and a urinary bladder haemorrhage secondary to heparin anticoagulation during dialysis sessions. Despite citrate dialysis he needed repeated surgical revisions within the next 2 weeks. A second biopsy 4 weeks post-RTx revealed discrete signs of capillaritis without positive C4d staining. Kidney function improved after 7 weeks and he could be discharged with a creatinine of 1.8 mg/dl. During the next 18 months kidney function stabilised with a creatinine level of 1.4 mg/dl (GFR 65 ml/min/1.73 m^2) under ongoing B-cell depletion.

Soon after the second aAMR, the known anti-HLA-DR 11(5) antibodies directed against the first graft tested positive again, but no specific antibody against an HLA antigen of the second transplant could be identified. AT1-receptor and MICA antibodies as alternative triggers for aAMR were excluded.

Discussion

We describe our experience in the therapy of four episodes of aAMR occurring early after RTx in three children. In three of these four episodes, aAMR could be successfully controlled by a combined therapy consisting of steroid pulses, IVIG, PE and rituximab. Renal function could be preserved under long-term triple immunosuppressive therapy (steroids, MMF, TAC) until

last follow-up. However, one graft had to be removed after treatment failure.

In the first case AT1-receptor antibodies were identified in addition to DSA. Clinically, the girl presented with severe hypertension. Dragun and Hegner [11] reported the presence of agonistic AT1 receptor antibodies in patients with AMR and severe hypertension in the absence of DSAs. In their cohort of 33 patients with AMR, almost half of them were identified with AT1-receptor antibodies without DSAs. All patients suffered from malignant hypertension. The successful therapy comprised the AT1-receptor blocker losartan combined with PE and IVIG. Retrospectively, it is impossible to discriminate whether the DSA or the AT1-receptor antibodies had induced the AMR in our patient. Fortunately, the intense therapy extended by an AT1-receptor blocker led to the favourable outcome.

The two patients receiving a second graft were tested positive for anti-HLA-class II antibodies before re-transplantation, but the HLA antibodies detected by ELISA in patients 2 and 3 were not CDC-reactive. In the era when the reported cases were transplanted (2008 and 2009), the standard immunological work-up of our local transplant centre consisted of a screening for HLA-specific antibodies and B-/T-cell-separated crossmatches. This procedure was in line with the recommended pre-transplant immunological work-up of the German Health authorities of that time [12]. In 2008 the experience with the interpretation of antibodies detected only by ELISA assays was rather limited. The significance of anti-HLA class II antibodies in renal transplantation is still controversial. Lefaucheur et al. [13] found the incidence of AMR 9-fold higher in patients with DSA regardless of the class. In contrast, Riethmüller et al. [14] found that pre-transplant DSAs against class I, but not against class II were predictive of AMR. In retrospect the decision to perform the re-transplantations in patients 2 and 3 under standard immunosuppression was wrong. However, whether intensified immunosuppressive protocols would have prevented the aAMR in our patients is uncertain.

In the third patient who experienced two episodes of aAMR no antibodies, neither DSAs nor non-HLA antibodies, could be detected after the second aAMR. However, he showed a booster of the DSAs against the first renal graft without developing DSAs against the second graft. Nevertheless, clinically and histologically, he fulfilled the criteria for aAMR and responded to the anti-rejection therapy.

According to the literature therapeutic options of AMR are:

1. An effective basic immunosuppression with TAC and MMF (at least most transplant units use TAC as the primary calcineurin inhibitor in re-transplantations and/or patients with aAMR)
2. Steroid pulses to treat the cellular component of the rejection
3. Use of antilymphocyte antibodies (ATG or OKT3)
4. Antibody binding with IVIG
5. Antibody removal with plasmapheresis or immunoadsorption
6. B-cell depletion with rituximab

The first two components (steroids and the basic immunosuppression with TAC + MMF) are commonly accepted [3–5, 7, 9, 15].

More than a decade ago the first therapeutic trials in resistant aAMR were performed with IVIG without knowing the exact mechanism of action [16, 17]. In the meantime IVIG has emerged to a main cornerstone in desensitisation protocols. Compared with antilymphocyte antibodies IVIG have not been proven to be absolutely superior regarding efficacy, but they offer an alternative therapeutic option with fewer side-effects [18].

Antibody removal by plasma exchange or immunoadsorption showed an additive aspect of aAMR therapy [4, 5, 15]. Both methods have been demonstrated to be effective, only the number of sessions recommended varies significantly [7, 19]. Several study groups added IVIG therapy administered after PE sessions [9, 15].

Jordan et al. [3] proposed the use of PE in those patients with severe histological signs of AMR (e.g. glomerulitis, thrombotic microangiopathy). On the other hand, patients with a moderate reduction of kidney function and positive C4d staining as an isolated histological sign of aAMR should be treated with rituximab and IVIG only [3]. However, the efficacy of these protocols still needs to be demonstrated.

Around 2000, the first reports describing the use of rituximab as effective therapy in aAMR were published [8].

Kaposztas et al. [6] compared the efficacy of PE combined with rituximab versus PE alone in the treatment of aAMR. The 2-year graft survival for patients treated with rituximab was 90% versus 60% in the group without rituximab. In a multivariate analysis rituximab was identified as a significant factor, whereas IVIG conferred an additional beneficial effect. Other studies further underlined the efficacy of rituximab [8, 9, 20]. However, the number of applications and the dosage varied considerably in these studies. Originally, the therapy was derived from the treatment protocols of non-Hodgkin's lymphoma with several courses. Rituximab applications in aAMR vary between 1 and 5 infusions of 375 mg/m^2 each [5, 7].

Reports of successful rituximab therapy in paediatric renal transplant recipients with AMR are scarce. Billing et al. [21] treated six children with chronic antibody-

mediated rejection with IVIG and rituximab successfully leading to an improvement of GFR within 12 months.

Recent studies of acute rejections in paediatric and adult renal transplant recipients revealed detection of intragraft B-cell infiltrates in a substantial number of patients. Standard anti-rejection therapy does not target B-cells, thus leading to therapy-resistant rejections. Zarkhin et al. [22] demonstrated the superiority of rituximab in the therapy of B-cell infiltrate-associated acute rejections in 10 paediatric renal transplant recipients in comparison to standard anti-rejection therapies. In all patients, biopsies confirmed improvement of acute rejection. Serious side-effects, especially infectious complications, did not occur.

In conclusion, the intense therapy with steroid pulses, TAC, MMF, plasmapheresis, IVIG and rituximab led to a favourable outcome in 3 out of 4 episodes of aAMR. In these cases a single dose of rituximab had been sufficient, although it was followed by plasmapheresis sessions starting the following day. In the episode that could not be controlled by this therapy the only obvious difference was that rituximab was administered rather late, after 10 PEs had failed. The documented B-cell depletion lasted at least 3 months, in the third patient it is still ongoing after 18 months.

Fortunately, the incidence of side effects seems to be low, but serious rare complications have been reported and nephrologists need to be aware of the potential development of progressive multifocal leukencephalopathy (PML) and rituximab-associated lung injury (RALI) in renal transplant recipients.

Currently, it is impossible to distinguish which therapy element is the most effective and whether this multimodal therapy might be adjusted individually.

Acknowledgements We thank Dr. Dragun (Berlin, Germany) for being so kind as to monitor the AT1-receptor antibodies in our children with acute AMR. Additionally, she supported us by giving advice on the cases described. We thank Dr. Grünewald (Great Ormond Street Hospital, UK) for revising the manuscript.

References

1. Solez K, Colvin RB, Racusen LC, Haas M, Sis B, Mengel M, Halloran PF, Baldwin W, Banfi G, Collins AB, Cosio F, David DS, Drachenberg C, Einecke G, Fogo AB, Gibson IW, Glotz D, Iskandar SS, Kraus E, Lerut E, Mannon RB, Mihatsch M, Nankivell BJ, Nickeleit V, Papadimitriou JC, Randhawa P, Regele H, Renaudin K, Roberts I, Seron D, Smith RN, Valente M (2008) Banff 07 Classification of renal allograft pathology: updates and future directions. Am J Transplant 8:753–760
2. Colvin RB (2007) Antibody mediated renal allograft rejection: diagnosis and pathogenesis. J Am Soc Nephrol 18:1046–1056
3. Jordan SC, Reinsmoen N, Peng A, Lai CH, Cao K, Villicana R, Toyoda M, Kahwaji J, Vo AA (2010) Advances in diagnosing and managing antibody-mediated rejection. Pediatr Nephrol 25:2035–2045
4. Ji SM, Liu ZH, Chen JS, Sha GZ, Ji DX, Li LS (2006) Rescue therapy by immunoadsorption in combination with tacrolimus and mycophenolate mofetil for C4d-positive acute humoral renal allograft rejection. Transplant Proc 38:3459–3463
5. Gomes AM, Pedroso S, Martins LS, Malheiro J, Viscayno JR, Santos J, Dias L, Henriques AC, Sarmento AM, Cabrita A (2009) Diagnosis and treatment of acute humoral kidney allograft rejection. Transplant Proc 41:855–858
6. Kaposztas Z, Podder H, Mauiyyedi S, Illoh O, Kerman R, Reyes M, Pollard V, Kahan MD (2009) Impact of rituximab therapy for treatment of acute humoral rejection. Clin Transplant 23:63–73
7. Faguer S, Kamar N, Guilbeaud-Frugier C, Fort M, Modesto A, Mari A, Ribes D, Cointault O, Lavayssière L, Guitard J, Durand D, Rostaing L (2007) Rituximab therapy for acute humoral rejection after kidney transplantation. Transplantation 83:1277–1280
8. Becker YT, Becker BN, Pirsch JD, Sollinger HW (2004) Rituximab as treatment for refractory kidney transplant rejection. Am J Transpl 4:996–1001
9. Mulley WR, Hudson FJ, Tait BD, Skene AM, Dowling JP, Kerr PG, Kanellis J (2009) A single low-fixed dose of rituximab to salvage renal transplants from refractory antibody-mediated rejection. Transplantation 87:286–289
10. Schwartz GJ, Haycock GB, Edelmann CM, Spitzer A (1976) A simple estimate of glomerular filtration rate in children derived from body length and plasma creatinine. Pediatrics 58:259–263
11. Dragun D, Hegner B (2009) Non-HLA antibodies post-transplantation: clinical relevance and treatment in solid organ transplantation. Contrib Nephrol 162:129–139
12. Bundesärztekammer D (2010) Richtlinie zur medizinischen Beurteilung von Organspendern und zur Konservierung Spender-organen. Dtsch Arztebl 107:A 1532–A 1541
13. Lefaucheur C, Suberbielle-Boissel C, Hill GS, Nochy D, Andrade J, Antoine C, Gautreau C, Charron D, Glotz D (2009) Clinical relevance of preformed HLA donor-specific antibodies in kidney transplantation. Contrib Nephrol 162:1–12
14. Riethmüller S, Ferrari-Lacraz S, Müller MK, Raptis DA, Hadaya K, Rüsi B, Laube G, Schneiter G, Fehr T, Villard J (2010) Donor-specific antibody levels and three generations of crossmatches to predict antibody-mediated rejection in kidney transplantation. Transplantation 90:160–167
15. Ibernon M, Gil-Vernet S, Carrera M, Seron F, Moreso F, Bestard O, Cruzado JM, Grinyo JM (2005) Therapy with plasmapheresis and intravenous immunoglobulin for acute humoral rejection in kidney transplantation. Transplant Proc 37:3743–3745
16. Jordan SC, Quartel AW, Czer LS, Admon D, Chen G, Fishbein MC, Schwieger J, Steiner RW, Davis C, Tyan DB (1998) Posttransplant therapy using high-dose immunoglobulin (intravenous gammaglobulin) to control acute humoral rejection in renal and cardiac allograft recipients and potential mechanism of action. Transplantation 66:800–805
17. Luke PP, Scantlebury VP, Jordan ML, Vivas CA, Hakala TR, Jain A, Somani A, Fedorek S, Randhawa P, Shapiro R (2001) Reversal of steroid- and antilymphocyte antibody-resistant rejection using intravenous immunoglobulin (IVIG) in renal transplant recipients. Transplantation 72:419–422
18. Casadei DH, del C Rial M, Opelz G, Golberg JC, Argento JA, Greco G, Guardia OE, Haas E, Raimondi EH (2001) A randomized and prospective study comparing treatment with high-dose intravenous immunoglobulin with monoclonal anti-

bodies for rescue of kidney grafts with steroid-resistant rejection. Transplantation 71:53–58
19. Nafar M, Farrokhi F, Pour-Reza-Gholi F, Firoozan A, Einollahi B (2006) Plasmapheresis in the treatment of early acute kidney allograft dysfunction. Exp Clin Transplant 4:506–509
20. Guilbeau-Frugier C, Kamar N (2009) Rituximab for humoral rejection after kidney transplantation: an update. Transplantation 87:1261
21. Billing H, Rieger S, Ovens J, Süsal C, Melk A, Waldherr R, Opelz G, Tönshoff B (2008) Successful treatment of chronic antibody-mediated rejection with IVIG and rituximab in pediatric renal transplant recipients. Transplantation 86:1214–1221
22. Zarkhin V, Li L, Kambham N, Sigdel T, Salvatierra O, Sarwal MM (2008) A randomized, prospective trial of rituximab for acute rejection in pediatric renal transplantation. Am J Transplant 8:2607–2617