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Chronic Antibody Mediated Rejection of Renal Allograft - Efficacy of Combined Treatment with Plasma Exchanges, Intravenous Immunoglobulin and Rituximab (One Center Experience)

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Abstract

Chronic antibody mediated rejection (CAMR) is the main cause for late kidney transplant loss, and the results of its treatment are dissatisfying. In our one center study we evaluated the efficacy of combined treatment with plasma exchanges, intravenous immunoglobulin and rituximab on the top of standard immunosuppression in 24 patients with chronic transplant glomerulopathy (TG), compared to control group of 26 patients, who did not receive additional treatment. At the time of diagnosis baseline estimated glomerular filtration rate (eGFR) did not differ between treatment and control subgroups (44.9 ± 21.3 vs 41.2 ± 14.6 ml/min, P = 0.47), as well as any other laboratory or pathology data, and subsequent decline of allograft function was also found in both subgroups. However, the rate of eGFR decline was significantly lower in the patients from the treatment subgroup compared to the controls: -0.47 ± 0.6 ml/min/month and -1.31 ± 1.6 ml/min/month respectively (P = 0.02). Thus 3-year transplant survival turned to be 21.3% in the control subgroup vs 64.8% in the treatment subgroup (p = 0.01). Our study demonstrated, that TG, which is the most often variant of CAMR, is characterized by unfavorable prognosis regardless of its pathology features and activity at the time of diagnosis. Combined treatment, including plasma exchanges (PE), intravenous immunoglobulin (IVIG) and rituximab (Rtx) allows slowing down the rate of the disease progression at least in some proportion of patients with lately diagnosed CAMR.

Keywords: Chronic antibody-mediated rejection; Transplant glomerulopathy; Plasma exchanges; Intravenous immunoglobulin; Rituximab

Background

Long-term renal transplant (RT) survival is in the focus of interest of many studies over last decades. Recent data indicate, that antibody mediated rejection (AMR), most often presenting as TG, is the main cause for late kidney transplant loss. Early stages of AMR are characterized by inflammatory microvascular lesions with inflammatory cells retention in the glomerular and peritubular capillaries (PTC). These lead to endothelial cell damage and subsequent capillary walls remodeling with double-contour pattern, and dissection of PTC basement membrane, which are characteristic for chronic antibody mediated rejection (CAMR) [1,2].

Above-mentioned pathology features, along with complement C4d expression and presence of donor specific antibodies (DSA) represent AMR diagnostic spectrum. Importantly, microvascular inflammation may preclude or coexist with chronic lesions [3-6]. Finding of even few double-contour capillary loops confirm the diagnosis of CAMR, considered as active if C4d staining on PTC is positive. Thus, acute AMR, as well as active and non-active CAMR, reflect consecutive stages of the single process, which lead to the kidney transplant dysfunction and finally to the loss of renal allograft.

However, treatment efficacy and prognosis in acute and chronic AMR significantly differ. Conventional therapy for AMR is directed to pre-existing DSA elimination and their production blockade. Several studies demonstrated that combined therapy, including PE, high dose IVIG and Rtx, was an effective treatment for acute AMR [7-10]. Unfortunately, the results of CAMR treatment are dissatisfying. Only few small studies with controversial results are published so far [11-15]. Despite the treatment efficacy in these patient series is not clear, all authors stress stabilization of transplant function even in patients with advanced chronic lesions, including TG. According to the Moscow Nephrology Centre Renal Biopsies Registry (data published in Russian) CAMR was diagnosed in 171 cases out of 1360 kidney transplant biopsies over last 10 years, which constituted 12.6%. CAMR was found mostly late (mean time after transplantation 85.5 ± 59.5 months). In cases when transplant biopsy was performed as late as in > 5-year post-transplant period, CAMR frequency turned to be 23.6% (99 out of 420 biopsies). 5-year transplant survival in cases of CAMR was 26%. We aimed to evaluate efficacy of PE, IVIG, and Rtx combination for treatment of late TG.

Materials and Methods

Study group included 50 patients (mean age 40.6 ± 12.5 years, M/F ratio - 30/20), with pathology proven chronic TG, diagnosed lately after renal transplantation - median follow-up after transplantation 81.4 [7.3; 285.0] months. In all cases indication for transplant biopsy was allograft dysfunction (mean serum creatinine 0.21 ± 0.08 mmol/l), isolated, or in combination with proteinuria (mean protein excretion 2.1 ± 1.9 g/day). Diagnosis of CAMR was based on pathology features of TG along with at least one of the following symptoms: C4d positivity on PTC, and/or presence of anti-HLA antibodies. Patients with only TG by pathology without C4d+ or DSA were excluded from the study [6]. Vast majority of subjects (n=44) received conventional 3-drug therapy,

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including cyclosporine-A (n=28) or tactolimus (n=16) in combination with steroids (all) and mycophenolates (n=41) or azathioprine (n=3). 2 patients received proliferative signal inhibitor (everolimus)-based 3-drug therapy, and 4 patients got 2-drug therapy with cyclosporine-A and steroids.

Depending on the additional treatment regimen, we selected two subgroups: treatment subgroup, including 24 patients treated with PE+IVIG+Rtx on the top of standard therapy; and control subgroup, comprised of 26 patients, who did not receive any additional therapy.

Pathology examination of renal allografts cores included light microscopy with H&E, PAS and Masson-trichrome staining. Pathology evaluation was based on Banff classification [3]. TG was diagnosed if double-contours were found in >10% of capillary loops in at least one glomeruli (Banff cg1). C4d staining was performed on cryo-sections by indirect immunofluorescence with FITC-conjugated anti-C4d monoclonal antibodies (Quidel Corporation, San Diego, CA). Staining was considered as diffuse in cases with C4d expression on > 50% of PTC, and focal in cases with C4d expression on 10-50% of PTC [3]. All patients were tested for anti-HLA antibodies class I and II by ELISA or Luminex method.

Patient's characteristics

31 out of 50 patients presented with all three symptoms (TG by pathology, C4d-positivity and anti-HLA antibodies), and were diagnosed with active CAMR. Other 15 had C4d-negative chronic rejection in presence of DSA; and in the rest 4 cases we did not find any anti-HLA antibodies at the time of biopsy, despite clear evidence of TG and diffuse staining for C4d on PTC. Severity of TG was considered as minimal, moderate and prominent in 24, 20 and 6 cases respectively. Complement C4d staining was diffuse in 26 and focal in 9 out of 35 C4d-positive cases. 13 patients demonstrated also features of acute cell-mediated rejection – interstitial (7 cases) or vascular (6 cases). Anti-HLA antibodies were mostly represented by class II (class II only, found in 30 patients; or class II plus class I - in 12 patients), and just 4 patients had anti-HLA antibodies class I only. Laboratory findings and pathology characteristics are shown in the (Table 1). As one can see from the table, there were no differences between the subgroups at the time of rejection diagnostics.

Treatment protocol

After the pathology confirmation of CAMR, patients, receiving 2-drug therapy and 3-drug therapy based on cyclosporine or everolimus, were converted to unified 3-drug therapy: tacrolimus plus mycophenolates plus steroids. Patients with concomitant cell-mediated rejection (which was found in 13 cases) received 3 methylprednisone i.v. pulses, 250-500 mg per pulse. Subsequently on top of this therapy 22 patients from treatment subgroup received combination of PE (№ 4-6), IVIG (0.5-1 g/kg) and Rtx (single dose 500 mg), another 2 patients from treatment subgroup with C4d-negative rejection, manifested with isolated proteinuria, received IVIG 0.5 mg/kg only. 26 patients, comprising control subgroup, did not receive any additional anti-CAMR treatment. Evaluation of treatment efficacy was performed by comparison of 3-years renal allografts Kaplan-Mayer survival curves between treatment subgroup and control subgroup. Kidney transplant function was estimated by serum creatinine level and eGFR, calculated by Cocroft-Gault equation. Rate of allograft function loss was calculated as delta eGFR per month [eGFR at the end of follow-up – baseline eGFR/duration of follow-up (months)].

Statistics

Statistical analysis was performed using SPSS 11.5 program package. Normally distributed variables presented as the mean ± standard deviation (SD). Comparison between mean data performed using Student criteria. Differences significance for categorical variables was evaluated by Fisher's exact test and χ^2 test. For abnormally distributed variables median value and interquartile range were calculated, Mann-Whitney test and Kruskall-Wallis test were used for comparison of these variables. P-value <0.05 was defined for statistical significance.

Results

Overall allografts survival at the end of 3 years follow-up period after the diagnosis was low - 41.2%. Iinterestingly, in patients with chronic rejection there were no differences in the allografts survival depending on C4d focal or diffuse expression and/or concomitant cell-mediated rejection, which was found in 13 patients [in 7 cases interstitial (Banff 1 a-b) and in 6 - vascular (Banff 2a)] (Figure 1). During the follow-up period study group demonstrated progressive loss of renal transplant function: eGFR declined from 43.1 ± 18.3 ml/min at the time of diagnosis to 33.6 ± 18.9 ml/min to the end of the study period. At the time of diagnosis baseline eGFR did not differ between treatment and control subgroups (44.9 ± 21.3 vs 41.2 ± 14.6 ml/min, P=0.47), and subsequent decline of allografts function was also found in both subgroups.

However, the rate of eGFR decline was significantly lower in patients from the treatment subgroup compared to the controls: -0.47 ± 0.6 ml/min/month and -1.31 ± 1.6 ml/min/month respectively (P=0.02) (Figure 2).

Totally 22 allografts were lost during the follow-up period, 15 in the control subgroup and only 7 in the treatment subgroup. Thus, 3-year transplant survival turned to be 21.3% in the control subgroup vs 64.8% in the treatment subgroup (P=0.01) (Figure 3). Multivariate Cox Regression model analysis revealed that only baseline eGFR and treatment modality were independent prognostic factors for the transplant function (Table 2). Other factors - demographic or clinical, like patient's age, time after renal transplantation and level of proteinuria, as well as pathology characteristics (C4d staining pattern, severity of TG, extent of interstitial fibrosis or proportion of totally sclerotic glomeruli) did not influence prognosis independently. Infectious complications were observed in both treatment and control subgroups, the differences were not significant. Treatment side effects occurred only in treatment subgroup, and were presented by allergic reactions, hypoproteinemia and leukopenia (Table 3). Totally 4 patients died during the study period: 2 in the treatment subgroup (1 from pneumonia and 1 from stroke), and 2 in the control subgroup (1 from pneumonia and 1 from infectious endocarditis).

Discussion

Recent studies showed that TG is the most often type of CAMR, characterized by unfavorable prognosis and rapid progression towards end stage of renal disease (ESRD). Allograft survival data in our study are completely consistent with the current view, as 3-year survival in our group of patients was found as low as 41.2%. That is even lower than in the study, performed by Gloor et al. [15], who described natural history of TG in 55 patients. The difference in survival rate might be caused by less severe baseline damage with predominantly sub-clinical course in patients from Gloor's cohort. Other studies with inclusion of clinically overt TG cases demonstrated lower allografts survival, which was not >50% to the end of 2-years follow-up [16,17] similarly to our data. Generally speaking the course of TG may significantly differ due

	Total (n=50)	PE/IVIG/Rx (n=24)	Control (n=26)	P
Age (mean±SD, years)	40.6 ± 12.5	42.7 ± 12.0	38.7 ± 12.9	NS
Time from transplantation (mean±SD, months)	81.4 ± 51.8	82.6 ± 67.5	80.4 ± 49.1	NS
Serum creatinine (mean±SD mmol/l)	0.21 ± 0.08	0.2 ± 0.06	0.2 ± 0.09	NS
GFR (mean±SD, ml/min)	43.1 ± 18.3	41.2 ± 14.6	44.9 ± 21.3	NS
Proteinuria (mean±SD, g/day)	2.07 ± 1.9	2.6 ± 2.1	1.7 ± 1.7	NS
Anti-HLA antibodies				
Positive class I	4 (8%)	2 (8%)	2 (8%)	NS
Positive class II	30 (60%)	16 (67%)	14 (54%)	
Positive class I+II	12 (24%)	5 (21%)	7 (27%)	
Negative	4 (8%)	1 (4%)	3 (11%)	
Transplant glomerulopathy (cg)				
1	24 (48%)	12 (50%)	12 (46%)	NS
2	20 (40%)	8 (33%)	12 (46%)	
3	6 (12%)	4 (17%)	2 (8%)	
mean score	1.6 ± 0.7	1.7 ± 0.8	1.6 ± 0.6	
C4d on PTC n (%)				
Negative	15 (30%)	6 (25%)	9 (35%)	NS
Focal	9 (18%)	3 (13%)	6 (23%)	
Diffuse	26 (52%)	15 (62%)	11(42%)	
Peritubular capillaritis				
0	19 (38%)	8 (33%)	11 (42%)	NS
1	19 (38%)	11 (46%)	8 (31%)	
2	9 (18%)	4 (17%)	5 (19%)	
3	3 (6%)	1 (4%)	2 (8%)	
mean score	0.92 ± 0.9	0.92 ± 0.9	0.92 ± 1.0	
Glomerulitis				
0	8 (16%)	3 (13%)	5 (19%)	NS
1	25 (50%)	13 (54%)	12 (46%)	
2	10 (20%)	6 (25%)	4 (16%)	
3	7 (14%)	2 (8%)	5 (19%)	
mean score	1.32 ± 0.9	1.29 ± 0.8	1.35 ± 1.0	
Intimal arteriitis n (%)				
0	44 (88%)	22 (92%)	22 (85%)	NS
1	6 (12%)	2 (8%)	4 (15%)	
2	0	0	0	
3	0	0	0	
Tubulitis				
0	26 (52%)	16 (67%)	10 (39%)	NS
1	13 (26%)	4 (16%)	9 (34%)	
2	9 (18%)	3 (13%)	6 (23%)	
3	2 (4%)	1 (4%)	1 (4%)	
	0.74 ± 0.9	0.54 ± 0.9	0.92 ± 0.9	
Glomerulosclerosis (%)	22.4 ± 25.3	14.8 ± 20.1	28.8 ± 27.6	0.05
Interstitial fibrosis (%)	25.6 ± 18.3	23.8 ± 14.9	27.4 ± 21.2	NS
(Banff score)	1.54 ± 0.9	1.54 ± 0.8	1.54 ± 0.9	

Table 1: Demographics, laboratory data and pathology.

to the heterogeneity of its pathology features. Despite of clearly defined pathology criteria for the diagnosis, pathology findings in CAMR may vary depending on TG stage, interstitial fibrosis extent, presence and type of C4d PTC positivity, and also presence and severity of concomitant cell-mediated rejection. In our patients all these peculiarities correlated with clinical manifestations of allograft rejection, however, we did not find any single pathology feature, directly influencing TG course and long-term outcomes. In particular, a concomitant cell-mediated rejection demanding high-dose steroid, which was found in 13 patients in our study group, finally did not influence significantly the outcomes. There were also no differences in allografts survival depending on the extent rejection activity, evaluated by the type of C4d expression.

According to the Banff classification, only diffuse C4d expression on PTC is considered as diagnostic for AMR [3], as that strongly correlate with DSA production and outcomes. However, these correlations were demonstrated first of all for acute AMR, whereas in CAMR C4d-positivity is seen not so often, and do not influence the course of the disease that much. Thus, the study performed by Haririan et al. did not show significant differences in the course of rejection depending on type of C4d positivity [18]; other investigators noticed

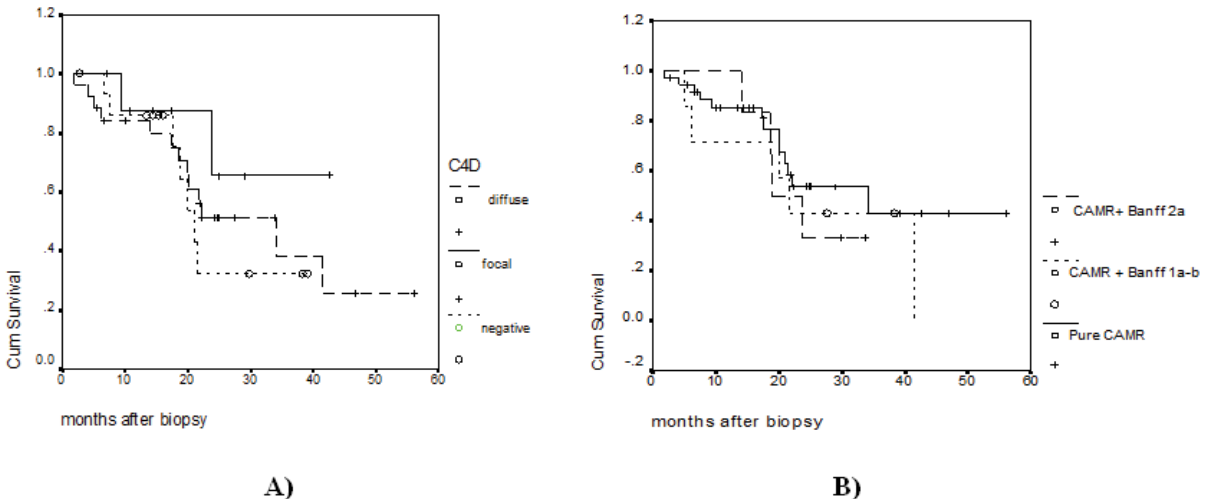

Figure 1: Graft survival according to the presence and character of C4d staining (A) and concomitant cell- mediated rejection (B).

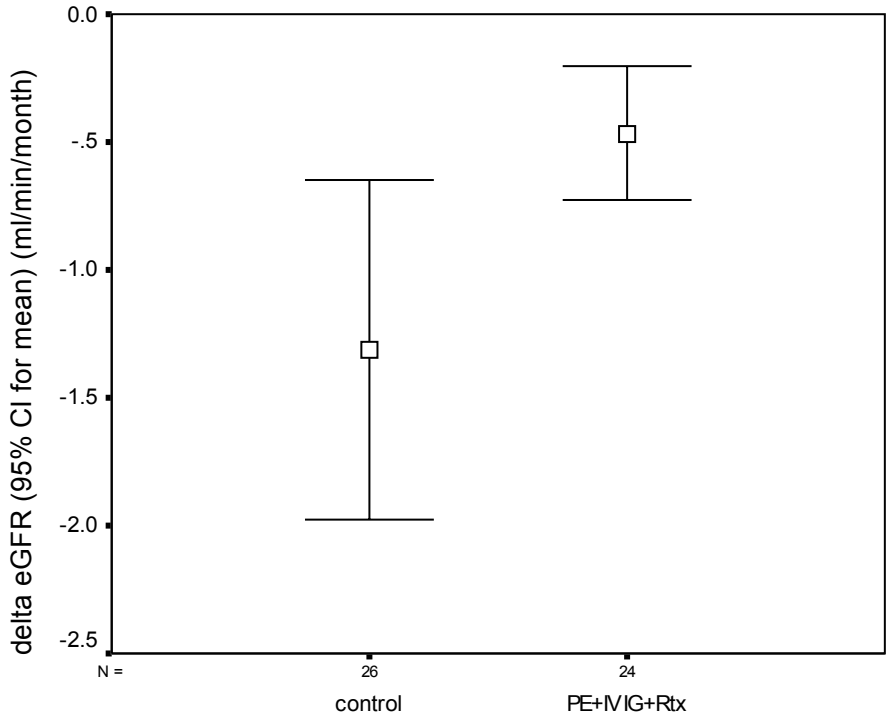

Figure 2: The rate of eGFR decline, calculated as delta eGFR per month [eGFR at the end of follow-up baseline eGFR/duration of follow-up (months)].

more favorable prognosis in patients with focal C4d expression [19]. In our study outcomes of TG were equally unfavorable both in cases with diffuse and focal C4d expression, which lead us to regard focal C4d-positivity as AMR criteria (same as diffuse C4d expression). Therefore, AMR prognosis in our patients did not depend on pathology findings, demanding the same treatment strategy regardless of its stage and activity.

Current approach to the AMR treatment includes measures directed to the already existing anti-donor antibodies elimination, and prevention of their further production. To achieve these goals most often PE, IVIG and Rtx (anti CD20-antibodies) are used in different regimens and combinations. That strategy already demonstrated its

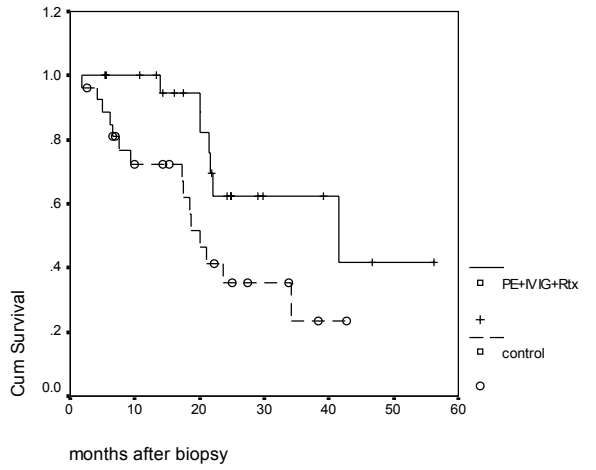

Figure 3: Graft survival according to according to the treatment strategy.

	P value	OR	95.0% CI	
			Lower	Upper
Treatment modality	0.002	0.1	0.026	0.439
Transplant glomerulopathy	0.398	0.64	0.232	1.787
Interstitial fibrosis	0.263	1.02	0.985	1.056
Glomerulosclerosis	0.12	0.97	0.937	1.008
C4D pattern	0.765	0.9	0.446	1.811
Patient's age	0.789	1	0.955	1.062
Time after renal transplantation	0.749	1	0.99	1.015
Cellular rejection	0.27	1.5	0.711	3.389
Proteinuria	0.557	1.1	0.809	1.482
eGFR	0.01	0.94	0.909	0.987

Table 2: Cox regression model.

efficacy in the treatment of acute AMR episodes [7-10]. In contrast, already developed chronic TG is characterized by the resistance to the treatment. Only few studies, approaching this issue, are published so far, and the results of these studies are controversial. These are mainly small patient's series, demonstrating partial effect of treatment with transplant function stabilization in some cases. Thus, Billing et al. used the combination of IVIG (1 g/kg) and Rtx (325 mg/m^2) and found stabilization of transplant function in 14 out of 20 children with active AMR [12]. Similar efficacy demonstrated the study, performed by Fehr et al. in 4 adult patients [13]. Kayler et al. describe delay of eGFR decline during 6 months after IVIG and Rtx treatment in 12 out of 18 patients with CAMR, compared to the rate of eGFR decline in the same patients during 6 months before that treatment [20]. The number of patients in above mentioned studies was 20 as maximum. Although in our study a small sample size is the main limitation, it included 50 patients and found statistically significant differences in the rate of transplant function decline as well as in the transplant loss proportion between the treatment and control subgroups. Moreover, post-hoc power calculation showed study power 69%.

Majority of authors, who used different treatment strategies

	Treatment subgroup	Control subgroup	P
Infectious complications	8 (33%)	4 (16%)	NS
Acute bronchitis	1	0	
Bacterial pneumonia	5	1	
CMV-pneumonia	1	0	
Infectious endocarditis	0	1	
Tuberculosis	0	1	
Soft tissues infection	0	1	
Erysipelas	1	0	
Non-infectious complications/side effects	6 (25%)	0	<0.05
Allergic reaction after Fresh Frozen Plasma infusion	2	0	
Hypoproteinemia	1	0	
Leukopenia	2	0	
Stroke	1	0	
Total	14 (58%)	4 (16%)	<0.05

Table 3: Complications and side effects.

for CAMR, found the effect only in some patients, but not in all of them, however, none of the studies were able to identify the factors, defining the response to treatment. Whereupon several causes that might explain treatment resistance are known. Prominent structural changes of capillary walls, characteristic for the late stages of CAMR and presenting with severe proteinuria, progress to ESRD even in the absence of immune activity [21,22]. On the other hand, predominance of B-memory cells and plasma cells in adults, compare to children, make the former less susceptible to Rtx treatment [23]. Despite majority of authors consider futility of anti-humoral therapy in CAMR, it is difficult to access true efficacy of such treatment in the above mentioned studies. The main pitfall is the absence of control groups, because the natural history of TG is characterized by alternating of progression and stabilization periods. Recently published study, conducted by Bachelet et al., also favors this hypothesis, demonstrating no difference in 2-year survival between patients, receiving IVIG and Rtx and control group (47% and 40% respectively, P=0.69) [16]. Our study with the similar design and compatible clinical and pathology characteristic's of patients population, however demonstrated significant differences in allograft survival between subgroups - 64.8% vs 21.3% (P=0.01). Possible explanation might be including of PE to the treatment protocol, as PE rapidly eliminate anti-donor antibodies and potentiate IVIG effects. Although PE, according to Cedar-Sinai Medical Center protocol [7], is considered to be necessary only if humoral rejection is accompanied by thrombotic microangiopathy, Lefaucheur et al. demonstrated the benefit of combination of PE, IVIG and Rtx compared to only IVIG and Rtx usage [24]. Interestingly, that the point of no-return for CAMR seems to be 2 years in our study 5 out of 7 allograft losses in the treatment subgroup occurred in the interval between 20 and 22 month after the treatment initiation. We suppose that 2-years follow-up period, which is often used for assessment of treatment results, may be not sufficient for accurate evaluation of CAMR therapy efficacy.

Conclusions

Our study demonstrated, that TG, which is the most often variant of CAMR, is characterized by unfavorable prognosis regardless of its pathology features and activity at the time of diagnosis. Combined treatment, including PE, IVIG and Rtx allows slowing down the rate of the disease progression at least in some proportion of patients with lately diagnosed CAMR.

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