Combination Therapy of Rituximab and Intravenous Immunoglobulin as an Effective Treatment for Chronic Antibody-Mediated Rejection in Kidney Transplant Recipients

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INTRODUCTION

Chronic antibody-mediated rejection (CAMR) is a representative cause of chronic allograft loss. Several studies have cited combination of rituximab and intravenous immunoglobulin (IVIG) as a treatment for CAMR, but the effects are still controversial.

OBJECTIVES

We investigated the efficacy of rituximab and IVIG on the progression of CAMR in kidney transplant recipients (KTRs).

METHODS

We retrospectively analyzed 27 KTRs with CAMR diagnosed by allograft biopsy–using the Banff 2005 classification. We divided into two groups as follows: combination group treated with rituximab (375 mg/m^2) and IVIG (2 g/kg) and control group not treated or used different protocols such as rituximab or IVIG only, steroid pulse therapy (non-rituximab and IVIG group). The change of graft function, and factors associated with graft survival were analyzed between two groups.

RESULTS

Table 1. Comparison of clinical and laboratory parameters according to treatment options

Valuables	Non-RIT+IVIG (n = 18)	RIT+IVIG (n = 9)	*p*-Value
Age at diagnosis (yr)	49 ± 11	47 ± 10	0.197
Gender (Male: Female), n (%)	12: 6	6: 3	1.000
Dialysis duration, months	73.7 ± 75.1	52.0 ± 45.6	0.467
Donor type (living: deceased), n (%)	12: 6	4: 5	0.411
Cause of end-stage renal disease, n (%)			0.854
Glomerulonephritis	14 (77.8)	8 (88.9)	
Hypertension	2 (11.1)	0	
Diabetes mellitus	1 (5.6)	1 (11.1)	
Polycystic kidney disease	1 (5.6)	0	
HLA mismatch number	3.3 ± 1.5	3.2 ± 1.5	0.529
PRA class I	14.8 ± 17.1	44.3 ± 35.8	0.045
PRA class II	38.3 ± 41.8	32.2 ± 38.3	0.746
PRA > 50%, n (%)	5 (45.5)	6 (66.7)	0.406
DSA, n (%)	6 (60.0)	6 (75.0)	0.638
Induction, n (%)			0.392
Basiliximab	10 (55.6)	3 (33.3)	
Antithymocyte globulin	1 (5.6)	2 (22.2)	
Main immunosuppressant, n (%)			
Tacrolimus: Cyclosporine			
At KT	10: 8	7: 2	0.406
At diagnosis	12: 6	8: 1	0.363
After diagnosis or treatment	11: 5	9: 0	0.125
Previous acute rejection, n (%)	3 (16.7)	3 (33.3)	0.367
Proteinuria at diagnosis (g/day)	1.5 ± 1.6	4.4 ± 3.7	0.047
High (≥1.3 g/day) : Low (<1.3 g/day)	7 : 11	6 : 3	0.236
Time from KT to diagnosis of CAMR, months	91.3 ± 54.7	125.8 ± 104.3	0.745
Graft failure, n (%)	11 (61.1)	4 (44.4)	0.448
Death, n (%)	4 (22.2)	2 (22.2)	1.000

Values are expressed as means ± SDs, n (%). HLA, human leukocyte antigen; PRA, panel reactive antibody; DSA, donor specific antibody; KT, kidney transplantation; MDRD eGFR, Modification of diet in the renal disease estimated glomerular filtration rate; CAMR, chronic antibody-mediated rejection.

Table 2. Comparison of clinical and laboratory parameters according to Graft failure

Valuables	Non-graft failure (n = 12)	Graft failure (n = 15)	*p*-Value
Age at diagnosis (yr)	49 ± 10	49 ± 11	0.942
Gender (Male: Female), n (%)	11 (91.7): 1 (8.3)	7 (46.7): 8 (53.3)	0.019
Dialysis duration, months	47.1 ± 35.6	82.0 ± 81.6	0.152
Donor type (living: deceased), n (%)	7 (58.3): 5 (41.7)	9 (60.0): 6 (40.0)	1.000
Cause of end-stage renal disease, n (%)			0.851
Glomerulonephritis	9 (75.0)	13 (86.7)	
Hypertension	1 (8.3)	1 (6.7)	
Diabetes mellitus	1 (8.3)	1 (6.7)	
Polycystic kidney disease	1 (8.3)	0	
HLA mismatch number	3.6 ± 1.4	3.1 ± 1.5	0.363
PRA class I	38.6 ± 33.7	20.0 ± 26.5	0.197
PRA class II	43.3 ± 41.7	28.3 ± 37.5	0.419
PRA > 50%, n (%)	6 (66.7)	5 (45.5)	0.406
DSA, n (%)	6 (75.0)	6 (60.0)	0.638
Induction, n (%)			0.063
Basiliximab	8 (66.7)	5 (33.3)	
Antithymocyte globulin	2 (16.7)	1 (6.7)	
Main immunosuppressant, n (%)			
Tacrolimus: Cyclosporine			
At KT	9 (75.0): 3 (25.0)	8 (53.3): 7 (46.7)	0.424
At diagnosis	9 (75.0): 3 (25.0)	11 (73.3): 4 (26.7)	1.000
After diagnosis or treatment	10 (83.3): 2 (16.7)	10 (66.7): 3 (20.0)	0.662
Previous acute rejection, n (%)	4 (33.3)	2 (13.3)	0.357
Proteinuria at diagnosis (g/day)	2.5 ± 3.6	2.7 ± 2.0	0.896
High (≥1.3 g/day) : Low (<1.3 g/day) in rituximab and IVIG	3 : 2	3 : 1	1.000
High (≥1.3 g/day) : Low (<1.3 g/day) in non-rituximab and IVIG	0 : 7	7 : 4	0.013
Time from KT to diagnosis of CAMR, months	96.7 ± 82.3	107.7 ± 70.6	0.710
Treatment, n (%)	9 (75.0)	6 (40.0)	0.121
Treatment options, n (%)			0.044
Rituximab + IVIG	5 (41.7)	4 (26.7)	
Rituximab	0	2 (13.3)	
IVIG	1 (8.3)	0	
Steroid pulse therapy	3 (25.0)	0	
None	3 (25.0)	9 (60.0)	
Death, n (%)	0	6 (40.0)	0.020

Values are expressed as means ± SDs, n (%). HLA, human leukocyte antigen; PRA, panel reactive antibody; DSA, donor specific antibody; KT, kidney transplantation; MDRD eGFR, Modification of diet in the renal disease estimated glomerular filtration rate; CAMR, chronic antibody-mediated rejection.

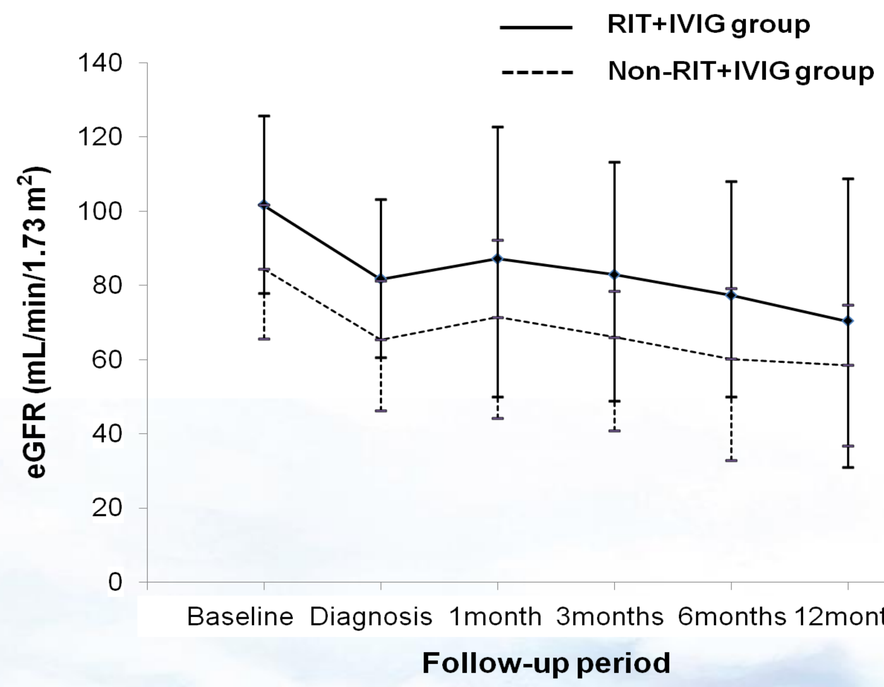

Figure 1. The change of graft function between RIT+IVIG and non-RIT+IVIG group.

CONCLUSIONS

The rate of graft failure was lower and the decline of graft function was lesser in rituximab and IVIG group. In KTRs diagnosed to CAMR with high proteinuria, combination therapy of rituximab and IVIG showed less progression to graft failure compared with other therapy. Combination therapy with rituximab and IVIG could be an effective treatment of CAMR in KTRs.

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