

Induction Therapy: Comparison between Poly and Monoclonal Antibodies

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Abstract

Objective: Compare the effects of 2 molecules as induction treatment in renal transplantation (RT): polyclonal antibodies (rATG or thymoglobulin) *versus* a monoclonal antibody antagonist of interleukin 2 receptors (basiliximub) in terms of occurrence of episodes of rejection, delayed graft function, graft loss, and the occurrence of infectious and neoplastic complications.

Patients and methods: A retrospective study involving 191 patients transplanted from 2007 to 2016 with a minimum follow-up of 3 months at department of nephrology, dialysis and transplantation Sahloul Sousse Tunisia. The induction treatment consists of the administration of a monoclonal antibody for 67 patients group 1 (G1) and polyclonal antibodies (anti-thymocyte anti-thymocyte globulin or thymoglobulin) for 124 patients group 2 (G2). In maintenance, patients were treated with ciclosporin or tacrolimus combined with MMF and corticosteroids or MMF alone with corticosteroids.

Results: We included 191 transplant patients with mean age of 33.13 ± 13.04 years. The occurrence of episodes of rejection was more frequent in patients treated with rATG (21.77% in G2 *versus* 14.92% in G1) but without significant difference ($p = 0.253$). The delay of occurrence of rejection was shorter in the G1. The uni-varied study showed that the occurrence of pneumopathies ($p = 0.005$, OR=6.626, CI [1.503-29.20]), urinary tract infections ($p = 0.020$, OR=2.044, CI [1.115-3.748]), cystitis ($p = 0.038$, OR=1.918, CI [1.032-3.564]), CMV infections ($p = 0.04$, OR=2.567, CI [0.996-6.615]) and digestive infections ($p = 0.035$, OR=4.472, CI [0.991-20.186]) are significantly observed with rATG treatment. In multi-variate analysis only pneumopathies ($p = 0.014$, CI [0.034-0.681]) and urinary tract infections ($p = 0.04$, CI [0.277-0.969]) were significantly frequent with ATG treatment. Neoplastic complications occurred exclusively in G2. We found no significant difference for delayed graft function and graft loss in both groups.

Keywords: Renal transplantation; Monoclonal antibody; Induction therapy

Introduction

Admittedly, immunosuppressive induction therapy in renal transplantation (RT) has proved its place in the prevention of graft rejection, especially in patients at high immunological risk [1]. Several molecules have been put on the market. They act by different mechanisms. These molecules are generally antibodies

that can target a single well-defined antigen (monoclonal antibody) or several antigens (polyclonal antibodies) whose role in the development of the rejection process has been well demonstrated.

Polyclonal antibodies are a mixture of antibodies directed against a multitude of surface molecules involved in intercellular communications (CD2, CD3, CD4, CD25 ...). However, basiliximab is a monoclonal antibody targeting the interleukin 2 receptor, a cytokine whose role is indisputable in the activation and proliferation of T lymphocytes once bound to its receptor.

The aim of our study is to compare these two induction treatment molecules in kidney transplant patients followed in our department of nephrology, dialysis and transplantation, in terms of efficacy concerning the occurrence of episodes of rejection, delayed graft function and graft loss, and safety regarding the occurrence of infectious and neoplastic complications.

Materials and Methods

This study is retrospective descriptive and analytical including all kidney recipients in our department between November 2007 and October 2016 with a minimum follow-up of 3 months.

We divided the patients into two groups: group 1 (G1) who received a monoclonal antibody basiliximub 20 mg on day 0 and day 4

after renal transplantation and group 2 (G2) who received polyclonal antibodies (rATG or thymoglobulin) to the dose of 1.25 and 2 mg/kg/day respectively for 3 to 5 days with a target lymphocyte count of 200 elements/mm³. All patients received methyl prednisolone and mycophenolic acid mofetil (MMF) in combination. Maintenance therapy was the calcineurin inhibitor (ciclosporin or tacrolimus) in combination with corticosteroids and MMF or MMF alone in combination with corticosteroids.

The demographic characteristics of patients in our population are: age, sex, initial nephropathy, donor type, number of mismatch, induction therapy, maintenance treatment, occurrence of rejection, time to onset rejection, infectious complications, neoplastic complications, delayed graft function, graft loss, and the occurrence of death.

All statistical analyzes were performed using the SPSS 20.0 software. The qualitative variables were summarized by numbers and percentages. Quantitative variables were expressed as means and standard deviations. The statistical analysis of the results was carried out by the Chi square test for the comparison of the percentages and

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the Student's t test for the comparison of two independent sample means. Alpha risk was judged to be statistically significant from a 5% threshold.

Results

We included 191 kidney recipients. 64.92% of the patients were received as induction therapy a polyclonal antibody and 35.07% received a monoclonal antibody (basiliximub). A high frequency of male sex was observed in both groups, 61.19% and 66.93% respectively with $p=0.427$. There was no significant difference for mean age in both groups, 31.73 ± 13.85 years in G1 versus 33.8 ± 12.57 years in G2, $p=0.279$. The most common initial nephropathy was chronic interstitial nephropathy in both groups, 65.67% and 42.74% respectively with significant difference, $p=0.013$. The mean number of mismatch was higher in the ATG group (3.33 ± 1.60 versus 2.32 ± 1.75) with a significant difference, $p=0.001$. Most patients in both groups received tacrolimus (50.74% in G1 versus 53.22% in G2) with p not significant $p=0.743$. 19.40% of G1 patients received ciclosporin versus 39.51% in G2, $p=0.005$ while treatment with MMF alone was more prescribed in G1 (26.86% in G1 versus 4.03% in G2) with $p=0.001$ (Table 1).

The occurrence of rejection was higher in the group treated with polyclonal antibodies compared with the basiliximub-treated group but without significant difference (21.77% in G2 versus 14.92% in G1), $p=0.253$. The mean time to onset of acute rejection was shorter in the basiliximub group (11.26 ± 21.98 days versus 20.21 ± 44.58 days) with no significant difference $p=0.37$.

Infectious complications were observed particularly in the group treated with polyclonal antibodies with a significant difference for the occurrence of pneumopathies ($p=0.005$), CMV infection ($p=0.045$), urinary tract infections ($p=0.020$), cystitis (0.038) and digestive tract infections ($p=0.035$) (Table 2).

The multivariate analysis revealed that the occurrence of pneumonia ($p=0.014$, IC [0.034-0.681]) and urinary tract infections,

Factor	High PRA	Low PRA	Significance
Overall	125 (18.7%)	543 (81.3%)	
Mean age	50.8	52.7	-
Elderly (>65)	17 (13.6%)	105 (19.3%)	-
Sex (male)	72 (57.6%)	170 (31.3%)	**
White	91 (72.8%)	384 (70.7%)	-
Black	28 (22.4%)	122 (22.5%)	-
Hispanic	4 (3.2%)	27 (5.0%)	-
Asian	2 (1.6%)	10 (1.8%)	-
Mean PRA	55.8	1.6	**
Retransplant	56 (44.8%)	124 (22.8%)	**

* $p < 0.05$, ** $p < 0.005$

Table 1: Recipient demographic and general information.

Disease/Infection	G1: basiliximub =124	G2: rATG=67	OR	IC (95%)	P
Pneumonia	2.98%	16.93%	6.626	[1.503-29.20]	0.005
CMV Infection	8.95%	20.16%	2.567	[0.996-6.615]	0.045
Urinary tract infections	38.80%	56.45%	2.044	[1.115-3.748]	0.020
Digestive infections	2.9%	12.09%	4.472	[0.991-20.186]	0.035
Candida	4.47%	2.41%			0.425
Tuberculosis	0	1.61%			0.296
Aspergillosis	0	2.41			0.199
Pneumocystis	0	2.41%			0.199

Table 2: Comparison of occurrence of infectious complications in both groups.

$p=0.04$, IC [0.277-0.969] were independently associated with treatment with rATG (Table 3).

No patient in group 1 developed neoplasia, while 10 patients in G2 (8.06%) had a neoplastic complication with a significant difference $p=0.017$. There were 3 cases of Kaposi's sarcoma, 2 cases of graft and cavum lymphoma, 1 luberkhunal adenocarcinoma of the colon, 2 common warts, 2 anal condylomas.

We also evaluated the impact of basiliximub induction versus polyclonal antibody on graft function.

The delayed graft function was observed more frequently in the group treated with r ATG 15.32% versus 11.94% but without significant difference $p=0.508$.

Graft loss was observed more frequently in the basiliximub group, 8.95% versus 8.06% but no significant difference $p=0.832$.

Regarding the impact of induction treatment on patient survival, our study showed that ATG treatment associated with a higher frequency of death (7.25% versus 4.47%) but without significant difference, $p=0.45$.

Discussion

Different types of induction treatments have been put on the market. All these molecules are not devoid of side effects. The occurrence of infectious and neoplastic complications and the significant risk of rejection of the graft observed with certain molecules are the main serious effects observed. Several studies have shown that induction therapy with polyclonal antibodies is associated with a lower risk of graft rejection due to strong immunosuppression. Indeed, Brennan DC in both studies, the first including transplant from cadaveric donors objectified significantly higher rejection rate in patients treated with basiliximub [1,2].

In addition, our study showed the opposite and we found a higher rejection frequency in the group treated with polyclonal antibodies but without significant difference. Our results agree with those of Wang W and all who also did not find a significant difference in the occurrence of rejection between the two groups (9.59% vs. 8.62%, $P=0.481$) [3]. Similarly for Sánchez-Escuredo A, who found no significant difference for rejection at 1 year between groups treated with polyclonal antibodies or basiliximub [4]. These results can be explained on the one hand by the interference of the several factors favoring the occurrence of rejection of the graft such as the poor therapeutic compliance and the occurrence of essentially viral infectious episodes requiring the decrease of the maintenance treatment. On the other hand, there is a possible selection bias seen that most of our patients are treated with polyclonal antibodies. However, the time to onset of rejection was shorter in the basiliximub-treated group, explained by the profound initial lymphopenia induced by rATG essentially T helper lymphocytes naive CD4 naive [5,6].

Disease/Infection	p	IC (95%)
Pneumonia	0.014	[0.034-0.681]
Urinary tract infections	0.04	[0.277-0.969]

Table 3: Occurrence of infectious complications in the two groups according to the multi-varied analysis.

Pulmonary and digestive infections are independently associated with rATG treatment. This can be explained by the strong immunosuppression induced by polyclonal antibodies. Wang W and all have also found a significantly higher frequency of lung infections when treating patients by rATG. Kim J.M. and all reported in their study a significant increase in CMV infections in the rATG treated group compared to that treated with basiliximub [7]. Hong-Feng Huang similarly demonstrated in his study that urinary tract infections mainly occur with rATG *versus* basiliximub [8].

In addition, neoplastic complications were observed exclusively in the group treated with polyclonal antibodies. For against, Brennan DC in his both studies did not show a significant difference in the occurrence of neoplasia between the two groups.

However, no significant difference was found in our study between the two groups for the impact on graft function. Indeed, like that of Wang W et al., our study did not find a significant difference for the occurrence of delayed graft function between the two groups. Similarly, rATG treatment was not associated with a significantly high incidence of graft loss compared to basiliximub induction therapy joining the study of Brennan DC et al. For against, Brennan DC., in his second study, was found that rATG therapy is associated in long term with a lower risk of graft loss compared to basiliximub therapy.

In another study including 200 kidney transplant recipients, the authors reported that creatinine clearance and the occurrence of acute rejection were similar at 1 year of transplantation between the two groups [9]. Huang HF. A has similarly demonstrated in his study including 213 transplanted patients followed for 3 months that there was no difference between the two groups treated with basiliximub *versus* rATG in terms of glomerular filtration rate, graft loss and death [10]. However the occurrence of infections mainly of the urinary tract and viral infections are significantly more observed in the group treated with rATG.

In the study of Brennan DC and all, the death at 5 years after transplantation was also significantly lower in the rATG group. In our study, there was no significant difference between the two groups in the occurrence of death joining the first study of Brennan DC.

Finally, the small number of our population may be the main limitation of our study.

Conclusion

The immunosuppressive induction therapy, whether it be basiliximab or polyclonal antibodies (rATG or thymoglobulin) aims to reduce the risk of rejection of the graft. The side effects particularly infectious and neoplastic remain inevitable mainly with polyclonal antibodies because of the profound immunosuppression induced. However, our study could not demonstrate the superiority of polyclonal antibodies in the prevention of rejection compared with basiliximub. Similarly to the occurrence of delayed graft function and loss of the graft. Moreover, the occurrence of infectious and neoplastic complications was significantly associated with treatment by polyclonal antibodies compared to the basiliximub. For this reason, many other treatments are being tested to minimize such effects and improve graft survival such as Tol 101, a non-depleting monoclonal murine antibody targeting TCR $\alpha\beta$ and causing a decrease in the production of cytokines and lymphocyte proliferation and which could be a solution for the future.

References

- Brennan DC, John MD, Daller A, Kathleen, Lake D, et al. (2006) Rabbit antithymocyte globulin versus basiliximab in renal transplantation. *N Engl J Med* 355: 1967-1977.
- Brennan DC, MA Schnitzler MA (2008) Long-term results of rabbit antithymocyte globulin and basiliximab induction. *N Engl J Med* 359: 1736-1738.
- Wang W, Yin H, Li XB, Hu XP, Yang XY, et al. (2012) A retrospective comparison of the efficacy and safety in kidney transplant recipients with basiliximab and anti-thymocyte globulin. *Chinese Medical J* 125: 1135-1140.
- Sánchez-Escuredo A, Alsina A, Diekmann F, Revuelta I, Esforzado N, et al. (2015) Polyclonal versus monoclonal induction therapy in a calcineurin inhibitor free immunosuppressive therapy in renal transplantation: a comparison of efficacy and costs. *Transplant Proc* 47: 45-49.
- Büchler M, Longuet H, Lemoine R, Herr F, Gatault P, et al. (2013) Pharmacokinetic and pharmacodynamic studies of two different rabbit anti thymocyte globulin dosing regimens/Results of a randomized trial. *Transplant Immunology* 28: 120-126.
- Pankewys O, Leca N, Kohli R, Wallace K, Said M, et al. (2011) Low dose rabbit anti thymocyte globulin induction therapy results in prolonged selective lymphocyte depletion irrespective of maintenance immunosuppression. *Transplantation Proceedings* 43: 462-465.
- Kima JM, Jangb HR, Kwona CHD, Huhb WS, Kimc GS, et al. (2012) Rabbit Antithymocyte Globulin Compared with Basiliximab in Kidney Transplantation: A Single-Center Study. *Transplantation Proceedings* 44: 167-170.
- Hong-Feng H, Jing-Yi Z, Wen-Qing X, Jian-Yong W, Deng H, et al. (2016) Basiliximab versus rabbit antithymocyte globulin as induction therapy for living-related renal transplantation: a single-center experience. *Int Urol Nephrol* 48: 1363-1370.
- Pilch NA, Taber DJ, Moussa O, Thomas B, Denmark S, et al. (2014) Prospective randomized controlled trial of rabbit antithymocyte globulin compared with IL-2 receptor antagonist induction therapy in kidney transplantation. *Ann Surg* 259: 888-993.
- Huang HF, Zhou JY, Xie WQ, Wu JY, Deng H, et al. (2016) Basiliximab versus rabbit antithymocyte globulin as induction therapy for living-related renal transplantation: a single-center experience. *Int Urol Nephrol* 48: 363-370.