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# Experience with different induction therapy protocols based on depleting antibodies for kidney transplantation

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**Aim.** *To analyze the efficacy and safety of different induction therapy protocols based on lymphocyte-depleting antibodies for kidney transplantation (ATGAM, Timoglobulin).*

**Material and methods.** *The study included 107 non-sensitized patients who underwent primary kidney allotransplantation in the period from January 2012 to March 2014. Patients were divided into 3 groups according to the ongoing induction immunosuppressive therapy: Group I, patients receiving the drug ATGAM (n = 67); Group II, patients receiving Thymoglobulin (n = 30); Group III, patients who received a combination of basiliximab and ATGAM (n = 10). All patients received basic triple immunosuppressive therapy: tacrolimus, mycophenolic acid, methylprednisolone.*

**Results.** *The incidence of acute rejection was 7.5% in group I, 0% in group II, 0% in group III (p=0.15). The incidence of severe thrombocytopenia was 2.7% in Group I, 0% in Group II (p <0.05), 10% in Group III. The incidence of CMV viremia was 6.16 % in group I, 6.6% in group II, 10% in group III (p>0.05). In Group II and III, CMV pneumonia (one case each) was registered in the early postoperative period.*

**Conclusion.** *The use of polyclonal lymphocyte-depleting antibodies as the agents of choice for induction therapy in primary renal transplantation in non-sensitized patients is warranted. Further research is necessary to evaluate 5 and 10-year outcomes.*

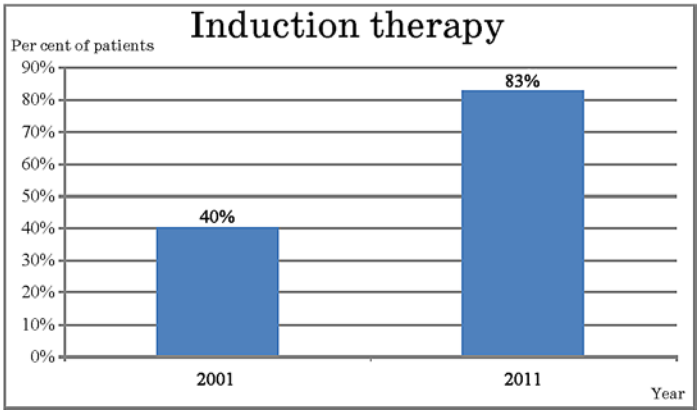
**Keywords:** lymphocyte-depleting antibodies, acute rejection, induction therapy, cytomegalovirus (CMV).

## Introduction

Solid organ transplantation has taken strong positions in the treatment of many chronic diseases in the terminal stage. Its efficacy would have been low without using the drugs aimed at alloimmunosuppression. Since the introduction of Minnesota antilymphocytic immunoglobulin (MALG) into clinical practice in the mid 80s of the last century, the induction therapy has been considered as one of the main factors of success in solid organ transplantation, alongside with the use of calcineurin inhibitors.

According to the Scientific Registry of Transplant Recipients (SRTR), the rates of the induction therapy use in the United States have double increased (from 40% to 83%) over the recent 10 years (Fig. 1, Graph 1). For example, in 2011, 58% of patients received the immunosuppressive therapy based on polyclonal depleting antibodies, 21% of patients received anti-interleukin-2 receptor (anti-IL-2R) monoclonal antibody therapy, 4% of patients received the combination of both (Fig. 1, Figure 2). Important to note that the growth was accounted for by an increased use of polyclonal antibodies [5].

**Graph 1**




**Graph 2**

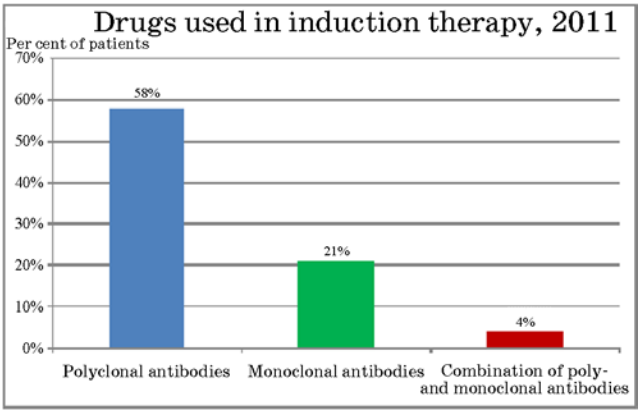



**Fig. 1. Data of Scientific Registry of Transplant Recipients (SRTR), USA, 2011**

Worthwhile to note the economic feasibility of induction therapy that is defined not so much by the cost of biological agents used but rather by the cost of treatment for potential complications associated with organ allotransplantation without adequate induction therapy, such complications as an acute chronic rejection, and the risk to return to an expensive renal replacement therapy with dialysis, and possible immunosuppressive therapy complications [3].

The aim of our study was to analyze the efficacy and safety of our clinical protocols of induction therapy based on the use of polyclonal lymphocyte-depleting antibodies (ATGAM, Thymoglobilun).

**Material and Methods**

The study included 107 non-sensitized patients who underwent primary kidney allotransplantation in the period from January 2012 to March 2014, including 37 cadaver transplantations and 70 living related donor transplants. Among all cases, 63% were men, 37% were women. The underlying diseases that resulted in terminal chronic renal failure were the following: chronic glomerulonephritis of unspecified morphology (n=75); Type I or II diabetes mellitus (n=10); abnormal genitourinary tract development and bladder dysfunctions leading to reflux nephropathy (n=7); polycystic kidney disease (n=4); urolithiasis (n=5); renal amyloidosis (n=1); Goodpasture syndrome (n=1); hemolytic-uremic syndrome (hus) (n=2); Alport syndrome (n = 2).

The mean age of live donors was 56.2 years (ranged from 25 to 62 years). The mean glomerular filtration rate in live donors until the moment of organ retrieval was 82.4 mL/min (MDRD), ranged from 72-102 mL/min.

The mean age of post-mortem donors was 43.4 years (ranged from 19 to 61 years), the main causes of death were: head trauma in 40.5 %, and acute ischemic stroke in 54%. The median cold ischemia time was 18.5 hours, ranging from 12 to 23 hours.

All patients received triple basic immunosuppressive therapy. Tacrolimus (standard or extended release) was given at a starting dose of 2 mg/kg/day. A target blood level of tacrolimus in the first postoperative month was defined as 8-12 ng/mL. Mycophenolic acid was admininstered at

a dose of 1440 mg/day for 2 weeks with further tapering to 720 mg/day (n=81). Azathioprine at a dose of 1 mg/kg of body weight was used instead of mycophenolic acid in 19 cases. Methylprednisolone was administered in a starting dose of 16 mg/day regardless of body weight followed by tapering to 4 mg by the 2nd postoperative month.

Patients were divided into three groups depending on the induction immunosuppressive therapy (Table. 1): Group I included the patients who received ATGAM at a dose of 10 mg/kg for 4-7 days (n=67); Group II patients received thymoglobulin 1 mg/kg for 3-7 days (n=30); Group III patients received a combination of basiliximab in a daily dose of 20 mg b.i.d. and ATGAM 250 mg/day q.i.d (n=10). The first dosing of drugs was undertaken intraoperatively prior to organ reperfusion.

**Table 1. Immunosuppressive induction therapy protocol established in our clinic**

| Group | Drug | Daily dose | Therapy duration, days |
|---|---|---|---|
| 1st | ATGAM | 10 mg / kg | 4-7 |
| 2nd | Thymoglobulin | 1 mg / kg | 3-7 |
| 3rd | Combination therapy (basiliximab + ATGAM) | 20 mg + 250 mg | 2-4 |

Anti-infection prophylactic valganciclovir was started in all patients on the 1st-2nd postoperative day (for 180 days). Antibiotic therapy with 2nd generation cephalosporins or with ciprofloxacin was given for 4-6 days,

including the day of surgery. In outpatient follow-up period all patients received a pneumocystic pneumonia (PCP) prophylaxis with cotrimoxazole for 90 days.

In cases of renal transplant dysfunction, a needle biopsy was performed with further histological and immunohistochemical examinations of biopsy specimens.

**Results**

The incidence of acute rejection made 7.5% (n=5) in Group I (ATGAM), 0% in Group II (thymoglobulin), 0% in Group III (ATGAM + basiliximab) ($p>0.05$). Four cases of acute rejection I were observed in Group at week 2-3 following surgery. In all the cases of acute rejection, a puncture biopsy of transplant kidney was performed for morphological and immunohistochemical studies of the specimens. The follow-up period was from 12 to 26 months post surgery in Groups I and III, and from 1 to 12 months in Group II (Fig. 2, Graph 3).

**Graph 3**

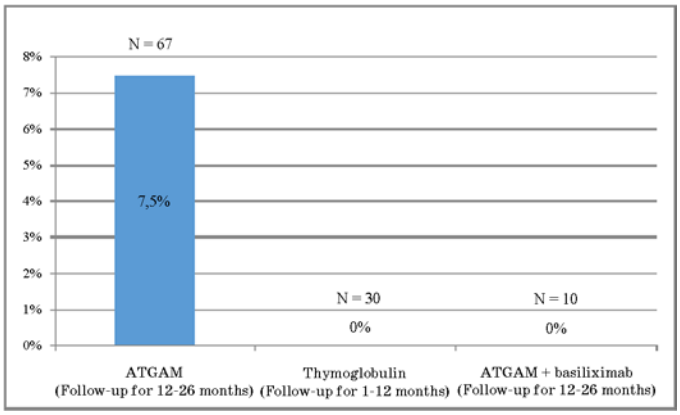



**Fig. 2. The incidence of acute rejection ($p>0.05$)**

A one-year incidence of acute post-transplant rejection in Group I was 5.3%.

The delayed graft function was observed in 50% of all cadaveric transplants and was unrelated to the induction therapy protocol. The median duration of the delayed graft function did not differ among the three groups making 16 days ($p<0.05$). Primarily non-functioning graft was reported in cadaveric transplants in Group I and II (one case each) as a result of pre-existing donor pathology.

A high incidence of thrombocytopenia (62.7%) defined as a decrease in platelet count below 100 $x10^3$/mL was noted in Group I, including 8.3% of moderate thrombocytopenia cases (platelet count of 30-50 $x10^3$/mL) and 2.7% of severe life-threatening thrombocytopenia cases (with platelet count of <30 $x10^3$/mL). In the group of patients who received induction with thymoglobulin, a transient thrombocytopenia was observed in 26% of cases only, without developing into a severe form ($p<0.05$). In Group III, the incidence of thrombocytopenia was 60%, including 10% of severe thrombocytopenia cases (n=2). Worthwhile to note that the platelet count in the peripheral blood returned to baseline values within a week after the withdrawal of induction agents (Fig. 3, Graph 4).

**Graph 4**

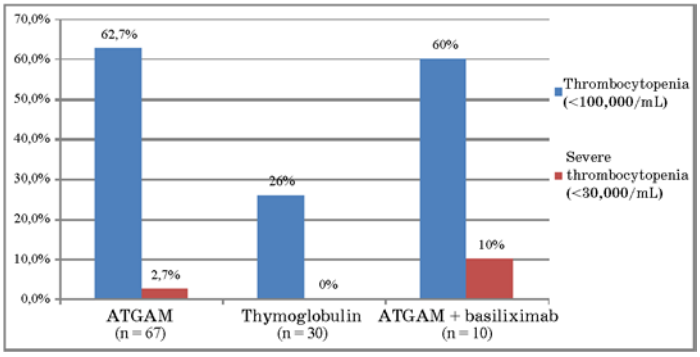



**Fig. 3. The incidence of thrombocytopenia ($p<0.05$)**

The incidence of life-threatening infections (Fig. 4, Graph 5) was 16.7%, 13.3%, and 20%, in Group I, II, and III, respectively (p>0.05), lower urinary tract and wound infections being included.

**Graph 5**

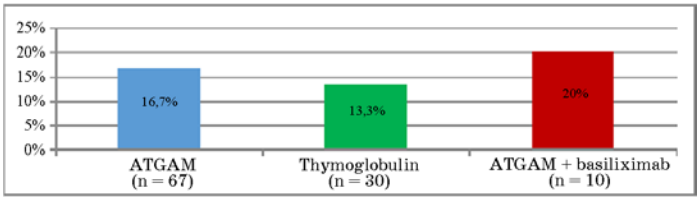



**Fig. 4. The incidence of life-threatening infection (p>0.05)**

We did not observe a great number of CMV viremia cases in any of the groups: 6.16%, 6.6%, and 10% in Group I, II, and III, respectively (p>0.05). Early postoperative CMV-pneumonia was registered in Group I and II (one case each), despite the undertaken prevention measures. One patient who received ATGAM as an induction therapy developed pneumocystis pneumonia at month 4 after transplantation that was successfully treated with co-trimoxazole course, but the patient died of recurrent pneumonia on the 6$^{th}$ month following transplantation (Fig. 5, Graph 6).

**Graph 6**

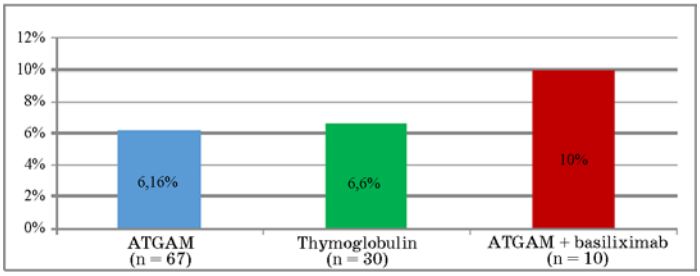



**Fig. 5. The incidence of CMV viremia (p>0.05)**

Cytokine release syndrome in association with the inductive therapy agent administration was observed in 15.5% of Group I patients, and in 6% of Group II patients ($p<0.05$). Also, there was a case of hardly correctable hyperkalemia associated with a thymoglobulin induction in a patient with a good graft function.

The mean course therapy dose calculated per 70 kg of body weight was 229.31 mg of thymoglobulin per patient, 2511.36 mg of ATGAM per patient. So, the cost of therapy was 229.31/25 x 10,040.00 = 92,090.89 rubles for thymoglobulin course, and 2511.36/250 x 47,008.07/5=94,443.34 rubles for ATGAM course. The combination therapy cost for Simulect + ATGAM course made 42,871.17 x 2 + 47,008.07/5 x 4 = 123,348.79 rubles (Table. 2).

**Table 2. The cost of induction immunosuppressive therapy course**

| Drug | Cost of therapy course, rubles |
|---|---|
| Thymoglobulin | 92 090.89 |
| ATGAM | 94 443.34 |
| Simulect + ATGAM | 123 348.79 |

**Discussion**

All the induction therapy protocols used in our study proved to be efficient in the prevention of acute graft rejection. Perhaps, the absence of acute rejection episodes in the Groups receiving thymoglobulin and the

combination of Simulect + ATGAM indicates a higher potency of this therapy protocols in the prevention of immunological conflict; however, a short follow-up period and a small sample size do not allow definite conclusions.

Thus, a low incidence of infectious complications and CMV viremia in early and late postoperative periods makes it possible to state with certainty that the selected dosing regimens of ATGAM and thymoglobulin were equally efficient and safe. However, as we noted, ATGAM use was associated with cytokine release syndrome manifestations significantly more often, although there were no reported severe anaphylactic reactions. Published reports have demonstrated no evidence of a significant superiority of thymoglobulin over ATGAM, but a 10-year study undertaken in the University of Missouri (USA) have shown a lower graft rejection rate (11%), and a lower incidence of all types of cancer (8%) when using thymoglobulin, compared to 42% and 21% of cases, respectively, when using ATGAM, the graft survival rates being similar. [9].

The results of using a dual induction therapy were rather ambiguous. We observed a high incidence of infectious complications and severe thrombocytopenia that were the issues of concern. On the other hand, there is evidence supporting the safety of this strategy even in elderly patients [10]. One should consider a cost-effective component of using each of the three induction therapy protocols, and here, the combination of Simulect + ATGAM therapy appears the most expensive without providing significant benefits for a patient.

The induction therapy is advantageous in providing the possibility to delay the administration of calcineurin inhibitors and to use them in lower doses. This is particularly important to reduce nephrotoxicity of the grafts

compromised by ischemia-reperfusion in cases of deceased donor donation, on the one hand, or in related transplantation from aged donors with decreased glomerular filtration rate, on the other hand [11].

One must remember that in terms of the drastic shortage of donor organs and the lack of renal replacement therapy options, the strategy of immunosuppressive therapy should be aimed at preserving any transplanted organ functions as a guarantee of a recipient survival.

## Conclusion

The chosen tactics of using lymphocyte-depleting polyclonal antibodies as the agents of choice for the induction therapy in renal transplantation in primary non-sensibilized patients has been warranted. Further studies are necessary to evaluate 5- and 10-year follow-up outcomes.

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