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Single dose thymoglobulin induction therapy in prevention of acute rejection in renal transplant recipients

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ABSTRACT

Introduction: The goal of induction therapy in developing countries should be prevention of acute rejection with access to immunosuppressive therapy on a cost-effective basis for maintaining allograft function.
Objectives: The objective of this study was to determine the incidence of acute rejection in the post-transplant period, on induction using single low dose thymoglobulin.
Patients and Methods: We conducted a prospective study of 98 renal transplant recipients to see the effectiveness of single dose induction therapy with thymoglobulin.
Results: The incidence of biopsy proven acute cellular rejection (ACR) was 8.16% in patients receiving thymoglobulin. The incidence of infection was 24.49%. We found a significant lymphocyte depletion in the immediate post-transplant period in thymoglobulin patients, with a mean of 500/µL in our cohort, for 4 to 10 post-operative days.
Conclusion: This prospective study favours the administration of low single dose thymoglobulin as an effective induction agent with low rejection rates and cost effectiveness in resource poor settings.

Original

Implication for health policy/practice/research/medical education:
In a prospective study of 98 renal transplant recipients to see the effectiveness of single dose induction therapy with thymoglobulin, we found, administration of low single dose thymoglobulin is an effective induction agent as shown by low rejection rates and cost effectiveness, which can be useful in resource poor settings.

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Introduction

Acute rejection episodes, which occur in the early engraftment period, could be either acute cellular rejection (ACR) or acute antibody-mediated rejection (AMR). ACR is largely preventable using induction therapy and maintenance triple immunosuppression. This has two objectives: to prevent acute rejection and to minimize infective complications due to high dose induction therapy. Bacterial, viral and fungal infections in allograft recipients are the major causes of morbidity and mortality in India (1-3). In developing countries such as India, where medical insurance covers only 5% of the population, the goal should be the prevention of acute rejection with access to immunosuppressive therapy on a cost effective basis for maintaining allograft function. The Kidney Disease Improving Global Outcomes (KDIGO) guidelines recommend using interleukin-2 (IL-2) receptor antagonist as the first line induction therapy in kidney transplantation (4). Basiliximab, an IL-2 receptor antagonist is a commonly used induction agent and costs INR 50 000 (US$727.5) per 20 mg in India. Thymoglobulin is a polyclonal antibody that causes lymphocyte depletion mainly by complement mediated cell lysis and is a potent induction agent (5-7). Thymoglobulin is a cheaper alternative to basiliximab in developing countries and costs about INR 12 500 (US$181.9) per 25 mg. Since thymoglobulin and basiliximab are used at different dosages with multiple injections, induction therapy has

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to be carefully monitored to prevent ACR and infections.

Objectives

With an increase in the access to renal transplantation services in India, many centres have used different protocols for induction therapy, with an objective to reduce the cost and improve the quality of life post-transplantation. The first author has used thymoglobulin in different dosages and combinations of maintenance immunosuppressive drugs for 30 years in developed and developing countries. This long experience enabled us to take up this study of low single dose thymoglobulin for induction. Hence this prospective study was undertaken to see the effectiveness of single-dose thymoglobulin induction therapy in South Asian patients from 2005 to 2015 in a single tertiary care center in South India.

Patients and Methods

Study population

We conducted a prospective study of 98 renal transplant recipients at the Madras Medical Mission Hospital, Chennai, India from 2005 to 2015. The donor-recipient relationship was first degree relatives, spouses or deceased donors. We looked at the incidence of ACR and infective episodes in these 98 patients.

Induction therapy

The dose of thymoglobulin used was 1 mg/kg body weight. If the patient weighed 70 kg, 75 mg thymoglobulin was given.

Postoperative surveillance

The cold ischemia time was up to 5 hours in deceased donor transplantation and 20 minutes in living donor transplantation. The warm ischemia time was 35 minutes. HLA typing for class 1 and class 2 antigen were done for all patients except in deceased donor transplantation. Perioperative antibiotic prophylaxis was given with intravenous ceftriaxone 1.5 g prior to recipient surgery. Peripheral lymphocyte count was monitored in all patients from the day of transplantation for 7–10 days in all recipients, and in the last 17 patients, we have measured CD3 and CD4 counts in addition to peripheral lymphocyte count. Further doses of thymoglobulin 1 mg/kg body weight were given if there was biopsy-proven ACR, which was not responsive to intravenous methyl prednisolone 500 to 1000 mg in 3 doses on consecutive days. Patients who received thymoglobulin were given valganciclovir 450 mg every other day for 6 weeks as cytomegalovirus (CMV) prophylaxis. The lower dosage of valganciclovir was given to reduce the cost and side effects as we inducted with a low dose of thymoglobulin. Cotrimoxazole double strength was given for all patients as PCP prophylaxis three times a week for one year unless contraindicated. All donors and recipients were positive for CMV IgG antibodies due to prior infection (Ig G CMV D and R positive). Indwelling urinary catheters were removed on the fifth post-operative day. Urine cultures were sent from the second postoperative day every other day until the patient was discharged from the hospital. All patients with graft dysfunction had an ultrasound-guided biopsy which was examined by light microscopy, C4d staining and immunofluorescence. All biopsy-proven ACR were treated with 500 mg to 1000 mg methyl prednisolone for 3 to 5 days. If there was no response to therapy, patients were given the second or third dose of thymoglobulin 1 mg/kg body weight. Acute rejections were diagnosed with an allograft biopsy according to Banff classification and C4d staining for AMR. Serial graft function estimations with serum creatinine and blood urea were done daily while in the hospital, then thrice a week after discharge for 2 weeks, and reduced to twice a week and once a week if the graft function is subsequently stable. All infections including UTI, wound infection and any other infections were documented and treated appropriately. The maintenance therapy consisted of prednisolone 0.5 mg per kg body weight. Microemulsion form of cyclosporine or tacrolimus (0.1 mg/kg body weight), mycophenolate mofetil (MMF) was given at a dose of 1 g twice daily for those 70 kg or more and 750 mg twice a day for those weighing <70 kg body weight. Trough levels were monitored for calcineurin inhibitor (CNI) to maintain appropriate dosage from the third day of engraftment, and prednisolone dosage was tapered to as low as 5 mg within the first 3 months of engraftment if the graft function was stable.

We collected the following data from the renal transplant recipients; the presence of diabetes mellitus and hypertension, the dosage of induction agent used, the presence of biopsy-proven ACR and AMR, infective episodes, absolute lymphocyte count, absolute CD4 count and absolute CD8 count.

Ethical issues

The research followed the tenets of the Declaration of Helsinki and its later amendments. Participants gave their written and informed consent to participate to the study by completing the consent form. This study was approved by the institutional ethics committee of Madras Medical Mission hospital, Chennai, India.

Statistical analysis

Continuous variables were reported as mean and standard deviation (SD). The incidence of rejection and infective episodes were reported as percentages.

Results

Out of the 98 patients, 24 (24.5%) were diabetics, and 67 (68.4%) were hypertensives. All the patients were followed for a minimum of 2 months and mean follow up time was 11 months. We report 7 (7.14%) cases of ACR, 1 (1.02 %) case of AMR, 1 (1.02 %) case of combined ACR and AMR,

1 (1.02%) case of hyper-acute rejection and 3 (3.06%) cases of borderline rejection during the follow up period. In a single patient who received single dose thymoglobulin induction therapy, a second dose of thymoglobulin was used due to ACR that failed to respond to intravenous methyl prednisolone. The incidence of infection was 24 (24.49%). We observed the following infective episodes; 18 urinary tract infections, 2 cases of pyelonephritis, 1 wound infection, 2 respiratory tract infections and 1 case of sepsis. Figures 1, 2 and 3 show the serial monitoring of total leukocyte count, absolute lymphocyte count, serum creatinine levels in the post-operative period and incidence of acute rejection. The average absolute lymphocyte count, CD4 count and CD 8 count before transplant as measured in our last 17 patients are 1274, 428 and 388/µL respectively. We found that there was a significant lymphocyte depletion to as low as 1.5 % in the immediate post-transplant period in some patients, with a mean of 524.4/µL in our study. This depletion was evident for 4 to 10 post-operative days.

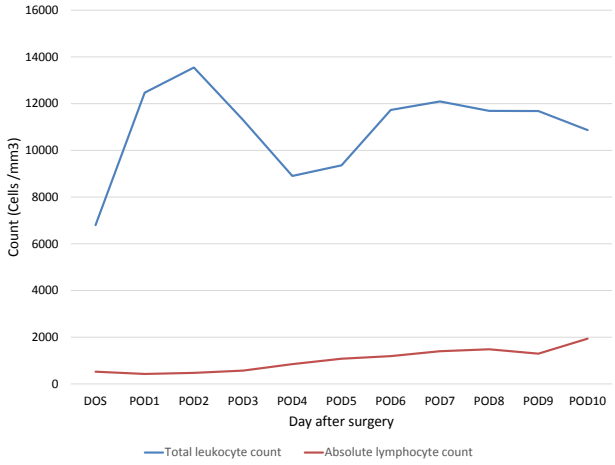

Figure 1. Serial monitoring of total count of leukocytes and absolute lymphocyte count under single dose thymoglobulin induction therapy.

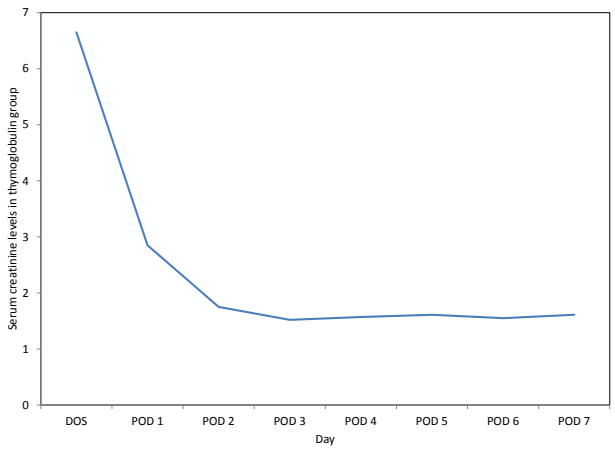

Figure 2. Serial serum creatinine level monitoring among the single dose thymoglobulin patients.

Discussion

Renal replacement therapy (RRT) is unaffordable to the majority of the CKD affected in India. Nationalized health programmes that focus on RRT are woefully inadequate to cater to the Indian population, where CKD is reaching epidemic proportions. The government of India has recently allocated a portion of its 2016-2017 financial budget for improving access to dialysis services at local district hospitals. However, there is a scarcity of nephrologists and other skilled healthcare personnel in district hospitals. Five North-Eastern states in India have no nephrologists. The vast majority of ESRD patients in India die within a few months of diagnosis because of lack of local access to dialysis on a sustained basis, and lack of access to affordable renal transplant services (11). This can be largely attributed to the health economics of India, where only a meager 4% of gross domestic product is being spent on healthcare, with 1.3% by the government (8,9). The deceased organ donation rate in India is one among the lowest in the world, but is steadily increasing. Various bacterial, viral, fungal and protozoal infections are major sources of morbidity and mortality in renal transplant recipients in India (1-3). The need of the hour is to develop and adopt cost effective treatment strategies to improve post-transplant care and outcomes.

There is no published data on acute rejection rates following single low dose thymoglobulin induction in Indian patients. Post-transplant immunosuppression has to be tailored to prevent acute rejection as well as infections. Various transplant centers in India have their own protocols on induction therapy. Basiliximab is considered to be the first line drug for preventing acute rejection according to KDIGO guidelines. In a developing country like India, it costs around INR 5 000 (US$727.5) per 20 mg, which is beyond the reach of potential transplant recipients. The annual gross domestic product (GDP) per person in India is about US $ 1709.4, which speaks for the

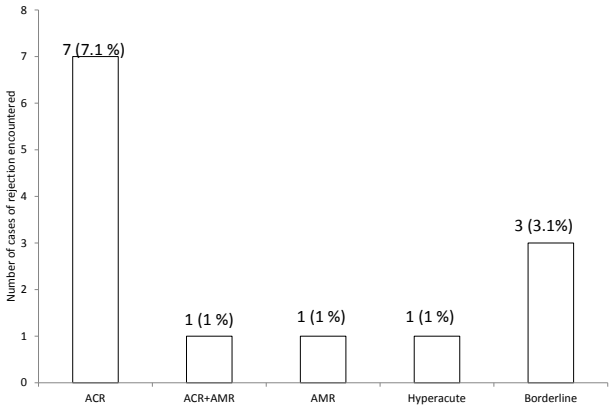

Figure 3. Number of cases of acute rejection encountered (n = 98)..

unaffordability to transplantation (12). There is a paucity of data on cost effective induction therapy to prevent ACR that can be followed in developing countries.

Several studies have been done on the comparison of thymoglobulin and basiliximab in preventing acute rejection (5,6,10). Thymoglobulin induction has been shown to have less rejection rates compared to basiliximab, and is cheaper than basiliximab. However, our prospective study looked at the outcome of single low dose thymoglobulin induction therapy in preventing acute rejection. In our study, the incidence of AVR was low in single dose thymoglobulin (8.16%). We measured the peripheral lymphocyte count of the patients on a daily basis which is cheap after single dose induction with thymoglobulin as a tool to measure lymphocyte depletion. For 4 to 10 post-operative days, there was a significant lymphocyte depletion to as low as 1.5 % in some patients, with a mean of 524.4/µL. The advantage of this is reflected in decreased rate of ACR in the immediate post-transplant period. In the six months period post-transplant, we did not observe development of any malignancy or other adverse effects of thymoglobulin therapy. We also had allograft biopsy in all graft dysfunction patients, which excluded ACR from other causes of graft dysfunction.

Conclusion

This prospective study favours the administration of low single dose thymoglobulin is an effective induction agent as shown by low rejection rates and cost effectiveness, which can be useful in resource poor settings.

Study limitations

This study does not report on the long-term graft function of renal allografts in patients who received single low-dose thymoglobulin, which has been planned in our institution.

Authors' contribution

GA, RP, MM, SS and PK made a substantial contribution to the conception, design, analysis and interpretation of data. MV and SN were involved in drafting the manuscript and revising it critically for important intellectual content. MV, SN and KS collected data. GA revised the manuscript critically for important intellectual content. All authors read and signed the final manuscript.

Conflicts of interest

The authors declare no conflict of interest.

Ethical considerations

Ethical issues (including plagiarism, data fabrication, double publication) have been completely observed by the authors.

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