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Prescription Trends of Immunosuppressant Drugs in Indian Renal Transplant Patients

Dharmik D Patel^{1*}, Ketan P Modi², Anil K Patel³

¹School of Pharmacy, R K University, Rajkot, Gujarat, India

²B K Modi government college, Rajkot, Gujarat, India

³Consultant Nephrologist Care Hospital, Surat, Gujarat, India

ABSTRACT

The present study was conducted to find out the changes in immunosuppressant drug prescription pattern and trends in kidney transplant patients. In this study 613 Indian transplant patients who underwent kidney transplantation between July 2004 and June 2011 were enrolled. Various data of all transplant patients including immunosuppressant drug medication, changes in the prescription, use of antibody for induction and antirejection treatment were collected during their hospital stay and ambulatory visit. Antibody use as an induction agent has increased from during the study period. Induction was used in 23.1% during the year 2005 and increased to 44.4% during the year 2009. Among induction agent ATG was most commonly preferred agent, followed by daclizumab and basiliximab (24% ATG Vs 6.9% daclizumab Vs 6.9% basiliximab). Use of tacrolimus has increased (94% on tacrolimus vs 6% on cyclosporine in 2010). Mycophenolate mofetil is most commonly used antiproliferative agent (80% on MMF vs 20% on azathioprine in 2010). Trend is towards more use of MMF though azathioprine is being used in significant number of patients. Analysis of maintenance immunosuppression after renal transplant showed 60% patient maintained their original regimen over 7 years of follow up. Sirolimus was introduced in 1.5 to 7% patients during follow up period. Anti rejection treatment was required in 22-47% renal transplant recipients and trend towards decreasing rejection episode was seen. Steroids were used in the treatment of rejection in 90-100% patients. Use of ATG for treatment of rejection has increased from 11.5% in 2005 to 40% in 2010-11. By this study we conclude that immunosuppressant drugs have passed through significant changes during the year 2005 to 2011. Use of ATG as an induction agent and for treatment of rejection has increased. Similarly MMF and tacrolimus are most commonly used in maintenance regimen for renal transplant patients.

Keywords: Immunosuppressant drug trends, Kidney transplant patients, Tacrolimus, mycophenolate mofetil.

INTRODUCTION

Renal transplantation has been the best renal replacement therapy that can be offered to patients

failure.

Lifelong

immunosuppressive agent is critical prevent early and late episodes of acute rejection as well as chronic allograft nephropathy.

Azathioprine was used as monotherapy or in combination with steroids in early 1960s until the discovery of cyclosporine. After introduction of significant

improvement in graft survival rates, the prescription

***Corresponding author: Mr. Dharmik D. Patel,**
Ph.D. Scholar, School of Pharmacy, R K University,
Rajkot, Gujarat, India; **Tel.:** +91-9228263190;
E-mail: dharmik_patel87@yahoo.co.in
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pattern was changing. Then standard immunosuppressive regimen consisted of cyclosporine and prednisone, often combined with azathioprine, in so-called triple therapy. [1]

First new immunosuppressant, Tacrolimus and new formulation of cyclosporine, micro emulsion were introduced in 1994 and then over the next decade, new immunosuppressant drug were introduced like, Mycophenolate mofetil (1995), Sirolimus (1999), Mycophenolate Sodium (2004) and also new antibody preparations like ATG (1999), Basiliximab (2000) and Daclizumab (1999) were also introduced. Introductions of these agents substantially increase the many options to the prescriber. It is required to know the prescription pattern and trends after introduction of this new immunosuppressant drug for Kidney transplant patients. Here in this study we retrospectively studied Immunosuppressant drug prescription pattern and trends of prescription in patients who underwent Kidney transplantation at Muljibhai Patel Urological hospital, Nadiad, Gujarat, India.

MATERIALS AND METHODS

This study was retrospective in nature. This study was performed on patients who underwent renal transplant procedure at Muljibhai Patel Urological hospital, Nadiad, Gujarat, India between July 2004 and June 2011. During this duration (7 years) total 632 patients underwent kidney transplantation. 14 subjects were Non Indian and 5 patients whose data not available so this subjects data were excluded from statistical analysis as per exclusion criteria. So data of remaining 613 Indian renal transplant recipients were included for the statistical analysis.

In this study, patients were followed up for a maximum available during the study period. Data of immunosuppressant medication was collected for all subjects during their hospital stay and their ambulatory follows up visits. Changes of immunosuppressant drug regimen were collected during each visit. Data about use of antibody for induction and treatment of rejection were also analyzed.

RESULTS

Induction immunosuppressant

It is observed that all patients were administered the higher dose of methylprednisolone on the day of a kidney transplant. Few patients received antibodies as an induction immunosuppressant along with methylprednisolone which includes Declizumab, Basiliximab or ATG. No other induction agent was used.

Trend of Use of these antibodies as an induction immunosuppressant in kidney transplant patient continued to vary each year. 20-44% patients received induction agent before kidney transplantation. From year 2005, there was a trend towards increasing use of antibody for induction agents. This trend continued up to 2009 after which there is a decline in use of

antibodies for induction (Figure 1). In 2005, 23.1% of kidney transplant recipient received antibody as an induction immunosuppressant which increased to 44.4% in year 2009.

When data was analyzed for the individual agent, ATG was most commonly used antibody for induction in kidney transplantation. It is clearly seen that trend is towards more common use of ATG compared to basiliximab and daclizumab since year 2006 except year 2011 (Figure 2). In 2004, Daclizumab (26%) was the most preferable antibody followed by basiliximab (15%) of in transplant patients. None of the patients received ATG till year 2006 as an induction agent. ATG was most commonly used inducing agent followed by daclizumab and basiliximab in 2010 (24% ATG Vs 6.9% daclizumab Vs 6.9% basiliximab).

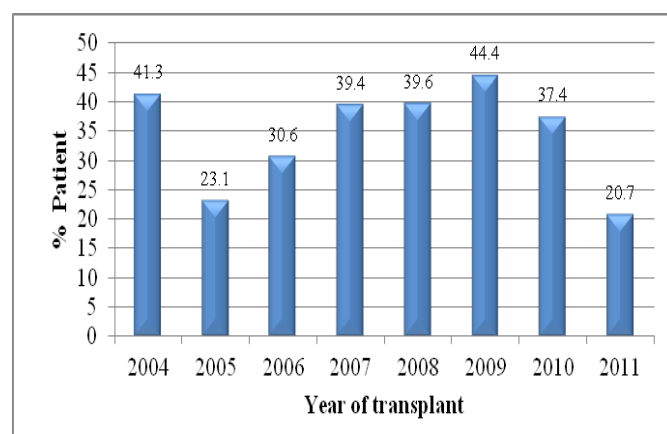


Fig. 1: Usage of Induction agent in percentage of renal transplant patients per year

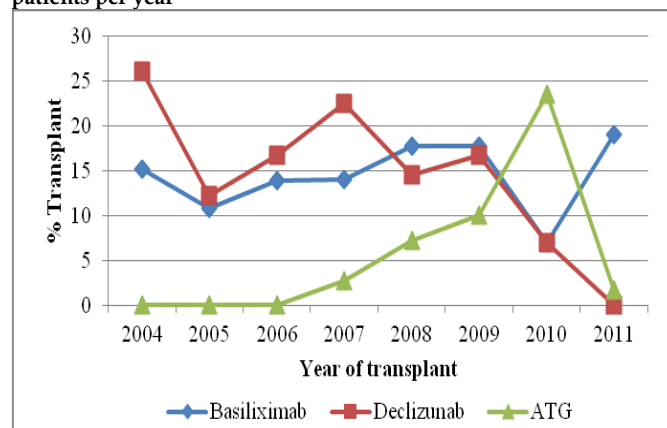


Fig. 2: Trends in usage of antibody as an induction agent

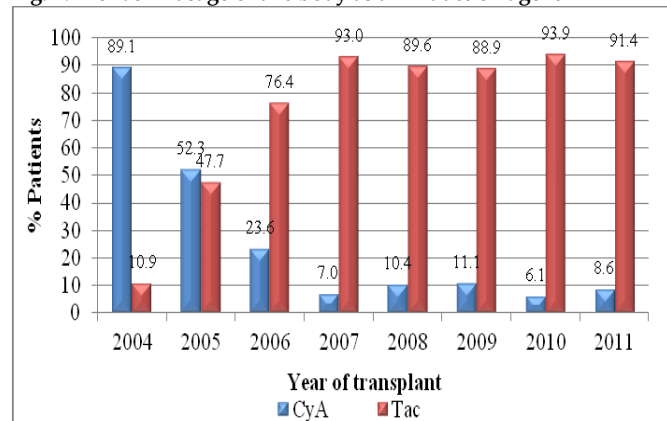


Fig. 3: Trends of Calcineurin inhibitor as a maintenance regimen

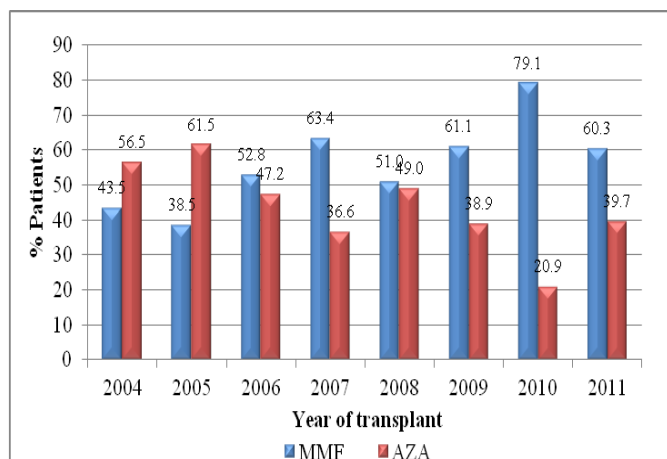


Fig. 4: trends of Antiproliferative agent as a maintenance regimen

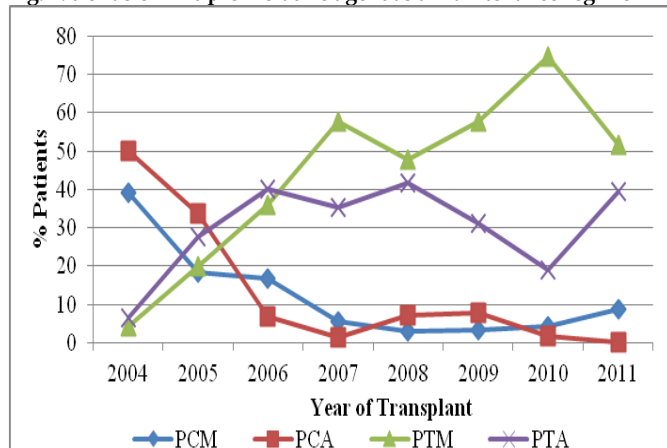


Fig. 5: Trends of Maintenance regimen at the time of transplant

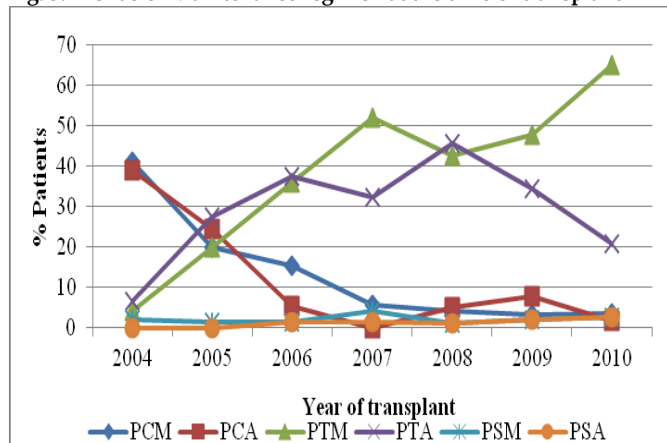


Fig. 6: Trends in immunosuppression maintenance regimens, 1 year post transplant

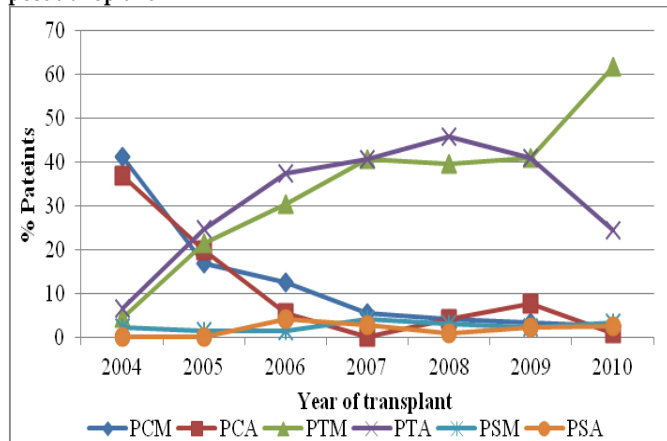


Fig. 7: Trends in immunosuppression maintenance regimens, 2 year post transplant

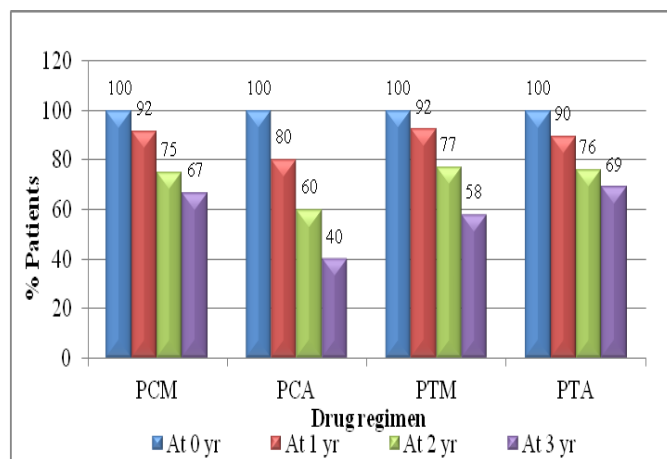


Fig. 8: Percentage of kidney transplant patients still on original discharge regimens at 1, 2 and 3 years post transplant

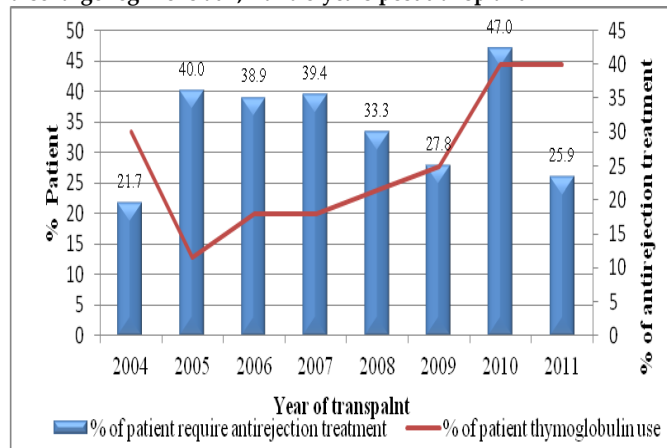


Fig. 9: Percentage of kidney transplants with antirejection treatments and thymoglobulin used as an antirejection treatment by year

Maintenance immunosuppressant before discharge

This study results shows that all patients were started on maintenance immunosuppressant drugs two days prior the day of transplant which includes Calcineurin inhibitor and antiproliferative agents. Steroids were started on the day of renal transplant before surgery, gradually tapered and continue indefinitely at a minimal dose. No steroid withdrawal protocol was used in our population. Tacrolimus is the Calcineurin inhibitor of choice and its use continues to grow, with 94% of patients treated with tacrolimus at discharge versus only 6% with cyclosporine in 2010 (Figure 3).

It was also observed that, use of mycophenolate mofetil, the most frequently used antiproliferative agent, is also still increasing, with 80% of patients discharged on mycophenolate mofetil compare to 20% of patients treated with azathioprine in 2010 (Figure 4). Still azathioprine is being used in a significant number of our patients. There was a definite trend towards fewer patients put on azathioprine through year 2008 to 2010. Again in 2011 uses of azathioprine has increased to near 40 % from 20% during the previous year.

Data show that use of the combination of tacrolimus/mycophenolate mofetil continues to increase. It is the most frequently utilized discharge regimen (75%), followed by tacrolimus/azathioprine

(19%). Use of cyclosporine/mycophenolate mofetil and cyclosporine/ azathioprine has continued to decline, reaching 4% and 2% in 2010 respectively. It is also observed that trends in prescription pattern for use of combination, tacrolimus/mycophenolate mofetil continues to increase as a discharge regimen when compare it with previous year data of this study (Figure 5).

Maintenance immunosuppressant 1 and 2 year post transplant

Results of the present study show that Tacrolimus/mycophenolate mofetil is also the most frequently used maintenance immunosuppressant combination at 1 and 2 years following transplantation and its prevalence for maintenance use has increased in recent years. At 1 year after transplantation in 2010, 65% of patients were receiving tacrolimus/mycophenolate mofetil, 21% were receiving tacrolimus/azathioprine, and 3% were receiving cyclosporine / mycophenolate mofetil, and 2% cyclosporine/azathioprine (Figure 6). Sirolimus was introduced after 1 and 2 years after transplant in combination with either mycophenolate mofetil or azathioprine and was found in 1.5% to 5.6% patients at 1 year and in 1.5% to 7% at 2 year follow up.

Maintenance regimen change and discontinuation

In these results, it is surprisingly observed that low percentage of patients continued their original immunosuppressive discharge regimen throughout the first 3 years following transplantation, as seen in Figure 8. Already at a year, a substantial number of patients were reported not to be on their original regimen.

There was significant variability in immunosuppressive regimen. Among patients transplanted in 2006, most were still on their original tacrolimus/azathioprine discharge therapy at both 1 (90%) and 3 years (69%) following transplantation. Patients on cyclosporine/azathioprine regimens showed high regimen change rates, with up to 60% of patients not on the original regimen in the cyclosporine/azathioprine group in 2006.

Patients were analyzed for change of their regimen (Switch) at various time periods following transplant (1, 2, 3, 4, 5, 6 and 7 year post transplant). It was seen that out of 613 patients 16.48% patient's initial regimen was changed during first year of renal transplant. It is seen that major changes in regimen occur during first three years of transplant and it was almost one third patient changed their regimen (31% at 3 year). Later up to 7 years regimen remains stable. It is seen from results that around 36% to 40% changes their regimen during later period. Almost 60% patients maintain their regimen during follow up through 7 years.

From 9.8% to 17.7% patients switched from azathioprine to MMF during their follow up. Similarly 6% to 22% patients switched from MMF to azathioprine during post transplant period (Table 1).

Similarly 1.6 to 5.8% patients' cyclosporine was changed to tacrolimus. Tacrolimus was switched to cyclosporine in 0 to 0.6% patients during post transplant period. It is also observed that 3.1 to 10.9% of patients were changed to sirolimus from either cyclosporine or tacrolimus (Table 2).

Table 1: Percentage of Antiproliferative Agent Treated Patients Switch Regimen.

Follow up Period	Total patients	% of patient switch	Aza treated patients	MMF treated patients	% of Aza treat patient switch	% of MMF treat patient switch	% of patient switch from Aza to MMF	% of patient switch from MMF to Aza	% of Aza withdrawn patients	% of MMF withdrawn Patients
0-1	613	16.48	255	358	18.04	15.36	9.80	7.82	4.71	0.28
0-2	513	25.15	225	288	24.00	26.04	10.67	17.01	5.33	0.69
0-3	393	30.79	193	200	29.53	32.00	11.40	20.00	6.74	1.00
0-4	306	36.60	147	159	36.05	37.11	15.65	22.01	7.48	0.63
0-5	216	37.96	110	106	39.09	36.79	14.55	21.70	9.09	0.94
0-6	147	40.14	84	63	42.86	36.51	14.29	15.87	11.90	1.59
0-7	83	37.34	51	32	47.06	21.88	17.65	6.25	11.76	0.00

Table 2: Percentage of Calciurine Inhibitor Treated Patients Switch

Follo w up Period	Total patie nt	% of patient switch	CyA treated patients	Tac treated patients	% of CyA treat patient switch	% of Tac treat patient switch	% of patient switch from CyA to Tac	% of CyA withdraw n patient	% of patient switch from Tac to CyA	% of Tac withdraw n patients	% of patients move on Siro
0-1	613	16.48	129	484	17.83	16.12	4.65	0.78	0.62	1.86	3.10
0-2	513	25.15	119	394	26.05	24.87	5.04	5.88	0.25	2.54	4.09
0-3	393	30.79	113	280	31.86	30.36	5.31	6.19	0.36	3.93	6.11
0-4	306	36.60	102	204	36.27	36.76	5.88	6.86	0.49	4.90	7.84
0-5	216	37.96	93	123	37.63	38.21	5.38	7.53	0.00	6.50	7.87
0-6	147	40.14	86	61	41.86	37.70	5.81	8.14	0.00	3.28	10.88
0-7	83	37.34	61	22	40.98	27.27	1.64	8.20	0.00	9.09	9.64

Antirejection treatment for kidney transplantation

Anti rejection treatment was required in 22-47% renal transplant recipients. It is found that percentage of patients treated for acute rejection has continued to decrease except year 2010 (Figure 9). During year 2005, 40% patients required anti rejection treatment out of

which 11.53% received thymoglobulin. Use of thymoglobulin for treatment of rejection has been increasing since then reaching a peak during the year 2010. During year 2010 and 2011, 40% rejection episodes were treated with thymoglobulin. No other antibodies like alemtuzumab, rituximab or bortezomib

were used for treatment of rejection. Corticosteroids still remain a principal element of rejection treatment. In 2011, 93% of patients requiring antirejection treatment received steroids.

DISCUSSION

Induction immunosuppressant

KDIGO guidelines for care of renal transplant patients recommends induction antibody for all renal transplant patients. [2] As a strategy to reduce drug cost KDIGO recommends use of induction agent in high risk patient's only. [3] In a study conducted by Meier-Kriesche HU *et al.*, [4] shows that use of antibody has continued to increase in American registry renal transplant patients. In this study, they found 72% patients of transplant patient's use inducing agent in 2003 Vs 46% in 1995. While ANZDATA Registry 2012 Report shows that most of the New Zealand kidney transplant patients were given induction therapy while in Australia all patients were given induction therapy on the day of transplant. [5]

In contrast to universal induction in New Zealand, Australia and high number in US renal transplant patient less than half of Indian patients receive antibody as an induction agent. Possible reasons behind less common use of induction might be following

1. High cost of induction agent
2. Low immunological risk - live related donors mostly from within family
3. High infective load in environment

If we compare the use of different antibodies as induction in renal transplant patients in New Zealand, Australia and Korea, receive Daclizumab and Basiliximab commonly. [4-6] Similar to US renal transplant patients, Indian patients also receive ATG as a first choice of induction agent. There is trend towards steroid free protocol in US in recent years. OPTN registry data of year 2012 shows that steroid free protocol was implemented in US in around 30% of renal transplant recipient. [7] This might be reason for compelling indication of use of induction. Steroid free protocol was not practiced at all in present study population.

Maintenance immunosuppressant before discharge

For use of calcineurin inhibitor in transplant patient, a study done by Meier-Kriesche HU *et al.*, [4] noted that in 2004 usage of tacrolimus and cyclosporine was 72% and 21% respectively in American patients. In Australian patients use of Tacrolimus was 87% and only 10% patients were on Cyclosporine while in New Zealand opposite trend was observed where 71% patients were on cyclosporine and 29% on tacrolimus in 2012. [5] Korean Organ Transplant Registry data shows that among the CNIs, 78.3% were treated with tacrolimus, whereas 20.3% with cyclosporine. [6] Use of tacrolimus in renal transplant patients is continued to be increased due to less number of rejection episodes in tacrolimus treated patients as compare to cyclosporine treated

patients. [8] Our study results also favor similar trends towards tacrolimus over cyclosporine as observed in most of the world.

Similar to tacrolimus, a same higher trend for use of mycophenolate mofetil as compare to azathioprine was also observed in OPTN 2012 reports, Korean registry data and ANZDATA Registry 2012 Report for use of antiproliferative agent. [5-7] Still azathioprine is being used in a significant number of our patients. In our study, there was a definite trend towards fewer patients put on azathioprine through year 2008 to 2010. Again in 2011 uses of azathioprine has increased to near 40% from 20% during the previous year. Reasons for these varying trends are not clear. It could be possibly due to the low cost of azathioprine, live related donor population and recent reports showing non inferiority of azathioprine compared to MMF in terms of similar long term outcomes- graft and patient survival. [9]

If considering drug regimen in transplant patients, OPTN & SRTR Annual Data Report 2011 shows that 86% registry patients were given tacrolimus/ mycophenolate mofetil combination. [10] In our study, we also show same trends towards this regimen means both results show that a trend has move towards the use of tacrolimus/ mycophenolate mofetil after development of these drugs.

Maintenance immunosuppressant 1 and 2 year post transplant

Study conducted by Meier-Kriesche HU *et al.*, [4] results shows that 51% of transplant patients were receiving same regimen Vs 60% from discharge in 2003 and comparing OPTN & SRTR Annual Data Report 2011 results it shows 78% of patients Vs 86% of patients are on same regimen then discharge this shows ratio of patients on same drug regimen means Tacrolimus/ mycophenolate mofetil was increase after 1 year of transplant. [10] If considering Australia registry data of year 2012 then it shows that less no. of patients were remaining on the original regimen still use of combination of Tacrolimus/ Mycophenolate mofetil is higher than other drug regimen. [5] Same higher trends were also observed in our study.

Sirolimus is mTOR inhibitor which is used as maintenance immunosuppressant in renal transplant recipient. Sirolimus was not used as an initial regimen in any patient in the present study. However, Sirolimus was introduced later during first or second year of renal transplant. It was found to replace calcineurine inhibitors. This study was not designed to know the causes of such shift or introduction of sirolimus. It requires further study to know the cause. We could presume that introduction of sirolimus could be attributable to CNI toxicity or poor graft function with creeping creatinine. Few patients were found to be on only two drugs after 1 and 2 year transplants. It could be due to drug side effects or depend on associate condition.

Maintenance regimen change and discontinuation

In our study around 40% patients change their regimen during their follow up. It may be due to side effect of a maintenance regimen or due to higher cost of the drug. Study conducted by Meier-Kriesche HU *et al.*, [4] results shows that more patients were their original tacrolimus/ mycophenolate mofetil discharge therapy at both 1 (75%) and 3 years (57%) following transplantation. But in contrast to this result, our result shows that more patients were remaining on tacrolimus/azathioprine group. When switch of antiproliferative (MMF to azathioprine or azathioprine to MMF) was considered almost similar number of patients changed their antiproliferative agents. There could be variety of reasons for these changes of immunosuppression which requires further studies to know the causes.

Antirejection treatment for kidney transplantation

Study conducted by Meier-Kriesche HU *et al.*, [4] results on American registry patients shows that use of antibody as antirejection treatment is increased and also among this antibodies use of ATG is increasing while use of steroids as an antirejection therapy has decreased. Same higher trends were also observed in our study. Our study patients have not received universal induction in all patients. This could be reason for significant rejection episodes occurring in the present study population. This issue requires further study addressing question about of universal induction in Indian renal transplant patients.

This study shows that noticeable changes were observed in the prescription pattern with the development of new drugs. Most of the patients are treated with triple combination immunosuppressant comprising of tacrolimus in combination of MMF and steroid in the majority of patients as initial maintenance regimen. Tacrolimus/mycophenolate mofetil is the most frequently used maintenance immunosuppressant regimen. Though use of MMF is increasing azathioprine is still in use in significant number of patients. Induction with antibody is not universal phenomena. ATG is used as induction agent of choice. Steroids pulse is still used as treatment of rejection in majority of patients. Use of ATG is increasing for treatment of rejection. Significant number of patients (40%) changes their initial regime and switch of various drugs is common phenomenon.

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