Immunosuppression strategies after liver transplantation: a single centre experience in 57 liver transplant recipients

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Abstract

Context The art of administering immunosuppression lies in the ability to achieve a delicate balance between rejection and infection, thus maximizing patient survival and minimizing morbidity.

Aims To analyze the effect of immunosuppression strategies following liver transplant on the incidence of acute rejection, bile leak, renal dysfunction and posttransplant graft unrelated infection.

Settings and Design A retrospective analysis of immunosuppression regimens in 57 liver transplant recipients between Jan 1998 to July 2004 at a single institution.

Methods and Material For the purpose of study, the patients were divided into two groups: **A** – Cyclosporine based therapy (n=37), and **B** – Tacrolimus based therapy (n=20). In addition, both groups received Azathioprine or Mycophenolate mofetil with steroids. There were two subgroups in each Group A and B: Group **C** – Received induction using IL2Rab (n=5), and **D** – Where Sirolimus was used instead of Mycophenolate mofetil (N=7). The

subgroups were equally distributed among the basic groups. The regimen was started based on one of the standard protocols but changes were made according to the clinical status of each patient.

Statistical analysis used The statistical analysis was done using Chi square test on SPSS12.

Results A lower incidence of rejection was observed in Tacrolimus group compared to Cyclosporine group. There was an unacceptably high incidence of bile leak in patients where Sirolimus was used as an adjunct. IL2Rab enabled us to maintain a lower trough level of Tacrolimus for maintenance and enabled us to discontinue steroids earlier.

Conclusions Based on this study we dropped Sirolimus from our immunosuppression protocol and the encouraging results obtained with tacrolimus based therapy have supported its use as standard therapy in our immunosuppression regimens.

Keywords Immunosuppression · Transplant · Rejection

Key Messages

- IL2Rab enabled us to maintain lower trough levels of Tacrolimus for maintenance.
- IL2Rab enabled us to discontinue steroids earlier.
- High incidence of bile leak was observed with sirolimus.
- Tacrolimus regimens have lower rates of acute rejection.

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Introduction

Current immunosuppressive regimens typically consist of an induction phase and maintenance therapy. Induction medications are given at the time of transplant to decrease the occurrence of early acute rejection and to avoid or minimize corticosteroids. Thereafter life long maintenance immunosuppression is required.

We performed this study to analyze the effect of various immunosuppression strategies following liver transplant on the incidence of acute rejection, bile leak, renal dysfunction and post transplant graft unrelated infection in an effort to minimize side effects and maximize allograft survival.

Subjects and Methods

We have done a retrospective analysis of immunosuppression regimens in 57 liver transplant recipients between Jan 1998 to July 2004.

The statistical analysis was done using Chi square test on SPSS12.

The patients were divided into two basic groups: **A** – Cyclosporine based therapy (n=37), and **B** – Tacrolimus based therapy (n=20). In addition both groups received Azathioprine or Mycophenolate mofetil with steroids. There were two subgroups in each Group A and B: Group **C** – Received induction using IL2Rab (n=5) and **D** – Where Sirolimus was used instead of Mycophenolate mofetil (N=7). The subgroups were equally distributed among the basic groups.

Immunosuppression regimen for an individual patient was tailor-made to suit the requirements. The choice of initial drugs depended on Pre-transplant renal dysfunction, nutritional status, pre-existing infection, viral/non viral aetiology, incidence of acute rejection and intolerable adverse reactions. Add-on agents, Sirolimus and IL2Rab, were used in patients with renal dysfunction (GFR < 45 ml/hr), or more than 15 % higher than baseline creatinine.

The drugs were used in following doses:

Azathioprine	1 mg / kg / day
Cyclosporine	8 mg / kg / day in divided doses
Tacrolimus	0.03 mg / kg / day in two divided doses
Mycophenolate mofetil	1 gm / day in two divided doses
Sirolimus	3 mg bolus followed by 2 mg / day
Steroids	50 mg / day for 7 days, tapered gradually over 2 - 6 months.
IL2Rab	20 mg IV on Day 0 and Day 4

The regimen was always started based on one of the standard protocols but changes were made according to the clinical status of each patient.

Doses were adjusted to maintain Cyclosporine levels between 200–240 mg/ml and Tacrolimus level between 3–5 ng/ml. Azathioprine or Mycophenolate mofetil were discontinued at a Platelet level < 50000 / cu.mm or TLC < 4000 / cu.mm.

The incidence of acute rejection, bile leak, renal dysfunction and post transplant graft unrelated infection were analyzed.

Results

A lower incidence of rejection was observed in Tacrolimus group (5.1%) compared to Cyclosporine group (18.91%) with a p value of 0.008 (Table 1). There was an unacceptably high incidence of bile leak in patients where Sirolimus was used as an adjunct (71.42%, p value 0.008) (Table 2). Five patients were given induction therapy with IL2Rab. It enabled us to maintain a lower trough level of Tacrolimus (3–5 mg / ml) for maintenance and enabled us to discontinue steroids earlier (mean 60 days vs. 116 days). There was a lower incidence of acute rejection (0%) and bile leak (0%) in the induction group, however graft unrelated infection remained high (40%).

Discussion

The success of clinical liver transplantation has been directly related to the development of newer immunosuppression agents. The art of administering immunosuppression lies in the ability to achieve a delicate balance between rejection and infection, thus maximizing patient survival and minimizing morbidity.

The greatest risk of rejection occurs in the immediate period after implantation. Thereafter, the risk is intermediate in the first year after placement and low for the rest of the life of transplanted organ. The aim of using *induction therapy* is to reduce early acute rejection episodes and prolong long term allograft survival. With the availability of IL2Rab and reports in literature supporting its use [1, 2], our last five patients were given induction therapy with IL2Rab. It enabled us to maintain a lower trough level of Tacrolimus (3–5 mg/ml) for maintenance and enabled us to discontinue steroids earlier (mean 60 days vs. 116 days). There was a lower incidence of acute rejection (0%) and bile leak (0%) in the induction group, however graft unrelated infection remained high (40%).

Maintenance immunosuppression regimens usually consist of a triple drug combination incorporating a calcineurin inhibitor, an antiproliferative agent and corticosteroids.

Table 1 Complications in Groups A & B

	Group A (n =37)	Group B (n = 20)	Overall (n = 57)	Statistical significance
Acute rejection	7 (18.91%)	1 (5 %)	8 (14.03 %)	p = 0.008
Bile leak	3 (8.10 %)	0	8 (14.03 %)	ns
Renal dysfunction	6 (16.21 %)	2 (10 .0 %)	8 (14.03 %)	p = 0.05
Graft unrelated infection	12 (32.43 %)	3 (15.0 %)	17 (29.82 %)	p = 0.02

Table 2 Complications in Groups C & D

	Group C (n = 5)	Group D (n = 7)	Statistical significance
Acute rejection	0	1 (14.2 %)	ns
Bile leak	0	5 (71.42%)	p = 0.008
Renal dysfunction	1 (20.0 %)	0	ns
Graft unrelated infection	2 (40.0 %)	0	ns

Corticosteroid regimens vary widely, typically with higher doses initially and then tapered over a period of 6 months to doses equivalent to prednisolone 5 to 10 mg which is further tapered slowly over time. Corticosteroids are associated with several adverse effects including hypertension, hyperlipidemia, posttransplant diabetes mellitus, osteoporosis and cataracts [3]. Concomitant use with other immunosuppressive agents can worsen these side effects. Hence there has been a trend towards reducing corticosteroid dosages or their early withdrawal [4], in an effort to avoid these long term adverse effects. In our study IL2Rab enabled us to discontinue steroids earlier (mean 60 days vs. 116 days). *Azathioprine* and *Mycophenolate mofetil* are the antiproliferative agents most commonly used. Routine therapeutic drug monitoring is not required with antiproliferative therapy. Most common adverse effects associated with mycophenolate mofetil are gastrointestinal side effects like nausea and diarrhoea and hematologic toxicities such as leukopenia and anaemia. An increased incidence of tissue invasive cytomegalovirus invasive disease, particularly gastrointestinal, is also associated with mycophenolate mofetil doses greater than 2 g/day [5].

Calcineurin inhibitors have been an integral part of immunosuppressive therapy. Cyclosporine and tacrolimus are both effective in reducing the incidence of acute rejection after transplantation. However, due to their narrow therapeutic index for efficacy and toxicity routine therapeutic drug monitoring is needed. The most well-known adverse effect of calcineurin inhibitors is nephrotoxicity. Tacrolimus is more frequently associated with neurotoxic effects while cyclosporine is associated with adverse cardiovascular and cosmetic effects. Further, tacrolimus has less nephrotoxicity

than cyclosporine and is preferred over cyclosporine. This confirms with studies reported in literature comparing the efficacy of these two drugs [6, 7, 8, 9]. In our study a lower incidence of rejection was observed in Tacrolimus group (5.1%) compared to Cyclosporine group (18.91%) with a p value of 0.008.

Sirolimus when used with calcineurin inhibitors allows lower calcineurin inhibitor doses to be used to minimise the risk for nephrotoxicity. However its use in liver transplant recipients immediately posttransplant is limited by the risk of hepatic artery thrombosis [10]. The most common adverse effects observed with Sirolimus include thrombocytopenia, leukopenia, anaemia, hypertriglyceridemia, hypercholesterolemia, diarrhoea and acne/mouth ulcers. Other adverse effects occur as a result of its antiproliferative properties. In our study there was an unacceptably high incidence of bile leak in patients where Sirolimus was used as an adjunct (71.42%, p value 0.008). Based on these results, Sirolimus was dropped from our protocol. This has however, not been reported in literature before and the exact mechanism for this observation is difficult to explain.

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