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Corticosteroid-free Immunosuppression in Liver Transplantation

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Abstract

Corticosteroid avoidance is at times desirable in liver transplantation because of real or perceived toxicity. The contribution of corticosteroids to posttransplant morbidity, such as diabetes mellitus, hypertension, and obesity, may be worth eliminating, but other objectives like corticosteroid avoidance in hepatitis C are less clear. A literature review was conducted using Medline from 1999 onward using the key terms "steroid-free immunosuppression" and "liver transplantation". Early studies established that about half of liver transplant patients can avoid corticosteroids with little modification of the maintenance immunosuppression regimen. However, better overall early results (up to three months) have been observed in more recent studies using dual therapy with tacrolimus and either mycophenolate or interleukin-2 antibodies.

The feasibility of corticosteroid-free immunosuppression was established in controlled trials by demonstrating non-inferiority with respect to patterns of rejection as well as patient and graft survival. However, the evidence available to date does not unequivocally establish the benefits of corticosteroid-free immunosuppression, although some advantage has been established relating to posttransplant diabetes mellitus, cytomegalovirus infection, and growth patterns in children. There is some concern that triple and quadruple regimens may be associated with signs of over-immunosuppression. The evidence available to date does not unequivocally establish an overall benefit of corticosteroid-free immunosuppression in hepatitis C patients. **(Trends in Transplant. 2009;3:77-84)**

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Key words

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Introduction

Corticosteroids have been a traditional component of immunosuppression regimens used in liver transplantation since the 1960s. Initially used in doses of 60 mg/day or higher, the daily dose was reduced significantly when calcineurin inhibitors (CNI) were introduced, and now maximum daily doses of prednisone as low as 20 mg are used, with tapering to withdrawal over three months being frequently practiced. The development of newer agents, particularly mycophenolate mofetil (MMF), sirolimus, and interleukin 2 (IL-2) antibodies, have increased the options and flexibility of immunosuppression regimens and have been used to further explore the feasibility of corticosteroid-free maintenance immunosuppression. Corticosteroids also play a role as first-line therapy for acute cellular rejection that is considered to be moderate or severe and, therefore, the incidence and severity of acute cellular rejection is pertinent to the evaluation of corticosteroid-free immunosuppression.

The main objectives of corticosteroid elimination have been to reduce the incidence of side effects associated with corticosteroid therapy (Table 1), or to abrogate the impact of hepatitis C recurrence in the graft. For the purpose of this review, corticosteroid-free immunosuppression is considered to be regimens that do not include a corticosteroid in the maintenance component, but protocols that allow the administration of single dose of high-dose corticosteroids intraoperatively were included.

Table 1. Side-effects seen after liver transplantation potentially modifiable by corticosteroid avoidance

Side-effect	Potential contributing factors
Impaired wound healing	Sirolimus
Diabetes	Tacrolimus
Hypertension	Cyclosporine, tacrolimus
Obesity	Cyclosporine, immobility, decreased metabolic rate
Osteopenia	Immobility
Dyslipidemia	Sirolimus, cyclosporine
Growth retardation	
Infection	All immunosuppressive agents

General studies

This section deals with studies involving largely unselected patient populations, especially with respect to etiology, and is subdivided into those that simply eliminated corticosteroids and those that compensated for the absence of corticosteroids with the addition of another agent. The latter practice raises the possibility that the price paid for eliminating corticosteroids may be an increase in the total burden of immunosuppression.

Simple elimination of corticosteroids

Six studies took the approach that corticosteroids could be eliminated from standard dual- or triple-drug immunosuppression regimens[1-6]. A CNI was used in all studies. One study used CNI monotherapy, two added azathioprine, two added mycophenolate, and one added basiliximab. The early studies functioned as "proof of concept" studies and established the feasibility of corticosteroid-free immunosuppression in approximately 50% of patients receiving liver transplants. However, better results with respect to outcome (acute cellular rejection rates, patient and/or graft survival) were seen in the latter studies that incorporated mycophenolate or basiliximab.

The first study was conducted at the Royal Free Hospital in London in 1996/7 and compared cyclosporine and tacrolimus monotherapy

in a prospective, randomized, open-label study using a cohort of 64 adult patients[1]. The long-term need for an additional immunosuppressive drug was avoided in 87% of patients on tacrolimus and 64% of patients on cyclosporine. However, acute cellular rejection requiring treatment occurred in 66% of 30 patients on tacrolimus and 65% of 34 patients on cyclosporine, and 21% of patients in both groups experienced a second rejection episode. This pattern of rejection would now be considered unacceptably high. Actuarial patient survival at 30 months was 80% in the patients on tacrolimus and 73.5% in the cyclosporine group, while graft survival rates were 73 and 62%, respectively. These data suggest that CNI monotherapy is inappropriate as a general approach to immunosuppression.

Better outcomes were seen in a small study of 20 adults conducted in 1998/9 that found that 52% of patients who were immunosuppressed with tacrolimus or cyclosporine and azathioprine did not require corticosteroids after liver transplantation[2]. Corticosteroids were not given intraoperatively, but were used to treat acute cellular rejection in 23.5% of transplant episodes, and in 28.5% to compensate for dose reduction or withdrawal of either tacrolimus or azathioprine. Hence, 48% of patients remained free of exposure to corticosteroids. All patients in this study were alive after three years of follow-up.

A prospective, randomized, open-labeled study compared outcomes in 22 patients who received triple immunosuppression with cyclosporine, prednisolone (initial dose of 20 mg/day tapered to complete withdrawal after three months), and azathioprine and 23 patients immunosuppressed with cyclosporine and azathioprine[3]. The incidence of acute cellular rejection of at least moderate severity was similar in the two groups at 60 and 55%, respectively. Actuarial two-year graft survival rates were also not different between the two groups (70.2 vs. 78.3%). Patients receiving corticosteroids tended to have higher HCV RNA and glucose and cholesterol levels in blood. The acute cellular rejection rates and graft survival rates in this study do not compare very favorably with later studies.

A different outcome was seen in another prospective, randomized, open-label study which planned to recruit 60 patients and compare tacrolimus, MMF, and corticosteroids with tacrolimus and MMF alone[4]. Corticosteroids were given initially in high dose at 200 mg/day tapering to 20 mg by day 6 and later tapered to withdrawal by the end of the third month. There was no difference in patient (100 vs. 91.7%) or graft (91.7 vs. 83.3%) survival, depending on whether corticosteroids were spared or administered, in the first 30 patients recruited into the trial. However, the incidence of acute cellular rejection was significantly higher at 75% in those not receiving corticosteroids, as compared with 16.7% in the other arm ($p = 0.002$), and this observation resulted in the discontinuation of the study.

More recently, a similar study design (tacrolimus and MMF as standard with and without corticosteroids) was employed in a prospective, randomized study of 72 patients[5]. There was a preponderance of hepatitis C patients in the corticosteroid group (67 vs. 39%; $p = 0.02$) and patients with autoimmune disease or colitis were excluded from this study. The use of basiliximab was allowed in patients with early renal dysfunction in order to delay initiation of tacrolimus therapy. However, preliminary analysis did not identify any significant differences between the two groups with respect to patient or graft survival or hepatitis C-related outcomes.

The largest study in this category was a prospective, randomized, open-label study comparing corticosteroid avoidance with a three-month tapering course of steroids in patients immunosuppressed with a combination of cyclosporine (using C2 monitoring with

target levels of 800-1200 ng/ml) and basiliximab (administered on day of transplant and four days later)[6]. Patients with autoimmune liver disease were also excluded from this study, and 45% of the patients recruited had hepatitis C. There was no difference in the incidence of acute cellular rejection (13 vs. 17%) or chronic rejection (1 vs. 3%) between the corticosteroid group and the corticosteroid-avoidance group, respectively. Actuarial patient and graft survival was similar between the two groups. Analyses of the secondary endpoints found a higher incidence of bacterial infections in a subset of patients with diabetes mellitus (54 vs. 14%; p = 0.005), as well as a higher incidence of diabetes mellitus (29 vs. 18%; p = 0.06), hypertension (44 vs. 25%; p = 0.006), and dyslipidemia in the steroid arm whilst taking corticosteroids. However, the latter differences were not sustained to the end of the study six months after transplantation. No significant differences were found between the two groups with respect to the histologic severity of HCV recurrence. This study concluded that corticosteroid avoidance in the context of immunosuppression with cyclosporine and basiliximab was safe and resulted in fewer infectious and metabolic complications.

Substitution for corticosteroids

In more recent times, a preferred approach to trial design has been to compensate for corticosteroid avoidance with addition of an antibody, mycophenolate, or both. Antibodies used include rabbit antithymocyte globulin (RATG), and the antibodies against the IL-2 (CD25) – daclizumab and basiliximab. This approach potentially increases the net burden of immunosuppression as the potency of the substituted agents may exceed that of corticosteroids, especially in regimens that curtail the maximum dose of maintenance prednisolone to 20 mg.

A pilot study of tacrolimus and MMF in 30 adult patients had an acute cellular rejection rate of 26.2% and two-year graft survival rate of 83.9%[7]. During the conduct of the study, 57% of patients were exposed to corticosteroids, but at its completion 73% of patients were not taking corticosteroids as part of their maintenance immunosuppression regimen. This study pointed to the feasibility of tacrolimus and MMF immunosuppression permitting corticosteroid avoidance.

A prospective randomized trial of RATG versus corticosteroids in patients also receiving tacrolimus and MMF has been reported in two parts[8,9]. Corticosteroids were commenced at 100 mg/day, decreasing to 20 mg by day 6 and weaned by three months. Of the first 71 patients randomized, 36 received RATG. There was no significant difference in the incidence of acute cellular rejection (32.0% with corticosteroids, 20.5% with RATG) or patient survival at a median of nine months (91% both groups)[8]. An advantage with steroid avoidance was seen with respect to the incidence of cytomegalovirus (CMV) antigenemia that was significantly higher at 20.6% in the corticosteroid arm as compared with 8.8% in the RATG arm. The second report from this study gave extended follow-up as well as an expansion of the numbers to 119 patients[9]. In addition, observations in a further 24 sequential patients treated with RATG were included. The 48 patients added to the trial received MMF for only two weeks. The rationale for this change in protocol was not given, but it might be a consequence of concern with the overall intensity of immunosuppression with this regimen. Corticosteroid avoidance did not increase the incidence of acute cellular rejection (25 and 32%), or chronic rejection (0%). However, acute cellular rejection appeared to be easier to manage in the RATG patients as only 6.6% required corticosteroids, as compared with 50% of the patients in the corticosteroid group (p = 0.03). One-year patient survival rates were 85% in both groups. The benefit

with respect to CMV was confirmed (5 vs. 23%; $p < 0.05$) and a trend to less posttransplant diabetes mellitus with avoidance of corticosteroids reached statistical significance (2 vs. 14%; $p = 0.03$). The remarkably low incidences of these complications were confirmed in a post-trial observational study of 24 consecutive patients managed with RATG.

The MASTER study was a prospective, randomized, open-labeled, parallel-group study conducted in 45 centers between 2000-2 that enrolled 706 patients who were randomized to tacrolimus and corticosteroids or tacrolimus and daclizumab after primary liver transplants[10]. Prednisone was started at 20 mg daily and tapered to 5 mg by the end of the study at three months. There was no difference in the incidence of acute cellular rejection requiring therapy (26.5% in the corticosteroid arm and 25.4% in the daclizumab arm). However, a significant benefit was seen with respect to corticosteroid-resistant rejection with the use of daclizumab (2.8 vs. 6.3%; $p = 0.027$). Patient and graft survival rates were similar at three months in both groups. There was evidence of benefit derived from the avoidance of corticosteroids with respect to diabetes mellitus (15.3 vs. 5.7%; $p < 0.001$) and CMV infection (11.5 vs. 5.1%; $p = 0.002$). Serum cholesterol levels increased 16% by the end of the study in patients receiving corticosteroids, while the levels were unchanged in the daclizumab arm. This study appears to demonstrate some advantages in efficacy and toxicity to justify substitution of corticosteroids with daclizumab, but a limitation of the study is the short period of follow-up.

The MARSILEA study was subsequently presented in abstract form[11]. This compared tacrolimus and daclizumab induction with tacrolimus and mycophenolate in 602 patients). This was also a three-month study and the primary endpoint was biopsy proven acute cellular rejection and there was no difference with respect to this parameter between the two groups (16%). There was also no difference between patient or graft survival rates.

Sirolimus

There is one small experience of sirolimus monotherapy (four patients), sirolimus combined with cyclosporine (seven patients), and triple therapy with sirolimus, cyclosporine, and prednisolone (four patients)[12]. These protocols were applied sequentially in reverse order in a patient population weighted to patients with malignant disease. Whilst the numbers are very small, the acute cellular rejection rates increased from 0 to 28% and 75% with progression from triple therapy to monotherapy. There has been no further enthusiasm for using sirolimus as a strategy to avoid corticosteroids after liver transplantation.

Pediatric transplantation

The rationale for corticosteroid avoidance is especially strong in pediatric patients because of the additional problem of growth retardation. One small study of 20 patients who were immunosuppressed with basiliximab and tacrolimus (first nine also receiving MMF) has been reported[13]. The outcomes were compared with 20 historical controls that received tacrolimus and prednisolone. Rejection-free survival was 90% in the tacrolimus/basiliximab group and 50% in the historical controls ($p < 0.05$). A significant catch-up in growth was observed in the basiliximab group starting within weeks of transplantation. An additional benefit of corticosteroid avoidance was a lower requirement for antihypertensive medication.

Hepatitis C

Recurrence of hepatitis C virus (HCV) infection is almost inevitable after liver transplantation and leads to significant disease in

up to 30% of patients within the first decade. A small percentage develop a devastating cholestatic illness, but most of these will develop cirrhosis at an accelerated pace, typically within 3-5 years of the transplant operation. Lesser degrees of chronic hepatitis are observed in most of the remaining patients. A number of factors have been implicated in accelerating disease progression (Table 2), and of these, donor age, pretransplant viral load, and repeated rejection episodes, leading to the use of high-dose corticosteroids or OKT3, seem particularly important[14]. In addition to general issues pertaining to immunosuppression, there has been significant interest in the possible benefits of corticosteroid avoidance in these patients.

Table 2. Factors that potentially accelerate hepatitis C disease after liver transplantation

Recipient age
Donor age
Era of transplantation
Pretransplant viral load
Repeated rejection episodes
High-dose corticosteroids
OKT3
Male gender
Alcohol consumption
Diabetes
Cytomegalovirus
Possibly genotype

The effect of tacrolimus monotherapy compared with a combination of tacrolimus and corticosteroids was assessed in a prospective, randomized trial carried out between 1998-2000[15]. Of the 60 patients enrolled, a cohort representing 58.3% were HCV positive and the incidence of severe recurrent disease tended to be higher in patients on tacrolimus and corticosteroids (67%) than those on tacrolimus alone (47%), without reaching statistical significance. However, the percentage progressing to cirrhosis by three years was significantly higher (45 vs. 9%; p = 0.04) in the patients receiving corticosteroids.

A prospective, double-blind, placebo-controlled, parallel-group trial has been performed in 10 Italian centers, assessing the effect of corticosteroids in conjunction with basiliximab, cyclosporine, and azathioprine[16]. Corticosteroids were given in an initial daily dose of 25 mg/day for 30 days, subsequently tapering to 5 mg/day by the end of the third month. Of 140 patients randomized, the impact of HCV could be evaluated histologically in 99, comprising 51 on corticosteroids and 48 on placebo. Recurrence of HCV was diagnosed in 41.2% of patients receiving corticosteroids and 37.5% of patients receiving placebo. Acute cellular rejection rates were lower with corticosteroids (24.3 vs. 39.4%; p = 0.04), but there was no difference in one-year graft survival rates (72.9 vs. 84.8%; p = NS). The HCV viral load rebounded more quickly over the first month in patients taking corticosteroids, but there was no difference between the two groups at subsequent time-points in the study. This study did not establish the superiority of the corticosteroid-free regimen, and since the conduct of this study, international consensus has emerged advising against the use of quadruple immunosuppression regimens in patients with HCV infection[17].

An interim analysis of a study comparing two triple immunosuppression regimens has reported on the first 39 patients recruited out of a planned total of 50 patients[18]. All patients received tacrolimus and MMF and were randomized to receive either daclizumab or corticosteroids. Corticosteroids were commenced at 200 mg/day and tapered to 20 mg at day 6 before being withdrawn by three months after transplantation. There was a trend towards less cellular rejection with daclizumab, especially in the first six months after transplantation. There

was no difference with regard to HCV recurrence other than that the small number of cases with advanced fibrosis all occurred in the corticosteroid arm of the trial. A unique feature of this trial was the inclusion in the protocol of preemptive antiviral therapy with peginterferon and ribavirin in both limbs. Fifty-seven percent of patients required dose-reductions or interruption of therapy because of side effects and the response rate was only 22% in the 23 patients who tolerated at least six months of therapy. Similar outcomes with respect to antiviral therapy have been reported for the cohort of the RATG studies described above[8,9].

Preliminary results from a large study, the multicenter Hepatitis C Three trial, have recently been published in abstract form[19,20]. A total of 312 patients with HCV were randomized to a three-arm study comparing tacrolimus and prednisolone with tacrolimus, prednisolone and MMF, and with tacrolimus, MMF and daclizumab. There was no difference in the incidence of acute cellular rejection between the three arms, with a range from 13-14% up to two years. Patient (81-87%) and graft (78-84%) survival rates did not differ between the three groups. There was no difference in the overall incidence of severe HCV recurrence defined as grade 3 fibrosis or higher (19-33%) at two years. However, a trend was noted suggesting that freedom from severe HCV recurrence at one year was more likely to be maintained in the corticosteroid-free patients[20]. There was no difference in HCV RNA levels with the different regimens.

Living related transplantation

Two series have been published that give some insight into the scope for corticosteroid-free immunosuppression in living related transplantation[21,22]. In one series of 26 patients, tacrolimus-based immunosuppression was combined with at least one additional oral agent (18 MMF, eight sirolimus, seven prednisolone) as well as an IL-2 antibody in 21 cases (19 basiliximab, two daclizumab). As a result, four patients with ABO-incompatible grafts received quadruple immunosuppression, while 20 of the rest received triple immunosuppression and two received dual therapy[21]. The overall acute cellular rejection rate was 30%, but was much higher in the five pediatric cases at 80% as compared with 19% in the adult cases. Total steroid avoidance was achieved in 46% of cases. A concern with this study was the poor patient and graft survival rates at 62 and 54%, respectively, during a period of follow-up ranging from 2-58 months.

In a pilot study, nine patients with chronic viral hepatitis-related liver disease were treated with a triple immunosuppression regimen using a CNI, MMF, and an IL-2 receptor monoclonal antibody after transplantation[22]. The outcome was compared with 13 historical controls that received corticosteroids at an initial dose of 100 mg daily that was rapidly tapered. Acute cellular rejection was observed in only two of the nine patients (22.2%), and all were alive at one year. This compared with a one-year survival rate of 74% in the historical controls. Prophylactic antiviral therapy was used in patients with hepatitis C, and HCV RNA negativity was documented in four of seven patients not receiving corticosteroids and two of four historical controls.

Conclusions

The use of corticosteroids in immunosuppression regimens in liver transplantation has been historically driven and it has proved difficult to evaluate their role. It is reasonable to conclude from early studies that about half of liver transplant patients can avoid corticosteroids with little modification of the maintenance immunosuppression regimen. However, better overall early results have been observed in more recent studies using dual therapy with tacrolimus and either MMF or

IL-2 antibodies. There is some concern that triple and quadruple regimens may be associated with signs of over-immunosuppression. The evidence available to date does not unequivocally establish an overall benefit of corticosteroid-free immunosuppression in HCV patients. However, specific benefits of corticosteroid avoidance are seen with growth in children, diabetes, CMV infection, dyslipidemia, and possibly infection.

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