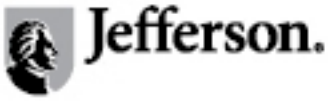

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Completely steroid-free immunosuppression in liver transplantation: a randomized study.

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FOOTNOTES TO THE TITLE:

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Abbreviations

ACR Acute cellular rejection

AST Aspartate aminotransferase

ALT alanine aminotransferase

CNI Calcineurin inhibitors

CS Corticosteroids

CMV Cytomegalovirus

DM Diabetes mellitus

EC-MPS Enteric-coated mycophenolate sodium

HCV Hepatitis C virus

INR International Normalized Ratio

I-R Ischemia-reperfusion injury

MAP Mean arterial pressure

MMF Mycophenolate mofetil

NGT Naso-gastric tube

NODM New onset- diabetes mellitus

POD Post-operative day

OLT Orthotopic liver transplantation

ABSTRACT

Background. Corticosteroids (CS) have always been part of the standard post-transplant immunosuppression to prevent and treat rejection. However, CS are associated with increased risk of infection, obesity, hypertension, hyperlipidemia, diabetes, and bone necrosis. They have also been implicated in accelerating Hepatitis C (HCV) recurrence post-liver transplantation (OLT). This study assesses the safety and efficacy of completely CS-free immunosuppressive regimen in adult OLT.

Methods. A 2-year, prospective, randomized study of CS or no-CS immunosuppressive regimen with basiliximab, tacrolimus and enteric-coated mycophenolate sodium (EC-MPS) was performed in 39 patients (CS=20, group A; No-CS=19, group B). The CS cohort received intra-operative methylprednisolone 1 gram intravenously tapered and weaned off by 6 months. HCV patients had HCV PCR pre-OLT, 0.5, 1, 3, 6 months post-OLT. Protocol liver biopsies were performed at OLT, 2 weeks, and 6 months post-OLT or when clinically indicated.

Results. CS-responsive acute rejection occurred in one patient in each group. Patient survival rates at 1 year (100% vs. 94%), 3 and 5 years (85% vs. 63%) post-OLT were similar between group A and B, respectively. Death-censored graft survival rates at 1 year (100% vs. 100%),

3 and 5 years (85% vs. 79%) were also similar between group A and B, respectively. The risk of new onset DM, hypertension, hypercholesterolemia, and weight gain was similar between 2 groups.

Conclusion. Complete CS-avoidance with basiliximab, calcineurin inhibitor (CNI), and EC-MPS is safe and effective as CS-containing immunosuppressive regimen in adult OLT.

INTRODUCTION

Corticosteroids (CS) have always been an integral part of standard post-transplant immunosuppression for prevention and treatment of rejection. First introduced in the early 1950s, CS have been used widely since the first successful orthotopic liver transplantation (OLT) in 1967 (1). CS exert potent immunosuppressive and anti-inflammatory effects through their action on leukocytes by stimulation or inhibition of gene transcription, altering gene expression responsible for mounting immune and inflammatory responses. However, CS use has been shown to cause long-term adverse effects, which include diabetes, increased susceptibility to infection, obesity, hypertension, hyperlipidemia, osteopenia, cataracts and growth retardation in children. CS have also been implicated in accelerating Hepatitis C (HCV) recurrence post-OLT (2-3). Consequently, several clinical trials which adopted early CS reduction and cessation after OLT were conducted and showed no increase in safety risks (4-6). In recent years, a small but increasing proportion of transplant centers, including our group, have demonstrated that adult and pediatric OLT may be successfully performed with CS minimization (7-11).

Prior to this study the standard immunosuppressive protocol at Thomas Jefferson University Hospital (TJUH) for OLT recipients included basiliximab induction and CS

intraoperatively, followed by calcineurin inhibitor (CNI), mycophenolate mofetil (MMF), and CS maintenance therapy.

RESULTS

Between February 2006 and November 2007, forty adult OLT recipients were enrolled in the study and 20 recipients were randomized to each group. One recipient in the CS-free group required a re-transplantation for hepatic artery thrombosis on post-OLT day 16. Since he expired within 10 days after re-transplantation, follow up data was short and untenable and therefore, he was excluded from the study analysis.

The mean overall follow-up was 47.3 months as of July 2011. Donor characteristics were comparable between the two groups (Table 1). Other than a significantly higher mean recipient age and longer mean hospital stay in group B compared to group A, recipient demographics and peri-operative data were similar between the two groups. There were 3 outliers in group B with mean hospital stay of 67.7 (range: 43-89) days. One had a protracted surgical ICU stay due to prolonged ventilator dependence, atrial fibrillation, and poor mental status. Another patient had ventilator-dependent adult respiratory distress syndrome, hepato-pulmonary syndrome, acute renal failure, sepsis, and massive colonic bleeding. The third patient had a MELD score of 35 at OLT with hepato-renal syndrome (Table 1).

Primary end points

There was no significant difference in patient and death-censored graft survival rates between the 2 groups. The 1-, 3-, and 5-year patient survival rates in group A and group B, respectively were: 100% vs. 94%, 85% vs. 63%, and 85% vs. 63% (Figure1). The 1-, 3-, and 5-year graft survival rates in group A and B, respectively were: 100% vs. 100%, 85% vs. 79%, and 85% vs. 79% (Figure 2). There were 10 deaths, 3 in group A and 7 in group B. The causes of death in group A were: cerebrovascular accident (n=1), and liver failure secondary

to severe progressive HCV recurrence (n=2). In group B, the causes of death were: cerebro-vascular accident (n=1), necrotizing pancreatitis post-endoscopic retrograde cholangio-pancreatography (n=1), self-inflicted gun shot wound to the head (n=1), and liver failure secondary to severe progressive HCV recurrence (n=4). The mean time to death from OLT was 21.5 months in group A and 24.7 months in group B (p= ns). CS-responsive biopsy-proven acute rejection occurred once in 1 patient (5%) in each group.

Secondary end points.

The mean peak aspartate aminotransferase (AST), alanine aminotransferase (ALT), total bilirubin and international normalized ratio (INR) levels and the mean days to peak post-OLT were similar between the 2 groups. The time to transaminase peak occurred on POD 2 and POD 1 in groups A and B, respectively, while the mean time to INR peak was <1day for both groups. Furthermore, there was no incidence of primary non-function in this cohort (Table 2).

The mean weight decreased in group A and group B from baseline to one month post-OLT. However, from 1-month to 1-year post-OLT, mean weight increased steadily in group A but decreased in group B, although the difference was not significant. Mean cholesterol levels were similar in both groups from baseline to 12 months post-OLT. The mean arterial pressure (MAP) in group A increased from baseline to 3 months before they started to decrease by 6 months post-OLT. Likewise, MAP in group B increased from baseline to 1 month before they trended downwards by the 3rd month post-OLT. Mean FBS levels at baseline, 1, 3, and 12 months post-OLT were similar, except at 6 months post-OLT when FBS levels were significantly higher (p=0.02) in group A compared to group B. Eight recipients in each group developed NODM with mean FBS levels (mg/dl) of 148 and 152 in group A and B, respectively (Table 2).

A total of 12 patients in each group developed bacterial infection. No single case of CMV infection/disease was observed in the cohort. Furthermore, there was no recurrent HCC or new malignancy noted on last follow-up.

There were more HCV recipients in group B (74%) than in group A (55%). We also observed an earlier peak (1 vs. 3 months post-OLT) and higher HCV PCR levels (16 million vs. 11.9 million, p=ns) in group A than in group B. However, the incidence and severity of HCV recurrence were similar in both groups based on liver biopsy results. Anti-viral treatment outcomes are listed in Table 3.

Mean tacrolimus trough levels (ng/ml) were similar at 1, 3, 6, and 12 month post-OLT in group A (11.3, 9, 7.8, 7.5) and B (8.1, 7.8, 9.4, 6), respectively. The mean duration on CS was 174 days in Group A. EC-MPS was given for a mean duration of 2.9 months post-OLT in both groups. EC-MPS dose reduction was carried out for gastro-intestinal symptoms (diarrhea, vomiting) in 4 patients in each group; and for neutropenia in 3 and 6 recipients in group A and B, respectively. EC-MPS was discontinued for GI symptoms in 1 recipient in each group; and for neutropenia in 2 and 1 recipient in group A and B, respectively.

DISCUSSION

Corticosteroids have been used widely for decades as part of immunosuppressive therapy in OLT despite their various associated long term adverse effects. In an attempt to reduce or avoid CS adverse effects, several transplant centers have successfully tried CS minimization or early CS withdrawal protocols post-OLT (4-11) and have reported similar graft failure rates with reduction and better control of hypertension, diabetes, obesity, and hypercholesterolemia, which are major risk factors known to accelerate atherosclerotic heart disease (10,12). In recent years, a few CS-free immunosuppressive protocols have been proposed post-OLT (7-8, 13-19). Some CS-free protocols included the use of intra-operative

dose of CS followed by post-OLT CS-free maintenance therapy (8, 20-24). Although CS-free protocols were reported to be safe compared to historical controls, these regimens have not been widely adopted by many transplant programs. Our aim was to evaluate the safety and efficacy of complete CS-avoidance compared to standard CS-containing immunosuppressive regimen consisting of basiliximab induction and tacrolimus, EC-MPS maintenance immunosuppression in adult OLT recipients.

The protective effect of CS treatment in ameliorating ischemia-reperfusion (I-R) injury and reducing acute rejection in deceased-donor OLT has been verified in a prospective randomized study (25). However, this approach was questioned by animal studies which showed that CS given at the time of transplantation could enhance I-R injury by increasing DNA fragmentation, and apoptosis after reperfusion (26), and by inhibiting TNF and IL-6 expression, which impairs cell-cycle progression, and hepatocyte regeneration (27). Our trial showed no difference in the incidence of I-R injury between CS-containing and CS-free groups, supporting Pirenne's (10) findings that intra-operative high dose CS bolus has no protective effect on I-R injury.

A recent meta-analysis of 19 randomized trials which compared CS-treated to CS-free immunosuppression reported that the CS-free groups demonstrated a trend toward lower hypertension and statistically significant reduction in cholesterol levels and CMV infection (28). Contrary to these results our prospective randomized trial did not show any difference between the two groups in the incidence of hypertension, cholesterol levels or CMV infection. Although not significant, our results showed a tendency toward increased weight gain in the CS-treated group, which is an anticipated consequence of long term CS use. This disparity may be explained by the heterogeneity of immunosuppressive protocols used by the individual centers, the short period of follow up and the small sample size of the various trials in the meta- analysis groups. The meta-analysis also suggested that the risk of NODM

would be markedly lower in the CS-free arm if CS were replaced with another immunosuppressive agent such as an anti-IL2 antibody, polyclonal anti-T-cell antibody or MMF, which was not demonstrated in our study. Our study also showed that FBS levels were similar between groups except at 6 months post-OLT when they were higher in the CS-treated group. The reason for this unexpectedly higher glucose level at 6 months is unclear considering that most recipients in the CS-treated group were no longer on CS by 6 months post-OLT.

Our study showed an overall low ACR rate of 5% and similar 1-, 3-, and 5-year patient and graft survival rates between CS-containing and CS-free groups. These may be attributed to the use of anti-IL2 induction in combination with dual CNI/MPA maintenance immunotherapy.

HCV recurrence post-OLT is almost a universal phenomenon. The incidence of histological HCV recurrence ranges from 14% to 72% (29-30). Furthermore, a severe cholestatic type of recurrent HCV, characterized by rapid progression to graft failure requiring re-transplantation within 2 years, has been reported in about 10% of HCV recipients (31-32). Contrary to these findings, our study showed higher overall incidence of histologic HCV recurrence (81%), and severe cholestatic HCV recurrence (28%). Furthermore, although the mean PCR levels peaked higher and earlier in the steroid group compared to steroid-free group, there was no difference in the incidence and severity of HCV recurrence, treatment outcomes, and graft loss rates between the two groups. These findings are consistent with the suggestions of Eghtesad et al. (33) that viremia or avoidance of specific immunosuppressive drug such as CS is not critical in promoting accelerated HCV recurrence post-OLT. Instead, they suggested that timing and continuity of immunosuppressive drugs post-OLT, which regulate the overall balance between virus

distribution and immune responsiveness, are more important factors affecting treatment outcomes in HCV recipients.

Mycophenolate mofetil has been one of the newer therapies in OLT in the last decade. However, MMF has been associated with diarrhea, nausea, vomiting, abdominal pain, etc. EC-MPS was developed in an effort to lessen these side effects. Renal transplant studies have shown the use of EC-MPS to be as effective and as safe as MMF (34- 35). However, studies on de novo use of EC-MPS in OLT recipients have been limited to conversion from MMF to EC-MPS (36-38). One study analyzed and showed that EC-MPS has similar efficacy to MMF as a primary immunosuppressant or as an MMF replacement in OLT recipients (39). Our data showed that EC-MPS was well tolerated with similar incidence of side effects between CS-treated and CS-free groups, most of which resolved with dose reduction. Neutropenia was observed less frequently in the CS-treated group, which could explain why over 90% in this group tolerated optimal dosing of EC-MPS. We suggest that the low incidence of neutropenia in the CS-treated group may be related to the effect of CS in increasing white blood cell count.

In this study, no recipient with autoimmune-mediated liver disorder, i.e., primary biliary cirrhosis, primary sclerosing cholangitis, and autoimmune hepatitis, was randomized in the CS-free group. It is well recognized that this subgroup of recipients may develop disease recurrence in the liver allograft and reported to have a higher incidence of acute and chronic ACR and perhaps may benefit from continuous, long term CS immunoprophylaxis (40-41). Consequently, extra caution should be exercised when selecting recipients who can safely be included in a completely CS-free regimen.

In conclusion, our analysis suggests that complete CS avoidance in adult OLT using basiliximab induction with CNI and EC-MPS maintenance is as safe and as effective as

standard CS-containing immunosuppression when evaluating for graft function, acute rejection, and patient and graft survival. Contrary to other studies, our results did not show any significant difference between CS-treated and CS-free groups in the incidence of hypertension, hypercholesterolemia, NODM, and weight gain. Furthermore, our data did not validate the common belief that CS-free immunosuppression has a beneficial effect in reducing the incidence, severity or degree of progression of HCV recurrence post-OLT.

MATERIALS AND METHODS

Institutional Review Board approval from TJUH was granted and informed consent was obtained from all subjects enrolled in this study, conforming to the ethical guidelines of the Declaration of Helsinki. Between February 2006 and November 2007, forty adult recipients of deceased donor primary OLT at TJUH were enrolled into this prospective, controlled, randomized, non-blinded, pilot trial. The primary objective was to assess the efficacy and safety of a completely CS-free immunosuppressive regimen in OLT, by comparing graft and patient survival rates and incidence and treatment of acute cellular rejection (ACR), between recipients treated with and without CS. The secondary objective was to compare the incidence of CS-related metabolic complications and HCV recurrence between recipients treated with and without CS. Common side effects associated with enteric-coated mycophenolate sodium (EC-MPS) use, i.e., neutropenia and gastro-intestinal symptoms, were also evaluated.

Inclusion criteria: adult recipients of primary cadaveric OLT between 18- 72 years old, liver graft cold ischemia time of <20 hours, and women of childbearing potential with negative pregnancy test. The exclusion criteria included: multiple organ transplant

recipients, women of childbearing potential not using the prescribed contraceptive methods, and use of any other investigational agent within 30 days prior to enrollment.

All recipients received basiliximab 20 mg IV intra-operatively and on post-operative day (POD) 4. Maintenance immunosuppression included tacrolimus and EC-MPS. Tacrolimus was started at 0.10 mg/kg/day by mouth (PO) or nasogastric tube (NGT) in 2 divided doses, within 48 hrs after reperfusion. The dose was adjusted to achieve target trough level 8-12 ng/ml in first month post-OLT, and 5-8 ng/ml, thereafter. All recipients received MMF 1 g every 12 hours via NGT until they could take oral medications, after which they were switched to EC-MPS 720 mg PO twice daily for three months post-OLT.

Recipients were randomized into either treatment arms: Control arm (group A) - standard immunosuppression with CS; and CS-free arm (group B) - standard immunosuppression without CS. Group A received methylprednisolone 1 g IV intra-operatively followed by a taper schedule as follows: methylprednisolone 50 mg IV every 6 hours on day 1; 40 mg IV every 6 hours on day 2; 30 mg IV every 6 hours on day 3; 20 mg IV every 6 hours on day 4; 20 mg IV every 12 hours on days 5; and thereafter, prednisone 20 mg PO daily which was tapered off by 6 months post-OLT. Group A and B recipients were on maintenance CNI monotherapy by 6 months and 3 months post-OLT, respectively.

All recipients received cytomegalovirus (CMV) prophylaxis with IV gancyclovir or valgancyclovir 450 mg PO daily for at least 3 months. They also received prophylactic doses of trimethoprim sulfa 3 times weekly and nystatin swish and swallow 3 times daily.

Liver biopsies were performed according to protocol intra-operatively, between days 7 and 21 post-OLT and at 3-6 months post-OLT, and when clinically indicated. For HCV (+)

recipients, quantitative HCV RNA PCR serum levels were performed at baseline, 0.5, 1, 3, and 6 months post-OLT.

Biopsy-proven ACR using the Banff Classification (42) was treated in both groups with methylprednisolone 1 g IV followed by a 5-day CS taper as described above. For recipients in group B who received CS for ACR, prednisone was tapered off by the third month after CS initiation. The protocol also required a repeat biopsy if there was no improvement in the liver function test at the end of CS taper.

A diagnosis of HCV recurrence was made based on liver biopsy findings and serum HCV RNA titers. Recipients with HCV recurrence were treated according to TJUH protocol as described below. Abnormal liver function tests were evaluated by hepatic ultrasound, and percutaneous liver biopsy. The TJUH protocol follows the modified Scheuer scoring system (43-44) to evaluate the need for anti-viral treatment in chronic hepatitis post-OLT. If the liver biopsy shows total score of >4 for necro-inflammatory activity (greater than mild portal and lobular inflammation) or > stage 1 (enlarged and fibrotic portal tracts), treatment with Peg-Interferon 180μg subcutaneously weekly for 2 weeks would be started. If the recipient tolerates peg-interferon without hematologic or neuro-psychiatric complications, ribavirin is added to Peg-interferon for a total duration of 48 weeks.

Weight, total cholesterol, fasting blood sugar (FBS), and mean arterial pressure (MAP) levels were measured and recorded at baseline, 1, 3, 6 and 12 months post-OLT. New onset diabetes mellitus (NODM) was defined as FBS ≥ 126 mg/dl (7 mmol/l), with fasting defined as no caloric intake for at least 8 hours.

STATISTICAL ANALYSIS: Statistical analysis was done to demonstrate equivalence or non-inferiority of the CS-free immunosuppressive regimen compared to the

standard protocol with CS for both primary and secondary end points. All continuous variables were summarized with mean and standard error and all categorical variables summarized as percentages. Statistical significance for each test was reported at $p \leq 0.05$. For continuous values, each group was compared using a two-tailed, independent Student's t-test assuming equal or unequal variance based on the results of an F-test. Each categorical variable was compared using a two-tailed Fisher's exact test. Survival analysis was done with Kaplan-Meier and significance was determined using a log-rank test. Analysis was performed using XLSTAT 2008 (Addinsoft, 2008) for Microsoft Excel.

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TABLES

Table 1. Recipient & Donor demographics and baseline (pre-OLT) characteristics

Donor Variables	Group A	Group B	p-value
Donor Age (years), mean± SD	48.1 ± 4.3	45.5 ± 3.5	ns
Donor Sex (M/F), n	12 /8	12 / 7	ns
Donor Race, n	Caucasian: 13 Non-Caucasian: 7	Caucasian: 13 Non-Caucasian: 6	ns
Donor HCV +, n	1	3	ns
Recipient Variables			
Age, (years), mean ± SE	50.40 ± 2.6	56.2 ± 1.1	0.05
Sex (M/F), n	15 / 5	14 / 5	ns
Race, n	Caucasian: 16 Non-Caucasian: 4	Caucasian: 16 Non-Caucasian: 3	ns
* Primary Diagnosis: n	Cryptogenic: 2 HCV: 11 HBV: 2 PSC: 2 HCC: 10 LC: 3 NASH: 1	Cryptogenic: 1 HCV: 14 HBV: 2 Budd-Chiari: 1 HCC: 11 LC: 6	ns
MELD Score, mean ± SD	23.2 ± 1.5	24.4 ± 2	ns
DM, n	5	4	ns
Hypertension, n	7	7	ns
Weight (lbs), mean ± SD	173.8 ± 9.6	171.5 ± 7.7	ns
Recipient Peri-operative Data (mean ± SE)			
Cold ischemia time (h:min)	7:25 ± 0:23	7:52 ± 0:38	ns
Intra-operative red blood cell transfusion (units)	7.9 ± 1.6	9.5 ± 1.5	ns

Total OR time (h:mm)	9:10 ± 1:19	8:44 ± 1:17	ns
Intensive care unit (days)	3.6 ± 0.39	5.8 ± 1.27	ns
Hospital length of stay (days)	16.7 ± 1.7	28.6 ± 5.1	0.04

* Some patients presented multiple diagnoses. HCV, hepatitis C virus; PSC, primary sclerosing cholangitis; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; NASH, nonalcoholic steatohepatitis; LC, Laennec's cirrhosis

Table 2. Recipient Metabolic Panels

Clinical Variables	Group A	Group B	p-value
Liver function tests			
Peak AST (IU/L)	2,357	1,503	ns
Peak ALT (IU/L)	1,151	813	ns
Total Bilirubin (mg/dl)	9.5	11.8	ns
INR	2.61	2.79	ns
Mean weight (lbs)			
Baseline	174	167	ns
1-month post-OLT	165	163	ns
3-months post-OLT	168	157	ns
6-months post-OLT	176	156	ns
12-months post-OLT	181	157	ns
Cholesterol (mg/dl)			
Baseline	94	91	ns
1-month post-OLT	155	157	ns
3-months post-OLT	151	143	ns
6-months post-OLT	165	149	ns
12-months post-OLT	146	160	ns
Mean arterial pressure (MAP)			
Baseline	84	89	ns
1-month post-OLT	93	96	ns
3-months post-OLT	99	91	ns
6-months post-OLT	98	94	ns
12-months post-OLT	96	91	ns
Fasting blood sugar (mg/dl)			
Baseline	148	148	ns
1-month post-OLT	111	103	ns
3-months post-OLT	117	106	ns

6-months post-OLT	144	98	0.02
12-months post-OLT	147	112	ns

Table 3. Hepatitis Recurrence

Clinical Variables	Group A	Group B	p-value
Total number of HCV recipients	11/20 (55%)	14/19 (74%)	ns
Mean HCV RNA PCR			
Pre-OLT	0.48 M	0.45 M	ns
2 weeks post-OLT	5.8 M	0.83 M	ns
1 month post-OLT	15.9 M	3.7 M	ns
3 months post-OLT	12.3 M	11.9 M	ns
6 months post-OLT	11.1 M	5.5 M	ns
Treatment for HCV recurrence	7/11 (64%)	9/14 (64%)	ns
No Treatment for HCV recurrence	4/11 (36%)	5/14 (36%)	ns
Mean duration of treatment (wks)	38.5 (4-52)	19.3 (2-46)	0.048
Sustained viral response (SVR)	2/11 (18%)	2/14 (14%)	ns
Non-responder to treatment	3/11 (27%)	3/14 (21%)	ns
HCV progression to cirrhosis	3/11 (27%)	4/14 (29%)	ns
Mean OLT to death interval (months)	25.9	25.4	ns