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Clinical Transplantation

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

Ramirez CB, Doria C, Frank AM, Armenti ST, Marino IR. Completely steroid-free immunosuppression in liver transplantation: a randomized study.

Abstract: Introduction: Corticosteroids (CS) have been standard immunosuppression to prevent and treat rejection. However, CS are associated with increased risk of infection, obesity, hypertension, hyperlipidemia, diabetes, and accelerated hepatitis C virus (HCV) recurrence post-orthotopic liver transplantation (OLT). This study assesses the safety and efficacy of CS-free immunosuppressive regimen in adult OLT.
Methods: A two-yr, prospective, randomized study of CS with delayed withdrawal (CS) or CS-free regimen with basiliximab, tacrolimus, and enteric-coated mycophenolate sodium (EC-MPS) was performed in 39 patients (CS=20; CS-free=19). CS group received intra-operative methylprednisolone weaned by six months. HCV patients had HCV PCR pre-OLT and 0.5, one, three, and six months post-OLT. Protocol liver biopsies were performed at OLT, 2 and 24 wk post-OLT or when indicated.
Results: Rejection occurred in two patients. Patient survival at one yr (100% vs. 95%), three yr (85% vs. 63%), and five yr (80% vs. 63%) post-OLT were similar between CS and CS-free group, respectively. Death-censored graft survival at one yr (100% vs. 95%), three yr (85% vs. 63%), and five yr (75% vs. 63%) were also similar. The risk of new-onset DM, hypertension, hypercholesterolemia, and weight gain was similar between groups.
Conclusion: CS avoidance with basiliximab, calcineurin inhibitor, and EC-MPS is safe and effective as CS- containing immunosuppression in adult OLT.

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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 virus (HCV) recurrence post-OLT (2, 3). Consequently, several clinical trials that 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.

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, 40 adult recipients of deceased donor primary OLT at TJUH were enrolled into this prospective, controlled, randomized, non-blinded, pilot trial (Clinical Trials.gov; ID: NCT00296244). 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, that is, neutropenia and gastrointestinal symptoms, were also evaluated.

The inclusion criteria included adult recipients of primary cadaveric OLT aged between 18 and 72 yr, liver graft cold ischemia time of <20 h, and women of childbearing potential with negative pregnancy test, and the patient has given written informed consent to participate in the study. The exclusion criteria included patients who have previously received an organ transplant, multiple organ transplant recipients, women of childbearing potential not using the prescribed contraceptive methods, known sensitivity to basiliximab or class of basiliximab, patients with severe medical condition(s) that in the view of the investigator prohibits participation in the study, and use of any other investigational agent within 30 d prior to enrollment.

Subjects were randomized immediately prior to OLT into one of two arms: control arm (CS): standard immunosuppression with CS and delayed CS withdrawal and study arm (CS-free): standard immunosuppression with complete CS avoidance. Randomization was performed by the TJUH Investigational Drug Pharmacy Service who dispensed study drug based on the computer-generated randomization schedule and the study protocol.

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/d by mouth (PO) or nasogastric tube (NGT) in two divided doses, within 48 h 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 h 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.

The CS group received methylprednisolone 1 g IV intra-operatively followed by a taper schedule as follows: methylprednisolone 50 mg IV every six h on day 1; 40 mg IV every six h on day 2; 30 mg IV every six h on day 3; 20 mg IV every six h on day 4; 20 mg IV every 12 h on days 5; and thereafter, prednisone 20 mg PO daily, which was tapered off by six months post-OLT. CS and CS-free groups were on maintenance CNI monotherapy by six and three months post-OLT, respectively.

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

Liver biopsies were performed according to protocol intra-operatively, between days 7 and 21 post-OLT and at three to six 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 (12) was treated in both groups with methylprednisolone 1 g IV followed by a five-day CS taper as described above. For recipients in the steroid-free arm 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.

Abnormal liver function tests were evaluated by hepatic ultrasound, and percutaneous liver biopsy. A diagnosis of HCV recurrence was made based on liver biopsy findings and serum HCV RNA titers. The modified Scheuer scoring system was used to evaluate biopsy findings of necroinflammatory activity in chronic hepatitis cases (13, 14). Recipients with HCV recurrence were treated for the virus, if the liver biopsy shows total score of >4 for necroinflammatory activity (greater than mild portal and lobular inflammation) or >stage 1 (enlarged and fibrotic portal tracts). Treatment consisted of peg-interferon 180 μg subcutaneously weekly for two wk. If the peg-interferon was tolerated without hematologic or neuropsychiatric issues during this time frame, ribavirin was added to peg-interferon for a total duration of 48 wk.

Weight, total cholesterol, fasting blood sugar (FBS), and mean arterial pressure (MAP) levels were measured and recorded at baseline, one, three, six, and 12 months post-OLT. New-onset diabetes mellitus was defined as FBS $\geq$ 126 mg/dL (7 mM), with fasting defined as no caloric intake for at least eight h.

Statistical analysis

Statistical analysis was carried out to demonstrate the 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 carried out with Kaplan–Meier, and significance was determined using a log-rank test. Analysis was performed using XLSTAT 2008 (Addinsoft, 2008, New York, NY, USA) for Microsoft Excel and IBM SPSS Statistics 20, 2004 (SPSS Inc, Chicago, IL, USA).

Results

Between February 2006 and November 2007, 40 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 retransplantation for hepatic artery thrombosis on post-OLT day 16. Because he expired within 10 d after retransplantation, follow-up data were short and untenable, and therefore, he was excluded from the study analysis (Fig. 1).

The mean overall follow-up was 64.4 (range: 10.6–79.6) months as of September 2012. Donor characteristics were comparable between the two groups (Table 1). Other than a significantly higher mean recipient age and longer median hospital stay in CS-free (23 d) compared with CS group (15 d), recipient demographics and peri-operative data were similar between the two groups. There were three outliers in the CS-free group with mean hospital stay of 67.7 d. 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 two groups. The one-, three-, and five-yr patient survival rates in CS and CS-free groups, respectively, were as follows: 100% vs. 95%, 85% vs. 63%, and 80% vs. 63% (Fig. 2). The one-, three-, and five-yr graft survival rates in CS and CS-free groups, respectively, were as follows: 100% vs. 95%, 85% vs. 63%, and 75% vs. 63% (Fig. 3). There were 12 deaths, five in the CS group and seven in the CS-free group. The causes of death in the CS group were cerebrovascular accident (n = 1), lung CA (n = 2), and liver failure secondary to severe progressive HCV recurrence (n = 2). The causes of death in the CS-free group were cerebrovascular accident (n = 1), necrotizing pancreatitis post-endoscopic retrograde cholangiopancreatography (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 57.5 months in the CS group and 24.7 months in the CS-free group (p = ns). CS-responsive biopsy-proven acute rejection occurred once in one 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 two groups. The time to transaminase peak occurred on POD 2 and POD 1 in the CS and CS-free groups, respectively, while the mean time to INR peak was <1 d for both groups. Furthermore, there was no incidence of primary non-function in this cohort (Table 2).

The mean weight decreased in both groups from baseline to one month post-OLT. However, from 1 month to 1 yr post-OLT, mean weight increased steadily in the CS group but decreased in the CS-free group, 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 the CS group increased steadily from baseline to three months and from six months to one yr post-OLT. On the other hand, while MAP in the CS-free group increased from baseline to one month, they trended downwards by three months post-OLT. MAP levels were significantly higher in CS vs. CS-free group at three and 12 months post-OLT. Mean FBS levels at baseline, one, three, and 12 months post-OLT were similar, except at six months post-OLT when FBS levels were significantly higher (p = 0.02) in the CS compared with the CS-free group. Eight recipients in each group

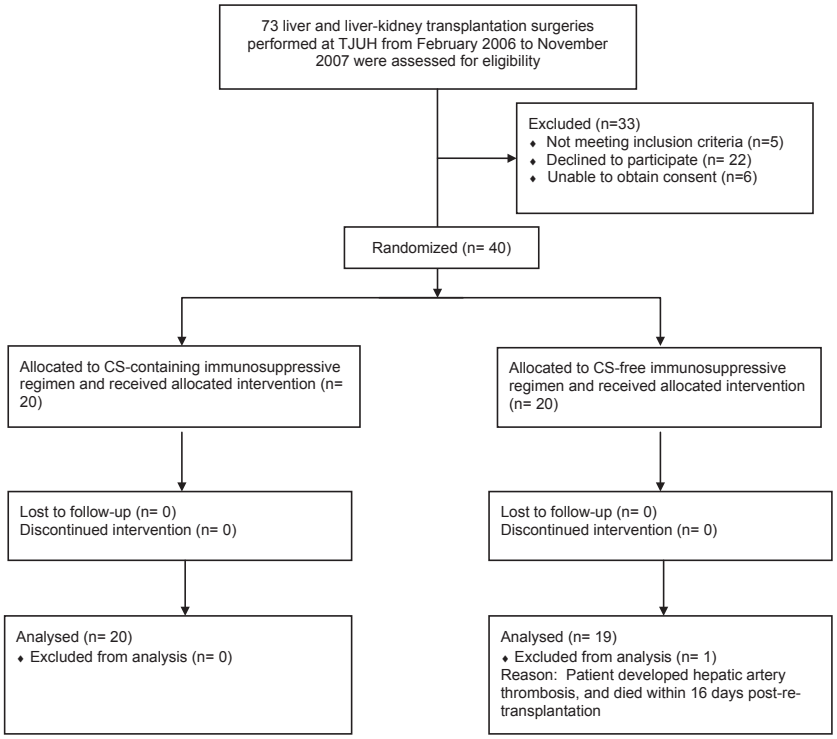

Fig. 1. The Flow Diagram illustrates the progress of patients through the trial, including enrollment, allocation, follow-up and analysis.

developed new-onset diabetes mellitus with mean FBS levels (mg/dL) of 148 and 152 in CS and CS-free groups, 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 the CS-free (74%) than in the CS group (55%). We also observed an earlier peak (one vs. three months post-OLT) and higher HCV PCR levels (16 million vs. 11.9 million, p = ns) in the CS than in the CS-free group. However, there was no significant difference in the incidence and severity of histologic HCV recurrence between the two groups. Comparison of degree of fibrosis based on liver biopsy at 24 wk post-OLT in the CS vs. CS-free group, respectively, showed no fibrosis in 45% vs. 43%, fibrosis grade 1–2 in 36% vs. 43%, and fibrosis grade 3 in 18% vs. 14% of recipients. Follow-up liver biopsy findings after a mean period of 25 months post-OLT in the CS vs. CS-free group, respectively, showed no fibrosis in 27% vs. 21%, fibrosis grade 1–2 in 36% vs. 42%, fibrosis grade 3 in 9% vs. 7%, and fibrosis grade 4 in 27% vs. 29% of recipients. Three recipients in the CS group (two developed cirrhosis within 22 months post-OLT), and two recipients in the CS-free group received liver grafts from donors older than 65 yr of age (donor mean age: 72.6, range: 66–81 yr old). Treatment outcomes for recurrent HCV are listed in Table 3. The duration of treatment for recurrent HCV was significantly shorter in the CS-free group compared with the CS group because three patients in the former and only one in the latter group had to discontinue treatment within four wk due to treatment non-response or progression to cirrhosis.

Two patients in the CS-free and one in the CS group developed biliary anastomotic stricture at 4.2 and 22.6 months vs. 0.9 post-OLT months, respectively. One patient in each group developed biliary anastomotic leak at mean of one month post-OLT.

Mean tacrolimus trough levels (ng/ml) were similar at one, three, six, and 12 months post-OLT in the CS (11.3, 9, 7.8, 7.5) and CS-free (8.1, 7.8, 9.4, 6) groups, respectively. The mean duration on CS was 174 d in the CS group. 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 gastrointestinal symptoms (diarrhea, vomiting) in four patients in each group and for neutropenia in three and six recipients in the CS and Cs-free groups, respectively. EC-MPS was discontinued for GI symptoms in one recipient in each group and for neutropenia in two and one recipient in the CS and CS-free groups, respectively.

Discussion

Corticosteroids have been used widely for decades as part of immunosuppressive therapy in OLT

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

Donor variables	CS Group	CS-free Group	p-value
Donor age (yr), 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	
Recipient variables			
Age, (yr), 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	
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			
OLT technique			
Classic bi-caval with bypass (n = 29)	14	15	NS
Piggyback (n = 10)	6	4	NS
Biliary reconstruction			
Choledocho-choledochostomy w/TT	4	6	NS
Choledocho-choledochostomy w/o TT	14	13	NS
Choledocho-jejunostomy	2	0	NS
Cold ischemia time (h:min)	7:25 ± 0:23	7:52 ± 0:38	NS
Warm Ischemia time (h:min)	1:16 ± 0:03	1:13 ± 0:04	NS
Intra-operative PRBC 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 (d)	3.6 ± 0.39	5.8 ± 1.27	NS
Median Hospital Length of stay (d)	15	23	NS

*Some patients presented multiple diagnoses. HCV, hepatitis C virus; PSC, primary sclerosing cholangitis; HCC, hepatocellular carcinoma; HBV, hepatitis B virus; NASH, non-alcoholic steatohepatitis; LC, Laennec's cirrhosis; post-OLT, post-orthotopic liver transplantation; NS, not significant.

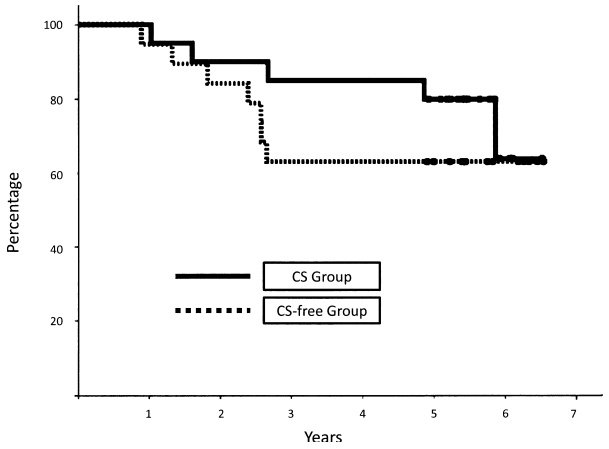

Fig. 2. Liver transplant patient survival (Kaplan–Meier). This graph illustrates patient survival rates in adult liver transplant recipients who received an immunosuppressive regimen consisting of basiliximab, tacrolimus, enteric-coated mycophenolate sodium with steroids, compared to patients who received a similar immunosuppressive regimen without steroids.

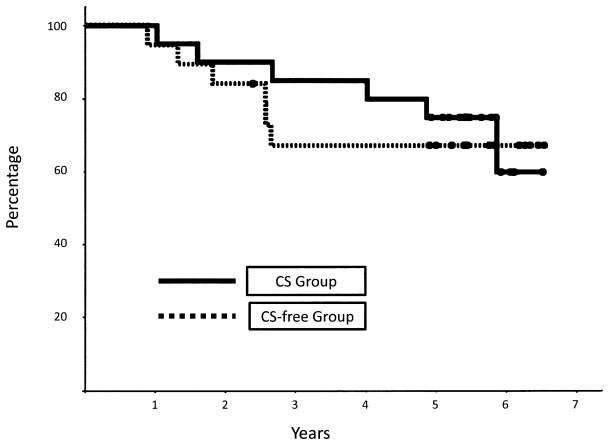

Fig. 3. Liver transplant death-censored graft survival (Kaplan–Meier). This graph illustrates death-censored graft survival rates in adult liver transplant recipients who received an immunosuppressive regimen consisting of basiliximab, tacrolimus, enteric-coated mycophenolate sodium with steroids, compared to patients who received a similar immunosuppressive regimen without steroids.

Table 2. Recipient metabolic panels

Clinical variables	CS Group	CS-free Group	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	90	0.02
6 months post-OLT	98	94	NS
12 months post-OLT	100	89	0.01
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

CS, corticosteroids; post-OLT, post-orthotopic liver transplantation; NS, not significant; INR, international normalized ratio.

Table 3. Hepatitis recurrence

Clinical variables	CS Group	CS-free Group	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 wk 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
Treated for HCV recurrence	7/11 (64%)	9/14 (64%)	NS
Mean duration of treatment (wks)	38.5 (4–52)	19.3 (2–46)	0.05
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

CS, corticosteroids; HCV, hepatitis C virus; post-OLT, post-orthotopic liver transplantation; NS, not significant.

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, 15). In recent years, a few CS-free immunosuppressive protocols have been proposed post-OLT (7, 8, 16–22). Some CS-free protocols included the use of intra-operative dose of CS followed by post-OLT CS-free maintenance therapy (8, 23–27). Although CS-free protocols were reported to be safe compared with 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 with 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 (28). 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 (29), and by inhibiting TNF and IL-6 expression, which impairs cell-cycle progression, and hepatocyte regeneration (30). Our trial showed no difference in the incidence of I-R injury between the CS 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 with 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 (31). 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 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 new-onset diabetes mellitus would be markedly lower in the CS-free arm if CS were replaced with another immunosuppressive agent such as an anti-IL-2 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 six months post-OLT when they were higher in the CS group. The reason for this unexpectedly higher glucose level at six months is unclear, considering that most recipients in the CS group were no longer on CS by six months post-OLT.

Our study showed an overall low ACR rate of 5% and similar one-, three-, and five-year patient and graft survival rates between the CS and CS-free groups. These may be attributed to the use of anti-IL-2 induction in combination with dual CNI/MPA maintenance immunotherapy.

HCV recurrence post-OLT is almost a universal phenomenon. The incidence of histologic HCV recurrence ranges from 14% to 72% (32, 33). Furthermore, a severe cholestatic type of recurrent HCV, characterized by rapid progression to graft failure requiring retransplantation within two yr, has been reported in about 10% of HCV recipients (34, 35). 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 CS group compared with the CS-free group, the incidence and severity of HCV recurrence, treatment outcomes, and graft loss rates were similar between the two groups. These findings are consistent with the suggestions of Eghtesad et al. (36). 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.

The higher incidence of histologic and advanced cholestatic HCV recurrence in this cohort could be due to a high overall immunosuppression in patients in both arms of this study. However, the low incidence of bacterial infection and absence of CMV infection and recurrent HCC observed in this study do not support this assumption. Perhaps other factors particularly the use of older donors may have also played a role in HCV progression. It remains unclear why CS-free immunosuppression did not demonstrate a beneficial effect in reducing the incidence, severity or degree of progression of HCV recurrence in this study. The authors think that the number of patients in the study is small that made it difficult to assess for any differences between the two groups.

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 (37, 38). However, studies on de novo use of EC-MPS in OLT recipients have been limited to conversion from MMF to EC-MPS (39–41). 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 (42). Our data showed that EC-MPS was well tolerated with similar incidence of side effects between CS and CS-free groups, most of which resolved with dose reduction. Neutropenia was observed less frequently in the CS 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 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, that is, 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 (43, 44). 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 and CS-free groups in the incidence of hypertension, hypercholesterolemia, new-onset DM, 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. Our study is limited due to its

small sample size, which may be a possible explanation for these findings.

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Authors' contributions

Carlo B. Ramirez, MD, principal author, involved in all aspects of the research project (research design, performance of the research, data collection, data analysis, and writing the manuscript). Cataldo Doria, MD, PhD, participated in research design, performance of the research, and writing the manuscript. Adam M. Frank, MD, participated in performance of the research, data analysis, and writing the manuscript. Stephen T. Armenti, BS, participated in the data analysis, and writing the manuscript. Ignazio R. Marino, MD, involved in research design, and writing the manuscript.

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