Corticosteroid-Free Immunosuppression With Tacrolimus Following Induction With Daclizumab: A Large Randomized Clinical Study

Olivier Boillot,[1] David A. Mayer,[2] Karim Boudjema,[3] Mauro Salizzoni,[4] Bruno Gridelli,[5] Franco Filipponi,[6] Pavel Trunecka,[7] Marek Krawczyk,[8] Pierre-Alain Clavien,[9] Christian Ducerf,[10] Carlos Margarit,[11] Raimund Margreiter,[12] José Mir Pallardo,[13] Krister Hoeckerstedt,[14] George-Phillipe Pageaux,[15] and the Monoclonal Antibodies vs. STERoids (MASTER) Study Group

This open, randomized (1 : 1), multicenter, 3-month study compared a dual tacrolimus plus steroids (Tac / steroids) regimen with a steroid-free immunosuppressive regimen of tacrolimus following daclizumab induction therapy (Tac / Dac) in adult liver transplant recipients. The full analysis set comprised 347 patients in the Tac / steroids group and 351 in the Tac / Dac group. Mean tacrolimus dose during month 3 was 0.11 mg/kg/day in both groups; mean whole-blood trough levels during month 3 were 10.9 ng/mL (Tac / steroids) and 10.6 ng/mL (Tac / Dac). The incidence of biopsy-confirmed acute rejection that required treatment was similar in both groups: 26.5% in the Tac / steroids group and 25.4% in the Tac / Dac group ($P = .727$). However, the incidence of biopsy-confirmed corticosteroid-resistant acute rejection was higher in the Tac / steroids group than in the Tac / Dac group (6.3 vs. 2.8%; $P = .027$). Kaplan-Meier estimates of graft survival (92.2 vs. 90.5%) and patient survival (94.5 vs. 93.7%) were similar in both groups. While also the overall adverse event profiles were similar, the incidences of diabetes mellitus (15.3 vs. 5.7%, respectively; $P < .001$) and cytomegalovirus infection (11.5 vs. 5.1%, respectively; $P = .002$) were higher in the Tac / steroids group compared with the Tac / Dac group. Mean cholesterol levels increased by 16% in the Tac / steroids group, but were unchanged in the Tac / Dac group during the study. In conclusion, tacrolimus monotherapy following daclizumab induction is an effective and safe regimen, with an advantage over concomitant steroid-maintenance therapy in terms of a lower incidence of diabetes and viral infection, and a lower incidence of steroid-resistant acute rejection. (*Liver Transpl 2005;11:61–67.*)

Tacrolimus is a potent immunosuppressant that provides excellent protection from graft rejection in liver transplant patients.[1] Maintenance therapy with corticosteroids remains an integral component of most immunosuppressive regimens. However, prolonged use of corticosteroids is associated with multiple side effects that are known to contribute to patient morbidity and mortality: these include osteoporosis,[2] diabetes mellitus, hypertension, and hyperlipidemia.[3] Therefore, the development of corticosteroid-sparing or corticosteroid-free immunosuppressive regimens is an important goal in the transplantation field.[4]

The corticosteroid-sparing effect of tacrolimus has been demonstrated in large, randomized, controlled trials with adult liver transplant patients.[5,6] In these studies, tacrolimus-based regimens were associated with reduced exposure to corticosteroids compared to those based upon cyclosporin. More recently, promising results were obtained in pilot studies that assessed the efficacy and safety of corticosteroid-free immunosuppression in adult liver transplant patients receiving

Abbreviations: Tac / steroids, tacrolimus plus steroids dual regimen; Tac / Dac, tacrolimus following daclizumab induction therapy; SD, standard deviation.

From the [1]Service de Transplantation, Hôpital Edouard Herriot, Lyon, France; [2]Liver and Hepatobiliary Unit, Queen Elizabeth Hospital, Birmingham, United Kingdom; [3]Centre de Chirugie Digestive et Hepato-biliare, Hôpital Pontchaillou, Rennes, France; [4]Azienda Ospedaliera S. Giovanni Battista, Unita Trapianto di Fegato, Torino, Italy; [5]Ospedali Riuniti di Bergamo, Chirurgia Generale III, Bergamo, Italy; [6]Azienda Ospedaliera Universitaria Pisana, Unità Trapianto di Fegato, Pisa, Italy; [7]Department of Hepatogastroenterology, IKEM, Praha, Czech Republic; [8]Department of General, Transplant, and Liver Surgery, Warsaw Medical University, Warsaw, Poland; [9]Department für Chirurgie, Universitätsspital Zürich, Zürich, Switzerland; [10]Hospital Croix Rousse, Service de Chirurgie, Lyon, France; [11]Hospital Vall d'Hebron, Servicio de Cirugia General y Digestiva / UTH, Barcelona, Spain; [12]Department of General and Transplant Surgery, University Hospital Innsbruck, Innsbruck, Austria; [13]Servico Cirugia General y Digestivo, Unidad de Transplante Hepatico, Valencia, Spain; [14]Department of Transplantation and Liver Surgery Unit, Helsinki University Hospital, Helsinki, Finland; and [15]Service d'Hepato-Gastroenterologie, Hôpital Saint-Eloi, Montpellier, France.

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Address reprint requests to Olivier Boillot, Unité de transplantation hépatique, Hôpital Edouard Herriot, Place D'Arsonval, 69437 Lyon Cedex 03, France. Telephone: 33 4721 16291; FAX: 33 4721 16783; E-mail: boillot@cismsun.univ-lyon1.fr

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tacrolimus in combination with azathioprine[7] or mycophenolate mofetil.[8]

Daclizumab, a novel anti-interleukin-2-receptor monoclonal antibody, has been successfully used as induction therapy to prevent acute rejection during the immediate posttransplant period,[9] when the risk of acute rejection is greatest. Therefore, a regimen of daclizumab induction therapy with tacrolimus as maintenance treatment may provide effective immunosuppression in liver transplant patients, without the need for corticosteroids.

To investigate this, we compared the efficacy and safety of tacrolimus monotherapy following daclizumab induction treatment (Tac / Dac) vs. a tacrolimus / steroids dual regimen (Tac / steroids) without induction treatment in adult liver transplant patients during the first 3 months following transplantation.

Patients and Methods

Study Design

This open-label, randomized, multicenter, parallel-group study compared the efficacy and safety of tacrolimus monotherapy after daclizumab induction treatment with a Tac / steroids dual regimen during the first 3 months following transplantation. The study was conducted at 45 transplantation centers in 15 European countries between July 2000 and February 2002 and in accordance with the Declaration of Helsinki. The ethics committee at each center approved the protocol before the study was implemented. Eligible patients were randomized (1 : 1) to the Tac / Dac group or the Tac / steroids group.

Patient Eligibility

Eligible patients were 18 years of age or older and undergoing orthotopic liver allograft transplantation, including partial organ transplantation. All eligible patients provided written or oral informed consent before any study-related procedure was conducted.

Exclusion criteria were multiorgan transplants; previous organ transplants, including liver retransplants; auxiliary grafts or bioartificial livers; living-related liver transplants; ABO blood group–incompatible grafts; initial, sequential, or parallel therapy with other immunosuppressive antibody preparations; corticosteroid therapy as well as chemotherapy before transplantation; symptoms or previous history of neoplastic disease, including leukemia, except for primary liver carcinoma with at most 3 nodes (no node larger than 5 cm), no metastases and no vascular tumoral invasion; significant, uncontrolled concomitant infections and / or severe diarrhea, vomiting or active peptic ulcer; patients or donors known to be human immunodeficiency virus–positive; allergy to or intolerance of study medications; pregnancy or breastfeeding; participation in another clinical trial and / or treatment with study drug within the previous 28 days; substance abuse or psychiatric disorder; and unlikely compliance with schedule.

Interventions

All patients received tacrolimus .075 mg/kg twice daily with subsequent dose adjustment to achieve target whole-blood trough levels of 10–20 ng/mL during the first 6 weeks and 5–15 ng/mL thereafter. A 24-hour intravenous infusion (.03 mg/kg/day) was permitted if the patient was initially unable to take medication orally or via a nasogastric / nasojejunal tube, or if trough levels were inadequate with oral dosing after the 1st 72 hours. The 1st dose was administered within 12 hours after transplantation. All patients also received methylprednisolone (500 mg) as a single intravenous bolus before reperfusion. Patients randomized to the Tac / Dac regimen received 2 intravenous doses of daclizumab: 2 mg/kg before reperfusion and 1 mg/kg between postoperative days 7 and 10. Patients randomized to the Tac / steroids regimen received oral prednisone 15–20 mg/day during month 1, 10–15 mg/day during month 2, and 5–10 mg/day during month 3.

Episodes of acute rejection were verified by histological examination of core biopsies except when biopsy was clinically contraindicated. Biopsy-confirmed acute rejection episodes were managed by increasing the dose of tacrolimus (if the trough level was below 15 ng/mL) and / or by giving intravenous pulses of methylprednisolone according to degree of severity. Corticosteroid-resistant biopsy-confirmed acute rejection episodes were to be treated with OKT3 antibodies according to local practice. When additional immunosuppressive drugs were used after occurrence of rejection, the patient was withdrawn from the study.

Antiviral prophylaxis was not mandatory and was administered according to local practice.

Efficacy and Safety Assessments

Patients were assessed at baseline (day 0) and days 1, 7, 14, 28, 61, and 91. The primary efficacy endpoint was the incidence of and time to 1st biopsy-confirmed acute rejection episode (within 3 months of transplantation) that required treatment. Acute rejection episodes that resolved after treatment with an increased tacrolimus dose, but without the need for corticosteroids, were also included in the primary endpoint analysis. For all assessments other than those at the primary endpoint, these episodes were classified as spontaneously resolving acute rejections. The time to 1st acute rejection was defined as the number of days from reperfusion to the 1st clinical, laboratory, or histologic signs of acute rejection. Local histopathologists, who were unaware of the treatment allocated to patients, performed the histological evaluations of biopsies.

Secondary efficacy endpoints were the overall incidence of biopsy-confirmed acute rejection episodes (including spontaneously resolving episodes), the incidence of and time to 1st corticosteroid-resistant acute rejection episode, the severity of biopsy-confirmed acute rejections, graft survival, patient sur-

vival, and treatment failure (defined as time to graft loss or withdrawal due to an adverse event).

Adverse events were monitored on an ongoing basis, irrespective of causality, coded using a modified Coding Symbols for Thesaurus of Adverse Reaction Terms dictionary and summarized by frequency count. An adverse event was defined as serious if it resulted in death, was life-threatening, resulted in persistent significant disability or incapacity, required in-patient hospitalization or prolongation of hospitalization, caused cancer or a congenital abnormality / birth defect, demonstrated signs and symptoms of overdose, or required intervention to prevent any of the above. Vital signs and selected laboratory parameters were assessed at every scheduled visit. Hematology as well as sodium, potassium, cholesterol, and serum creatinine levels were assessed at baseline and day 91.

Statistics

A sample size of 600 patients was calculated in order to detect a 12% difference between treatment arms for the primary endpoint using a Wilcoxon-Gehan test, based on an estimated incidence of 40% for the Tac / steroids arm, a 5% level of significance, a power of 80%, and a dropout rate of 10%. Efficacy and safety were analyzed using the intent-to-treat population, which included all randomized patients who received at least 1 dose of study medication.

Continuous variables were analyzed using Student's *t*-test, or the Wilcoxon rank sum test if the data was not normally distributed. Categorical variables were analyzed using Pearson's chi-square test or Fisher's exact test if any expected cell frequency was less than 5. Time-to-event data were analyzed using Kaplan-Meier methods and compared using the Wilcoxon-Gehan test. A P value $< .05$ was considered significant.

Results

Patients

A total of 708 patients were recruited, with 352 randomized to the Tac / steroids group and 356 to the Tac / Dac group. A total of 10 patients were excluded from the intent-to-treat analysis: 4 in each group received no study medication, 1 in the Tac / steroids group was not transplanted, and 1 in the Tac / Dac group did not provide informed consent. The number of patients completing the study was 281 (81.0%) in the Tac / steroids group and 259 (73.8%) in the Tac / Dac group. Most discontinuations occurred within the 1st 2 weeks of the study. Protocol violations (Tac / steroids: 4.9%; Tac / Dac: 8.0%) and adverse events (Tac / steroids: 5.2%; Tac / Dac: 7.7%) were the most common reasons for withdrawal. Protocol violations resulting in withdrawal were mainly addition of mycophenolate mofetil (MMF) or sirolimus to the immunosuppressive regimen. The incidences of any adverse event leading to withdrawal did not differ between the treatment groups. The rate of withdrawal due to lack of efficacy was low in both groups (1.7 and 1.1%). Other reasons for withdrawal were retransplantation (2.6 and 3.4%), loss to follow-up (0.3 and 0.9%), and not specified other reasons (0.9 and 1.1%) in the Tac / steroids and the Tac / Dac group, respectively.

Patient demographics and baseline characteristics were comparable between the 2 groups (Table 1). Whole-blood trough levels of tacrolimus were maintained in the target range throughout the study period, and the mean daily dose of oral tacrolimus was similar in both groups (Fig. 1). A total of 7 patients in the Tac / steroids group and 2 patients in the Tac / Dac group received intravenous tacrolimus during the study.

Efficacy

The incidence of biopsy-confirmed acute rejection that required treatment did not differ between the 2 treatment groups: 92 patients in the Tac / steroids group (26.5%) and 89 patients in the Tac / Dac group (25.4%) experienced at least 1 biopsy-confirmed acute rejection episode by month 3 that required treatment ($P = .727$; Fig. 2). Kaplan-Meier estimates of the incidence of and time to 1st biopsy-confirmed acute rejection requiring treatment were also similar, with 71.8% of patients in the Tac / steroids group and 72.0% in the Tac / Dac group free from biopsy-confirmed acute rejection requiring treatment at month 3 ($P = .580$).

The overall incidence (including spontaneously resolving episodes) of biopsy-confirmed acute rejection was similar between the groups: 28.5% in the Tac / steroids group vs. 27.6% in the Tac / Dac group ($P = .793$; Fig. 2). However, the incidence of biopsy-confirmed corticosteroid-resistant acute rejection was significantly higher in the Tac / steroids group compared with the Tac / Dac group: 6.3 vs. 2.8%, respectively ($P = .027$; Fig. 2). Although there were no substantial differences in grading between the treatment groups, the incidence of severe rejections was slightly higher in the Tac / steroid group (6.9%) than in the Tac / Dac group (4.8%). The majority of biopsy-confirmed acute rejections in both groups had a histological grade of mild (Tac / steroids: 8.1%; Tac / Dac: 9.7%) or moderate (Tac / steroids: 13.5%; Tac / Dac: 13.1%).

At month 3, Kaplan-Meier estimates showed no difference between the Tac / steroids and the Tac / Dac groups in terms of graft survival (92.2 vs. 90.5%, respectively; $P = .424$), patient survival (94.5 vs. 93.7%, respectively; $P = .634$) and patients free from treatment failure (88.4 vs. 84.2%, respectively; $P =$

Table 1. Patient Demographics and Baseline Characteristics

	Tac/steroids (N = 347)	Tac/Dac (N = 351)	*P**
Mean age, years ± SD	51.0 ± 9.8	50.9 ± 10.4	.923
Male–female ratio	238:109	239:112	.888
Primary diagnosis, n (%)			
Cirrhosis	256 (73.8)	240 (68.4)	.1329
Carcinoma	50 (14.4)	53 (15.1)	.8314
Sclerosing cholangitis	18 (5.2)	29 (8.3)	.1305
Budd-Chiari syndrome	7 (2.0)	4 (1.1)	.3815
Metabolic disease	2 (0.6)	7 (2.0)	.1769
Other	14 (4.0)	18 (5.1)	.5881
Viral status, n (%)			
CMV-positive†	248 (71.5)	240 (68.4)	.308
EBV-positive†	237 (68.3)	236 (67.2)	.304
HBV-positive†	55 (15.9)	63 (18.0)	.460
HCV-positive†	103 (29.7)	106 (30.1)	.921
CMV mismatch, n (%) (negative recipient/positive donor)	82 (23.6)	68 (19.4)	.141
Diabetes mellitus, n (%)	55 (15.9)	57 (16.2)	.9181

Abbreviations: CMV, cytomegalovirus; EBV, Epstein-Barr virus; HBV, hepatitis B virus; HCV, hepatitis C virus; N, intent-to-treat patients; SD, standard deviation.
* Fisher's exact test.
† Variable not recorded for all patients.

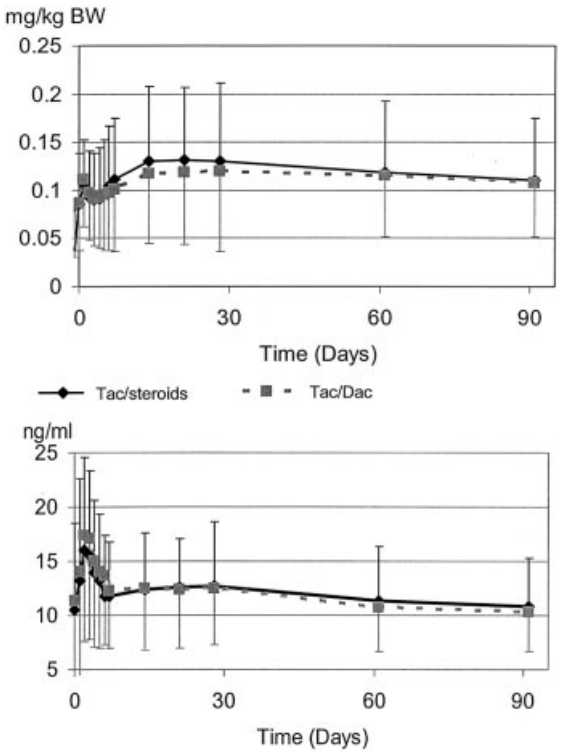

Figure 1. Mean daily dose (± SD) and mean whole-blood trough levels of oral tacrolimus. N, intent-to-treat patients.

.105). A total of 28 patients (8.1%) in the Tac / steroids group and 36 patients (10.3%) in the Tac / Dac group lost their graft. Of these, 10 patients in the Tac / steroids group and 15 in the Tac / Dac group were retransplanted. A total of 45 patients died: 20 in the Tac / steroids group and 25 in the Tac / Dac group. The causes of death are summarized in Table 2.

Safety

Overall, 94.5% of patients in the Tac / steroids group and 94.9% of patients in the Tac / Dac group reported

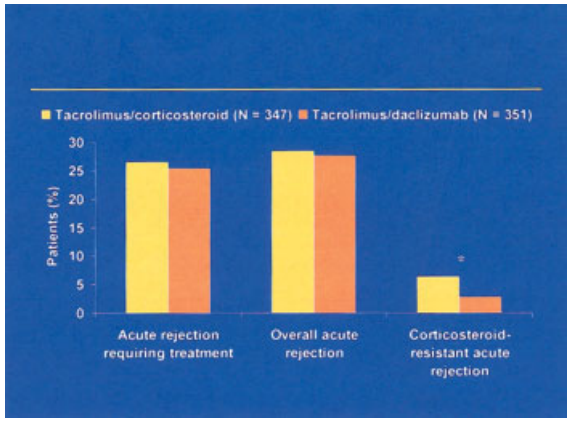

Figure 2. Incidence of biopsy-confirmed acute rejection. N, intent-to-treat patients; *$P = .027$.

Table 2. Causes of Death

	Tac/steroids (N = 347)	Tac/Dac (N = 351)	*P**
Total deaths,† n	20	25	.5383
Shock/multiorgan failure	9	18	.1150
Cardiovascular event	7	3	.2209
Hemorrhage	1	4	.3732
Liver necrosis	1	0	.4971
Pulmonary hypertension	1	0	.4971
Pneumonia	1	0	.4971

Abbreviation: N, intent-to-treat patients.
* Fisher's exact test.
† Includes those that occurred either during the study or after withdrawal.

at least 1 adverse event. Table 3 shows the most frequently reported adverse events. Among these, the incidences of spontaneously reported posttransplant diabetes mellitus and cytomegalovirus infection were significantly higher in the Tac / steroids group compared with the Tac / Dac group. Concomitant systemic antiviral medication was administered to 66.0% of the patients in the Tac / steroids group and to 60.4% of the patients in the Tac / Dac group.

The incidence of long-term (>30 consecutive days) insulin use in previously nondiabetic patients was 17.8% in the Tac / steroids group and 5.1% in the Tac / Dac group.

In both groups, there was a similar overall incidence of serious adverse events other than death that were considered to be causally related to treatment: 29.1% of patients in the Tac / steroids group vs. 28.5% of patients in the Tac / Dac group. Table 4 shows the most frequently reported treatment-related serious adverse events. The overall incidences of neurological disorders, gastrointestinal disorders, and cardiac events were also similar in both treatment groups (data not shown).

Clinical laboratory data did not differ significantly between the treatment groups. However, a trend was observed in mean serum cholesterol levels (± standard deviation [SD]), which increased during the study in the Tac / steroids group (3.8 ± 1.8 mmol/L at baseline and 4.5 ± 1.4 mmol/L at month 3), but were basically unchanged in the Tac / Dac group (4.0 ± 2.4 mmol/L at baseline and 3.9 ± 1.1 mmol/L at month 3). Antihyperlipidemic medication was reported in 1 (0.3%) of the patients in the Tac / Dac group; no patient in the Tac / steroids group received antihyperlipidemic therapy.

Overall renal function, as assessed by measuring serum creatinine levels, was within the normal range in both groups: mean serum creatinine levels were 86.4 ± 27.8 μmol/L at baseline and 116.6 ± 48.5 μmol/L at month 3 in the Tac / steroids group compared with

Table 3. Most Frequently Reported Adverse Events

	Tac/steroids (N = 347) n (%)	Tac/Dac (N = 351) n (%)	*P**
Kidney function abnormal	82 (23.6)	98 (27.9)	.2257
Liver function tests abnormal	53 (15.3)	59 (16.8)	.6070
Posttransplant diabetes mellitus	53 (15.3)	20 (5.7)	<.001
Hypertension	50 (14.4)	45 (12.8)	.5816
Cholestatic jaundice	45 (13.0)	43 (12.3)	.8200
Hyperglycemia	45 (13.0)	41 (11.7)	.6458
CMV infection	40 (11.5)	18 (5.1)	.002
Infection	39 (11.2)	39 (11.1)	1.000

Abbreviations: CMV, cytomegalovirus; N, intent-to-treat patients.
* Fisher's exact test.

Table 4. Most Frequently Reported Treatment-Related Serious Adverse Events

	Tac/steroids (N = 347) n (%)	Tac/Dac (N = 351) n (%)	*P**
CMV infection	18 (5.2)	6 (1.7)	.013
Hepatitis	13 (3.7)	4 (1.1)	.028
Sepsis	10 (2.9)	11 (3.1)	1.000
Kidney function abnormal	9 (2.6)	18 (5.1)	.1150
Kidney failure	9 (2.6)	10 (2.8)	1.0000

Abbreviations: CMV, cytomegalovirus; N, intent-to-treat patients.
* Fisher's exact test.

88.2 ± 38.2 μmol/L at baseline and 126.3 ± 69.4 μmol/L at month 3 in the Tac / Dac group.

Discussion

This large, randomized, multicenter study demonstrates that tacrolimus monotherapy with daclizumab induction treatment provides effective immunosuppression during the first 3 months after liver transplantation, without the need for corticosteroids. There was no difference between the Tac / steroids and Tac / Dac regimens in the incidence of and time to biopsy-confirmed acute rejection that required treatment, which was the primary endpoint. Graft and patient survival rates were similarly high in both treatment groups.

Corticosteroid-free immunosuppression was feasible for most patients in the Tac / Dac group, with 96.9% (251 / 259) receiving tacrolimus monotherapy at the end of the study. Moreover, the incidence of acute rejection was comparable with other randomized, multicenter liver transplantation studies that used tacrolimus-based immunosuppression. The 3-month incidences of overall (including spontaneously resolving) biopsy-confirmed acute rejection were 28.5% in the Tac / steroids group and 27.6% in the Tac / Dac group in the present study. The incidences of biopsy-confirmed acute rejections are lower than those reported in a previous study comparing a Tac / steroids dual regimen with cyclosporin-microemulsion plus steroids (36.1 vs. 40.0%, respectively; P = not significant).[10]

A substantial number of acute rejections reversed under increased doses of tacrolimus without the need of steroids. The results of a French pilot study[16] showed that by using increased tacrolimus doses alone, early acute rejection episodes, including the severe grade, can be resolved, while tacrolimus toxicity remains limited.

In addition, the incidence of corticosteroid-resistant biopsy-confirmed acute rejection was significantly lower in the Tac / Dac group than in the Tac / steroids group. This is consistent with a study, which showed that the use of anti-interleukin-2-receptor monoclonal antibody induction therapy reduced the incidence of corticosteroid-resistant acute rejection during the first 3 months after liver transplantation in patients receiving a cyclosporin / corticosteroid / azathioprine triple regimen.[11]

In general, the pattern of adverse events was similar in both treatment groups. However, there was a significantly higher incidence of posttransplant diabetes mellitus in the Tac / steroids group compared with the Tac / Dac group. It is also worth noting that the mean serum cholesterol level was 16% higher by the end of the study compared with baseline in the Tac / steroids group, but was unchanged in the Tac / Dac group. The higher incidence of diabetes mellitus and elevated serum cholesterol concentrations in the Tac / steroids group can be attributed to corticosteroid administration. Indeed, a previous study with liver transplant patients found an association between early corticosteroid withdrawal from immunosuppressive regimens and a lower incidence of diabetes mellitus as well as lower serum cholesterol levels.[12] Diabetes mellitus and hypercholesterolemia are risk factors for cardiovascular disease, which is a major cause of posttransplant mortality.[2] A corticosteroid-free Tac / Dac regimen may, therefore, improve long-term transplant outcome by reducing the cardiovascular risk. A longer follow-up period would be necessary to determine the effect on long-term morbidity and mortality.

Infection, including cytomegalovirus infection, is another common and potentially serious complication in transplant patients.[13] The incidence of cytomegalovirus infection, as well as the overall incidence of viral infections, was significantly higher in the Tac / steroids group compared with the Tac / Dac group. This may indicate overimmunosuppression with corticosteroids,

although the overall incidence of other types of infection was similar in both treatment groups.

Importantly, there was no increased risk of renal toxicity with the Tac / Dac regimen. Patients in this group did not require higher daily doses of tacrolimus to compensate for the absence of corticosteroids—in fact, the mean daily dose of tacrolimus was slightly lower in the Tac / Dac group throughout the study—and overall renal function, as assessed by the measurement of serum creatinine levels, was within the normal range in both groups.

Noncompliance with immunosuppressive therapy remains a major factor contributing to organ rejection in transplant recipients.[14,15] Restricting the role of corticosteroids to rescue therapy will minimize the overall risk of corticosteroid-related adverse events and simplify immunosuppressive regimens. A Tac / Dac regimen may therefore improve long-term tolerability and patient compliance.

In conclusion, adult liver transplant patients receiving tacrolimus monotherapy with daclizumab induction treatment are not exposed to a greater risk of acute rejection compared with a standard Tac / steroids dual regimen. Patient and graft survival was high in both groups. The tacrolimus / daclizumab regimen showed advantages in terms of a lower incidence of corticosteroid-resistant acute rejection, and lower incidences of posttransplant diabetes mellitus and viral infection.

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