Steroid avoidance in liver transplantation
José Oberholzer MD, Mohammed Al-Saghier MD, Norman M Kneteman MD

Corticosteroids have always played a valuable role in transplantation. Unfortunately, they are subject to a wide range of side effects, such as hyperlipidemia, hypertension, diabetes mellitus, osteoporosis, growth retardation and Cushingoid appearance. Steroids may also exacerbate problems that existed before surgery, including malignancy, hepatitis B and hepatitis C. New, powerful immunosuppressants have allowed steroid use to be reduced or avoided altogether, but use of these regimens is not simple and may be associated with late acute rejection and recurrence of autoimmune disease. The present review examines the rationale for steroid avoidance in liver transplantation and assesses the new regimens that are currently being developed.

Key Words: Immunosuppression; Liver transplantation; Mycophenolate mofetil; Steroids

A variety of nonsteroidal immunosuppressive agents have become available, thereby increasing interest in effective strategies that reduce the use and considerable morbid impact of corticosteroids.

STEROIDS IN PEDIATRIC TRANSPLANT RECIPIENTS
Most steroid-induced side effects seen in adults are also encountered in children. In addition, growth retardation and Cushingoid features are of particular concern in the pediatric transplant population.

Growth retardation
Growth after transplantation is determined by a variety of factors, including the underlying disease, pretransplant nutritional status, post-transplant complications and the nature of the immunosuppressive regimen. Steroids inhibit the growth of children undergoing solid organ transplantation (12). Although the underlying mechanisms have not been completely elucidated, an inverse correlation between the degree of suppression of endogenous cortisol production and growth velocity has been described (13).

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Steroid withdrawal in pediatric liver transplant recipients was described as early as 1989 by Margarit et al (14). In this pilot trial, patients were given cyclosporine (CsA)- and prednisolone-based immunosuppression. Prednisone dosage was reduced every second week by 0.1 mg/kg/day, reaching 0.2 mg/kg/day at month 6 after transplantation; thereafter, steroids were withdrawn within two months. Five of the 15 patients presented with a cellular rejection episode and two patients developed chronic rejection requiring retransplantation.

Dunn et al (15) attempted steroid withdrawal in 28 of 37 children beyond 18 months after liver transplantation on CsA-based immunosuppression. Increased growth velocity was observed after steroid withdrawal. Three of the 28 children experienced cellular rejection, requiring the reintroduction of steroids. Subsequent studies using tacrolimus showed that steroids could be withdrawn safely in most pediatric liver transplant recipients with an acceptable risk of reversible rejection of approximately 30% (16), and a beneficial effect on growth (17). Growth velocity after liver transplantation seems to be inversely related to the cumulative yearly steroid dosage (expressed as mg/kg); after steroid withdrawal, it returns nearly to normal (18).

**Cushingoid side effects**

Physiognomic disfigurement induced by corticosteroids is a significant problem in pediatric organ transplant recipients, especially female adolescents, and may result in nonadherence with treatment. Work involving kidney transplant recipients suggests that the development and persistence of Cushingoid features may be related to decreased total body clearance of prednisolone (19,20), which in turn may be due to impaired renal or hepatic function. Minimizing steroid dosage may improve both quality of life and adherence in children and adults.

**DIABETES MELLITUS**

Post-transplant diabetes mellitus (PTDM) occurs in up to 20% of patients undergoing organ transplantation (21). On the other hand, diabetes mellitus may be a complication of end-stage liver disease, which can improve after liver transplantation. A study from Berlin found that 66 of 618 patients were diabetic before transplantation and that, in 37 (56%) of these cases, it seemed to resolve after the procedure (22).

New-onset glucose intolerance and diabetes mellitus are major problems after liver transplantation. Several risk factors have been identified, including obesity, genetic predisposition to type II diabetes (23), hepatitis C virus (HCV) infection (24) and calcineurin inhibitors (CNIs) (25). New-onset PTDM was observed in 39 of 552 patients (7.2%) in the Berlin series (22).

In a recent retrospective analysis, Baid et al (26) showed that the prevalence of PTDM was significantly associated with HCV positivity (64% versus 28%, P=0.0001). Among HCV-positive patients, cumulative mortality was significantly higher in patients with PTDM (56% versus 14%, P=0.001). HCV infection and methylprednisolone boluses were found to be independent risk factors for the development of diabetes mellitus after transplantation (26).

It is widely accepted that steroid withdrawal is beneficial for glucose homeostasis (27-29), although the Berlin study (22) failed to show a difference in the prevalence of diabetes mellitus between conventional and steroid-free regimens (10.4% versus 12.5%, respectively). Animal studies in islet transplantation have shown that steroids dramatically exacerbate the diabeticogenic potential of CNIs (30).

PTDM worsens the long-term prognosis of transplant recipients (31). Insulin-dependent diabetes mellitus is a major risk factor for cardiovascular disease, which is the leading cause of long-term morbidity and mortality in liver transplant recipients (22).

**STEROIDS AND RECURRENCE OF VIRAL HEPATITIS**

**Hepatitis B**

In vitro data indicate that steroids, but not azathioprine, tacrolimus or CsA, increase the expression of viral antigen in cultured hepatocytes isolated from hepatitis B virus (HBV)-infected patients (32,33). Petersen et al (34) showed that steroids increase the replication rate of woodchuck hepatitis virus in a mouse model of hepatocyte xenotransplantation. In clinical practice, the impact of steroids on HBV recurrence after liver transplantation is not clear, but several observations outside the context of transplantation support the view that they have an adverse effect on the course of HBV infection. Pilot studies indicate that steroids increase the rate of HBV replication in patients with chronic, but not acute, hepatitis (35,36). Severe forms of hepatitis have been observed in HBV carriers who were given steroids for the treatment of hematological malignancy (37,38).

Modern antiviral strategies, including lamivudine and hepatitis B immune globulin, have greatly reduced the rate of HBV recurrence after liver transplantation (39-43).

**HCV**

To date, there is no completely effective treatment for HCV, and recurrence after transplantation is universal (44). HCV reinfection after liver transplantation significantly impairs patient and graft survival (45-47), particularly if it occurs early (48,49).

The pathogenesis of HCV recurrence after liver transplantation is poorly understood. The severity of its impact on the liver graft probably depends on both the pathogenicity of the virus and the immune responsiveness of the recipient. Although the former may be related to the viral genotype (45,50), the viral load is also likely to influence the course of HCV recurrence (51,52). A retrospective analysis of the consequences of using OKT3 (Jansen-Ortho, Canada) (for steroid-resistant liver graft rejection) showed that increased immunosuppression contributes to poor outcome in HCV-infected recipients (53). Both experimental and clinical data indicate that immunosuppression, especially with steroids, increases the severity of HCV recurrence by affecting the viral load and the immune responsiveness of the recipient (54,55).

A four- to 10-fold increase in serum HCV RNA levels has been documented after the administration of methylprednisolone to treat acute rejection (56), and other investigators have also shown that steroids boost HCV replication (56-59). However, no correlation was found between quantities of genomic HCV RNA in serum and relative intrahepatic viral replication, either before or after liver transplantation (52).

Therefore, it is possible that the increased HCV RNA levels observed after steroid treatment are due to decreased immune-mediated viral clearance, rather than to increased viral replication.

Thus far, there are no conclusive clinical data comparing steroid-free immunosuppressive protocols with classical regimens that include steroids (60). A retrospective analysis by Brillanti et al (55) suggests that long-term steroid therapy,
slowly tapered over time, may actually prevent the most aggressive forms of recurrent HCV disease in liver transplant recipients. Only preliminary data are currently available from ongoing comparative studies investigating the effects of early steroid withdrawal or complete steroid avoidance on HCV recurrence (60,61).

STEROIDS AND RECURRENCE OF LIVER MALIGNANCIES

Liver transplantation is an excellent therapeutic option for selected patients with hepatocellular carcinoma (62-64), although immunosuppression likely accelerates recurrence. In a recent retrospective multivariate analysis (64), the amount of CsA given in the first 12 months post-transplantation and the tumour stage (according to the International Union Against Cancer Tumour, Node, Metastases [TNM] classification system) were independent prognostic factors for tumour recurrence. A high dosage of CsA administered during postoperative months three to 12 was associated with a significantly lower recurrence-free survival. A cut-off in the cumulative CsA dosage was determined by applying a receiver-operating characteristic curve. Recurrence-free survival at five years was 78% for patients receiving more than 116,834 mg of CsA in the first 12 postoperative months, compared with 93% for those receiving lower dosages. The same retrospective analysis found that the cumulative dosage of steroids and azathioprine administered during the first postoperative year was not correlated with tumour recurrence. Moreover, immunosuppressive regimens that included CsA, azathioprine and steroids had similar effects to those that included only CsA and steroids, and that CsA was equivalent to tacrolimus (64).

It has been found that recurrent hepatocellular carcinomas grew significantly more quickly in transplant recipients under immunosuppression than in patients with the same disease who underwent liver resection without transplantation (65). CsA also accelerates tumour progression in animal models of hepatocellular carcinoma (66).

On the other hand, the effect of steroids per se on tumour recurrence has not been extensively investigated. Early clinical trials suggested that discontinuation of corticosteroids soon after transplantation may reduce recurrence rates (62). In a retrospective analysis by the Milan group (67), steroid treatment beyond six months after transplantation increased the risk of tumour recurrence fourfold. Patients weaned from steroids at six months post-transplantation and maintained on CsA monotherapy (43 cases) or on CsA plus azathioprine (four cases) had four-year tumour-free survival rates of 86% and 75%, respectively, whereas patients on CsA and steroids (22 cases) or azathioprine (nine cases) had four-year tumour-free survival rates of 44% and 37%, respectively. Controlled trials on the impact of steroid withdrawal or steroid avoidance on tumour recurrence have not yet been reported.

These clinical and experimental data indicating a relationship between CNIs and tumour recurrence suggest that the recommendation of steroid avoidance in favour of increasing the CNI dosage should be approached with caution. Steroid withdrawal should serve to decrease the total immunosuppressive load, which may be one of the most important determinants of tumour recurrence. If steroid tapering or avoidance are unlikely to increase the risk of organ rejection, then regimens that reduce or avoid the use of steroids and CNIs would be appropriate for patients undergoing transplantation for liver malignancies. Newer agents with antitumour activity, such as sirolimus (68,69), may have theoretical advantages but need further exploration.

Steroid avoidance has only recently been introduced in liver transplantation. Long term follow-up studies, ideally prospective trials, are needed to evaluate its impact on tumour recurrence.

APPROACHES TO STEROID AVOIDANCE

Although most candidates for liver transplantation are prone to steroid-induced side effects (Figure 1), some are at particularly high risk. Patients with cholestatic liver disease frequently have osteoporosis even before transplantation, and this would be adversely affected by steroid therapy. HCV and obesity are both associated with an increased risk of PTDM. Given the overall risk of PTDM of 10% to 15% and the fact that it may not be reversible with steroid withdrawal, one could argue for the routine avoidance of steroids, unless a contrary argument exists.

Despite the availability of more potent immunosuppressents, steroids continue to be used in the short or long term in most liver transplantation protocols. The use of such agents as tacrolimus and mycophenolate mofetil (MMF) allows most patients to taper off steroids, or avoid them altogether, without increasing the risk of immunological graft loss.

Steroid withdrawal or avoidance may not always be possible. For example, steroid reintroduction may be necessary for late rejection episodes, recurrent autoimmune disease or renal impairment due to CNIs. Other medical conditions, such as inflammatory bowel disease in patients with primary sclerosing cholangitis, may require chronic steroid treatment. In the majority of cases, however, steroid withdrawal can be attempted safely, and its reintroduction always remains an option (70).

Several trials have shown that steroid therapy can be successfully withdrawn shortly after liver transplantation, thereby decreasing cardiovascular risk factors and improving bone metabolism (29,71-73). Other investigators have reported less of an impact (74,75) (Tables 1 and 2). Unfortunately, most studies have been small and either uncontrolled or retrospective; caution must be used when interpreting the results.
Steroid avoidance – too much of a good thing?

There are several advantages to the complete avoidance of corticosteroids after liver transplantation. Especially important are the prevention of increased viral replication early after transplantation and the prevention of side effects, such as osteoporosis and atherosclerosis, that last long beyond withdrawal. The rejection rate appears to be low with appropriate use of newer immunosuppressive agents, and these agents can reverse acute rejection episodes. These theoretical advantages have to be carefully balanced against the potential risks of increasing nonsteroidal immunosuppression, such as greater nephrotoxicity associated with CNIs (76), a higher incidence of viral infections (eg, cytomegalovirus, Epstein-Barr virus, post-transplantation lymphoproliferative disorder and HCV) with MMF (77) and severe hepatitis C with the use of anti-IL-2-receptor antibodies (78).

Early studies of complete steroid avoidance in liver transplantation yielded various success rates; a significant number of patients subsequently required steroid treatment for rejection (58,79). The first trials in liver transplantation using steroid-free immunosuppressive protocols are summarized in Table 3.

In an uncontrolled trial, Ringe et al (76) treated 30 patients with tacrolimus, MMF and intraoperative steroids, but no steroids after transplantation. The incidence of acute rejection in this trial was 26%, and all episodes were reversed with short-term steroid administration (17 patients received steroids temporarily or permanently). Only 13 of 30 patients (43%) in their series never received steroids after liver transplantation. Nevertheless, 73% were ultimately maintained on steroid-free immunosuppression at two years. Ten patients presented within the first two months after transplantation with renal impairment requiring hemofiltration. In seven patients, renal failure was associated with high tacrolimus levels (20 µg/L or greater).

Of particular interest is the randomized, controlled study of 71 patients by Eason et al (80). Rabbit antithymocyte globulin, without steroids, was compared with the combination of steroids, tacrolimus and MMF. Seven of the 36 patients randomized to receive antithymocyte globulin experienced rejection, which resolved in all cases after the dosage of tacrolimus was increased.

<table>
<thead>
<tr>
<th>Reference (year), n</th>
<th>Immunosuppression</th>
<th>Time of SW</th>
<th>Frequency of rejection</th>
<th>Rate of SW*</th>
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<td>Margarit et al (14) (1989), n=18</td>
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<td>12/154 (7.8%)</td>
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<td>CsA + AZA + P (n=31) versus CsA + AZA (n=33) (randomized)</td>
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<td>Gomez et al (29) (1998), n=86</td>
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*Percentage of patients ultimately withdrawn from steroids. AZA Azathioprine; CsA Cyclosporine; P Prednisone; Sir Sirolimus; Tac Tacrolimus

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<td>&gt;2 weeks</td>
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### Table 1

Studies on late steroid withdrawal (SW) after liver transplantation

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### Table 2

Studies on early steroid withdrawal (SW) after liver transplantation

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<th>Reference (year), n</th>
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<td>58/71 (82%)</td>
<td>Early SW decreased post-transplant diabetes, hypercholesterolemia and hypertension compared with historical control (CsA + P)</td>
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<td>Trotter et al (82) (2001), n=39</td>
<td>Tac + Sir (n=17) or CsA + Sir (n=22)</td>
<td>3 days</td>
<td>10/33 (30%)</td>
<td>26/33 (79%)</td>
<td>Compared with historical control: identical patient and graft survival rates, less rejection, less need for OKT3</td>
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TABLE 3
Prospective studies on steroid avoidance in liver transplantation

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<tr>
<th>Reference (year), n</th>
<th>Immunosuppression</th>
<th>Rate of rejection with steroid treatment</th>
<th>Rate of long-term steroid treatment</th>
<th>Remarks</th>
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</thead>
<tbody>
<tr>
<td>Tsone et al (58) (1999), n=45</td>
<td>CsA + AZA + P (n=22) versus CsA + AZA (n=23) (randomized)</td>
<td>10% (2/19) in each group (3 and 4 early deaths in the steroid and control group unrelated to rejection)</td>
<td>0% in both groups beyond three months after transplantation</td>
<td>Patients in the steroid avoidance group showed lower levels of alkaline phosphatase and gamma-GT early post-transplant, lower lipid levels, and less diabetes</td>
</tr>
<tr>
<td>Rolles et al (79) (1999), n=64</td>
<td>CsA (n=34) versus Tac (n=30) monotherapy (randomized)</td>
<td>14/34 (42%) (CsA group); 18/30 (60%) (Tac group)</td>
<td>36% (CsA group); 13% (Tac group) after median follow-up of 26 (range 19 to 33) months</td>
<td>Only eight patients in each group did not receive any steroids</td>
</tr>
<tr>
<td>Watson et al (81) (1999), n=15</td>
<td>Sir + CsA + P (n=4) versus Sir + CsA (n=7) versus Sir (n=4)</td>
<td>3/4 (Sir group); 2/7 (Sir + CsA group)</td>
<td>0% beyond 3 months after transplantation</td>
<td>High mortality in this pilot study (five of 15 patients died)</td>
</tr>
<tr>
<td>Ringe et al (76) (2001), n=30</td>
<td>Tac + MMF pilot study</td>
<td>8/30 (26%)</td>
<td>8/30 (27%) after mean follow-up of 597 (range 44 to 1224) days</td>
<td>Renal impairment in 30% of patients consequent to higher Tac levels</td>
</tr>
<tr>
<td>Eason et al (80) (2001), n=71</td>
<td>RATG + Tac + MMF (n=36) versus Tac + MMF + P (n=35) (randomized)</td>
<td>0% (RATG group); 7/36 (20%) (steroid group)</td>
<td>0% at any time point in the steroid-free group</td>
<td>In the steroid-free group, the study showed a trend toward a lower rejection rate, decreased incidence of postorthotopic liver transplantation diabetes, less recurrent hepatitis C and decreased CMV infection</td>
</tr>
</tbody>
</table>

AZA Azathioprine; CMV Cytomegalovirus; CsA Cyclosporine; GT Glutamyltransferase; MMF Mycophenolate mofetil; P Prednisone; RATG Rabbit antithymocyte globulin; Sir Sirolimus; Tac Tacrolimus

was increased. None of these patients required steroids. The long-term prevalence of renal dysfunction and post-transplantation lymphoproliferative disorder are not yet reported in this patient group.

Three preliminary studies of sirolimus have been conducted (81-83). In a pilot study (81) of 15 patients, acute rejection occurred in two of seven patients (29%) receiving CsA and sirolimus but no steroids; in none of four patients treated with CsA, sirolimus and steroids (for 42 to 84 days); and in three of four patients on steroid-free sirolimus monotherapy. Two of the patients in the last group had steroid-resistant rejection. Four patients required dialysis in the early postoperative period. In a pilot study of early steroid withdrawal, 39 patients were randomized to sirolimus and either CsA or tacrolimus, and all patients received a tapering schedule of methylprednisolone for three days (82). Rejection was experienced by 10 of 33 patients (30%), and comparison with a historical control showed similar results for patient and graft survival. A third study was a nonconsecutive series of 36 patients treated with tacrolimus, sirolimus and steroids (83). Steroids were discontinued between three and 12 months after surgery in 91% of patients, and were restarted for immune suppression in one patient and for colitis exacerbation in another. The incidence of acute rejection was 14%. Sirolimus dosage reduction was required in 22 patients, primarily for hematological abnormalities, and there was one episode of hepatic artery thrombosis. This combination allowed a reduction of the tacrolimus dosage, which resulted in improved renal function compared with conventional tacrolimus or CsA use in this population.

**CONCLUSIONS**

Corticosteroids have historically been part of immunosuppression regimens in liver transplant recipients. There are ample accumulated data to document the adverse effects of steroids in important patient groups. Steroids have been reported to adversely affect HBV, HCV and hepatocellular carcinoma, and to promote the development of PTDM and metabolic bone disease. Nevertheless, well-structured prospective trials documenting the benefits of steroid avoidance or early withdrawal are lacking.

More recent studies with CNIs and more potent adjuvant agents, such as MMF and sirolimus, with or without induction therapy, suggest that complete steroid avoidance is achievable, with acceptable rates of rejection. These studies suggest that steroid avoidance may be at least as easily achievable as steroid weaning. New immunosuppressive agents will need to be equally easy to handle and monitor, and be comparable with steroids in cost. Prospective randomized trials are needed to determine the role of steroids and how to balance efficacy in preventing rejection, the risk of disease recurrence and safety.

**REFERENCES**


