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# Long-term immunosuppression after liver transplantation: are steroids necessary?

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**Abstract.** Steroid therapy was withdrawn in 85% of 152 orthotopic liver transplant recipients with grafts surviving for more than 3 months, and 87% of these remained steroid-free. Steroid therapy was restarted in 8% for reasons other than rejection. The most common was conversion of immunosuppression because of cyclosporine nephrotoxicity. The incidence of rejection after steroid withdrawal was low: 3.8% for chronic rejection (CR) and 4.5% for acute rejection. Only 3 grafts (1.9%) were lost because of CR. No risk factors have been identified for the development of CR after steroid withdrawal, but a protective role for azathioprine has been suggested.

**Key words:** Immunosuppression – Steroids – Liver transplantation

Maintenance immunosuppression (IS) after orthotopic liver transplantation (OLT) in the cyclosporine (CyA) era has consisted of CyA in combination with prednisolone (PRED) or PRED and azathioprine (AZA). Long-term IS without steroids is not widely practised in liver transplant recipients.

Long-term IS without steroids is possible in approximately 30%–50% of kidney recipients [1–4]. Cessation of steroids at 3–6 months in patients with stable graft function has been achieved at the expense of higher rates of rejection, but with no difference in long-term patient or graft survival. In one randomised controlled trial, there was a significant reduction in the incidence of steroid-related complications in the patients who remained free of steroids [1].

It has been the policy of the Birmingham unit to taper the PRED dose down to withdrawal from the IS regimen by the end of the 3rd postoperative month. The aims of this study were to examine the rate of graft rejection in patients after cessation of PRED and to identify retrospectively risk factors for the development of chronic rejection (CR) in this cohort.

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## Materials and methods

*Patients and grafts.* There were 312 grafts in 271 adult (>15 y) patients transplanted between Jan 1982 and June 1990 (M:F = 32%:68%). A total of 197 (63%) grafts in 177 patients (65%) survived for more than 3 months and were therefore eligible for steroid withdrawal. PRED was stopped in 168 (85%) of these grafts. Reasons for the non-withdrawal of PRED are given in Table 1.

In 14 grafts steroids were recommenced for reasons other than rejection (Table 2); it is the remaining 154 grafts in 152 patients (M:F = 31%:69%; median age 48 years, range 16–68) that were studied (i.e. in patients in whom PRED had been stopped and was restarted only if a rejection episode occurred). In this group there were 143 first grafts, 10 second grafts, and 1 third graft.

*Immunosuppression.* There were 2 induction IS protocols used during this period, the details of which are given in Table 3. Episodes of acute rejection were treated with 200 mg p. o. prednisolone for 3 consecutive days and repeated if necessary for incomplete resolution.

**Table 1.** Reasons for non-withdrawal of steroids at 3 months after transplantation

| | No. of patients |
|---|---|
| Early ductopoenic rejection | 8 |
| Poor condition and biliary complications | 7 |
| Previous graft loss (rejection) | 3 |
| Followed elsewhere | 3 |
| Miscellaneous | 3 |
| Unknown | 3 |

**Table 2.** Reasons for recommencement of steroids

| | No. of patients |
|---|---|
| CyA nephrotoxicity | 6 |
| CyA neurotoxicity | 1 |
| Musculoskeletal pain | 4 |
| Colitis | 2 |
| Other | 1 |

CyA, cyclosporine A

**Table 3.** Immunosuppression protocols

| | 1982–1987 Double | Route of application | 1987→ Triple |
|---|---|---|---|
| Induction | | | |
| Hydrocortisone | 200 mg/day | p.o. | 200 mg/day |
| Prednisolone | 20 mg/day | p.o. | 20 mg/day |
| CyA | 2–5 mg/kg | i.v. | 2 mg/kg |
| | 10–15 mg/kg | p.o. | 10 mg/kg |
| AZA | | | 1–1.5 mg/kg |
| Prednisolone reduction | | 20 mg for weeks 1–3<br>15 mg for weeks 4–6<br>10 mg for weeks 7–9<br>5 mg for weeks 10–12<br>cease at week 12 | |
| Maintenance | CyA alone | | CyA alone or CyA + AZA |

AZA, azathioprine

**Table 4.** Primary indications for orthotopic liver transplantation in study cohort

| Primary diagnosis | Frequency | Chronic rejection |
|---|---|---|
| Primary biliary cirrhosis (PBC) | 72[a] | 1 |
| Fulminant | 23[a] | 1 |
| Primary sclerosing cholangitis | 13 | 2[b,c] |
| Cryptogenic cirrhosis | 13 | |
| Tumours | 12 | 2[b] |
| Metabolic | 8 | |
| Hepatitis B | 6 | |
| Autoimmune CAH | 3 | |
| Budd-Chiari syndrome | 3 | |
| Other | 1 | |

[a] One patient had 2 grafts
[b] NS compared with PBC
[c] One patient had an incidental cholangiocarcinoma

**Table 5.** Influence of the severity of acute rejection

| Acute rejection | Chronic rejection | No chronic rejection |
|---|---|---|
| None/mild, no treatment | 2 | 31 |
| Mild-moderate | 4 | 75 |
| Moderate-severe | 0 | 35 |

For severe or recurrent episodes 1 g methylprednisolone i.v. was given. OKT3 was given if the rejection was steroid-resistant (that is, failure to respond to 2 courses of increased quantities of steroids).

PRED was stopped at 3 months or later if the graft function was not stable at this time (median 3 months, range 1–15). AZA, used as part of the triple therapy protocol from 1987 onwards, was stopped in some patients and continued in others at the discretion of the attending consultant (mean 3 months range 1–32; $n = 67$). In 57 grafts, the long-term IS regimen was CyA and AZA double therapy, and in the other 97, CyA monotherapy (induction IS: 30 CyA + PRED; 67 CyA + AZA + PRED). The CyA dose was adjusted to maintain whole blood levels between 100 and 250 ng/ml as measured by monoclonal whole blood radioimmunoassay.

*Biopsies, follow-up, and rejection.* Percutaneous biopsies were performed routinely 7 days post-OLT and as clinically indicated thereafter. Protocol biopsies were also performed during patient readmission for annual review.

Follow-up in these patients was continued until July 1991, giving a minimum potential follow-up of 12 months (actual follow-up mean 28 months, range 5–109). At 12 months or later biopsies were obtained in 137 grafts (mean 24 months, range 8–78). In 8 grafts the biopsies were either contraindicated or the patients refused, and in a further 9, death or graft loss occurred prior to 12 months.

Definitions of graft rejection were as follows:

Acute rejection (AR) histological features of acute cellular rejection with biochemical changes (bilirubin, aspartate aminotransferase, AST, and alkaline phosphatase, ALP). Episodes of AR were graded histologically as mild, moderate, or severe [5].

Chronic rejection, histological features of chronic or ductopoenic rejection [5] with biochemical changes.

*Risk factors.* The following risk factors for the development of CR were examined (comparisons by univariate analysis, $\chi^2$ or Fisher's exact test; significance level $P = 0.01$): the primary indication for OLT, previous AR, previous OKT3 for steroid-resistant rejection, retransplantation, ABO blood group donor/recipient match, cytomegalovirus (CMV) infection, and maintenance CyA monotherapy versus CyA/AZA double therapy.

## Results

### *Rejection*

There were 13 episodes of rejection in 12 grafts (8%) after steroid withdrawal. Five grafts developed CR (mean 4.5 months, range 1–44 after PRED withdrawal), 6 grafts developed AR (mean 7 months, range 1 week–33 months), and 1 graft developed AR at 33 months, which resolved, but CR appeared 11 months later. This gives a CR and AR rate of 3.8% and 4.5%, respectively.

Steroids were restarted in 8 of these patients (5%) either permanently or until resolution of the rejection episode. Therefore, of the original 168 who ceased taking PRED, 146 (87%) remained steroid-free.

The AR resolved in all 7 grafts. Of the 6 grafts developing CR, 1 resolved, 2 were regrafted (1 of whom died), 1 is awaiting regraft, and 2 died, principally because of recurrent tumour, but with histological evidence of CR in postmortem sections of the liver. Thus, excluding these latter 2 patients, the incidence of graft loss due to rejection was 1.9% and patient loss, less than 1%.

### *Risk factors*

The primary indications for OLT in the 154 grafts are listed in Table 4. In all, 121 grafts had an episode of treated AR prior to the cessation of PRED (Table 5). None of the grafts which had had a moderate/severe acute rejection developed CR after steroid withdrawal. Moreover, in 5 of these grafts, OKT3 had been used for steroid-resistant rejection. Similarly, CR did not occur in any of the 11 regrafts in this series, 5 of whom had been regrafted because of CR.

Five of the grafts with CR were from the set of 137 ABO blood group identical donor/recipient matches. CR developed in 1 of 4 with an ABO mismatch, and there was no CR in 11 with an ABO compatible match (NS).

A symptomatic cytomegalovirus (CMV) infection occurred in 15 patients. Two of these patients developed CR compared with 4 of the remaining 139 (NS).

CyA monotherapy was the IS regime in all 6 patients with CR versus none of the 57 on CyA and AZA double therapy ($P = 0.058$, NS).

## Discussion

It is clear from this study that the cessation of steroid therapy is a safe undertaking in OLT recipients. The incidence of CR developing in grafts in this series (3.8%) is identical to the incidence of CR developing after 3 months in patients maintained on 10–20 mg/day of PRED as reported by Klintmalm and associates [6]. Furthermore, the incidence of AR of 4.5% in the present series compares favourably with an incidence of 7.7% (8/104) occurring after 3 months in their patients. While these 2 groups of patients are not necessarily directly comparable, it is apparent that withdrawing steroids after 3 months, or when graft function is stable, does not lead to an increased rate of rejection.

This is in contrast to the experience with renal grafts. Rejection may occur in 24%–47% of renal recipients following steroid withdrawal [1, 2], although long-term patient and graft survival is not compromised. Moreover, successful steroid withdrawal may be achieved in a greater proportion of liver recipients. Some 56% of renal recipients in whom steroid therapy was withdrawn remained steroid-free [3] (representing 43% of all recipients with a primary functioning graft), whereas 87% of the liver recipients in the present series did not require further steroids.

There were no definite risk factors identified for the development of CR after steroid withdrawal. A protective effect of AZA on ductopoenic rejection has been previously described by van Hoek et al. [7], and it is possible that the rejection rate may have been reduced if all patients had remained on CyA and AZA double therapy. However, because the rate of CR is low, further follow-up of these patients is required to determine whether or not there is a clinically significant difference.

It is noteworthy that a number of the risk factors examined may have been considered contraindications to steroid cessation. Grafts in which there had been a previously moderate to severe AR, steroid-resistant AR, and even regrafts, some of which were for CR, were not more susceptible to the development of CR after steroid withdrawal. We propose that the most important factor is stable graft function and that once this has been achieved, steroids may be successfully withdrawn in almost all patients.

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