USE OF TACROLIMUS IN RESCUE THERAPY OF ACUTE AND CHRONIC REJECTION IN LIVER TRANSPLANTATION

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PURPOSE: To study the indications and results of tacrolimus as rescue therapy for acute cellular or chronic rejection in liver transplantation.

PATIENTS AND METHODS: Eighteen liver transplant recipients who underwent rescue therapy with tacrolimus between March 1995 and August 1999 were retrospectively studied. The treatment indication, patients, and graft situation were recorded as of October 31st, 1999. The response to tacrolimus was defined as patient survival with a functional graft and histological reversal of acute cellular, or for chronic rejection, bilirubin serum levels decreasing to up to twice the upper normal limit.

RESULTS: Fourteen cases (77.8%) presented a good response. The response rate for the different indications was: (1) acute cellular + sepsis - 0/1 case; (2) recurrent acute cellular - 1/1 case; (3) OKT3-resistant acute cellular - 2/2 cases; (4) steroid-resistant acute cellular + active viral infection - 3/3 cases; (5) chronic rejection - 8/11 cases (72.7% response rate). The 4 patients who did not respond died.

CONCLUSION: Tacrolimus rescue therapy was successful in most cases of acute cellular and chronic rejection in liver transplantation.


After the advent of cyclosporin in 1980, the survival rate of patients undergoing liver transplantation (LTx) improved dramatically. At our unit, cyclosporin in combination with azathioprine and corticosteroids constitutes the drug of choice for immunosuppressive therapy in LTx. With this therapeutic regimen, about 30% of the patients undergoing LTx presented episodes of acute cellular rejection (ACR). Recent studies have shown that up to 13% of the episodes of ACR are refractory to the standard treatment with corticosteroids. For this reason, ACR continues to be a cause of graft loss.

The most widely used agent in the treatment of steroid-resistant ACR is OKT3, a monoclonal antibody that blocks lymphocyte-mediated cytotoxicity by binding with the CD3 receptor. However, its use is limited by adverse reactions, by an increased occurrence of opportunistic infectious diseases, and by lymphoproliferative disorders, as well as the high cost. More recently, tacrolimus (FK506) made its appearance as an alternative immunosuppressive drug. It became available in Europe in 1990. FK506 is a macrolide compound isolated from Streptomyces tsukubaensis and has an immunosuppressive potential approximately 100 times more powerful than cyclosporin. The drug acts by binding to cytoplasmic proteins of the lymphocytes, primarily FKBP12, forming a complex that associates with calcineurin. Some direct or indirect substrates of calcineurin act as transcription factors and promote the activation of genes that encode cytokine production.

This activation is dependent on the calcium influx into the cell. The association of calcineurin to the FK506 complex prevents stimulatory signal
transduction, inhibiting the formation of interleukin-2 by the T-lymphocytes and the formation of other soluble mediators, such as interleukin-3 and interferon-γ.11,12

The introduction of FK506 has added an alternative to OKT3 for rescue therapy of steroid-resistant ACR. It also has opened new possibilities for the pharmacological control of chronic liver graft rejection (CR), which until that time, was treated exclusively by retransplantation.13

The purpose of this study was to analyze the indication criteria and the results of employing FK506 in rescue therapy of acute and chronic rejection in LTx.

PATIENTS AND METHODS

All 244 LTx performed at our unit between March 1995 and August 1999 were retrospectively studied. Among these, we identified and analyzed 7 cases of ACR and 11 cases of CR that had been converted to FK506 for rescue therapy.

Eight of the 18 patients who underwent rescue therapy with FK506 were males. The mean age was 39.1 ± 15.4 years (16 to 64 years). The indications for LTx for these patients are shown in table 1.

Table 1 - Indications for liver transplantation in patients undergoing rescue therapy with tacrolimus for acute and chronic rejections.

<table>
<thead>
<tr>
<th>Indications</th>
<th>n</th>
</tr>
</thead>
<tbody>
<tr>
<td>primary sclerosing cholangitis</td>
<td>4</td>
</tr>
<tr>
<td>hepatitis C cirrhosis</td>
<td>4</td>
</tr>
<tr>
<td>acute liver failure</td>
<td>2</td>
</tr>
<tr>
<td>ductopenic disease</td>
<td>1</td>
</tr>
<tr>
<td>primary biliary cirrhosis</td>
<td>1</td>
</tr>
<tr>
<td>alcoholic cirrhosis</td>
<td>1</td>
</tr>
<tr>
<td>cryptogenic cirrhosis</td>
<td>1</td>
</tr>
<tr>
<td>familial amyloidotic polyneuropathy</td>
<td>1</td>
</tr>
<tr>
<td>hemochromatosis</td>
<td>1</td>
</tr>
<tr>
<td>α-1-antitrypsin deficiency</td>
<td>1</td>
</tr>
<tr>
<td>autoimmune hepatitis</td>
<td>1</td>
</tr>
</tbody>
</table>

The primary immunosuppressive therapy for all patients was based on cyclosporin, prednisone, and azathioprine, according to the standard service protocol. According to this regimen, 1 g of methylprednisolone was delivered intravenously at the time of revascularization, and 200 mg of prednisone or methylprednisolone were delivered on the immediate postoperative day (PO). This dosage was tapered to 40 mg/day until the maintenance dosage of 20 mg/day was achieved on the sixth PO. Azathioprine was administered orally, at a daily dosage of 1 mg/kg. Cyclosporin was introduced orally between the first and third PO, 10 mg/kg, divided into 2 daily doses. The dosage was adjusted daily to achieve a target trough blood level between 300 and 350 ng/mL (monoclonal TDX). During the first year PO, the dosage of cyclosporin was progressively reduced to attain a trough blood level of approximately 100 ng/mL. During the same period, the dosage of prednisone was reduced to 5 mg/day. ACR episodes were treated with 1 to 3 pulses of 1 g of methylprednisolone, followed by a 6-day taper from 200 to 20 mg/day.

Rescue therapy with FK506 was individualized in each case. Only the oral formulation of FK506 was used. The initial dosage ranged from 0.1 to 0.3 mg/kg/day, and was adjusted according to the trough blood level. Initially the target blood level was maintained around 15 ng/mL. However, the target level was set on an individual basis according to the patient’s clinical response and the severity of the side effects. One month after conversion, the mean dosage of FK506 was 0.2 ± 0.1 mg/kg/day. During this period, the mean blood level was 13.8 ± 5.9 ng/mL. Corticosteroid administration was maintained in all cases. Five patients received combination therapy with mycophenolate mofetil (MMF) in dosages ranging from 1.0 to 3.0 g/day.

The diagnosis of ACR and CR was suspected because of clinical and laboratory alterations. All ACR episodes
were histologically confirmed. The 11 diagnoses of CR were established using one of the following three criteria: 1- characterization of ductopenia in liver biopsy, in 5 patients (Fig. 1); 2- presence of bile duct damage in the biopsy, with normal cholangiography and hepatic angiography, in 5 cases (Fig. 2); 3- presence of duct aggression with angiographic demonstration of multiple intrahepatic arterial strictures in 1 case (Fig. 3).

Steroid-resistant ACR was defined as the persistence of the clinical, biochemical, and histopathological signs of rejection after treatment with at least 2 pulses of 1.0 g of methylprednisolone. OKT3-resistant ACR was defined as the persistence of the clinical, biochemical, and histopathological signs of rejection after treatment with the drug for at least 10 days.

In the 18 cases studied, the following data were recorded: date of LTx, indication for rescue therapy, date of conversion, follow-up period, and patient and graft situation on October 31st, 1999.

The response to FK506 was defined as patient survival with functional graft and histological reversal of ACR, or for CR, bilirubin serum levels decreasing to up to twice the upper normal limit.

The patients’ actuarial survival rates were calculated using the Kaplan-Meier method.

RESULTS

Five different indications for rescue therapy with FK506T were identified: 1) ACR plus bacterial sepsis (n=1); 2) recurrent ACR (n=1); 3) OKT3-resistant ACR (n=2); 4) steroid-resistant ACR plus active viral disease (n=3); 5) chronic rejection (n=11).

The patient with recurrent ACR presented 4 rejection episodes in a 4-month period. Among the 3 patients with ACR plus active viral disease, 2 presented cytomegalovirus (CMV) hepatitis, and 1 had herpetic gastroenterocolitis.

Table 2 shows the response rate to FK506 for each indication. Fourteen patients (77.8%) were considered “patients who responded”. All 4 patients with no response died. The mean follow-up time after conversion to FK506 was 19.8 months, ranging from 10 days to 48 months.

The 47-month actuarial survival rates were up to 61.5% in cases of CR (Fig. 4). Figures 5, 6, and 7 show the evolution of the serum levels of total bilirubin, alkaline phosphatase, and alanine transaminase (ALT) during the first 12 months of treatment with FK506.
Table 2 - Results: indication for conversion to tacrolimus, percentage of response and mean follow-up.

<table>
<thead>
<tr>
<th>Indication for conversion to tacrolimus</th>
<th>n</th>
<th>Response</th>
<th>Mean follow up (months)</th>
</tr>
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<tbody>
<tr>
<td>ACR + bacterial sepsis</td>
<td>1</td>
<td>0</td>
<td>0.3</td>
</tr>
<tr>
<td>Recurrent ACR</td>
<td>1</td>
<td>1</td>
<td>2.0</td>
</tr>
<tr>
<td>OKT3-resistant ACR</td>
<td>2</td>
<td>2</td>
<td>43.5 (39-48)</td>
</tr>
<tr>
<td>Steroid-resistant ACR + viral infection</td>
<td>3</td>
<td>3</td>
<td>39.3 (31-46)</td>
</tr>
<tr>
<td>Chronic rejection</td>
<td>11</td>
<td>8 (72.7%)</td>
<td>13.5 (0.5-47)</td>
</tr>
<tr>
<td>Total</td>
<td>18</td>
<td>14 (77.8%)</td>
<td>19.8 (0.3-48)</td>
</tr>
</tbody>
</table>

ACR= acute cellular rejection.

DISCUSSION

Several clinical studies have evaluated the effects of FK506 on rescue therapy of CR or ACR in LTx recipients. Most have demonstrated the beneficial effects of the drug, with a success rate of up to 89% for steroid-resistant ACR. Sher et al. obtained a response rate of 70.3% in patients with CR, while Platz et al. reported a success rate of 88.9% in patients with steroid-resistant ACR. In the present study, the response rate was 72.7% and 85.7% in cases of CR and ACR, respectively.

In the present study, the survival rate of the patients undergoing rescue therapy for CR was 61.5% at 2 years (Fig. 4). Sher et al. observed an 81.2% survival rate with the same follow-up, while Jonas et al. obtained a 76% survival rate.

In the present study, only 3 patients (16.7%) were less than 18 years old; the youngest patient was 16. Thus, our results refer basically to an adult population. Other authors, however, have shown positive long-term results with FK506 rescue therapy for pediatric patients. Reyes et al. studying pediatric LTx recipients, obtained a patient survival rate of 78.1%.
RESUMO


OBJETIVO: Estudar os critérios de indicação e o resultado do uso de tacrolimus na terapia de resgate de rejeições agudas ou crônicas no transplante de fígado.

CASUÍSTICA E MÉTODO: Foram estudados 18 pacientes transplantados de fígado, submetidos a terapia de resgate com tacrolimus entre março de 1995 e agosto de 1999. Foram
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registradas a indicação do tratamento e a situação de pacientes e enxertos em 31/10/1999. Considerou-se “respondentes” pacientes vivos, com enxerto funcionante e regressão histológica da terapia de resgate de rejeições agudas, ou com bilirrubina até 2 vezes o valor normal, no caso de terapia de resgate de rejeições crônicas.

RESULTADO: Observou-se resposta em 14 casos (77,8%). A taxa de resposta nas diferentes indicações foi: (1) terapia de resgate de rejeições agudas + sepse bacteriana - 0/1 caso; (2) terapia de resgate de rejeições agudas recorrente - 1/1 caso; (3) terapia de resgate de rejeições agudas resistente a OKT3 - 2/2 casos; (4) terapia de resgate de rejeições agudas resistente a corticóide + doença viral ativa - 3/3 casos; (5) terapia de resgate de rejeições crônicas - 8/11 casos (72,7% de resposta). Os quatro casos sem resposta (22,2%) evoluíram para óbito.

CONCLUSÃO: O tacrolimus é eficaz na terapia de resgate da maioria dos casos de rejeição celular aguda e crônica no transplante de figado.


REFERENCES


