

Single-dose daclizumab induction therapy in patients with liver transplantation

Lu-Nan Yan, Wei Wang, Bo Li, Shi-Chun Lu, Tian-Fu Wen, Qi-Yuan Lin, Yong Zeng, Nan-Sheng Cheng, Ji-Chun Zhao, Yue-Meng Dai

Lu-Nan Yan, Wei Wang, Bo Li, Shi-Chun Lu, Tian-Fu Wen, Qi-Yuan Lin, Yong Zeng, Nan-Sheng Cheng, Ji-Chun Zhao, Yue-Meng Dai, Liver Transplantation Center, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China

Correspondence to: Dr. Lu-Nan Yan, Department of Surgery, West China Hospital, Sichuan University, Chengdu 610041, Sichuan Province, China. yanlunan@hotmail.com

Telephone: +86-28-85422072 **Fax:** +86-28-85423724

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Abstract

AIM: To investigate the efficacy and safety of a single-dose daclizumab induction therapy in orthotopic liver transplantation (OLTx).

METHODS: A retrospective study was made for 54 cases of OLTx in recent three years. The daclizumab group consisted of 23 cases of OLTx who received single-dose of 2 mg/kg intravenously after postoperative 24 hours. The control group consisted of the remaining 31 patients. Additional immunosuppressors included steroids, mycomphenolate mofetil, tacrolimus or microemulsion cyclosporine used in all patients. Meta-statistical analysis was made for general data, incidence of acute rejection and infection, postoperative clinical course, complications and prognosis between two groups.

RESULTS: Pretransplant demographics were not significantly different between two groups. In the induction group there were significantly less acute rejection episodes (5 of 23, 21.74 %) than those in the control group (12 of 31, 38.71 %), which were proved by pathologic diagnosis ($P < 0.05$). The incidence of infection at the early stage was not significantly different between two groups.

CONCLUSION: Induction therapy with single-dose of daclizumab is safe and effective and appears to be able to reduce the incidence of acute rejection.

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INTRODUCTION

One of the key elements for successful liver transplantation is to effectively prevent acute rejection in patients with liver transplantation. Even the routine immunosuppressants such as azathioprin (AZA), cyclosporin (CSA), mycomphenolate mofetil (MMF) and tacrolimus (FK506) were used, the acute rejection rate in liver transplantation was still as high as 30-40 %^[1-3]. Daclizumab, a humanized form of murine monoclonal antibody, has been recently shown to be able to decrease the acute rejection in liver transplanted recipients^[4-7].

In this retrospective study, whether daclizumab induction therapy was effective and safe in orthotopic liver transplantation (OLTx) was evaluated.

MATERIALS AND METHODS

General data

We retrospectively reviewed the results of 54 consecutive OLTx performed from February, 1999 to January, 2002 at the West China Hospital in Sichuan University. There were 44 males and 10 females, their age ranged from 11 to 68 years old (average 38.98 years old). 42 patients had benign hepatic diseases, 29 had cirrhosis due to hepatitis B, 2 had diffuse intrahepatic stones with liver cirrhosis, 1 had alcoholic cirrhosis, 1 had polycystic liver with cirrhosis, 2 had Budd-Chari's syndrome, 3 had unibobar carolis syndrome, 1 had alcoholic cirrhosis and 3 had alveolar echinococcosis. 12 patients had hepatocellular carcinoma. According to the Child's classification, 39 of the 54 patients were grade A, 2 were grade B and 13 were grade C. According to the classification of the united network of organ share (UNOS), 14 were grade I, 40 were grade II.

Among them, 14 cases were performed emergency liver transplantation because of acute hepatic failure with severe jaundice (total bilirubin 129-676 nmol/L), large volume of ascites (2 500-11 000 ml) or severe coagulopathy, and 4 cases had hepatic encephalopathy. 23 patients received induction therapy with daclizumab and 31 patients were managed with conventional immunosuppression (non induction). In the control group (non-induction), oral cyclosporin was administered at a dosage of 6-10 mg/kg/day, starting within 24 hours before the operation. Dosage adjustments were based on achieving serum level of CSA between 200 ng and 300 ng/dL. Patients received methylprednisolone during surgery 200 mg intravenously, which was decreased by 40 mg daily over a period of 5 days. On postoperative day 5, patients started to administer prednisone at 20 mg/day. MMF was administered at a dosage of 0.75 g, twice daily.

In the induction group, daclizumab was given 2 mg/kg intravenously within the postoperative 24 hours, cyclosporin, steroid and MMF were identical to the control group.

Tacrolimus was used in patients with CSA toxicity and occasionally as the primary therapy.

Diagnosis of rejection

Rejection was suspected by biochemical evidence of deteriorating liver function and/or clinical signs. Pathological examination was done in all patients suspected of rejection. The patients in both groups received methylprednisolone every day for the treatment of acute rejection at 500 mg intravenously for 3 days.

Concomitant therapy

The patients in both groups received losec for prophylaxis of stress ulcer (40 mg, intravenously, daily). Cephaloxin was used for postoperative infection prophylaxis. HBV-DNA positive patients were given lamivudine (100 mg, orally, daily). The

patients accompanied by suspected virus infection were treated with acyclovir (800 mg, orally twice daily) or ganciclovir (5 mg/kg, intravenously twice daily).

Liver transplantation

Operative procedures were performed according to standard surgical techniques, and all grafts were perfused with the University of Wisconsin solution^[8]. Veno-venous bypass was used in all cases. Buct-to-duct over a T-tube biliary anastomosis or choledochojejunostomy was performed.

Statistical analysis

All the patients received a minimum follow-up for 60 days. Values of the descriptive variables between groups were compared with a nonparainetric wilcoxon rank sum test. Chi-square test or Fisher exact test was used to evaluate the data of the independent groups.

RESULTS

Survival rate

The general data of patients in this study are shown in Table 1, which were similar in two groups.

Table 1 General data in two groups

	Induction group (n=23)	Non-induction group (n=31)
Average age(yr)	39.17(19-68)	38.76(11-57)
Male/female	21/2	23/8
Indication with		
Liver cirrhosis	15	18
Liver cancer	6	6
Other	2	7
UNOS classification		
Grade I	5	10
Grade II	18	21
Child classification		
Grade A	4	9
Grade B	2	0
Grade C	17	22
Blood type		
ABO-identical	14	23
ABO-compatible	9	8

The 1-, 3-, and 6-month survival rate in patients receiving the induction therapy with daclizumab was 91.3 %, 86.9 % and 86.9 %, respectively vs 90.0 %, 83.9 % and 83.9 %, respectively for patients not receiving induction therapy ($P>0.05$). There was a significant difference between two groups. Six months after the transplantation, 20 of the 23 patients with daclizumab induction were still alive. Deaths occurred in this group were due to the following reasons: complications of intercerebral bleeding (1case), heart failure (1case) and pulmonary infection (1case). In the non induction group, 26 of 31 patients survived for 6 months. Deaths occurred in this group were due to the following reasons: complications of intracerebral bleeding (1case), pulmonary fungus infection (2case), MOF(1case) and recurrent of cancer (1case).

No patients in either group developed primary dysfunction or died of blood vessel complications.

Complications

Complications especially infection were less in the induction group than those in the non induction group, without significant difference (Table 2).

Table 2 Postoperative complications in two groups

	Induction (n=23)	Non-induction (n=31)
Intraperitoneal bleeding	1	3
Ascite infection	0	1
Stress ulcer bleeding	1	3
Stress ulcer perforation	0	1
Pulmonary infection	5	11
Heart failure	1	3
Biliary leakage	1	3
Chronic oral ulcer	2	3
Bowel fungal infection	1	2
Intracerebral bleeding	1	3
Total	13	32

Rejection

Overall, in the first month, acute rejection occurred less in patients of the daclizumab induction group than that in the non-induction group(21.74 % vs 38.71 %, $P<0.05$). None in either group had acute rejection after the first month and occurred chronic rejection during the first 6 months. None in the induction group and one patient in the noninduction group had OKT₃ added to their immunosuppression for intractable rejection.

Tolerance of daclizumab

None in the daclizumab group required reduction of their dose or cessation of daclizumab for side effects. Daclizumab was well tolerated without apparently clinical or biochemical toxicity.

DISCUSSION

In the recent 30-40 years, with the development of organ transplantation biology, many immunosuppressive agents have been introduced to reduce the incidence of acute rejection^[9-12]. The introduction of azathioprine (AZA) was in 1960s by Starzl. Cyclosporin A has (CSA) achieved long-term survival rate since early 1980s^[13-17], and occurrence of tacrolimus (FK506)^[18-22] and mycomphenolate mofetil (MMF)^[23-27] has prolonged the long-term survival. In spite of these major advances in liver transplantation, there are a number of problems associated with its use. For example, the incidence of acute rejection is still as high as 30-40 %^[11].

Thus, the next advance that is required in immunosuppression in recipients with liver transplantation is an agent that can either decrease the rejection without increase of toxicity or decrease toxicity with maintenance of effective immunosuppression.

Daclizumab, a humanized anti-IL-2R α -chain (CD25) antibody, is a new immunosuppressant, its proposed actions include blockade of signaling *via* the high-affinity IL-2R, down-modulation of CD25, depletion of CD25+ cells, and interaction with its FC fragments and FCRs on activated T cells^[28, 29]. Induction therapy with daclizumab has been shown effective in preventing acute rejection in kidney transplantation patients^[30-32]. Routine use of antibody induction therapy in liver transplantation has not gained widespread acceptance^[11].

This study explored the results of adding daclizumab to conventional immunosuppressive therapy in 23 liver recipients with liver transplantation compared to the results in 31 control recipients. It was found that adding daclizumab appeared to be able to decrease the incidence of acute rejection from 38.71 % to 21.74 % without any apparent toxicity or opportunistic infections.

In this study, a different dosing schedule for daclizumab was used. Ciancio *et al* reported their dosing schedule was that daclizumab (1 mg/kg) was given on the day of surgery and every other week for a total of 5 doses^[31]. Devin's schedule

was that the first dose (2 mg/kg) was given before organ engraftment and the second dose (1 mg/kg) was given on postoperative day 5^[1]. Both results suggest the efficacy of their dosing schedule. Our dosage of daclizumab was smaller than that in other transplant centers, but we still found that daclizumab appeared to be able to reduce the incidence of acute rejection significantly without apparent toxicity and was well tolerated. In conclusion, the induction therapy with single-dose of daclizumab is safe and effective.

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