Efficacy and Safety of Basiliximab with a Tacrolimus-Based Regimen in Liver Transplant Recipients

Ignazio R. Marino,[1,5] Cataldo Doria,[1] Victor L. Scott,[2] Carlo Scotti Foglieni,[3] Augusto Lauro,[4] Tommaso Piazza,[3] Davide Cintorino,[3] and Salvatore Gruttadauria[3]

Background. Induction with monoclonal antibodies for prevention of acute cellular rejection (ACR) may avoid many of the adverse events associated with polyclonal antibodies. Basiliximab, a chimeric monoclonal antibody directed against the α-chain of the interleukin 2 receptor (CD25), has been extensively evaluated as an induction therapy for kidney transplant recipients, more frequently in combination with a cyclosporine-based regimen. In this study, we assessed the efficacy and safety of basiliximab in combination with a tacrolimus-based regimen after liver transplantation.

Methods. Fifty consecutive liver transplants (47 cadaveric donors; 3 living donors) were analyzed. All patients received two 20-mg doses of basiliximab (days 0 and 4 after transplantation) followed by tacrolimus (0.15 mg/kg/day; 10–15 ng/mL target trough levels) and a tapered dose regimen of steroids. Follow-up ranged from 404 to 1,364 days after transplantation (mean 799.89 days, SD$\pm$257.37; median 796 days).

Results. A total of 88% of patients remained rejection-free during follow-up with an actuarial rejection-free probability of 75% within 3 months. The actuarial patient survival rate at 3 years was 88%, and the graft survival rate was 75%. Twelve (24%) patients experienced one episode of sepsis, requiring temporary reduction of immunosuppressive therapy. There were no immediate side effects associated with basiliximab and no evidence of cytomegalovirus infection or posttransplant lymphoproliferative disorder.

Conclusions. Basiliximab in combination with a tacrolimus-based immunosuppressive regimen is effective in reducing episodes of ACR and increasing ACR-free survival after liver transplantation. In addition, basiliximab does not increase the incidence of adverse effects or infections.

Keywords: Clinical transplantation, Liver, Immunosuppression, Monoclonal antibodies, Rejection, Infections.

(*Transplantation* 2004;78: 886–891)

Orthotopic liver transplantation (OLTx) has become the standard treatment for both chronic and acute end-stage liver disease. However, despite advances in immunosuppression, acute cellular rejection (ACR) remains an important risk factor. Antibody induction is a means of reducing the risk of ACR in the early posttransplantation period while simultaneously attempting to avoid adverse effects such as nephrotoxicity.

Antibodies may be either polyclonal or monoclonal. Polyclonal antibodies have been associated with numerous adverse effects including anti-antibody formation, serum sickness, leukopenia, cytokine release syndrome, and an increased risk of infection and malignancy (*1*, *2*). Monoclonal antibodies specifically targeting the interleukin 2 receptor (IL-2R) were developed to reduce these adverse effects (*2*). IL-2 receptor antibodies include the chimeric IL-2R antibody basiliximab (Simulect) and the humanized IL-2R antibody daclizumab (Zenapax). Both are directed against the α-chain (CD25), which is expressed on activated T cells. As inhibitors of IL-2 binding, they prevent ACR by inhibiting IL-2–driven T-cell proliferation. A meta-analysis of randomized trials with anti–IL-2R antibodies showed that in kidney transplant recipients the addition of IL-2R antibodies to cyclosporine-based immunosuppression reduced the risk of ACR at 6 months by 49% without increasing the overall incidence of infection including cytomegalovirus (CMV) infection, mortality, or risk of malignancy at 1 year (*3*).

Randomized trials of basiliximab in kidney transplantation have shown its safety and effectiveness as an induction agent (*4–7*). Patients in these studies had a reduction in ACR when compared with patients receiving placebo. In addition, the incidence of infection and other adverse effects was comparable between recipients of basiliximab and placebo.

Experience with basiliximab in OLTx has been less extensive than in KTx. Furthermore, basiliximab has been evaluated more frequently with a cyclosporine-based than with a tacrolimus-based regimen. This is the first study evaluating the efficacy and safety of basiliximab and tacrolimus as standard immunosuppression in adults undergoing OLTx.

MATERIALS AND METHODS

A prospective study was conducted in consecutive recipients of primary orthotopic liver transplants from January 2000 to November 2002 at Ismett, a transplant program started in July 1999. Recipients of either cadaveric-donor or living-donor grafts were eligible for the analysis. Standard immunosuppression was used for all primary OLTx for the study period, which included 20 mg of basiliximab and 1 g of

[1]Division of Liver Transplantation and Hepatobiliary Surgery, Department of Surgery, Thomas Jefferson University Hospital, Philadelphia, PA.
[2]Department of Anesthesiology, Maricopa Medical Center, Phoenix, AZ.
[3]Istituto Mediterraneo per i Trapianti e Terapie ad Alta Specializzazione (IsMeTT), Palermo, Italy.
[4]U.O. Centro Trapianti di Fegato e Multiorgano, Policlinico S. Orsola-Malpighi, Bologna, Italy.
[5]Address correspondence to: Ignazio R. Marino, M.D., F.A.C.S., Professor of Surgery, Jefferson Medical College Director, Division of Liver Transplantation and Hepatobiliary Surgery, Thomas Jefferson University Hospital, 1025 Walnut Street, 605 College Building, Philadelphia, PA 19107-5083. E-mail: ignazio.marino@jefferson.edu.
Received 10 March 2004. Revision requested 7 April 2004. Accepted 22 April 2004.

ISSN 0041-1337/04/7806-886
DOI: 10.1097/01.TP.0000134970.92694.68

methylprednisolone at the time of liver reperfusion; both were given by intravenous (IV) bolus. An additional 20-mg dose of basiliximab was administered by IV bolus on day 4 after transplantation. Tacrolimus (Prograf) was administered at 0.15 mg/kg per day by mouth or through a nasogastric tube, starting not earlier than 24 hr after the OLTx but always within 48 hr from liver reperfusion, and adjusted to achieve trough levels in the range of 10 to 15 ng/mL. At 30 days after transplantation, the target trough level was lowered to 5 to 10 ng/mL. Corticosteroids were administered in a standard rapid taper regimen for the first month (methylprednisolone at 50 mg IV every 6 hr on day 1; 40 mg IV every 6 hr on day 2; 30 mg IV every 6 hr on day 3; 20 mg IV every 6 hr on day 4; 20 mg IV every 12 hr on day 5; 20 mg of prednisone by mouth or through the nasogastric tube on days 6 through 15, and then 10 mg/day for 1 week and 5 mg/day for 1 additional week).

In case of ACR, the protocol comprised a 1,000-mg IV bolus of methylprednisolone, followed by the 5-day taper regimen of IV corticosteroids described above. Simultaneously, the tacrolimus target level was increased to 15 to 20 ng/mL. The protocol also included a second liver biopsy if the liver parameters were not improving by day 5; in case of steroid-resistant ACR, the protocol included 5 mg of OKT3, given IV daily for 5 to 10 days.

CMV pp65 antigenemia-guided preemptive therapy was used for CMV prophylaxis: surveillance for CMV antigenemia was performed at weeks 2, 4, 6, 8, 12, and 16 after transplantation. If positive, oral ganciclovir was used for 6 weeks as previously reported (*8*).

Follow-up ranged from 404 to 1,364 days after transplantation, with a mean of 799.89 days (SD±257.37) and a median of 796 days. Parameters evaluated included graft failure, need and indication for retransplantation, and number of retransplants. Patient survival/death, ACR-free time, number of ACRs per month, and infection rate were also measured. The diagnosis of ACR was always biopsy proven.

Statistical Analysis

Continuous variables are presented as the mean ± SD, and categorical variables are shown as rates. For continuous variables, paired sample *t* tests determined whether there was a difference between groups. For survival, the Kaplan-Meier method was used. The analyses were performed using SPSS (SPSS Inc., Chicago, IL).

RESULTS

Patient demographics are shown in Table 1. Fifty patients were included in the analysis; 47 received cadaveric livers and 3 received livers from living donors. The cohort included 35 men and 15 women; patients ranged in age from 15 to 64 years, with a mean age of 49.78 years. The most common CMV status was donor-positive/recipient-positive (31 patients); however, all combinations of CMV status were represented (Table 1). The liver diseases leading to OLTx are also listed in Table 1. All patients received tacrolimus at a median time of 48 hr after OLTx (mean, 45.6 hr). The mean total ischemia time from the time of cross-clamping during the donor operation to liver reperfusion was 10 hr and 42 min (SD±0.13). Of 50 OLTx, 16 were performed with a standard hepatectomy with the use of venous-venous bypass, 15 with a standard hepatectomy without the use of venous-venous bypass, 12 with the so-called "piggyback" technique without venous-venous bypass, and 7 with the "piggyback" technique with the use of venous-venous bypass. All 47 cadaveric livers were perfused with University of Wisconsin solution, whereas the 3 live donor grafts were perfused with histidine-tryptophan-ketoglutarate solution (to prevent the need for flushing before reperfusion during the recipient operation).

TABLE 1. Patient demographics

Baseline patient characteristics	n=50
Mean age (range)	49.78 (15–64)
Male/female, n	35/15
Race/ethnicity	100% Caucasian
Mean baseline creatinine level (mg/dL)	0.9 (SD±0.6)
CMV status, n	
Donor +/recipient +	31
Donor +/recipient −	4
Donor −/recipient +	12
Donor −/recipient −	3
Cadaveric donor, n	47
Living donor, n	3
Primary liver disease	**n=50**
HCV-related cirrhosis	21
HBV/HDV-related cirrhosis	10
HCC	6
Alcohol-related cirrhosis	5
PBC	3
Autoimmune hepatitis	2
Cryptogenic cirrhosis	2
Sclerosing cholangitis	1

CMV, cytomegalovirus; HCV, hepatitis C virus; HBV, hepatitis B virus; HCC, hepatocellular carcinoma; PBC, primary biliary cirrhosis.

The majority of patients experienced a successful outcome. The actuarial patient survival rate at 3 years was 88% and the graft survival rate was 75% (Figs. 1 and 2). Graft loss occurred in nine patients (18%). Two patients underwent retransplantation as a result of hepatic artery thrombosis and one patient as a result of late graft dysfunction; five patients underwent retransplantation for primary nonfunction. In addition, one patient underwent two retransplantations for prolonged primary graft dysfunction. There were six deaths: four as a result of late graft failure and two as a result of sepsis.

Forty-four (88%) patients were free of ACR episodes during the follow-up period. Five patients (10%) had one ACR episode: one within 3 months (mild in severity); two within 3 to 6 months (one mild, one moderate in severity); and two within 6 to 12 months (one mild, one moderate in severity). One patient (2%) had three ACR episodes (severe, moderate, and mild in severity), two of which occurred at 6 to 12 months after transplantation. OKT3 or other antibody therapy was never required to treat rejection. The mean ACR episodes per month were 0.15 (±0.21; range, 0 to 0.58). Rejection-free probability was 75% within the first 3 months after transplantation.

Basiliximab was well tolerated by all patients. No acute

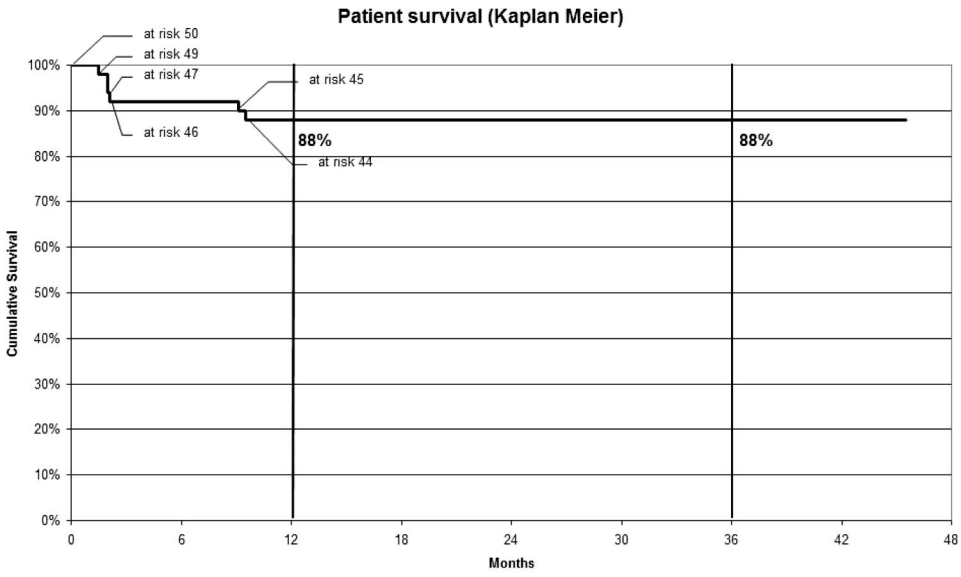

FIGURE 1. Kaplan-Meier estimates of patient survival (n=50).

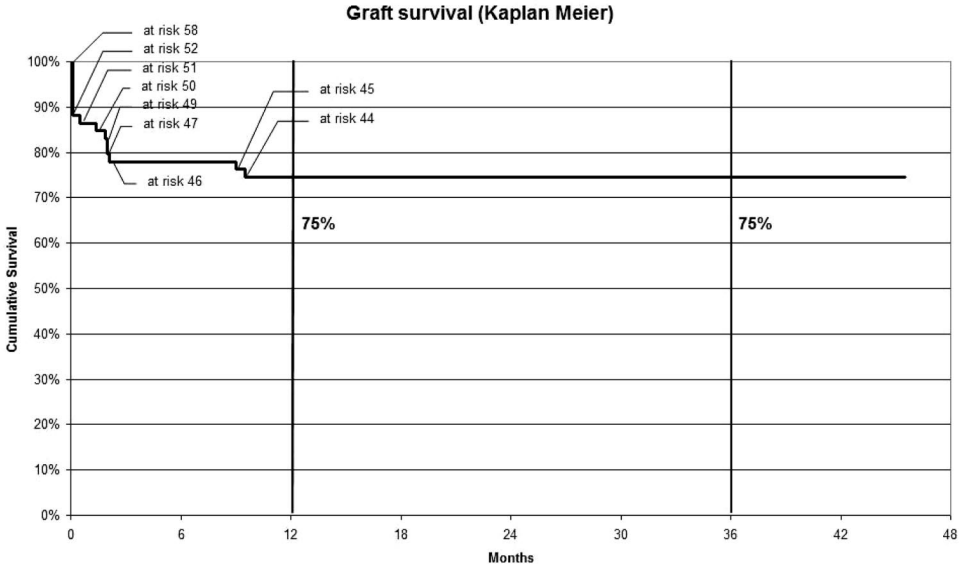

FIGURE 2. Kaplan-Meier estimates of graft survival (n=50).

side effects were noted, including acute infusion reactions. The mean baseline creatinine level in the 50 primary recipients was 0.9 mg/dL (SD±0.6). The mean creatinine level at day 10 after transplantation was 1.3 mg/dL (SD±0.7), statistically different from the preoperative value ($P=0.0037$). Thrombocytopenia was seen in the early postoperative period, as usually observed after OLTx and described by us elsewhere (*9*). The mean baseline platelet count was 68,080/mm^3 (SD±42,077). Mean platelet count at day 10 after transplantation was 104,700/mm^3 (SD±53,317), statistically different from the preoperative value ($P=0.0002$).

Twelve patients experienced at least one episode of infection, whereas four experienced more than one episode. In case of infection, immunosuppression was always reduced. Respiratory infection occurred in seven patients: three related to *Klebsiella pneumoniae*, four to *Pseudomonas aeruginosa*. Bronchoalveolar lavage (BAL) was positive for *Xanthomonas* in two patients. Four patients had one episode of CMV antigenemia diagnosed by pp65. Three patients had a wound infection from *Escherichia coli*, one patient had a positive *Escherichia coli* culture in the ascites fluid, one patient had *Escherichia coli* urinary tract infection, one patient had a positive *Escherichia coli* culture in the bile and blood, and one patient had a positive *Escherichia coli* culture simultaneously in wound, ascites, and bile. Among the hepatitis C virus (HCV)-positive recipients, 42% (9/21) developed biopsy-proven HCV recurrence within the follow-up period. None of the patients in this study experienced posttransplant lymphoproliferative disorder. No recurrent or de novo malignancies have occurred in any patient to date.

DISCUSSION

This study showed that basiliximab in a tacrolimus-based immunosuppression regimen is well tolerated and effective in both reducing episodes of ACR and increasing

ACR-free survival after OLTx. Our results may be compared with those of a large retrospective analysis using data from 15 Italian liver transplant centers in which 3,026 orthotopic liver transplant recipients of similar demographics received immunosuppression with a calcineurin inhibitor and either mycophenolate mofetil or azathioprine (*10*). A total of 12% of patients in the current study experienced at least one episode of ACR, representing a substantial improvement compared with the 43.5% rejection rate seen in the Italian multicenter study, in which monoclonal antibodies were not used. The addition of basiliximab to the immunosuppression regimen also seems to improve actuarial graft and patient survival rates at 3 years. In the current study, actuarial graft and patient survival rates at 3 years were 75% and 88%, respectively. This compares favorably with the results seen in the Italian multicenter study, in which 3-year graft and patient survival rates were 70.2% and 72.3%, respectively (*10*). The results of our study might also represent an improvement compared with nationwide data provided by the United Network for Organ Sharing Transplant Liver Registry, which found graft and patient survival rates at 3 years to be 71.5% and 77.9%, respectively (*11*).

Our results may also be compared with literature data related to tacrolimus-steroids protocols. The 12% ACR rate of our study compares favorably with the 38% 1-year rejection rate recently reported by Boillot et al. (*12*) as well as the 45.2% 1-year rejection rate reported by Jain et al. (*13*) from the Pittsburgh group. The difference is even more dramatic when our results are compared to the U.S. and European multicenter FK506 liver study groups, in which the 1-year rejection rates with steroids and tacrolimus were 68%, and 40.5%, respectively (*14*, *15*).

Although our study was not designed to evaluate the pharmacokinetics and immunodynamics of basiliximab, we want to mention these topics. As previously reported by Kovarik et al. (*16*, *17*), basiliximab was measurable in drained ascites fluid and clearance by this route was about 20% to 29% of the total body clearance. Patients with more than 5 L of posttransplantation ascites fluid drainage tended to have CD25 saturation duration in the lower adult distribution quartiles (*17*). However, although ascites fluid drainage and postoperative bleeding are potential sources of basiliximab loss, these events did not seem to jeopardize the maintenance of immunoprophylactic drug concentration (*16*). Conversely, it was suggested that an additional dose of basiliximab may be considered on a case by case basis depending on the volume of the ascites drained (*17*). However, in this study we never felt that the fluid or blood loss was so significant to justify an extra basiliximab dose.

The use of monoclonal antibodies in OLTx has been less studied than in KTx. However, recent studies (mostly pediatric) have demonstrated that the addition of basiliximab to tacrolimus- or cyclosporine-based regimens could reduce ACR rates in OLTx (*18–21*).

Reding et al. (*21*) recently reported on their experience with a steroid-free tacrolimus-basiliximab protocol in 20 pediatric orthotopic liver transplant recipients. In these children, the 12-month rejection-free survival rate was 75%, statistically better ($P=0.05$) than a similar population treated with tacrolimus and steroids. Furthermore, growth in the first year after transplantation was significantly better in the tacrolimus-basiliximab group than in the steroid group. This finding may also encourage new studies to further assess the efficacy and safety of a steroid-free tacrolimus-basiliximab regimen in adults. However, the current study is the first to show that the addition of basiliximab to a standard tacrolimus-based immunosuppressive regimen is effective and well tolerated in adults undergoing OLTx. The effects of basiliximab on ACR and patient survival in OLTx have been more extensively studied in standard cyclosporine-based regimens (*22–25*). In a phase III study involving 381 orthotopic liver transplant recipients, the addition of basiliximab to cyclosporine- and steroid-based immunosuppression reduced the overall rate of biopsy-confirmed ACR at 6 months from 43.5% to 35.1%. Rates of death, graft loss, or first biopsy-confirmed ACR decreased from 52.8% to 44.1%, representing a 19% relative reduction (*22*). Although both HCV-positive and -negative patients treated with basiliximab had reduced ACR rates compared with recipients of placebo, this reduction was most evident in HCV-negative patients (*22*). Some of this difference may have been caused by elevated baseline levels of immune system activity in the HCV-positive patients. Standard immunosuppression may have been insufficient to overcome this elevated activity in HCV-positive patients, therefore resulting in higher ACR rates.

It has been shown that basiliximab is well tolerated in pediatric orthotopic liver transplant recipients, including HCV-positive recipients (*18–25*). Basiliximab did not seem to increase opportunistic infection rates or CMV or posttransplant lymphoproliferative disorder (*18–25*). Consistent with data previously reported, this was confirmed in the current study.

HCV recurrence developed in 42% of HCV-positive recipients during the 3-year follow-up. This rate compared favorably with that previously observed in Pittsburgh (42–53%) (*26*, *27*). Although the intensity of immunosuppression has been shown to correlate with recurrent HCV hepatitis after OLTx (*27*), the addition of basiliximab to baseline immunosuppression in our study did not increase the HCV recurrence rate. This is particularly relevant because patients with recurrent HCV hepatitis show a higher incidence of late-occurring infections, mostly as a result of pathogens associated with depressed cell-mediated immunity (*27*). It is also interesting to note that, as reported by Kato et al. (*28*) from the Miami group, tacrolimus along with another IL-2R antibody—daclizumab—and a steroid-free regimen resulted in fewer HCV infection recurrences after OLTx. In their study, biopsy-proven recurrent HCV was 0% at 3 months, whereas the control arm (patients not treated with daclizumab and receiving steroids) had a 27% HCV recurrence rate. A literature meta-analysis on daclizumab induction in organ transplantation confirmed this finding; this salutary effect could be related to the steroid-sparing immunosuppression allowed by IL-2R antibody induction (*29*). This is similar to our study in which patients underwent an early (1 month) steroid withdrawal. A second possible mechanism justifying a lower HCV histologic recurrence rate may be related to an immunomodulatory role of basiliximab and daclizumab in HCV-positive subjects. In fact, in this population it seems that the mean serum IL-2 soluble receptor (sIL-2R) concentration correlates with the Knodell histology index and therefore with the impaired liver function (*30*). In other words, the presence of

viral replication is not sufficient to induce the release of large amounts of sIL-2R, which, instead, correlates with the degree of liver damage related to HCV. Therefore, it would be interesting in future studies to investigate the role of IL-2R antibodies and sIL-2R to prove beneficial effects and reductions of HCV histologic recurrence in HCV-positive liver recipients, independently from a steroid-free immunosuppression.

Our data support the use of basiliximab in adult OLTx treated with tacrolimus-based immunosuppression as a strategy for decreasing ACR in OLTx while avoiding the serious adverse effects associated with broad T-cell depletion. However, monoclonal antibodies may also be beneficial to patients when used in calcineurin inhibitor–sparing regimens. In such regimens, monoclonal antibodies could facilitate the early withdrawal of calcineurin inhibitors, thus reducing the risk for nephrotoxicity, and neurotoxicity. Favorable results using monoclonal antibody therapy in calcineurin inhibitor–sparing regimens have already been observed in small series of kidney transplant patients with delayed graft function (*31–34*). Our previous use of basiliximab in selected patients, particularly those with a rising serum creatinine level, prompted us to include it in our standard immunosuppression protocol. Therefore, we believed it unethical to conduct the present study in a randomized manner and deny potential benefits to patients.

The improved rates of ACR and patient survival without malignancies or significant adverse events seen during 3 years of follow-up in the current study support the further investigation of basiliximab as an agent that facilitates the withdrawal of cyclosporine or tacrolimus over time. Based on the positive results obtained in this study thus far, plans are underway to start weaning our patients from immunosuppression at year 4 after transplantation. This approach has previously been explored in a prospective study of liver transplant recipients, in which 19% of patients could be maintained drug-free with low ACR rates from 10 months to 4.8 years (*35*). Kidney transplant recipients treated before transplantation with antithymocyte globulin and with posttransplantation tacrolimus monotherapy have also been successfully weaned from tacrolimus (*36*). These results suggest that, through the avoidance of early posttransplantation overimmunosuppression, a degree of partial tolerance may develop that is sufficient to allow for dose reduction (*36*, *37*). The role of nondepleting monoclonal antibodies in achieving a tolerant state remains to be explored.

CONCLUSION

This study demonstrated that basiliximab, a chimeric monoclonal antibody directed against the IL-2R (CD25), was effective in reducing the number of ACR episodes and increasing the probability of remaining rejection-free after OLTx, which could potentially result in improved long-term outcomes. In addition, the study showed that basiliximab was safe and did not increase the adverse event profile or rate of infection. Investigation of the potential of this regimen for allowing later weaning from maintenance immunosuppressants is needed. Based on the favorable outcome observed in our patient population reported here, we believe that it would be appropriate to test a steroid-free immunosuppressive regimen based on tacrolimus and basiliximab in adult liver recipients, similarly to what has been performed in children by Reding (*21*), with particular attention to HCV recurrence in this subgroup of recipients.

ACKNOWLEDGMENTS

The authors thank Dr. Maurizio Iaria for useful suggestions.

REFERENCES

1. Brennan DC. Action, efficacy and toxicities: polyclonal antilymphocyte antibodies. In: Norman DJ, Turka LA, eds. Primer on transplantation [ed 2]. Mt. Laurel, NJ, American Society of Transplantation 2001, p. 152.
2. Moser MAJ. Options for induction immunosuppression in liver transplant recipients. *Drugs* 2003; 62: 995.
3. Adu D, Cockwell P, Ives NJ, et al. Interleukin-2 receptor monoclonal antibodies in renal transplantation: meta-analysis of randomised trials. *BMJ* 2003; 326: 789.
4. Nashan B, Moore R, Amlot P, et al, for the CHIB 201 International Study Group. Randomised trial of basiliximab versus placebo for control of acute cellular rejection in renal allograft recipients. *Lancet* 1997; 350: 1193.
5. Kahan BD, Rajagopalan PR, Hall M, for the United States Simulect Renal Study Group. Reduction of the occurrence of acute cellular rejection among renal allograft recipients treated with basiliximab, a chimeric anti-interleukin-2-receptor monoclonal antibody. *Transplantation* 1999; 67: 276.
6. Ponticelli C, Yussim A, Cambi V, et al, for the Simulect Phase IV Study Group. A randomized, double-blind trial of basiliximab immunoprophylaxis plus triple therapy in kidney transplant recipients. *Transplantation* 2001; 72: 1261.
7. Lawen JG, Davies EA, Mourad G, et al, for the Simulect International Study Group. Randomized double-blind study of immunoprophylaxis with basiliximab, a chimeric anti-interleukin-2 receptor monoclonal antibody, in combination with mycophenolate mofetil-containing triple therapy in renal transplantation. *Transplantation* 2003; 75: 37.
8. Singh N, Paterson DL, Gayowski T, et al. Cytomegalovirus antigenemia directed pre-emptive prophylaxis with oral versus I.V. ganciclovir for the prevention of cytomegalovirus disease in liver transplant recipients: a randomized, controlled trial. *Transplantation* 2000; 70: 717.
9. Chang FY, Singh N, Gayowski T, et al. Thrombocytopenia in liver transplant recipients: predictors, impact on fungal infections, and role of endogenous thrombopoietin. *Transplantation* 2000; 69: 70.
10. Fagiuoli S, Mirante VG, Pompili M, et al, and the Monotematica AISF 2000-OLT Study Group. Liver transplantation: the Italian experience. *Dig Liver Dis* 2002; 34: 640.
11. 2003 Annual Report of the U.S. Organ Procurement and Transplantation Network and the Scientific Registry of Transplant Recipients; Transplant Data 1993–2002. Department of Health and Human Services, Health Resources and Services Administration, Office of Special Programs, Division of Transplantation, Rockville, MD; United Network for Organ Sharing, Richmond, VA; University Renal Research and Education Association, Ann Arbor, MI.
12. Boillot O, Baulieux J, Wolf P, et al. Low rejection rates with tacrolimus-based dual and triple regimens following liver transplantation. *Clin Transplant* 2001; 15: 159.
13. Jain A, Kashyap R, Dodson F, et al. A prospective randomized trial of tacrolimus and prednisone versus tacrolimus, prednisone and mycophenolate mofetil in primary adult liver transplantation: a single center report. *Transplantation* 2001; 72: 1091.
14. The U.S. Multicenter FK506 Liver Study Group. A comparison of tacrolimus FK506 and cyclosporine for immunosuppression in liver transplantation. *N Engl J Med* 1994; 331: 1110.
15. Neuhaus P, Pichlmayr R, Williams R, and the European FK506 Multicentre Liver Study Group. Randomised trial comparing tacrolimus (FK506) and cyclosporin in prevention of liver allograft rejection. *Lancet* 1994; 344: 423.
16. Kovarik J, Breidenbach T, Gerbeau C, et al. Disposition and immunodynamics of basiliximab in liver allograft recipients. *Clin Pharmacol Ther* 1998; 64: 66.
17. Kovarik J, Gridelli BG, Martin S, et al. Basiliximab in pediatric liver transplantation: a pharmacokinetic-derived dosing algorithm. *Pediatr Transplant* 2002; 6: 224.

18. Asensio M, Margarit C, Chavez R, et al. Induction with basiliximab reduces acute rejection in pediatric liver transplant patients treated with tacrolimus and steroids. *Transplant Proc* 2002; 34: 1970.
19. Arora N, McKiernan PJ, Beath SV, et al. Concomitant basiliximab with low-dose calcineurin inhibitors in children post-liver transplantation. *Pediatr Transplant* 2002; 6: 214.
20. Aw MM, Taylor RM, Verma A, et al. Basiliximab (Simulect) for the treatment of steroid-resistant rejection in pediatric liver transplant recipients: a preliminary experience. *Transplantation* 2003; 75: 796.
21. Reding R, Gras J, Sokal E, et al. Steroid-free liver transplantation in children. Lancet 2003; 362: 2068.
22. Neuhaus P, Clavien P-A, Kittur D, et al, for the CHIC 304 International Liver Study Group. Improved treatment response with basiliximab immunoprophylaxis after liver transplantation: results from a double-blind randomized placebo-controlled trial. Liver Transpl 2002; 8: 132.
23. Calmus Y, Scheele JR, Gonzalez-Pinto I, et al. Immunoprophylaxis with basiliximab, a chimeric anti–interleukin-2 receptor monoclonal antibody, in combination with azathioprine-containing triple therapy in liver transplant recipients. *Liver Transpl* 2002; 8: 123.
24. Ganschow R, Broering DC, Stuerenburg I, et al. First experience with basiliximab in pediatric liver graft recipients. *Pediatr Transplant* 2001; 5: 353.
25. Ganschow R, Lyons M, Grabhorn E, et al. Experience with basiliximab in pediatric liver graft recipients. *Transplant Proc* 2001; 33: 3606.
26. Singh N, Gayowski T, Wannstedt CF, et al. Interferon-alpha therapy for hepatitis C virus recurrence after liver transplantation: long-term response with maintenance therapy. *Clin Transplant* 1996; 10: 348.
27. Gayowski T, Singh N, Marino IR, et al. Hepatitis C virus genotypes in liver transplant recipients: impact on post-transplant recurrence, infections, response to interferon-α therapy and outcome. *Transplantation* 1997; 64: 422.
28. Kato T, Neff G, Montalbano M, et al. Steroid-free induction with tacrolimus and daclizumab in liver transplant recipients with hepatitis C: a preliminary report of a prospective randomized trial. *Am J Transplant* 2001; 1(1 suppl): 179.
29. Carswell CI, Plosker GL, Wagstaff AJ. Daclizumab: a review of its use in the management of organ transplantation. *BioDrugs* 2001; 15: 745.
30. Gessoni G, Valverde S, Giacomini A, et al. In subjects with antibody to hepatitis C virus a high serum level of interleukin-2 soluble receptor suggests activity of liver disease. *J Viral Hepat* 1998; 5: 99.
31. Flechner SM, Goldfarb DA, Fairchild R, et al. A randomized prospective trial of OKT3 vs. basiliximab for induction therapy in renal transplantation [abstract 169]. *Transplantation* 2000; 69: S157.
32. Mourad GJ, Rostaing L, Legendre C, et al. A sequential protocol using Simulect vs Thymoglobulin in low immunological risk renal transplant recipients: six-month results of a French multicenter, randomized trial [abstract 1212]. *Am J Transplant* 2003; 3: 462.
33. Pelletier RP, Bumgardner GL, Davies EA, et al. Delayed cyclosporine administration following Simulect induction does not increase acute rejection in renal transplant recipients [abstract 176]. *Transplantation* 2000; 69: S158.
34. Hong JC, Kahan BD. A calcineurin antagonist-free induction immunosuppression strategy for delayed graft function in renal transplantation. *Transplant Proc* 2001; 33: 1271.
35. Mazariegos GV, Reyes J, Marino IR, et al. Weaning of immunosuppression in liver transplant recipients. *Transplantation* 1997; 63: 243.
36. Shapiro R, Jordan ML, Basu A, et al. Kidney transplantation under a tolerogenic regimen of recipient pretreatment and low-dose postoperative immunosuppression with subsequent weaning. *Ann Surg* 2003; 238: 520.
37. Calne R. "Almost tolerance" in the clinic. *Transplant Proc* 1998; 30: 3846.