

Prophylactic Use of OKT3 in Liver Transplantation

A Review

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Liver rejection in the era of cyclosporine-based immunosuppression is approximately 60–70%. Approximately 15–25% of liver transplant patients will require hemodialysis following transplantation. These facts argue for a potent, less nephrotoxic immunosuppressive regimen, especially during the period of vulnerability to these events. Prophylactic use of OKT3 has been suggested as a means to decrease the need for hemodialysis while maintaining potent immunosuppression. The goal of this review is to examine potential benefits and pitfalls of this regimen. A lack of documentation of long-term patient and graft survival, the potential susceptibility to infectious complications, development of sensitization, and the cost must be weighed against the decreased need for hemodialysis and the control of early rejection episodes.

KEY WORDS: OKT3; liver transplantation.

OKT3 (orthoclone) is a murine monoclonal anti-human T-cell antibody with clinically proven efficacy in the reversal of acute renal and liver allograft rejection (1–7). While the major impact in improvement in patient and graft survival appears to be in patients with acute cellular rejection, the early postoperative use of OKT3 has been shown to be of benefit in a subpopulation of patients after liver transplantation (5). This is related to decreased graft loss from rejection during a period in which cyclosporine use has been minimized because of renal dysfunction. Since OKT3 is capable of preventing alloactivation *in vitro*, its prophylactic use should delay the onset of rejection, at least during the period of administration of the agent.

The rationale for the prophylactic use of OKT3 in liver transplantation is primarily to decrease or mod-

ulate the early cyclosporine-related renal dysfunction seen in many liver transplant patients and possibly to decrease the incidence and severity of acute rejection episodes. Renal dysfunction, either measured by elevated serum creatinine or by the need for hemodialysis, occurs relatively frequently after liver transplantation. McCauley et al (8) noted an incidence of acute renal failure after liver transplantation with cyclosporine-based immunosuppression of 15–20%. The causes of renal failure following liver transplantation are multifactorial and include perioperative hypotension, use of nephrotoxic antibiotics, and preoperative hepatorenal syndrome (9). The use of cyclosporine was determined to be the sole cause of renal failure in 20% of patients with renal failure following liver transplantation and can certainly augment other causes of renal failure.

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SURVIVAL, RENAL FUNCTION, AND REJECTION EPISODES

Several studies have compared prophylactic OKT3 following liver transplantation to standard

cyclosporine immunotherapy. Millis et al (10), presented the results of 52 patients randomized to either cyclosporine, azathioprine, and steroids (27 patients), or to azathioprine, steroids, and OKT3, followed by conversion to cyclosporine at 14 days (25 patients). The incidence of rejection within the two weeks following transplantation was significantly lower in the prophylactic group (41%) than in the control cyclosporine-treated group (72%, $P < 0.02$). In addition, rejection occurred earlier in the control group (9.5 days vs 12.2 days, OKT3-treated group). Early renal function was better preserved in the prophylactic OKT3-treated group as determined by serum creatinine (1.14 mg/dl vs 1.45 mg/dl for the control group). However, patient and graft survival was not significantly better, with the overall six-month survival for the control group being 86% vs 75% for the OKT3 prophylactic group.

McDiarmid et al (11) reported the results of the long-term follow-up of the patients reported by Millis et al (10). In a larger series of 85 liver transplant recipients, 46 patients were randomized to receive prophylactic OKT3, while 39 patients were randomized to standard cyclosporine immunosuppression. Patients dying during the first post-transplant week were excluded from analysis. Long-term follow-up, with a mean survival of two years in both groups, showed a 69% survival in the OKT3 prophylactic group and an 84% survival with the standard cyclosporine immunosuppressive regimen. Graft survival greater than 90 days was 61% in the OKT3 group and 74% in the control group. The incidence of rejection after 30 days was not different between the two groups. Renal function was not different between the two groups at 6, 12, or 24 months. Eight patients in the prophylactic group required a second course of OKT3. Reuse of OKT3 was successful in reversing rejection only in five patients, primarily due to the presence of anti-OKT3 antibodies. They conclude from this study that no long-term benefits of OKT3 prophylaxis could be demonstrated with regards to graft or patient survival, incidence of rejection after 30 days, or renal function.

Muhlbacher et al (12), studied 88 consecutive patients following liver transplantation. Following transplant, 58 patients received cyclosporine and steroid, while 30 received prophylactic OKT3, steroids, and azathioprine. Cyclosporine was substituted for OKT3 on day 10 posttransplantation. In this study, the overall one-year patient survival was

control group. Again, the incidence of rejection was statistically significantly reduced in the OKT3 prophylactic group (56% vs 80%, control group, $P = 0.03$). Renal function also was better preserved with a mean serum creatinine of 1.3 ± 1.0 mg/dl in the control cyclosporine-treated group while the prophylactic group had a mean serum creatinine of 0.7 ± 0.4 mg/dl ($P < 0.05$).

Cosimi and coworkers (13) studied 79 patients randomized into a cyclosporine control group consisting of triple drug immunosuppression with cyclosporine, steroids, and azathioprine (42 patients), and 37 patients treated with prophylactic OKT3, azathioprine, and steroids followed by conversion to cyclosporine at 14 days. The incidence of rejection during the first two weeks was 42% in the prophylactic group versus 70% in the control group ($P < 0.02$). Renal function was reportedly better in the OKT3 group. The 14-month patient survival was 87% in the OKT3 group and 76% in the control group.

INFECTIONS

There are potential pitfalls of OKT3 use. The major problem is the potentiation of infectious complications brought about by the use of OKT3. OKT3 is associated with an increase in the incidence of viral infections. Singh et al (14) examined the incidence of cytomegalovirus (CMV) and other herpes virus infections in liver transplant patients and the effect of OKT3, given to treat rejection, on the severity of the viral disease. Symptomatic herpes simplex virus was increased from 31% to 53% ($P = 0.05$) in patients receiving OKT3. Disseminated CMV occurred more frequently with OKT3 use ($P < 0.04$). These findings were even more impressive in pediatric liver recipients. Bowman et al (15) found that primary invasive CMV was three fold higher in OKT3-treated patients than in children not receiving OKT3 (58% vs 19%, $P < 0.03$). Adenovirus infections, not commonly seen in adults, was seen in 14% of pediatric patients receiving OKT3, as compared to 2% in those not requiring OKT3. Muhlbacher et al (12) could not demonstrate an increased incidence of viral infections in patients receiving prophylactic OKT3, although all of the patients that died of severe viral illnesses had received OKT3. In contrast, Millis et al (10) concluded that there was not a significant increase in incidence of infectious complications. These

n the adult/pediatric composition of the patient populations studied.

DISCUSSION

The purpose of this review is to summarize some of the available information regarding the prophylactic use of OKT3 following liver transplantation and to clarify the situation(s) in which this agent might be utilized. The main questions are: (1) whether prophylactic use versus selective use of OKT3 in liver transplant patients can effect patient and graft survival, (2) whether a decrease in the incidence of rejection during the first few weeks following transplantation is helpful in the overall management of these patients, (3) if the avoidance of cyclosporine during the early posttransplant period results in an improvement in renal function, (4) if the nonselective use of OKT3 adversely affects the requirement for subsequent use of OKT3, and (5) whether the infectious complications outweigh the potential benefits of prophylactic use of OKT3. It may not be possible to answer all of these questions at this time; however, several general conclusions can be made.

Prophylactic OKT3 has not been determined in any study to lead to an increased patient or graft survival. In a study by Fung et al (7), the more selective use of OKT3 early in the posttransplant period, in patients with renal dysfunction or early liver allograft dysfunction, was associated with a "normalization" in patient and graft survival. These figures were not better than those obtained with more "blue ribbon" patients, but were better than those previously reported in patients with such complications.

The avoidance of cyclosporine during the immediate posttransplant period appears to benefit early renal function following liver transplantation. It is also clear that the long-term nephrotoxicity of OKT3 is not influenced by these early posttransplant events. Nevertheless, prevention of early renal dysfunction allows the transplant team to manage fluid and electrolytes more easily and decrease the morbidity associated with the need for hemodialysis. Selective administration of OKT3 to patients manifesting the hepatorenal syndrome prior to transplantation or to those who develop early postoperative oliguria may reduce the early need for hemodialysis, although this question has not been prospectively studied in a randomized fashion.

The rate of sensitization to the murine and allo-type components of OKT3 occurs at a rate to 20-40% (16). Various strategies have been developed to overcome such a sensitization state, such as increasing the dose of OKT3 and carefully monitoring T-cell subpopulations. The success of reuse of OKT3 is less than that for primary use, both when OKT3 is used for prophylaxis or for treatment (5, 18). This strategy may be associated with an even higher incidence of infectious complications (19). Perhaps with the availability of "humanized" OKT3, the difficulty with sensitization precluding successful reuse of OKT3 may be avoided.

It is clear that OKT3 can potentiate the susceptibility to viral infections when used to treat acute allograft rejections. It is not clear that prophylactic use of OKT3 does the same. In a kidney transplant study using prophylactic OKT3, the incidence of viral infections was higher in the prophylactic group when compared to azathioprine and steroids (18); however, the length of OKT3 prophylaxis and the nature of the control groups were different than what is the current standard for liver transplantation. Generally, the development of viral infections can be managed by specific antiviral therapy; however, the ominous development of lymphoproliferative disease (LPD), is associated with increased mortality. In several reports, the development of EBV-associated LPD was associated with the use of OKT3 (20, 21). Whether the addition of prophylactic antiviral therapy can decrease the incidence and severity of viral infections, in the context of OKT3 immunoprophylaxis, is currently being evaluated (22).

It can be argued that the tradeoff of sensitization and susceptibility to infections with the ease in the management of liver transplant patients during the first few weeks after liver transplantation is justified. However, without an appreciable impact on long-term graft or patient survival, cost analysis becomes a paramount factor in determining the usefulness of prophylactic OKT3. If one were to take 100 liver transplant patients and treat them with prophylactic OKT3 for 14 days, the drug costs alone will be \$840,000, assuming a cost to the patient of \$600/5 mg. Once the costs of drug administration and premedication charges are added, this cost will rise to \$1,000,000. If monitoring of drug levels of OKT3 and/or determination of T-cell subpopulations are added, these costs could add an additional \$1000 per patient (assuming that only two determinations were made during the course of prophylaxis). If one assumes that 20% of these patients will require a second

course of OKT3, then the additional drug charges will be \$200,000, and the monitoring charges will be \$40,000. The total charges would be expected to approach \$1,500,000. On the other hand, selective use of OKT3 for those with early renal dysfunction (20%) or those requiring OKT3 for steroid-resistant rejection (25%) would decrease the total charges for OKT3 and monitoring to about one third that of the prophylactic group. The savings of \$1,000,000 alone would serve as justification for a more judicious use of OKT3.

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