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TEMPORARY WITHDRAWAL OF IMMUNOSUPPRESSION FOR LIFE-THREATENING INFECTIONS AFTER LIVER TRANSPLANTATION[1]

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The outcome of a transplanted organ depends frequently upon the occurrence of allograft rejection and infection episodes. These 2 events are closely related. On one side, immunosuppressive therapy is required to avoid allograft rejection, but on the other side this therapy facilitates the occurrence of infections (1). A better understanding of allograft rejection mechanisms along with new immunosuppressive therapies and antimicrobial prophylaxis has increased graft and patient survival. However, infectious complications continue to be a common cause of morbidity and mortality after organ transplantation.

The managements of these infections depend primarily upon identification of infectious causative agents. Specific antibacterial, antiviral, antifungal, and antiprotozoal therapy provides the mainstay in treatment of these infections. However, it also is important to lower the immunosuppressive background to allow the host immunological response to these infections, particularly when infections are considered life threatening. Although discontinuation of immunosuppression is a generally accepted option in these situations of life-threatening infections, no information it is available about graft and patient outcomes in these circumstances. In kidney transplantation, immunosuppression may be stopped completely in the setting of life-threatening infections, since return to dialysis and retransplantation is always an option (2,3). In contrast, in liver transplantation discontinuation of immunosuppression is considered “very risky,” because it may lead to graft loss and patient death. The following is a report of the circumstances and outcome of patients with life-threatening infectious complications after liver transplantation, all of whom were managed with a temporary discontinuation of the immunosuppression therapy.

Between 1987 and 1991, 31 patients underwent liver transplantation and developed severe opportunistic infections. The management included, along with the specific anti-infectious therapy, a temporary withdrawal of immunosuppression for at least 15 days. The patients were

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on 2 different immunosuppressive protocols, as described previously (4): (1) CsA and steroids (12 patients) and (2) FK506 with low dose steroids (19 patients). Table 1 shows the types of infection seen and the immunosuppression that patients were receiving. The change in their immunosuppression management followed 1 of 2 patterns when infection was diagnosed: total discontinuation of immunosuppressive agents (in 1 CsA and 19 FK506 patients) or a maintenance dose of 5 mg/day prednisone only was given (11 CsA patients). Thirteen patients (42%; 5 CsA and 8 FK506 patients) died at a median time of 23 days after their immunosuppression therapy was discontinued (range 16–56 days) because of complications related to the infections. Autopsy examination was performed in 8 of these patients, with no evidence of allograft rejection in any of them.

Eighteen patients (7 CsA and 11 FK506) who survived had their immunosuppression discontinued at a median interval of 140 days (range 44–779) after liver transplantation. They were a median of 17 days (range 15–43) without detectable levels of CsA or FK506. All patients had their baseline immunosuppression resumed. However, the maintenance dose of either CsA and FK506 was reduced a median of 50% (range 0–89%) in comparison with the baseline immunosuppression before the discontinuation. Only 4 patients (3 CsA, 1 FK506) required reinstitution of immunosuppression because of rejection. The median interval from liver transplantation to discontinuation of immunosuppression was 129 days (range 44–411) in those patients who had rejection and 143 days (range 53–779) in patients who did not have rejection (NS). The median period with undetectable levels of CsA or FK506 was 27 days (range 20–43) in those patients who had rejection and 16 days (range 15–27) in patients who did not have it (P=0.01). No differences were found in the dose of CsA before the discontinuation among the 3 CsA patients who had rejection and the 4 who did not. In those patients who did reject, all rejection episodes were controlled with the resumption of baseline immunosuppression. With a median follow-up of 942 days (range 440–2022 days), all patients who survived are alive, none required retransplantation, and only 2 (11%; 1 CsA and 1 FK506 patient) have signs of chronic rejection in their liver biopsy (5).

The fact that most of the patients reported here had their immunosuppression stopped without emergence of rejection could be explained by more than a single mechanism. On the one hand, the infection itself may produce immunosuppression, particularly viral infections (CMV or EBV), which are well-known immunosuppressive agents (6,7). In addition, these patients were by definition iatrogenically “overimmunosuppressed,” as none of the 8 who came to an autopsy had evidence of rejection; for those who survived, a 50% reduction in baseline maintenance immunosuppression when this was resumed did not lead to rejection.

A second explanation for the ability to stop treatment is that the first stage of donor recipient nonreactivity was well underway. This tolerance induction, which has been associated with cell migration and chimerism (8–10), allowed global immunologic recovery without rejection of the graft. The variable and unpredictable completeness of this process of “graft acceptance” was evident even at such an early time. Rejection emerged in 4 of the 18 survivors when reinstitution of treatment was withheld beyond 2 weeks, by freedom of this complication in the other 14. However, even in the recipients who developed rejection, secondary rescue therapy at a lower level of immunosuppression was successful in all cases. Reyes et al. (11) have shown that some recipients in a similar series of cases could be left permanently drug free, but which recipients cannot be predicted.

In summary, we have shown here that in selected patients after liver transplantation, temporary withdrawal of immunosuppression therapy may be indicated in the management of severe infectious complications, without the development of immediate rejection. Reinstitution of immunosuppression in reduced doses at a later time can be done on a case to case basis to prevent the emergence of rejection.

REFERENCES

1. Rubin RH. The compromised host as a sentinel chicken. N Engl J Med 1987;317:1151. [PubMed: 3657881]
2. Scherbaum WA, Zanker B. Infectious complications in immunosuppressed patients after kidney transplantation. Immun Infekt 1988;16:6. [PubMed: 3129358]
3. Bass M. Infection in renal transplantation. Crit Care Nurs Clin North Am 1990;2:133. [PubMed: 2357309]
4. Fung J, Abu-Elmagd K, Jain A, et al. A randomized trial of primary liver transplantation under immunosuppression with FK506 vs cyclosporine. Transplant Proc 1991;23:2977. [PubMed: 1721333]
5. Demetris AJ, Fung J, Todo S, et al. Conversion of liver allograft recipients from cyclosporine to FK506 immunosuppressive therapy: a clinicopathologic study of 96 patients. Transplantation 1992;53:1056. [PubMed: 1374944]
6. Rouse BT, Horohov DW. Immunosuppression in viral infections. Rev Infect Dis 1986;8:850. [PubMed: 3025993]
7. Kaposi K, Rice GPA. Cytomegalovirus infection of peripheral blood mononuclear cells: effects on interleukin-1 and -2 production and responsiveness. J Virol 1988;62:3603. [PubMed: 2843662]
8. Starzl TE, Demetris AJ, Murase N, Ildstad S, Ricordi C, Trucco M. Cell migration, chimerism, and graft acceptance. Lancet 1992;339:1579. [PubMed: 1351558]
9. Starzl TE, Demetria AJ, Trucco M, et al. Chimerism after liver transplantation for type IV glycogen storage disease and Type I Gaucher's disease. N Engl J Med 1993;328:745. [PubMed: 8437594]
10. Starzl TE, Demetris AJ, Trucco M, et al. Cell migration and chimerism after whole organ transplantation: the basis of graft acceptance. Hepatology 1993;17:1127. [PubMed: 8514264]
11. Reyes, J.; Tzakis, A.; Zeevi, A., et al. Chimerism and the frequent achievement of a drug free state after orthotopic liver transplantation. Abstracts of the 19th Annual Meeting of the American Society of Transplant Surgeons; May 19–21; Houston, TX.

TABLE 1

Infection, immunosuppression, and outcome in the 31 patients[a]

Patient	Infection	Immunosuppression	Outcome
1	CMV retinitis	FK	Alive
2	CVM retinitis	FK	Alive
3	CMV retinitis	FK	Alive
4	CMV pneumonitis	FK	Died (28 days)
5	CMV pneumonitis	CSA	Alive
6	CMV + PCP pneumonitis	FK	Died (18 days)
7	Disseminated CMV	FK	Died (27 days)
8	Disseminated CMV	FK	Died (16 days)
9	Disseminated CMV + PTLD	FK	Died (21 days)
10	Disseminated TB	FK	Alive
11	Dissemmated TB	CSA	Alive
12	PCP pneumonia	FK	Alive
13	PCP pneumonia	FK	Alive
14	Aspergillosis	FK	Alive
15	Aspergillosis	FK	Died (30 days)
16	Aspergillosis	FK	Died (50 days)
17	Cryptococcal meningitis	FK	Died (56 days)
18	Cryptococcal meningitis	CSA	Died (21 days)
19	Cryptococcal meningitis	CSA	Died (23 days)
20	PTLD	CSA	Died (20 days)
21	PTLD	CSA	Died (25 days)
22	PTLD	CSA	Died (23 days)
23	PTLD	CSA	Alive
24	PTLD	CSA	Alive
25	PTLD	CSA	Alive
26	PTLD	CSA	Alive
27	PTLD	CSA	Alive
28	PTLD	FK	Alive
29	PTLD	FK	Alive
30	PTLD	FK	Alive
31	PTLD	FK	Alive

[a] PCP, *Pneumocystis carinii* pneumonia; PTLD, posttransplant lymphoproliferative disorder.