The Spectrum of Aspergillosis in Liver Transplant Patients: Comparison of FK 506 and Cyclosporine Immunosuppression

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Aspergillosis is the second most important cause of fungal infection after liver transplantation (LTx), with a mortality approaching 100%. In a previous study, we observed a 4% frequency of invasive aspergillosis in 101 consecutive LTx recipients.[1] Outcome depends on early treatment, however, the diagnosis of this disease is very difficult.[2]

The introduction of FK 506, allowed us to evaluate the impact of this new immunosuppressive agent on the incidence and outcome of aspergillosis following LTx, and to compare this to a group of patients under traditional cyclosporine (CyA) therapy.

METHODS

Patient Selection

Pathology and microbiology records were reviewed during the period from 1981 to 1990, and 32 cases of invasive aspergillosis occurring after liver transplantation were identified. Their inpatient and outpatient charts were reviewed.

Definitions

Definitive diagnosis—Histologic evidence of tissue invasion at biopsy or autopsy (24 of 32, 75%).

Probable diagnosis—Characteristic clinical picture combined with lack of response to antibacterial agents and presence of repeated positive cultures for Aspergillus species (8 of 32, 25%).

Disseminated aspergillosis—Histologic proven invasion in autopsy of two or more noncontiguous organs (16 of 32, 50%).

Immunosuppression

Two protocols were used: (a) CyA and steroids, and (b) FK 506 with low-dose steroids (20 mg/d).

Rejection episodes were treated with a 1-g dose or 5-day recycle of methylprednisolone. OKT3 monoclonal antibody was used for treatment of steroid-resistant rejection.

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Antibiotic Prophylaxis

Perioperative IV cefotaxime and ampicillin 4 g/d were administered to all patients. Fungal prophylaxis included oral nystatin 2 millions units daily.

Risk Factors

We analyzed four pretransplant (hepatocellular disease, ALT >60 and steroid use) and seven posttransplant variables (IV antibiotics >5 days, cumulative surgical time > 12 hours, retransplantation, additional abdominal operations, choledochojejunostomy, OKT3, and additional steroids).

Statistics

Proportions were analyzed with chi-square test or Fisher's Exact Test when data were scarce.

RESULTS

The characteristics of the population are shown in Table 1. During the 10-year study period, 2180 patients underwent OLT at our institution, and 32 patients developed invasive aspergillosis for an overall rate of 1.5%.

CyA and steroid immunosuppression were used in 1247 patients, and 30 patients were identified with invasive aspergillosis, for an incidence of 2.4%, and a mortality of 94% (29 of 30). Two cases of aspergillosis occurred from among 933 patients receiving FK 506 and low-dose steroids for an incidence of 0.2% ($P < .01$), and a mortality of 50% (1 of 2).

The mean time to diagnosis after OLT was 101 ± 160 days in the CyA group and 31 ± 13 days in the FK 506 group. The median time of diagnosis was 35 days in the CyA group and 31 days in FK 506 group. One FK 506 patient died of disseminated aspergillosis on day 219, which was significantly longer than the mean survival time of 119 days seen in CyA patients. The other patient is free of disease after completing 6 months of treatment that included amphotericin B and itraconazole.

The presenting symptoms in FK 506 patients included fever and respiratory complaints in both, and skin involvement in one. Fever, respiratory, and neurological manifestations were the most frequent presenting symptoms in the CyA group. In both FK 506 and CyA patients, concomitant bacterial, fungal, and viral infections were frequent.

When four pretransplant risk factors were analysed, a higher occurrence of hepatocellular disease in FK 506 patients was found. No patient receiving FK 506 required OKT3 or retransplantation, whereas in the CyA group, 73% of patients were treated with OKT3 and 70% needed retransplantation. These findings were the most significant of the seven posttransplant variables analysed.

DISCUSSION

Aspergillosis continues to be associated with very high mortality after liver transplantation. In this series, only two patients survived, and in only 56% of patients was the diagnosis made before death. Variables found to be correlated with higher rates of fungal infection in our previous reports[1,3] are also associated with aspergillosis in this series. The typical patient at risk for aspergillosis is relatively young, has undergone a long cumulative surgical time, and demonstrates persistent fever despite antimicrobial therapy in the first months after transplantation.

With the introduction the new immunosuppressive agent, FK 506, we observed a decrease in the incidence of aspergillosis. This phenomenon occurred in spite of the potent immunosuppressive properties of FK 506, suggesting that this new drug has the ability to decrease other factors for infection, such as lowering steroid usage without increasing the risk of rejection and the subsequent need for augmented immunosuppression and/or retransplantation.

Improvement in patient management after LTx has allowed us to increase patient and graft survival to levels unparalleled only a few years ago. The introduction of novel agents such as FK 506 will contribute to a further improvement in overall morbidity.

References

1. Kusne S, Dummer JS, Singh N, et al. Medicine 1988;67:132. [PubMed: 3280944]
2. Denning DW, Stevens DA. Rev Infect Dis 1990;12:1147. [PubMed: 2267490]
3. Kusne S, Dummer JS, Singh N, et al. Transplant Proc 1988;20:650.

Table 1

Comparison of Aspergillosis on FK 506 and CyA

	Total	CyA	FK506
Total OLT	2180	1247	93
Aspergillus	32(1.5%)	30 (2.4%)[*]	2 (0.2%)[*]
Time diagnosis (mean ± SD)	97 ± 162	101 ± 168	31 ± 13
Time diagnosis (median)	34.5	35	31
Died	30 (94%)	29 (97%)	1 (50%)

[*] $P< 01$.