Itraconazole Therapy for Acute Invasive Pulmonary Aspergillosis in Heart Transplantation


TREATMENT OF acute invasive pulmonary aspergillosis (AIPA) in immunocompromised hosts remains difficult and has a high mortality rate.1 In patients treated with cyclosporin A (CyA) the additional side effects of the common antifungal agents may have important sequelae on renal and hepatic function, therefore limiting their use.2-4 We report the results obtained using Itraconazole, a new, orally active, antifungal agent, in the treatment of AIPA after heart transplantation (HTx), occurring in two out of 64 patients (3%) who were discharged after HTx at our department from November 1985 to July 1988.

CASE REPORTS

Case 1
A 44-year-old man underwent orthotopic HTx for dilated cardiomyopathy on November 1985. Immunophrophylaxis for allograft rejection utilized a five-day course of equine antilymphocytic globulin, CyA, azathioprine (Aza) and oral prednisone. CyA was titrated to maintain a whole blood level between 400 to 500 ng/mL as assessed by radioimmunoassay (Sandoz kit, Sandoz, Basel, Switzerland). Serial endomyocardial biopsies revealed no signs of rejection throughout the 1st post-HTx month and the patient was discharged in good clinical condition. One week later he was readmitted because of fever and increased bilirubin level. Clinical and laboratory data suggested a non A-non B viral hepatitis. Thirty days after readmission, while his bilirubin level was at the highest values (30 mg/dL), a right apical, round shaped, infiltrate was noted on chest x-ray. Suspecting a pulmonary fungal infection bronchoscopy with brushing was performed and both microscopic and cultural examinations of the aspirate revealed the presence of Aspergillus fumigatus. Treatment with amphotericin B was started and after a total dose of 2 g clear improvement of the pneumonic process was noted with normalization of subsequent cultures. However, persistence of severe liver dysfunction and development of renal failure, led to suspension of antifungal treatment. Immunosuppression protocol was then modified by progressive reduction and suspension of CyA and by maintaining the patient only on Aza and steroids. In the following days a relapse of the fungal pneumonia was observed (Fig 1) with appearance of multiple, bilateral, confluent infiltrates, with positive cultures of bronchoaspirates, and increased titer of serum specific IgG for A. fumigatus. The patient also developed a large pericardial effusion which required pericardiotomy, yielding 900 cc of serous fluid from which Aspergillus was also cultured. It was then decided to try a new antymycotic drug, Itraconazole (Janssen Pharm., N.V. Beersel, Belgium), which was administered in a dose of 200 mg/day po maintaining serum levels around 700 ng/mL. After ten days of treatment negativization of cultures and reduction of serum antibodies occurred together with improvement of the chest x-ray. Both renal and liver functions improved with a fall in creatinine and bilirubin levels, so that it was possible to resume CyA treatment. It appeared that during Itraconazole treatment lower doses of CyA (2 mg/kg/day) were needed to maintain therapeutic levels. After two years of continuous treatment the chest x-ray is clear except for a small residual aspergilloma (Fig 2), without any clinical sign of infection.

Case 2
A 36-year-old man underwent orthotopic HTx for dilated cardiomyopathy in February 1987. The immunosuppressive treatment was the same as for Patient 1. In the early postoperative period the patient developed acute renal insufficiency as a consequence of right ventricular failure which required ultrafiltration and hemodialysis and temporary suspension of CyA. One month post-HTx, serial endomyocardial biopsies revealed two episodes of moderate acute rejection which were treated with a total of 6 g of methylprednisolone. At this time bilateral lung infiltrates were noted on the chest x-ray. Bronchoscopy and brushing were performed disclosing the presence of A. fumigatus. Since the patient was still on hemodialysis we then decided to use Itraconazole (400 mg/day) as first choice drug and already after 15 days of treatment, maintaining serum levels around 800 ng/mL, improvement of the chest x-ray was noted followed by complete restoration of the renal function two months post HTx. CyA was then resumed, and again lower doses (2.6 mg/kg/day) were needed to maintain therapeutic levels. After 12 months of continuous treatment the chest x-ray completely cleared, cultures and serology became negative and the treatment was suspended; and four months later the patient had no evidence of any relapse.

DISCUSSION

Infectious complications represent the main cause of mortality and morbidity after orthotopic HTx,1-3 Because of the chronic immunosuppressive regimen HTx recipients are particularly prone to infections caused not only by common pathogens, but also by other less frequent microorganisms such as fungi. Fungal infections are extremely difficult to treat and carry a dismal prognosis.5 Amphotericin B is considered the treatment of choice for pulmonary aspergillosis but it is associated to important side effects especially on the renal function.4

In the two patients herein reported pulmonary aspergillosis developed after two months post-HTx in the first and early postoperatively in the second, in the latter most likely following increased immunosuppression for ongoing rejection. Since both of them developed severe renal failure, the

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use of amphotericin B had to be either suspended or avoided. As gratifying results had been reported in experimental aspergillosis using Itraconazole, a new orally active triazole with minimal collateral effects, we decided to treat such complications with this drug in both our patients. After 24 and 12 months of treatment, respectively, aspergillus infection appears to be controlled in both.

Despite the limited experience we believe that our results indicate that: (1) Itraconazole appears to be effective in the treatment of AIPA in chronically immunosuppressed patients; (2) since it does not have important side effects, it can be administered even in patients with liver and/or renal failure; (3) Itraconazole might interfere with CyA clearance or absorption, requiring careful monitoring of CyA therapy; and (4) since this drug is still in an experimental clinical trial the length of treatment has yet to be defined; we believe that it should be continued, if well tolerated, until serology becomes negative.

REFERENCES