

Original Article

Pretransplant Antitubercular Therapy - How Long?

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ABSTRACT

Objective: To define a safe duration of antitubercular therapy in patients on dialysis awaiting a kidney transplant. Patients with chronic renal failure are more prone to develop tuberculosis than the general population. Continuing dialysis till completion of antitubercular therapy (ATT) has its problems both in terms of morbidity and finances. Since most patients in developing countries have to pay for their dialysis, it is important to define a safe duration of ATT prior to renal transplantation which balances the risk of flare up of tuberculosis with the problems of prolonged dialysis.

Design: Retrospective.

Setting: Department of Urology, Christian Medical College, Vellore, Tamil Nadu, India.

Materials and methods: Records of 1360 patients who had received renal allograft at our hospital were reviewed retrospectively. Patients who were found to have tuberculosis prior to transplantation and received

therapy according to our hospital protocol were assessed for the duration of pre transplant ATT and their outcome after transplantation.

Results: Out of 96 patients who received ATT starting at a mean of 122 ± 82 days before transplant, only one developed tuberculosis in the post transplant period. Of the 96 patients, a subgroup of 23 patients had received an allograft between six to eight weeks after initiating ATT, while the rest were transplanted at varying periods after that. At a mean follow up of 29 months post transplant, none of these 23 patients developed recurrence of tuberculosis. This compares favorably with a 13.3% incidence of post transplant tuberculosis among those patients who did not have the disease preoperatively.

Conclusion: Renal transplantation after 6-8 weeks of ATT is probably associated with a minimal risk of flare up of the disease in the post transplant period.

KEYWORDS: allograft, ESRD, *Mycobacterium*, renal transplant, tuberculosis

INTRODUCTION

Tuberculosis (TB) is a common disease in India. It is estimated that at least 50% of the Indian population above the age of 20 years is infected with the tubercle bacillus and remains at risk of the disease^[1]. The prevalence of tuberculosis in the urban population in India is 1.3%^[2]. Compared to the general population, the risk of tuberculosis in India, in patients undergoing dialysis, is reported to be as much as 13 times higher^[3]. Reports from the US put the relative incidence at 10-15 folds^[4,5] while in Turkey it is reported to be between 24 and 273 times^[6,7]. With increasing number of end-stage renal disease (ESRD) patients undergoing renal transplantation, the problem of balancing the risk of flare-up of the disease in the post transplantation period and the risk and expense of maintaining these patients on dialysis assumes greater significance. We attempted to review the outcome of management of these patients at our hospital and identify a reasonably safe period after starting ATT when renal transplantation could be performed.

MATERIALS AND METHODS

We reviewed the records of 1360 patients for whom adequate information was available and who had undergone renal transplantation at our centre between 1985 and 2001. Patients who had tuberculosis prior to renal transplantation and received ATT in the peritransplant period were included in the study. The predominant location of tubercular involvement and the duration of antitubercular therapy prior to renal transplantation were studied. We also looked at the post-transplantation period for possible recurrence or reinfection with the tubercular bacillus.

Patients suspected of having tubercular lung involvement were assessed by chest X-ray, sputum acid fast bacillus (AFB), gastric juice AFB or bronchoalveolar lavage specimen for AFB smear and culture. Tissue diagnosis was obtained from accessible lymph nodes, pleura or from the pericardium in patients requiring an open pericardiostomy for effusion with tamponade. Pleural or pericardial fluid was also stained and

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Table 1: Distribution of site of pre transplant tuberculosis (n = 96)

Site of infection	n	%
PUO	29	30.2
Lymph node	26	27.0
Pulmonary	19	19.8
Pleural effusion	6	6.3
Positive gastric juice AFB	6	6.3
TB Spine	3	3.1
Abdominal tuberculosis	3	3.1
Genitourinary tuberculosis	2	2.1
Miscellaneous	2	2.1
Total	96	100

cultured for AFB. Patients suspected to have disseminated disease or those without localizing signs underwent bone marrow aspiration for AFB smear and culture. Patients with suspicious lymph nodes in areas difficult to access, those with pyrexia of unknown origin or those with lymphocytic exudative collections negative for AFB on smear, were assessed by their response to a therapeutic trial of anti tubercular drugs, while awaiting culture reports. A positive therapeutic response is usually seen by about two weeks in the form of resolution of fever, weight gain, improvement in appetite and a feeling of general well being. Serological tests and PCR were not routinely performed for the diagnosis of tuberculosis in these patients.

All patients received 18 months of antitubercular therapy beginning with rifampicin (10 mg/kg/d), isoniazid (INH - 5 mg/kg/d), ethambutol (25 mg/kg/d) and pyrazinamide (35 mg/kg/d). Doses of drugs were modified according to the renal function. Ethambutol and pyrazinamide require 50% dose reduction in ESRD while INH is given at 150-200 mg per day in adults. Five days prior to transplantation rifampicin was substituted with ofloxacin (400 mg in adults) at the time when cyclosporine is started. Ofloxacin was continued for nine months while pyrazinamide was stopped after three months. Isoniazid and ethambutol were continued for 18 months after which all patients were put on lifelong secondary INH prophylaxis at a dose of 300 mg per day. We follow this intensive ATT regimen since another study from our institution showed a very high incidence of primary single and multi-drug resistant tuberculosis in our population⁸. In patients with atypical mycobacterial infection, treatment was initiated with amikacin and clarithromycin in addition to other drugs, according to sensitivity reports. Patients with ESRD were considered for renal transplantation after six weeks of ATT, if no other contraindication was noted.

Table 2: Distribution of findings in patients with PUO (n = 34)

Site of infection	n	%
PUO only	20	58.8
PUO with		
Pleural effusion	5	14.8
CXR suggestive	3	8.8
Pericardial effusion	1	2.9
Ultrasound / CT / CXR diagnosis of		
Mass at Porta hepatis	1	2.9
Para aortic lymph nodes	2	5.9
Para tracheal lymph nodes	1	2.9
Mediastinal lymph nodes	1	2.9
Total	34	100

Patients received prednisolone and azathioprine (2 mg/kg/d) immunosuppression until 1989 and thereafter cyclosporine (8 mg/kg/d in two divided doses) with prednisolone (20 mg/d) and azathioprine was used. Before 1989 prednisolone was started at a dose of 80 mg per day when used as part of two drug regimen and gradually tapered. Those with an uncomplicated course were given the option of withdrawal of cyclosporine at one year. Monoclonal antibody (OKT3) was used for the treatment of recurrent or refractory rejection from 1994. Mycophenolate mofetil and rapamycin have been used in a few patients during drug trials, as rescue therapy for cyclosporine toxicity and for recurrent rejections.

All patients were followed up in-centre three times a week for the first two months, twice a week for the next two months and once weekly for the subsequent two months. Thereafter they were seen at nine and twelve months and whenever required.

RESULTS

Out of 1360 patients studied, 112 had developed tuberculosis prior to transplantation. Of them 16 had completed antitubercular therapy prior to transplantation. Thus 96 patients could be evaluated in the peritransplant period and formed our study group. These patients were diagnosed to have TB at varying periods after the diagnosis of CRF. Thus patients required renal replacement therapy after varying periods of ATT. The common indications for starting antitubercular therapy in these patients are shown in Table 1. Forty three patients were already on dialysis at the time of diagnosis of tuberculosis. Of the 34 patients started on ATT for pyrexia of unknown origin (PUO), 20 (58.8%) had fever only, while the rest had other features suggestive of tuberculosis in addition to fever (Table 2). Two patients were diagnosed as having atypical mycobacterial infection.

Out of the 96 patients who were on ATT in the peritransplant period 11 (11.45%) patients expired due to various causes while still on ATT. Fourteen (14.58%) patients were lost to follow up before completing ATT. Seven (7.29%) patients were still on ATT at the time when this study was undertaken.

Patients underwent renal transplantation at a median of 90 days after the initiation of ATT (range 27 - 420 days). The mean duration was 122.25 ± 82.49 days. The time between diagnosis of tuberculosis and the development of ESRD, other co-morbidities, donor preparation and financial constraints influenced the time when renal transplantation could be performed. This resulted in the wide range of time between initiating ATT and performing the transplantation. These patients were followed up for a mean of 36.79 ± 34.65 months (range 2 - 216 months). Twenty three patients received an allograft between six to eight weeks of initiation of antitubercular therapy. These patients had a mean follow up of 29 months (range 7 - 120 months). Of these 23 patients, 19 had microbiologically or pathologically confirmed tuberculosis. Eight had sputum positive for AFB, three grew AFB from pleural fluid and two from gastric aspirate, and five had a histologically positive lymph node while one patient had pleural biopsy suggestive of tuberculosis. Of the four patients with PUO in this group, two had only fever while two had PUO with pleural effusion. The only patient who developed recurrence of tuberculosis in the post transplant period developed combined tubercular and cryptococcal meningitis three years after renal transplantation. His primary disease was tuberculosis of the spine and he received an allograft nine months after initiation of antitubercular therapy.

Out of 96 patients, 19 (20%) had expired at the time when this study was undertaken. Except the above mentioned patient who expired due to combined tubercular and cryptococcal meningitis, the other deaths were unrelated to tuberculosis.

DISCUSSION

The prevalence of tuberculosis in patients with ESRD on hemodialysis is 13.6%^[9]. The prevalence of tuberculosis in CRF patients awaiting renal transplant at our centre was 8.45%. Inability to make a definitive microbiological or tissue diagnosis of tuberculosis is common^[10]. This problem is more in endemic areas and in children where antitubercular therapy is often started on the basis of clinical, biochemical and radiological features^[11,12] or scoring systems^[13] to assist in diagnosis. Such patients are also diagnosed by response to a therapeutic trial of ATT^[12]. A definite diagnosis of tuberculosis was made in 78 of the 112

patients (70%) in our study. Patients on hemodialysis are known to have a higher incidence of predominant or exclusive extrapulmonary disease. It is reported to constitute between 40%^[4] to 92%^[15] of the total cases. In our study 41 of the 78 patients (52.5%) in whom tuberculosis could be localized, had extra pulmonary involvement. Lymph node was the commonest extra pulmonary site constituting 39.7% (31/78) of the proven presentations. About 30% of our patients presented with pyrexia of unknown origin, 41% of whom had other clinical or radiological features suggestive of tuberculosis. In these patients, when a detailed workup failed to identify any cause, response to a therapeutic trial of ATT confirmed the diagnosis.

The ideal duration of antitubercular therapy before renal transplantation is not defined. Most centers offer therapy with two or three drugs usually rifampicin, INH and ethambutol for about 12 to 24 months. We prefer to stop rifampicin since the dose requirement of cyclosporine is known to go up by at least two times^[16], significantly increasing the cost of treatment. Some studies have demonstrated unpredictable variation in blood levels of cyclosporine and a higher rate of acute rejection when both these drugs were used together. Rifampicin is known to increase the clearance of corticosteroids two fold^[17] and that of cyclosporine about two to five-folds^[18-20] by its effect on cytochrome P-450. Not much is written in the literature regarding the ideal duration of anti tubercular therapy prior to renal transplant. Malhotra *et al* in their study of tuberculosis and renal transplant have mentioned performing renal transplantation in 11 patients three to six months after initiation of ATT^[3]. They continued the medication for two years and observed one recurrence. In another study, four out of eight patients received an allograft in less than six months after starting ATT. They observed no recurrence^[9].

In India, the cost of maintaining a patient on dialysis with erythropoietin therapy would be about Rs. 30,000/- (US\$ 600) per month. The mean per capita monthly income of a salaried citizen of this country is Rs. 17,188/- (US \$ 350)^[21]. Since most patients have to pay for their transplants by themselves, it is important to define a shorter, but safe duration of ATT that prevents recurrence of TB in this population, allowing earlier transplantation. While cost certainly is a cause for concern, the much higher mortality in patients awaiting renal transplant is also a reason for attempting surgery earlier. Even in developed countries, mortality rates from sepsis are one to several hundred fold higher in dialysis patients as compared to the general population^[22]. Renal transplant recipients have

sepsis associated mortality rates approximately 20 folds higher than those of the general population but 15 folds lower than those of dialysis patients. We believe that with the protocol of therapy mentioned earlier, it is safe to perform renal transplantation after six weeks of initiation of antitubercular therapy. Even in established ESRD patients however, donor preparation, economic considerations and other comorbidities in the recipient at that time influence our ability to do so. In the study population, 23 of the 96 patients (23.95%) could actually receive an allograft between six to eight weeks. At a mean follow up of 29 months, none of these 23 patients developed recurrence of the disease. We know that about 58% cases of post transplant tuberculosis manifest within the first year after transplant^[23]. Thus a mean follow up of 29 months in these 23 patients appears adequate to demonstrate the safety of performing a renal transplant after six weeks of ATT. Among the entire group of 96 patients, at a mean follow up of 36.79 months, only one patient developed a recurrence of tuberculosis in the post transplant period. They had received a mean of 122.25 days of ATT prior to transplantation. Of the 19 patients who expired in the post transplant period only one (5.3%) did so of tuberculosis. In another study from our hospital, which looked at post transplant tuberculosis in the period 1986 -1999^[24], 166 of 1251 (13.3%) renal transplant recipients developed tuberculosis in the post transplant period. These patients had no evidence of tuberculosis prior to transplant. Out of 53 patients who expired; 17 (32%) were due to post transplant tuberculosis. This particular study, which looked at the same patient population and over a period almost equal to our study, provides data on the population which could serve as a control in our study. A comparison of these two studies suggests a reduction in risk of post transplant tuberculosis from 13.3% to about 1% and reduction in the risk of death due to tuberculosis from about 10% to 1%. Thus it appears that using the treatment protocol mentioned above and also using secondary INH prophylaxis, renal transplantation can be performed safely within six to eight weeks of initiation of antitubercular therapy with very little risk of flare up of the disease or of its recurrence in the post transplant period. To the best of our knowledge, this study has evaluated the largest number of patients reported till date on the necessary duration of pretransplant antitubercular therapy.

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