Original Article

Tuberculosis in renal transplant recipients on various immunosuppressive regimens

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Abstract

Background. Mycophenolate mofetil (MMF) and tacrolimus (TAC) are more potent than conventional immunosuppressive drugs, i.e. azathioprine, cyclosporin and prednisolone, and may be associated with an increase in the incidence of infections in the post-transplantation (post-tx) period. The aim of this study was to determine if the use of either or both of MMF and TAC for immunosuppression in renal transplant recipients increases the prevalence or modifies the clinical presentation of tuberculosis (TB), when compared with conventional therapy.

Methods. The medical records of 443 adult patients who received a kidney transplant between 1994 and 2002 were reviewed retrospectively. Comparisons were made between patients who had conventional immunosuppressive treatments (cyclosporin, azathioprine and prednisolone) or an alternative regimen (including MMF, TAC or both).

Results. We found 20 patients (4.5%) to have post-tx TB. There were 13 cases of TB (age 38.9±10.6 years) among 328 patients who received conventional immunosuppressants (group I) (4.0%) and seven cases (age 24.2±7.4 years) among 115 (6.1%) who received an alternative immunosuppressive regimen (group II) (P>0.05). The patients in group II were younger than the patients in group I (P=0.002). A significantly higher number of patients in group II developed TB within the first 6 months post-tx (P=0.042). However, there was no significant difference between the two groups regarding clinical and radiographic presentations or outcomes.

Conclusions. Immunosuppression with TAC or MMF is associated with the development of TB earlier in the post-tx period and in younger patients.

Keywords: mycophenolate mofetil; renal transplantation; tacrolimus; tuberculosis

Introduction

Tuberculosis (TB) is still one of the most serious infections worldwide among renal transplant recipients, because of their chronic immunosuppression. Conventional immunosuppressive regimens include azathioprine (AZA), cyclosporin (CsA) and prednisolone. Mycophenolate mofetil (MMF) and tacrolimus (TAC) are potent immunosuppressive agents that have been included more recently in most post-transplantation immunosuppression protocols. MMF, developed as a replacement for AZA in maintenance immunosuppression, impairs lymphocyte function by blocking purine synthesis via inhibition of the enzyme inosine monophosphate dehydrogenase [1]. TAC selectively inhibits the transcription of interleukin-2 and several other cytokines, mainly in T-helper lymphocytes. It may therefore be used instead of CsA [2]. These drugs are efficacious either as primary or as rescue immunosuppressants after renal transplantation [1].

When compared with the combination of TAC and prednisolone, immunosuppressive regimens that comprise TAC, MMF and prednisolone have been reported to be associated with fewer episodes of rejection, a lower need for steroids and better peri-operative graft function [3]. In solid organ transplant recipients, the combination of TAC and MMF had a higher immunosuppressive potency than CsA plus MMF [4].

The potency of immunosuppressive drugs may, however, be associated with increases in the prevalence or severity of infections in the post-tx period. In simultaneous kidney–pancreas transplant recipients, MMF was found to be more efficacious than AZA, but the incidence of opportunistic infections was higher...
among patients treated with MMF (54 vs 38%) [5]. Data are scarce with regards to TB in patients treated with different immunosuppressive regimens. Reactivation of TB has been reported in one patient after conversion from AZA to MMF 16 years after renal transplantation [6]. In a prospective study, treatment with CsA and TAC was associated with an earlier onset of TB when compared with prednisolone and AZA [7].

Therefore, the aim of this study was to determine if immunosuppressive therapy with newer agents increases the prevalence of TB or modifies its clinical presentation, management or outcome when compared with conventional therapy. To this end, the clinical records of adult kidney recipients who developed TB were analysed retrospectively for findings at presentation and for outcome, and comparisons were made between patients who received conventional regimens (CsA, AZA and prednisolone) or alternative ones (including MMF, TAC or both).

Subjects and methods

We reviewed the clinical records of all adult patients who received kidney grafts at two referral centres between 1994 and 2002. The data collected for analysis included: demographic features, risk factors, graft origin, mean time of onset of TB since transplantation, diagnostic methods, manifestations of TB, relationship to rejection treatment, serum levels of CsA and TAC, concomitant infections and their outcomes, immunosuppressive regimen changes, delayed graft function, use of anti-thymocyte globulin (ATG), acute rejection episodes, pulse corticosteroid treatment, infections and diabetes mellitus that developed during the post-tx period.

The patients were grouped according to the immunosuppressive regimen they had received following transplantation. Group I consisted of transplant recipients on conventional treatment with CsA, AZA and prednisolone, and group II included those who received an alternative immunosuppressive regimen, including TAC, MMF or both. We then compared the two groups.

Immunosuppressive protocols

There were no criteria for assigning a particular patient to any particular immunosuppressive regimen. Thus choosing the immunosuppressive regimen was at the discretion of the attending physicians, and the choice was largely made at random. The donor type, the recipient's characteristics or other parameters did not influence the treatment given. No patient was switched from conventional to the TAC/MMF-based regimen, or vice versa, during the study period.

CsA was administered at a starting dose of 2 mg/kg intravenously (i.v.) on the day of transplantation and 4 mg/kg on the first post-operative day, followed by a maintenance dose of 8 mg/kg/day orally. Its target serum level for the first 3 months was 200–400 ng/ml, and 100–300 ng/ml thereafter. AZA was administered at a dose of 2 mg/kg i.v. on the day of operation and 1.5–2 mg/kg/day during the post-operative period. Methylprednisolone was given as a bolus of 1000 mg on the day of operation followed by doses of 250 and 100 mg/day on the first and second post-operative days, respectively. Its maintenance doses were 30 mg/day for the first 3 months and 10–15 mg/day for the second 3 months.

Patients in group II received one of the following regimens: (i) CsA, prednisolone and MMF (n = 57); (ii) TAC, prednisolone and AZA (n = 38); or (iii) TAC, prednisolone and MMF (n = 20). The doses for CsA, AZA and prednisolone were the same in the two groups. Tacrolimus was administered at a dose of 0.2 mg/kg/day on the first post-surgical day and 0.1 mg/kg/day on the following days. Its target serum level was 10–15 ng/ml for the first 3 months and 5–10 ng/ml thereafter. MMF was given in a 1 g dose the first night after the operation followed by a maintenance dose of 2 g/day, when combined with CsA, or 1 g/day, when combined with TAC.

ATG was given to the patients who experienced delayed graft function (i.e. renal dysfunction during the early post-operative period).

Diagnosis of TB

Post-tx TB was clinically suspected when a patient presented with one or more of: fever, respiratory symptoms and symptoms of other organ involvement. A chest X-ray was routinely obtained if a pulmonary infection was suspected. The diagnosis of TB was made when acid-fast bacilli were present on the Ziehl–Neelsen-stained smear of respiratory specimens and *Mycobacterium tuberculosis* grew on the culture (Lowenstein–Jensen medium) of appropriate samples (sputum, bronchoalveolar lavage and pleural fluid, tissue specimen), or caseating granulomas were detected on histopathological examination of biopsy samples. Sputum examination was done in six patients (46.2%) in group I and five patients (71.4%) in group II. We examined bronchoalveolar lavage material from six patients (46.2%) in group I and six patients (85.7%) in group II. The sites of the biopsies made to reach a definite diagnoses of TB were: lung, pleura, lymph node, skin, bone marrow and liver.

TB was classified according to the type and extent of involvement. Thus, pulmonary disease was defined as the involvement of the lungs only, and extrapulmonary TB signified the involvement of a single extrapulmonary site. ‘Disseminated TB’ referred to the concomitant involvement of at least two separate sites. Primary TB was defined as the involvement of the lung parenchyma together with the involvement of hilar and mediastinal lymph nodes or pleura, or both [8].

Anti-TB treatment

The standard treatment for TB at our institution includes isoniazid (5 mg/kg/day), rifampin (10 mg/kg/day), pyrazinamide (15–30 mg/kg/day) and ethambutol (15–25 mg/kg/day) for the first 2 months, followed by isoniazid and rifampin for another 7 months.

Statistical analysis

For parametric measures, the Student t-test was used. We analysed categorical variables using the $\chi^2$ test and Fisher’s exact test. A value of $P<0.05$ was considered significant for all statistical analysis.
Results

We reviewed the records of 443 renal transplant recipients, whose demographic features are shown in Table 1. Of these patients, 20 (4.5%) were found to have developed TB during the post-tx period. There were 13 cases of TB among 328 patients who received the conventional immunosuppressive regimen (group I) (4.0%), and seven cases (6.1%) among 115 patients who received an alternative immunosuppressive regimen (group II) (P > 0.05). Of these seven patients, three were receiving TAC, prednisolone and AZA; two were receiving CsA, prednisolone and MMF; and the last two were on TAC, prednisolone and MMF. There was no difference between these subgroups with regards to the incidence of TB; however, the numbers were too small to reach a definite conclusion.

TB developed at a younger age in group II patients (24.2 ± 7.4 years) than in group I patients (38.9 ± 10.6 (P = 0.002), although the mean ages of the two groups were similar (30.4 vs 30.8 years, respectively).

There was no difference between the two groups regarding potential risk factors for the development of TB. Within the study population, four patients had a history of acute rejection: three in group I (6, 8 and 9 months post-tx) and one in group II (7 months post-tx). All four were treated with pulse corticosteroids. ATG was administrated to one patient in group I and to three patients in group II for DGF. There was no difference between the two groups regarding the administration of ATG, history of rejection and use of pulse corticosteroids. There was also no temporal relationship between the administration of ATG and when TB developed. None of the patients reported recent contacts with active cases of TB. One patient in group I had had TB 18 years earlier. No patient in either group had a past family history of TB. Tuberculin testing was not done on patients in the pre-tx period. Four patients in group I (30.8%) but none in group II had radiographic findings suggestive of inactive TB. None of the patients in either group had received chemoprophylaxis.

Post-tx infections tended to occur more frequently (53.8 vs 14.3% in group II, P = 0.106) and diabetes mellitus developed more frequently in group I (38.5 vs 14.3% in group II, P = 0.277), but neither tendency reached statistical significance.

The median time interval between transplantation and the development of TB was 53.1 ± 73.1 (2–255) months in group I and 46.1 ± 55.8 (3–145) months in group II (P > 0.05). A significantly higher number of patients in group II developed TB during the first 6 months post-tx (P = 0.042) (Table 2). The mean duration of symptoms of TB until diagnosis was 32.5 ± 16.1 (7–60) days in group I and 18.9 ± 11.6 (12–30) days in group II (P > 0.05). There was no difference between the groups for symptoms at presentation. The tuberculin skin test was performed on five patients in group II and was negative in all except one.

The sites of TB are summarized in Table 2. A higher percentage of patients in group II (71.4 vs 38.4% in

Table 1. Demographic features of the patients on conventional treatment (group I) and alternative treatment (group II)*

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 13)</th>
<th>Group II (n = 7)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)b</td>
<td>38.9 ± 10.6</td>
<td>24.2 ± 7.4*</td>
</tr>
<tr>
<td>Sex (male/female)c</td>
<td>8/5</td>
<td>4/3</td>
</tr>
<tr>
<td>Duration of haemodialysis (months)b</td>
<td>19.6 ± 25.0</td>
<td>10.4 ± 9.2</td>
</tr>
<tr>
<td>Cause of renal diseasec</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Unknown</td>
<td>7</td>
<td>3</td>
</tr>
<tr>
<td>Chronic pyelonephritis</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Diabetic nphopathy</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Amyloidosis</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Acute glomerulonephritis</td>
<td>0</td>
<td>2</td>
</tr>
<tr>
<td>Chronic glomerulonephritis</td>
<td>1</td>
<td>1</td>
</tr>
<tr>
<td>Previous diseasesc</td>
<td></td>
<td></td>
</tr>
<tr>
<td>TB</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>Pneumonia</td>
<td>0</td>
<td>1</td>
</tr>
<tr>
<td>Inactive TB lesions on CXRc</td>
<td>4</td>
<td>0</td>
</tr>
<tr>
<td>Donor type (living related/cadaveric)c</td>
<td>10/3</td>
<td>5/2</td>
</tr>
</tbody>
</table>

*Group I consisted of patients on conventional treatment with CsA, AZA and prednisolone, whereas group II consisted of patients on TAC, MMF or both.

Values represent the number of patients.

aGroup I consisted of patients on conventional treatment with CsA, AZA and prednisolone, whereas group II consisted of patients on TAC, MMF or both.
bWhen two percentage values are given to reflect the time-related incidence of TB, the first is the rate among all TB patients in that group and the second is the rate among all transplant recipients in (all the members of) that group.
cLymph node (one patient), pleura (one patient), liver (one patient).
dPleura.
eLung and lymph node (one patient), pleura (two patients), skin (one patient) or bone marrow (one patient).

Table 2. The time and site of tuberculosis development in the conventional and alternative treatment groupsa (groups I and II, respectively) in the post-transplantation period

<table>
<thead>
<tr>
<th></th>
<th>Group I (n = 13/328)</th>
<th>Group II (n = 7/115)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Time when TB was diagnosed</td>
<td></td>
<td></td>
</tr>
<tr>
<td>First 6 monthsb</td>
<td>2 (15.4%, 0.6%)</td>
<td>5 (71.4%*, 4.3%**)</td>
</tr>
<tr>
<td>6–12 months</td>
<td>4</td>
<td>1</td>
</tr>
<tr>
<td>After 1 year</td>
<td>7</td>
<td>1</td>
</tr>
<tr>
<td>Site of TB</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Pulmonary</td>
<td>5</td>
<td>2</td>
</tr>
<tr>
<td>Extrapulmonary</td>
<td>3c</td>
<td>1d</td>
</tr>
<tr>
<td>Disseminated</td>
<td>5e</td>
<td>4f</td>
</tr>
</tbody>
</table>

Values represent the number of patients.

*P = 0.002.
**P = 0.036.
TB = tuberculosis; CXR = chest X-ray.
group I) developed primary TB, but this did not reach statistical significance.

There was no statistically significant difference between the two groups with regards to the elevation of liver function tests, occurrence of toxic hepatitis, acute rejection, need for dose adjustments of the immunosuppressants and concomitant infections. With the administration of anti-TB treatment, there was a need to increase the daily dose of CsA in group I from 208.5 ± 44.6 to 366 ± 95.5 mg (P = 0.011); in group II, the daily dose of TAC was increased from 6.9 ± 2.4 (range: 4–10 mg/day, mean: 0.13 ± 0.02 mg/kg/day) to 19.6 ± 3.3 mg (range: 16–22 mg/day, mean: 0.40 ± 0.11 mg/kg/day) (P = 0.004).

The duration of follow-up was 55.4 ± 28.8 (5–104) months in group I and 15.1 ± 3.5 (8–19) months in group II. During follow-up, there were no relapses in any of the patients who received anti-TB treatment. In group II, two patients (28.6%) died on days 21 and 30 of anti-TB treatment. One of them had pulmonary TB and developed toxic hepatitis while under treatment. This patient had also been diagnosed to have bacteraemia due to methicillin-resistant Staphylococcus aureus (MRSA) prior to the diagnosis of TB. He had been treated with glycopeptide antibiotics, with which his clinical condition had improved, and no organism was grown in the post-treatment cultures of blood and respiratory specimens. The second who died had disseminated TB (lung and bone marrow), and he died with toxic hepatitis and acute pancreatitis, possibly due to the anti-TB treatment. The higher TB-related mortality in group II (two out of seven, 28.6%) was not significantly different from that in group I (none out of 13 patients) (P > 0.05).

**Discussion**

This study showed that immunosuppression with one or both of TAC and MMF is associated with the development of TB at a younger age and at a higher frequency during the first 6 months after transplantation when compared with conventional therapy.

Among the 443 renal transplant recipients in this study, TB developed in 20 patients (4.5%). Previous studies in Turkey also reported rates between 2.4 and 4.2% [9,10]. These rates are almost 10 times as high as the prevalence of TB in the general Turkish population (27 in 100 000) [11]. There was no difference in the prevalence of TB between the two groups treated with different immunosuppressive regimens.

Active TB infection in transplant recipients can be due to airborne spread in the community or transmission with the transplanted organ, but the disease is believed to develop mainly because of the reactivation of an old, pre-existing focus [12]. Patients who receive kidney grafts are at an increased risk for the development of mycobacterial disease, because of uraemia and the immunosuppressants used in the post-tx period, all of which interfere with T-cell function [13]. The presence of co-existing infections [deep mycoses, and infections due to cytomegalovirus (CMV), Pneumocystis carinii or Nocardia] is also closely related to the development of TB [14].

The optimal dose of maintenance immunosuppressive therapy in renal transplantation is not established. The major immunosuppressive agents that are currently being used are corticosteroids (primarily oral prednisolone), AZA or MMF and CsA or TAC. TAC and MMF are considered to be potent immunosuppressants, as they prevent early acute rejection; however, the incidence of opportunistic infections increases when such potent agents are used. In a large European trial, treatment with CsA and TAC was associated with the development of infection in ~40% of patients, sepsis in 20% and CMV infection in 15–25% [15]. Treatment with TAC was found to be associated with an increased incidence of severe infections (37 vs 12%) in recipients of heart transplants [16]. In our study, there was also a tendency toward the more frequent occurrence of post-tx infections in patients using TAC or MMF. On the other hand, the incidence of post-tx diabetes mellitus was higher in the conventional therapy group than in the alternative therapy group, in spite of non-significant differences in corticosteroid doses, and in contrast to previous reports on the association of TAC with diabetes mellitus. However, group I patients had other risk factors for diabetes. Age and hepatitis C seropositivity have been reported to be important risk factors for post-tx diabetes mellitus [17]. In our study, the patients in group I were older, had a higher positivity for hepatitis C antibody and had longer follow-ups than the patients in group II. Moreover, nearly half of the patients in group II (57 out of 115, 49.6%) were not treated with TAC, all of which may explain the lower rate of diabetes mellitus in this group.

There are no data on whether or not the immunosuppression protocol is associated with any change in the rate, clinical presentation and outcome of TB except for the report on a patient with a history of pulmonary TB during childhood, who developed axillary lymph node TB after conversion from AZA to MMF therapy 16 years after renal transplantation [6]. That report concluded that, in renal allograft recipients, MMF therapy may cause reactivation of old, dormant TB even in the late post-tx period.

In this study, TB developed earlier and at a younger age in patients receiving an alternative regimen of immunosuppression, with one or both of TAC and MMF. This may be related to the higher potency of immunosuppression in these patients, who therefore would be more prone to develop primary TB following exposure to the bacilli. Somewhat supportive of this hypothesis is the statistically non-significant observation that group II patients (treated with TAC, MMF or both) more frequently had concomitant TB involvement of their lungs together with the involvement of hilar and mediastinal lymph nodes or pleura. There was no significant difference between the two groups, however, regarding the frequency of rejection episodes,
pulse corticosteroid therapy and the administration of ATG, as has already been reported [18]. The difference between the two groups in the incidence of TB in the early post-tx period is not likely to be due to differences in the lengths of follow-up, as the difference was still significant when the incidence rates were calculated using the total number of patients in each group as the denominator (Table 2).

Another important consideration in the management of transplant recipients who develop TB is the potential for drug interactions. Rifampin deserves special attention in this regard, with its induction of the hepatic microsomal P-450 system. When CsA is used in conjunction with rifampin, its serum level must be monitored closely. In this study, with dose adjustments made as required, serum levels of CsA were kept within the therapeutic range, and no acute rejection occurred. Experience regarding a possible interaction between rifampin and TAC has been rather limited to date. There is only one report where a late graft rejection occurred, following the substitution of CsA with TAC. The concomitant use of rifampin caused an abrupt decrease in the blood concentrations of TAC, leading to a 10-fold increase in its daily dose [19]. Our observations in this study support that previous observations in this study support that previous case report where a late graft rejection occurred, following the substitution of CsA with TAC. The concomitant use of rifampin caused an abrupt decrease in the blood concentrations of TAC, leading to a 10-fold increase in its daily dose [19].

In this study, tuberculin testing was not done routinely and isoniazid prophylaxis was not given to the transplant recipients, in accordance with the usual practices of the country. The tuberculin reaction is unreliable in the diagnosis of latent TB infection in this group of patients, because of immunosuppression and the regular use of bacille Calmette–Guérin (BCG) vaccination in childhood in this country [10]. Regarding the treatment of latent infection, two different studies showed that the prevalence of post-tx TB was not changed by the administration of isoniazid prophylaxis [9,20]. Besides, the risk of hepatotoxicity is relatively higher in patient populations such as this one, with high prevalence of infection with one or both of hepatitis B and C.

Post-tx TB occurring after 2 years of transplantation independently carries a 1.8 times higher risk of death compared with patients who do not develop the disease [14]. Mortality in transplant recipients with TB was 21.4% [16] and 22.2% [9] in two different studies, and it was mostly related to the severity of TB and complications of anti-TB therapy, mainly liver failure. In our study, the mortality rate was somewhat higher in the patients receiving TAC or MMF (28.6% vs 0%), but this difference did not reach statistical significance.

In conclusion, an alternative immunosuppressive therapy that includes TAC, MMF or both causes the earlier development of TB and may modify its clinical presentation, but it is not associated with significant drug interactions. The early development of TB in patients receiving alternative therapy may be significant because of the higher level of immunosuppression and the higher risks of concomitant medical problems during the first 6 months after transplantation.

Conflict of interest statement. None declared.

References


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