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Original article

Active tuberculosis in renal transplant recipients in a tertiary-care center, in Mexico City: a retrospective analysis of a cohort

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ABSTRACT

Background: The recipients of a renal transplant have a 50-100 times greater probability to develop active tuberculosis. The use of isoniazid has proven to decrease the reactivation frequency in high-risk patients. In this study we assess adherence to a prevention program of tuberculosis and outcomes in patients who are renal transplant recipients at tertiary care center located in Mexico City. **Material and methods:** At the end of 2003 we reviewed and updated the prevention and treatment program of tuberculosis (Tb) in candidates for a renal transplant. The program includes: 1) risk assessment before the transplant: clinical history, tuberculin skin test (TST), radiographic studies and mycobacterial cultures; 2) treatment of high-risks patients: isoniazid for six months in cases of latent Tb (LTb), defined as positive TST (over 5 mm) with no clinical evidence of the disease; 3) treatment of patients with demonstrated active tuberculosis. A revision was conducted of the files of all the patients who received a renal transplant from January 2004 to December 2009. We assessed adherence to the program, the frequency of LTb and active Tb during the follow up period. **Results:** All the files of the 230 patients who received a renal transplant in the study period were reviewed. 55% were men, with a mean age of 33.9 ± 11.9 years; 74.2% were kidney transplant recipients from a living donor, and 91.6% received induction immunosuppressive therapy. Assessment of tuberculosis risk: 30.4% (70/230) of the patients had TST + (> 5 mm), only 17 (8.1%) had a history of exposure and eight (3.8%) of previous Tb infection. 3.9% (9/230) of the chest radiographies had findings pointing to Tb, however a Chest CT was conducted in 22 patients, out of which six (27%) showed findings of pulmonary Tb and only one of these was diagnosed active disease, with ganglionar involvement. Pre-transplant treatment of high-risk patients: 98.5%

RESUMEN

Antecedentes: *Los receptores de un trasplante renal tienen una probabilidad 50-100 veces mayor de desarrollar tuberculosis activa. El uso de isoniacida ha demostrado disminuir la frecuencia de reactivación en pacientes de alto riesgo. En este estudio evaluamos la adherencia a un programa de prevención de la tuberculosis y los resultados en pacientes trasplantados renales en un centro de atención terciaria ubicado en la Ciudad de México.* ***Material y métodos:*** *A finales de 2003 revisamos y actualizamos el programa de prevención y tratamiento de la tuberculosis (Tb) en candidatos a trasplante renal. El programa incluye: 1) evaluación del riesgo antes del trasplante: historia clínica, prueba cutánea de tuberculina (PCT), estudios radiográficos y cultivos de micobacterias; 2) tratamiento de pacientes de alto riesgo: isoniacida durante seis meses en casos de Tb latente (LTb), definida como PCT positiva (más de 5 mm) sin evidencia clínica de la enfermedad; 3) tratamiento de pacientes con tuberculosis activa demostrada. Se realizó una revisión de los expedientes de todos los pacientes que recibieron un trasplante renal entre enero de 2004 y diciembre de 2009. Se evaluó la adherencia al programa, la frecuencia de TbL y Tb activa durante el periodo de seguimiento.* ***Resultados:*** *Se revisaron todos los expedientes de los 230 pacientes que recibieron un trasplante renal en el periodo de estudio. El 55% eran hombres, con una edad media de 33.9 ± 11.9 años; el 74.2% eran receptores de trasplante de riñón de un donante vivo y el 91.6% recibía tratamiento inmunosupresor de inducción. Evaluación del riesgo de tuberculosis: el 30.4% (70/230) de los pacientes tenía PCT + (> 5 mm), sólo 17 (8.1%) tenían antecedentes de exposición y ocho (3.8%) de infección previa por Tb. El 3.9% (9/230) de las radiografías de tórax presentaba hallazgos que apuntaban a Tb; sin embargo, se realizó una TC torácica en 22 pacientes; de los cuales, seis (27%) mostraron hallazgos de Tb pulmonar y sólo uno de ellos fue diagnosticado con enfer-

(69/70) of the patients with LTb received isoniazid, two of them suspended it before the end of six months due to poor adherence. In addition one case was diagnosed with active Tb and treated accordingly. Incidence of tuberculosis: During the follow up period [(average of 49.6 m (3.6-72)], there was only one case of splenic tuberculosis in a patient in hemodialysis previously treated for humoral rejection which included rituximab. **Conclusions:** A complete assessment of the risk for developing tuberculosis is carried out in our Institution to all patients who are candidates for renal transplantation. All high-risk patients received isoniazid with good tolerance. Despite the high prevalence of TST+ there is a very low incidence of tuberculosis and this is probably due to proper pre-transplant screening and the treatment of LTb for six months in nearly all high-risk patients.

Key words: Tuberculosis, renal transplantation, isoniazid prophylaxis.

medad activa, con compromiso ganglionar. Tratamiento pretrasplante de pacientes de alto riesgo: el 98.5% (69/70) de los pacientes con LTb recibió isoniacida, dos de ellos la suspendieron antes del final de los seis meses debido a una adherencia deficiente. Además, se diagnosticó un caso de Tb activa y se trató en consecuencia. Incidencia de la tuberculosis: durante el periodo de seguimiento [(promedio de 49.6 m (3.6-72)], sólo hubo un caso de tuberculosis esplénica en un paciente en hemodiálisis previamente tratado por rechazo humoral que incluía rituximab. ***Conclusiones:*** *En nuestra institución se realiza una evaluación completa del riesgo de desarrollar tuberculosis a todos los pacientes candidatos a trasplante renal. Todos los pacientes de alto riesgo recibieron isoniacida con buena tolerancia. A pesar de la alta prevalencia de PCT+, la incidencia de tuberculosis es muy baja y esto se debe probablemente a un adecuado cribado previo al trasplante y al tratamiento de LTb durante seis meses en casi todos los pacientes de alto riesgo.*

Palabras clave: *Tuberculosis, trasplante renal, profilaxis con isoniacida.*

INTRODUCTION

Infectious complications are the main cause of morbidity and mortality in renal transplant (RT) recipients during the first year and they are as well responsible for 25% of complications in the long term.[1-4] With the purpose to reduce its incidence, diverse strategies for screening, prophylaxis and treatment have been used in these patients. In spite of this, tuberculosis has been reported among RT recipients who have a significant risk, 50 to 100 times, greater than the general population.[1-4] In a previous report we described an incidence rate of 0.6% (2/350 patients) during a period of 14 years (1990 to 2003).[5] This risk is proportional to the prevalence of tuberculosis by geographic region. Mexico is considered a country with an intermediate prevalence of the disease, 13.5 cases per 100,000 inhabitants according to the report from 2009.[6,7] Furthermore, in the United States in 2007, 29% of the cases of active tuberculosis (ATb) were diagnosed in Hispanics, the majority of them being Mexican.[8,9]

In Mexico, there are reports of a frequency of 1.7% of ATb in the post-RT period, corresponding to a risk increased by a factor of 130 when compared to the non-transplanted general population.[10] Additionally, there is worldwide recognition that one of the most important risk factors for developing ATb in the immunocompromised patients is the prior evidence of latent tuberculosis (LTb), and the WHO has estimated that a third of the world population is living with this condition. Thus the prophylactic use of isoniazid in patients with LTb has shown to decrease the reactivation of tuberculosis after a transplant or administration of immunosupressive therapy. In the meta-analysis conducted by Currie et al (n = 704 patients) a significant decrease in the risk of developing post transplant ATb (RR 0.31) was seen after isoniazid therapy for 12 months without risk of hepatitis.[11] Accordingly, screening for ATb and LTb as well as the administration of prompt therapy are the most important measures to improve the outcome of these patients. For this reason, the aim of this study was to assess adherence to the ATb prevention program in patients who were candidates for RT and who subsequently underwent a RT as well as to evaluate the pretransplant assessment and posttransplant outcome.

MATERIAL AND METHODS

We conducted a descriptive, observational, retrospective cohort study in patients (n = 230) who underwent RT after the implantation of a more strict prevention program of tuberculosis at a tertiary care center in Mexico City from January 2004 to December 2009. Patients included had a minimum follow-up of 12 months after RT. Briefly, we reviewed the clinical files, looking for demographics and relevant clinical variables, as well as the chest X-ray, TST and cultures for *Mycobacterium tuberculosis*. The assessment for

LTb and ATb was initiated in candidates for a RT since 1971. However, the protocol was reinforced in 2002 in the following manner a detailed clinical history, an in-depth investigation for possible contacts, a TST (≥ 5 mm was considered as positive), a regular TST booster was placed in patients with a negative result in the first test. Once ATb was excluded, patients with LTb (TST ≥ 5 mm) received isoniazid 300 mg per day for six months, before RT.

Statistical analysis. A descriptive statistical analysis was performed according to the measurement level: mean and standard deviation for continuous variables and mean with interquartile intervals for categorical variables. We calculated the prevalence of the pretransplant ATb, post RT incidence and its confidence intervals at 95%.

RESULTS

During the study period, 230 patients were included, with a mean age of 33.9 ± 11.9 years and 55% of them were men. Other demographic and transplant characteristics are summarized in *Table 1*.

Program of tuberculosis prevention, risk assessment and outcome. All the patients underwent chest X-ray, TST and general urinalysis. Chest X-ray showed lesions suggesting ATb 8 patients (3.5%), all of them with negative sputum cultures for *M. tuberculosis*. Sixty of the 230 patients (26%) had a first TST positive. A booster was conducted in 80 of the 170 initial TST negative patients (47%), and 10 of them had a positive result. Therefore, 70/140 patients (50%) tested properly had a positive result or evidence of LTb *(Figure 2)*.

Other subsequent studies were conducted based on clinical suspicion, thus from 22 chest CT done, six showed findings suggestive of Tb (only one suggestive of ATb).

Because persistent hematuria or leukocyturia in the urinalysis or positive TST, 52 patients underwent urine cultures for *M. tuberculosis* (three samples per patient) and all of them were negative. Other cultures for *M. tuberculosis* from sputum or gastric lavage were requested in 32 patients (three samples per patient) and none were positive.

In one patient, enlarged lymph-nodes in the neck were detected and resected, the histopathological analysis disclosed granulomas with positive acid-fast stain and culture negative. As a result of this strategy, one of the 230 patients 0.43% (95% CI, 0.01 to 2.4) was confirmed to have ATb before RT.

The patient was a 35-years-old woman from State of Mexico, with positive TST and lymph-node enlargement in the neck, which was surgically removed and described above. She received complete treatment (four drugs) for 12 months. After six months, the RT was conducted from a living related donor. She received daclizumab induction and triple drug maintenance immunosuppression therapy based on tacrolimus, MMF and prednisone. After 4 years, she has remained cured and the renal function continued normal.

Treatment and outcome of latent tuberculosis. Sixty-nine of the 70 patients diagnosed with LTb were treated with isoniazid, 67 of them (97.1%) completed the six-month term of therapy. Two patients developed gastric intolerance and stopped the treatment after three months of therapy. No liver toxicity was seen in any of the patients.

Table 1. Demographic and transplant characteristic of study population.

Variable	n = 230 n (%)
Age	33.9 (± 11.9)
Male	127 (55.2)
Etiology of CKD	
Unknown etiology	140 (61.3)
Diabetic nephropathy	25 (10.8)
Systemic lupus erythematosus	21 (9.1)
Second transplant	12 (5.2)
Focal segmental glomerulosclerosis	10 (4.3)
Polycystic kidney disease	8 (3.4)
Other causes	14 (6)
Rural origin	52 (22.6)
Donor type	
Live donor	170 (73.9)
Deceased donor	60 (26)
HLA shared haplotypes	
Cero haplotypes	115 (50)
One haplotype	92 (40)
Two haplotypes	23 (10)
Induction therapy	
Daclizumab	153 (66.5)
Basiliximab	31 (13.4)
Thymoglobulin	17 (7.39)
w/o Induction	29 (12.6)
Maintenance immunosuppression	
Tacrolimus	187(81.3)
Cyclosporin	34 (13.9)
Antiproliferative	
Mycophenolate mofetil	184 (80)
Azathioprin	38 (16.5)
mTOR inhibitor	8 (3.4)
Prednisone	228 (99.1)

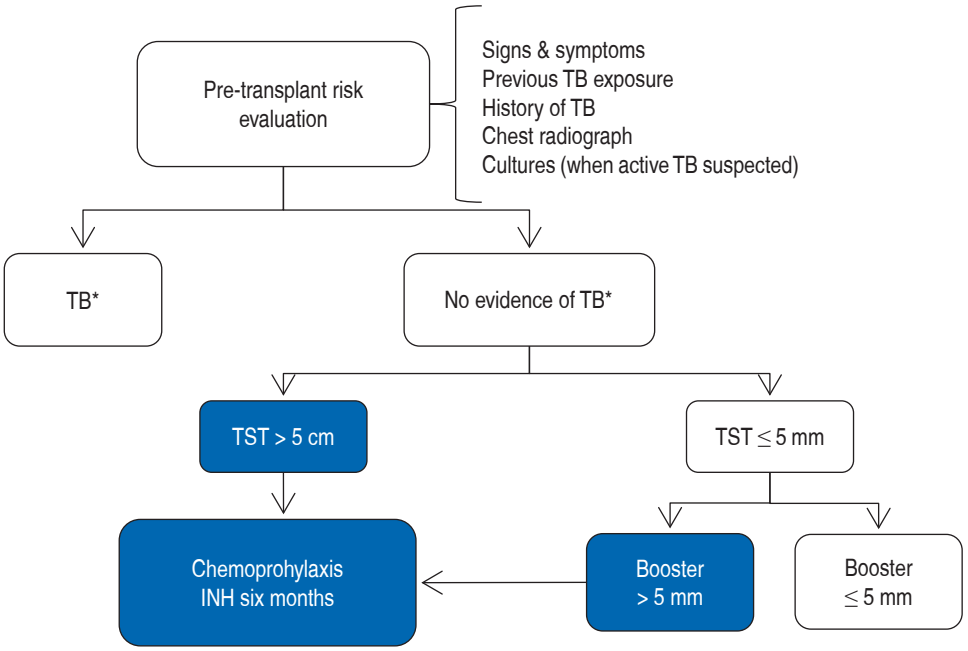

Figure 1.

Pre-transplant risk assessment.

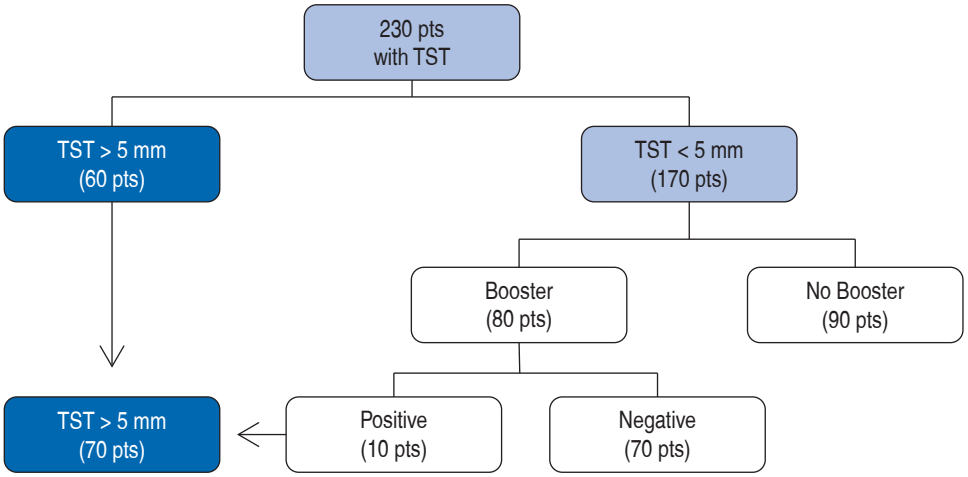

Figure 2.

LTb in transplant recipients 30.4% of the patients had a positive tuberculin skin test.

Follow up and active posttransplant tuberculosis. The median length of posttransplant follow up was 50 months (IQR 31 to 71). During the study period, only one of the 230 patients developed extrapulmonary Atb. A 40-year old woman with a negative TST in the pretransplant assessment, who underwent RT in 2005. After two years, because of biopsy-proven acute humoral rejection, she received standard treatment with plasmapheresis, IV immunoglobulin and rituximab. Six months after rejection treatment, she lost graft function and started on hemodialysis. Six months later (about three years after the RT), she was hospitalized because of high fever, sweets and chills. After an exhaustive clinical study, she underwent exploratory laparotomy with splenectomy. The histopathological study of the spleen demonstrated numerous caseous granulomas with positive acid-fast stain with culture negative. Treatment for tuberculosis with 4-drug regimen was administered during 12 months and the patient was cured and stayed on hemodialysis. She has been followed for 72 months and remained cured.

During the study period the incidence of posttransplant ATb was 0.43% (95% CI, 0.01 to 2.4)

or 430 per 100,000 inhabitants at risk, there were no significant differences in induction or maintenance immunosuppression therapy or the type of renal transplant (living or deceased donor) between the patients with pre-transplant LTb in comparison with those with LTb.

DISCUSSION

This study assesses adherence to a pretransplant tuberculosis prevention program in a tertiary care hospital located in a country with a medium prevalence of the disease. The program is based on pre-transplant screening and early treatment of patients with reactivation risk. In the first stage the patients are categorized as high or low risk of presenting ATb. In this study, 100% of the patients underwent this assessment. Subsequently we classified the high-risk patients, defined as those who have a TST > 5 mm or those with signs or symptoms suggesting ATb (radiographic findings, sterile leukocyturia, history of infection or contact with infected persons). Once that ATb was ruled out and with otherwise positive TST the patients were diagnosed as LTb carriers and considered for therapy with isoniazid.

The globally used screening strategies of patients at risk of developing active post-transplant Tb are highly varied. Currently there are no completely reliable tools to determine who could benefit from prophylaxis or which cases there should be a more exhaustive search for ATb. In high-risk countries, in the majority of cases, screening for LTb is conducted based on radiographic findings or history of infection with *M. tuberculosis*, however the reactivation index is still high.[12-14] The use of TST or IGRAS is also very controversial and currently many authors recommend using both tests as sources of supplementary information.[15,16] In this study, from 230 patients evaluated during the pre-transplant period, only one case of ATb was diagnosed; the prevalence of pre-transplant ATb was 0.43% (95% CI, 0.01 to 2.4), which is 16 times greater than the average rate in the country. In our setting, during the study period there was no availability of IGRAS.

All the patients with a positive TST, without any other suggestive clinical, radiographic or microbiological data of ATb, received prophylaxis with isoniazid 300 mg per day for six months. Adherence was at 97% and no relevant adverse events were reported which conditioned INH to be suspended. It is worth mentioning that 90 of the 170 patients who were negative TST did not undergo a Booster for reasons undisclosed in the file, which underestimates the LTb diagnosis, nevertheless one of these patients developed extrapulmonary post-transplant TB after three years of the RT.

The prevalence of LTb in this study is lower than in the general population in Mexico which, depending on the geographical zone and group of patients, has been reported between 40 and 70%.[17] These findings are to be expected in the group of patients in dialysis therapy, where the high prevalence of anergy has already been reported.[18] However it is also lower than the rate found in other centers in patients with dialysis therapy, which varies between 35 and 45%.[19]

The frequency of infection by *M. tuberculosis* in transplant recipients has been highly variable and depends on the prevalence seen in the general population of the studied geographical region. In a recent published meta-analysis Reis-Santos et al. pooled the data of 41 studies and found a prevalence of 2.51% (CI 95% 2.17-2.85).[18] The origins of this disease in the majority of the cases are attributed to a reactivation of a latent infection while in others, mainly late infections, to a primary infection. Therefore in all transplant centers, but especially in those located in countries with a high prevalence of tuberculosis, there should be a clinical and laboratory screening program in order to identify active pre-transplant infections and those patients with a high-risk of developing post-transplant tuberculosis.

The presentation of posttransplant ATb is varied, where 45% to 63% of the cases occur during the first year, with an average start time of nine months. There can also be late cases with presentation starting from the second year after surgery.[20-22]

In this study, the posttransplant observation period was extensive with a mean of 49 months, during which no patient from the LTb group developed ATb and only one case from the group unaffected with LTb presented the disease. The disease developed 31 months post-transplant, which is considered late and makes the disease most probably a primary infection. An important risk factor in this patient was the administration of Rituximab as part of treatment for humoral rejection six months prior to the presentation of ATb.

Counting the case of the posttransplant Tb the incidence in this study was 0.43%(CI 95% 0.01 to 2.4), which is a much lower percentage than that previously reported for Mexico by Melchor et al, which was 1.8%.[10] In the meta-analysis above mentioned about the prevalence of post-transplant Tb, they also divide

the studies in three groups, based in the prevalence of Tb by country (high, medium and low incidence). They found in high prevalence group, 43 times greater prevalence than in the general population (6.88% versus 0.16%); in the medium prevalence group, the prevalence of Tb in transplant patients was 83 times greater than in the general population (2.61% versus 0.03%) and in the low prevalence group, transplant patients had Tb prevalence rates 56 greater than the general population (0.56% versus 0.01%). Taking this facts, and if Mexico is consider a medium to high Tb prevalence country, in our cohort we find only 13 to 31 times greater prevalence than in general population depending the reference (0.43% versus 0.03 to 0.012%).[4,7] This is much lower than the growing of the prevalence reported in the groups of high and medium incidence (6.88% and 2.61%), that are 43 and 83 times, as above mentioned.[18]

This low incidence can be explained by the frequent treatment with isoniazid in patients identified as at risk and the previously demonstrated efficacy of isoniazid in this group of patients.[11]

We admit that this study has drawbacks. Firstly, the retrospective design type. The efficacy of both screening and presentation of ATb in the post-transplant period requires prospective observation. However, the findings become relevant when considering that the cohort of patients with transplants are followed in the same institution, the average follow up time was 49 months after the transplant and the patients live in a country with a high prevalence of the disease, which leads us to conclude that the measures adopted in the pre-transplant study, based on clinical observation and basic tests such as TST, Urianalysis and RxT, are efficient means of identifying the existence of LTb and ATb. Due to the type of study conducted we do not have information about the patients who underwent a pre-transplant assessment and did not receive a renal transplant, we also lack information of the causes of this situation. In the case of the patient reported with ATb, the transplant was merely postponed and was performed upon finishing the Tb treatment.

CONCLUSION

At the INCMNSZ we conduct a complete risk assessment of tuberculosis in all patients who are candidates for a RT based on the clinical assessment protocol and basic laboratory tests. The great majority of the patients with LTb received prophylaxis with isoniazid (97%). The prevalence of active posttransplant Tb was found to be 0.43%. Despite the high prevalence of TST+ there is a low prevalence of posttransplant ATb, possibly as a consequence of adequate pre-transplant screening including TST and the administration of isoniazid in cases of LTb.

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