Tuberculosis in Liver Transplant Recipients: Prophylaxis in an Endemic Area


ABSTRACT

Background. Tuberculosis (TB) has a high prevalence in Brazil. The scenario of liver transplantation (LT) creates challenges: atypical presentation, treatment hepatotoxicity, and increased mortality. The majority of TB cases after transplantation represent reactivation of latent infections; therefore, prophylaxis (PX) plays a major role. The aim of this study was to evaluate the benefits of PX after LT based on a pretransplantation tuberculin test (TT) in an endemic area.


Results. Among 191 selected patients, 137 (71%) showed a pretransplant TT including 41 (30%) with a TT ≥5 mm. The 17 (40%) of these patients who were prescribed PX did not experience TB. Prophylaxis was discontinued in 5 patients (20%) owing to suspicion of hepatotoxicity (medium serum alanine transaminase 175 U/L). In the group without PX, we diagnosed 1 case of pulmonary TB. The overall prevalence of anergic patients in the cirrhotic phase was 65% and prevalence of TB 1%.

Conclusions. The prevalence of TB was similar to that reported in the literature, but positivity to TT was higher (34% vs 25%), possibly because of the endemicity of the area. There was a lower prevalence of extrapulmonary disease and no mortality. No patient undergoing PX with isoniazid, although incomplete due to suspicion of hepatotoxicity displayed TB. One patient without PX was affected by TB. The drug was effective but not always safe.

Tuberculosis is a major public health problem worldwide, especially in developing countries. In Brazil there are ~50 million infected people, with ~85,000 new cases per year (corresponding to an incidence of 47/100,000 inhabitants) and 6,000 deaths per year.1 Thus Brazil is among the 22 countries that include 80% of all tuberculosis cases.1 Rio de Janeiro is the Brazilian state with the highest incidence and mortality rates of tuberculosis. In Rio de Janeiro city, in 2006, the 5,749 new cases of tuberculosis corresponded to an incidence of 93.7/100,000 inhabitants and a mortality rate of 5.4/100,000 inhabitants.3 The chaotic urbanization, the massive urban population (96.4% in 2000, the country’s highest rate) and the deficiencies in public health care are the possible reasons for these high rates.1

At present, there is sufficient evidence of the efficacy of current drugs. In studies of drug resistance, Brazil shows a low rate of primary resistance; apparently this is not responsible for the high mortality rates. Therefore, tuberculosis is an avoidable cause of death.2

The emergence of acquired immunodeficiency syndrome elevated tuberculosis as an opportunistic disease. At the same time, improved immunosuppressive drugs in the transplantation scenario created a new pool of susceptible patients. The prevalence of tuberculosis ranges from 0.5% to 11% among patients undergoing a solid
organ transplantation, depending on the endemicity of the area. After liver transplantation (LT), the rate ranges from 0.9 to 2.3%. A recent meta-analysis revealed values of up to 6%, with an annual incidence of about 450/1,000,000 in habitants. The peak incidence occurs in the fourth month after liver transplantation, with more than one-half of the patients showing an extrapulmonary presentation with the risk for graft infection. The challenges that delay diagnosis consist of atypical presentations and the high frequency of coinfections.

The mortality rate can reach 40% despite treatment; without treatment it is 100%. Predictors of mortality have been recently suggested to be symptoms-diagnosis interval >1 month, treatment with <3 drugs, and absence of therapy.

Although most LT candidates are anergic on the tuberculin test (TT) because of immunodepression due to cirrhosis, positivity (TT ≥5 mm) occurs among up to 25%. This subgroup of patients shows a 4-fold risk for tuberculosis after LT, because in most cases this state represents “latent disease” (LTBI) rather than previous vaccination. These transplant recipients are more susceptible to reactivation of the latent disease after immunosuppression.

Because TT underestimates LTBI among cirrhotic patients, an earlier TB diagnosis (not adequately treated), a recent high-risk contact, or a chest radiograph suggesting past infection help to identify subjects with LTBI. Tuberculosis in organ transplant recipients may also develop, albeit much less commonly, either after a new exposure or by transmission from an organ donor.

Prophylaxis (PX) for 9 months with isoniazid is indicated in LTBI, but there are reports of 6-month treatment, as currently used in Brazil. It is recommended to start as soon as liver function and liver enzymes are stable, but within the first 6 months after LT. Not only TT ≥5 mm indicates PX, but also an abnormal thoracic image, a history of incompletely treated tuberculosis, recipients from living donors with a TT ≥10 mm, and/or a recent high-risk contact.

Many authors consider that the risk of isoniazid hepatotoxicity in transplantation patients may be greater than the benefit, as recently discussed in a large meta-analysis. Liver enzyme alterations after LT are generally due to acute rejection episodes, reactivation of underlying disease (principally viral hepatitis), vascular/biliary complications, or opportunistic infections (such as cytomegalovirus). In these cases, isoniazide may be a confounding variable; therefore, clinical suspicion must be high.

Hepatotoxicity criteria are not well defined in the literature. Benito et al defined hepatotoxicity as a fold increase in serum aspartate-transaminase, improvement or resolution after isoniazid withdrawal, and histologic features of hepatitis on liver biopsy. They found a 17% rate of patients who met criteria for hepatotoxicity; almost one-half of them showed alterations in liver enzymes. Drug suspension rates were 6% to 42%, but multidrug regimens did not appear to be a better choice.

An alternative approach prescribe isoniazid chemoprophylaxis during the period of transplant candidacy. This approach can prevent toxicity to the graft, but the tolerability of isoniazid and the possibility of hepatotoxicity in end-stage liver failure patients make this a fraught option. Singh et al reported series of compensated cirrhotic patients (Child 6–8, average Model for End-Stage Liver Disease 13). Both series noted good results, suggesting also the possibility of using rifampin which is commonly used in cholestatic patients for pruritus, for 4 months as a safe prophylaxis. It should be avoided after LT, because it accelerates the metabolism of immunosuppressive drugs.

Established disease, does not entail a focus on “risk versus benefit” as does PX, but rather consideration of which therapeutic regimen is more safe and efficient. The most commonly used agents in Brazil—isoniazid, rifampin, and pyrazinamide—are prescribed for 6 months but frequently changed to other drugs such as ethambutol or ofloxacin. In a recent meta-analysis of 139 treated patients, Holty et al showed a high rate of hepatotoxicity (73%), although the criteria for the diagnosis were not defined. Thirty percent of subjects changed drugs or stopped treatment; the average time between starting treatment and hepatotoxicity was 3 months, and isoniazid was the most hepatotoxic drug. The literature has failed to identify notable differences in the natural history or management of TB infections between live- and deceased-donor liver transplantation cases. The aim of the present study was to evaluate prophylaxis after LT in an endemic area, based on the pretransplantation TT.

METHODS

This retrospective study reviewed hospital records of patients who underwent a deceased- or live-donor primary LT between 2001 and 2009. Exclusion criteria were: patients transplanted due to acute liver failure, age <13 years at transplantation date, patients deceased ≤6 months from the procedure and history of correctly and fully treated tuberculosis or PX due to a high-risk contact. The inclusion criterion for TT results before LT was induration ≥5 mm in diameter at 48–72 hours after administration of tuberculin intradermally. Furthermore, we included living-donor liver recipients from donors whose was TT ≥10 mm.

Patients with TT ≥5 mm or donor TT ≥10 mm underwent administration of isoniazid after transplantation. Drug suspension, mean alanine transaminase (ALT) at suspension, tuberculosis diagnosis, and death were the endpoints. Patients in whom PX was not performed, despite these indications, were also analyzed for group comparisons. We secondarily evaluated the response to TT among the whole study population.

RESULTS

We performed 376 LTs from 2001 to 2009. The recipient gender distribution was almost equal (52% male/48% female), with a median age of 38.4 years at transplantation. The principal etiology was hepatitis C, followed by hepatitis
C and hepatocellular carcinoma, corresponding in aggregate to 33% of cases. After applying the exclusion criteria, 191 patients were considered for the study. Fifty-four patients (29%) had not had a TT performed during the candidacy period. The other 137 patients (71%) had a pretransplant TT: the majority were anergic (90 patients, 66%), 6 patients showed a TT < 5 mm (4%), and 41 (30%) ≥ 5 mm, thereby meeting one of the inclusion criteria (Fig 1).

Among this study group, 41% had undergone 6 months of PX with isoniazid (300 mg daily) started within the first 6 months after transplantation. Three other patients who were selected as the study group because their donors had a TT ≥ 10 mm received the same prophylaxis. No patient received it because of an abnormal thoracic and image a history of untreated tuberculosis. Almost 60% of the group had no PX even though it was indicated.

Analyzing the principal outcome, no patient (including those with drug discontinuation) in the PX group displayed tuberculosis after transplantation, with a median follow-up of 5.3 years.

No standard criteria were used to define hepatotoxicity. The median serum ALT value at the time of the drug suspension was 175 U/L, namely, a 3-fold increase above the normal value. After a median of 3 months of isoniazid use, PX was discontinued in 5 patients (20%).

Among the group not undergoing PX, there was 1 case of pulmonary tuberculosis. This patient did not receive PX, principally owing to an acute rejection episode in the first months after LT. The diagnosis was established at 2 years 2 months after LT. He underwent the standard treatment (rifampin + isoniazid + pyrazinamide) for 9 months without major complications.

The other 2 tuberculosis cases occurred in a patient who was previously anergic and a patient with unknown TT status. The former experienced a pleural-pulmonary form at 1 year 4 months after transplantation; standard treatment was suspended within 1 month owing to hepatotoxicity, requiring a 1-year course of a alternative regimen of streptomycin, ethambutol, and ofloxacin. The patient with unknown TT status had pulmonary involvement at 10 months after transplantation, also with pleural involvement. Owing to preexistent hepatic injury from cytomegalovirus infection as well as biliary stenosis and an acute rejection episode, the subject received the alternative regimen for 1 year.

The overall prevalence of TB among the transplanted population was 1%. If exclusion due to death before 6 months after transplantation is not considered, the overall prevalence among cirrhotic phase of TT ≥ 5 mm was 30%, with 66% anergic and 4% TT < 5 mm.

DISCUSSION

Limitations to our study exist. It was not a prospective controlled study. The evaluation of the enzyme profiles during PX was only partial. No biopsy was undertaken in a majority of patients with enzyme elevations. In contrast, we have reported many more patients tested with TT before LT compared with the literature (71% vs 47%). The positivity to TT among our sample was higher than in the literature (34% vs 25%), possibly because of the endemicity of the geographic area. Although observations regarding the stage of liver disease and the correlation with the grade of immune response were not possible, we can, however, confirm that the poor immune responses among cirrhotic patients in general can result in false negative tests. Our sample included 1 TT-anergic case among 90 anergic patients who developed TB. Curiously, a patient with a history of previously treated tuberculosis was also anergic. Quantiferon TB Gold, an interferon-release assay, does not appear to overcome the shortcomings associated with TT, because it also measures the cellular immune response to Mycobacterium tuberculosis.12 Our prevalence of tuberculosis was similar to the literature, despite the fact that we are in an endemic area. We had a lower prevalence of extrapulmonary disease and no mortality. The prevalence of tuberculosis in our study was similar to another Brazilian study, although the latter comes from a less endemic Brazilian state.13

No patient undergoing PX with isoniazid, although incomplete due to hepatotoxicity, displayed tuberculosis. The drug was effective but not always safe. The rate of interruption due to hepatotoxicity was similar to the literature,9 but higher than that in a recent meta-analysis.6 Nevertheless, the median ALT serum level at suspension was lower than that used in the literature.10

Among the patients with an indication for but not undergoing PX, 1 experienced tuberculosis. Although it was not statistically significant, owing to the sizes of the groups, there was another case of tuberculosis in whom we did not know the TT status.
All cases of tuberculosis were diagnosed after ≥1 year after LT, contradicting the 4th-month occurrence peak. In 1 case, the diagnosis was established >2 years after transplantation, suggesting an exogenous infection. In 50% of cases, there was a history of an acute rejection episode, with aggressive immunosuppression and coinfection, confirming risk factors cited in the literature. The tolerability of LT patients to standard treatment is poor; the majority of patients had to change their drug regimen.

REFERENCES