Abstract

Tuberculosis is a major problem in the posttransplantation period, because of its high incidence and prevalence, difficulty in diagnosis as well as high risk of morbidity and mortality. In solid-organ transplant recipients, the diagnosis of tuberculosis is complex because it is paucisymptomatic. Tuberculin skin testing results may be negative, and interferon-gamma release assays may be insufficiently sensitive. Furthermore, imaging technique findings are mostly atypical, and sputum smear results can be negative despite the presence of active disease. Therefore, most tuberculosis cases are overlooked, and thus, treatment initiation is often delayed.

The treatment of tuberculosis falls under 2 headings: that of active disease and latent disease. The drugs for treating these 2 entities are similar; however, their protocols are completely different. Active disease in the immunocompetent patient is treated mostly by giving isoniazid, rifampicin, pyrazinamide, and ethambutol for 2 months (intensive phase), followed by isoniazid and rifampicin for 4 months (continuation phase). The treatment of immunosuppressed patients is controversial; a similar protocol or longer duration of treatment has been suggested as compared to immunocompetent patients. Because there is a drug interaction between antituberculosis drugs (rifamycins) and immunosuppressants (calcineurin/mammalian target of rapamycin inhibitors and glucocorticoids), the risk of graft rejection increases during the treatment of tuberculosis.

For the treatment of latent tuberculosis, in regions with a high prevalence of tuberculosis, universal prophylaxis with isoniazid for 6 months (preferably 9 months) has been recommended. In countries where the risk of tuberculosis is lower, no prophylaxis has been proposed. We propose that the best solution is to individualize therapy for patients at greatest risk of the disease.

To conclude, posttransplant tuberculosis is still an important source of morbidity in transplant recipients because of its high frequency, problems in diagnosis and treatment and association with increased risk of morbidity and mortality.

Key words: Antituberculosis drugs, Immunosuppression, Solid-organ transplant, Tuberculosis prophylaxis, Tuberculosis treatment

Introduction

Tuberculosis is a major problem in transplant patients during the posttransplant period because of many factors. First, tuberculosis has a high incidence and prevalence. In a prospective analysis of 4388 patients from Spain,1 tuberculosis incidence was found to be 512/100 000 patients per year among transplant recipients, whereas incidence was only 19/100 000 per year in the general population. These statistics indicate that the incidence of tuberculosis is 27-fold higher in solid-organ transplant recipients than in the general population.1 With regard to prevalence, it is well known that the frequency of tuberculosis varies significantly worldwide; although it is quite rare in some countries, in others, estimated new cases exceed 30/100 000.2 As a result, the prevalence of tuberculosis in transplant patients in such countries may reach 10% to 15% of all cases, compared with approximately 1% to 5% in more developed countries.3,4

Second, several mechanisms underlie the pathogenesis of tuberculosis in transplant patients, such as (1) reactivation of a latent infection, (2) acquisition of a new infection after transplant, (3) nosocomial transmission, and (4) transmission of the disease
from donors. A retrospective cohort study from Spain, which included more than 19,000 donors between 1998 and 2011, found that when a donor had tuberculosis, the possibility of transmitting the disease was 27%. Because of all these factors, the risk of contracting tuberculosis is high in the post-transplant period, and may in some cases be unavoidable.

Third, several factors contribute to the complexity of treating these patients: (1) impaired immune response due to pharmacological immunosuppression; (2) increased risk of drug toxicities because of coadministered prescription drugs and other medications that frequently cause liver problems, seen in up to 37% of patients in some series, and (3) increasing numbers of patients with drug-resistant disease.

Fourth, tuberculosis is a major cause of morbidity in transplant patients. There is a significant interaction between drugs used to treat tuberculosis (the rifamycins) and those used to suppress the immune system and prevent graft rejection (calcineurin inhibitors [CNIs] and/or mammalian target of rapamycin inhibitors [mTORi’s]). This interaction results in a dramatic decrease in serum levels of immunosuppressants; as a result, the risk of graft rejection increases, resulting in a 25% incidence of graft loss among these patients.

Fifth, posttransplant tuberculosis is a major cause of mortality; in the literature, mortality rates of 29% have been reported. According to a previous report from our center, tuberculosis was diagnosed in 22 of 520 (4%) transplant recipients. Among these cases, 6 died despite all therapeutic interventions, corresponding to a mortality rate of 27%. Disseminated infection, prior rejection episodes and receipt of antithymocyte globulin have been found to be predictors of mortality.

Clinical findings
In general, when a person is infected with *Mycobacterium tuberculosis*, the body can eliminate these microbes. If this does not, active disease develops. Alternatively, the bacteria can be controlled initially and a latent infection can develop, without signs or symptoms of active disease. In such a case, over the years, the bacteria may be eliminated or there may be a lifelong containment of the pathogen. Another possible course, especially in the at-risk population, is the development of active tuberculosis disease in the long term. With this possibility in mind, the disease may appear at any time after solid-organ transplant. In a prospective study of more than 4300 patients, tuberculosis was detected in 21 cases (0.5%); disease onset occurred after a median of 183 days (range, 28-499 d) posttransplant, and 20 of the cases (95%) appeared within the first year. Another study, by the Haberal group from Turkey, reported 19 cases of tuberculosis out of nearly 1000 transplant patients (2%). In the authors’ experience, 16 (85%) of the cases appeared within the first 6 months after transplant. In short, although the timing of disease onset varies, most tuberculosis cases appear within the first year after transplant.

Regarding the clinical presentation, the vast majority of the immunocompetent patients with suspected tuberculosis are admitted to hospitals with pulmonary symptoms. Typical clinical findings include cough, bloody sputum and constitutional symptoms. However, in immunocompromised hosts, the findings may be quite nonspecific, as in the following cases: (1) one third to one half of patients are admitted with cases of disseminated or extrapulmonary tuberculosis; in addition, pyomyositis, skin ulcers or abscess formation, tenosynovitis or tuberculosis lymphadenitis are frequent manifestations; or (2) fever may or may not be present, and the patient may be admitted with fever of unknown origin.

It has been reported that patients who have received antithymocyte globulin or who have diabetes mellitus, chronic liver disease or coexisting infections (eg, cytomegalovirus, mycosis, *Pneumocystis jiroveci* pneumonia) are more prone to developing tuberculosis.

Diagnosis
In the immunocompetent host, diagnosis is made using a variety of techniques. These include clinical findings, tuberculin skin testing (TST), interferon-gamma release assays (IGRAs), imaging techniques, sputum examination for staining and culture, nucleic acid amplification testing and molecular testing, and finally (albeit rarely), invasive procedures such as bronchoscopy or lung biopsy (Figure 1).

In contrast, in the immunocompromised host, the diagnosis of tuberculosis is often complex. First, from a clinical point of view, the disease shows a paucisymptomatic presentation, and extrapulmonary
tuberculosis is more common. Many clinical findings, such as fever and other constitutional symptoms, may be absent. Also, other frequently encountered infections (eg, Nocardia, community acquired pneumonia, aspergillosis) may modify already nonspecific symptomatology. Second, tuberculin skin testing is usually negative; up to 70% of the cases may be anergic. \(^4\) Third, IGRAs (including Quantiferon-TB Gold (QIAGEN Company, Victoria, Australia) and enzyme-linked immunosorbent spot assays) may be less sensitive in immunosuppressed patients. \(^1\) When a comparison is made between the 2 testing types, TST is less expensive, similarly sensitive, but less specific than IGRAs. \(^2\) (It should be noted that neither TSTs nor IGRAs distinguish between active and latent tuberculosis; however, the enzyme-linked immunosorbent spot assay is capable of predicting active tuberculosis development in kidney transplant recipients with negative TST results. \(^2\)\(^,\)\(^1\)\(^2\))

Fourth, findings from the chest radiographs of immunosuppressed patients are also mostly atypical (eg, they feature focal infiltrate, miliary patterns, nodules, pleural effusions or interstitial infiltrates), whereas cavities, which are mostly associated with tuberculosis, are quite rare. \(^1\)\(^4\) Not infrequently, sputum smear results are negative despite the presence of active disease. \(^1\)\(^4\) In addition, nucleic acid amplification tests are sensitive for identifying \(M.\) \(tuberculosis\) in populations with positive sputum smears for acid-fast bacilli but less sensitive in sputum-smear-negative populations. \(^1\)\(^4\) Xpert MTB/Rif (Cepheid GeneXpert System, Sunnyvale, CA) is a rapid nucleic acid amplification technique that, within 2 hours, can identify \(M.\) \(tuberculosis\) DNA and resistance to rifampicin using a nucleic acid amplification test, with an assay sensitivity that is much higher than that of smear microscopy. It is available in Europe and is being examined for approval in the United States. \(^2\) Positron emission tomography also may be useful; however, there has not been enough experience with this test to show its usefulness in solid-organ recipients. A definitive diagnosis of tuberculosis can be done only by isolating \(M.\) \(tuberculosis\) from clinical samples, but this may take up to 6 weeks. \(^4\) Therefore, most of the time, more invasive techniques (eg, fiberoptic bronchoscopy, mediastinoscopy, laparoscopy, tissue biopsies) are required for definitive diagnosis (Figure 1).

**Treatment**

The treatment of tuberculosis falls under 2 main headings: that of active disease and latent disease. In practice, drugs for the treatment of these 2 entities are similar; however, their protocols are completely different. Antituberculosis medications are classified as first-line and second-line drugs. First-line drugs include isoniazid, rifampicin, pyrazinamide, ethambutol, and streptomycin, whereas second-line drugs include kanamycin, amikacin, rifabutin, levofloxacin, ethionamide, cycloserine, and capreomycin. (Rifapicin is one of the medications included in the group of rifamycins; the other 2 drugs in this context are rifabutine and rifapentine.)

**Active Disease**

In newly diagnosed cases in immunocompetent patients (who are not multidrug-resistant), the standard protocol for treating tuberculosis comprises isoniazid, rifampicin, pyrazinamide and ethambutol given for 2 months (intensive phase), followed by isoniazid and rifampicin for 4 months (continuation phase).

Recently, the most significant emerging problem has been treating multidrug-resistant tuberculosis, which is caused by an organism that is resistant to at least isoniazid and rifampicin, the 2 most potent antituberculosis drugs. In addition, there is a form of extensively drug-resistant tuberculosis, which is a rare type of multidrug-resistant tuberculosis that is resistant to isoniazid and rifampicin plus any fluoroquinolone and at least 1 of the 3 injectable second-line drugs (ie, amikacin, kanamycin or capreomycin). \(^1\)\(^5\) Extensively drug-resistant tuberculosis is of special concern to immunosuppressed patients. \(^2\)
In immunocompetent patients, multidrug-resistant tuberculosis is treated using a regimen of 4 second-line antituberculosis drugs (as well as pyrazinamide), including a fluoroquinolone, a parenteral agent (ethionamide or prothionamide) and either cycloserine or para-aminosalicylic acid, if cycloserine cannot be used. Therapy should continue for ≥ 20 months in patients who have not received previous treatment, and for 30 months in those who have been treated for multidrug-resistant tuberculosis. It should be noted that all these proposed treatment protocols are based mainly on the results of randomized controlled trials in immunocompetent hosts.

Data on tuberculosis therapy in solid-organ transplant recipients are both scarce and of low quality; as a result, many controversies surround such therapy. For example, with regard to selecting the treatment regimen, the American Society of Transplantation underlines that a rifamycin-containing regimen should be mandatory in all cases because of rifampicine’s potent sterilizing activity and ability to prevent the emergence of resistance. However, guidelines from the Spanish Group for the Study of Infection in Transplant Recipients (GESITRA) reserve the use of rifamycins only for severe cases. The latter protocol suggests using 2-drug regimens (isoniazid and either ethambutol or pyrazinamide) for 12 to 18 months as an alternative.

All protocols take into account the interaction between rifampicin and the CNI/mTORi drugs and glucocorticoids. All these drugs are metabolized by the hepatic cytochrome p450 isoenzyme CYP3A4; thus, induction of immunosuppressive drug metabolism by rifampicin results in lower levels of the former, and an increased risk of graft rejection. As a result, the vast majority of treatment protocols suggest a 3- to 5-fold increase in the dose of the CNI or mTORi as well as monitoring serum levels very closely. Also, guidelines recommend that the dosage of steroids be doubled. Almost all authors agree that the antibiotic streptomycin should be avoided because of its nephrotoxicity. In addition, local resistance patterns and epidemiologic and susceptibility data from the individual patient’s bacterial isolate should be considered. In general, a reduction in immunosuppressive drug dose is not suggested during the treatment of active tuberculosis.

Controversy continues regarding the duration of treatment as well. Although some authors suggest that 6 months of a rifampicin-containing regimen may be adequate (in the absence of disseminated/cavitary/bone and/or joint or central nervous system tuberculosis), most other experts propose ≥ 9 months of treatment be given to all solid-organ transplant recipients.

**Latent Disease and Tuberculosis Prophylaxis**

Many diseases can be prevented by immunization both of the general population and of renal transplant recipients. However, vaccination for tuberculosis with Bacillus Calmette-Guérin is definitely contraindicated in immunocompromised hosts because this application can be complicated by disseminated infection due to the patient’s immunosuppressed status. Therefore, the only way of preventing tuberculosis in these patients is chemoprophylaxis.

Overall, 20% to 50% of solid-organ transplant recipients with a positive tuberculin skin test who do not receive prophylaxis subsequently develop active tuberculosis; therefore, the vast majority of authors suggest treating latent infection. Moreover, at least 2 guidelines (those of the European Respiratory Society and the British Thoracic Society) recommend the treatment of all solid-organ transplant recipients (universal prophylaxis) who live in regions with a high prevalence of tuberculosis.

For immunocompetent patients, the drug of choice for the treatment of latent tuberculosis infection is isoniazid at a dosage of 300 mg/day, supplemented with vitamin B6 for a duration of ≥ 6 months (preferably 9 months). For immunosuppressed patients, some authors have suggested a similar duration of prophylaxis, while others’ protocols recommend prophylaxis for a 1-year period. Alternatively, 2 months of rifampicin + pyrazinamide or 6 months of levofloxacin + ethambutol may be given. This advice should be taken with caution because prophylaxis is not devoid of adverse events, and one always must consider the risk of hepatotoxicity, which can be seen in 37% of patients. Thus, considering the facts that hepatotoxicity risk is high, that tuberculosis is rare in many countries, and that tuberculosis is a manageable disease, prophylaxis is not practiced widely. The diversity of opinions shows wide disagreement among experts: some suggest 6 months of treatment, whereas others recommend 9 months of treatment. Still others propose 1 year of treatment, while some authors suggest no prophylaxis at all. Therefore, we conclude that the best solution is to
individualize the treatment of latent tuberculosis for patients at risk. Indications for such treatment can be summarized as follows: (1) an initial or boosted TST with induration of > 5 mm or a positive IGRA, (2) a history of untreated latent tuberculosis, (3) receiving a transplant from a donor with untreated latent tuberculosis, and (4) being at high risk for primary tuberculosis (eg, recent history of contact with an individual with active disease). 17

Prophylaxis can be performed in both the pre-transplant and the post-transplant periods. The advantages of pretransplant prophylaxis are myriad: higher efficacy in boosting immunocompetency, fewer drug-drug interactions, lower medication, and pill burden resulting in better patient compliance, and better tolerance compared with the posttransplant period. Unfortunately, pretransplant prophylaxis may not always be possible because of insufficient time to complete therapy. The advantages of posttransplant prophylaxis include treating the patients when the risk is greatest for tuberculosis reactivation. The disadvantages of posttransplant prophylaxis include (1) lowered efficacy owing to immunosuppressed status, (2) additional pill burden along with many other medications, (3) interactions of antituberculosis drugs with immunosuppressants, and (4) a higher reported rate of drug-induced liver injury. 11

Many Unknowns Remain

Although tuberculosis is a longstanding and well-understood disease, and renal transplant has been performed as the treatment of choice for end-stage renal disease patients for more than a half century, many unknown factors remain in treating transplant recipients who develop the complication of tuberculosis. These unknowns include, but are not limited to: (1) screening strategies for latent tuberculosis diagnosis; (2) the role for a dual strategy that uses both TST and IGRA and appropriate timing of the 2 tests; (3) risk stratifying solid-organ transplant recipients to identify individuals who would benefit from chemoprophylaxis despite negative results on screening tests; (4) implementing safer drug regimens for chemoprophylaxis with respect to toxicities and interactions with immunosuppressive regimens; (5) additional testing to evaluate for active tuberculosis; and (6) the risk for disease recurrence in solid-organ transplant recipients with a history of treated active tuberculosis. 11

Conclusions

Although during recent decades significant progress has been made in both the diagnosis and treatment of tuberculosis, as well as immunosuppression protocols, posttransplant tuberculosis continues to be a significant problem in solid-organ transplant recipients. These problems can be summarized as follows: frequency is still high in many countries; there are many problems in diagnosing and treating the disease; handling immunosuppression is complex and still problematic: and morbidity and mortality rates are considerably high. Therefore, well-designed studies in solid-organ transplant recipients are needed, and even more important, collaboration with many other experts is required to best treat transplant patients whose condition is complicated by tuberculosis.

References