LETTER TO THE EDITORS

Antibiotic prophylaxis for preventing postorthotopic liver transplant tuberculosis: is there a safe alternative to isoniazid?

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Dear Editors,

We read with interest the research paper by Yoo *et al.* [1] who studied the prevalence of TB in subjects who underwent hematopoietic stem cell transplantation (HSCT) and solid organ transplantation (SOT). These authors also reported the effectiveness of isoniazid (INH) prophylaxis since the introduction of latent tuberculosis infection (LTBI) screening.

The study shows that drug prophylaxis significantly lowers the prevalence of active TB in all cohorts, from 1.6% to 0.5% in kidney transplant (KTx), from 4.7% to 1.9% in heart transplant (HTx), and from 1.3% to 0.9% in HSCT. Surprisingly, TB prophylaxis was not provided to any of the 3796 orthotopic liver transplant (OLTx) recipients as LTBI screening was not systematically performed. As prevalence of TB in OLTx was close to other subgroups (1.79%), it is not immediately clear why so many OLTx recipients were not screened for LTBI, also considering high TB endemicity in a country like South Korea, up to 90 cases per 100 000 person-years [2]. It is noteworthy that a recent study from the Spanish Network for Research on Infection in Transplantation (RESITRA) found a much higher incidence of active TB in OLTx recipients compared with the general population (512 cases per 100 000 person-years) in a country with low TB endemicity like Spain [3].

Despite these data, the issue of TB prophylaxis in OLTx recipients with LTBI is still controversial. Irreversible liver damage is a rare side effect of INH [4–7], yet mild hepatotoxicity is still a concern in subjects who are strictly followed up for organ rejection and HCV recurrence. INH is usually deferred at least 6 months after transplantation, and, thereafter, it can be carefully considered whether OLTx is performing well [4].

Avoiding liver toxicity with alternative to INH prophylaxis would be highly appealing in OLTx, but, at present, validated options are missing. Torre-Cisneros *et al.* [8] proposed levofloxacin (500 mg q24h for 9 months) as a safe alternative to INH for TB prophylaxis in OLTx recipients, but, sadly, the study was interrupted because of high incidence of tenosynovitis.

We would like to report our experience in the setting of LTBI prophylaxis in OLTx recipients. All procedures followed were in accordance with the ethical standards of the responsible committee on human experimentation (institutional and national) and with the Helsinki Declaration of 1975, as revised in 2008. All subjects gave their informed consent prior to their inclusion in the study.

Our approach was inspired by Directly Observed Therapy short course (DOTS) DOTs protocol [9] or treating active TB in developing countries where therapy is administered only three times a week with similar efficacy to the daily schedules used in Western countries [10,11]. A combination of levofloxacin and ethambutol is administered OD from day 1 postsurgery till hospital discharge and then three times a week for 1 year.

From January 2006 to December 2015, 646 OLTx recipients were screened for LTBI by interferon-gamma release assays (IGRAs)–QuantiFERON TB Gold

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Table 1. Characteristics of 35 orthotopic liver transplant (OLTx) patients following TB prophylaxis.

Characteristic	Value
Sex, % male/female	91/9
Recipient age, mean years SD	58.8 ± 6.6
CMV serological mismatch (D+/R)	3/35
ALD, %	11.4
HBV infection, %	17.1
HCV infection, %	40
HBV/HDV, %	5.7
HCV/HDV, %	11.4
HCV/Hemochromatosis, %	2.9
HCV/ALC, %	5.7
HCV/HBV/ Hemochromatosis, %	2.9
HBV/autoimmune, %	2.9
Allograft rejection, %	28.6
Hepatitis recurrence, %	45.7
Immunosuppressive therapy	
Cyclosporine, %	28.5
Tacrolimus, %	71.4
Mycophenolate, %	5.7
Sirolimus, %	11.4
Methylprednisolone, %	100
Basiliximab, %	85.7
Duration of follow-up, median, months (range)	38 (22–69)
Global mortality, %	17.1

(Cellestis, Melbourne, Victoria, Australia). Thirty-five subjects (5.4%) with a positive test were started on the above-described protocol (Table 1).

Subjects were evaluated for evidence of active TB monthly for at least 1 year from prophylaxis completion. Four patients experienced side effects which prompted us to discontinue prophylaxis: two (5.5%) had tenosynovitis, one (2.7%) had transient optical neuritis, and one (2.7%) had transaminitis (10-fold increase) without histological evidence of rejection or viral hepatitis.

Among 35 subjects who were started on TB prophylaxis, one (2.7%) was diagnosed with active TB. He was a 69-year-old male with HCC/HCV who was diagnosed with TB based on a CT scan showing two apical nodules and a rise in QuantiFERON titer 7 months from completion of TB prophylaxis. At that time, he was on pegylated IFN-α and ribavirin. Sputum was negative for AAFB, as well as PCR and cultures. He received TB therapy with levofloxacin/Ethambutol daily and amikacin 1000 mg three times a week for 2 months, with full resolution of lung nodules. Then, he was started on levofloxacin/Ethambutol three times a week for further 16 months. No recurrences were detected at follow-up.

Remarkably, among the four patients who discontinued prophylaxis, TB was diagnosed in a 56-year-old male who experienced a rise in QuantiFERON titer concomitantly to CT scan detection of right pleural effusion and 1.5-cm right apical nodules. He received levofloxacin/Ethambutol daily associated with amikacin 1000 mg three times a week for 2 months. A follow-up CT scan showed resolution of pleural effusion and apical nodules. Neither therapy-related liver toxicity nor TB recurrences were observed at 16-month follow-up.

Drug-related liver toxicity and the very low risk of active TB in OLTx recipients in a low endemicity country like Italy (from 7.3 to 5.3 cases per 100 000 person-year in the 2006–2013 period) [12] may further hinder the use of INH in this setting. In this short observational study with few events, levofloxacin and ethambutol appear safe alternatives to INH prophylaxis. RCTs are needed to assess the efficacy and toxicity in comparison with INH.

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