Tuberculosis Prophylaxis With Levoﬂoxacin in Liver Transplant Patients Is Associated With a High Incidence of Tenosynovitis: Safety Analysis of a Multicenter Randomized Trial

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**Background.** It is necessary to develop a safe alternative to isoniazid for tuberculosis prophylaxis in liver transplant recipients. This study was designed to investigate the efficacy and safety of levoﬂoxacin.

**Methods.** An open-label, prospective, multicenter, randomized study was conducted to compare the efﬁcacy and safety of levoﬂoxacin (500 mg q24h for 9 months) initiated in patients awaiting liver transplantation and isoniazid (300 mg q24h for 9 months) initiated post-transplant when liver function was stabilized. Efficacy was measured by tuberculosis incidence at 18 months after transplantation. All adverse events related to the medication were recorded.

**Results.** CONSORT guidelines were followed in order to present the results. The safety committee suspended the study through a safety analysis when 64 patients had been included (31 in the isoniazid arm and 33 in the levoﬂoxacin arm). The reason for suspension was an unexpected incidence of severe tenosynovitis in the levoﬂoxacin arm (18.2%). Although the clinical course was favorable in all cases, tenosynovitis persisted for 7 weeks in some patients. No patients treated with isoniazid, developed tenosynovitis. Only 32.2% of patients randomized to isoniazid (10/31) and 54.5% of patients randomized to levoﬂoxacin (18/33, \( P = .094 \)) completed prophylaxis. No patient developed tuberculosis during the study follow-up (median 270 days).

**Conclusions.** Levoﬂoxacin prophylaxis of tuberculosis in liver transplant candidates is associated with a high incidence of tenosynovitis that limits its potential utility.

**Keywords.** tuberculosis; levoﬂoxacin; tenosynovitis; investigator-driven clinical trial.

Less than 30% of liver transplant recipients with a positive tuberculin purified protein derivate (PPD) skin test currently receive prophylaxis with isoniazid because of its potential hepatotoxicity [1–3], which can destabilize chronic liver disease when used in the pretransplant period. For this reason some experts recommend that isoniazid prophylaxis should not be initiated until after transplantation when liver function is stable [1–3]. However, the prophylaxis with isoniazid is frequently never initiated or discontinued due to the elevation of transaminase levels. In fact, some experts believe that, in this scenario, the risks of using isoniazid outweigh its potential benefits [4]. Other alternatives [5, 6] are not free of hepatotoxicity [2, 7–11].

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The use of quinolones (ofloxacin, levofloxacin, moxifloxacin, gatifloxacin) for prophylaxis of latent tuberculosis infection could be a good alternative, but there is insufficient evidence of their efficacy and safety in liver transplant candidates or recipients [1], and moxifloxacin has been associated with severe hepatotoxicity [12].

In this study we decided to evaluate the efficacy and safety of levofloxacin administered to candidates awaiting transplantation compared to conventional isoniazid prophylaxis initiated after transplantation.

**METHODS**

**Study Design**

An open-label, prospective, multicenter, randomized clinical trial was conducted. The efficacy and safety of levofloxacin initiated in candidates on the waiting list (500 mg q24h for 9 months, experimental arm) was compared to isoniazid (300 mg q24h for 9 months, control arm) initiated between 3 and 6 months post-transplant for tuberculosis prophylaxis. The trial was conducted according to the principles of the Declaration of Helsinki and Good Clinical Practice guidelines in compliance with Spanish legislation. The trial was approved by the Clinical Research Ethics Committees of the participating centers and registered at clinicaltrials.gov (NCT01761201, registered 22 November 2012) and EudraCT (2010-022302-41, registered 20 January 2012). The Spanish Regulatory Agency (AEMPS) authorized the study and permitted the labeling and distribution of the study drug to all the participating sites. This is an investigator-driven study whose sponsorship was initially conducted by CAIBER (Consortio de Apoyo a la Investigación Biomédica en Red, Instituto de Salud Carlos III) and then by the Foundation of one of the participating hospitals (FISEBI). The foreseen recruitment period was 2 years, and the approximate duration of the trial 3 and a half years from the inclusion of the first patient to the last visit of the last enrolled patient. The setting for the study was 18 public and academic hospitals with research groups pertaining to the Spanish Network for Research in Infectious Diseases (REIPI).

The study included liver transplant candidates ≥18 years of age without evidence of active tuberculosis, who met one of the following criteria: (1) PPD >5 mm; (2) interferon gamma release assay (IGRA) reactive; (3) history of improperly treated tuberculosis; or (4) recent contact with a patient with active tuberculosis or chest radiograph compatible with past untreated tuberculosis (apical fibronodular lesions, nodules/calcified lymph nodes, or pleural thickening). Written informed consent signed by the patient or legal representative was required. Exclusion criteria were: (1) intolerance or prior adverse reactions to isoniazid or levofloxacin; (2) prior contact with a case of isoniazid-resistant or levofloxacin-resistant tuberculosis; and (3) treatment with active drugs against *Mycobacterium tuberculosis* (including quinolones) in the previous month. Women at childbearing age were required to have a negative pregnancy test at screening and effective contraceptive method was indicated (including abstinence) during the study period.

Patients were randomized sequentially when placed on the transplant waiting list of each center in order to receive levofloxacin or isoniazid. The assignment of treatment was automatically generated through the electronic case report form (eCRF) with a permuted-block randomization system, stratified by centers, in a 1:1 ratio.

 Patients randomized to levofloxacin began prophylaxis immediately prior to transplantation while they were on the waiting list. Patients randomized to isoniazid began prophylaxis after transplantation when liver function was considered stable, between 3 and 6 months post-transplant. Liver function was considered stable when transaminases, alkaline phosphatase, and bilirubin did not exceed twice the upper limit of normality.

Both isoniazid (300 mg tablets) and levofloxacin (500 mg capsules) were administered orally in a single daily dose on an empty stomach. When treatment was discontinued for a period of less than two weeks, it was allowed to be reintroduced for a period of up to 9 months. In transplanted patients on levofloxacin prophylaxis, the medication was allowed to be discontinued for a maximum period of two weeks Interruptions of >2 weeks or a change in the prophylaxis regimen resulted in exclusion from the study. Patients withdrawn from the study would be subject to follow-up for an established time period to determine the appearance of tuberculosis.

**Follow-up**

During the 9 months of prophylaxis, patients were followed up monthly to assess the efficacy and safety (adverse events [AE]) of the drugs studied. At the end of prophylaxis, patients were followed up at least every 3 months until month +6 and every 6 months until month +18. Patients were also assessed whenever there was clinical suspicion of tuberculosis or adverse effects. Patients who missed 2 consecutive visits were excluded from the study.

**Objectives**

The primary efficacy endpoint was the proportion of patients who developed tuberculosis at 18 months after transplantation. To diagnosis tuberculosis, isolation of *M. tuberculosis* or detection of *M. tuberculosis* DNA by polymerase chain reaction in a representative clinical sample, organic fluid or tissue, were requested. Cases with histological demonstration (typical granulomas with or without visualization of acid-fast bacilli) and clinical compatibility were also accepted.

A secondary objective was to demonstrate if adverse effects, paying particular attention to hepatotoxicity, limit the efficacy of levofloxacin.
Adverse Events

AE were assessed clinically and analytically at each monthly follow-up visit. The severity of AE were classified according to the National Cancer Institute Common Toxicity Criteria version 4.0 [13]. Following the onset of the first cases, the criteria for considering the presence of tenosynovitis were established as spontaneous pain that increased with movement in any tendon insertion with tenderness at that level and observation of localized inflammatory signs of at least 72 hours in duration.

Patients were considered to have hepatotoxicity when they presented alanine transaminase, aspartate aminotransferase, or bilirubin elevations more than 2 times the upper limit of the normal
Toxicity was considered severe, and therefore the drug was discontinued when symptomatic elevations were more than 3 times or asymptomatic elevations were more than 5 times the normal levels. All AE were recorded and additional information was required in case of serious adverse events.

**Statistical Methods**

The sample size was calculated to demonstrate that the incidence of tuberculosis in the levofloxacin arm was not higher than that of the isoniazid arm. With a significance level of $a = 0.025$, a type 2 error of $b = 0.20$, a loss to follow-up of 20%, and assuming a 0.5% incidence of tuberculosis in the first 18 months, 870 subjects (435 per arm) were needed to demonstrate that the incidence in the levofloxacin arm did not exceed that of the isoniazid arm by 1.5%.

An intention-to-treat (ITT) analysis was performed. All the randomized patients were included in the efficacy analysis, including those of the isoniazid arm that could not initiate treatment due to nonstabilized liver function. All randomized patients who received at least 1 dose of the study drugs and who had at least 1 follow-up visit were included in the AE analysis.

Differences in the efficacy and safety endpoints were tested using the $\chi^2$ or Fisher exact test when indicated. Quantitative endpoints were compared using the Student $t$-test.

**RESULTS**

Summary of study characteristics and study report according with the CONSORT guidelines [14] are detailed in Table 1.

**Patients**

At the time of the safety analysis, which resulted in the suspension of the study, 64 patients from 18 centers (31 patients in the isoniazid arm and 33 patients in the levofloxacin arm) had completed the study medication period. The number of patients accounts for the 7.5% of the sample size needed. The study has been active from January 2012 to February 2014. Table 2 compares the baseline characteristics of both groups by ITT, including patient followed-up after transplantation. The patients were between 34 and 71 years of age. Only 18 patients (58.1%) underwent prophylaxis in the isoniazid group compared to 33 (100%) in the levofloxacin group ($P < .01$) (Figure 1). Thirteen patients (41.9%) in the isoniazid group did not start treatment.

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**Figure 1.** Patient flow through the study.
due to nonstabilized liver function. Of the 18 patients who initiated isoniazid prophylaxis, only 10 patients (55.7%) com- pleted 9 months of prophylaxis. Therefore, in the ITT analysis only 32.2% of patients randomized to isoniazid (10/31 patients) completed prophylaxis compared with 18 patients (54.5%) who completed levofloxacin prophylaxis \( (P = .094) \). The reasons for discontinuing prophylaxis in each arm are shown in Figure 1.

**Efficacy**

No cases of tuberculosis were diagnosed in either group, including patients who never received isoniazid during the follow-up period.

**Safety**

In the monitoring procedures of the study it was detected that several patients suffered AE which were recorded as AE and properly registered in the eCRF for the study but were not communicated with additional information as they were not classified as "severe" according to the pharmacovigilance criteria described in the protocol. This was the reason for performing a specific analysis of those that occurred at the time information was received. No serious unexpected adverse events occurred during the study.

Twenty-six patients (51.0%) had AE related to the medication: 10 (55.5%) of those receiving isoniazid and 16 (48.5%) receiving levofloxacin (Table 3). The most frequent AE were tenosynovitis in the levofloxacin group and hepatotoxicity in the isoniazid group. The remaining AE are listed in Table 3. The AE resulted in the permanent discontinuation of medication in 7 patients (38.9%) of the isoniazid group and in 11 patients (33.3%) of the levofloxacin group (Table 3).

Six patients (18.2%) in the levofloxacin group had tenosynovitis (Table 4). All cases presented prior to transplantation and were bilateral. Tenosynovitis occurred at knee level in 5 patients and affected the Achilles tendon in one case. A patient with bilateral knee tenosynovitis also presented concomitant tenosynovitis of both ankles. The range of days with levofloxacin treatment until onset of tenosynovitis was 14–133 days. The medication was discontinued in all patients, who were cured in a period ranging from 5 to 50 days. The symptoms were mild and improved with anti-inflammatories in one patient in whom medication was restarted after interruption. Medication was permanently discontinued in 5 patients (83.3%). The case with bilateral Achilles tendinitis was especially crippling and persisted for 50 days despite discontinuing the medication and anti-inflammatory treatment. No patient took corticoste-roids upon developing tendinitis. There were no differences in the creatinine clearance and model for end-stage liver disease score between patients with and without tenosynovitis. No cases of tenosynovitis in patients treated with isoniazid \( (P = .05) \) were observed.

### Table 3. Adverse Events Reported During the Treatment Period in Patients Who Received at Least One Dose of the Drug

<table>
<thead>
<tr>
<th>Adverse events associated with the medication</th>
<th>Isoniazid ( n = 18 )</th>
<th>Levofloxacin ( n = 33 )</th>
</tr>
</thead>
<tbody>
<tr>
<td>Total</td>
<td>10 (55.5%)</td>
<td>16 (48.5%)</td>
</tr>
<tr>
<td>Tenosynovitis</td>
<td>0</td>
<td>6 (18.2%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>3 (9%)</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>7 (38.9%)</td>
<td>2 (6.1%)*</td>
</tr>
<tr>
<td>Diarrhea due to <em>C. difficile</em></td>
<td>1 (3%)</td>
<td>0</td>
</tr>
<tr>
<td>Urinary infection due to quinolone-resistant <em>E. coli</em></td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Nosocomial pneumonia</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Impaired renal function</td>
<td>1 (5.5%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Gastrointestinal bleeding</td>
<td>1 (5.5%)</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Hematologic toxicity</td>
<td>1 (5.5%)</td>
<td>0</td>
</tr>
<tr>
<td>Adverse events requiring permanent withdrawal of prophylaxis</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Total</td>
<td>7 (38.9%)</td>
<td>11 (33%)</td>
</tr>
<tr>
<td>Tenosynovitis</td>
<td>0</td>
<td>5 (15%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>7 (38.9%)</td>
<td>2 (6%)</td>
</tr>
<tr>
<td>Diarrhea due to <em>C. difficile</em></td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Impaired renal function</td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Urinary infection due to quinolone-resistant <em>E. coli</em></td>
<td>0</td>
<td>1 (3%)</td>
</tr>
<tr>
<td>Exitus during treatment</td>
<td>2 (11.1%)</td>
<td>4 (12.1%)</td>
</tr>
</tbody>
</table>

* Statistical significance of the comparison of the two groups: \( P = .01 \).

In the levofloxacin group, 2/33 patients (6%) developed severe hepatotoxicity prior to transplantation that was resolved by discontinuing the drug. Three patients (9%) in the levofloxacin group developed gastrointestinal toxicity (vomiting), which resulted in discontinuation of the drug in one case. Levofloxacin was discontinued in 2 additional patients due to bacterial infections (Clostridium difficile and urinary tract infection due to quinolone-resistant *Escherichia coli*). Two patients developed other toxicities that did not require discontinuing the medication (nosocomial pneumonia, gastrointestinal bleeding).

Seven out of 18 patients in the isoniazid group who met the established criteria for initiating prophylaxis (38.9%) developed hepatotoxicity \( (P = .01) \). In all these patients, the researchers decided to discontinue the drug and the toxicity disappeared in all cases. Three other patients did not present toxicities, and it was therefore not necessary to discontinue the drug: mild impairment of renal function, gastrointestinal bleeding, and hematologic toxicity (pancytopenia).

**DISCUSSION**

Although quinolones have activity against *M. tuberculosis* (including in vitro or modeling data) [15], there is little evidence...
of their usefulness in the treatment of latent tuberculosis infection [16, 17] and are only recommended when the index case has resistance to first-line drugs [18]. Given the high risk of hepatotoxicity in these patients, liver transplantation is a good scenario for studying the efficacy and safety of quinolones in comparison with isoniazid.

There are several reasons to study levofloxacin rather than other quinolones in liver transplantation. Moxifloxacin, which may be the quinolone with greatest in vitro efficacy against \textit{M. tuberculosis}, has a hepatotoxicity warning that advises using this drug only in the event that no other therapeutic alternatives are available. Levofloxacin, which has also been demonstrated to have in vitro efficacy [15, 19, 20], has a very favorable pharmacokinetic profile with a better area under the curve/minimal inhibitory concentration ratio than other quinolones [21] and has proven to be clinically effective in the treatment of tuberculosis as a second-line drug [1, 15, 22].

There is abundant evidence that levofloxacin is a safe drug [23, 24]. This quinolone is used regularly and for long periods for the treatment of osteoarticular infections and prophylaxis of spontaneous bacterial peritonitis in cirrhotic patients [23, 24]. According to a report published by the American Thoracic Society, the hepatotoxicity profile of levofloxacin is better than other treatment options, although some grade of hepatotoxicity cannot be ruled out as occurred in our study and in others [25, 26]. Six percent of the patients treated with levofloxacin prior to transplantation, developed hepatotoxicity that reversed upon discontinuing the drug. Obviously, in these patients with terminal liver disease is very difficult to determine whether the impaired liver function was due exclusively to the use of this drug. A three-year case-control study including 102 patients with a levofloxacin regimen and 358 patients with a first-line regimen for treatment of tuberculosis reported a similar rate of adverse advents in the levofloxacin-containing regimen and the front-line treatment [27]. Since it is considered a safe drug, levofloxacin is recommended for even longer regimens than those used in our clinical trial [1, 22]. Nevertheless, the 6% incidence of hepatotoxicity observed in our study in the levofloxacin group is well below the 38.9% observed in the isoniazid group.

Levofloxacin is known to produce arthropathy (tendinitis, synovitis, etc.) but with a frequency <1% [28]. In some cases it can be severe and tendon rupture has been reported [29–31]. In a prospective, randomized clinical trial on the prevention of BK virus-associated nephropathy in renal transplant recipients, arthropathy was observed in 8% of patients treated with levofloxacin [32]. In our study, the use of levofloxacin as tuberculosis prophylaxis in liver transplant candidates was associated with an 18.2% incidence of tenosynovitis. In five of the six cases we were forced to permanently discontinue the medication. In all cases tenosynovitis was bilateral. All patients improved after

<table>
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<tr>
<th>Table 4. Description of Tenosynovitis Cases Reported in the 33 Patients Treated With Levofloxacin</th>
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<tbody>
<tr>
<td>Case</td>
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<tr>
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</tr>
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<td>1</td>
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<td>2</td>
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<tr>
<td>3</td>
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<tr>
<td>4</td>
</tr>
<tr>
<td>5</td>
</tr>
<tr>
<td>6</td>
</tr>
</tbody>
</table>

NOTE: Creatinine clearance was >60 mL/min in all cases.
discontinuing the medication, but in one case the symptoms persisted for weeks. Due to high frequency and intensity of this unexpected side effect the trial was definitively stopped. Unfortunately, a pharmacokinetic study was not foreseen that would have allowed us to determine if the levofloxacin levels were above the therapeutic levels due to some kind of pharmacological interaction or metabolic disorder. It has been reported that concomitant treatment with corticosteroids may increase the risk of tendinitis [30, 31], this was not the case in our study since all cases developed tenosynovitis prior to transplantation. Otherwise, it is unlikely that this secondary effect was due to impaired liver function because the drug undergoes only a 5% of liver metabolism, and more than 85% of levofloxacin is eliminated unchanged by renal route. Creatinine clearance was normal in patients with tenosynovitis. Nevertheless, it could be underestimated in patients with cirrhosis.

In conclusion, the use of levofloxacin in liver transplant candidates has been associated with a high incidence of tenosynovitis. Whether tolerance and safety could be improved using lower doses of levofloxacin or other quinolones prior to transplantation or full-dose after transplantation are issues that should be clarified in future studies.

Notes

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Potential conflicts of interest. All authors: No potential conflicts of interest.

All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

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18. Targeted tuberculin testing and treatment of latent tuberculosis infection. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. This is a Joint Statement of the American Thoracic Society (ATS) and the Centers for Disease Control and Prevention (CDC). This statement was endorsed by the Council of the Infectious Diseases Society of America (IDSA), September 1999, and the sections of this statement. Am J Respir Crit Care Med 2000; 161(4 Pt 2): S221–47.


