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Empiric vs screening-based use of isoniazid for tuberculosis prophylaxis: Safety and effectiveness in lung transplant recipients in Saudi Arabia

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Abstract

Background: Tuberculosis (TB) is a major complication following transplantation. The likelihood of TB may be increased in transplant patients living in TB-endemic areas such as Saudi Arabia. In areas where TB is less common, guidelines recommend isoniazid (INH) for TB prophylaxis depending on patient and donor screening results. However, in TB-endemic regions, studies have supported its use in all transplant patients regardless of TB screening results. This study aimed to compare the safety and effectiveness of administering INH prophylaxis therapy based on the TB screening results of lung transplant (LT) recipients.

Methods: We conducted a single-center retrospective cohort study on LT recipients. The outcomes were compared between patients who were administered screening-based prophylaxis (SBP) with INH based on their tuberculin skin tests (TSTs) or QuantiFERON results and those who were administered empirical prophylaxis (EP) with INH regardless of TB screening results. The primary endpoint was the incidence of TB infection, and the secondary endpoints were INH-induced hepatotoxicity and INH resistance.

Results: A total of 50 patients received SBP and 30 received EP. TB incidences were 8% and 0%, respectively ($P = .0487$). One of these patients had INH resistance, and one patient experienced INH-induced hepatotoxicity ($P = .1591$); both were in the SBP group.

Conclusion: The low rates of TB infection, INH-induced hepatotoxicity, and INH resistance in the EP group suggest that INH prophylaxis appears to prevent TB and can be safely used in all LT recipients. However, prospective studies using large sample sizes are required to confirm these findings.

KEYWORDS

isoniazid, latent tuberculosis, lung transplantation, tuberculosis, tuberculosis prophylaxis

Dema A. Alissa has equally contributed as the primary author.

1 | INTRODUCTION

Tuberculosis (TB) is a major post-transplant complication in solid organ transplant (SOT) recipients. Both de novo TB and the reactivation of latent TB infection (LTBI) may occur post-transplantation.[1,2] SOT recipients have a higher rate of TB-associated mortality than other TB patients. The fatality rate among SOT recipients who developed TB was 9.5%–29%.[3,4] The rate of post-transplant TB varies based on the transplanted organ and is highest among lung transplantation (LT) recipients.[2] The risk of TB in LT recipients may be up to 5.6-fold higher than in other SOT recipients.[3] The reported incidence of TB post-LT ranges from 3.8% to 10%.[2,5,6]

Most new TB cases and instances of reactivation occur within the first year post-transplantation.[3] Therefore, The American Society of Transplantation (AST) recommends the use of universal isoniazid (INH) prophylaxis for the first year post-transplantation in TB endemic areas,[7] while in areas with low TB prevalence, the use of INH for TB prophylaxis is not supported in patients with negative tuberculin skin tests (TSTs) or QuantiFERON tests.[7] Treatment using INH is recommended for 9-12 months post-transplantation for TB prophylaxis, based on recipients' TB exposure, their screening test results,[1] their risk factors for TB, and the donor TB history.[2,8] Risk factors associated with post-transplant TB infections include recipients' advanced age, previous exposure to TB, pre-transplant comorbidities (dialysis, diabetes, cirrhosis, and hepatitis C virus infection), and intensity of immunosuppression (IS), especially when using azathioprine and mammalian target of rapamycin inhibitors.[3,9,10] Other risk factors may be donor-driven, such as the history of residence in high TB-endemic areas and history of latent or active TB.[3,8-12]

Tuberculosis infection risk may be especially high in transplant populations living in TB-endemic areas such as Saudi Arabia.[2,13,14] In particular, when the donors are also from Saudi Arabia or are expatriates from other TB-endemic countries. Therefore, the use of INH for latent TB treatment may be essential.[2] A prospective study conducted in Spain, a TB-endemic region, reported that using INH prophylaxis was safe and effective in preventing TB even in LT recipients with negative purified protein derivative (PPD) skin tests.[15] Similarly, in Saudi Arabia, a retrospective study reported a lower rate of TB infection in kidney transplant recipients with evidence of LTBI who received universal INH prophylaxis.[2] However, concerns exist regarding the possibility of developing INH resistance and INH-induced hepatotoxicity.[5] The most effective and safest strategy for TB prevention in LT recipients remains undetermined. Therefore, we undertook this study to compare the outcomes of using TB prophylaxis based on recipients' TB screening test results with those using INH empirically in all LT recipients.

2 | METHODS

2.1 | Patients and methods

This retrospective cohort study reviewed the records of adult patients aged 14 years and older (based on the criteria of the institute indicating that patients are considered an adult at 14 years of age) who underwent lung transplantation at the King Faisal Specialist Hospital and Research Centre (KFSH & RC) in Riyadh, Saudi Arabia, between 1 January 2010, and 31 December 2017. The lung transplant program at KFSH and RC is the only program in Saudi Arabia and the Arabic Gulf region currently performing more than 30 lung transplants annually. In this study, patients were excluded if they (a) had received other solid organ transplants (heart, liver, kidney, pancreas, or intestine) alone or concomitantly, or (b) had a history of active liver disease, viral hepatitis, or known hepatotoxicity. The included subjects were divided into two main groups. Subjects who were prescribed INH based on recipients' and or donors' PPD or QuantiFERON-TB Gold In-Tube (Cellestis, Melbourne, Australia) test results were grouped under the "screening-based prophylaxis" (SBP) group. In contrast, patients who were prescribed INH regardless of the recipients' and donors' PPD or QuantiFERON test results for LTBI were grouped as "empirical TB prophylaxis" (EP). Ethical approval was obtained from the KFSH & RC Institutional Review Board (RAC # 218 175).

2.2 | Anti-tuberculosis prophylaxis

The approach of prescribers to TB prophylaxis varied in our institution. Before the study by Al-mukhaini et al in KFSH & RC,[2] a majority of the practitioners prescribed INH 300 mg plus pyridoxine 50 mg daily for 9-12 months as LTBI therapy if the PPD or QuantiFERON test results of either the LT recipient or donor or both were positive. However, this practice was later changed to prescribing INH 300 mg plus pyridoxine 50 mg daily for 9-12 months regardless of the recipient's TB screening test results.[2] Moreover the IS and antimicrobial prophylaxis regimens were administered to LT recipients based on the institutional protocol, as mentioned in detail in the supplementary material.

2.3 | Patient characteristics

The recipient' 1-year post-transplantation data were collected from their electronic medical records using the Research Electronic Data Capture (REDCap) 8.9.0 software. To ensure patient privacy, a serial number was linked to each patient's medical record number for tracking. Data collected from donors included age, sex, blood type, and history of TB. Data on recipients comprised demographics, TSTs, blood test results, operative, postoperative, IS regimen, and antimicrobial prophylaxis.

2.4 | Clinical outcomes

The study hypothesized that the rate of pulmonary TB infection at one year after lung transplantation would be lower in patients administered with empiric INH as anti-TB prophylaxis than in

patients administered INH as LTBI treatment based on the TB test results of the donor or recipient. The primary endpoint was the incidence of TB infection within the first-year post-transplantation. The secondary endpoints were INH-induced hepatotoxicity and INH resistance.

The criteria for diagnosing active TB infection was through microbiological confirmation either by a single respiratory culture growing *Mycobacterium tuberculosis* (MTB) from recipient specimens and or DNA detected by a polymerase chain reaction in the sputum clinical sample or sputum smears positive for acid-fast-bacilli.

INH-induced hepatotoxicity was defined as alanine aminotransferase (ALT), and aspartate aminotransferase (AST) levels more than three times the upper limit of normal (ULN) defined as ALT or AST ≥ 120 U/L in the presence of hepatitis symptoms and or jaundice, or five times the ULN defined as ALT or AST ≥ 200 U/L in the absence of signs and symptoms of hepatotoxicity (eg jaundice, flank pain, abdominal pain, epigastric pain, vomiting, and tea-colored urine). Other causes of hepatotoxicity, such as medications or comorbidities, needed to be excluded to confirm INH-induced hepatotoxicity. INH resistance was identified using culture-based drug susceptibility testing, or if patients developed TB infection while adherent to the INH prophylaxis regimen.

Vital signs of subjects, laboratory test results, including results of renal function tests and liver function tests, and body mass index were recorded at baseline, on day 7, and 1, 3, 6, and 12 months post-transplantation.

2.5 | Statistical analysis

The findings in the two groups were compared using chi-square statistics for categorical variables, and continuous variables were compared using the *t*-test. Differences were considered significant if *P*-values were less than .05. To determine the differences in magnitude, Cramer's effect size was obtained for chi-square and Cohen's *D* effect size for the *t*-test. The rates of TB infection, patient survival, and graft rejection were calculated at a 1-year follow-up. Survival analysis was performed on time to death. All analyses were performed using JMP software version 14 (SAS Institute, Cary, NC, USA).

3 | RESULTS

3.1 | Study population

In total, 81 LT recipients met the inclusion criteria. One patient was later excluded because of death from hemorrhage during transplantation surgery. Donors were mostly East Asian (61%), with a mean age of 39 ± 13 years. Most of the donors (60) had an unreported history of TB, and none had a respiratory culture positive for TB at baseline. Therefore, patient categorization into SBP or EP groups depended solely on the recipients' available data on TB screening testing and INH administration. The SBP group comprised 50 patients, of whom seven (14%) were administered INH according to the recipient's positive screening test result. The EP group included 30 subjects, all of whom were administered INH regardless of the recipients having a known negative TB test result or undetermined test results. Two subjects in the EP group were administered 150 mg (pediatric dose) of INH instead of 300 mg because of their age (16 years) and low body weight.

The baseline characteristics of both groups were similar, as presented in Table 1. However, the length of both hospital stay (LOS) and intensive care unit (ICU) stay was significantly longer in the EP group with a median of 14 and 19 days, respectively ($P = .005$ and $P = .002$). For the 37 patients who were administered INH, the duration of INH prophylaxis and the grouping based on their TB screening test were significantly different at baseline, as shown at the bottom of Table 1. The mean age of the study subjects was 38 ± 15 years. Most patients (65%) were male and of Arab ethnicity (98%). Most recipients (94%) underwent bilateral lung transplantation. On day one post-transplantation, all patients were started on a triple IS regimen; they all had FK included. However, seven patients later had FK replaced with cyclosporine because of FK-related neurological side effects. MMF was switched to azathioprine in 28 patients because of gastrointestinal or hematological side effects.

3.2 | Tuberculosis infection

Four patients (5%) developed pulmonary TB infection during the first year post-transplantation. All were in the SBP group. Among these four patients, three patients had unknown TST test results and negative QuantiFERON; therefore, they were not administered INH. The remaining patient had an unknown TST result and positive QuantiFERON results; therefore, INH was administered. The patient had a sputum culture positive for MTB despite being on INH. This infection in this patient was found to be INH resistant (Figure 1). The time to TB infection occurrence in the patient who was administered INH was 106 days, while the time to TB occurrence in patients who were not administered INH was a mean of 96 ± 14 days.

3.3 | INH safety

Most patients tolerated INH well. One patient, however, experienced INH-induced hepatotoxicity. In patients who were administered INH, the mean maximum AST levels within the 12 months were 75 ± 54 U/L in the EP group and 66 ± 50 U/L in the SBP group. The mean maximum ALT levels, 59 ± 50 U/L in the EP group and 78 ± 58 in the SBP group ($P = .1591$, $V = 0.07$). One patient had resistance to INH in the SBP group ($P = .0631$), suggesting that INH resistance was associated with TB occurrence ($V = 0.72$).

TABLE 1 Baseline recipients characteristics

Recipients' baseline characteristics	Total (n = 80)	Screening-based prophylaxis (n = 50)	Empiric prophylaxis (n = 30)	*P*-value
Age in years, mean ± (SD)	38 ± 15	37 ± 16	39 ± 14	.600
Male gender, n (%)	52 (65)	34 (68)	18 (60)	.457
Arab ethnicity, n (%)[a]	78 (98)	49 (98)	29 (96)	.715
Occupation, n (%)[a]				
Healthcare employee	0 (0)	0 (0)	0 (0)	.308
Non-healthcare employee	19 (30)	14 (38)	7 (23)	
Unemployed	5 (6)	3 (6)	2 (7)	
History of smoking, n (%)[a]				
Smoker	49 (61)	28 (56)	21 (70)	.011
Former smoker	8 (10)	6 (12)	2 (7)	
History of TB infection, n (%)[a]				
Positive	2 (2.5)	1 (2)	1 (3)	.481
Negative	52 (65)	35 (70)	17 (57)	
TB screening test, n (%)				
PPD +, Quant +	0 (0)	0 (0)	0 (0)	.8257
PPD +, Quant −	1 (1)	1 (2)	0 (0)	
PPD +, Quant UnK	1 (1)	1 (2)	0 (0)	
PPD −, Quant −	1 (1)	0 (0)	1 (3)	
PPD −, Quant +	0 (0)	0 (0)	0 (0)	
PPD −, Quant UnK	0 (0)	0 (0)	0 (0)	
PPD UnK, Quant UnK	8 (10)	6 (12)	2 (7)	
PPD UnK, Quant −	61 (76)	37 (74)	24 (80)	
PPD UnK, Quant +	8 (10)	5 (10)	3 (10)	
Underlying lung disease, n (%)[b]				
Interstitial lung disease	39 (49)	25 (50)	14 (47)	.766
Pulmonary fibrosis	32 (40)	22 (44)	10 (33)	
Bronchiectasis	31 (39)	20 (40)	11 (37)	
COPD	6 (8)	4 (8)	2 (7)	
Lung cancer	1 (1)	1 (2)	0 (0)	
Other[c]	14 (18)	6 (12)	8 (27)	
History of transplantation, n (%)	1 (1)	1 (2)	0 (0)	.088
Comorbidities, n (%)[b]				
Pulmonary hypertension	36 (45)	23 (46)	13 (43)	.816
Diabetes mellitus	17 (21)	13 (26)	4 (13)	.1800
Hypertension	11 (14)	8 (16)	3 (10)	.441
Cardiovascular disease	8 (10)	5 (10)	3 (10)	1.000
Renal failure	2 (2.5)	1 (2)	1 (3)	.7115
Transplantation & post-transplantation information				
Unilateral lung transplantation, n (%)	5 (6)	4 (8)	1 (3)	.38
Duration of transplant in hours, mean ± SD	12.5 ± 48	15.36 ± 61	7.81 ± 2	.388
Cold ischemia time in minutes, mean ± SD	320 ± 96	323 ± 112	317 ± 66	.785
Underwent re-exploration surgery, n (%)	36 (45)	20 (40)	16 (53)	.246

(Continues)

TABLE 1 (Continued)

Recipients' baseline characteristics	Total (n = 80)	Screening-based prophylaxis (n = 50)	Empiric prophylaxis (n = 30)	*P*-value
Hospital length of stay for transplantation in days, median ± SE	26 ± 56	11 ± 3	25 ± 9	.005
ICU length of stay during transplantation in days, median ± SE	16 ± 36	23 ± 3	42 ± 15	.002
Initial immunosuppression regimen, n (%)				
FK + MMF + Corticosteroids	78 (98)	48 (96)	30 (100)	.5253
FK + AZA + Corticosteroids	2 (3)	2 (4)	0 (0)	
Patients initiated on INH prophylaxis, n (%)	N = 37 (46)	N = 7 (14)	N = 30 (100)	
INH reception according to TB screening, n (%)				
PPD +, Quant −	1 (3)	1 (14)	0 (0)	.0001
PPD +, Quant UnK	1 (3)	1 (14)	0 (0)	
PPD −, Quant −	1 (3)	0 (0)	1 (3)	
PPD UnK, Quant UnK	2 (5)	0 (0)	2 (7)	
PPD UnK, Quant −	24 (65)	0 (0)	24 (80)	
PPD UnK, Quant +	8 (22)	5 (71)	3 (10)	
INH prophylaxis duration in days, mean ± SD	343 ± 184	40.6 ± 115	352.6 ± 198	.0001
INH interruption, n (%)	15 (41)	1 (14)	14 (47)	.061
INH interruption duration in days, mean ± SD	29 ± 37	5 ± 37	30.57 ± 10	.519

Abbreviations: AZA, azathioprine; FK, tacrolimus; MMF, mycofenolate mofetil; UnK, unknown.

[a]Remaining subjects' data are missing, SE, standard error; TB, tuberculosis; INH, isoniazid; PPD, purified protein derivative; Quant, QuantiFERON; +, positive; −, negative; COPD, chronic obstructive pulmonary disease.

[b]Each subject may has more than 1 disease.

[c]Others including Karagener syndrome, emphysema, sarcoidosis, acute respiratory distress syndrome.

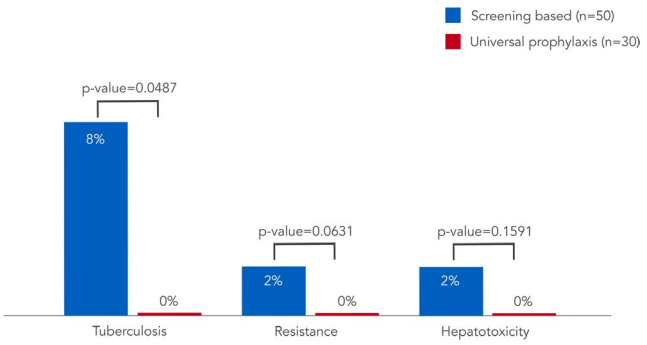

FIGURE 1 INH effectiveness and safety outcomes in the empiric prophylaxis compared to screening-based prophylaxis

3.4 | Patient and graft survival

The one-year graft survival rate was 100%. However, 22 of the 80 patients (28%) experienced biopsy-proven graft rejection at 12 months post-transplantation; eight of these patients were in the EP group and 14 in the SBP group (P = .89). None of the patients who had TB growth experienced an organ rejection episode during the 1-year follow-up period. Of the 80 patients, seven died within 1 year of transplantation, yielding a 91% patient survival rate. Four of the patients who died were in the EP group, and three were in the SBP group. The Kaplan-Meier probability of time to death was 97.7 ± 75.8 days in the EP group and 134.6 ± 110.6 (P = .492) in the SBP group. The causes of death of the four patients in the SBP group were pulmonary related complications, such as multi-organ failure, lung failure, pulmonary hemorrhage, and chronic allograft dysfunction. The remaining three patients in the EP group also died of multi-organ failure, including pulmonary failure, and one patient died from pan-resistant pneumonia.

4 | DISCUSSION

In this study, we compared two groups that were administered INH to prevent post-LT TB infection using different approaches. We found that none of the patients who were administered INH empirically developed TB infection. The 5% incidence of TB infection in this study is similar to those previously reported in LT recipients.[2,5,6] The fact that all TB infection cases (n = 4) were in the SBP group, of which

three were not administered INH, demonstrates the effectiveness of administering INH for TB prevention. Moreover it has been reported that most transplant patients who develop active TB post-transplantation tested negative for TB before transplantation.[7] Similarly, in the present study, most of the LT recipients who developed active TB post-transplantation tested negative in the QuantiFERON test before transplantation. This result may indicate that the risk of TB infection in transplant recipients remains high regardless of their TB screening results prior to transplantation, thus supporting INH's use empirically to prevent TB occurrence in LT recipients.

Even though donors' TB screening information was unavailable, their probability of carrying active or latent TB infection is possible in such highly endemic areas. Most of these donors came from the East Asian region, including well-known TB-endemic countries such as Saudi Arabia, India, Indonesia, Philippines, Pakistan, and Bangladesh. Therefore, we cannot rule out that patients who developed TB post-transplantation were probably related to donor's reactivation of TB. In addition, LOS and ICU stays were significantly longer in the EP group. This increased duration might indicate that these patients were very sick to start with, thus were a greater risk of developing TB.

The reported onset of TB post-LT varies between previous studies, with medians ranging from 3.2 to 9.0 months.[2-4] In the current study, the median time to develop post-LT TB was 3.3 months, which was less than the previously reported time for solid organ transplants 9.2 months.[2] TB infection occurrence in the patients who were administered with INH was 106 days, which was similar to the mean time to occurrence that has been reported in patients who were not administered with INH at 96 ± 14 days. There is no consensus on the optimal time to begin TB prophylaxis post-transplantation or the optimal duration.[1] It may be reasonable to start the prophylaxis before transplantation and continue with it post-transplantation for 9-12 months.[9,16] The agent of choice for TB prophylaxis may vary depending on local rates of anti-TB drug resistance, drug interactions with IS, and patients' adherence, comorbidities, and illness.[3]

INH prophylaxis appears to be a safe and TB-preventative treatment in TB-endemic areas in LT recipients with negative TST tests.[15] In the present study, only one subject experienced INH-induced hepatotoxicity; this rate of INH-induced hepatotoxicity during clinically monitored preventive therapy was lower than that reported previously.[17,18] The administration of INH 300 mg daily for 9-12 months for TB prophylaxis appears safe. In this study, there was only one case of INH resistance; this rate is consistent with that found in studies of renal transplant recipients.[19,20] However, due to the infrequent occurrence of INH-induced toxicity and INH resistance, it is difficult to draw a definitive conclusion.

To the best of our knowledge, the present study is the first to compare the safety and effectiveness of two TB prophylactic approaches in LT recipients. Even though the sample size was very small, it is comparable to that of other studies assessing the LT population.[2,15] However, our limitations include the fact that the study was a single-center retrospective observational study lacking randomization. Additionally, data on most of the donors and some of the recipients could not be retrieved. Information about the IS levels during TB infection, which is a major driver of infection risk in LT recipients, was not collected; this may limit inferring a reliable conclusion about INH's empiric use in all LT recipients. Nonetheless, the study results will contribute to developing rigorous protocols for TB prophylaxis, especially in TB-endemic areas.

5 | Conclusion

This study proposes that in TB-endemic countries, such as Saudi Arabia, the use of empiric INH prophylaxis in LT recipients may be essential. However, practitioners should always assess INH's benefit in preventing TB against its risks, including side effects, drug interaction with IS, and the development of INH resistance. The low rates of TB infection, INH-induced hepatotoxicity, and INH resistance in the EP group may advocate the safe and effective use of INH in all LT recipients. However, prospective studies using a larger sample size needs to be conducted to confirm these findings.

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CONFLICT OF INTEREST

None declared.

AUTHOR CONTRIBUTIONS

GBK: contributed to the conception or research design of the work; or the acquisition, analysis, or interpretation of data for the work; participated in the performance of the research; participated in drafting the work or revising it critically for important intellectual content; served as scientific advisors, critically reviewed the study proposal, participated in writing or technical editing of the manuscript; agreed on the approval of the version to be published; agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; DAA: contributed to the conception or research design of the work; or the acquisition, analysis, or interpretation of data for the work; participated in the performance of the research; participated in drafting the work or revising it critically for important intellectual content; agreed on the final approval of the version to be published; served as scientific advisors, critically reviewed the study proposal; agreed to be accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved; equally contributed as the primary author; NIA: contributed to the conception or research design of

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SUPPORTING INFORMATION

Additional supporting information may be found online in the Supporting Information section.

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