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RESEARCH ARTICLE

Management of Latent Tuberculosis Infection in Solid Organ Transplant Candidates: Short Regimens

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ABSTRACT

Tuberculosis reactivation causes significant morbidity and mortality especially in immunocompromised patients such as solid organ transplant (SOT) recipients. Therefore, treating latent tuberculosis infection (LTBI) is critical. The treatment of LTBI with former first line regimen, isoniazid monotherapy for 9 months, can be challenging, as it is associated with higher toxicity risk and lower treatment completion rates. Isoniazid monotherapy for 9 months is more likely to cause liver toxicity compared to other regimens and its rate of completion can be lower than 50%. As of result of this, there has been a shift in the treatment of LTBI. The following short-regimens: 3 months of weekly isoniazid plus rifapentine, 4 months of daily rifampin and 3 months of daily isoniazid plus rifampin, have replaced 9-month isoniazid monotherapy as first line treatments for LTBI, after the new guidelines of LTBI management were published in 2020 by the Centers for Disease Control and Prevention (CDC) and National Tuberculosis Controllers Association. These short regimens for LTBI are effective and safe in SOT candidates. However, close monitoring for drug-drug interactions are paramount.

Introduction

Latent tuberculosis infection (LTBI) is very common and its treatment is highly effective in preventing tuberculosis (TB) reactivation, which is associated with significant morbidity and mortality especially in vulnerable patients such as solid organ transplant (SOT) recipients[1]. Screening for LTBI is standard of care in all the patients that are being evaluated for transplantation. Treatment of LTBI is recommended for those that screen positive after active TB is ruled out[1]. Isoniazid (INH) monotherapy for 9 months was the first line treatment for LTBI for many years until 2020 when the LTBI guidelines were updated and INH monotherapy became just an alternative treatment[2]. INH monotherapy is highly effective[3], however, it is associated with higher toxicity risk and lower treatment completion rates[4]. A 2-month regimen of rifampin (RIF) and pyrazinamide (PZA) was an alternative treatment for LTBI several years ago until it was discovered to be associated with fatal and severe hepatitis[5]. Other shorter regimes have become the treatments of choice, as they are very efficacious and are associated with higher completion rates and lower toxicity risk[2]. The data of shorter regimens in SOT patients is scarce. The rifamycins included in the shorter regimens can potentially be problematic in SOT candidates that are taking drugs that can interact with rifamycins, which are inducers of cytochrome P-450 (CYP)[6]. Investigation for potential drug-drug interactions (DDI) is essential prior to initiating treatment with shorter regimens. In this review, we described the different shorter regimens that are being used to treat LTBI in SOT patients.

Epidemiology of LTBI in the general population

It is estimated that more than one third of the world population has *Mycobacterium tuberculosis* infection[7], including more than 10 million people in the United States (US)[8]. A systematic review demonstrated that the global prevalence of LTBI was 24.8% and 21.2% by interferon gamma release assay (IGRA) and tuberculin skin test (TST), respectively[9]. The LTBI prevalence is very high in countries such as Haiti, Peru, Ethiopia, Somalia, Buthan and Vietnam (range: 42% to 55%)[10]. The estimated prevalence of LTBI in US is only 2.7%[11]. The prevalence of LTBI may vary based on age group and ethnicity. In a study performed in US, the highest prevalence of LTBI was noted in persons ≥ 65 years among US-born persons and in persons between the ages of 45 and 64 years among non-US-born persons[11].

Epidemiology of LTBI in SOT patients

In a study conducted at a large transplant program in Miami, US, it was noted that the prevalence of LTBI among kidney transplant candidates was higher in patients that were born in South America (33%), followed by the Caribbean (26%), Central America (21%) and North America (8%)[12]. Haitians had the highest prevalence of LTBI (51%), and kidney transplant candidates with LTBI were more likely to be older compared to patients without LTBI (60.6 ± 11.3 vs. 55.3 ± 14.18 years, $P < 0.001$)[12]. The prevalence of LTBI among SOT recipients is unknown as TST and IGRA may yield false negative and indeterminate results in immunocompromised patients[13]. The prevalence of LTBI can also be difficult to measure with certainty in SOT candidates due to anergy associated with end-stage organ disease. In a retrospective study, the prevalence of indeterminate IGRA result was 25% among liver transplant candidates[14]. On a different cohort of liver transplant candidates, it was discovered that those patients with a MELD score greater than 25 were greater than 16 times more likely to have an indeterminate IGRA result[15].

Short regimens

The shorter regimens that have become preferred treatments for LTBI after the 2020 LTBI guidelines came out are: 3 months of weekly INH Plus Rifapentine (RPT), 4 months of daily RIF and 3 months of daily INH Plus RIF[2]. The treatment doses are included in Table 1. These short regimens are effective in preventing active TB, and are more likely to be completed than the longer 9-month INH regimen[16]. There were no significant differences in efficacy and completion rate among the different short regimens[16]. These short regimens have been used in SOT candidates, but to our knowledge, they have not been used in SOT recipients as no reports were found in the medical literature. As per LTBI guidelines in SOT (published in 2019), the use of RIF to treat LTBI should be avoided if possible or at least used with caution in the post-transplant setting given DDI with immunosuppressive drugs[1]. This should also apply to other rifamycins.

Of note, 1 month of RPT Plus INH was found to be non-inferior to 9 months of INH in preventing TB in HIV-infected patients[17]. However, this study was criticized as included many patients at low risk for progression to active TB[18]. This regimen is not recommended as a preferred therapy neither as an alternative[2].

TABLE 1. Dosages of short regimens used for treatment of latent tuberculosis infection

Regimens	Dosages	Food effect
Weekly isoniazid and rifapentine (3 months)	**Adults and children aged ≥12 years**	
	Isoniazid: 15 mg/kg rounded up to the nearest 50 or 100 mg; 900 mg maximum	Take without food
	Rifapentine:	Take with food
	10–14.0 kg, 300 mg	
	14.1–25.0 kg, 450 mg	
	25.1–32.0 kg, 600 mg	
	32.1–49.9 kg, 750 mg	
	≥50.0 kg, 900 mg maximum	
	Children aged 2–11 years	
	Isoniazid: 25 mg/kg; 900 mg maximum	Take without food
	Rifapentine: see above	Take with food
Daily rifampin (4 months)	**Adults:** 10 mg/kg	Take without food
	Children: 15–20 mg/kg	Take without food
	Maximum dose: 600 mg	
Daily isoniazid and rifampin (3 months)	**Adults**	
	Isoniazid: 5 mg/kg; 300 mg maximum	Take without food
	Rifampin: 10 mg/kg; 600 mg maximum	Take without food
	Children	
	Isoniazid: 10–20 mg/kg; 300 mg maximum	Take without food
	Rifampin: 15–20 mg/kg; 600 mg maximum	Take without food

Three Months of Weekly INH Plus RPT

The 3-month regimen of weekly INH Plus RPT was found to be non-inferior to 9-month INH in preventing active TB. In addition, it was associated with higher completion rates and lower rates of hepatotoxicity[4]. This treatment is recommended for children and adults, including HIV-positive persons if drug interactions allow[2]. In a systematic review, it was noted that this regimen had a lower frequency of adverse events compared to INH monotherapy [INH/RPT: 11.5% (1.9%-41.5%) vs. 9-month INH: 17.6% (0.18%-71.8%)][19]. In a small study, soluble triggering receptors expressed on myeloid cells were found to be useful biomarkers for predicting systemic adverse reactions during the INH/RPT regimen[20]. However, this has not been validated in other studies.

This regimen when administered through directly observed therapy (DOT) is associated with higher completion rates. The completion rate by self-administered therapy was inferior to the rate with DOT[21]. However, self-administered therapy is still an approved option[22]. A strategy of sending weekly reminders to patients was effective in maintaining a high treatment completion rate in a cohort of patients that were self-administering this regimen[23].

In SOT, this shorter regimen has been used in renal and liver transplant candidates[23,24]. A retrospective study, performed in renal transplant candidates (RTC) showed higher compliance rate in the 3-month INH Plus RPT compared to the 9-month INH regimen (93% vs. 47%, $P < 0.001$), and no transaminase elevations were observed in the INH/RPT group, but occurred in 5% of the patients taking INH monotherapy[23]. This short regimen was also used among potential living kidney donors with LTBI and was not associated with significant adverse reactions[25]. As previously mentioned, DDI can occur with the shorter regimens. Eight (22%) RTC developed severe hypertension (≥180/110 mmHg) after starting INH/RPT[26]. RPT can decrease the efficacy of certain antihypertensive drugs through the induction of CYP3A4—CYP2C9[6]. RPT can also cause significant DDI with other drugs such as warfarin and statins[24].

Four Months of Daily Rifampin

The 4-month course of daily rifampin was found non-inferior to 9-month course of INH. This shorter regimen is recommended for adults[27] and children[28] but it is not approved for HIV-positive patients as no efficacy data is available among those patients with HIV[2]. This regimen is associated with lower hepatotoxicity risk (0.1% vs 1%), higher completion rate [53.5% (95% CI: 50.2–56.8) vs. 36.9% (95% CI: 35.9–37.8)] and lower costs compared to 9 months of INH[29]. The potential DDI with the rifamycins are more pronounced with RIF. Rifabutin (it causes less marked DDI) can sometimes be used instead of RIF when RIF is contraindicated due to DDI and INH cannot be used[6].

In a small prospective study in liver transplant candidates with compensated cirrhosis, LTBI treatment with RIF for 4 months was associated with no liver toxicity and 100% completion rate[30]. No other studies of this regimen performed in transplant candidates were found in the literature.

Three Months of Daily Isoniazid Plus Rifampin

The 3-month of daily INH plus RIF is recommended for adult and children with HIV (if allowed by potential DDI) or without it. This regimen was found to have similar risk for TB reactivation, hepatotoxicity, and adverse effects requiring discontinuation of therapy when compared to 6 months or more of INH[31,32].

This regimen was used in a small cohort of lung transplant candidates and it appeared to be safe and effective[33]. Of the 22 patients that received this regimen, none developed TB reactivation post-transplant and only two had adverse effects[33]. No additional data with this regimen in transplant candidates were found.

Conclusions

The short regimens [3 months of weekly INH Plus RPT, 4 months of daily RIF and 3 months of daily INH Plus RIF] are effective in preventing active TB and potentially safe as long as patients are monitored closely for DDI and therapeutic interventions are done if needed (e.g. adjusting the dose of an anti-hypertensive drug). Unfortunately, these short regimens are restricted to the pre-transplant setting given DDI with immunosuppressive drugs. Therefore, treatment of LTBI should be attempted prior to SOT if possible (e.g. non-urgent transplantation). The short regimens have probably no value in liver transplant candidates with decompensated cirrhosis as the LTBI treatment is usually postponed until after the transplant in these patients. Additional data for these short regimens for the treatment of LTBI in SOT candidates, especially the 4 months of daily RIF and 3 months of daily INH Plus RIF, are needed.

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