Current Treatment Options for Latent Tuberculosis Infection

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ABSTRACT. Treatment of latent tuberculosis infection (LTBI) is a key component in TB control strategies worldwide. However, as people with LTBI are neither symptomatic nor contagious, any screening decision should be weighed carefully against the potential benefit of preventing active disease in those who are known to be at higher risk and are willing to accept therapy for LTBI. This means that a targeted approach is desirable to maximize cost effectiveness and to guarantee patient adherence. We focus on LTBI treatment strategies in patient populations at increased risk of developing active TB, including candidates for treatment with tumor necrosis factor-α blockers. In the last 40 years, isoniazid (INH) has represented the keystone of LTBI therapy across the world. Although INH remains the first therapeutic option, alternative treatments that are effective and associated with increased adherence and economic savings are available. Current recommendations, toxicity, compliance, and cost issues are discussed in detail in this review. A balanced relationship between the patient and healthcare provider could increase adherence, while cost-saving treatment strategies with higher effectiveness, fewer side effects, and of shorter duration should be offered as preferred. (J Rheumatol Suppl. 2014 May; 91:71–7; doi:10.3899/jrheum.140105)

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Latent tuberculosis infection (LTBI) is defined as an infection with mycobacteria of the *Mycobacterium tuberculosis* complex, in which the bacteria are alive but not currently causing active disease. Once infected, the chance of a given immune-competent individual developing active TB is highest within the first 2 years after exposure, with half the cases occurring within 5 years, accounting overall for the 5–10% of cases[1]. The remaining 90–95% of subjects with LTBI stay healthy over their lifetime, representing the largest reservoir of the tubercle bacilli. It is estimated that about one-third of the world's population has LTBI, the majority of the cases being distributed in 22 high-burden countries. Airborne infection control measures, with early diagnosis and treatment of active TB, remain the top priority to limit person-to-person transmission in resource-poor countries in which the prevalence of TB is high[2]. Although treatment of LTBI is an essential component of TB control in low-prevalence countries such as the United States, where a significant proportion of cases of active TB is due to reactivation of an old infection[3], it is not widely practiced in most endemic countries.

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Targeting LTBI Treatment

Because people with LTBI are neither symptomatic nor contagious, any screening decision should be weighed carefully against the potential benefit of preventing active disease in those who are known to be at higher risk and are willing to accept therapy for LTBI. A targeted approach is therefore desirable to maximize cost-effectiveness. Treatment of contacts should be tailored on the basis of risk assessment algorithms that consider a range of factors, including type of contact (close or casual), tuberculin skin test (TST) and/or interferon-γ release assay (IGRA) results, bacillus Calmette-Guérin vaccination status, place of birth (foreign-born or resident), and age group (cutoff 35 yrs). Current guidelines suggest treatment in recently infected cases due to close exposure to patients affected by active pulmonary TB. Additional high-risk populations are reported in Table 1[4,5]. The targeted policy comprises no therapy in casual contacts with a positive vaccination history even with a positive TST result[6]. Conversely, treatment of LTBI must be offered to individuals infected by human immunodeficiency virus (HIV), foreign-born subjects younger than 35 years, immune-suppressed patients, and children under the age of 5 years with a recent contact with a case of active TB regardless of TB infection screening results[6,7].

It is mandatory that before starting any treatment, active TB should be carefully excluded in all cases. All close contacts (household, close friends, and job colleagues) of patients with active TB and vulnerable subjects (cases with

Table 1. Risk factors for progression of latent tuberculosis (TB) infection into active disease.

- Recent close exposure to active pulmonary TB (within 2 years)
- Human immunodeficiency virus infection
- Recently exposed infants and children aged < 5 years
- Silicosis
- Radiographic findings consistent with prior untreated or not adequately treated TB
- Immigrants from high TB burden areas
- Residents and employees of congregate living facilities
- Solid organ transplantation/solid organ tumors (neck, head, lung)/lymphoma, leukemia
- Gastrectomy/jejunoileal bypass
- Chronic renal failure/hemodialysis
- Diabetes mellitus/low body mass index (< 18.5)
- Longterm therapies with corticosteroids/immunosuppressive drugs or with tumor necrosis factor-α blockers
- Cigarette smokers/drug or alcohol abusers

1 or more known TB risk factors) must be offered a chest radiograph and a screening test for TB infection (that is, TST and/or any IGRA). All cases tested positive by the TST and/or IGRA with no evidence of clinical and radiographic signs suggestive of active TB should be treated for LTBI. In the case of suspicion of a false-negative TST and/or IGRA result, retesting should be considered after a window period of at least 8 weeks from the last exposure to the index case while still infectious[8,9]. In the case of suspicion of active TB, the patients should have 3 daily sputum specimens (or additional site-specific samples, if requested) cultured for mycobacteria. Further investigations should be tailored based on the clinical and radiological presentation.

Therapy Options

Current standard monotherapy with daily self-administered isoniazid (INH) is the preferred regimen in the United States and European countries because it reduces the risk of active TB by as much as 90% if taken for 9 months[10,11]. Prospective randomized controlled trials (RCT) have largely established the protective efficacy of INH given for 6–12 months among both non-HIV-infected and HIV-infected subjects[12,13]. A 6-month (m) regimen also provides protection, being more favorable from a cost-effectiveness point of view[11]. Pina, *et al* found that the number of patients to be treated to prevent 1 TB case was 33 and 26, using 6m-INH or 9m-INH, respectively, with an estimated cost ratio of 0.98 (95% CI 0.6–1.5)[14]. Shortening the treatment duration to 6 months is actually recommended in immune-competent adults[11,15]. Intermittent INH therapy (i.e., twice weekly with increased dosage) is allowed as directly observed treatment. Longterm INH therapy may be an effective and quite safe option in HIV-infected patients in high TB-burden settings[16].

Daily rifampicin (RMP) monotherapy for 24 weeks is well tolerated[17], but efficacy data are currently limited[18,19,20], and concerns remain over possible selection of RMP-resistant mutants in HIV-infected patients receiving antiretroviral therapies[21]. With an assumed 4m-RMP efficacy of 60%, this regimen has been estimated to be cheaper and more effective than 9m-INH, offering a challenge to cost savings within 10 years along with a significant reduction in the risk of noncompletion and liver toxicity[22,23]. Treatment with RMP alone is indicated for people who cannot tolerate INH, or close contacts of patients affected by INH-resistant TB[10].

Combination therapy with RMP and pyrazinamide (PRZ) for 2 months, given either daily or twice weekly, was advocated as an alternative choice in the American Thoracic Society (ATS)/US Centers for Disease Control (CDC) guidelines in 2000[10]. Despite the initial promising results in HIV-infected patients[24,25], further reporting of severe liver toxicity and death mainly in non HIV-infected patients[26,27], as confirmed later in a metaanalysis by Gao, *et al*[28], led to a revision of the ATS/CDC recommendations in 2003[29]. As a consequence, this regimen should not generally be offered. In selected cases (patients poorly compliant to longer therapies or intolerant to INH), clinical surveillance and liver function monitoring are required.

Daily or intermittent combined treatment with RMP plus INH for 3 months has proven efficacy, is well tolerated, and is safe[30,31]; however, adverse effects (AE) may be more frequent than with monotherapy regimens[32]. Salinas, *et al* recently reported an increased rate of treatment completion (84.9% vs 92.5%) and lower hepatotoxicity (1.6% vs 2.4%) in patients treated with 3m-RMP/INH in comparison with 6m-INH[33].

Three RCT have shown that a new combination regimen of INH and rifapentine (RPT) administered weekly for 12 weeks as directly observed treatment is as effective at preventing TB as other regimens[32,34]. Sterling, *et al* reported that active TB developed in 7 of 3986 subjects in the combination-therapy group (cumulative rate, 0.19%) and in 15 of 3745 subjects in the INH-only group (cumulative rate, 0.43%), for a difference of 0.24 percentage points. Rates of treatment completion were 82.1% and 69.0%, respectively ($p < 0.001$), with the proportions of drug discontinuation due to an AE being 4.9% and 3.7%, respectively ($p = 0.009$). Rates of investigator-assessed drug-related hepatotoxicity were 0.4% and 2.7%, respectively ($p < 0.001$)[35]. The CDC

recommends this regimen as an equal alternative to the 9m-INH regimen for otherwise healthy patients aged ≥ 12 years who have LTBI and factors that are predictive of the development of TB (e.g., recent exposure to contagious TB). The new regimen can also be considered for other categories of patients when it offers practical advantages. Although the INH-RPT regimen was well tolerated in treatment trials, monitoring for AE is recommended[36]. RPT-based regimens for treating LTBI are being considered for future clinical trials, but even if they prove effective, high drug costs may limit their economic viability. Holland, *et al* have estimated that both daily INH/RPT for 1 month and weekly INH/RPT for 3 months were less expensive and more effective than other strategies under a wide variety of clinically plausible variable estimates, the former being the least expensive and most effective[37]. Current treatment regimens with their doses/schedules are reported in Table 2.

Management of Suspected Drug-resistant LTBI

Expert opinions differ on whether to treat contacts of patients with multidrug-resistant TB. A reasonable option may be close clinical monitoring for at least 2 years for contacts who are healthy and do not have risk factors for disease progression. Regarding treatment, further concerns that have not yet been resolved include the choice and number (at least 2) of drugs to be used, and for how long. Regarding this issue, the 2000 ATS/CDC guidelines recommend combining PRZ with ethambutol or with a quinolone (i.e., levofloxacin or ofloxacin) for 6–12 months, respectively, in immune-competent and HIV-infected contacts[10]. However, poor tolerance and high rates of liver toxicity have been observed with PRZ-containing regimens[38,39,40]. Fluoroquinolone monotherapy has been suggested as a safe alternative, but emergence of drug resistance is a matter of concern[41]. More recently, thiorizadine alone, or with other antibiotics, has been proposed for the treatment of drug-resistant LTBI as inexpensive, effective, safe, and unlikely to induce resistance[42]. In a computerized Markov model assessing the cost and effectiveness of 6 different therapy options, the combination of moxifloxacin with ethambutol was estimated as the preferred strategy under a wide array of assumptions[43].

Toxicity Issues

Hepatotoxicity is the most severe AE related to LTBI treatment. Drug administration should be discontinued if transaminase levels are greater than 3 times the upper limit of normal in symptomatic patients or 5 times the upper limit of normal in asymptomatic patients. In a retrospective study done from 1999 to 2005 among 219 adults patients initiating INH treatment, Vinnard, *et al* found that 8% of cases discontinued therapy because of liver toxicity, the median time to onset of this toxicity being 3 months[44]. Discontinuation was not associated with advancing age, while a predictive factor was hepatitis C infection. Conversely, in a retrospective evaluation of 11 studies addressing this issue in the general population (n = 6) and in transplant recipients (n = 5), chronic viral hepatitis was not an established risk factor for INH hepatotoxicity[45]. In a further analysis of a historical cohort including all residents given therapy for LTBI (95% INH, 5% RMP) in Quebec, the risk of hepatotoxicity requiring hospital admission increased significantly among patients over 65 years old[46]. Previously, in a systematic review including 7 studies (18,610 participants), the rates of INH- and/or RMP-associated liver injury were higher among persons aged ≥ 35 years[47]. Recently, based on data in a passive surveillance system, the CDC reported the occurrence of 17 serious AE in INH-treated patients (15 adults and 2 children) in the period 2004–2008, suggesting the need for liver function monitoring while receiving therapy[48].

Table 2. Treatment regimens and doses/schedules of latent tuberculosis (TB) infection.

Regimen	Dose/Schedule	Recommendation
Isoniazid for 9 mos	Daily, self-administered 5 mg/kg (max 300 mg/day) Twice weekly, DOT 15 mg/kg (max 900 mg/dose)	ATS/CDC, preferred regimen for all risk groups
Isoniazid for 6 mos	Same dose/schedule of INH-9 months	NICE (UK), recommended regimen for HIV-infected/uninfected people of any age
Rifampicin for 4 mos	Daily, self-administered 10 mg/kg (max 600 mg/day)	Alternative to INH 9 mos for contacts of INH-resistant TB
Rifampicin plus isoniazid for 3 mos	Daily, self-administered RMP: 10 mg/kg (max 600 mg/day); INH: 5 mg/kg (max 300 mg/day)	NICE (UK), equal alternative to INH 6 mos for non-HIV adults
Rifapentine plus isoniazid for 3 mos	Once weekly, DOT; INH: 15 mg/kg (max 900 mg/dose) RPT: 10.0–14.0 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 kg: 900 mg max	CDC, equal alternative to self-administered 9m-INH in persons ≥ 12 yrs. Not recommended for children < 2 yrs, HIV-infected persons taking ART, pregnant women

INH: isoniazid; RMP: rifampicin; RPT: rifapentine; ART: antiretroviral therapy; ATS: American Thoracic Society; CDC: US Centers for Disease Control and Prevention; NICE: UK National Institute for Health and Clinical Excellence; DOT: directly observed treatment; HIV: human immunodeficiency virus.

A metaanalysis of 4 RCT comparing conventional INH treatment with the association of RMP/PRZ in 2657 HIV-infected patients showed that the rate of development of severe hepatotoxicity was lower in the RMP/PRZ group than in the 6–12m-INH group[49]. A combined clinical picture of INH-induced eosinophilic exudative pleural effusion and systemic lupus erythematosus was also found in a 75-year-old woman[50]. Finally, AE, including low rates of hepatotoxicity, flu-like syndrome, and thrombocytopenia, have been reported in 87 patients under LTBI treatment with RMP, with 2 cases developing active TB during 21.8 months of followup[51]. Negligible rates of hepatotoxicity were reported in 205 adults with LTBI treated with RMP who had poor adherence to clinic visits and treatment[52]. Four months of treatment with RMP was associated with significantly better completion rates and less hepatotoxicity, albeit at a higher total cost[53].

Compliance

Although INH reduces the risk of active TB by as much as 90% if taken daily for 9 months, acceptance and adherence to prolonged therapy are less than desired because completion is less than 50% in many programs. The relationships between medication adherence and demographics, sex, self-reported health, and side effects are inconclusive[54,55].

Of 101 household contacts of hospitalized patients with pulmonary TB in Brazil, 53.5% completed a 6m-INH regimen, the risk of treatment noncompletion being significantly higher in household contacts who reported side effects; 28.7% of cases were lost to followup because of difficulties reaching the hospital[56]. A previous survey study including 380 LTBI patients attending the Wetmore TB Clinic (New Orleans, Louisiana, USA) estimated that the adherence rate to treatment was very low, at 19%[57]. A more comprehensive systematic review of 78 studies in the United States and Canada, published between 1997 and 2007, found suboptimal adherence and completion rates across high-risk groups, with no consistent associations with patient-related factors, clinic facilities, or treatment characteristics[58]. Completion rates of 59% and 67% were reported for 9m-INH and 6m-INH regimens, respectively, in a retrospective review of pharmacy records from 2000 to 2006[59]. A completion rate of 45.2% was estimated in New York City among a total of 15,035 patients. Treatment completers were more likely to be 35 years old or more, contacts of patients with pulmonary TB, receiving directly observed treatment, and to have received the RMP-based regimen, with no differences between HIV-negative and HIV-positive individuals[60]. In a retrospective survey in 19 regions of the United States and Canada, the risk factors for failure to complete treatment included starting the 9m-INH regimen, residence in a congregate setting (nursing home, shelter, or jail), injection drug use, age 15 years or more, and employment at a healthcare facility[61]. In a randomized prospective study by Trajman, *et al* treatment completion was higher with RMP than with the conventional INH regimen. Early predictors of nonadherence were late first visit attendance, > 20% of missed doses, and greater variation of hours between doses. Serious AE were not associated with irregularity of treatment[62]. Marriage and alcohol use were significant predictors of completion and noncompletion in 2 RCT comparing 6-12m-INH to 9m-INH self-administered regimens, with an overall treatment adherence rate of 44%[63]. A further retrospective evaluation including 599 LTBI cases in Spain found a very high rate of treatment completion (80.8%), with no differences according to therapy duration. Again, low adherence was associated with age < 36 years, male sex, immigrant status < 5 years of residence, and the presence of social risk factors[64].

LTBI Management in Candidates for Tumor Necrosis Factor-α Blockers

Although there is wide agreement among scientists and experts about the need to treat LTBI in candidates for anti-tumor necrosis factor-α (TNF-α) therapy, the choice of the best timing for initiation is still a matter of debate. In the United States, the CDC suggest completing LTBI therapy before starting treatment with TNF-α blockers[65].

Conversely, in the European setting, the current opinion is to start anti-TNF-α treatment at the completion of an induction period of 3–8 weeks of LTBI therapy; both treatments can then be continued together for the required period[66,67,68]. More recently, a board of experts fixed the so-called induction period of LTBI therapy at 4 weeks[69].

Treatment management of LTBI is largely based on INH monotherapy at the dosage of 5 mg/kg per day for 9 months. This is also the safest regimen in terms of occurrence of hepatotoxicity and of other AE[70]. An increased rate (39%) of gastrointestinal intolerance or high transamine levels was recently reported in a small cohort of patients treated with INH or RMP while taking antirheumatic drugs[71].

Currently no regimens have been validated as alternatives to INH for LTBI treatment in this specific clinical setting. However, further options may be represented by the daily or intermittent association of INH and RMP, or by RMP monotherapy in INH-intolerant patients.

In the last 40 years, INH has been the keystone of LTBI treatment in all clinical settings, with few alternative and equally effective options available. Targeted testing of high-risk populations is pivotal in TB control programs as "intention to test is intention to treat." A balanced relationship between patients and the healthcare provider could increase adherence, while cost-saving treatment strategies with greater effectiveness, fewer side effects, and shorter duration should be offered as consistently preferred.

In summary:

- LTBI screening and treatment decisions should be weighed carefully against the benefit of preventing active disease in high-risk patients
- Longterm administration of INH has been the keystone of LTBI therapy over the last 40 years
- Effective, well-tolerated, shorter lasting, and cost-saving alternative therapy regimens are becoming available

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