Pharmacologic Issues in LTBI Treatment

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Disclosure Statement

• I am on the speaker bureau for Merck, Inc. vaccines division

Learning Outcomes

• Review the current recommended treatment options for latent tuberculosis infection (LTBI)
• Compare and contrast the advantages and disadvantages of each regimen and its appropriate use in clinical practice
• Identify possible adverse reactions and side effects that may result from LTBI therapy and possible drug-drug interaction
• Given a patient case identify appropriate treatment and rationale for choosing one regimen over another
Background

• Treatment of latent tuberculosis (TB) infection (LTBI) is crucial to controlling and eliminating TB in the US because it reduces the risk that TB infection will progress to disease
• Groups at high risk for developing TB disease once infected should be identified
• TB in the US decline to historical lows until the HIV epidemic in the early 1990’s due to co-infection rates
• Current recommendations in place since 2003 (update coming??)
• Drug development is focused on new agents to treat drug resistant organism as well as decreasing duration of therapy

Background

• Once a diagnosis of LTBI is made, healthcare providers must choose an appropriate regimen that is effective and make every effort to ensure those individuals complete the full course of treatment
• However, if exposed to and infected by a person with multidrug-resistant TB (MDR TB) or extensively drug-resistant TB (XDR TB), preventive treatment may not be an option
• Most recent up to date to LTBI treatment recommendations was in December 2011 – CDC MMWR published on Recommendations for Use of an Isoniazid-Rifapentine Regimen with Directly Observation to Treat Latent Mycobacterium tuberculosis infection

Epidemiology
Epidemiology

• In 2011, approximately 62% of TB cases in the US occurred in foreign-born persons
• Majority of US cases among foreign-born persons are from 7 countries (Mexico, Philippines, Vietnam, India, China, Haiti, and Guatemala)
• Identifying persons from high risk countries should be based on the following
  – Local epidemiologic profiles are the most useful resources in identifying countries of highest risk
  – This should guide health care providers testing and treatment decisions on local immigration patterns

LTBI: Pre-treatment Evaluation

Definition of LTBI

• A person infected with tuberculosis
• Small amount of TB bacteria in the body (alive but inactive)
• Cannot spread TB bacteria to others
• Does NOT feel sick, may become sick if bacteria becomes active
• Usually has a TB skin test or TB blood test indicative of TB infection
• Radiograph is typically normal
• Sputum smears and cultures are negative
• Should consider treatment for LTBI to prevent disease
• Does NOT require respiratory isolation
Pretreatment Evaluation

• The decision of whether an individual who has a positive tuberculin skin test (TST) or interferon gamma release assay (IGRA) result is a candidate for LTBI treatment includes
  – Determine the benefits of treatment by evaluating the individuals risk for developing disease
  – Assessing the persons level of commitment to completion of treatment and resources available to ensure adherence to therapy

Pretreatment Evaluation

• Once the decision to treat has been made the healthcare provider must establish a rapport with the patient as well as the following
  – Discuss benefits and risk of treatment
  – Review possible side effects and drug interactions
  – Emphasize the importance of adherence, identify possible barriers to adherence and establish a plan to ensure adherence

Diagnosis

• Diagnostic Tools
  – Mantoux tuberculin skin test
    • Purified Protein Derivative (PPD)
  – Interferon Gama Assays (Blood test)
    • Quantiferon (QFT-Gold and QFT-GIT In Tube)
    • T-Spot® TB Test
  – Radiologic Evidence
    • Chest X-Ray (standard screening)
    • Computerized tomography (CT) Scan
• Review of symptoms
  – Fever, cough, weight loss, night sweats, fatigue, or anorexia

Pharmacological Issues in LTBI Treatment
Risk Assessment

- Persons with the following risk factors should be tested for TB infection:
  - Testing is not indicated only if documentation of previous positive PPD skin testing or IGRA
- Individuals with the following risk should be assessed:
  - Recent close or prolonged contact to someone with infectious TB disease
  - Foreign-born person from or recent traveler to high prevalence area
  - Chest radiographs with fibrotic changes suggestive of inactive or past TB
  - HIV infection
  - Organ transplant recipient

Risk Assessment

- Individuals with the following risk should be assessed:
  - Immunosuppression secondary to the use of prednisone (equivalent of ≥ 15 mg/day for ≥ 1 month) or other immunosuppressive medication such as TBF-alpha antagonists
  - Injection drug use
  - Resident or employee of high risk congregate setting (prison, long term care facility, hospital, homeless shelter)
  - Medical conditions associated with risk of progressing to TB disease if infected (DM, Silicosis, cancer of head or neck, Hodgkin's disease, Leukemia, ESRD, intestinal bypass or gastrectomy, chronic malabsorption syndrome, low body weight (10% or more below ideal for population)
  - Signs and symptoms of TB

Candidates for Treatment

Positive IGRA or 5mm or more TST reaction
- HIV-infected persons
- Recent contact to TB case
- Person with fibrotic changes on chest radiograph consistent with old TB
- Organ transplant recipients
- Person who are immunosuppressed for other reasons (taking prednisone or TNF-alpha antagonists)

**Recent data may support increase this time frame to ≤ 9 years**

Groups that should be given high priority for LTBI treatment

Positive IGRA or 10mm or more TST reaction
- Recent immigrants (< 5 years) from high prevalence countries**
- Injection drug user
- Residents and employees of high congregate settings (correctional facilities, nursing homes, homeless shelters, hospitals, and other health care facilities)
- Mycobacteriology laboratory personnel
- Children under 4 years of age and adolescents exposed to adults in high-risk categories

**Pharmacological Issues in LTBI Treatment**
Candidates for Treatment

- Persons with no known risk factors for TB may be considered for treatment of LTBI if the following
  - Positive TST 15mm or larger
  - Positive IGRA (QFT or T-Spot)
- TB testing programs should only be conducting testing in high risk groups (TARGETED TESTING)
- All testing activities should include a plan for follow-up care for persons identified with infection or disease

Literature Review

Persistent Latent Tuberculosis Reactivation Risk in United States Immigrants Am J Respir Crit Care Med Vol 189, Iss 1, pp 88-95, Jan 1, 2014

- Objective
  - Estimate reactivation and imported TB in an immigrant cohort
- Methods
  - California bound Filipino immigrants pre-immigration records reviewed during 2001 to 2010
  - TB was likely LTBI reactivation if immigrant had no evidence of active TB at pre-immigration evaluation,
  - Likely imported if pre-immigration radiography was abnormal and TB was reported less than or equal to 6 months after arrival
  - Likely reactivation of inactive TB if radiography was abnormal but TB was reported more than 6 months after arrival

Literature Review

Persistent Latent Tuberculosis Reactivation Risk in United States Immigrants Am J Respir Crit Care Med Vol 189, Iss 1, pp 88-95, Jan 1, 2014

- Study Results
  - 123, 114 Immigrants charts reviewed
  - 793 cases of TB were reported
  - Within one year of pre-immigration examination 85% of TB was imported; 6% were reactivation of LTBI and 9% inactive TB
  - Conversely, during years 2-9 after US entry 76% were reactivation LTBI and 24% inactive TB
  - Rate of LTBI reactivation (32 per 100,00 didn’t decline during years 1-9
Literature Review

Persistent Latent Tuberculosis Reactivation Risk in United States Immigrants. Am J Respir Crit Care Med Vol 189, Iss 1, pp 88-95, Jan 1, 2014

- Conclusions
  - High postarrival TB rates were caused by detection of imported TB through active surveillance
  - Immigrants without active TB at baseline, reported TB did not decline over 9 years indicating sustained high risk for LTBI reactivation
  - Revised guidelines should support LTBI screening and treatment more than 5 years after arrival in the US

Latent TB Infection Treatment Regimens

- Choose the most effective regimen
- Treatment of LTB should be initiated after the possibility of TB disease has been ruled out
- Persons suspected of having TB disease should receive the recommended multidrug regimen for treatment until the diagnosis can be confirmed or ruled out
- Consult with a TB expert of known source of TB infection has drug resistant TB
- Regimens are broadly applicable but modifications should be made in special circumstances including the following
  - HIV infection, suspected drug resistance, pregnancy, or treatment of children
LTBI Treatment Regimens

Isoniazid (INH)
- Standard treatment regimen for LTBI for 9 months of therapy at daily dosing (270 doses)
  - Weight based dosing
  - Self administered
  - Adherence can be challenging given the extended duration
  - Can be administered twice weekly (under Directly Observed Therapy (DOT)) (76 doses)
- Note: Can be given a minimum of 6 months if elevated LFT or unable to tolerate (180 doses daily or 52 doses 2x/weekly)
  - Very effective
  - Preferred regimen in HIV positive persons on antiretroviral therapy and children aged 2 to 11 years

LTBI Treatment Regimens

Isoniazid + Rifampin
- Alternative treatment regimen for LTBI for 4 months of therapy at daily dosing (120 doses)
  - Preferred in patients with evidence of old healed granulomatous disease or fibrotic changes on chest radiography
  - Weight based dosing
  - Self administered or twice weekly (DOT)
  - Shorter duration of therapy may improve adherence
  - Combination therapy may increase possible adverse effects
  - Rifamycin component increase risk of drug-drug interactions

LTBI Treatment Regimens

Rifampin
- Alternative treatment regimen for LTBI for 4 months (120 doses of therapy at daily dosing (6 months (180 doses) in pediatric patients)
  - Indicated when individuals are unable to tolerate INH or source case of exposure is known to be INH resistant
  - Weight based dosing
  - Self administered
  - Shorter duration of therapy may improve adherence
  - Rifamycin component increase risk of drug-drug interactions
  - Should not be used in HIV positive individuals on ART
LTBI Treatment Regimens

- **3HP (Isoniazid + Rifapentine (RPT)) Regimen**
  - This regimen does not replace other recommended LTBI treatment regimens.
  - 12 dose regimen of INH and RPT.
  - Once weekly dosing under DOT (11 doses within 16 weeks is considered complete).
  - Not indicated in those with known exposure to INH or RIF-resistant case.
  - Eligible Individuals (otherwise healthy)
    - ≥ 12 years of age who have predictive factors for greater likelihood of TB developing including:
      - Recent exposure to contagious TB.
      - Conversion from negative to positive TB testing.
      - Radiographic findings of healed TB disease.

LTBI Treatment Regimens

- **3HP (Isoniazid + Rifapentine (RPT)) Regimen**
  - Not recommended for the following:
    - Children younger than 2 years of age.
    - People with HIV/AIDS who are taking antiretroviral therapy.
    - Persons presumed to be infected with INH or RIF-resistant M. tuberculosis.
    - Pregnant women or women expecting to become pregnant within the 12-week timeframe.

Adverse Reactions
Adverse Drug Reactions

- Patient receiving treatment for LTBI should be instructed to report any signs and symptoms of adverse drug reaction
- Adverse reactions including (specific to INH)
  - Asymptomatic elevation of serum liver enzyme concentrations (occur in 10-20% of persons on INH), typically return to normal even if treatment is continued
    - INH should be withheld if transaminase level exceeds 3 times the upper limit of normal if symptomatic or 5 times the upper limit of normal if asymptomatic
  - Clinical hepatitis occurs in 0.1% of persons on INH and is more common when INH is combined with other hepatotoxic drugs
    - Factors that increase rates include – underlying liver disease, daily alcohol consumption, and concurrent use of other medications which are metabolized by the liver

- Adverse Drug Reactions

  - Peripheral neuropathy occurs in less than 0.2% person taking INH at conventional doses
    - More likely if they have the following conditions – HIV, renal disease, diabetes, or alcoholism
    - B6 supplementation is recommended in those at risk and pregnant or breastfeeding women to prevent neuropathy

  - Adverse reactions including (specific to RIF or RPT)
    - Hepatotoxicity, evidenced by transient asymptomatic hyperbilirubinemia, may occur in 0.6% of persons taking RIF (more likely when combined with INH)

  - Cutaneous reactions such as pruritis (with or without rash), occur in 0.6% of persons taking RIF
    - Generally self-limiting and may not be true hypersensitivity, continued treatment is possible
    - Symptoms include fever, headache, dizziness/lightheadedness, musculoskeletal pain, petechiae, and pruritis
    - Gastrointestinal symptoms including nausea, anorexia, and abdominal pain (rarely severe enough to discontinue therapy)
    - Orange discoloration of bodily fluids are expected and harmless (advise patient in advance)
Adverse Drug Reactions

- CDC collects reports of all severe adverse events that lead to hospitalization or death of a person receiving treatment for LTBI
- Adverse events can be reported to the Division of Tuberculosis Elimination via email (LTBIdrugevents@cdc.gov)
- Serious Adverse Events Include
  - Anaphylaxis
  - Liver injury
  - Metabolic Acidosis
  - Seizure
  - Severe dermatitis
- Post implementation surveillance was conducted to observe patients taking the 3HP regimen to determine if adverse effects occurred at a higher rate than the other regimens

Monitoring Parameters

- Baseline laboratory monitoring is not always indicated
- Laboratory monitoring during LTBI treatment is indicated when patients have one of the following
  - History of liver disease
  - HIV infection
  - Pregnancy (or 3 months post partum)
  - Regular alcohol use
- Laboratory Testing including
  - Liver function test (AST, ALT, and bilirubin) *signs of hepatitis
  - CBC w/differential (Rifamycin based regimens)
- Clinical monitoring
  - Brief physical examination should occur to assess adherence, rationale for treatment, and possible signs and symptoms of adverse effects (should occur at monthly visit)

Patient Counseling

- Explain disease process and rationale for medication in absence of symptoms or radiologic abnormalities
- Review importance of completing the full course of treatment
- Review possible side effects of LTBI medication (things to look for while on treatment)
  - Arthralgia
  - Fever
  - Rash
  - Unexplained anorexia, dark urine (coffee colored or cola like), icterus, abdominal tenderness specifically right upper quadrant, easy bruising or bleeding, nausea or vomiting
  - Persistent paresthesia of hands and feet
  - Persistent fatigue or weakness lasting 3 or more days
### Drug Interactions

**Pharmacological Issues in LTBI Treatment**

All patients on LTBI therapy should provide a current list of medications to avoid possible drug-drug interactions.

**Drug Interactions with Isoniazid**
- Increased blood levels of phenytoin (Dilantin) and disulfiram (Antabuse)

**Drug Interactions with RIF or RPT**
- Rifamycins decrease the blood levels of many drugs
  - Oral contraceptives, warfarin, sulfonureas, and methadone
  - Contraindicated in HIV-infected persons being treated with protease inhibitors (PIs) and most nonnucleoside reverse transcriptase inhibitors (NNRTIs)

### Based on University of Texas Health Science Center at Tyler - Heartland National TB Center Recommendation Charts

- Rifamycins and Anti-Diabetic Agents
  - Biguanides (Metformin) Based
    - Increased monitoring due to possible decrease in glycemic control
  - Sulfonlurea Based
    - Increased monitoring due to possible decrease in glycemic control
  - Meglitinide analogue
    - Increased monitoring due to possible decrease in glycemic control, consider dosage adjustment or an alternative agent
Drug Interactions

Based on University of Texas Health Science Center at Tyler - Heartland National TB Center Recommendation Charts

- Rifamycins and Anti-Diabetic Agents
  - Thiazolidinedione (PPAR agonists)
    - Increased monitoring due to possible decrease in glycemic control, consider dosage adjustment or an alternative agent
  - Dipeptidyl Peptidase IV Inhibitor
    - Increased monitoring due to possible decrease in glycemic control

- Rifamycins and Psychotropic Drugs
  - Anti-psychotics
    - Increased clinical monitoring, consider dose adjustment when RIF therapy is initiated
  - Anti-anxiety agents
    - Increased clinical monitoring, consider dose adjustment when RIF therapy is initiated or consider switching to alternative agent
  - Anti-depressants
    - Increased clinical monitoring, consider dose adjustment, or consider switching to alternative agent

- Rifamycins and Cardiovascular Agents
  - Angiotensin Converting Enzyme (ACE) Inhibitors
    - Increase BP monitoring, consider dose adjustment
  - Angiotensin Receptor Blockers (ARBs)
    - Increase BP monitoring, consider dose adjustment
  - Beta Blockers
    - Increase BP monitoring, consider dose adjustment
  - Calcium Channel Blockers (CCBs)
    - Increase BP monitoring, consider dose adjustment or switching to other antihypertensive
Drug Interactions

Based on University of Texas Health Science Center at Tyler - Heartland National TB Center Recommendation Charts

- Rifamycins and Cardiovascular Agents
  - HMG CoA Inhibitors (Statins)
    - Increase BP monitoring, consider dose adjustment or consider switching to Rifabutin
  - Ionotropic/Chronotropic Agents
    - Measure digoxin levels before and during treatment and increase digoxin if need to keep therapeutic levels
- Antiplatelet Agents
  - Monitor for antiplatelet effects such as easy bruising and bleeding

Case Studies

Case Study #1

- 34 y/o female originally from Ethiopia who immigrated to the US June 2011
- Currently asymptomatic (denies cough, weight loss, fever, night sweats, or cough)
- Wt: 105 lbs
- PMH – HTN; Home Medication (metoprolol) and Oral Contraceptive (from country of origin)
- Denies ever having TB or prior TB treatment
- Family History – aunt died of TB
- Social History – smoker x 5 years (states she quit when entering the US)
- Labs
  - HIV – non-reactive, Past PPD positive (unknown duration)
  - Sputum Cultures (negative x 2), Sputum Culture (positive x 1 – M. avium)
  - Chest X-Ray – abnormal (granulomatous disease seen in the left upper lobe) Sputum Smears (negative x 3)
Which of the following LTBI regimens would be MOST appropriate?

A. INH 300mg daily x 9 months
B. INH/RPT once weekly (DOT) x 12 weeks
C. RIF 600mg daily x 4 months
D. INH/RIF 300mg/600mg daily x 4 months

Case Study #2

- 37 year old Asian female born in China arrived in the US in October 2013
- Patient denies history of tuberculosis diagnosis or TB treatment
- Family History mother being sick when she was a very young child for which she took medications for an extended period of time
- Denies any constitutional symptoms including night sweats, fever, cough, or chills
- Weight: 56kg
- PMH - C-section and tubal ligation in 2009
- Medications - Multivitamin daily
- Labs
  - QFT positive with 0.50 IU/mL, HIV non-reactive
  - Sputum smears and culture negative x 3 consecutive samples
  - Chest X-RAY interpreted as normal free of infiltrates or fibrosis

Which of the following LTBI regimens would be MOST appropriate?

A. INH 300mg daily x 9 months
B. INH/RPT 900mg/900mg once weekly (DOT) x 12 weeks
C. RIF 600mg daily x 4 months
D. INH/RIF 300mg/600mg daily x 4 months
Case Study #3

- 44 y/o male born in Russia who immigrated to the US in 2012 for completion of his residency education. Currently working as a physician resident in a local hospital.
- Pt was referred for evaluation following a positive QFT test (MTB likely) from an employee health screening.
- Say he will complete therapy only if he can be finished with treatment in the next 6 months, he is moving to Colorado to complete an infectious disease fellowship.

Which of the following LTBI regimens would be MOST appropriate?

A. INH 300mg daily x 9 months
B. INH/RPT once weekly (DOT) x 12 weeks
C. RIF 600mg daily x 4 months
D. INH/RIF 300mg/600mg daily x 4 months

Case Study #4

- 5 y/o US born male household contact to an Active Pulmonary Case of TB disease. Contact has positive sputum smears of 2+ at time of diagnosis.
- Contact organism is resistant to Streptomycin and INH at the lower concentration.
- Wt: 32lbs (15kg).
- PMH – Asthma, atopic dermatitis, and allergic rhinitis.
- Labs – PPD + (11mm induration)
- Sputum Smears/Cultures – not performed *Source case susceptibilities
- Chest X-Ray – normal.

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Which of the following LTBI regimens would be MOST appropriate?

A. INH 300mg daily x 9 months
B. INH/RPT once weekly (DOT) x 12 weeks
C. RIF 300mg daily x 4 months
D. RIF 150mg daily x 6 months
E. INH/RIF 300mg/600mg daily x 4 months

Summary

- Treating latent tuberculosis infection crucial to controlling and eliminating TB in the US because it reduces the risk that TB infection will progress to disease
- Groups at high risk for developing TB disease once infected should be identified
- Pretreatment evaluation and risk assessment should be used in addition to laboratory targeted testing to ensure candidates will successful complete treatment
- Current recommendations including INH or RIF alone, or INH in combination with Rif or RPT
- Appropriate regimens are determined by assessing the individual for possible adverse effects as well as possible drug-drug interactions
- Rifamycin based regimens are the most likely to cause drug interactions and should be avoided in patients on multiple medications
- Treating LTBI is safe and effective when thoughtful consideration is given to each individual patient needs

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