TB Intensive
Tyler, Texas
June 2-4, 2010
ATS/CDC Guidelines for Treating Latent TB Infection
Timothy R. Aksamit, MD

June 2, 2010

ATS/CDC Guidelines for Treating LTBI
Tuberculosis Intensive
University of Texas Health Science Center at Tyler
Heartland National TB Center
June 2, 2010

Timothy R. Aksamit, MD
Assistant Professor of Medicine
Mayo Clinic
College of Medicine
Consultant
Pulmonary Disease and Critical Care Medicine
Department of Internal Medicine
Mayo Clinic
Rochester, Minnesota
ATS/CDC Guidelines for
Treating LTBI

DISCLOSURE

Relevant Financial Relationship(s)
None

Objective

• Discuss the ATS/CDC guidelines for treating LTBI
Latent Tuberculosis Infection (LTBI) Update

• Background
• Diagnosis
• Treatment
• Summary
ATS/CDC Guidelines for Treating LTBI

CC: Positive TST

HPI: 35 year-old male non-smoker

• Immigration evaluation, 20 mm positive TST
• No cough, sputum, hemoptysis, fever, chills, sweats, weight loss
• No known TB exposure or BCG

• No DM, polyneuropathy, h/o hepatitis, renal insufficiency, sz disorder
• HIV unknown, no risk factors;
• NO EtOH or IDU

SHx: School teacher, married without children.

EXAM: Mild obese Somali male NAD VSS WNL
ATS/CDC Guidelines for Treating LTBI

The chance of this patient developing active TB disease over his life time is greater than the chance of an American personal injury attorney flying on commercial airlines with active pulmonary XDR tuberculosis?

A. True
B. False
ATS/CDC Guidelines for Treating LTBI

CDC Clinician Communication
Information from Clinician Outreach and Communication Activity (C COCA)

May 20, 2007

The following is an official CDC Health Advisory distributed via the Health Alert Network on May 20, 2007 at 12:40 p.m. EDT.

CDC Health Advisory

Investigation of U.S. Traveler with Extensively Drug Resistant Tuberculosis (XDR TB)

Targeted Tuberculin Testing and Treatment of Latent Tuberculosis Infection, 2005

Applying CDC/ATS Guidelines in Your Clinical Practice

Division of Tuberculosis Elimination
Centers for Disease Control and Prevention
For more than 3 decades, an essential component of TB prevention and control in the U.S. has been the treatment of persons with LTBI to prevent TB disease.

1965: American Thoracic Society (ATS) recommends treatment of LTBI for those with previously untreated TB, tuberculin skin test (TST) converters, and young children.

1967: Recommendations expanded to include all TST positive reactors (>10 mm).
Treatment of LTBI – Milestones

1974: CDC and ATS guidelines established for pretreatment screening to decrease risk of hepatitis associated with treatment

- Treatment recommended for persons ≤ 35 years of age

1983: CDC recommends clinical and laboratory monitoring of persons ≥ 35 who require treatment for LTBI

1998: CDC recommends 2 months of rifampin (RIF) plus pyrazinamide (PZA) as an option for HIV-infected patients (later changed)
Treatment of LTBI – Milestones

2000: CDC and ATS issue updated guidelines for targeted testing and LTBI treatment\(^1\)
- 9-month regimen of isoniazid (INH) is preferred
- 2-month regimen of RIF and PZA and a 4-month regimen of RIF recommended as options (later changed)

\(^1\) MMWR June 9, 2000; 49(No. RR-6)

2001: Owing to liver injury and death associated with 2-month regimen of RIF and PZA, use of this option de-emphasized in favor of other regimens\(^2\)

2003: 2-month regimen of RIZ and PZA generally not recommended — to be used only if the potential benefits outweigh the risk of severe liver injury and death\(^3\)

\(^2\) MMWR August 31, 2001; 50(34): 733-735
\(^3\) MMWR August 8, 2003; 52(31): 735-739
What’s New: ATS/CDC Guidelines for Treating LTBI

Tuberculin skin testing

- Emphasis on targeting persons at high risk
- 5-mm induration cutoff level for organ transplant recipients and other immunosuppressed patients being treated with prednisone or TNF-α antagonists
- Skin-test conversion defined as increase of ≥10 mm of induration within a 2-year period, regardless of age

---

**MMWR** August 61, 2004; 53(33): 683-686

What’s New: ATS/CDC Guidelines for Treating LTBI

Treatment of LTBI

- HIV-negative persons – INH for 9 months preferred regimen
- HIV-positive persons and those with fibrotic lesions on chest x-ray (consistent with previous TB) – INH should be given for 9 months
- For all persons – RIF for 4 months is an option
What’s New: ATS/CDC Guidelines for Treating LTBI

Clinical and laboratory monitoring

- Routine baseline and follow-up monitoring not required except for
  - HIV-infected persons
  - Pregnant women or those in early postpartum period
  - Persons with chronic liver disease or who use alcohol regularly
- Monthly monitoring for signs or symptoms of possible adverse effects

Latent TB Infection (LTBI)

LTBI is the presence of *M. tuberculosis* organisms (tubercle bacilli) without symptoms or radiographic evidence of TB disease.

No GOLD STANDARD
Latent TB Infection (LTBI)

LTBI is the presence of *M. tuberculosis* organisms (tubercle bacilli) without symptoms or radiographic evidence of TB disease.

No GOLD STANDARD – Natural history is uncertain

“LTBI” = Persistent adaptive M. *Tb* immune response
## LTBI vs. Pulmonary TB Disease

<table>
<thead>
<tr>
<th>Latent TB Infection</th>
<th>Pulmonary TB Disease</th>
</tr>
</thead>
<tbody>
<tr>
<td>• TST* or IGRA† positive</td>
<td>• TST or IGRA usually positive</td>
</tr>
<tr>
<td>• Negative chest radiograph</td>
<td>• Chest radiograph may be abnormal</td>
</tr>
<tr>
<td>• No symptoms or physical findings suggestive of TB disease (pulmonary or XP)</td>
<td>• Symptoms may include one or more of the following: fever, cough, night sweats, weight loss, fatigue, hemoptysis, decreased appetite</td>
</tr>
<tr>
<td></td>
<td>• Respiratory specimens may be smear or culture positive</td>
</tr>
</tbody>
</table>

* *tuberculin skin test  ††IGRA (interferon gamma release assay) is a blood test to detect *M. tuberculosis* infection.*

## Testing for Latent TB Infection

**PPD (TST):**

"...A purified protein derivative (PPD) - TST ... at initial evaluation, ... a negative PPD-TST does not exclude the diagnosis of active tuberculosis...

...However, a positive PPD-TST supports ... diagnosis of culture-negative pulmonary tuberculosis, as well as LTBI in persons with stable abnormal chest radiograph consistent with inactive tuberculosis."

*AJRCCM 187: 603, 2003*
Terminology

• “Treatment of latent TB infection” replaces the terms “preventive therapy” and “chemoprophylaxis” to promote greater understanding of the concept for both patients and providers.

• Targeted tuberculin testing is used to focus program activities and provider practices on groups at the highest risk for TB.

Testing for TB Disease and Infection
Targeted Tuberculin Testing

- Detects persons with LTBI who would benefit from treatment
- De-emphasizes testing of groups that are not at high risk for TB
- Can help reduce the waste of resources and prevent inappropriate treatment

Testing for Latent TB Infection

Targeted Tuberculin Testing:

“… strategic component of TB control … identify (patients with high) risk for developing TB …

... residents immigrating from high prevalence countries (and other individuals at risk for infection)

... recent M Tb infection (new conversion)...

... clinical conditions associated with progression to active tuberculosis.”

AJRCCM 161: S221, 2000
Testing for Latent TB Infection

What areas of the world are considered high TB incidence or prevalence?

- Asia
- Africa
- Latin America
- Eastern Europe
- Russia

Core Curriculum on Tuberculosis CDC 2000

Testing for Latent TB Infection

Targeted Tuberculin Testing:

“… individuals at risk for exposure to or infection with TB…

... residents immigrating from high prevalence countries (select foreign-born individuals)

- close contacts new/suspected disease
- residents and employees high-risk settings
- HCWs serving high-risk individuals
- medically underserved
- those using IV drugs.”

Core Curriculum on Tuberculosis CDC 2000
Testing for Latent TB Infection

Targeted Tuberculin Testing:

“... individuals at higher risk for TB disease once infected ...

...recent M Tb infection (new conversion)

... clinical conditions associated with progression to active tuberculosis
  • HIV infection
  • certain medical conditions
  • those using IV drugs
  • h/o inadequately treated TB”

Core Curriculum on Tuberculosis CDC 2000

Conditions That Increase the Risk of Progression to TB Disease

- Diabetes mellitus
- Silicosis
- Prolonged corticosteroid therapy
- Other immunosuppressive therapy
- Cancer of the head and neck
- Hematologic and reticuloendothelial diseases
- End-stage renal disease
- Intestinal bypass or gastrectomy
- Chronic malabsorption syndromes
- Low body weight (10% or more below the ideal)
Latent Tuberculosis Infection (LTBI) Update

- Background
- Diagnosis
- Treatment
- Summary

Testing for Latent TB Infection

- Tuberculin Skin Test (TST)
- or
- Interferon-γ Release Assay (IGRA):
  - QuantiFERON®-TB Gold
  - QuantiFERON®-TB Gold-IT (In-Tube)
  - T-SPOT®.TB
Testing for Latent TB Infection

Tuberculin Skin Test (TST)

or

Interferon-γ Release Assay (IGRA):
QuantiFERON®-TB Gold
QuantiFERON®-TB Gold-IT (In-Tube)
T-SPOT®.TB

New Insights in the Diagnosis of Tuberculosis Infection

Tuberculin Skin Test (TST)

- Century old
- False +ve: BCG and Non-tuberculous mycobacteria
- Limited sensitivity: LTBI and active disease
- Variable interpretation and need for return visit
Classifying the Tuberculin Reaction

5 mm is classified as positive in

- HIV-positive persons
- Recent contacts of TB case
- Persons with fibrotic changes on chest radiograph consistent with old healed TB
- Patients with organ transplants and other immunosuppressed patients

Classifying the Tuberculin Reaction (cont.)

10 mm is classified as positive in

- Recent arrivals from high-prevalence countries
- Injection drug users
- Residents and employees of high-risk congregate settings
- Mycobacteriology laboratory personnel
- Persons with clinical conditions that place them at high risk
- Children <4 years of age, or children and adolescents exposed to adults in high-risk categories
Classifying the Tuberculin Reaction (cont.)

15 mm is classified as positive in

- Persons with no known risk factors for TB
- Targeted skin testing programs should only be conducted among high-risk groups

Boosting

- Some people with LTBI may have negative skin test reaction when tested years after infection
- Initial skin test may stimulate (boost) ability to react to tuberculin
- Positive reactions to subsequent tests may be misinterpreted as a new infection
Two-Step Testing

Use two-step testing for initial skin testing of adults who will be retested periodically

- If first test positive, consider the person infected
- If first test negative, give second test 1-3 weeks later
- If second test positive, consider person infected
- If second test negative, consider person uninfected

Testing for Latent TB Infection

Tuberculin Skin Test (TST)

or

Interferon-γ Release Assay (IGRA):

QuantiFERON®-TB Gold

QuantiFERON®-TB Gold-IT (In-Tube)

T-SPOT®.TB
New Insights in the Diagnosis of Tuberculosis Infection
IFN-γ Release Assays (IGRAs)

- Quantifies IFN-γ release by peripheral blood cells (T-cells CMI response) after stimulation with *M. tuberculosis* specific:
  - **ESAT-6**: early-secreted antigen target 6
  - **CFP-10**: culture filtrate protein 10
  - **TB 7.7(p4)**: (QuantiFERON®-TB Gold IT only)
New Insights in the Diagnosis of Tuberculosis Infection
IFN-γ Release Assays (IGRAs)

- ESAT-6 and CFP-10 (and TB 7.7(p4))
  - no cross reactivity with
    - BCG (TST no impact)
    - most NTM, except M. kansasii, M. szulgai, and M. marinum
  - + reactivity with M. bovis, africanum, microti

- Control antigens
  - nil (negative) control antigen
  - mitogen phytohemagglutinin (positive) control antigen

New Insights in the Diagnosis of Tuberculosis Infection
IFN-γ Release Assays (IGRAs)

- POSITIVE IFN-γ signal:
  - ESAT-6 - nil or
  - CFP-10 - nil or
  - (or TB 7.7(p4) - nil)

- NEGATIVE IFN-γ signal:

- INDETERMINATE:
  - Low mitogen response (positive control)
  - Large nil response (negative control)
New Insights in the Diagnosis of Tuberculosis Infection

IFN-γ Release Assays (IGRAs)

Advantages over TST:
• Single visit
• Blood draw versus ID injection - acceptance
• Less variation in application and interpretation
• No cross reactivity with BCG
• No boosting with serial IGRA testing
• Cost-effectiveness in select populations
  • Contacts
  • HCW
  • FB(?)

Diagnosis of LTBI:

1. TST versus IGRAs ?
2. QFT-Gold IT versus T-SPOT.TB ?
New Insights in the Diagnosis of Tuberculosis Infection

Diagnosis of LTBI:

1. TST versus IGRAs?: DEPENDS

2. QFT-Gold IT versus T-SPOT.TB?: DEPENDS

New Insights in the Diagnosis of Tuberculosis Infection

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

Gardner CA Smith, J F Par

BMJ 327:1459, 2003

Parachutes reduce the risk of injury after gravitational challenge, but their effectiveness has not been proved with randomised controlled trials
New Insights in the Diagnosis of Tuberculosis Infection

Parachute use to prevent death and major trauma related to gravitational challenge: systematic review of randomised controlled trials

BMJ 327:1459, 2003

New Insights in the Diagnosis of Tuberculosis Infection-LTBI
5 Aug 2008

Annals of Internal Medicine


**New Insights in the Diagnosis of Tuberculosis Infection- LTBI**

**Systematic Review: Pai, et al.**

**Sensitivity:** studies of microbiologically confirmed TB disease, not only immunocompromised patients

**Specificity:** studies of healthy, low-risk individuals without known exposure to tuberculosis who were from low TB incidence countries

Separated BCG-vaccinated from non-BCG patients

Included: TST, QFT (QFT-Gold and -IT), and T-SPOT

38 articles; at least 10 participants/study


<table>
<thead>
<tr>
<th>Test</th>
<th>Sensitivity*</th>
<th>Pharma (range)</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>0.77 (0.71-0.82)</td>
<td>0.75: 0.64 - 0.88</td>
</tr>
<tr>
<td>QFT-Gold</td>
<td>0.78 (0.73-0.82)</td>
<td>0.84: 0.64 - 1.00</td>
</tr>
<tr>
<td>QFT-IT</td>
<td>0.70 (0.63-0.78)</td>
<td>0.91: 0.70 - 1.00</td>
</tr>
<tr>
<td>T-SPOT</td>
<td>0.90 (0.86-0.93)</td>
<td>0.96: 0.92 - 0.98</td>
</tr>
</tbody>
</table>

*(95%CI)*


**Specificity***

<table>
<thead>
<tr>
<th></th>
<th>BCG</th>
<th>non-BCG</th>
<th>Pharma</th>
</tr>
</thead>
<tbody>
<tr>
<td>TST</td>
<td>0.59</td>
<td>0.97</td>
<td>0.87</td>
</tr>
<tr>
<td>QFT-G &amp; IT</td>
<td>0.96</td>
<td>0.99</td>
<td>0.99</td>
</tr>
<tr>
<td>T-SPOT</td>
<td>0.93</td>
<td></td>
<td>0.97</td>
</tr>
</tbody>
</table>

*(95%CI)*


---

New Insights in the Diagnosis of Tuberculosis Infection IFN-γ Release Assays (IGRAs)

<table>
<thead>
<tr>
<th></th>
<th>QFT-Gold-IT</th>
<th>T-SPOT®.TB</th>
</tr>
</thead>
<tbody>
<tr>
<td>Immunocompromised</td>
<td>X</td>
<td>XX</td>
</tr>
<tr>
<td>Children less than 5 yr</td>
<td>X</td>
<td>XX</td>
</tr>
<tr>
<td>Contact investigations</td>
<td>X</td>
<td>XX</td>
</tr>
<tr>
<td>Indeterminate results</td>
<td>X</td>
<td>XX</td>
</tr>
<tr>
<td>Specificity</td>
<td>XX</td>
<td>XX</td>
</tr>
<tr>
<td>Laboratory intensity</td>
<td>XX</td>
<td>X</td>
</tr>
<tr>
<td>Specimen time to process</td>
<td>XX</td>
<td>X</td>
</tr>
</tbody>
</table>

ERJ 28: 24, 2006
Lancet 367: 1328, 2006
New Insights in the Diagnosis of Tuberculosis Infection
IFN-γ Release Assays (IGRAs)

Serial IGRAs testing for response to treatment to LTBI
or TB disease?

**NO** (at this time...)

- Natural history of conversion and reversions is unknown and unpredictable.
- IGRA may increase, decrease, or demonstrate no change

IJTLD 9: 1034, 2005

New Insights in the Diagnosis of Tuberculosis Infection
IFN-γ Release Assays (IGRAs)

Does boosting occur with IGRAs testing following TST testing?

Boosting of QFT-GIT is possible from serial TST testing.

ERJ 29: 1212, 2007
IUTLD 9:985, 2005
IUTLD 11: 788, 2007
**New Insights in the Diagnosis of Tuberculosis Infection**

**IFN-γ Release Assays (IGRAs)**

Does a positive IGRAs mean that an individual with latent TB infection is at greater risk of developing TB disease in the future?

- **Uncertain**
  - Longitudinal studies pending
  - Contacts at increased risk, relative to TST (BCG exposure 46%)

*ARJCCM 177: 1164, 2008*

---

**New Insights in the Diagnosis of Tuberculosis Infection**

**IFN-γ Release Assays (IGRAs)**

Is IGRAs testing cost effective for testing for latent TB infection?

- **Yes, but depends…on local culture**
  - Single visit
  - Higher specificity than TST (BCG, NTM)
  - Reduce personnel cost, time away
  - Less chest x-rays, investigation, LTBI treatment
  - Direct and indirect costs
New Insights in the Diagnosis of Tuberculosis Infection
IFN-γ Release Assays (IGRAs)

- Markov models
  - Close contacts: Diel et al. (Western Europe)
  - HCW: dePerio et al. (Cincinnati VA)
- Both suggest that IGRAs are cost-effective

Can IGRAs testing be used in place of TST?
- Yes

CDC Guidelines QFT-Gold 2005:
  QFT-Gold can be used in all circumstances in which the TST is used including:
  - contact investigations
  - evaluation of recent immigrants (BCG)
  - TB screening HCW, including serial screening
New Insights in the Diagnosis of Tuberculosis Infection

Should IGRAs testing always be used first for LTBI testing in place of TST?

- No

- National Institute for Health and Clinical Excellence (NICE) UK

- Two step strategy: 1st TST, if positive TST then IGRA

- If +ve TST, -ve IGRAs: consider false positive TST, infection unlikely

HPE guideline March 2008  NICE NHS guideline March 2006

New Insights in the Diagnosis of Tuberculosis Infection

Should IGRAs testing always be used first for LTBI testing in place of TST?

- No

- IGRAs as sole testing:
  - those with potential false negative TST, immunocompromised
  - screening large numbers PHD
  - HCW

HPE guideline March 2008  NICE NHS guideline March 2006
New Insights in the Diagnosis of Tuberculosis Infection
IFN-γ Release Assays (IGRAs)

Future directions

- Predictive of TB disease in LTBI (natural history)
- Indeterminate results
- Cut points – TST (5,10,15) vs. IGRAs (0.35 QFT, 8 spots T-SPOT)
- Specific IGRAs for specific patients – TNF inhibitor, immunocompromised
- Cost-effectiveness for varying practices

Latent Tuberculosis Infection (LTBI)

Update

• Background
• Diagnosis
• Treatment
• Summary
LTBI Treatment Regimens

Initiating Treatment

Before initiating treatment for LTBI
- Rule out TB disease (i.e., wait for culture result if specimen obtained)
- Determine prior history of treatment for LTBI or TB disease
- Assess risks and benefits of treatment
- Determine current and previous drug therapy
Isoniazid Regimens

- 9-month regimen of isoniazid (INH) is the preferred regimen
- 6-month regimen is less effective but may be used if unable to complete 9 months
- May be given daily or intermittently (twice weekly)
  - Use directly observed therapy (DOT) for intermittent regimen

ATS/CDC Guidelines for Treating LTBI

![Graph depicting case rate percentage over months of treatment](source)
Isoniazid Regimens

- INH daily for 9 months
  (270 doses within 12 months)
- INH twice/week for 9 months
  (76 doses within 12 months)
- INH daily for 6 months
  (180 doses within 9 months)
- INH twice/week for 6 months
  (52 doses within 9 months)
- INH twice/week for 9 months
  (76 doses within 12 months)
- INH daily for 6 months
  (180 doses within 9 months)
- INH twice/week for 6 months
  (52 doses within 9 months)

Rifampin Regimens

- Rifampin (RIF) given daily for 4 months is an acceptable alternative when treatment with INH is not feasible.
- In situations where RIF cannot be used (e.g., HIV-infected persons receiving protease inhibitors), rifabutin may be substituted.
Rifampin Regimens

- RIF daily for 4 months
  (120 doses within 6 months)
- RIF and PZA for 2 months should generally not be offered due to risk of severe adverse events\(^6\)

\(^{\text{\textsuperscript{6}}}$MMWR August 8, 2003; 52 (31): 735-739

Completion of Therapy

Completion of therapy is based on the total number of doses administered, not on duration alone.
Management of Patient Who Missed Doses

- Extend or re-start treatment if interruptions were frequent or prolonged enough to preclude completion
- When treatment has been interrupted for more than 2 months, patient should be examined to rule out TB disease
- Recommend and arrange for DOT as needed

ATS/CDC Guidelines for Treating LTBI

<table>
<thead>
<tr>
<th>Drug</th>
<th>Treatment Duration</th>
<th>Comment</th>
<th>Rating/Evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>Daily for 9 months</td>
<td>In HIV-infected persons, isoniazid may be administered concomitantly with nucleoside reverse transcriptase inhibitors (NRTIs), protease inhibitors, or non-nucleoside reverse transcriptase inhibitors (NNRTIs).</td>
<td>A (B) A (B)</td>
</tr>
<tr>
<td></td>
<td>Twice weekly for 9 months</td>
<td>Directly observed therapy (DOT) must be used with twice-weekly dosing.</td>
<td>B (B) B (B)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>Daily for 4 months</td>
<td>DOT must be used with twice-weekly dosing.</td>
<td>B (B) C (I)</td>
</tr>
<tr>
<td></td>
<td>Twice weekly for 4 months</td>
<td>DOT must be used with twice-weekly dosing.</td>
<td>B (B) C (I)</td>
</tr>
</tbody>
</table>

MMWR 52: 735, 2003
Short Course Therapy with RIF plus INH 3 Months versus Standard INH

- Not CDC approved for LTBI (as of 2000 with updates)
- Meta-analysis LTBI treatment
- Pooled 1926 patients (5 studies) Hong Kong, Spain, and Uganda

- Equivalent to standard therapy with INH (IR3 vs I6-12):
  - Efficacy (4.2% vs. 4.1%)
  - Severe side effects (4.9% vs. 4.8%)
  - Mortality (9.5% vs. 10.4%)

- Also equally effective in pediatric population, better completion (Greece)

CID 40: 670-676, 2005
CID 45: 715-722, 2007

Latent TB Infection (LTBI) Treatment

- Prospective MC treatment trial 4RIF vs 9INH - LTBI
- N=847 Canada, Saudi Arabia, Brazil
- Treatment completion: 78% vs. 60% (p<0.001)
- AE: 1.7% vs. 4.0%
  - Grade 3-4 hepatitis: 0.7% vs. 3.8%

Latent TB Infection (LTBI) Treatment

- Prospective MC treatment trial 4RIF vs 9INH - LTBI
- N=847 Canada, Saudi Arabia, Brazil
- Treatment completion: 78% vs. 60% (p<0.001)
- AE: 1.7% vs. 4.0%
  - Grade 3-4 hepatitis: 0.7% vs. 3.8%

---

Class V versus LTBI

- Class V pulmonary TB evaluation and treatment
- Start treatment for culture negative disease
- Four drugs: RIF, INH, EMB, and PZA
- Reassess at 2 months
- If no change in radiograph noted and patient felt to have LTBI – receives credit for LTBI treatment and medication discontinued
Inhibition of tumor necrosis factor and tuberculosis infection

• Increased incidence of tuberculosis infection (and other infections) with FDA approved exposure to TNF inhibitors
  
  • **Infliximab (Remicade®)** chimeric, murine-human monoclonal antibody, soluble and transmembrane TNF
  
  • **Etanercept (Enbrel®)** recombinant fusion protein, soluble TNF
  
  • **Adalimumab (Humira®)** humanized monoclonal antibody against TNF

• Increased extrapulmonary TB disease (57%) and disseminated TB disease (25%) with TNF inhibitor Rx

• **TBI rate** inhibitor specific (?)
  
  - infliximab (33-54/100k) > etanercept (27-28/100k)
  
  - ? adalimumab (27.1/100k)

• **Onset of TB disease** inhibitor specific
  
  - Infliximab (median 3 mo) > etanercept (median 11.5 mo)
Inhibition of tumor necrosis factor and tuberculosis infection

- Guidelines for evaluation and treatment:
  - Screening required for all prior to TNF-Rx
  - Exclude active disease prior to LTBI
  - TBI pre-test assessment, CXR, TST > 5 mm
  - Two-step testing “boosting” may increase sensitivity but decrease specificity
  - Consider LTBI even if TST negative if risk sufficiently high
  - INH 9 months (RIF 4 months alternative)

Nature Clinical Practice Rheum 2: 602, 2006

Inhibition of tumor necrosis factor and tuberculosis infection

TB disease despite LTBI

- Retrospective study of 613 patients Aristotle University, Greece receiving TNF inhibitors for rheumatic disease
- All screened with TST (10mm) and CXR
- 36 of 45 “LTBI” patients received proper LTBI therapy
- 11 patients TB disease (2-35 mos into TNF-Rx, 7/11 <6 mos)
  - 7/11 correct Rx, 2 incorrect, 1 declined, 1 neg TST and CXR
  - Of correct Rx:
    - 3/7 while on LTBI, 4/7 after LTBI
    - TNF inhibition stopped, +/- etanercept restarted after TB Rx

Int J Tuberc Lung Dis 10: 1127, 2006
Clinical Monitoring

Instruct patient to report signs or symptoms of adverse drug reactions

- Rash
- Anorexia, nausea, vomiting, or abdominal pain in right upper quadrant
- Fatigue or weakness
- Dark urine
- Persistent numbness in hands or feet
Clinical Monitoring

Monthly visits should include a brief physical exam and a review of:

- Rationale for treatment
- Adherence with therapy
- Symptoms of adverse drug reactions
- Plans to continue treatment

Clinical Monitoring

- Incidence of hepatitis in persons taking INH is lower than previously thought (0.1 to 0.15%)
- Hepatitis risk increases with age
  - Uncommon in persons < 20 years old
  - Nearly 2% in persons 50 to 64 years old
- Risk increased with underlying liver disease or heavy alcohol consumption
Laboratory Monitoring

Baseline liver function tests (e.g., AST, ALT, and bilirubin) are not necessary except for patients with the following risk factors:

• HIV infection
• History of liver disease
• Alcoholism
• Pregnancy or in early postpartum period

Laboratory Monitoring

Repeat laboratory monitoring if patient has
• Abnormal baseline results
• Current or recent pregnancy
• High risk for adverse reactions
• Symptoms of adverse reaction
• Liver enlargement or tenderness during examination
Laboratory Monitoring

- Asymptomatic elevation of hepatic enzymes seen in 10%-20% of people taking INH
  - Levels usually return to normal after completion of treatment
- Some experts recommend withholding INH if transaminase level exceeds 3 times the upper limit of normal if patient has symptoms of hepatotoxicity, and 5 times the upper limit of normal if patient is asymptomatic.

Fibrotic Lesions

Acceptable regimens include
- 9 months of INH
- 2 months RIF plus PZA
- 4 months of RIF (with or without INH)

Pregnancy and Breast-feeding
- INH daily or twice weekly
- Pyridoxine supplementation
- Breast-feeding not contraindicated
Contacts of INH-Resistant TB

- Treatment with a rifamycin and PZA
- If unable to tolerate PZA, 4-month regimen of daily RIF
- HIV-positive persons: 2 month regimen with a rifamycin and PZA

Contacts of Multidrug-Resistant TB

- Use 2 drugs to which the infecting organism has demonstrated susceptibility
- Treat for 6 months or observe without treatment (HIV-negative)
- Treat HIV-positive persons for 12 months
- Follow for 2 years regardless of treatment

Latent Tuberculosis Infection (LTBI) Update

- Background
- Diagnosis
- Treatment
- Summary
Meeting the Challenge of TB Prevention

For every patient

• Assess TB risk factors
• If risk is present, perform TST or QFT
• If TST or QFT is positive, rule out active TB disease
• If active TB disease is ruled out, initiate treatment for LTBI
• If treatment is initiated, ensure completion

Case Studies
Case Study A

Patient history
• 29-year-old African-American female
• History of diabetes
• 35 weeks pregnant
• TST = 20 mm of induration
• No symptoms of TB disease
• CXR, CBC, LFTs normal
• No known contact with TB patient

Questions
1. What are this patient’s risk factors for TB infection or disease?
2. What is the appropriate management for this patient?
Case Study A

Discussion of risk factors

• Persons with diabetes mellitus are 2 to 4 times more likely to develop TB disease than those without diabetes
• Risk may be higher in insulin-dependent diabetics and those with poorly controlled diabetes

Case Study A

Discussion of management

• Pregnancy has minimal influence on the pathogenesis of TB or the likelihood of LTBI progressing to disease
• Pregnant women should be targeted for TB testing only if they have specific risk factors for LTBI or progression to disease
Case Study A

Discussion of management

• Some experts prefer to delay treatment until after the early postpartum period, unless the person has recent TB infection or HIV infection

Case Study B

Patient history

• 47-year-old Hispanic male
• Moved to U.S. from Bolivia 4 years ago
• Known contact of infectious TB case
• TST = 5 mm of induration
• 3 months later TST = 23 mm of induration
• No symptoms of TB disease
• Normal CXR, CBC, AST, and bilirubin
Case Study B

Questions
1. What are the patient’s risk factors for TB infection or disease?
2. Has the management of this patient to date been appropriate?

Discussion of risk factors
- Patient is a contact of an infectious TB case
- Recent immigrant to the U.S. from a country with a high prevalence of TB
Case Study B

Discussion of risk factors

• If the patient had not been a contact, the recency of his immigration (less than 4 years) would have made him a candidate for TB testing, but the 5-mm reaction would not be considered positive.

• Persons who immigrate from TB-endemic countries have increased rates of TB for 5 years after arrival in the U.S.

These increased rates most likely result from recent *M. tuberculosis* infection in their native country.
Case Study B

Discussion of management

- Should be treated for LTBI if TST reactions ≥ 10 mm of induration
- As a contact of an active TB case, 5 mm of induration is considered positive
- This patient should have been treated for LTBI immediately after the first TST

Case Study C

Patient history

- 36-year-old Asian female
- Moved to U.S. from Philippines > 15 years ago
- Plans to work in a correctional facility
- TST result negative 1 year ago
- TST for pre-employment physical = 26 mm of induration
- CXR normal
- No symptoms of TB disease
- No known contact with a TB patient
Case Study C

Questions

1. What are the patient’s risk factors for TB infection or disease?

2. What is the appropriate management for this patient?

Discussion of risk factors

- Patient’s TST converted from negative to positive (within a 2-year period)
- TST conversion increases risk for progressing from LTBI to TB disease
- Foreign-born status is less of a risk factor, i.e., she immigrated more than 5 years ago
Case Study C

Discussion of management

• Patient’s TST conversion indicates failure to identify this person as high risk for recent exposure to TB
• Patient may have had extended travel to her country of origin or other high-prevalence parts of the world

Case Study C

Discussion of management

• Patient is a recent converter and, as such, is a candidate for treatment of LTBI with INH
Meeting the Challenge of TB Prevention

For every patient

• Assess TB risk factors
• If risk is present, perform TST or QFT
• If TST or QFT is positive, rule out active TB disease
• If active TB disease is ruled out, initiate treatment for LTBI
• If treatment is initiated, ensure completion

Think and act globally!

Think and act locally!