The Role of Rifampin for the Treatment of Latent TB Infection

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Introduction

• Treatment of LTBI is a major priority in the quest for TB elimination in the US
• A major activity of TB control programs is to identify persons with LTBI and treat those with increased risk for developing active TB
• Treatment can provide individual and public health benefits

Introduction

• Current recommended standard therapy is 270 doses of INH (at least 9 mos.)
• Mainstay for almost 4 decades
• Known efficacy of more than 90%
• However, only about 65% or fewer complete therapy under routine program conditions
Contacts to Smear Positive
TB Cases - 2003

<table>
<thead>
<tr>
<th>National Objectives</th>
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<tbody>
<tr>
<td>73,319</td>
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<tr>
<td>14.0</td>
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<tr>
<td>80%</td>
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<tr>
<td>95%</td>
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<tr>
<td>1%</td>
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<tr>
<td>95%</td>
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<tr>
<td>73%</td>
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<tr>
<td>26%</td>
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<tr>
<td>59%</td>
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<td>85%</td>
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Introduction

• A very serious limiting factor is the occasional occurrence of drug-induced hepatitis and INH’s well known reputation for such despite the decrease in the incidence of such complications through the years
• Approach to TLTBI must be improved if it is to have an impact on the problem of TB

Introduction

• Interest in finding shorter, well tolerated regimen for TLTBI
• In the 2000 ATS/CDC/IDSA statement, 2 alternative regimens are recommended: 2 months RIF/PZA; and 4 months RIF
• 2RZ associated with serious hepatotoxicity and deaths, causing CDC to subsequently advise against its use
Introduction

• 4R is now the only ATS/CDC/IDSA recommended alternative to 9H for HIV (-) persons
• Limited published information on safety, tolerability, and efficacy

Introduction

• Considering the Role of 4 Months Rifampin in the Treatment of LTBI

  • Reichman LB, Lardizabal A, Hayden CH. Am J Respir Crit Care Med 2004; 170:832-835

Efficacy

• Bactericidal for M. tuberculosis
• Acts well against mycobacterial sub-populations with short bursts of metabolic activity
• Main reason for today’s “short-course” chemotherapy for TB
Efficacy

- Animal studies with mice: sub-clinical infection after BCG vaccination and challenging with MTB
- Received 4 treatment regimens: 6H, 3R, 2RZ, 2HRZ
- Bacilli cultured from spleen significantly lower with 4R and 2RZ compared to 6H

**Efficacy**

- The only randomized clinical trial that evaluated rifampin alone revealed 3R given to persons with silicosis had an efficacy rate of 63% compared to 48% for 6H

**Efficacy**

- Several studies have shown that rifampin was efficacious in treatment of LTBI among contacts of INH-resistant cases
Hepatotoxicity

- The Hong Kong study showed that 3R was least toxic regimen vs. 6H and 3HR
- Patients treated for active TB developed fewer serious side effects and no hepatitis from rifampin compared to H or Z

INH Resistance

- 57% of TB cases in the US are in foreign born (CDC, 2006)
- Higher levels of INH resistant TB among foreign born
  - Vietnam 21%, So. Korea 17%, Haiti 16%, Philippines 16%, China 16%, India 11%, Mexico 9% (CDC)

Adherence

- Shorter rifampin-based regimens have been shown to increase adherence rates
Adherence

- San Diego reported from a cohort of about 4000 patients on 6H only 64% completed the regimen

Rifampin in Treatment of Latent Tuberculosis Infection – 1

We argue that 4R is an effective, relatively nontoxic, affordable strategy that clinicians and program managers should consider for more widespread use in selected populations and settings to effectively and efficiently treat LTBI, thereby accelerating the decline of TB in their communities.

AJRCCM 2004;170:832-835

Rifampin in Treatment of Latent Tuberculosis Infection – 2

- Our own experience in Middlesex Co., NJ has shown that when we shifted to 4R for a majority of patients starting late 2002, completion rates have increased to 85%, compared to 66% from January 1999 to June 2000
• Study in County Chest Clinic
• 474 Patients
• 2000 Predominantly 9 months Isoniazid (9H)
• 2003 Predominantly 4 months Rifampin (4R)
• Treatment completion
  – 9H 53%
  – 4R 80.5% \( P < 0.0001 \)
• Treatment completion predicted by regimen (OR
  5.1; 95% CI 3.3, 8.1)

Lardizabal, A. et al. Chest 2006;130: 1712-1717

Comparison of Regimen Features: 9H and 4R

<table>
<thead>
<tr>
<th>Regimen Feature</th>
<th>9H</th>
<th>4R</th>
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<tbody>
<tr>
<td>High efficacy</td>
<td>X</td>
<td>*</td>
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<tr>
<td>Lower hepatotoxicity</td>
<td>X</td>
<td></td>
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<tr>
<td>Lower overall cost</td>
<td>X</td>
<td></td>
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<tr>
<td>Higher adherence</td>
<td></td>
<td></td>
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<tr>
<td>More effective against INH-resistant strains (e.g., among foreign-born persons)</td>
<td>X</td>
<td></td>
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<tr>
<td>Shorter duration</td>
<td>X</td>
<td></td>
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<tr>
<td>Fewer drug-drug interactions</td>
<td>X</td>
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* Good evidence that 3R is at least as efficacious as 6H. Inferential reasoning from other evidence suggests that efficacy of 4R may approach that of 9H.

AJRCCM 170; 832-835, 2004

• Confirms patient acceptance and compliance with treatment significantly improved with 4R
• Large scale study to assess safety and efficacy of rifamycins in TLTBI is ongoing
Recommendations

- Advocate broader use of rifampin for TLTBI for specific patient populations
- Strong caution against use among individuals known to be HIV (+) or have risk factors for HIV co-infection
- Many drugs that a patient may be on can have interactions with rifampin making its use problematic