Short-course Chemotherapy for Tuberculosis  
with Largely Twice-weekly Isoniazid-Rifampin*  

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Although short-course, largely twice weekly chemotherapy has been shown to be effective in other countries, when given under closely controlled conditions, it has not been adopted in this country where most patients are older and are treated as outpatients. Since January, 1976, 315 patients (mean age 55.5 years) with proven pulmonary tuberculosis have been treated with rifampin (RIF) 600 mg and isoniazid (INH) 300 mg daily for one month, followed by RIF 600 mg and INH 900 mg twice-weekly for another eight months, self-administered except for a few patients. By three months, 95 percent had converted to negative culture. There were only ten failures among 185 patients in whom final results could be assessed. There has been only one relapse during 1-21 months of follow-up in 175 patients. Serious side effects were few; six instances of jaundice, two of "flu-like syndrome," and one of thrombocytopenia. This form of initial therapy for tuberculosis is safe, effective, and economical.

Prolonged chemotherapy for tuberculosis, as presently used in the United States, has several disadvantages. Ingestion of daily medications for long periods is associated with a troubling incidence of both noncompliance and drug toxicity, as well as considerable expense.¹ The possibility of developing short-course chemotherapy for tuberculosis arose from two key experimental studies of tuberculosis in mice which showed the effective antibacterial activity of pyrazinamide (PZA),² and of rifampin (RIF).³ Several workers have confirmed the efficacy of rifampin both alone and in combination with isoniazid (INH) in experimental murine tuberculosis.⁴⁻⁶ Moreover, less than daily, or "pulse therapy," with RIF for tuberculosis in mice and guinea pigs was associated with little reduction in efficacy.⁷⁻¹⁰

Fox and associates¹¹⁻¹⁴ under the auspices of the British Medical Research Council, have employed INH and RIF in several short-course regimens in the treatment of advanced human tuberculosis among persons living in developing countries. Daily administration of INH and RIF for nine months with an initial supplement of streptomycin (SM) or ethambutol (EMB) for the first two months was shown to be highly effective in the treatment of advanced tuberculosis.¹⁵⁻¹⁶ Also, INH and RIF given twice weekly was effective and produced few adverse reactions.¹⁷⁻¹⁹

The extensive favorable experience with both short-course and twice-weekly therapy for tuberculosis thus seemed to leave little doubt as to efficacy and safety when administered under closely controlled conditions.²⁰⁻²⁸ However, it remained to be demonstrated that they would be applicable in the United States where tuberculosis develops more commonly in elderly persons, and is only rarely treated in hospitals.

The excellent results obtained in controlled clinical trials are often not applicable to outpatient treatment programs which rely upon patients to take medication with little supervision.²⁹⁻³¹ We felt our public health nurses would be able to achieve adequate compliance in most patients. However, another advantage of giving medications twice a week and for less than a year is that poorly cooperative patients can more readily be treated with direct observation of drug ingestion.¹⁷

Following careful consideration of the literature and shortly after the September, 1975, meeting of the International Union Against Tuberculosis in Mexico City, a protocol for short-course chemotherapy with INH and RIF was developed and distributed to the 75 chest clinics held in county health departments. These clinics are operated by qualified private physicians who are assisted by public health nurses and are under central guidance from the

For editorial comment, see page 415

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office of the Tuberculosis Program of the Arkansas Department of Health in Little Rock. For cases meeting the criteria set forth in the protocol, the approximately 40 physicians in this program were given the option of employing our standard form of therapy (INH an EMB) for 18-24 months supplemented by SM for 2-3 months in cavity cases or of instituting INH-RIF therapy under the terms of the protocol. If the latter course was elected, it was with the understanding that the protocol would be followed unless adverse side effects necessitated a change in therapy. Treatment of patients under this protocol was initiated in January, 1976, and we are reporting the results of 30 months’ experience.

MATERIALS AND METHODS

Newly diagnosed cases of pulmonary tuberculosis are eligible for treatment under the protocol if: (1) the sputum smear is positive for acid-fast bacilli and the chest roentgenogram is compatible with active tuberculosis; (2) the sputum culture is positive (despite negative initial smears) before any therapy has been initiated; (3) there is no history of prior chemotherapy or likelihood of bacterial resistance (eg, patients from the Philippines, SE Asia, etc); and (4) no other chemotherapy has been given for more than ten days.

Protocol for Short-course Therapy Used in this Program

Treatment Schedule: INH 300 mg (about 5 mg/kg body weight) and RIF 600 mg (about 10 mg/kg) given daily for one month (range accepted for inclusion in analysis was 28-40 days), followed by INH 900 mg (about 15 mg/kg) and RIF 600 mg twice each week for another eight months. Medications were given in a single dose, preferably before breakfast to facilitate rapid absorption.

Bacteriologic monitoring is by smear and culture of sputum: weekly, at first, until three consecutive specimens have been reported negative by culture. Then monthly sputum samples are submitted until six months after completion of therapy. Sputum is then checked every three months for another 21 months, giving a total of 36 months of observation.

Baseline Studies: blood counts, urine analysis, and both renal and liver function tests are obtained at the start of therapy and repeat studies are ordered thereafter as indicated by clinical signs or symptoms suggestive of drug toxicity.

Surveillance for compliance and toxicity: each patient is seen weekly by a public health nurse for two months to check urine for presence of INH and the red color of RIF. Appropriate questions are asked for symptoms of side effects of the drugs at each visit. If all is well after two months of therapy (one month of daily and one of twice weekly administration), further observations are made at least monthly during the entire course of therapy.

It is important to realize that this is not a report of a study of a new form of chemotherapy, but is a report of the practical use of a form of therapy which has already been pioneered by others. Not every patient with a positive sputum smear who was started on this form of therapy could be included in the analysis of results, because some were found later not to have met the conditions for inclusion. Of the 426 patients in whom this form of therapy was initiated, the diagnosis of tuberculosis was not confirmed in 34 patients.

Table 1—Age Distribution of 315 Patients

<table>
<thead>
<tr>
<th>Years</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>20</td>
<td>8</td>
</tr>
<tr>
<td>21-40</td>
<td>66</td>
</tr>
<tr>
<td>41-60</td>
<td>76</td>
</tr>
<tr>
<td>61-80</td>
<td>137</td>
</tr>
<tr>
<td>80-100</td>
<td>28</td>
</tr>
</tbody>
</table>

Mean age: (range 15-92 years) 55.5 years

(sputum smears positive but cultures negative for mycobacteria), in 34 daily therapy had inadvertently been continued for more than 40 days, and in 28 therapy had been initiated with additional drugs and given for more than 10 days. In six patients, the organisms were found to have been resistant to INH at the start and in nine others to have been mycobacteria other than M tuberculosis. Thus, for the above reasons, these 111 patients could not be included in the analysis or results, leaving 315 patients for analysis.

Medications were self-administered in all but 28 patients who were closely supervised in their drug administration because of suspicion of poor compliance or of being institutionalized (nursing home, prison, etc). The sputum smear was positive in all but 42 patients. An additional drug, usually SM or EMB, was given for less than 10 days in 18 patients.

Age, Sex, Race, and Extent of Disease

The majority of the patients were elderly, with a mean age of 55.5 years, ranging from 15 to 92 years (Table 1). There were 203 males, and 192 of the patients were white, the remainder black. In all but 35, the disease was considered to be moderately to far advanced.

RESULTS

Termination of Therapy under Protocol during Daily Administration of Drugs

Therapy under this protocol had to be terminated during the daily phase in 27 of the 315 patients: in 24 (7.6 percent) due to side effects of the drugs, and in three due to death from overwhelming tuberculosis on the 5th, 24th, and 28th day of treatment. Two of the 24 patients who showed side effects were moribund from multiple causes when therapy was started. Both developed jaundice, presumably due to the drugs, and died on the 8th day of treatment.

Termination during Twice-weekly Administration of Drugs

It was possible to continue therapy in 288 of the original 315 patients into the twice-weekly phase (Table 2). Of these, 175 have now completed the

Table 2—Duration of Treatment during Intermittent Phase in 288 Patients

<table>
<thead>
<tr>
<th>Months</th>
<th>Number</th>
</tr>
</thead>
<tbody>
<tr>
<td>1-2</td>
<td>47</td>
</tr>
<tr>
<td>3-4</td>
<td>31</td>
</tr>
<tr>
<td>5-6</td>
<td>23</td>
</tr>
<tr>
<td>7-8</td>
<td>12</td>
</tr>
<tr>
<td>Completed therapy</td>
<td>175</td>
</tr>
</tbody>
</table>
full course of treatment and therapy is still in progress in 78. Medication had to be terminated in 35 patients during the twice-weekly phase for a variety of reasons: in 12 due to side effects of drugs, in seven due to deaths from other causes, in three with psychiatric problems who refused treatment, and in six who moved from the state during the course of treatment. Two patients were removed from the protocol despite bacteriologic conversion due to a misunderstanding by the treating clinicians. In five patients, therapy was changed because sputum had not converted to negative by five to nine months and they were considered bacteriologic failures.

**Bacteriologic Conversion**

The bacteriologic conversion of sputum by smear and culture is shown in Figure 1. Of the 315 patients, 42 were initially negative on smear. Thus, 218 (96.9 percent) of the 223 patients with positive sputum smears who completed three months of treatment had negative sputum smears, as had 179 (96.2 percent) of 186 of those who completed six months and 155 (96.9 percent) of 160 at completion of eight months of therapy. Cultures were negative in 247 (95 percent) of 260 patients at the completion of three months of therapy, 208 (97.7 percent) of 213 patients by the end of six months of treatment and 181 (97.3 percent) of 186 patients at eight months of therapy. This includes the five patients in whom adequate therapy failed to convert to negative smears.

**Treatment Failures**

As mentioned above, three patients died of overwhelming tuberculosis during daily therapy and another two patients with extensive disease died of tuberculosis complicated by drug toxicity. In five additional patients, treatment failed to achieve bacteriologic conversion. Thus, there were ten treatment failures (5.4 percent) among the 185 patients at the time of this report. The sputum of one patient was persistently positive for *M tuberculosis* by smear and culture at seven months of therapy. A susceptibility test at that time revealed bacterial resistance to INH but by mistake, a pretreatment test had not been performed. According to the assessment of the clinician and public health nurses, the patient had taken medication regularly. It is probable that this patient harbored bacilli resistant to INH from the beginning of treatment. The second patient (a maximum security prisoner) remained bacteriologically positive throughout five months of therapy. Medication was given to him regularly, but his ingestion of it was not observed. It is unlikely that the patient took the medication. The susceptibility test performed on organisms obtained after five months of protocol therapy showed full susceptibility to both INH and RIF and he later showed a good response to supervised therapy. The third patient remained bacteriologically positive during five months of therapy, after which the organisms became resistant to INH. This patient was an alcoholic and compliance was seriously doubted. The fourth patient had cavitary silicotuberculosis, and although the sputum became negative on culture during the fourth month of therapy, the sputum smears remained positive throughout treatment. This patient was fully cooperative. Sputum cultures again became positive for *M tuberculosis* within three months after therapy was stopped and the organisms showed susceptibility to both INH and RIF. The fifth patient remained bacteriologically positive after five months of therapy in spite of good cooperation. Although initial susceptibility tests showed the organisms to be susceptible to all drugs, the organism was recently found to be resistant to isoniazid, but sensitive to rifampin. Therapy has

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**Figure 1. Bacteriologic conversions in 315 patients (42 with negative smear).**
been changed to other drugs.

Drug Side Effects

Side effects from the drugs were encountered in 36 patients (11.4 percent) (Tables 3 and 4), in 24 of 315 (7.6 percent) during the daily phase and in 12 of 288 (4.2 percent) during twice-weekly administration of drugs. Most of the side effects in the daily phase were minor and consisted of gastrointestinal intolerance or minor allergic reactions. The serious reactions were six instances of jaundice; five during daily therapy and one within two weeks after entering the twice weekly phase of therapy. Of the patients with jaundice, INH was thought to be responsible in one, RIF in three and assignment was impossible in the two fatal cases.

The total incidence of side effects during the twice-weekly phase was 4.2 percent (12 of 288 patients) (Table 4). Hypersensitivity reactions to RIF were encountered as “flu-like syndrome” of moderate clinical severity in two patients. Thrombocytopenia with petechiae occurred in one patient during the fourth month of twice-weekly administration. Renal failure has not been encountered. In the other eight patients, the drugs were changed because of minor drug intolerance.

Table 4—Drug Side-effects in 12/288 Patients during Twice-Weekly Therapy

<table>
<thead>
<tr>
<th>Side-effects</th>
<th>Drugs and patients</th>
</tr>
</thead>
<tbody>
<tr>
<td>Drug intolerance</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Gastrointestinal upset</td>
<td>2</td>
</tr>
<tr>
<td>Pain in joints, etc.</td>
<td>2</td>
</tr>
<tr>
<td>Minor allergy</td>
<td>Rifampin</td>
</tr>
<tr>
<td>Rash, fever, etc</td>
<td>2</td>
</tr>
<tr>
<td>Hepatotoxicity</td>
<td>INH</td>
</tr>
<tr>
<td>Jaundice, enzyme rise</td>
<td>1</td>
</tr>
<tr>
<td>Vomiting, enzyme rise</td>
<td>2</td>
</tr>
</tbody>
</table>

(2) INH and/or Rifampin

Completion and Follow-up

At the time of this report, 175 patients have successfully completed the full nine-month course of chemotherapy. Lengths of post-therapy observations are shown in Table 5. Sixty-nine patients have been observed from 12-21 months after termination of therapy. During followup, nine patients died of non-tuberculous causes (myocardial infarction, cerebrovascular accident, carcinoma of the lung, etc.). Two patients, both bacteriologically negative at the first and fourth months of post-therapy follow-up, had moved from the state.

Of the remaining 164 patients who completed therapy and who remain under observation, one has relapsed four months after completion of therapy. This elderly woman was mentally deficient and had been given medication by personnel in a boarding home. Tests of the organisms obtained after relapse showed complete susceptibility to both INH and RIF.

Discussion

We were able to find only one experience with short-course therapy with daily INH-RIF reported from the United States, a brief report with no information on relapse. Therefore, this report is the first detailed account of short-course treatment for tuberculosis from the United States. Under a protocol employed in chest clinics throughout Arkansas, INH and RIF were given daily for one month followed by an additional eight months in which these medications were given twice-weekly.

In several studies, SM or EMB was given at the outset in order to assure administration of two effective drugs even if the organisms were resistant to INH. However, the addition of a third drug (SM or EMB) is of little benefit in patients with susceptible organisms. The incidence of INH resistance in newly discovered cases in Arkansas remains quite low (6/315 or 1.9 percent). For this reason the use of two bactericidal agents together was thought to be sufficient. It must be stressed, however, that among patients with a possibility of
harboring organisms resistant to INH (i.e., previous treatment or persons from SE Asia, the Philippines, etc.), a third drug should be used until the results of susceptibility tests of the organisms are known.

All patients included in the analysis of results had culture-proven pulmonary tuberculosis, and 87 percent of them had positive sputum smears. Almost all had moderately to far-advanced disease. The relapse of one of the 175 patients followed for up to 21 months compares favorably with what one would expect with any other regimen. In this relapse case, the organisms were susceptible to both INH and RIF, as were those observed by Fox et al. Daily administration of INH and RIF appears to reduce bacterial growth rapidly and the irradiation can be completed by twice-weekly administration of the drugs. Conversion to negative occurred among many of our patients after change to twice-weekly therapy.

Girling and associates have pointed out that reducing the number of doses of RIF by twice-weekly administration greatly reduces the cost of treatment. In our protocol, utilizing less than 100 doses of RIF, the total cost of medicine for a full course of treatment is about $75 compared to approximately $310 for an INH and EMB therapy program for 18 months with three months of SM initially, or $454 for INH and RIF given daily for 18 months. Twice weekly administration for most of the treatment period lowers the cost of using the most expensive drug (RIF) to considerably less than that of "standard" therapy. In addition, giving dosage twice a week makes it relatively simple to supervise the ingestion of each dose of medication when this is indicated.

Bacteriologic monitoring was more frequent than usual among these patients because we were using this form of therapy for the first time in this country. It was important that we determine the rapidity of conversion and to have clear evidence if therapy failed. Twice-monthly bacteriologic monitoring would probably be sufficient in routine use of the regimen.

Treatment failed in 10 of the 185 patients in whom results could be judged. Five of these died in the first month and five failed to convert to positive bacteriology under the treatment. It seems possible that noncompliance and pre-existing resistance to INH may explain three of these instances, but in two, there was a clear failure of the regimen. The two patients who died with jaundice were moribund at the beginning of chemotherapy and unable to survive even a transient hepatic reaction. A 5 percent treatment failure among patients with advanced tuberculosis accompanied by old age and other diseases compares favorably with results of other two- or three-drug regimens. Resistance to INH developed in three of the five treatment failures but to RIF in none. The same was observed by Girling et al which suggests that RIF may not be as effective a drug as INH.

Since both INH and RIF are potentially toxic, careful clinical monitoring for evidence of side effects is necessary although serious side effects were few in this series. Transient elevation of hepatic enzymes without clinical evidence of hepatitis are common with antituberculosis chemotherapy regimens containing INH or RIF either alone or in conjunction with other antituberculosis drugs. Significant reduction in the platelet count may be seen in patients receiving twice weekly RIF without clinical manifestation of bleeding diathesis. Periodic laboratory monitoring has been shown to add little advantage and even to lead to confusion at times. Jaundice occurred in six of our 315 patients, five during the daily phase of therapy, but cleared without incident in all but the two patients who were moribund when therapy was started.

In view of the reported adverse hypersensitivity and hematologic side effects of less-than-daily therapy with RIF, clinical surveillance for toxicity has been particularly close when the drugs are being given twice-weekly. These side effects have been found to be more common when larger doses of RIF (900-1200 mg) were given or when a dose of 600 mg was given as infrequently as once a week. Reactions have been infrequent when RIF is given at the lower dosage of 450 mg or 600 mg two to three times per week. We observed only two instances of "flu-like syndrome" and one of thrombocytopenia with petechiae, none of which was life-threatening. Surveillance for thrombocytopenia in our clinics is done by advising the patients to check for any "red spots" on the body, or legs, before taking each dose.

Rifampin antibodies have been demonstrated in several studies, but only a portion of the patients having demonstrable antibodies have developed clinical hypersensitivity manifestations. We were unable to demonstrate antibodies in any of our patients by in vitro studies performed by the method of Worlledge despite checking our methods by a visit to her laboratory in London. The relationship of rifampin-dependent antibodies and hypersensitivity reactions in patients remains unclear. Further study of patients in the United States who are receiving RIF at greater than daily intervals is necessary.

Finally, some have raised a question about compliance when patients are asked to take medications...
twice a week. Our observations indicate that patients who have taken the drugs daily for a month are very pleased when they are permitted to reduce the frequency of medication to twice a week. They find little trouble in remembering the medication when they are furnished a calendar to mark as they take the medications. Certainly our frequent observations of the patients including examination of urine for INH excretion and our favorable therapeutic results all indicate regular ingestion of the drugs in the great majority of our patients.

Our experience over a 30-month period with this short-course, largely twice-weekly regimen has shown it to be a safe and effective therapy for pulmonary tuberculosis. Bacteriologic conversion is generally prompt, serious side effects infrequent, and relapse rare. This form of therapy has now been shown to be safe in the older patients commonly seen in this country. The cost of medication (which is largely dependent upon the total number of doses of rifampin) is less than that of "standard" regimens in use currently. The shortening of treatment is gratifying for the patients.

ADDENDUM

The results have not significantly changed on updating the data through January 1, 1979. During this period, 375 patients have been treated, and 214 of them have completed therapy. There were three (1.4 percent) relapses during followup of 1 to 27 months with susceptible bacilli to INH and RIF.

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