these results we suggest that Z-containing regimens are well tolerated by alcoholic tuberculous patients who have adequate liver function, that histologic and biochemical alterations observed on admission improve or disappear after two months' treatment, and that Z, as well as I and R, are nontoxic to the liver.

**SUMMARY**

A group of alcoholic tuberculous patients was given a pyrazinamide-containing regimen, and the liver was studied on admission and after two months of intensive treatment with I and R. Alterations in liver histology and in liver function tests found on admission improved or disappeared after two months' chemotherapy. A control group, given I and R, showed similar results. A third group of nonalcoholic patients was given Z alone for 15 days, and liver tolerance was also excellent.

These data support the conclusion that tuberculous alcoholic patients, in the absence of significant and persistent hepatic dysfunction, can be given Z-containing regimens. In all cases, a careful monitoring of hepatic function, with monthly SGPT and bilirubin determinations, is recommended.

**REFERENCES**


**BTA Short-course Chemotherapy Studies**

**J. H. Angel, M.D.*

The advent of rifampicin and the re-emergence of pyrazinamide have allowed the possibility of reducing the duration of chemotherapy from the previous standard 18 months to two years. The Research Committee of the British Thoracic Association (BTA) has organized two separate studies of short-course chemotherapy, both of them multicenter controlled clinical trials and both of them leaving the degree of supervision of the chemotherapy in the hands of the cooperating physician. The criterion for admission to the studies was that patients should have pulmonary tuberculosis, with sputum positive on either smear or culture. Patients who were known to be alcoholic or who had any significant impairment of hepatic, renal or visual function were excluded.

In the first study, initiated in 1972, four different durations of regimens of rifampicin plus isoniazid—6, 9, 12, and 18 months, allocated at random—were investigated. For patients under the age of 60 years, there was a further random allocation to either ethambutol or streptomycin as the third drug for the first eight weeks. The dosages of the drugs used are shown in Table 1; the oral drugs were all taken together in a single daily dose on an empty stomach.

**RESULTS**

Of the 802 patients who satisfied the requirements of the protocol, 106 did not complete the allocated duration; 37 absconded from treatment or were otherwise uncooperative, 6 emigrated, 19 died (9 of pulmonary tuberculosis), and 15 were withdrawn from the study by their physicians for miscellaneous reasons. Twenty-nine had toxic reactions to rifampicin or isoniazid, or both. There remained 696 patients for analysis.

Only one patient (in the six-month group) was a failure of chemotherapy in that he still had positive cultures at five and six months. There was no difference in the rate of sputum conversion according to whether the patients received ethambutol or streptomycin as the third drug initially, but there was a difference in the incidence of adverse effects; none of the patients receiving ethambutol experienced these, while 8 percent of those receiving streptomycin had to discontinue use of the drug.

In 29 (3.6 percent) of the 802 patients, there were adverse effects to the rifampicin-isoniazid regimen severe enough to warrant discontinuation of treatment. The majority of these reactions occurred early, most in the first month of treatment. Fourteen of the 29 patients had hepatotoxicity, of whom six had persistently raised serum transaminase levels and eight had jaundice. All but one of the patients regained normal liver function after they stopped receiving the chemotherapy.

The patients have now been followed up for a total of 54 months from the start of treatment and have had intensive bacteriologic surveillance throughout the period of observation; 92 percent were available for follow-up at 33 months, and 84 percent for the whole of the 54-month period.

Relapse has been defined in purely bacteriologic terms as the occurrence of two or more positive cultures in any period of four months in specimens taken at least two weeks apart. It occurred in 11 patients...
Table 1—BTA First Short-course Chemotherapy Study

<table>
<thead>
<tr>
<th>Drug</th>
<th>Dosage</th>
</tr>
</thead>
<tbody>
<tr>
<td>Ethambutol</td>
<td>25 mg/kg daily (in one dose)</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>0.75 g daily, 6 days/week</td>
</tr>
<tr>
<td>Isoniazid</td>
<td>300 mg daily (in one dose)</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>450 mg daily for patients weighing &lt; 50 kg (in one dose)</td>
</tr>
<tr>
<td></td>
<td>600 mg daily for patients &gt; 50 kg</td>
</tr>
</tbody>
</table>

(Table 2), nine of them in the six-month group (7 percent) and two in the 12-month group (1.4 percent); in 10 of the 11 patients the relapse occurred within two years of stopping the chemotherapy. At 54 months there had been no relapses among the 116 patients in the nine-month group, but we have since been notified of two late relapses in this group, occurring 62 and 69 months after the start of chemotherapy. All 13 patients had relapses with organisms fully sensitive to the antituberculosis drugs used in the study, and all but one (who died shortly after his relapse) responded to further chemotherapy.

It was concluded from this study that the rifampicin-isoniazid regimen was acceptable to and well tolerated by patients. A six-month duration produced an unacceptably high incidence of relapse, but it was felt that a nine-month duration, supplemented for the first two months by ethambutol, could be recommended as the treatment of choice for pulmonary tuberculosis, at least in Great Britain.

The second BTA Study attempted to improve the results of the six-month duration by the addition of pyrazinamide for the first two months. The design of the study is shown in Figure 1. Patients were allocated at random to either isoniazid and rifampicin plus streptomycin and pyrazinamide for the first two months (SHRZ6 regimen), isoniazid and rifampicin for six months plus ethambutol and pyrazinamide for the first two months (EHRZ6 regimen), or isoniazid and rifampicin for nine months plus ethambutol for the first two months (EHR9 regimen). The dosages of the drugs were the same as in the first study; pyrazinamide was given in a dose of 1.5 g daily for patients weighing less than 50 kg, 2.0 g for those between 50 and 74 kg, and 2.5 g for those more than 75 kg.

The criteria for admission to the study were the same as in the first study, and known alcoholics were again excluded. Between January 1977 and January 1979, 511 patients were admitted. The age and sex distribution was similar in all three treatment series. All patients initially had sputum positive on culture for Mycobacterium tuberculosis, and 58 percent were also positive on direct smear. The radiologic extent was similar in the three treatment series, one third having slight disease, another third limited, and the remainder having moderate, extensive, or gross disease. Half of the patients showed cavitation.

Of the 511 patients, 67 did not complete the allocated regimen; 6 died (2 from pulmonary tuberculosis), 15 defaulted from treatment, and 27 patients had their chemotherapy changed because of adverse reactions to one or more of the drugs. In 19 patients, the chemotherapy regimen differed significantly from that laid down by the protocol.

The rate of sputum conversion was more rapid in the two pyrazinamide regimens than in the control EHR9 regimen. At two months, 77 percent of the patients in the pyrazinamide regimens had negative cultures compared with 64 percent in the control regimen. At three months, the figures were 98 percent and 88 percent, respectively. All the patients in the three regimens had negative cultures by the end of the fifth month, and there were no failures of chemotherapy. Those whose pretreatment smears were positive became culture-negative more slowly than those with negative pretreatment smears.

Urine was examined monthly for six months for isoniazid metabolites; 97 percent of these tests were positive, indicating that the patients were taking their drugs as prescribed.

The study has been particularly concerned with changes in liver function tests during chemotherapy.

Table 2—BTA First Short-course Chemotherapy Study—Relapses After Cessation of Chemotherapy

<table>
<thead>
<tr>
<th>Duration of Chemotherapy</th>
<th>No. of Patients</th>
<th>Months from Start of Chemotherapy</th>
<th>Relapses</th>
<th>Alive and Well at 54 Mos</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td>7-18</td>
<td>18-33</td>
<td>33-54</td>
</tr>
<tr>
<td>6</td>
<td>182</td>
<td>5</td>
<td>3</td>
<td>1</td>
</tr>
<tr>
<td>12</td>
<td>181</td>
<td>1</td>
<td>1</td>
<td>0</td>
</tr>
<tr>
<td>9</td>
<td>153</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>18</td>
<td>149</td>
<td>0</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Total</td>
<td>665</td>
<td>6</td>
<td>4</td>
<td>1</td>
</tr>
</tbody>
</table>

*There were two late relapses in the nine-month group, at 62 and 69 months.
and in the comparison of the incidence of adverse effects, particularly of hepatitis, in the regimens containing pyrazinamide with the incidence in the control regimen. Biochemical monitoring included measurement of serum bilirubin, SCOT, alkaline phosphatase, albumin, and uric acid. These were measured pretreatment and at 1, 2, and 6 months. Clinical observations were made throughout the course of chemotherapy.

The serum bilirubin did not exceed the normal range; the mean value rose during the six-month period by 2 mmole/L; this rise occurred (and was statistically significant) in all three regimens. The mean values of serum alkaline phosphatase and SGOT (AST) also remained within the normal ranges; the values remained virtually unchanged throughout the course of chemotherapy and again were similar in all three regimens. In contrast, the mean values for serum uric acid levels rose sharply and significantly in patients receiving the pyrazinamide-containing regimens during the two months that the patients were taking pyrazinamide. By six months the values had returned virtually to the pretreatment levels and were no different from the values in the control regimen.

Hepatitis presented in three different ways: (1) persistently abnormal liver function tests without symptoms (3 patients); (2) abnormal liver function tests associated with gastrointestinal symptoms, such as nausea, vomiting, and abdominal pain (10 patients); and (3) jaundice (8 patients). The incidence of hepatitis was 4 percent in both the pyrazinamide-containing regimens and was also 4 percent in the control group. These results suggest that the pyrazinamide was not contributing to the incidence of hepatitis.

Other adverse reactions occurred rather more frequently in the pyrazinamide-containing regimens than in the control regimen. The chief of these was drug rash/es; arthralgia occurred in only two patients.

All patients in the two pyrazinamide-containing regimens have now been followed up for a minimum of 12 months from the end of chemotherapy. Bacteriologic relapse has occurred in four of the 287 patients admitted to these two groups, compared with two of the 157 patients admitted to the control EHR9 regimen.

It is too early to make any definite recommendations about the usefulness of these pyrazinamide-containing regimens in routine clinical practice, but it is clear that they do not produce undue toxicity and merit further study.

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Short-course Chemotherapy
The Arkansas Experience

Asim K. Dutt, M.D., F.C.C.P.,* and William W. Stead, M.D., F.C.C.P.†

By the end of 1975 it had been shown that a combination of rifampin (RIF) and isoniazid (INH) could cure tuberculosis within six to nine months. Therefore, in January 1976, the Arkansas Department of Health began to use a short-course regimen of these drugs in smear-positive cases. In October 1976 the regimen was adopted as our standard treatment for tuberculosis. Our total experience now comprises a total of more than 1,000 cases.

Choice of Regimen

Several well-controlled clinical trials under the guidance of Fox and associates by 1975 had shown the efficacy of RIF and INH in various short-course regimens among young hospitalized patients. Daily treatment with INH and RIF for nine months with initial supplement of streptomycin (SM) or ethambutol (EMB) for two to three months already were in wide use in France and the United Kingdom. Also, "pulse therapy" of RIF-INH once or twice a week after an initial daily treatment supplemented by SM for two weeks had been proved effective in Singapore. All that remained to be determined was whether therapy that involved two potentially hepatotoxic drugs in combination would be applicable for routine treatment patients in the United States who are often elderly and cared for largely as outpatients.

We devised our own regimen of largely twice-weekly administration of RIF and INH without the addition

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