The management of pulmonary tuberculosis in adults notified in Scotland in 1993

A. J. SIMPSON*, B. WATT†, S. H. HEALD*, M. F. SUDLOW* AND A. G. LEITCH*

*Royal Victoria Chest Clinic, Chalmers Hospital, Royal Infirmary NHS Trust, Edinburgh EH3 9HQ
†Scottish Mycobacteria Reference Laboratory, City Hospital, Greenbank Drive, Edinburgh EH10 5SB
*Hospital and Community Information Unit, Information and Statistics Division, Trinity Park House, Edinburgh EH5 3SQ, U.K.

The management of pulmonary tuberculosis (TB) in Scotland in 1993 was studied by asking the physicians responsible for all 321 adult cases of the disease notified that year to complete a standardized questionnaire relating to drug treatment and bacteriology. The response rate to the questionnaire was 100%. Isoniazid and rifampicin were used together in initial therapy in 98.4% of cases, while pyrazinamide was prescribed in 90.3% of cases, broadly in keeping with existing treatment guidelines. However, considerable variability was observed both in the drug regimens employed, and in the duration of initial and continuation phases of chemotherapy. Treatment regimens were therefore frequently at variance with published recommendations. Among patients prescribed drug regimens other than those recommended satisfactory completion of therapy was less common. Microbiological confirmation was provided for 84% of cases in which clinical samples were submitted. However, in approximately 11% of cases, no clinical samples were submitted. Closer adherence to existing treatment guidelines and more rigorous pursuit of microbiological confirmation should further improve the overall management of pulmonary TB in Scotland.

Introduction

In 1990 the British Thoracic Society (BTS) published recommendations for the treatment of pulmonary tuberculosis (TB) (1). These were based on evidence generated from important clinical trials (2–6), and proposed that isoniazid (H), rifampicin (R) and pyrazinamide (Z) be used together in the initial 2 months, to be followed by isoniazid and rifampicin together for a further 4 months continuation therapy (1).

The extent to which these recommendations have been implemented in Scotland has not been formally assessed. The Scottish Respiratory Tuberculosis (SRTB) Survey published comprehensive data relating to the clinical management of pulmonary TB between 1977 and 1985 (7). Among several interesting findings, the Survey noted that ethambutol (E) was far more commonly used as part of initial therapy in the early 1980s than was pyrazinamide though the latter was gaining in popularity (7).

We aimed to determine how widely the BTS guidelines have been implemented in Scotland by examining data pertaining to treatment of pulmonary TB in adults in Scotland in 1993. We also sought to examine whether changes in treatment or microbiological information had emerged when compared to historical data from the 1980s (7).

Methods

The Consultant in Public Health Medicine for each of Scotland's Health Board areas (to whom notifications of TB are made) kindly supplied us with details of all notified cases of TB in 1993. The named specialist physician responsible for each case was sent a standardized questionnaire designed to determine details of the initial and continuation therapy used, and to establish microbiological details. Questions asked in the questionnaire are presented in the Appendix. In all cases microbiological information was derived from reports issued by the local microbiology laboratory, together with identification and sensitivity testing of Mycobacterium tuberculosis cultures by the Scottish Mycobacteria Reference Laboratory, which also acted as the primary laboratory for the Lothian region.

Several items in the questionnaire were identical to questions posed in previous SRTB Surveys, allowing broad comparisons to be made with data generated up to 1985. The response rate to the questionnaire was 100%.

The derivation of the patient groups studied is illustrated in Fig. 1. In total 369 patients were diagnosed as having TB confined solely to the lungs (as detailed in 8). Eighteen were
399 patients notified with pulmonary TB

18 under age of 15

30—no information on treatment regimen

321 with information pertaining to initial chemotherapy

32 died before continuation therapy started

20—insufficient information regarding continuation therapy

3 lost to follow-up

266 with information pertaining to continuation chemotherapy

Fig. 1. Derivation of the patient groups studied.

under 15 years of age and were excluded from analysis. In 30 of the remaining patients no information relating to treatment was available; in 12 of these the diagnosis of pulmonary TB was made after death, one left the country, and no treatment details were provided for the remaining 17. In keeping with data presented by other groups (7,9) these patients were excluded from analysis, leaving a population of 321 adult patients with a diagnosis of pulmonary TB for whom detailed information was available.

Information pertaining to initial chemotherapy was available for all 321 patients. However, no data were generated relating to continuation therapy in 55 cases—32 died before continuation treatment was considered, insufficient information was available to determine details of continuation treatment in 20 and three were lost to follow-up. Information on continuation treatment was therefore available for 266 patients (Fig. 1).

Patient details were coded numerically to ensure confidentiality, and stored in a computerized registry.

Results

Patients

The median age of the patients was 62 years (range 15-92 years). Two hundred and eighty-seven patients (89.4%) were Caucasian. The ethnic origin of the remaining patients was as follows, Indian sub-continent in 27 (8.4%), African continent in 6 (1.9%), and Chinese sub-continent in one.

Therapy

Initial therapy

The frequency of use of individual drugs in initial therapy is shown in Table 1. The combination of isoniazid and rifampicin comprised part of initial therapy in 316 patients (98.4%). The use of at least three drugs in initial treatment was recorded in 307 patients (95.6%).

The duration of initial treatment was extremely variable. This is exemplified by the duration of initial treatment prescribed for patients receiving isoniazid, rifampicin and pyrazinamide as initial therapy, followed by isoniazid and rifampicin as continuation therapy (the HRZ/HR regimen) shown in Fig. 2. Of the 171 patients receiving HRZ/HR for whom information was available, 103 (60.2%) received the recommended 8 or 9 weeks of initial treatment. However, 11 patients (6.4%) received less than 8 weeks of HRZ, and 57 (33.3%) were prescribed more than 9 weeks of HRZ, of whom 18 (10.4%) were not switched to HR continuation treatment until after 12 weeks. A similar pattern was observed for the other treatment regimens employed (data not shown).

Continuation therapy

The frequency with which individual drugs were used in continuation therapy is shown in Table 2. The combination
TABLE 2. Frequency with which individual drugs were used in the continuation phase of chemotherapy. A total of 266 patients received continuation phase treatment.

<table>
<thead>
<tr>
<th>Drug</th>
<th>n</th>
<th>%</th>
</tr>
</thead>
<tbody>
<tr>
<td>Isoniazid</td>
<td>255</td>
<td>95.9</td>
</tr>
<tr>
<td>Rifampicin</td>
<td>249</td>
<td>93.6</td>
</tr>
<tr>
<td>Ethambutol</td>
<td>28</td>
<td>10.5</td>
</tr>
<tr>
<td>Streptomycin</td>
<td>3</td>
<td>1.1</td>
</tr>
<tr>
<td>Ciprofloxacin</td>
<td>3</td>
<td>1.1</td>
</tr>
</tbody>
</table>

![Fig. 3. Distribution of drug regimens prescribed to patients receiving initial and continuation chemotherapy, n=266. x/E, Drug regimen in which ethambutol featured in continuation therapy. All other abbreviations are as explained in text.](image)

of isoniazid and rifampicin alone was used in continuation in 221 cases (83.1%) for which information was available, while a further 19 patients (7.1%) received these drugs in combination with others.

Continuation therapy could be broadly divided according to individual drugs prescribed, giving rise to five groups, namely HRZ/HR; HRZE/HR; HRE/HR; treatments in which ethambutol featured as part of continuation therapy; and other miscellaneous treatments. The proportion of patients in each group is shown in Fig. 3. A high proportion of patients in each group was treated for longer than the recommended 6-month period (as illustrated in Fig. 4, using the example of patients completing treatment with the recommended HRZ/HR regimen), while a minority received treatment for less than 6 months.

The attending physician considered that chemotherapy was completed as planned in 135 (78.5%) of the patients prescribed the recommended HRZ/HR regimen. Of the remaining 37 patients 13 were still receiving some form of chemotherapy 1 year after diagnosis, 13 died during treatment, five were lost to follow-up, two were non-compliant with treatment, and incomplete information was available on the final four. Satisfactory completion of treatment was achieved in a lower proportion of patients when other treatment regimens were employed: 67.7% for those receiving HRZE/HR, 75.0% for those receiving HRE/HR, 42.9% for the group receiving ethambutol in continuation, and 45.8% for the group receiving other regimens. In total 193 patients (60.1%) among the total population of 321 were considered to have completed treatment as planned.

Sixty-two patients died within 1 year of the diagnosis of pulmonary TB. The mean age of this group of patients was 71.3 years. The majority of deaths were considered to be unrelated to TB. TB was considered to be a primary cause of death in 17 of these patients, for whom the mean age was 71.5 years. Detailed information was available for 10 of these 17 patients. Six had received anti-tuberculous chemotherapy for between 5 and 11 days before death and two had received prolonged, non-standard regimens.

Among patients in whom chemotherapy was completed 18 (9.3%) were said to have required a modification of treatment because of drug toxicity.

**MICROBIOLOGY**

In 36 cases (11.2%) no microbiological samples were received, and in 11 cases (3.4%) no data regarding microbiology were available, leaving detailed information for 274 cases. *Mycobacterium tuberculosis* was identified on both sputum smear and culture in 139 cases (50.8%), on culture alone in 66 cases (24.1%), and by sputum smear alone in 25 cases (9.1%). In total bacteriological confirmation by smear and/or culture was obtained for 230 patients (83.9%) from whom samples were sent. In the remaining 44 cases (16.1%) samples were sent but no bacteriological confirmation was obtained. The rate of microbiological confirmation was higher in patients receiving recommended chemotherapeutic regimens than in those prescribed non-standard regimens.

Drug sensitivity results were available to the attending physician in 194 of the 205 culture positive cases (94.6%). Isoniazid resistance was reported in 12 cases and rifampicin....
resistance in six (representing 5.7% and 2.9% of cases in which information was available, respectively). No cases of combined isoniazid and rifampicin resistance were identified.

Discussion

These data indicate that since the publication of BTS recommendations for the management of pulmonary TB (1) there has been a considerable rise in the use of pyrazinamide as part of initial therapy in Scotland (from approximately 35% of cases in 1985 to around 90% in 1993) with a reduction in the administration of ethambutol (92% in 1985 compared with 20% in 1993). These findings are in keeping with the increased use of pyrazinamide in England and Wales (9,10). However, the prescription of pyrazinamide was already increasing steadily prior to the publication of the BTS recommendations (7,9). The combination of isoniazid and rifampicin remained the backbone of both initial and continuation treatment.

The continued use of ethambutol in 20% of initial therapy may reflect a preference on the part of some physicians to cover the possibility of drug resistance or atypical mycobacteria while awaiting culture and sensitivity results. BTS recommendations suggest incorporating ethambutol where isoniazid resistance is suspected (1). Our data suggests an approximate rate of isoniazid resistance of 6% while almost 20% of patients received ethambutol in initial therapy. Reasons for the high prevalence of ethambutol prescription in continuation therapy remain unclear.

Several comparisons can be made between elements of our data and information generated in Scotland in 1985 by the SRTB survey (7), and in England and Wales in 1988 and 1993 (9,10). It should be noted however that there were small differences in the composition of cases included in these studies. The SRTB survey, unlike this study, included only patients admitted to hospital as part of pulmonary TB management, and among this number included 5% of patients under the age of 15. The BTS study in England and Wales differed from this study in that 36% of patients were non-Caucasian and that patients with no known bacteriological results were excluded from final analysis. However, allowing for these small differences broad comparisons can be made.

A high proportion of patients received chemotherapy for longer than 6 months in Scotland in 1993. This was largely attributable to prolongation of the initial phase of treatment. A similar pattern emerged in England and Wales in 1988 (9). A continued tendency to prescribe 9 months of chemotherapy partly explained the prolonged mean duration of treatment in England and Wales, but this accounted for few cases in Scotland.

Our findings indicate that treatment was completed as intended by the attending physician in only 60% of cases. This compares with a corresponding figure of 59.3% in 1985 (7). Approximately 58% of patients completed therapy as planned in England and Wales in 1988 (9).

The proportion of patients with pulmonary TB who died within 1 year of treatment was higher in 1993 (16.8%) than in 1985 (13.5%). However, a higher proportion of those who died in the 1993 survey were over the age of 65 (data not shown) and it seems likely that the increased death rate simply reflects the more elderly age distribution. The proportion of deaths in which TB was considered a primary cause was higher than in England and Wales (9). Interestingly, in the few cases in which detailed information was available there was a distinct trend for deaths attributable to TB to occur early in the course of treatment. This might imply that technologies allowing earlier diagnosis and treatment (11) may reduce mortality attributable to TB. An alternative inference might be that extra vigilance is required in elderly patients newly diagnosed, and treated, for pulmonary TB.

The incidence of recorded drug toxicity necessitating modification of therapy was lower (9%) than that in England and Wales (14%) (9). A possible explanation for this observation is under-reporting of drug reactions by patients and/or physicians. The current study did not allow for an assessment of whether toxicity contributed to mortality.

The percentage of patients in whom bacteriological confirmation was obtained via sputum smear and/or culture was almost identical to that observed in Scotland in 1985, and slightly higher than in 1983 and 1984 (7). Despite the high rate of microbiological confirmation, the diagnosis of TB was apparently made in the absence of any clinical samples being submitted in over 10% of patients. This compares with a rate of approximately 5% in the 1980s. Furthermore, a high proportion of cases proved to be culture positive but sputum-smear negative, or sputum-smear positive and culture negative, while in 44 cases samples were sent but no bacteriological confirmation was possible. The absence of concomitantly positive smear and culture results may reflect laboratory techniques, insufficient or technically inadequate clinical sampling, or the coincidental use of treatments that might clear M. tuberculosis in clinical samples (e.g. ciprofloxacin or aminoglycosides). In cases where no bacteriological confirmation could be obtained an alternative possibility could have been diagnostic inaccuracy. Where possible clinical samples of high quality should be sent for bacteriological confirmation, not least to prevent emergence of multi-drug resistance in Scotland (12).

Taken together, these data illustrate that the rate of satisfactory completion of treatment, and the rate of microbiological confirmation were no different from rates recorded in Scotland 8 years previously. There has been some movement toward adoption of the drug regimens recommended in published guidelines, but major obstacles still lie in the way of their widespread application. Principal among these are trends for prolonged duration of treatment regimens, continued use of non-standard regimens, and frequent cases in which no clinical samples are sent to the laboratory. Closer adherence to existing guidelines, and increased pursuit of microbiological confirmation appear not only to be practicable, but also highly desirable given that less satisfactory completion of therapy and lack of laboratory data were associated with non-standard drug regimens in this study.
Acknowledgements

The compilation of this study could not have proceeded without the expertise, organization and enthusiasm of G. Leitch who tragically died in 1996. The authors are also grateful to all of the physicians in Scotland who completed questionnaires, and to J. Helliwell who co-ordinated their return—the success of these efforts is reflected in the almost unique response rate of 100%. Thanks are also due to A. Rayner and G. Harris of the Scottish Mycobacteria Reference Laboratory for technical assistance in the processing of clinical samples and sensitivity testing of isolates, and to the Scottish Thoracic Society for its support.

References


Appendix

QUESTIONNAIRE USED

Date of birth
Site of disease
Date of notification or commencement of treatment (whichever was first)

Initial treatment regimen
Was chemotherapy initiated for treatment of TB? Yes/no
Date chemotherapy commenced
Which of the following were used in initial therapy?
- isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, PAS, ethionamide, cycloserine, capreomycin, viomycin, other (please state)
What was duration of initial treatment regimen in weeks?

Continuation phase regimen
Was initial therapy followed by a continuation phase of chemotherapy? Yes/no
If yes, state date commenced
if no, state reason
Which of the following drugs were used as continuation therapy?
- isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, PAS, ethionamide, cycloserine, capreomycin, viomycin, other (please state)
Was chemotherapy continuing 1 year after notification/start of treatment? Yes/no
If no, give date treatment ended or date patient died
If chemotherapy not continuing 1 year after notification/start of treatment, had patient died within the year? Yes/no
If yes, give date of death, and give cause of death in opinion of physician from the following - TB primary cause, TB secondary cause, late effects of TB, death not related to TB.
If chemotherapy not continuing 1 year after notification/start of treatment, was treatment completed as planned? Yes/no
If no, state reason from the following list – patient stopped treatment, physician stopped treatment, patient lost to follow-up, patient died, other (please specify)
If chemotherapy was completed as planned were there any modifications in treatment regimen after initial chemotherapy was commenced? Yes/no

If yes, state reason for modification from the following list – drug toxicity, initial drug resistance, bacteriological relapse during therapy, bacteriological relapse on stopping therapy, default by patient, other (please specify)

Bacteriology

State laboratory used for initial bacteriological confirmation from the following list – Scottish Mycobacteria Reference Laboratory, local laboratory, both, no bacteriology

Was disease confirmed bacteriologically? Yes/no

if yes, was disease confirmed with positive smear? Yes/no

was disease confirmed with positive culture? Yes/no

From the following list state drugs tested for sensitivity, and for each state whether organism sensitive or resistant – isoniazid, rifampicin, ethambutol, pyrazinamide, streptomycin, PAS, ethionamide, cycloserine, capreomycin, viomycin, other (please specify)