Surveillance report

GREAT DIVERSITY OF TUBERCULOSIS TREATMENT IN FINLAND

T Vasankari^{1,2}, M Kokki¹, P Holmström¹, K Liippo², S Sarna³, P Ruutu¹

1. Department of Infectious Disease Epidemiology, Helsinki, Finland

2. Department of Respiratory Medicine, Turku University Hospital, Preitilä, Finland

3. Department of Public Health, University of Helsinki, Helsinki, Finland

We investigated the treatments given and the outcome in a national cohort of culture-verified pulmonary tuberculosis cases in Finland. Our aim was to find out how adequate TB treatment was, and the outcome of treatment. Medical records of all culture-verified pulmonary tuberculosis cases in 1995-1996 were abstracted to assess treatment and outcome, using the European recommendations for outcome monitoring. There were 689 cases, 429 in men (62.3%) and 260 in women (37.7%), mean age 63.1 years. A total of 377 (54.7%) cases were > 65 years old. There were 29 (4.2%) cases in people who had migrated to Finland. Great diversity was observed in treatment combinations and duration. A favourable outcome was achieved in 446 (64.7%) cases. Non-favourable outcomes consisted of defaulting and transfer out (N=33; 4.8%), premature cessation of treatment by a physician (51; 7.4%), or death (132; 19.2%). Treatment was still continuing in 27 (3.9%) cases at 12 months. The outcome categorisation in the European recommendations and the WHO target level for outcome are problematic in a country where the majority of tuberculosis cases are in older people. The diversity in treatment suggests a need for training and centralisation of treatment for the decreasing number of cases.

Introduction

The recurrence of tuberculosis in eastern Europe, the emergence of multidrug resistance (MDR), immigration from countries where tuberculosis (TB) is endemic, as well as transferring from vertical TB control programmes including a special hospital system dedicated for TB treatment and follow-up to programmes integrated in the general health care system call for intensified monitoring of TB programmes in Europe [1]. The components of an effectively functioning control programme are a high case finding rate, a high cure rate, and a low level of acquired resistance [2]. It is also essential to collect up-to-date surveillance data at the international level to identify determinants of failure [1, 3-4].

Outcome monitoring is an integral part of the vertical tuberculosis control programmes, but may be more complex in the new integrated health care systems. The World Health Organization (WHO) and the International Union Against Tuberculosis and Lung Disease (IUATLD) have issued joint recommendations aiming at standardised reporting of the outcome of tuberculosis treatment in Europe [5-7].

The few national cohort analyses of all pulmonary tuberculosis cases that exist have reported favourable outcomes rates ranging between 58%-80% [8-12], and the routine outcome monitoring in European Union (EU) countries since 2001 have reported favourable

outcome rates between 54%-88% [13], with the lowest rates often associated with high rates of loss to follow-up. Little information is available about the compliance with recommendations of TB treatments given.

In Finland, tuberculosis surveillance and care was integrated into the general health care system in 1987. The incidence of tuberculosis has decreased steadily, and was 13 per 100,000 population at the time of the study year, including a high proportion of cases in people aged 65 and over together with a low proportion of cases in people who were born in countries other than Finland [13]. Our aim was to find out how TB is treated in Finland, and what the outcome of treatment is. We assessed the TB treatments given and the feasibility of monitoring treatment outcome according to the European recommendations in a national, population-based two-year (1995 and 1996) cohort of all culture-verified pulmonary tuberculosis cases in Finland.

Material and methods

Study cohort, case definitions and data collection

The method of identifying all culture-confirmed tuberculosis cases in Finland in 1995-1996 (N=1059) has been described

FIGURE 1

Composition of the national study cohort of culture-confirmed pulmonary tuberculosis cases, Finland, 1995-96

TABLE 1

Definitions used in describing the treatment given to the cases in a national cohort of patients with pulmonary tuberculosis

Treatment group	Drugs used in intensive phase	Duration of intensive phase [days]	Drugs used in continuation phase	Total duration of treatment [months]
Standard treatment A	HRZ	At least 54	HR	At least 5.5
Standard treatment B	HRE or HRS	At least 54	HR	At least 8
Standard treatment with short intensive phase C	HRZ or HRE or HRS	Less than 54	HR	At least 5.5 for HRZ At least 8 for HRE and HRS
Standard treatment D	≥ 4 tuberculosis drugs, including HRZ or HRE or HRS	At least 54	HR ± any other anti-tuberculosis drug(s)	At least 5.5 for HRZ At least 8 for HRE or HRS
Other combination of tuberculosis drugs	Non-standard combinations of tuberculosis drugs, excluding the combinations above	NA ²	Any combination of antituberculosis drugs	NA ²
Ineffective treatment	One antituberculosis drug used alone or in combination with a drug with limited antituberculosis activity ¹	NA ²	NA ²	NA ²

1 E.g. fluoroquinolones

2 NA = not applicable

H = isoniazid, R = rifampicin, Z = pyrazinamide, E = ethambutol, S = streptomycin

elsewhere [14]. All culture-verified pulmonary TB cases diagnosed during years 1995 or 1996 were included in the present study. Collection of the cases was implemented first within the national surveillance system with independent mandatory laboratory and physician notification components, and was complemented later by a separate inquiry to each clinical microbiology laboratory in Finland. Data was then retrieved from patient records of 97% of the cases in the cohort, ensuring a standardised assessment by the study team, in contrast to routine outcome surveillance.

A case was defined as pulmonary with a culture finding for *Mycobacterium tuberculosis* in sputum or bronchoalveolar lavage (BAL), or as a culture finding for *M. tuberculosis* from another sample type in a case with sputum smear positive for acid fast bacilli. The final number of the pulmonary tuberculosis cases for outcome evaluation was 689 [Figure 1].

Definitions of treatment

Tuberculosis treatment given to each patient, according to record review, was grouped into six categories [Table 1]. Definitions for the grouping were based on the national recommendations in Finland following the recommendations by WHO, American Thoracic Society and British Thoracic Society [15-20].

Non-standard combinations of tuberculosis drugs of any duration including more than one effective drug were grouped together (other combination of tuberculosis drugs). In the 'ineffective treatment' group, one antituberculosis drug was used alone or in combination with a drug with a limited antituberculosis activity. Interruptions of chemotherapy lasting less than one week were not recorded.

Directly observed therapy short course (DOTS) was seldom used after discharge from hospital. If a case died during treatment, the treatment immediately preceding death determined the treatment group. In cases with a shift to another group during medication, treatment group was assigned according to the final combination given.

Definitions of outcome

The categories of WHO/EuroTB recommendation [7] for outcome monitoring are cure, treatment completed, failure, death, treatment interrupted (default), transfer out, and on treatment at 12 months.

The duration of the follow up period is defined as 12 months from the beginning of the treatment or the date of diagnosis, and the first outcome registered as final.

The WHO/EuroTB 'treatment interrupted' category includes all interruptions, whether caused by a patient or by a treating physician. In order to analyse these two subcategories separately, we divided 'treatment interrupted' into 'physician's decision to stop early' and 'default' for interruptions due to patient only. The outcome was recorded as 'death' if the case died before treatment or during treatment. We included also those dying within 14 days after cessation of antiTB drugs, because the death could be due to side effects in those cases.

Definitions of origin, social and medical risk factors

A case was defined as an immigrant if the country of birth was not Finland or the nationality was other than Finnish. Immunosuppressive treatment was defined as corticosteroid treatment (>40 mg per day of any duration, or any daily dose with duration exceeding one month), cytotoxic or cyclosporine treatment, or irradiation treatment during the preceding year. For inclusion

FIGURE 2

The age and gender distribution of cases, Finland, 1995-96

TABLE 2

Treatment outcome in the study cohort according to the WHO/EuroTB classification, modified for 'default' and 'physician's decision to stop early', Finland, 1995-96

Treatment group	FAVOURABLE			UNFAVOURABLE ¹					On treatment at 12 months	Total
	Cured	Treatment completed	Subtotal	Death	Transfer out	Default	Physician's decision to stop early	Subtotal		
Standard treatment A	87 27.4%	133 42.0%	220 69.4%	64 20.2%	1 0.3%	12 3.8%	12 3.8%	91 28.7%	8 2.5%	317 100%
Standard treatment B	15 26.8%	13 23.2%	28 50.0%	7 12.5%	0	4 7.1%	15 26.8%	26 46.4%	2 3.6%	56 100%
Standard treatment with short intensive phase C	8 24.2%	18 54.5%	26 78.8%	1 3.0%	1 3.0%	1 3.0%	4 12.1%	7 21.2%	0	33 100%
Standard treatment D ²	82 48.0%	37 21.6%	119 69.6%	24 14.0%	5 2.9%	6 3.5%	6 3.5%	41 24.0%	11 6.4%	171 100%
Other combination of tuberculosis drugs	9 12.2%	41 55.4%	50 67.6%	8 10.8%	0	3 4.1%	9 12.2%	20 27.0%	4 5.4%	74 100%
Ineffective treatment	2 18.2%	1 9.1%	3 27.3%	4 36.4%	0	0	2 18.2%	6 54.5%	2 18.2%	11 100%
Overall outcome with any treatment	203 30.6%	243 36.6%	446 67.2%	108 16.3%	7 1.4%	26 3.9%	48 7.2%	189 28.8%	27 4.1%	662 100%
No treatment	NA	NA	NA	24 88.9%	0	0	3 ³ 11.1%	27 100%	NA	27 100%
Total	203 29.5%	243 35.3%	446 64.7%	132 19.2%	7 1.0%	26 3.8%	51 7.4%	218 31.6%	27 3.9%	689 100%

1 There were no failures in the cohort

2 Only one patient had a combination of isoniazid + rifampicin + ethambutol and another drug

3 The treating physician decided not to give any treatment

in the group of social risk factors, a case should have a history of alcohol abuse, unemployment, imprisonment or homelessness. Diabetes was defined as juvenile or adult onset disease on drug treatment.

Ethical review

The ethics approval was acquired from the National Research and Development Centre for Welfare and Health.

Statistical methods

Median age comparisons were calculated using Mann-Whitney U test. For comparison of proportions Chi-square or Fisher's generalised exact test was used. StatXact software version 6.2 (Cytel Software Corporation, MA, USA) was used for statistical calculations.

Results

In the study cohort of 689 cases, there were 429 men (62.3%) and 260 women (37.7%). The mean age was 63.1 years, the median 67. The proportion of cases aged >65 years was 377 (54.7%). The proportion of immigrants was 4.2% (29 cases), mainly from developing countries [Figure 2]. The proportion of those having a risk factor for TB was 13.5% (93), 44.9% (308) and 15.0% (103) for immunosuppressive treatment, social risk factor and diabetes mellitus, respectively. Only two patients in the cohort had TB/HIV-co infection. No prisoners were included.

Treatment given

Tuberculosis chemotherapy was given to 662 (96.1%) of the 689 cases. Half of the cases (317/662; 47.9%) received standard treatment A, 56 (8.5%) received standard treatment B, and one quarter (171; 25.8%) received standard treatment with additional drugs (D) [Table 2]. The median age varied between groups from 55.8 to 82.0 years. In 33 (5.0%) of the cases the intensive

phase was short (category C). A total of 85 cases (12.8%) received either other combinations of tuberculosis drugs or ineffective treatment. Most of the cases (451/662; 68.1%), were treated with the same combination during the whole treatment. Twenty-seven (3.9%) cases were untreated, the majority (24) of whom died before the diagnosis of tuberculosis was established.

Outcome of treatment

A favourable outcome was achieved in 446 (64.7 %) of the cases, consisting of those cured (29.5%) and treatment completed (35.3%) [Table 2]. The proportion with favourable outcome varied between 27.3 to 78.8 % in different treatment groups. There were no treatment failures in the cohort.

The proportion of cases defaulting or transferring out was 33/689 (4.8 %). Among 51 cases treatment was stopped prematurely by physician, the decision being in 36 cases (70.6 %) due to miscalculation or lack of knowledge on the correct recommended duration. Death was the outcome in 19.2 % (132/689) cases, including 27 cases not treated. Death took place in the intensive phase in 62.5% (60/96), and in the continuation phase in 37.5% (36/96) in standard groups A-D.

The proportion of cases with favourable outcome differed between groups ($P=0.029$), and was smallest in treatment groups B and ineffective (50.0% and 27.3%). The proportion of cases for whom the treating physician decided to stop the treatment prematurely differed significantly between groups ($P<0.001$), being larger in group B than in the other groups (26.8% vs. 5.4%). The proportion of deaths differed significantly between groups ($P=0.015$), and was lowest in treatment group C (3.0%). In the ineffective treatment group the proportion of deaths was higher (36.4% versus 10.8% $P=0.045$) than in the other combinations of TB drugs.

TABLE 3

Duration of treatment in different treatment groups and subgroups, excluding cases who died during or within 14 days from the end of treatment, transferred out or defaulted, Finland, 1995-96

Group/subgroup	Total in group	Duration of intensive phase				Total duration of treatment					
		Number analysed	<54 days	54–67 days	>67 days	Short		Standard		Long	
			n (%)	n (%)	n (%)	Cut-off (days)	n (%)	Time range (days)	n (%)	Cut-off (days)	n (%)
Standard treatment A	317	240	3* (1.3%)	130 (54.2%)	107 (44.6%)	<167	11 (4.6%)	167–213	124 (51.7%)	>213	105 (43.8%)
Standard treatment B	56	45	NA	5 (11.1%)	40 (88.9%)	<243	16 (35.6%)	243–304	24 (53.3%)	>304	5 (11.1%)
Standard treatment with short intensive phase C, HRZ	32	29	29 (100%)	NA	NA	<167	3 (10.3%)	167–213	15 (51.7%)	>213	11 (37.9%)
Standard treatment with short intensive phase C, HRE or HRS	1	1	1 (100%)	NA	NA	<243	1 (100%)	243–304	0	>304	0
Standard treatment D/ combination + extra drug(s)	156	124	NA	53 (27.6%)	71 (68.7%)	<167	4 (3.2%)	167–213	25 (20.2%)	>213	95 (76.7%)
Standard treatment D, combination as in HRE or HRS + extra drug(s)	15	12	NA	1 (8.3%)	11 (91.7%)	<243	5 (41.7%)	243–304	5 (41.7%)	>304	2 (16.7%)
Total	577	451	33 (7.3%)	189 (41.9%)	229 (50.8%)	40 (8.9%)		193 (42.8%)		218 (48.3%)	

* Died >14 days after premature cessation of treatment during intensive phase, due to progressive clinical deterioration with severe co-morbidities

H = isoniazid, R = rifampicin, Z = pyrazinamide, E = ethambutol, S = streptomycin

Duration of treatment

Duration of treatment was analysed in groups A to D [Table 3]. The duration of intensive phase exceeded the recommended duration with at least a week in 229/451 (50.8%) cases. The total duration of treatment was short, i.e. < 5.5 months in treatment groups with a recommendation of six months, or < 8 months in groups with a recommendation of nine months, in 40/451 (8.9%) cases. The total duration was long (> 7 months and > 10 months, respectively), in 218/451 (48.3%) cases [Table 3]. The mean duration of treatment was 37 weeks in the group of other combination of tuberculosis drugs.

Discussion

In a large two-year national cohort of culture-proven pulmonary tuberculosis cases, we observed a great diversity of treatments in an integrated TB management system. We also observed that the outcome categorisation in the European recommendations can be improved to better reveal needs for system development or clinical training. The category default is heterogeneous, and for the purpose of implementing corrective measures, it should be divided to two separate categories of default due to patient and due to physician. Furthermore, the target levels presented by WHO on favourable outcomes are problematic in a country where the majority of tuberculosis cases are diagnosed in people 65 years and over, which calls for analysis of outcome in more specific ways than comparing the national annual success rate.

Our data were from years 1995 – 1996 but there have been no significant changes in TB treatment recommendations or treatment system after that in Finland, or the epidemiology TB concerning the proportion of foreign born nor the age-distribution during the past ten years. Mortality for pulmonary TB in 2004 was 18% (unpublished data), identical to study years.

The treatment combinations used in Finland were observed to be variable both regarding the combination and duration of drugs. The long duration of the intensive phase and total treatment in a considerable proportion of the cases was an unexpected finding, because all cases of tuberculosis are treated in the public healthcare

sector, and the great majority of the treatments are initiated and supervised by the approximately 20 pulmonary units of central hospitals. The short total duration of treatment, particularly in our standard treatment group B, may be partly due to the national recommendations not including explicit instructions on the extended total duration of the treatment, when PZA was replaced with another drug [15, 20]. The diversity may also reflect the presence or perceived risk of adverse effects from the drugs in older patients. It is of major concern that in 7% of the cases treated, the treating physician stopped treatment prematurely. Previously published outcome evaluations have very little information on treatment combinations used [12]. In a smaller study from Switzerland, treatment did not conform to recommendations in half of the patients [21].

A striking finding was the high proportion of death as outcome, in almost one fifth of the cases. High proportions of death as outcome, ranging from 6.8% to 21% have been reported from a number of low-incidence countries [9-12, 21-24], where tuberculosis is mainly the disease of the elderly. In those aged 65 and over, it is often difficult to determine the causal relationship between tuberculosis and death. Multiple variables including age, comorbidities and treatment can confound the interpretation of this effect, and we will report this analysis separately. In our study, most of the deaths occurred before or shortly after the initiation of the antituberculosis treatment, which could reflect a delay in seeking care and delay in starting treatment [25], or faster deterioration of vital status in the presence of old age and underlying diseases [26]. Based on the findings of an earlier Finnish study, it is probable that about a third of the deaths in our study were not directly attributable to tuberculosis [27]. From all these findings, it is obvious that the overall 5% targeted proportion for death as outcome by WHO should not be used as an indicator for satisfactory performance in populations, where disease is mainly in older people.

Our findings indicate that the outcome category 'default' [7], incorporates subgroups of very different character and consequence. We divided the 'default' group into two groups: defaulting patient, and a decision by the treating physician to stop

the treatment prematurely. Altogether, these two constituted 77 (11.2%) outcomes, close to the target limit of 10% of unfavourable outcomes set by WHO [2]. Unexpectedly, the physician made the decision to stop treatment prematurely more often than the patient. When a premature decision was taken by the physician, the treatment was commonly of the standard alternative (B), discontinued already after six months, either because of lack of knowledge of the recommended duration or due to miscalculation. In an outcome surveillance system based on notification by the treating physician, the physician would certainly have reported outcome as cured or treatment completed, and the need for strengthening national recommendations and training would be missed. Routine national outcome surveillance systems may be subject to varying interpretation of criteria for outcome categories by multiple notifiers.

Out of the parameters reflecting quality of the tuberculosis control programme in Finland, this national cohort outcome analysis revealed a proportion of favourable outcomes far below the target of 85% set by WHO, mainly due to a high proportion of deaths. On the other hand, there were no treatment failures. Furthermore, rates of *M. tuberculosis* strains resistant to drugs have been very low, and the incidence of tuberculosis in the paediatric and working age population is very low [13]. Of concern is the diversity of treatment combinations and duration observed in the study, requiring further training and specific focus on guidelines.

In conclusion, data from routine, continuous outcome surveillance in integrated health care systems in low incidence countries may be difficult to interpret, and therefore age distribution and comorbidities need careful consideration before making international comparisons or comparisons over time. The complexity of issues affecting outcome in this type of population and the limitations of outcome surveillance in reflecting management practises may make periodic, high quality cohort studies more efficient in supporting the development of national control programmes in low incidence countries than continuous outcome surveillance with varying coverage and representativeness. Our study revealed a need for further training of physicians treating TB, and constituted a major reason for developing and publishing a national TB programme in September 2006 [28].

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