Peer reviewed article

Directly observed therapy for tuberculosis in a low prevalence region: first experience at the Tuberculosis Dispensary in Lausanne

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Summary

Aim: Evaluation of first experience of the directly observed therapy (DOT) programme for tuberculosis introduced in the Canton of Vaud in 1997.

Method: Retrospective analysis of tuberculosis patients included in a DOT programme from October 1997 to March 2000 under the supervision of the TB Dispensary in Lausanne.

Results: 54 patients were included, 49 of whom were new cases and 5 relapses. 70% were asylum seekers and illegal immigrants. The indications for DOT were immigrant status, social problems, and physical or psychiatric comorbidities. Treatment was fully supervised in 67% and partially in 33%. The outcome was favourable (cure or treatment completion) in 88.9% and unfavourable in 11.1%. A similar success rate was observed in full and partial DOT and there was no difference in success rates between the various structures where DOT was administered. By comparison, the success rate in a historical group from the same institution was 70% in 1990.

The biggest problem was communication with the patients and within the team.

Conclusion: Treatment of tuberculosis under DOT in the Canton of Vaud resulted in improvement of the treatment success rate.

Key words: tuberculosis; directly observed treatment; DOT; therapeutic adherence

Introduction

Tuberculosis (TB) is on the decline in Switzerland [1–2]. In 2003 the incidence was 8.6 per 100 000 population per year [3]. Since 1994 the number of cases notified among foreign-born patients, especially asylum seekers from countries with a high incidence, was higher than that observed in the native Swiss population.

Regularity and completeness is paramount in the treatment of tuberculosis, since default, interruption and incorrect dosing may cause failure or relapse and development of drug resistance. The WHO reports worldwide success rates for tuberculosis treatment ranging from 20–87% [4]. Factors influencing the success rate relate to patient adherence but also to the health care system (e.g. adequate case management, drug availability). Several studies have tried to define the factors associated with poor therapeutic adherence eventually resulting in an unfavourable outcome: age, sex and nationality do not usually influence adherence [5]; long and complex treatment, difficult access to health care facilities, communication problems between patients and health partners, physical or psychiatric comorbidities, alcohol abuse or i.v. drug consumption, social marginalisation and relapse after prior TB treatment seem to be risk factors for decreased therapeutic adherence [5–7]. Many authors have proposed methods of improving the control of drug intake, such as blood or urine tests to check the presence of the TB drugs and electronic devices to monitor time of drug intake and improve adherence to TB treatment by educating the patients and their families, incentives (bus fares, meals etc), letters or phone calls to recall appointments [6, 8]. Fixed drug combinations have also been advocated as a means of making treatment less complex [9]. All these methods are effective to some degree when used separately.

Directly observed therapy (DOT) has been promoted as one method of ensuring regular intake of drugs until complete cure. Introduced by Fox in the fifties, the method involves observing the patient taking the drugs [10]. This ensures intake of the full treatment, regular follow-up of patients, early detection of adverse events and immediate awareness of non-adherent patients who fail to keep appointments. For some experts DOT should be offered to all tuberculosis patients [11, 12]. Others consider that its effectiveness has not been proven by controlled studies [13]. Its cost-ef-

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fectiveness has also been questioned, particularly in relation to programmes attaining a high rate of cure and completion. DOT is seldom used in low prevalence countries in Europe and requires highly coordinated teamwork.

In our institution we have been using DOT since 1997 for immigrants and for patients with social problems and physical or psychiatric comorbidities potentially associated with default and non-compliance. We also included all cases in retreatment, with drug resistance or following intermittent treatment (3 doses per week).

The aim of the study was to evaluate experience of the DOT programme in a region with a low incidence of tuberculosis but a high proportion of immigrants and potentially non-compliant patients, in order to study the outcome of treatment in tuberculosis patients on the basis of the duration and location of DOT, and to compare the outcome with data from the period preceding the implementation of DOT.

Method

The DOT programme was introduced in the Canton of Vaud in 1997, under the supervision of the TB Dispensary of the Lausanne University Medical Policlinic. The patients included in the programme were immigrants or patients with severe psychiatric comorbidities (psychosis etc.), alcohol or drug abusers, patients presenting social problems (homeless, illegal immigrants, prison inmates), and HIV-infected patients. We also included all the retreatment cases, the intermittent treatment cases and all drug resistant TB. All patients were treated and followed up according to Swiss guidelines [14, 15]. The inclusion criteria remained the same throughout the study.

Once a patient with tuberculosis was included in the programme the medical staff of the dispensary decided on the type of supervision according to the patient's needs: either supervision entirely at the dispensary (patients visited the dispensary daily to take their TB drugs) or another structure (social health structures with nurses visiting the patients at home or patients coming to the centre, health centres for refugees and asylum seekers and shelters with nurses or social workers supervising treatment, general practitioners, pharmacies, daily supervision by a family member collecting the drugs weekly from the dispensary, drug distribution in prison). We endeavoured to find a structure located near the patient's home or workplace. Many treatments were started in the dispensary and later transferred to another supervision structure if this was more convenient to the patient. Women with small children were usually visited at home by a nurse who could not only deliver DOT to the mother but also preventive chemotherapy to the children. The patients with the worst social and psychiatric problems were supervised only at the dispensary, where we could use the other structures of the institution if patients did not appear in time (our pharmacy and the emergency ward). In all cases of drug distribution by an external structure the dispensary provided overall supervision of treatment. All patients were usually followed up monthly in the dispensary and staff were in regular contact with the other structures to ensure therapeutic adherence. The nurses kept a file on all patients and the type of DOT, and kept a daily record of the doses given. Dispensary nurses phoned or visited patients at the workplace or at home when they missed appointments. We were able to hire interpreters to explain the treatment and role of supervision to some non-French speaking patients. Asylum seekers received bus fare to attend the dispensary. If the nurses discovered other problems (social, financial), they could refer the patients to social workers. In very compliant patients with negative cultures and stable social conditions the treatment was self-administered after the intensive phase.

All the patients who were started in the DOT programme from October 1997 to March 2000 and had ended treatment by March 2001 were included in this retrospective study. Data was collected at least 6 months after completion of treatment. We analysed the patient records and contacted all the supervisors to discuss the problems that had occurred during treatment. We analysed the population included in the study and the treatment outcome in patients treated under full DOT (whole duration of treatment), partial DOT (intensive phase only, i.e. 2 months), and patients treated in a single institution (TB Dispensary) or in other institutions under the Dispensary's supervision.

Definitions

Therapeutic success is the sum of cases *cured* (with bacteriological confirmation) and those who received a *full course of treatment* (without bacteriological confirmation of cure) [16, 17].

The *unfavourable outcomes* are represented by therapeutic *failure* (sputum still positive after 5 months of treatment), *defaulters* (interruption of treatment for more than 2 months), *death* (whatever the cause) and *transfer* (patient transferred out of our health care system leaving us no possibility of ascertaining the result of the treatment). *Relapse* is defined as a new diagnosis of TB in a patient who was declared cured or who had completed a full course of treatment.

Full DOT is treatment supervised throughout its course. Included in this group were patients who received at least 5 doses under supervision during the week and the weekend doses in self-administration. Intermittent treatments (3 times a week) were always administered under full DOT. We define as *partial DOT* the courses with supervision during only part of the treatment, usually the intensive phase.

Statistical analysis

Statistical analyses were performed by GraphPad InStat version 3.05 (GraphPad Software, San Diego, California). Comparison of results between different subgroups and with historical control groups was calculated by Fisher's exact test.

Results

Between 1997 and 2000, 54 patients among the 257 tuberculosis cases notified in the Canton of Vaud (21%) were included in the DOT programme. The patients' demographics are shown in Table 1. Most were asylum seekers or refugees (62.9%) or foreign residents (24.1%) and born either in the Balkans (24.1%) or in Africa (51.8%). The mean age was 31.6 years (range 15–74) (Fig. 1). Of the 203 patients not included in the DOT programme 37 were followed up by the Dispensary and 166 by other medical structures (chiefly general practitioners).

The main comorbidities were 11 HIV infections (including one with cerebral toxoplasmosis), 9 psychiatric disorders, 6 alcohol abusers, 5 pregnancies and 3 IV drug users.

Disease: Types of TB are reported in Table 2. Most patients were smear- or culture-positive (53.7%) and 9.3% were on retreatment. Among new cases, two patients had received preventive chemotherapy. Among the retreatment cases, no patient had received the first course of treatment under supervision. There were 3 cases of resistance to antibiotics, one of which was multiresistant.

The smear- and culture-negative patients had been diagnosed on the basis of clinical and radiological criteria.

Treatment: Treatment was administered according to the usual recommendation of 2 months' intensive phase with HRZE (H = isoniazid, R = rifampicin, Z = pyrazinamide, E = ethambutol) and 4 months' continuation with HR, and was adapted if necessary according to drug sensitivity, side effects and contra-indications. The mean duration of treatment was 6.5 months. Seventeen treatments were longer (maximum 21 months), chiefly due to use of second line antibiotics (resistance, side effects) or concomitant HIV infection. Six treatments were shorter (1–5 months), due to default, death or transfer.

Supervision: Supervision was complete in 36 cases (67%) and partial in 18 cases (33%). The proportion of patients under partial DOT increased from 22.2% in 1997 to 36.4% in 2000. Mean duration of supervision was 4.6 months.

The indication for DOT was chiefly social status (refugee, asylum seeker, illegal immigrant) (74%) and language problems which were often associated conditions. Patients under intermittent therapy, retreatment, drug-resistant TB, smear-positive cases who left hospital before sputum became negative, and patients who had been non-adherent during previous treatment or during hospitalisation were always included in the DOT programme. Several associated conditions such as HIV infection, psychiatric disorders, alcohol or drug abuse were also indications for DOT. Many patients had more than one indication.

For 27 patients DOT was administered only by the Dispensary, 10 by both the Dispensary and another structure (pharmacy, family, prison, social health structures), 13 by social health structures only and 4 by other structures (general practitioners, asylum seeker centres).

Treatment outcome: Overall the outcome was favourable in 48 patients (17 cured and treatment completed in 31) i.e. 88.9% of cases. There were 6 unfavourable outcomes (3 defaulters, 2 transfers out and 1 death) i.e. 11.1% of cases. There were no treatment failures. During the 3½ years of the

Table 1
Demographics of 54 patients under DOT.

Demographics	%
Patients	100.0
Males	57.4
Females	42.6
Birthplace	
Switzerland	5.6
Balkan countries	24.1
Other European countries	3.7
Africa	51.8
South America	5.6
Asia	9.2
Immigration status	
Swiss nationality	5.6
Foreign residents	24.1
Asylum seekers and refugees	62.9
Illegal immigrants	7.4

Figure 1
Age distribution of patients treated under DOT, by gender.

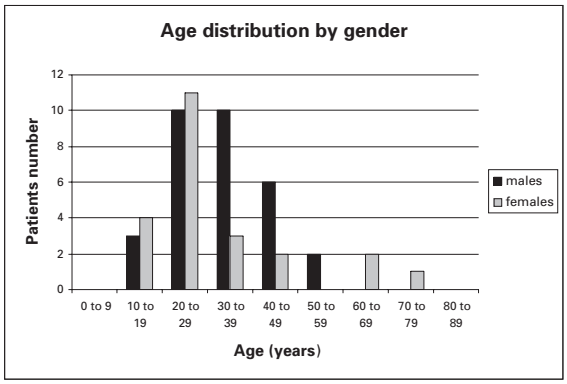

Table 2
Type of tuberculosis among 54 patients under DOT.
S = smear,
C = culture

Type of TB	%
New cases	
S+ pulmonary	33.3
S-/C+ pulmonary	14.8
S-/C- pulmonary	25.9
Extrapulmonary	16.7
Retreatment	
S+ pulmonary	3.7
S-/C+ pulmonary	1.9
S-/C- pulmonary	0
Extrapulmonary	3.7

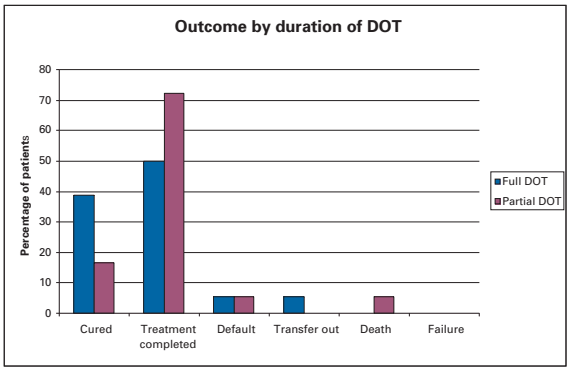

Figure 2
Outcome of treatment by duration of DOT.
Full DOT = whole duration of treatment. Partial DOT = intensive phase only. Favourable outcome (cured and treatment completed) is similar for both groups (88.9%), with no statistical difference (p = 1.00).

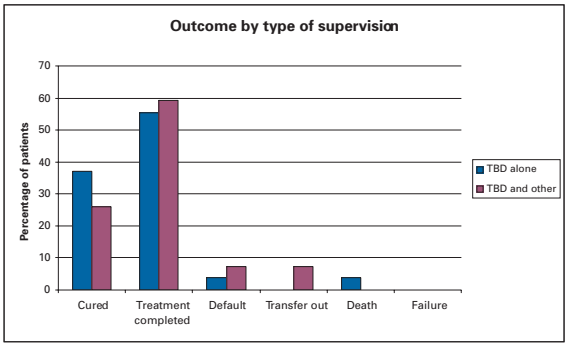

Figure 3
Outcome of treatment by type of supervision.
TBD alone = DOT administered only by TB Dispensary.
TBD and other = DOT administered by TBD and other structures (social health structures, asylum seeker health centres, pharmacies, general practitioners, families, prison etc).
Favourable outcome (cured and treatment completed) is 92.6% for TB Dispensary alone and 85.2% for TBD and other structures, with no statistical difference between the two groups (p = 0.67).

study we observed one relapse. All cases in retreatment and the patients with drug-resistant TB were treated successfully.

A similar success rate was observed in the partial and full DOT groups (Fig. 2). There was no statistical difference between the two groups (p = 1.00).

Allocation of patients to the two successful categories "cured" and "treatment completed" depends on the result of the initial bacteriological examination. The proportion of patients cured and treated completely differs between the two groups because more patients with culture- or smear-positive TB were included in the full DOT group.

The success rate in the group supervised by the TB Dispensary alone was 92.6% vs 85.2% in the group supervised by TB Dispensary and other structures (Fig. 3). This difference was not statistically significant (p = 0.67).

The 2 patients transferred out had very good therapeutic adherence during the initial phase of treatment. They had to leave Switzerland and received sufficient antibiotics to complete the treatment in their own countries.

The 4 other unfavourable outcomes had several associated conditions such as HIV infection, severe psychiatric disorders, alcohol and drug abuse or other social problems (imprisonment). In two cases the patients disappeared and could not be traced.

Discussion

According to the World Health Organization a TB programme should attain a success rate of more than 85% [16, 18]. In low-endemic countries the target is even higher and aims not only to lower TB incidence but eventually eliminate the disease; the rate of unfavourable outcomes should be under 10% after exclusion of death cases [19].

A programme should provide adequate case finding and diagnosis, health care accessibility, a continuous drug supply, regular follow-up of patients to ensure therapeutic adherence and a record of the outcome (all these conditions are summarised under the acronym DOTS). After analysis of many programmes which did not reach the WHO target, consideration was given to ways of improving adherence [5–7, 10–12, 20–22]. Directly observed therapy has been introduced in numerous TB programmes to enhance adherence and so increase the success rate.

In Switzerland DOT was first considered unnecessary in view of the highly developed health care system and as an intolerable limitation of patients' rights. Several studies in the nineties revealed that the WHO target of 85% was not being reached: the success rate was 70% in the Canton of Vaud [23] and 71% in Zurich [24]. An overall success rate of 79% was observed in 1996 but the rate was much lower (54%) among illegal immigrants [25]. In some studies asylum seekers were also associated with a lower success rate [23, 26]. In view of these results, DOT was proposed to ensure adherence in some patient groups considered at higher risk of decreased adherence, i.e. chiefly immigrants and patients with social or psychiatric comorbidities [14, 15, 27]. A first study analysed the results of a DOT programme introduced in the Canton of Zurich between 1991 and 1993, for the population considered at high risk of non-adherence [28]. The success rate increased from 59% in the first year to 73% in the third year of the study. Implementation of this new programme gradually became more effective, though not reaching the WHO target.

Our study shows that implementation of a DOT programme is possible in a population considered at risk of decreased adherence. The success rate in this group (88.9%) reaches the WHO target of 85% and even the target for low-incidence countries after exclusion of death cases (90.6%).

The treatment results of the 203 patients not included in the DOT programme were not known. As the study was retrospective and there is no provision for systematic recording of the outcome of treatment in Switzerland, the patients treated out-

side our institution by other doctors could not be traced and we did not have sufficient information on follow-up of the patients treated in our institution without DOT. Moreover, these patients had different demographic characteristics and so could not serve as a valid comparison. We therefore had to rely on historical comparison with the results obtained from former studies performed locally. The staff, the treatment and the characteristics of the patients in this historical comparison bore a closer resemblance than the group of patients treated in the Canton of Vaud without DOT during the period of the DOT study. The outcome of treatment under DOT is superior to the historical results previously obtained in the same region [23] (success rate 88.9% vs 70%). This difference was statistically significant ($p = 0.007$). The success rate was enhanced under DOT with an odds ratio of 3.43 (95% CI 1.35–8.73).

Coulon's study pointed to several difficulties with the treatment of immigrants. With the DOT programme, patients who are often unstable (language problems, frequent changes of residence, financial difficulties) were followed more closely, wherever possible with the help of interpreters, and this contributed to an increase in the success rate. The awareness of the risk factors for non-adherence and the need for better and closer follow-up of these patients resulted in an improved outcome not only within the migrant population but also in other groups (e.g. subjects with psychiatric disorders or alcohol or drug abusers).

Several studies in other countries have analysed the impact of DOT on the outcome of TB treatment. The results are divergent. In some randomised studies the outcome is no better with DOT than with self-administered treatment [13]. Zwarenstein in rural South Africa reported no advantage from DOT [29]. However, the success rate in that study was very low in both DOT and self-administered treatment and we may therefore presume that other factors influenced these results [30]; for example, there was no recall for patients in the DOT group who missed an appointment. In Pakistan, the outcome in patients supervised by health centres or family members was similar to that in self-administered treatment [31]. On the other hand, American [32, 33] and other Asian [34, 35] studies report a significant increase in success rate after implementation of DOT (25–55% before DOT compared to 70–90% with DOT programmes) and also a significant decrease in relapse rate and resistance to antibiotics [36, 37].

Many authors insist on the fact that to increase adherence [8, 38] the programme must be tailored to patients' needs. In our programme we endeavoured to adjust the type of supervision and its duration to the needs of the patient. Most patients were supervised throughout treatment. For a third of them we stopped supervision earlier, usually at the end of the intensive phase, when the first part of the treatment had been followed without major difficulties and with good adherence. We continued to follow up these patients monthly at the dispensary. The final outcome in this group was the same as the group supervised throughout treatment (success rate 88.9% in both groups), with no statistical difference between the two groups. This suggests that it would be possible to taper off supervision in a selected number of patients without unfavourable consequences for the outcome. However, as described in an American study [37], we must be aware that this involves a risk of lowering the success rate. In this study, the success rate of partial DOT was only 78–82% vs 85–87% under full DOT.

We found no statistical difference between the different types of supervision (TB Dispensary alone vs TB Dispensary and other structures). The other structures could not be analysed separately since the number of patients followed in each structure was too small.

The biggest problem was communication. Not only communication with the patients, most of whom did not speak French, but also within the health care system. This led to errors in therapeutic regimen and some brief treatment interruptions because the Dispensary and the external structures omitted to transmit information. One pharmacy did not report bad adherence to the Dispensary and one patient was lost to follow-up. Eight patients were irregular in their visits to the Dispensary. After phone calls or visits by the nurses at the patients' workplace the situation improved and treatment could be continued. The use of incentives (for instance bus fare to travel to the dispensary), and the involvement of interpreters and social workers if other problems occurred (financial etc) helped to follow up patients and continue treatment not only with regard to TB therapy but psychosocial conditions.

The unfavourable outcomes included two transfers. These patients adhered well to DOT at the beginning of treatment and left Switzerland with a sufficient supply of drugs to complete the treatment in their own countries. Considering the good adherence at the beginning, we can assume that they have continued to take their drugs, in which case the success rate would even attain 92.6%. The other four unfavourable outcomes were in patients who had multiple other somatic or psychiatric disorders, alcohol or drug abuse and social problems. Awareness of these problems should prompt staff to follow up these patients even more closely and endeavour to help them not only to take their drugs but if possible also with their other problems. For example, one alcoholic patient was hospitalised after irregular Dispensary follow-up of simultaneous treatment for TB and alcohol cessation, and the treatment was eventually successful. In nearly all cases the unfavourable outcomes seem to be due to factors other than defects in the programme itself (death from HIV complications, severe psychiatric disorder, illegal immigration, judicial problems). Only in one case may the lack of rapid communication between pharmacy and dispensary have contributed to inadequate follow-up of a patient.

As the overall TB incidence is declining in

Switzerland and the disease is increasingly diagnosed only in groups of patients from high-endemic countries or with comorbidities such as HIV, there is a danger that the general practitioner will experience difficulties in managing the patients under treatment. The role of specialised TB centres which can supervise programmes, update guidelines and deliver regular information is crucial in this situation [39].

Another problem we met with during the study was a lack of information on the outcome of treatment. TB is an infectious disease notifiable by law, and hence all cases occurring during the study period were recorded. Though in the Dispensary the nurses recorded drug intake daily, this was not done as systematically in the other structures. In some cases we had only oral information from the supervisors about completion of treatment. To improve follow-up of patients, it may be useful to record adherence and treatment outcome more systematically.

Conclusion

The implementation of DOT in selected TB patients in our country is possible by use of the pre-existing medical and social structures, and may improve the success rate of TB treatment. Under the DOT programme the TB treatment success rate reaches the WHO target. DOT was not only watching the patients as they swallowed their drugs but also pursued a policy of following patients on an overall basis and identifying problems (in relation to the disease, the treatment or patients' social or financial situation) which may interfere with TB treatment. DOT can be used in programmes which focus not only on TB treatment but also on the medical and psychosocial history of the patients, and can be tailored as far as possible to the patient's needs.

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Erratum

In issue 29–30 (Swiss Med Wkly 2004;134: 430–4), we regret that, by error, the article "Oguzulgen IK, Ozis T, Gursel G. Is the fall in platelet count associated with intensive care unit acquired pneumonia?" was given the wrong category heading. The correct heading is not "Short communication" but "Original article". We apologize to the authors for this oversight.

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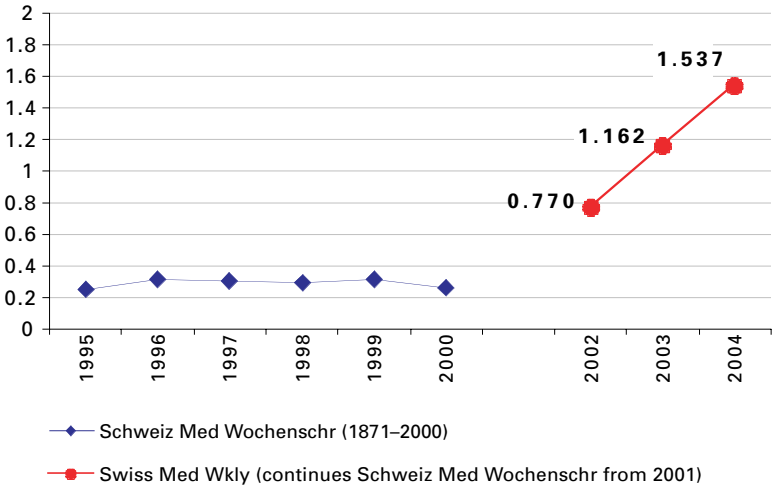

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