Annals of Clinical Microbiology and Antimicrobials

Research

Antituberculosis drug resistance patterns in two regions of Turkey: a retrospective analysis

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Published: 16 December 2002

Annals of Clinical Microbiology and Antimicrobials 2002, **1**:6

Received: 11 October 2002
Accepted: 16 December 2002

This article is available from: http://www.ann-clinmicrob.com/content/1/1/6

Abstract

Backround: The emergence of *Mycobacterium tuberculosis* strains resistant to antituberculosis agents has recently received increased attention owing largely to the dramatic outbreaks of multi drug resistance tuberculosis (MDR-TB).

Methods: Patients residing in Zonguldak and Kayseri provinces of Turkey with, pulmonary tuberculosis diagnosed between 1972 and 1999 were retrospectively identified. Drug susceptibility tests had been performed for isoniazid (INH), rifampin (RIF), streptomycin (SM), ethambutol (EMB) and thiacetasone (TH) after isolation by using the resistance proportion method.

Results: Total 3718 patients were retrospectively studied. In 1972–1981, resistance rates for to SM and INH were found to be 14.8% and 9.8% respectively (n: 2172). In 1982–1991 period, resistance rates for INH, SM, RIF, EMB and TH were 14.2%, 14.4%, 10.5%, 2.7% and 2.9% (n: 683), while in 1992–1999 period 14.4%, 21.1%, 10.6%, 2.4% and 3.7% respectively (n: 863). Resistance rates were highest for SM and INH in three periods. MDR-TB patients constituted 7.3% and 6.6% of 1982–1991 and 1992–1999 periods ($p > 0.05$).

Conclusion: This study demonstrates the importance of resistance rates for TB. Continued surveillance and immediate therapeutic decisions should be undertaken in order to prevent the dissemination of such resistant strains.

Background

Infection with *Mycobacterium tuberculosis* is a current global health problem [1]. Following a constant decrease in the attack rate of this disease in developed countries during the past decades, a marked increase in its incidence has been recently recognized worldwide [1,2]. The emergence of multiple drug resistant tuberculosis (MDR-TB) is of great concern. Epidemiological studies for the assessment of local resistance rates and the detection of MDR-TB are therefore crucial in order to optimize empiric drug therapy and to prevent the dissemination of resistant strains in the community.

The emergence of *M. tuberculosis* strains resistant to antituberculosis agents has recently received increased attention owing largely to the dramatic outbreaks of MDR-TB [1,3]. These outbreaks have been characterized by delayed diagnoses, inadequate treatment regimens, high mortality, and significant rates of nosocomial transmission [4]. Drug resistance may occur, the latter as a result of inappropriate regimens prescribed by providers, or of non-compliance by patients [5].

Our aim was to study the prevalence of MDR-TB cases and the patterns of resistance to anti-TB drugs in two regions of Turkey, to find out and the difference between three decades, in 1972–1999.

Methods

The study was conducted in Zonguldak and Kayseri, the northwest and central regions of Anatolia in Turkey, respectively. TB cases registered to the Tuberculosis Dispensary in Zonguldak and Tuberculosis Hospital in Kayseri were enrolled to this retrospective study. TB control system and health care system for TB referrals did not change significantly in Turkey during the last 30 years except therapeutic approach to these patients.

In 1996 treatment regimens have changed substantially in; (*1*) allocation of multiple drug regimens and (*2*) utilization of short-course supervised chemotherapy. This survey marks the disappearance of "conventional" 18-month chemotherapy of TB disease with INH-RIF-SM or INH-EMB. All programs now use shorter-course therapies of 6 to 9 mo in duration, except under "special" circumstances that are usually related to poor compliance or initial drug resistance.

Patients

All enrolled cases were adults who are older than 18 years residing in Zonguldak and Kayseri provinces with culture-proven *M. tuberculosis* disease diagnosed between 1972 and 1999. Data was broken down into three period categories and resistance rates at 10-year intervals were analyzed. Risk factors for drug resistance could not be evaluated as there was insufficient data in the charts.

Characterization of mycobacterial isolates

The analyzed *M. tuberculosis* strains were isolated at the TB Laboratory in central laboratory for the Zonguldak, Kayseri TB Hospital laboratory and the National Reference Laboratory (Institute of Refik Saydam Hifzisihha) in Ankara. The species identification of the isolates was based on standard microbiological tests: colony morphology, acid-fast staining, and biochemical tests [6].

Drug susceptibility testing

Culture positivity for *M. tuberculosis* for each patient had been recorded in data files. Data regarding the source of the culture as well as drug susceptibilities were obtained from the archives. Identification of *M. tuberculosis* was performed based on standard physical and biochemical characteristics. Samples were inoculated on Lowenstein-Jensen media and incubated at 37°C in 5–10% CO2 atmosphere for 8 weeks. Positive cultures were identified following the guidelines of conventional methods [6]. Susceptibility tests were performed using the resistance proportion method for INH, RIF, SM, EMB and TH; strains were considered highly resistant if the same growth was observed on Lowenstein-Jensen medium containing the following drug concentrations, respectively: 0.2–1 μg/ml, 40 μg/ml, 4 μg/ml, 2 μg/ml and 2–4 μg/ml. All susceptibility analyses were performed in the same laboratories for Zonguldak and Kayseri. To detect TB drug resistance proportional method was used and it has not been changed during study period (1972–1999).

Resistance in new cases (primary) was defined as in vitro resistance in patients who did not have a history of anti-TB treatment, while retreatment resistance (secondary) was defined as in vitro resistance in patients previously treated with any anti-TB medication.

Definition

The definition of MDR-TB cases recommended by WHO and IUATLD is the pattern of drug resistance to at least INH and RIF. Resistance to several agents except these agents was referred to as poly drug resistance TB (PDR-TB) [7].

Statistics

The statistical evaluations were done using SPSS 9.0 software (SPSS Inc., Chicago, IL, USA). The results were given as the percentage and prevalence, and were assessed by Chi-square test. Significance was taken as a p value of <0.05.

Results

Total number of TB patients included was 3718. Two-thousand-seven-hundred-sixty-one culture proven TB cases were registered in Zonguldak Tuberculosis Dispensary, 957 TB patients were registered in Kayseri Tuberculosis Hospital. Patients were primarily men (74.5%) with a median age of 35 year (range: 20–78) in two regions.

Anti-TB drug susceptibility test results according to number of drugs were given in Table 1. MDR-TB constitutes 7.3% and 6.6% of all the isolates in 1982–1991 and 1992–1999 periods. But single drug resistance was higher in 1992–1999.

Table 1: Drug resistance patterns according to number of drugs and MDR-TB status.

	1972–1981 (n = 2172)		1982–1991 (n:683)		1992–1999 (n:863)		1972–1999 (n:3718)	
Resistance	n	%	n	%	n	%	n	%
One drug	319	14.7	100	14,6	278	32,2	713	19,1
Two drugs	96	4,4	47	6,8	18	2,0	166	4,4
Three drugs	-	-	19	2,7	28	3,2	57	1,5
More than three drugs*	-	-	13	1,9	11	1,2	24	1,5
At least one drug	415	19.1	179	26,2	335	38,8	929	25,0
PDR-TB	108	5,0	29	4,2	0	0	137	3,7
MDR-TB*	-	-	50	7,3	57	6,6	107	6,9

* Susceptibility test to RIF, EMB and TH had been performed after 1982 (n: 1546)

Table 2: Total anti-tuberculosis drug resistance for the study period.

	1972–1981 (n = 2172)		1982–1991 (n:683)		1992–1999 (n:863)	
Drugs	n	%	n	%	n	%
SM	322	14.8	99	14.4	182	21.1
INH	213	9.8	97	14,2	125	14.4
RIF[1]	-	-	72	10.5	92	10.6
EMB[1]	-	-	19	2,7	21	2.4
TH[1]	-	-	20	2.9	15	3.7
Total	535	24.6	179	26.2	335	38.8

1: Susceptibility test to RIF, EMB and TH had been performed after 1982 (n: 1546)

INH resistance rates were increased after 1982. Also, SM resistance rates were increased after 1992. TH resistance rates were found to be higher in 1992–1999, but there was statistically difference between two decades ($p > 0.05$). RIF and EMB resistance rates were similar in 1982–1991 and 1992–1999 periods. (Table 2)

Among patients with at least one drug resistance high resistance rates were reported for SM (16.2%) and INH (11.6%). The resistance rates to at least one drug were increased significantly between three periods ($p < 0.05$).

In Figure 3 totally primary and secondary drug resistance were shown. There was significantly increasing in primary and secondary resistance ratio in 1992–1999 period ($p > 0.05$).

Discussion

A third of the world's population is estimated to be infected with *M. tuberculosis* [8]. Recently MDR-TB has increased from an occasional infection to outbreak proportions. The WHO's global surveillance for anti-TB drug resistance from 1994 to 1997 had reported high resistance to anti-TB drugs in 35 countries including Argentina, Asia, the Dominican Republic, and the former Soviet Union. From 1998 to 1999 alone, there were repeated reports in the medical literature of MDR-TB in countries like Australia, Azerbaijan, Canada, Estonia, Ethiopia, Guatemala, Hungary, India, Kenya, Korea, Russia, Scotland, Taiwan, Thailand, The Netherlands, and West Africa [9,10]. Although MDR-TB patients are an epidemiologic threat to the community in Turkey [11], it is not easy to improve the management significantly.

One study evaluated the resistance of the microorganisms to primary anti-TB drugs over the 21 years period in Turkey. It was found that 60.8% of the isolated strains were susceptible, whereas 39.2% were resistant to at least one drug. MDR-TB was found in 194 (5.8%) materials. Over the 21 years period studied, total resistance to INH, RF and SM were determined as 10.5%, 6.9% and 7.0%, respectively [12]. The single drug resistance rate reported in this study is much higher than in our survey (39.2% versus 25.0%). MDR-TB and INH resistance rates are approximately correlating to our results, but SM and RIF's resistance rates lower than our rates (Table 2).

Recently, Cohn et al performed a Medline search of the worldwide literature between 1985 and 1994 for the results of antimicrobial susceptibility testing of *M. tubercu-*

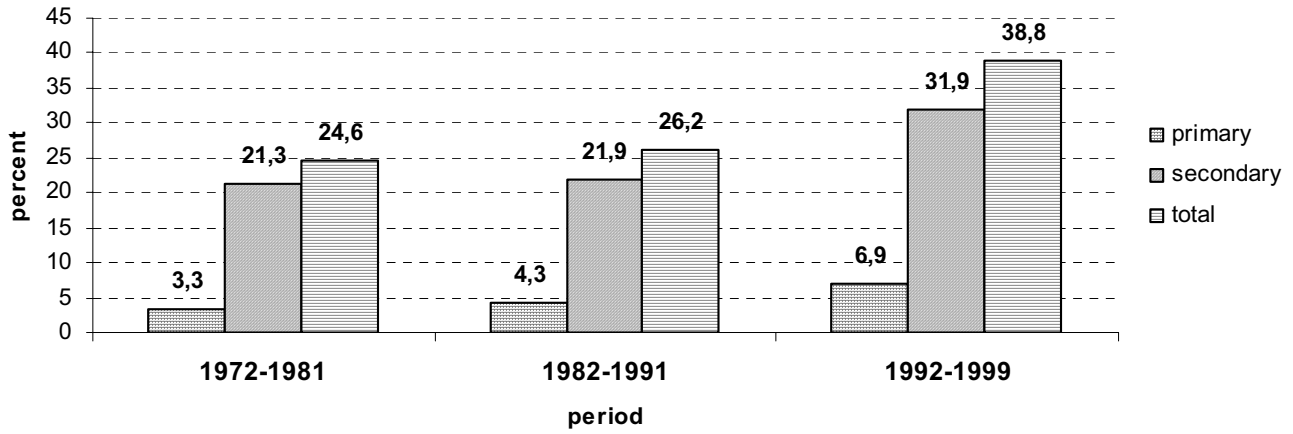

Figure 1
Primary and secondary resistance of all drugs according to period.

losis isolates [13]. They found that the highest rates of MDR-TB were reported from Nepal (48%), Gujarat, India (34%), New York City (30%), Bolivia, and Korea (15% each). In our retrospective study, MDR-TB patients constituted 7.3% and 6.6% in 1982–1991 and 1992–1999 periods respectively and resistance rates to at least one drug were 19.1%, 26.2% and 38.8% in three periods. MDR-TB rate could not be calculated as data of RIF's resistance is unavailable for 1972–1981 periods (Table 1). Additionally, the data of one, two, three drug resistance rate in 1972–1981 period compared to other two periods was insufficient because of different kinds of drug resistance were detected.

According to the Centers for Disease Control and Prevention, when INH resistance rates are > 4%, quadruple empiric therapy with INH, RIF, PZA and EMB or SM is indicated [14,15]. As INH resistance rates were > 4% overall in both study periods, quadruple empiric therapy at least is indicated for every suspected or diagnosed TB case in our populations. In our study resistance rates to INH were 11.6 % (Table 2) and resistance rates to SM were 16.2%. Thus in both regions SM should not be preferred as the fourth drug of choice in four drug regimens. Instead EMB might be chosen.

Both primary and secondary drug resistance may occur, the latter as a result of inappropriate regimens prescribed by providers, or of non-compliance by patients [5]. We differentiate between primary and secondary resistance totally in three periods (Figure 1). In a Mexican study primary resistance was found to be higher than previous report. However, acquired resistance was similar [16]. In our study primary and secondary resistance rates were higher in 1992–1999 periods. The prevalence of primary and secondary resistance in our country has been studied [11,17]. Our data was similar with these Turkish reports. However, secondary drug resistance is a measure of the quality of a TB control program and should be vigorously sought and reported. Continued surveillance in the next few years is warranted.

In Turkey, the majority of the patients are diagnosed as being TB by a positive acid-fast bacilli stain and most of the cases are confirmed by culture. Many patients have adequate access to health care and health care facilities. However some of the regions of Turkey do not possess the appropriate infrastructure (for example they are deficient in trained staff or simply lack the appropriate microbiologic laboratories) to allow accurate and rapid isolation and susceptibility testing. It is important to improve microbiologic laboratories around the country as well as expand resources and education in order to enhance the quality of treatment programs for all patients. In this manner, the incidence and development of drug resistant cases may be decreased. Additionally, directly observed therapy (DOT) is not available currently in Turkey, we think that implementation of good programs might have played a role in decrease in anti-TB drug resistance rates. A reasonable solution would be to develop a national specialized

unit or team for the treatment of MDR-TB, as recommended in the WHO guidelines for the management of drug-resistant TB [18,19].

In conclusion, although MDR-TB patients are an epidemiologic threat to the community, it is not easy to improve their management significantly. Continued surveillance and immediate therapeutic decisions should be undertaken in order to prevent the dissemination of such resistant strains to the general population.

Abbreviations

MDR-TB: multi drug resistance tuberculosis

PDR-TB: poly drug resistance TB

INH: isoniazid, RIF: rifampin, SM: streptomycin, EMB: ethambutol and TH: thiacetasone

WHO: World Health Organization,

IUATLD: International Union Against Tuberculosis and Lung Disease

Authors' contributions

LK had primary responsiblity for protocol development, patient screening, enrollment, outcome assessment, preliminary data analysis and writing the manuscript. AL and MT participated in the development of the protocol and analytic framework for the study, and contributed to the writing of the manuscript. IG contributed as AL and MT, and was responsible for patient screening. SFO, HMA and FE supervised the design and execution of the study, performed the final data analyses and contributed to the writing of the manuscript.

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