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RETROSPECTIVE STUDY OF MEASURING TUBERCULOSIS THERAPY COMPLIANCE: GREECE AS A HOST COUNTRY FOR VULNERABLE POPULATIONS BEFORE AND DURING THE FINANCIAL CRISIS

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ABSTRACT

Background: For the realization of "2015 UN Millennium Development Goals", a question arises pertaining to the course of tuberculosis in Greece and its relationship to patient adherence to treatment, given the fact that the country is undergoing a financial crisis and is a gateway for economic migrants. **Methods:** The study concerned 1179 patients of the anti-TB department, "Sotiria" General Chest Diseases Hospital, Athens, Greece collaborating with the National Reference Centre of Mycobacteria, covering a year before the financial crisis, 2007 and 2010-11, the first years of the crisis. A special recording form was used, on the basis of a specific protocol. **Results:** Out of 954 patients were diagnosed with tuberculosis disease, 657 of which were foreigners. Out of 791 patients residing in the same area, 632 were foreigners. Of the patients who proceeded to a first self-discontinuation of the medication, only 38.3% (n=18) completed the treatment, while 40.4% of them self-discontinued within the first month. Duration of treatment was 6.68 ± 3.54 months for those (n=805) with no discontinuation and 7.48 ± 3.68 months for those (n=149) with at least one discontinuation, regardless of the etiology $p = 0,032$. Cases increased during financial crisis, with gradual decrease in mean treatment duration for patients with first line treatment to 7.77 ± 3.81 months in 2007, and 6.53 ± 3.47 and 6.40 ± 3.31 months in 2010 and 2011, respectively. **Conclusions:** Since the beginning of treatment measurable signs of either adherent/non-adherent behavior appeared, affecting mean treatment duration and completion. Duration of treatment decreased in the years of financial crisis. Migrants ghettoization calls for implementation of DOTS.

Key words: Tuberculosis, DOT, migrants, adherence, treatment completion, ghettoization, financial crisis.

1. INTRODUCTION

As ascertained by the United Nations High Commissioner for Refugees, due to its geographical location, Greece serves as a gateway country and an escape path for economic migrants coming from areas of low socioeconomic status (1) and on their way to Europe (2, 3). WHO in its "Global tuberculosis report 2013" states that the efforts to fulfill the "2015 UN Millennium Development Goals (MDGs)" by 2015 seem to be successful (4). At the same time point—May 2010—Greece is undergoing financial difficulties, with a large budget deficit. In order to

meet its borrowing needs, it signs a Memorandum of Understanding with the IMF, the European Union and the ECB (5). The two major mechanisms through which financial crisis affects infectious diseases relate to: firstly, the reduction of national revenues and personal income resulting in lower health care and social welfare expenses; and secondly, to increased poverty and anxiety creating more numerous high risk groups for infectious diseases (6, 7). With the financial crisis still present, the vulnerable population groups are more affected as the price of the crisis becomes larger (8).

In its “Adherence to Long-Term Therapies—Evidence for Action, 2003” report WHO points out that non-adherence patient of patients to long term therapies is a serious problem worldwide and for developed countries it reaches 50% (9). In the Oxford dictionary, “adherence” is defined as “obedience to the rules or requests posed by an authority’s people” (10). In the healthcare domain it concerns a patient’s compliance with taking medication and following the treating physician’s instructions (11). In studies it has been shown that long term treatment has an adverse effect on adherence (12, 13, 14) and so do medication side effects (15).

Under these circumstances, a question is posed regarding the course of tuberculosis in Greece and its correlation with patient adherence to treatment, the answer being searched through an effort for a retrospective measurement of the disease.

2. MATERIALS AND METHODS

The present retrospective study was carried out in the Out-patient Unit of the Treatment Section of the Anti-TB Department of “Sotiria” General Chest Disease Hospital of Athens which falls under the Ministry of Health, in the 1st Health Region of Attica.

Usually the patients have been previously hospitalized in a clinic, where they have been diagnosed with tuberculosis and treatment has been initiated. Upon discharge, they are referred to the anti-TB department where they pay scheduled visits at regular intervals in order to receive follow-up care by the treating physician and to have scheduled laboratory tests, mainly of blood, urine and sputum as well as imaging ones. The data source for the study were the patients’ records in the Anti-TB Department for the years 2007, 2010 and 2011 (284, 484 and 432 in number, respectively) and the accompanying hospitalization records from the clinics for previously hospitalized cases, which are estimated to comprise approximately 75% of the total of cases. As for the years selected, 2007 was the year prior to financial crisis, for which the patients had all completed their treatment when data collection started, while 2010 was the year when financial crisis broke out and 2011 was the first full year within the financial crisis. Data collection was carried out from September 2010 to December 2012. A recording form was specifically prepared/ designed to be used as a tool for the collection process in the study. In all, there were recorded the demographic data, and data about the foreign patients’ residence time in Greece and their ability to communicate. As regards the disease (16), diagnosis and duration of treatment were recorded and occurrence time, frequency and duration of voluntary and iatrogenic discontinuations of the medication were measured. Finally, data regarding patient adherence and sensitivity to anti-tuberculosis drugs (17, 18, 19) were identified and collected. In Greece, most laboratory diagnosis and sensitivity testing is carried out in the Microbiology Laboratory – National Reference Centre of Mycobacteria of “Sotiria” General Chest Diseases Hospital of Athens.

Patients sensitive to anti-tuberculosis drugs based on bacteriological diagnosis as well as patients diagnosed on a different criterion but taking first line medication were included in a common group, that of patients sensitive to first-line drugs.

The study protocol and the recording form were submitted to the General Assembly of Special Composition of the School of Medicine of the University of Thessaly. In its No. 4143/04-

10-2010 meeting, the Assembly gave its approval for initiation (Reference No.4921/05-11-2010)

Descriptive and inferential statistical analysis was carried out. For quantitative variables the t-test and ANOVA parametric methods were used, while for qualitative variables the chi-square method with Yate’s correction for fourfold tables was used. The statistical significance level was set to $p=0.05$.

3. RESULTS

Out of 1200 medical files recorded in the registries of the Anti-TB Department, were available and studied along with the accompanying files from the clinics, in cases of previously hospitalized patients. Result analysis shows that 954 of the subjects had been diagnosed with tuberculosis and were under first-line treatment. 35 subjects were followed-up in the Treatment Section, without medication. Such cases are, for example, patients with older, inactive forms of tuberculosis, patients in close contact with active disease, presented with pulmonary shadowing and negative sputum smear tests. Out of these 954 patients, 519 were sensitive to anti-tuberculosis drugs and 435 did not have a bacteriological diagnosis and were taking first-line drugs.

Region of Origin	N %
Greece	297 31.1
Pakistan – Bangladesh	236 24.7
Asian countries	159 16.7
Somalia	71 7.3
African countries	67 7.2
Balkan countries	60 6.3
Ex-USSR	29 3.0
Albania	26 2.7
Europe	8 0.8
USA-Canada	1 0.1
Total	954 100.0

Table 1. Distribution of population on the basis of region of origin

Regarding the country of origin, as listed in Table 1, 297 patients were from Greece, 236 from Pakistan and Bangladesh, 159 were Asians, 71 Somalian, 67 Africans, 60 from Balkan countries, 29 from the Former Soviet Union, 26 from Albania, 8 from Western Europe and 1 from USA- Canada.

As can be seen, 791 patients were residents of the same area, out of whom 632 were foreigners. Mean residence time in Greece for migrant patients with drug-sensitivity ($n=416$) was $4,28 \pm 5,83$ months, with a median value of 2 years and an InterQuartileRange–IQR– of 1 to 6. During treatment, taking into consideration the long-term receipt of drugs required by the patients, it was observed that there were intervals of non-receipt for various reasons. In total (Table 2), the population ($n=954$) did 199 treatment discontinuations, out of which 76 were voluntary (self-decided) and corresponded to 47 patients, who proceeded to a first self-discontinuation and 123 were iatrogenic discontinuations ($n=102$). There were recorded up to three treatment discontinuations and interim administration intervals.

Thus, with regard to medication discontinuation and to drug sensitive patients, it appears that $n=149$ subjects did a first discontinuation, $n=42$ did a second discontinuation and $n=8$ did a third discontinuation. Of those who did the first discontinuation, 68.5% ($n=102$) discontinued for iatrogenic

It concerns all patients treated for the disease n=954	1st discontinuation	2nd discontinuation	3rd discontinuation
Voluntary (self-decided)	47	24	5
Iatrogenic	102	18	3
Total	149	42	8

*If at least one stop: mean treatment duration: 7.38±3.68 vs 6.68±3.54, p=0.032
 ** if 1st self-discontinuation: mean treatment duration: 4.75±3.18 vs 8.09±3.78, p<0.001

Table 2. Repeated Treatment Discontinuations and their Causes.

reasons, 31.5% (n=47) discontinued voluntarily (self-decided). Yet it should be noted that 5 out of these 47 patients were staying in various Institutions, like psychiatric hospitals, prisons or homeless shelters for the homeless, and they were all foreign males. Also, of all those—namely n=149 subjects—who, regardless of reason, did the first discontinuation, 50,3% discontinued within the first 15 days of treatment, and of these 46,3% discontinued due to hepatotoxicity while 22,5% due to the presence of allergic reactions.

It is noted that in the population of sensitive patients who did the first treatment discontinuation voluntarily there were 1 Somalian, 4 Pakistanis, 3 Africans, 3 Asians, and one Greek, all with poor understanding, as results from medical files. For the same patients who did the first treatment discontinuation voluntarily, it seems that 29.8% discontinued within the first fifteen days of treatment and 10.6% within the second fortnight, that is 40,4% decided and proceeded to discontinuation within the first month of treatment. A percentage of about 17,4% did the first self-decided discontinuation within the second month of treatment and 14,9% within the third month.

	2007	2010	2011
It concerns only patients treated for the disease n=954			
Greeks (n): Foreigners (n)	76:132	94:267	112:208
Location of disease (n):			
Pulmonary	141 65%	179 49.7%	152 47.4%
Extra-pulmonary	62 28.6%	129 35.7%	112 34.9%
Pulmonary shadowing	9 4.1%	25 7%	40 12.4%
Unknown Activity	1 0.5%	16 4.4%	8 2.5%
Unknown	4 1.8%	12 3.3%	9 2.8%
Incidence, (n):			
Drug-sensitive tuberculosis	237	378	339
Mean duration of treatment: (net number of treatment months)			
MT±TA	7.77±3.81	6.53±3.47	6.40±3.31
Drug-sensitive tuberculosis			

Table 3. Presentation of the problem of tuberculosis prior to and during financial crisis

Out of n=47 patients who proceeded to the first self-decided discontinuation, n=34 received treatment for up to 6 months, while n=13 received treatment for over 6 months, and of those the vast majority 57.4% (n=27) gave up treatment. It should be pointed out that in total only 38.3% (n=18) of the patients who did the first discontinuation self-decided, completed their treatment. As regards treatment duration, measured in net number of months of administration in patients with drug sensitivity, mean duration is 6.74±3.60 months with a maximum 24 months.

Treatment duration (Figure 1), is 6.68±3.54 months for

patients (n=805) who did no treatment discontinuation and 7.38±3.68 months for those (n=149) with at least one discontinuation for any reason p= 0.032. As for those (n=47) with first self-decided discontinuation, they received 4.75±3.18 months of treatment, while for the ones (n=102) with first iatrogenic discontinuation, mean treatment duration was 8.09±3.78 months p< 0.001

Table 3 shows the problem of tuberculosis prior to and during the financial crisis. It seems that in the year 2010, when the financial crisis broke out, Greek to Foreigner patient ratio was approximately 1:3, unlike 2007 and 2011 when it was 1:2. Pulmonary sites for the years 2007, 2010 and 2011 accounted for 65%, 49.6% and 47.4% of each year's cases respectively. In comparison with 2007, there is a significant increase in extra-pulmonary site cases, by 35.7% in 2010 and 34.9% in 2011, accounting for 28.6% of total sites for 2007 respectively.

As far as the incidence of the disease is concerned, a considerable increase of cases is observed during the financial crisis. In 2007 there were 237 cases with first line treatment, while in 2010 and 2011 these cases rose to 378 and 339, respectively.

The processing of the data about mean treatment duration measured in net number of months of therapy,— that is after deducting the interim intervals of non-receipt of therapy due to voluntary (self-decided) or iatrogenic discontinuation, — reveals that there was a gradual decrease in the number of patients treated with first line therapy at 7.77±3.81 months for the year 2007, and 6.53±3.47 and 6.40±3.31 months for the years 2010 and 2011, respectively.

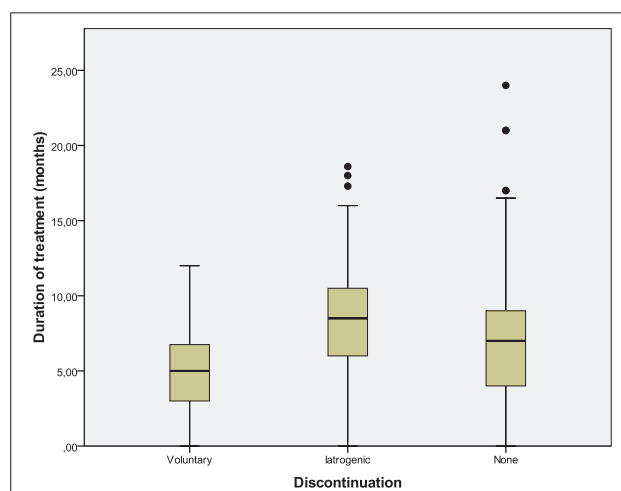


Figure 1. Difference in anti-TB treatment duration between patients with voluntary/self-decided and iatrogenic discontinuation and patients with no discontinuation "Stoppers – non stoppers"

The median residence time in Greece for the foreigners with good adherence was 2.5 years (IQR:1-7) years, while for those with poor adherence it was 2 years (IQR: 0.6-5) (p<0.0024). Among non-adherent patients, 84% were men and it seems that those that were on average 6.57 years older –mean age of the participants 37.4 ±17.34 years- were more adherent. Among adherent patients (n=562), 1.1% (n=6) of the population had a self-decided discontinuation during treatment, but among non-adherents this rate was equal to 15.4% (n=29).

In regard of visit adherence, 1% (n=5) of the population was completely adherent and self-discontinued, while among those frequently non-adherent the rate reached 17.6% (n=12). As for

treatment-adherence – i.e. proper dosage, everyday administration, proper timing and method – of the patients completely adherent 0.9% (n=5) proceeded to self-discontinuation, but for the ones frequently non-adherent the rate for self-discontinuation was 27.6% (n=8).

4. DISCUSSION

According to the findings of the present study, the tuberculosis cases in Greece tend to increase in time. On the basis of the World Bank Group and official data from the Greek Ministry of Health and given the restrictions in the national surveillance system for the disease (20, 21), the longitudinal trend of the reported cases is identified as decreasing until 2010 in the total and in the Greek population but increasing in the foreign population. From 2011 on an increasing trend is noticed in the total population, mostly in Greeks, but a slightly decreasing trend is seen in foreigners (22).

Nearly all the foreign patients who served as subjects in the present study were residents of the same area and their average residence time in Greece justifies immediate infection and initiation of anti-tuberculosis treatment upon entering the country (23). Due to its geographical location, Greece receives every year a significant number of economic migrants (3) who, as a result of insufficient national policies, are ghettoized with subsequent adverse effects (24, 25). Their identification and implementation of DOT programs (26, 27, 28), based on WHO guidelines (29), as designed for Greece and presented in the Post-Graduate Seminars in Pulmonology (30) sponsored by the Hellenic Thoracic Society, would be an excellent solution for control of the disease, adherence of the population (31) and prevention of creation of resistance.

Pertaining to adherent behavior, the population under study which self-discontinued treatment, for the most part decided to do so only once. With regard to iatrogenic discontinuations, those also occurred once for the most part. One of the most important findings of the present study is that more than half of the discontinuations took place immediately, within the first fortnight of medication administration, half of the self-discontinuations happened in the first month of treatment, and the vast majority occurred in the first quarter. Only 1/3 of the patients who self-discontinued completed treatment. These behaviors indicate that a patient's adherence-related intention can be detected early enough for health care providers to be able to evaluate the case and take proper measures (32) in order to prevent case loss and ensure public health.

Non-adherent behavior was also evident in the reduction of mean treatment duration due to the decision for self-discontinuation of treatment, especially if this was the first in the row. On the other hand, when iatrogenic discontinuations were present, duration was extended in order to complete the required treatment time (33, 34), at any cost involved.

Patients with at least one self-discontinuation had the lower mean duration of treatment compared to those with no discontinuation and those with at least one iatrogenic discontinuation. It is obvious and expected as well that the least adherent behaviors dealt with in this study had the lower mean duration of treatment.

As established in our study, in the years of financial crisis in Greece, incidence of tuberculosis rose. In addition, extra-pulmonary sites were very highly increased, in contrast with

the ECDC statement that in 2011 12.9% of the sites were extra-pulmonary (35, 36) usually occurring in 10–42% of the patients, depending on race, nationality, age, presence of underlying disease, genotype of the *M. tuberculosis* strain, and immune status (37). During the financial crisis, mean duration of net treatment gradually decreased over the years.

In relation to the financial crisis, incidence of tuberculosis is a marker of the population's development status. Therefore, the World Bank shows that the specific marker in Greece is comparable to Europe and WHO (20). However, it seems that in countries experiencing a financial crisis and being forced to follow strict financial control programs incidence, prevalence and mortality of the disease were significantly increased. Following completion of fiscal adjustment programs, incidence returned to previous levels (38, 39, 40, 41). Due to the imperative necessity to ensure continuous service provision and administration of anti-tuberculosis drugs, any cuts or stops in financing seem to have had serious consequences in public health (42, 43).

5. CONCLUSION

In conclusion, it seems that from the beginning of treatment the patients showed signs of adherent or non-adherent behavior, which affected not only the mean duration of treatment but also its completion. The duration of the latter was affected and gradually diminished in the years of financial crisis. Furthermore, ghettoization of foreigners is a reason for local administration of therapy with safe implementation of DOT, as instructed by WHO.

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CONFLICT OF INTERESTS: NONE DECLARED.

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