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The Treatment of Latent Tuberculosis Infection: Province Based Practice and Problems

Latent Tüberküloz Enfeksiyonu Tedavisi: İl Bazlı Uygulamalar ve Sorunlar

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ABSTRACT Objective: To investigate the treatment indications and compliance of individuals who underwent preventive treatment for latent tuberculosis infection (LTBI) in Turkey at the provincial level. **Material and Methods:** The data were collected retrospectively from records of 1,147 tuberculosis (TB) patients who have been followed-up in Elazığ TB Dispensary between the years 2005 and 2013. **Results:** Preventive treatment of LTBI was applied to 1,264 registered individuals for the indication of various factors. The causative factors for initiating preventive therapy were the history of contact with TB patients (55.1%), immunosuppression (28.2%), tuberculin skin test (TST) positivity (8.2%), TST conversion (0.1%) and for other reasons (8.4%). Of the patients, 66.3% had completed preventive treatment with success, however, 33.4% have abandoned their therapies. All of the patients have used isoniazid as preventive drug treatment. **Conclusion:** Preventive treatment for LTBI was applied most frequently with the indication of contact history with TB and the second indication was immunocompromised patients either by getting the drug or having a disease that is susceptible to TB infection. Unfortunately, the results of the study suggested that rates of completed treatment were not high enough.

Keywords: Latent tuberculosis; prevention and control

ÖZET Amaç: Türkiye'de latent tüberküloz enfeksiyonu (LTE) için önleyici tedavi gören bireylerin il düzeyinde tedavi endikasyonlarını ve uyumlarını araştırmak. **Gereç ve Yöntemler:** Elazığ Verem Savaşı Dispanseri'nde 2005-2013 yılları arasında kayıtlı koruyucu ilaç tedavisi alanlara ait veriler dosyalardan kaydedilmiştir. **Bulgular:** LTE için koruyucu tedavi, farklı endikasyonlarda 1.264 kişiye uygulanmıştır. Koruyucu tedavi alan bireylerin %55,1'ine tüberküloz hastası ile temas öyküsü, %28,2'sine (n=357) bağışıklığın baskılanması, %8,2'sine tüberkülin deri testi (TDT) pozitifliği, %0,1'ine TDT konversiyonu, %8,4'üne ise diğer nedenlerle koruyucu ilaç tedavisi başlanmıştır. Koruyucu tedavi alan bireylerin %66,3'ünün tedavileri tamamlanmış, %33,4'ü ise koruyucu ilaç tedavisini terk etmiştir. Koruyucu ilaç tedavisinde bireylerin tamamı izoniyazid kullanmıştır. **Sonuç:** Koruyucu ilaç tedavisi alan bireylerin çoğunluğunu tüberküloz hastası ile temas öyküsü olanlar oluştururken; ikinci sırada ise gerek ilaç kullanımı gerekse bir hastalık nedeni ile tüberküloza yatkınlık gösteren bağışıklığı baskılanmış bireyler yer almaktadır. Çalışmamızın sonuçlarına göre tedaviyi tamamlama oranları yeterince yüksek değildir.

Anahtar Kelimeler: Latent tüberküloz; önleme ve kontrol

Tuberculosis (TB) is still an important global public health problem. TB is a disease that can be treated and also be prevented. Latent tuberculosis infection (LTBI) is an ongoing immune response situation against *Mycobacterium tuberculosis* with a lack of clinical, radiological and microbiological active disease. This is also called "TB infection". The purpose of the LTBI treatment is to prevent TB infection in individuals that encountered TB bacilli and to eliminate the residual bacilli that have the potential to cause the

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disease.[1] Infected individuals have got active TB risk with a percentage of 5-10% in their overall life time.[2,3]

LTBI treatment is important for TB control programs' success because it avoids new bacilli sources via inhibiting the development of disease in infected individuals. It is considered to be an important part of TB control programs in countries that are in the elimination phase.[2] Modelling studies have shown that even with the lack of additional TB control preventions; when the 8% of individuals with LTBI are treated in every year the total global incidence will be 14 times lower by 2050 compared with the incidence in 2013.[4] The risk of active TB is higher in the individuals who are affected by household TB infection and among these individuals the early detection of TB is an important strategy.[5] To start LTBI treatment by contact investigation and screening of high-risk groups, to make effort for compliance and completion of treatment is necessary for TB control programs.[6]

LTBI treatment has always been a part of the TB control program in Turkey. This treatment is applied to TB dispensaries. A recent contact of a person with TB disease, tuberculin skin test (TST) measurements, TST conversion, age and immunosuppression states are indicative factors taken into consideration in Turkey to apply preventive treatment.[7]

In Turkey, LTBI treatment is a continuous issue for many years. Indications of the LTBI treatment have been published in the Ministry of Health TB control guidelines. Records of all patients receiving LTBI treatment are given as a report to the TB Department of the Turkish Ministry of Health by dispensaries monthly. The total number of patients receiving LTBI treatment is used to be published in the annual TB report.

The aim of the study was to investigate the indications for LTBI treatment and to observe the results of the LTBI treatment in Elazığ.

MATERIAL AND METHODS

STUDY POPULATION-WRITTEN CONSENT

This study was carried out in Elazığ located in Eastern Anatolia of Turkey. The population was recorded as 568,239 in 2013.[8] Data were obtained from LTBI treatment records in Elazığ TB Dispensary between January 2005 and December 2013. Because of information security, descriptive data were obtained from the provincial directorate of public health. The rough data based on the privacy of patients were not shared. Thus it was not possible to perform analytic studies because of the lack of rough data. Our study was designed as a retrospective one with the written consent of the provincial directorate of public health. Permission was obtained from patients and, if necessary, from their legal representatives. All procedures performed in the study involving human participants were following the ethical standards of the National Research Committee and with the 1964 Helsinki Declaration and its later amendments or comparable ethical standards. Written consent was obtained from the Public Health Directorate by official correspondence; number 87673967-902.15.

STATISTICAL ANALYSIS

All the statistical analyses were performed using the Statistical Package for the Social Sciences software version 24.0 (SPSS IBM Corp.; Armonk, NY, USA).

LTBI TREATMENT

According to the recommendations, 6-month isoniazid treatment for adults (5 mg/kg/day; maximum 300 mg) and children (10 mg/kg/day; maximum 300 mg) was applied.

DEFINITIONS OF INDICATIONS OF LTBI TREATMENT[7,9]

A recent contact of a person with TB disease: Drug treatment that is started to an individual; either he/she has a positive or a negative TST; in case of contact with TB patient. In some cases index case may not have a positive smear.[7,9] The contact criteria were to share the common air with a TB patient or exposure to TB bacilli.[7]

TST positive: Drug treatment started due to the detection of positive TST. There is no recent contact of a person with TB disease.[7,9] The skin test was defined as positive when the induration was ≥15 mm in BCG vaccinated individuals.[7] Individuals without BCG vaccination were considered as positive when induration was ≥10 mm.[7] In immunocompromised conditions, those have a risk for TB, positivity criterion was defined as the induration ≥ 5 mm.[7]

Immune suppression: Drug treatment is given to TST positive immunocompromised patients with an

increased risk of TB. In this group of patients, TST is positive when skin induration is measured ≥5 mm.[7,9]

Conversion of TST: Converting of a TST from negative to positive with at least a 6 mm increase in diameter in the last 2 years providing that BCG vaccine is not performed in the meantime.[7,9]

Fibrotic sequelae: Patients who have Chest X-ray lesions compatible with TB sequelae, previously untreated for TB and active TB has been excluded by a specialist physician.[9] Active TB infection was excluded by physicians, especially chest and infectious diseases, with a detailed medical approach by considering physical examination, anamnesis, radiological and necessary bacteriological evaluations.

Other: LTBI treatment started for any reason other than the above mentioned.

DESCRIPTION OF RESULTS OF LTBI TREATMENT (STATUS AFTER ONE-YEAR FOLLOW-UP)[9]

Completion of LTBI treatment: Completion of an LTBI treatment after at least a 6-month treatment duration. However, this duration is prolonged to 9 months in patients receiving immunosuppressive treatments.

LTBI treatment default: Patients those detected to receive LTBI treatment with a period of shorter than six months.

Diagnosis of TB: TB diagnosed after initiation of LTBI treatment

Death: Death for any reason during LTBI treatment.

Transferred patients: Patients who migrated to another dispensary region during LTBI treatment.

Other: Termination of LTBI treatment for any reason other than listed above.

RESULTS

A total of 1,147 TB patients' records that underwent to anti-TB treatment between years 2005 and 2013 were investigated. 58.2% (n=667) of the patients had pulmonary TB, 41.8% (n=480) of the patients had extrapulmonary TB (Figure 1). All the patients were

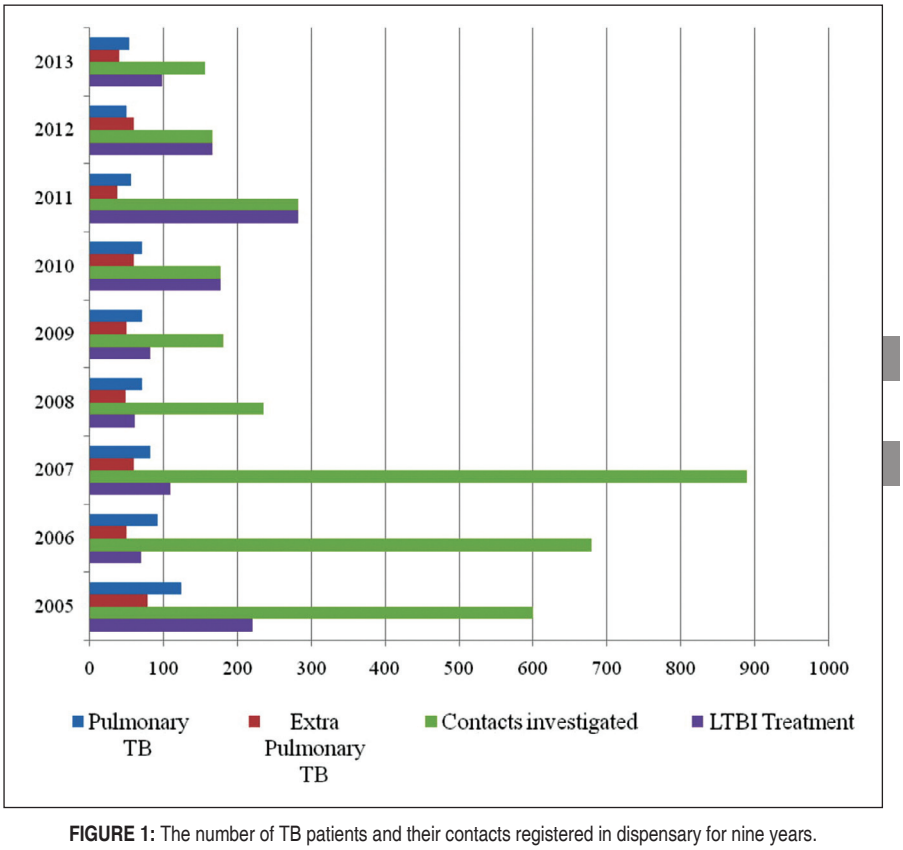

FIGURE 1: The number of TB patients and their contacts registered in dispensary for nine years.

registered at the Dispensary of Elazığ, but detailed information about their addresses was not evaluated in our study.

3,364 TB contact of 667 pulmonary TB patients identified and clinically evaluated registered for TB in the dispensary between 2005 and 2013 (5.04 per patient). In the dispensary, the individuals who cover the definition of LTBI including the ones who have positive TST were applied anti-TB treatment. In this regard, LTBI treatment was given to 1,264 individuals. All of the patients have used isoniazid as preventive drug treatment. In the follow-up records of dispensary no multi-drug resistant TB patients were detected, therefore it was determined that isoniazid was preferred in all cases, it was routinely given for 6 months and those who received immunosuppressive treatment were given 9 months of treatment. Among all the individuals who received LTBI treatment, 51.6% (n=652) were male and the remaining 48.4% (n=612) were female. The percentage of individuals and age intervals are as follows: 14.2% were 1-15, 61.4% were 16-35, 21.3 were 36-64 and 3.1% were over 65 years of age (Table 1). Indications of this treatment were 55.1% (n=697) history of contact with TB patients, 28.2% (n=357) immunosuppression, 8.2% (n=103) TST positivity, 0.1% (n=1) TST conversion and 8.4% (n=106) initiation of preventive drug treatment for other reasons. The presence of fibrotic sequelae as a radiological finding was not an indication to initiate preventive drug treatment (Table 2).

Among the individuals who had contact with active TB patients, the age and percentage distribution was found to be: 23% of the patients were ≤15 years of age, 48.6% were 16-35 years and 28.4% were ≥36 years. In the patient group with ≤15 years of age, only 13.5% of them received preventive treatment according to TST positivity. We were unable to reach the data concerning the indications of preventive treatment in the remaining age groups. 89 patients were detected in the other age groups who have been started preventive treatment for TST positivity. 67.7% of the immunocompromised patients those received preventive treatments took place in the 16-35 years of age.

Table 2 represents the results of preventive therapy. 66.3% of the patients (n=838) completed and 33.4% (n=422) abandoned the treatment. The reasons why the patients abandoned their treatments couldn't have been found in the dispensary records. Two patients were transferred to another dispensary and two patients were diagnosed as TB during preventive treatment. Death was not detected during protective treatment (Table 2). Among the patients who have been started treatment for TB contact; 63.5% (n=443) of them completed the treatment. 35.9% (n=250) of them abandoned and 0.3% (n=2) had developed active TB.

Completion rates were lower among TST positive patients (50.5%, n=52) in our study. It was determined that adherence and completion of patients were better in LTBI treatment due to immunosuppression (72.5%, n=259).

TABLE 1: Distribution of age and gender of the patients who received LTBI treatment.

	0-15		16-35		36-64		65 and +		Patients who recieved LTBI treatment
Years	Male	Female	Male	Female	Male	Female	Male	Female	Total
2005	12	8	80	58	32	30	-	-	220
2006	11	9	25	10	9	5	-	-	69
2007	7	13	38	42	-	-	9	-	109
2008	2	-	13	12	23	11	-	-	61
2009	9	7	33	28	5	-	-	-	82
2010	11	12	44	56	26	28	-	-	177
2011	25	23	78	68	35	23	15	15	282
2012	5	6	63	49	20	23	-	-	166
2013	10	9	49	30	-	-	-	-	98
Total %	92 (7.3)	87 (6.9)	423 (33.5)	353 (27.9)	150 (11.8)	120 (9.5)	24 (1.9)	15 (1.2)	1,264

TABLE 2: Distribution of LTBI indications and drug treatment results for preventive treatment.

Years	TB contact		TST positive		Immunesupression		Conversion of TST		Fibrotic sequelae	Completion of LTBI treatment		LTBI treatment abandonment		Progression to active TB		Death	Transferred patients		Other		Patients who received LTBI treatment Total
	n	%	n	%	n	%	n	%		n	%	n	%	n	%		n	%	n	%	
2005	113	51.4	16	7.2	72	32.7	-	-	-	190	86.4	30	13.6	-	-	-	-	-	19	8.6	220
2006	38	55	10	14.5	17	24.6	-	-	-	58	84	11	16	-	-	-	-	-	4	5.8	69
2007	78	71.6	11	10.1	17	15.6	-	-	-	85	78	24	22	-	-	-	-	-	3	2.8	109
2008	55	90.2	-	-	6	9.8	-	-	-	41	67.2	19	31.1	1	1.7	-	-	-	-	-61	
2009	54	65.9	9	11	18	22	-	-	-	49	59.8	33	40.2	-	-	-	-	-	1	1.2	82
2010	69	39	6	3.4	84	47.5	-	-	-	104	58.8	73	41.2	-	-	-	-	-	18	10.2	177
2011	134	47.5	40	14.2	63	22.3	-	-	-	152	53.9	129	45.7	-	-	-	1	0.4	45	16	282
2012	98	59	1	0.7	56	33.7	1	0.7	-	108	65	56	33.7	1	0.65	-	1	0.65	10	6166	
2013	58	59.1	10	10.2	24	24.5	-	-	-	51	52	47	48	-	-	-	-	-	6	6.2	98
Total	697	55.1	103	8.2	357	28.2	1	0.1	-	838	66.3	422	33.4	2	0.15	-	2	0.15	106	8.4	1,264

DISCUSSION

The purpose of the LTBI treatment is to prevent the development of TB in contacts of TB cases or to prevent the development of TB disease in infected patients.[1]

This study was based on the records of the Elazığ TB Dispensary. Data about LTBI treatment were recorded on a regular basis; so access to data was easy and reliable. The data belonged to a period of nine years therefore it is useful to shows changes and approaches to LTBI treatment over time.

The limitation of our study is while using the retrospective data of TB patients followed-up in dispensaries, we were unable to reach the detailed information about the clinical situations such as the presence of pregnancy, drug abuse or HIV positivity patients. Also, there was a lack of detailed data for immunocompromised patients. The data recording documents (VSD-16 form) used for preventive drug treatment in the dispensary included the option of suppressing immunity for reasons of protection, and the forms did not contain more detailed information about immunosuppression. Therefore, drug side effects, type of immunocompromised situations and the causative factors for treatment defaulters could not be analyzed. A monthly follow-up of patients with a lack of primary health care contribution and monthly given preventive drugs without directly observed treatment approaches may be a cause of treatment failures. Therefore, we need more detailed further studies concerning the reasons for treatment defaults. The male predominance in receiving LTBI treatment can be explained that male individuals have relatively more social activities, which can be a possible cause for TB bacilli contact. Moreover, considerable LTBI treatment in the younger population indicates ongoing contamination.

LTBI treatment indications according to the local TB treatment guidelines are given in Table 3. In our study, 28.4% of the patients who had contact with TB patients were ≥ 36 years of age and also 13.5% of patients with TST positivity were ≤ 15. These two results revealed that there was no compliance with the national guidelines of diagnosis and treatment concerning the preventive treatment in TB.

TABLE 3: LTBI Treatment Indications in Turkey.[4,6]

Reference Book for the Control of TB in Turkey-2003	The Guideline of TB Diagnosis and Treatment - 2011
TST positive children under age 15	TST positive children under age 15
TST conversion	TST conversion
Increased risk of TB immunocompromised TST positive patient	Increased risk of TB immunocompromised TST positive patient
Contacts of active TB patients younger than 35 years old	Contacts of active TB patients younger than 35 years old
Sequelae of TB lesions in chest X-ray	

This situation indicates that there is a problem with the compliance of the TB control program, thus an efficient and regular education given among dispensary physicians is essential.

Compliance with LTBI treatment reduces when the individuals with no complaints (especially in pediatric age group) are ordered to use the drug treatment for an extended period of time with the information of possible drug side effects.[10] Even in healthcare workers the initiation and to complete the LTBI is an important problematic issue.[11-13] Health care professionals have to educate and support and encourage patients for regular drug use and treatment completion. If necessary, LTBI treatment should be directly supervised. Moreover, the patients who are diagnosed as LTBI and under treatment should be provided knowledge about their health as well as the fight against their anxiety and fear.[14] Innovative interventions can significantly improve compliance with treatment and reduce the risk of future TB development.[15] For instance, patients treated with directly observed treatment treatments performed by video-assistant technologies had more rates of treatment completition.[16]

One-quarter of the world's population is infected by TB.[17] LTBI treatment is rather important for the preventive purpose among close contact of persons with infectious TB.[18] Moreover, LTBI treatment is an important portion of TB elimination and control.[19] Even in countries with low TB burden, some obstacles have prevented the implementation or expansion of LTBI treatment programs.[20] There is globally a concern about maintaining and compliance. Maintaining the LTBI treatment perpetually is essential. If there are short-term intervals, this should be added at the end of LTBI treatment.[7] In a previous study performed in Providence-USA, only 61.7% of individuals with LTBI completed the treatment.[21] Similarly in a meta-analysis performed in USA and Canada revealed that compliance to LTBI rates were 30-90%.[22] In this study it was emphasized that preventive treatment for TB elimination needs to be done effectively. It is also stated that to ensure compliance, innovative approaches are necessary. In a study from Manitoba-Canada between the years 1999 and 2014 of the total 5.515 individuals LTBI treatment was completed with a percentage of 60.2%.[23] In a study performed in Iqaluit-Canada between 2012 and 2016, 439 (19.1%) of the 2,303 patients tested with TST were diagnosed with LTBI, 328 patients were offered treatment, 246 (75.0% of those offered) were started and 186 were (75.6% of initiators) completed the treatment.[24] In a USA study focused on the treatment outcomes of LTBI (n=12.495) between the years 2009 and 2015, 48.4% of the patients were unable to complete the treatment.[25] In a Japanese study, the rate for treatment completion was 71.9%, and also the treatment duration was shorter than 180 days in 20% of the patients.[26] In a study performed in Porto ve Lisbon-Portugal between the years 2013 and 2017, 13.8% of the patients were unable to complete the LTBI treatment.[27] In a prospective cohort study performed in Norway, treatment completion rate was 91%.[28] The completion rate of LTBI treatment in patients aged 65 years and older has been investigated and the competition rate was found as 83.1%.[29] In a study that evaluates 415 LTBI treatment initiated patients at a university hospital in Stockholm-Sweden, treatment completion rates in 2002 and 2007 were 71% and 87%; respectively, that indicated an increase in the rate for 5 years.[30] Contrary to this literature; in our study rates of completion of treatment declined from

86.4% in 2005 to 52% in 2013. Family medicine system was introduced in 2007 at Elazığ. Having experienced dispensary physicians as family doctors, frequent changes and short-term work of dispensary doctors, reduction of the complete protection would be related with an increased number of patients leaving the treatment. Moreover, the reduction in reported TB contact people within years and the discrepancies between the number and treated individuals with TB contact can be attributed to the changes in duties among dispensary physicians (Figure 1). During the transition to family medicine practice in Turkey, educated and experienced physicians about TB, transferred to family medicine centers from the dispensaries which was a negatively affecting factor for TB control. An immediate educational program against TB fight should be performed for the beginner physicians in these dispensaries as well as the educational approaches for the actual health care professionals. Some innovative and personal approaches should be developed concerning the enhancement of compliance to the LTBI within the national TB control program.

There are not many comprehensive studies regarding the LTBI treatment in Turkey. In a retrospective study, 61.6% of the patients completed the treatment by using their drugs regularly or irregularly (59.4% and 2.4% respectively) in dispensaries of Eskişehir between January 1996 and December 2000.[31] A study conducted at dispensaries in İzmir, health professionals asked about their patients' compliance with LTBI treatment. They stated noncompliance with treatment as occasionally in 56% of patients and rarely in 44% of patients. Causes of noncompliance are accounted to being forced to take the drug while feeling healthy, a long-term course of drug therapy (78%) and forgetting to take the drug, respectively.[32] A previous study performed between the years 2016 and 2017 in Samsun dispensary reported that among 233 patients who were started LTBI treatment, 19.5% of the males and 21.2% of the females abandoned their treatments.[33] In our study, LTBI treatment was completed in 66.3% of the patients. Contacts of active TB patients completed the treatment by 63.5%.

CONCLUSION

In our study, we have revealed the outcomes of preventive treatment for LTBI based on the results of a province in Turkey. Most of the individuals who had received the treatment were those who had close contact with TB patients. The rate of completion of treatment was relatively low. The rate of treatment completion has not developed and improved. For the TB infection control, the main target should be screening patients who had a history of contact with TB patients, initiation of TB treatment when the active disease is detected and to give preventive treatment when necessary. Also, sustainable efforts have to be given and innovative methods should be improved to increase the rate of patients' treatment compliance as well as encouragement for completion of treatments.

Source of Finance

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Conflict of Interest

No conflicts of interest between the authors and / or family members of the scientific and medical committee members or members of the potential conflicts of interest, counseling, expertise, working conditions, share holding and similar situations in any firm.

Authorship Contributions

Idea/Concept: *Mustafa Hamidullah Türkkanı, Tarkan Özdemir;* ***Design:*** *Mustafa Hamidullah Türkkanı, Tarkan Özdemir, Çiğdem Özdilekcan;* ***Control/Supervision:*** *Canan Küçük, Çiğdem Özdilekcan;* ***Data Collection and/or Processing:*** *Tarkan Özdemir, İbrahim Halil Akkuş;* ***Analysis and/or Interpretation:*** *Tarkan Özdemir, İbrahim Halil Akkuş;* ***Literature Review:*** *Mustafa Hamidullah Türkkanı, Tarkan Özdemir, Çiğdem Özdilekcan;* ***Writing the Article:*** *Mustafa Hamidullah Türkkanı, Tarkan Özdemir, Çiğdem Özdilekcan, Canan Küçük;* ***Critical Review:*** *Mustafa Hamidullah Türkkanı, Çiğdem Özdilekcan;* ***References and Fundings:*** *Mustafa Hamidullah Türkkanı, Tarkan Özdemir, Çiğdem Özdilekcan.*

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