

Recommendations of the Turkish Society for Rheumatology on tuberculosis screening and treatment in patients receiving advanced antirheumatic drug therapy

Gelişmiş antiromatizmal ilaç tedavisi alacak hastalarda tüberküloz taraması ve tedavisi için Türkiye Romatoloji Derneği önerileri

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Abstract

Tuberculosis (TB) remains a significant public health concern in endemic countries despite widespread Bacillus Calmette-Guérin vaccination. In rheumatology practice, biologic and targeted synthetic disease-modifying anti-rheumatic drugs (b/tsDMARDs) alter immune responses and increase the risk of reactivation of latent TB infection or development of new TB. Therefore, appropriate screening, treatment, and follow-up strategies before, during, and after initiation of advanced therapies are essential. These recommendations were developed by the Tuberculosis Working Group of the Turkish Society for Rheumatology through a systematic literature review, an evaluation of national and international guidelines, and a Delphi consensus process involving 12 experts. The recommendations address key clinical questions, including the definition of latent TB, the interpretation of the tuberculin skin test and the interferon-gamma release assay, the selection and duration of treatment regimens, management during pregnancy and lactation, the approach to patients with prior TB, and the management of TB occurring during advanced therapies. Isoniazid is

Özet

Tüberküloz (TB), Bacillus Calmette-Guérin aşılmasına rağmen ülkemizde önemini koruyan bir halk sağlığı sorunudur. Romatolojik hastalıkların tedavisinde kullanılan biyolojik ve hedefe yönelik sentetik hastalık modifiye edici antiromatizmal ilaçlar (b/tsDMARD'ler), immün yanıtı baskılamaları nedeniyle latent tüberkülozun reaktivasyonu ve yeni TB gelişimi açısından ek risk oluşturur. Bu nedenle gelişmiş tedavi öncesinde, sırasında ve sonrasında uygun tarama, tedavi ve izlem stratejilerinin belirlenmesi kritik öneme sahiptir. Türkiye Romatoloji Derneği Tüberküloz Çalışma Grubu tarafından hazırlanan bu öneriler, sistematik literatür taraması, ulusal ve uluslararası kılavuzların incelenmesi ve 12 uzmanın katıldığı Delphi konsensus süreci ile oluşturulmuştur. Rehber; latent tüberküloz tanımı, tüberkülin deri testi ve interferon gamma salınım testlerinin kullanımı ve yorumlanması, latent tüberküloz tedavi rejimleri ve süreleri, gebelik ve emzirme döneminde yaklaşım, geçirilmiş TB öyküsü olan hastalarda izlem, gelişmiş tedavi altında TB gelişimi ve yeniden tedavi planlaması gibi başlıkları kapsamaktadır. Latent tüberküloz saptanan hastalarda öncelikli

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Abstract

recommended for nine months as the first-line treatment, with alternative options specified for particular clinical scenarios. The timing of advanced therapy initiation relative to latent TB treatment should be individualized based on disease activity and TB risk assessment. These recommendations aim to provide clinicians with a practical roadmap for latent and active TB screening and management in patients receiving b/tsDMARD treatments, and are consistent with national data.

Keywords: Latent tuberculosis, biologic therapy, bDMARD, tsDMARD, anti-TNF, IGRA, tuberculin skin test, rheumatic diseases, Delphi consensus

Introduction

Tuberculosis (TB) remains an important public health problem in countries where it shows endemic characteristics despite Bacillus Calmette-Guérin (BCG) vaccination.^[1] Advanced therapies used in the treatment of rheumatologic diseases, namely biologic and targeted synthetic disease-modifying anti-rheumatic drugs (bDMARDs and tsDMARDs), may create an additional risk for the development of TB or reactivation of latent TB infection due to their effects on the immune response.^[2] Therefore, it is essential to define appropriate screening, adequate treatment for latent TB, and safe follow-up strategies before, during, and after advanced therapy.

On behalf of the Turkish Society for Rheumatology (TSR), the Tuberculosis Working Group planned to develop practical and applicable recommendations that are consistent with scientific evidence and national real-life data, while taking into account the conditions of Türkiye, to address clinical problems frequently encountered in rheumatology practice related to TB. The aim in developing these recommendations is to provide up-to-date, consistent, and practical information on latent TB screening, definitions, and treatment approaches for patients who will receive b/tsDMARD agents. In addition, it is intended to create a guide to assist clinicians in (a) the follow-up of patients receiving b/tsDMARD therapy with respect to TB risk, and (b) the determination of treatment strategies for patients diagnosed with latent or active TB.

Materials and Methods

Study Group

These recommendations were developed with participation from members of the “Tuberculosis Working Group” established by the TSR. Twelve rheumatology specialists participated in the group. All participants declared potential conflicts of interest. This study is based on a systematic literature review and expert opinion; it does not include patient or public participation.

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latent tüberküloz tedavi rejimi izoniazid 9 ay olarak önerilmiş, alternatif şemalar tanımlanmıştır. Latent tüberküloz tedavisi ve gelişmiş tedavilerin zamanlamasının hastalık aktivitesine göre planlanması önerilmiştir. Bu rehber ile, b/tsDMARD tedavilerinde latent ve aktif TB tarama ve yönetimi hakkında klinisyenlere pratik ve ulusal verilerle uyumlu bir yol haritası sunulması amaçlanmıştır.

Anahtar Kelimeler: Latent tüberküloz, biyolojik tedavi, bDMARD, tsDMARD, anti-TNF, IGRA, tüberkülin deri testi, romatolojik hastalıklar, Delphi konsensus

Development of Clinical Questions

Thirteen research questions were identified concerning TB-related issues that are frequently encountered and difficult to resolve in rheumatology practice. These questions cover focus areas such as latent TB screening, interpretation of the tuberculin skin test (TST) or interferon-gamma release assay (IGRA), duration of latent TB treatment and drug selection, approach during pregnancy and lactation, follow-up of patients with a history of TB, and the interaction between advanced therapies and TB. To structure clinical decision-making, all guideline questions were addressed using the PICO system.

The PICO questions that need to be answered regarding TB in rheumatology practice are listed below:

Question 1: What is the definition of latent TB?

Question 2: What are the screening methods? Which of the TST, IGRA, chest radiography should be used? Which should be chosen: TST or IGRA test? What are the advantages over each other?

Question 3: What should be the TST cut-off value for the definition of latent TB?

Question 4: Latent TB treatment: which drug should be used and for how long?

Question 5: What should be the screening and latent TB treatment approach in pregnant and breastfeeding women?

Question 6: What is the duration of protection in patients receiving treatment for latent TB? Is repeat treatment necessary; after how many years should it be repeated?

Question 7: How should screening be performed in patients receiving immunosuppressive drugs?

Question 8: If b/tsDMARD therapies are to be initiated in patients who have previously had TB, how should TB screening and treatment be performed?

Question 9: In patients receiving b/tsDMARD therapy, how frequently and how should patients be screened in terms of TB frequency and development?

Question 10: In patients who develop TB under b/tsDMARD therapy, how should anti-TB treatment be managed, and if advanced therapy is to be restarted, what should be the timing and drug selection?

Question 11: In patients who have received TB treatment or completed latent TB treatment, what should be the follow-up protocol and screening approach?

Question 12: After initiating latent TB treatment, when can b/tsDMARD therapies be started, and can latent TB treatment and b/tsDMARD therapies be given simultaneously?

Question 13: Is there a difference between drugs in terms of TB development risk in b/tsDMARD therapies?

Literature Search

In line with the defined questions, a systematic search was conducted in PubMed, Scopus, and Web of Science, and national guidelines, international recommendations, and real-life data were reviewed.

Delphi Consensus Process

For each PICO question, draft recommendations were prepared by combining evidence from the literature with experts' experience. All group members expressed their opinions on the draft recommendations, which were then finalized. The recommendations were submitted to Delphi voting within the group and scored using a Likert scale (1: strongly disagree - 5: strongly agree). The level of agreement for each recommendation was provided.

Recommendations

This section presents the recommendations and summaries that the working group developed and agreed upon by combining the systematic literature review conducted within the scope of the research questions with expert opinions.

1. What is the Definition of Latent TB?

Recommendation 1: It is defined as cases without clinical complaints or findings related to TB, having positive IGRA or TST results indicating prior encounter with the TB bacillus, typically having normal chest radiographs, or, in those with abnormal chest radiographs, cases in whom active TB has been excluded by appropriate methods (agreement score: 5.0).^[1,2]

2. Recommendations for Latent TB Screening

2.1. How should patients be screened for latent TB before receiving advanced therapy?

Recommendation 2: For latent TB screening, TST or IGRA testing should be performed in addition to chest radiography (agreement score: 5.0).^[3-6]

2.2. Which test should be preferred in latent TB screening?

Recommendation 3: TST or IGRA may be preferred in latent TB screening, and there is no drawback in using either of them; however, if available, IGRA should be preferred (agreement score: 5.0).^[7-14]

IGRA should be preferred in latent TB screening because it shows high specificity and sensitivity and is less affected by BCG vaccination.^[5,6,15-22]

2.3. What should be the approach according to the TST result before advanced therapy?

Recommendation 4: When TST is preferred as the first test in latent TB screening, induration of 5 mm and above is accepted as positive and treatment for latent TB is given (agreement score: 4.83).^[23-25]

Recommendation 5: In cases with induration below 5 mm, IGRA or repeat TST (booster) after 1-3 weeks is recommended (agreement score: 4.83).^[24-26]

2.4. When should screening tests be repeated in patients with negative TST and/or IGRA before advanced therapy?

Recommendation 6: In high-risk patients receiving bDMARD or tsDMARD therapy whose initial screening TST or IGRA is negative, repeat latent TB screening is recommended after the first year following physician evaluation (agreement score: 4.92).^[27-31]

2.5. What should be done in patients found to have a positive follow-up screening test?

Recommendation 7: If positivity is detected in the repeated test, latent TB treatment should be given (agreement score: 4.92).^[19,32,33]

Recommendation 8: It is appropriate that screening be performed primarily with IGRA blood tests, and if access is not available, by using TST (agreement score: 5.0).^[27-31]

2.6. How should patients with unclear treatment information for latent TB or previous active TB be approached?

Recommendation 9: In patients with positive TB screening tests whose treatment history for latent TB is unclear or who have not received treatment, with no findings of active TB infection at the current visit, a standard latent TB treatment regimen should be planned by approaching them as if latent TB were present (agreement score: 4.83).

3. Drug Options and Duration of use for Latent TB Treatment

3.1. Which drug should be used for latent tb treatment and for how long? What should be the priority of isoniazid (INH), rifampicin (RIF), pyrazinamide (PRZ), and ethambutol (ETB) options in treatment?

Recommendation 10: For latent TB treatment, INH monotherapy should be given as the first option at a dose of 300 mg/day for 9 months (agreement score: 4.92).^[3,34-37]

Recommendation 11: Even if the advanced antirheumatic agent is discontinued, if latent TB treatment has been started, it should be completed if possible (agreement score: 5.0).^[37]

As long as they are receiving INH, neuropathy prophylaxis with pyridoxine supplementation is recommended for patients (agreement score: 4.83).

3.2. What should be the alternatives, drug combinations, and recommended duration in patients who cannot receive INH?

Recommendation 12: In patients who cannot use INH, the first alternative should be RIF 600 mg/day as a treatment for 4 months treatment (agreement score: 4.92).^[3,34,36-39]

Recommendation 13: Alternatively, the combination of RIF 600 mg + INH 300 mg for 3 or 4 months, INH 900 mg once weekly and rifapentine 900 mg once weekly as a 3 months combination, daily combination of RIF and PRZ for 2 months with attention to hepatotoxicity, or the combination of levofloxacin (1000 mg/day) or moxifloxacin (400 mg/day) with ETB (2000 mg/day) or ethionamide (750 mg/day) for 6 months may be given (agreement score: 4.92).^[3,27,34,36,37,39-46]

4. How Should Screening be Performed When Advanced Antirheumatic Therapy Will be Initiated in Patients Who Have Had TB?

Recommendation 14: In patients who have previously had TB, tests such as TST and IGRA are not appropriate for screening; screening for active TB should be performed using clinical, laboratory, and imaging methods (agreement score: 5.0).^[37]

5. Follow-up Recommendations in Patients Who Have Received Latent TB Treatment

5.1. For how long is this treatment considered protective in patients who have received latent TB treatment?

Recommendation 15: Those who complete INH monotherapy for 6 months are considered protected for 7 years; those who complete 9 months are considered protected for 10 years; and those who complete uninterrupted TB treatment of appropriate duration according to organ involvement are considered protected for 10 years (agreement score: 4.92).^[47-53]

Recommendation 16: In patients who have completed latent TB treatment, protection has been shown to continue for more than 10 years, and there are no data regarding the administration of repeat treatment (agreement score: 4.92).^[54]

Recommendation 17: Re-treatment is recommended in individuals who are approaching the end of the specified periods

and who are in high socioeconomic-risk conditions/high-risk populations for TB contact/activation (high-risk population: if there is an active TB case in the immediate environment such as home or workplace, history of imprisonment, substance use, military barracks living, daily use of public transportation...) (agreement score: 4.83).^[37]

Recommendation 18: Advanced therapy may be started directly in patients with a history of completed TB treatment within 10 years (the durations given above) and without findings suggestive of TB infection (agreement score: 4.92).^[54,55]

5.2. How should the adequacy and effectiveness of treatment given for latent TB be evaluated?

Recommendation 19: Whether TB treatment has been received appropriately, uninterruptedly, and for a sufficient duration should be verified with TB Dispensary records and patient documents (agreement score: 4.83).^[37]

5.3. When can bDMARD or tsDMARD therapy be started after initiating latent TB treatment?

Recommendation 20: In patients in whom latent TB is detected and treatment for it is started, bDMARD or tsDMARD should be started 4 weeks later if rheumatologic disease activity permits (agreement score: 4.92).^[32,34,36,37,56]

5.4. Can latent TB treatment and bDMARD or tsDMARD therapy be given simultaneously?

Recommendation 21: If there is severe rheumatologic disease activity, bDMARD or tsDMARD therapy may also be started together with latent TB treatment without waiting 4 weeks; however, close follow-up with clinical, laboratory, and when necessary imaging is recommended in terms of TB development (agreement score: 5.0).^[28,34,57]

Recommendation 22: According to real-life data from Türkiye, since no TB flare was observed in patients in whom latent TB treatment and b/tsDMARD were started simultaneously, latent TB treatment and advanced therapies may be started simultaneously in patients with severe rheumatologic activity and in whom active TB infection has been shown to be absent (agreement score: 4.92).

6. Is There a Difference Between bDMARD or tsDMARDs in Terms of the Risk of TB Development?

Recommendation 23: Among biologic drugs, the risk of TB development is higher in the anti-tumour necrosis factor- α (TNF- α) drug group than in non-anti-TNF- α drugs (agreement score: 4.92).^[28,29,31,58,59]

Recommendation 24: Within the anti-TNF- α class, the risk of TB development under chimeric (infliximab), monoclonal antibody (adalimumab, golimumab), and pegylated anti-TNF- α

(certolizumab) treatment is higher than with the TNF- α receptor fusion protein (etanercept) (agreement score: 4.92).^[28,30,38,60-62]

Recommendation 25: Among drugs outside the anti-TNF- α group, the risk of TB development from highest to lowest is as follows: Janus kinase inhibitors (tsDMARD group drugs: tofacitinib, baricitinib, upadacitinib), interleukin-6 (IL-6) antagonists (tocilizumab, sarilimumab, calakizumab), cytotoxic T-lymphocyte associated protein 4 (CTLA-4) inhibitor (abatacept), IL-1 antagonists (anakinra and canakinumab), anti-CD-20 (rituximab), anti-IL-17 (ixekizumab, secukinumab), rituximab, anti-IL-17 (ixekizumab, secukinumab), ustekinumab, and IL-23 inhibitors (guselkumab, risankizumab) (agreement score: 4.75).^[2,28,63-83]

7. Active TB Evaluation and Management

7.1. How should patients be approached if there is suspicion of active TB?

Recommendation 26: The presence of active TB clinical findings should be investigated with imaging, clinical, and laboratory examinations (agreement score: 5.0).^[3]

Recommendation 27: If there is suspicion of active TB in patients receiving bDMARD or tsDMARD therapies, advanced therapies should be discontinued until the investigations are completed (agreement score: 4.92).^[3]

Recommendation 28: If there is active disease, the patient should be evaluated with the relevant specialties in order to restart TB treatment, and advanced therapy should not be given until TB is controlled (agreement score: 4.92).^[84]

7.2. In patients who develop TB while receiving bDMARD or tsDMARD drug treatment, how should anti-TB treatment be managed; if bDMARD and tsDMARD therapies are to be restarted, what should be the timing and drug selection?

Recommendation 29: In patients who develop TB under bDMARD or tsDMARD drug treatment, anti-TB treatment is initiated in accordance with the National Tuberculosis Diagnosis and Treatment Guideline (agreement score: 5).^[3,34,37]

Recommendation 30: If advanced therapy is to be restarted in patients who develop TB, completion of TB treatment is recommended first. In patients with high disease activity, b/tsDMARD agents may be given at the earliest 2 months after TB treatment has been started (agreement score: 4.92).^[27,85]

7.3. How should antirheumatic drug selection be made in patients who develop TB under bDMARD and tsDMARD therapies?

Recommendation 31: Drugs carrying a lower risk in terms of TB reactivation should be preferred in patients. Monoclonal

anti-TNF antibodies are associated with a higher risk of TB than receptor fusion proteins. The TB risk associated with tocilizumab (anti-IL-6), abatacept, ustekinumab, secukinumab, apremilast, and rituximab is lower compared with anti-TNF group drugs (agreement score: 5).^[2,66,86-92]

8. What Should be the Long-term Follow-up Protocol, Screening, and Re-treatment Approach in Those Who Complete TB Infection or Latent TB Treatment?

Recommendation 32: In those who complete TB infection treatment or latent TB treatment, follow-up with physical examination every 3 months and, if necessary, further evaluation directed to the affected system is recommended. In these patients, TST and IGRA are not recommended because they do not assist in diagnosis. TB activity should be sought according to clinical, laboratory, and imaging methods (agreement score: 4.75).^[37,66]

Recommendation 33: If active TB is detected, anti-TB treatment is given. If active disease has not been detected but there is a suspicious situation in terms of previous treatment and re-infection, the patient should be re-evaluated by the relevant specialist in terms of preventive treatment (agreement score: 4.92).^[37]

9. Recommendations for Special Groups

9.1. How should latent TB screening be performed in pregnant women?

Recommendation 34: TST and IGRA tests are safe for latent TB screening in pregnant women, and both methods may be used (agreement score: 4.83).^[26,93-95]

9.2. How should latent TB treatment be performed in pregnant women?

Recommendation 35: In pregnant women diagnosed with latent TB and planned to receive bDMARD treatment, INH treatment for 9 months is the first choice for treatment. These patients should be followed closely in terms of hepatotoxicity risk, and daily 25-50 mg pyridoxine prophylaxis is recommended due to the risk of peripheral neuropathy (agreement score: 4.92).^[96-100]

Recommendation 36: In pregnant women who cannot use INH, RIF treatment may be used as an alternative.^[97,99,101] Administration of vitamin K at birth is recommended for newborns exposed to RIF during pregnancy because of the risk of "hemorrhagic disease of the newborn" (agreement score: 4.92).^[102-104]

9.3. How should latent TB screening be performed in breastfeeding mothers?

Recommendation 37: In breastfeeding patients, TST or IGRA tests may be used for latent TB screening similarly to the normal population (agreement score: 4.92).

9.4. How should latent TB treatment be performed in breastfeeding mothers?

Recommendation 38: In breastfeeding patients with latent TB detected and planned to receive bDMARD treatment, use of INH for 9 months should be preferred as the first choice for treatment.^[105,106] During treatment, use of pyridoxine prophylaxis is recommended for both the mother and the infant (agreement score: 4.92).^[107]

Recommendation 39: In breastfeeding patients in whom use of INH is not appropriate, RIF treatment may be preferred as an alternative (agreement score: 4.92).^[108,109]

Discussion

This set of recommendations was prepared to guide clinicians in assessing TB-related risks, performing appropriate screening, and determining treatment protocols for patients for whom b/tsDMARD therapy is planned or who have already started these treatments. Türkiye's conditions regarding TB were considered, and recommendations were developed by combining evidence from the literature with approximately twenty-five years of experience in the use of biologic agents. Overall, the mean agreement scores for the recommendations are high. The application of the recommendations to each patient is possible only if the individual and medical characteristics of the patient are taken into account, and the preference of the clinician following the patient should take priority.

In Türkiye, the Ministry of Health's Tuberculosis Diagnosis and Treatment Guideline is updated periodically. The most recent update was made in 2019.^[37] The TB guideline for patients using biologic agents was prepared in 2016 to include only anti-TNF drugs.^[110] The guideline published in 2016 was prepared with relatively limited clinical experience, based only on anti-TNF drugs, and reflected the opinions and recommendations of chest diseases and TB specialists interested in TB rather than rheumatology specialists. Over the past ten years, the diversity of bDMARDs has increased, tsDMARDs have become widely used, and new scientific evidence regarding TB data in patients using these agents has been published in many sources, including registries. In this set of recommendations, those related to anti-TNF agents (infliximab, adalimumab, golimumab, certolizumab, and etanercept) were updated, and the recommendations were also expanded to include other bDMARDs such as IL-6 antagonists (tocilizumab, sarilimumab, calakizumab), the CTLA-4 inhibitor

(abatacept), IL-1 antagonists (anakinra and canakinumab), anti-CD-20 (rituximab), anti-IL-17 (ixekizumab, secukinumab), IL-23 and 12/23 inhibitors (guselkumab, risankizumab, ustekinumab), and Janus kinase inhibitors in the tsDMARD category (tofacitinib, baricitinib, upadacitinib). In the guideline published in 2016, TST and IGRA were considered to have similar effectiveness for latent TB screening, and the preferential use of IGRA was recommended only for patients with psoriasis. In our study, IGRA tests were prioritized, when available, before all b/tsDMARDs because they show high specificity and sensitivity in latent TB screening and are less affected by BCG vaccination. In addition, recommendations were presented regarding TB screening, treatment, and bDMARD use in special situations such as pregnancy and lactation.

European Alliance of Associations for Rheumatology (EULAR) and American College of Rheumatology (ACR), the largest professional organizations in the field of rheumatology, publish guidelines on many issues, including diagnosis, treatment, and associated conditions of rheumatic diseases. These organizations have also provided recommendations on TB at different times. In 2022, EULAR presented recommendations for screening and prophylactic treatment for chronic and opportunistic infections including TB.^[3,34] In this set of recommendations, the primary emphasis regarding TB is to follow national guidelines because of differences in BCG vaccination, TB burden, and drug resistance. ACR's approach, on the other hand, has been to implement Centers for Disease Control and Prevention (CDC) and American Thoracic Society (ATS) recommendations. ATS and CDC recommendations were developed based on TB data in the United States of America.^[111] Our recommendations were also prepared to guide physicians in Türkiye, based on TB data in Türkiye, BCG vaccination, and clinical experience. National TB data may change over time. Therefore, the National Tuberculosis Guideline, published and revised over the years by the Republic of Türkiye Ministry of Health, Turkish Public Health Institution, should be followed, and updates to the recommendations should be considered when necessary.

The use of drugs that increase the risk of TB and TB activation or reactivation is not solely of interest to rheumatology specialists. However, rheumatology is the specialty that uses b/tsDMARDs most widely, for the longest time, and with the greatest experience. Gastroenterology, dermatology, and ophthalmology, which are involved in the treatment of diseases with inflammation-based pathogenesis, have an undeniable interest in this subject. Although prepared by a working group composed solely of rheumatology specialists, these recommendations will guide the management of latent and active TB in other specialties that use b/tsDMARDs as much as in rheumatology. One of the most important limitations of this set of recommendations is that chest and infectious disease

specialists experienced in TB management and representatives from other scientific fields experienced in the use of b/tsDMARDs were not included in the working group. It is our hope that a national consensus report will be prepared by a working group formed with participation from all parties involved.

Conclusion

In conclusion, this set of recommendations was prepared as a guiding source on TB screening and treatment for clinicians managing patients receiving bDMARD and tsDMARD agents in Türkiye.

Footnotes

Author Contributions

Concept: C.B., R.D., M.E., U.İ., B.İ., Z.Ö., Ş.Ç.S., M.S., V.Y., Ş.E., T.K., İ.E., Design: C.B., R.D., M.E., U.İ., B.İ., Z.Ö., Ş.Ç.S., M.S., V.Y., Ş.E., T.K., İ.E., Data Collection and Processing: C.B., R.D., M.E., U.İ., B.İ., Z.Ö., Ş.Ç.S., M.S., V.Y., Ş.E., T.K., İ.E., Analysis or Interpretation: C.B., R.D., M.E., U.İ., B.İ., Z.Ö., Ş.Ç.S., M.S., V.Y., Ş.E., T.K., İ.E., Literature Search: C.B., R.D., M.E., U.İ., B.İ., Z.Ö., Ş.Ç.S., M.S., V.Y., Ş.E., T.K., İ.E., Writing: C.B., R.D., M.E., U.İ., B.İ., Z.Ö., Ş.Ç.S., M.S., V.Y., Ş.E., T.K., İ.E.

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