ORIGINAL ARTICLE

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Are Patients with Different Rheumatologic Diseases Under Immunosuppressive Therapies Adequately Screened and Protected Against Viral Hepatitis?

İmmünosupresif Tedaviler Altında Farklı Romatolojik Hastalıklarla İzlenen Hastalar Viral Hepatitlere Karşı Yeterince Taranıyor ve Korunuyor mu?

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ABSTRACT

Aim: The aim of this study is to determine the screening rates for hepatitis B (HBV) and C virus (HCV) in patients with rheumatologic diseases who receive immunosuppressive therapies, to evaluate the prevalence of HBV reactivation during the regimens and also to reveal the frequency of vaccination.

Materials and Methods: This retrospective study included the patients who were followed-up with different rheumatologic diseases in two rheumatology outpatient clinics. The immunosuppressive regimens were categorized into two groups as biologic (bDMARDs) and conventional synthetic disease modifying anti rheumatic drugs (csDMARDs). The markers of HBsAg, anti-HBs, anti-HBc-IgM and anti-HBc-IgG, HBV DNA, anti-HCV levels were all taken from the patients' charts checked prior and during the immunosuppressive treatments.

Results: There were 451 patients [61.9% female, mean age 41.1 years, (standard deviation: 13.78)] who were taking bDMARDs (n=348) and csDMARDs (n=103). The data for HBV for 20 (4.4%) patients and HCV for 23 (5%) patients were missing, all in the csDMARDs group. Also, HBV serology tests were found to be incomplete in 51 patients (14.7%) in the bDMARDs group, as not checking the anti-HBc-IgM and anti-HBc-IgG. During the follow-up, HBV reactivation was not observed in the whole cohort. In the bDMARDs group, there were 39 patients who did not receive prophylaxis despite having HBsAg negative phase of chronic HBV infection; no HBV reactivation was observed also in this group. One hundred twenty nine (28.6%) of the patients were evaluated as never infected and unvaccinated prior to immunosuppressive therapies. Recurrent HBV serology controls were performed in nearly half (n=75) of them during their follow-up and it was observed that all were still non-immune.

Conclusion: The screening rates of HBV and HCV serology were detected as successful in rheumatology patients under immunosuppressive therapies. No HBV reactivation was observed in the entire group. Also, the study showed that there was a significant deficiency in immunizing patients against HBV in follow-up.

Keywords: Hepatitis B virus, hepatitis C virus, immunosuppressive therapies, anti-rheumatic drugs, hepatitis B immunization

ÖZ

Amaç: Çalışmanın amacı immünosupresif tedavi altındaki romatoloji hastalarının viral hepatit B (HBV) ve C (HCV) için taranma sıklığının değerlendirilmesi, HBV reaktivasyon sıklığının tespit edilmesi, HBV aşılanma oranlarının değerlendirilmesidir.

Gereç ve Yöntem: Bu retrospektif çalışmaya romatoloji polikliniğinde izlenmekte olan immünosupresif tedavi alan hastalar dahil edilmiştir. İmmünosupresif tedaviler biyolojik (bDMARD) ve konvansiyonel sentetik (ksDMARD) hastalığı modifiye eden antiromatizmal ilaçlar olarak sınıflandırılmıştır. Hastaların İmmünosupresif tedavi başlanmadan hemen önce veya tedavi esnasında bakılan serum HBsAg, anti-HBs, anti HBc-IgM, anti HBc-IgG, HBV DNA ve anti-HCV belirteçleri dosya taramalarından elde edilmiştir.

Bulgular: Çalışmada 451 hasta yer almıştır [%61,9 kadın, ortalama yaş 41,1 yıl, (standart sapma: 13,78)]. Bu hastalar bDMARD (n=348) ve ksDMARD (n=103) kullananlar olarak iki gruba ayrılmıştır. Tüm hasta grubunda 20 (%4,4) hastanın HBV verisi, 23 (%5) hastanın ise HCV verisi olmadığı

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izlendi, bu hastaların tamamının ksDMARD grubunda olduğu görüldü. Ayrıca bDMARD grubundaki 51 hastanın (%14,7) HBV seroloji tetkiklerinin yeterli ayrıntıda olmadığı izlendi (anti-HBc-IgM ve anti HBc-IgG tetkikleri izlenmedi). Tüm kohortta izlem esnasında akut HBV enfeksiyonu veya HBV reaktivasyonu hiç izlenmedi. bDMARD hasta grubunda HBsAg negatif fazda kronik HBV'si olmasına rağmen profilaksi almayan 39 hastada da HBV reaktivasyonu izlenmediği görüldü. Hastalardan 129'unun (%28,6) immünosupresif tedavi öncesinde non-immün/aşısız olduğu görüldü. Bu hastalardan izlemleri esnasında tekrarlayan HBV serolojisi kontrol edilenlerin (n=75) halen non-immün/aşısız olduğu gözlendi.

Sonuç: İmmünosupresif tedavi altındaki romatoloji hastalarının yapılan HBV ve HCV serolojilerinin tarama sonuçları başarılı olarak değerlendirildi. Tüm grupta hiç HBV reaktivasyonu izlenmedi. Bu çalışmanın sonuçları ayrıca HBV non-immün olan romatoloji hastalarının takipte aşılanmalarının yetersiz düzeyde olduğunu göstermiştir.

Anahtar Kelimeler: Hepatit B virüsü, hepatit C virusü, immünosupresif tedavi, anti romatizmal ilaçlar, hepatit B aşılama

INTRODUCTION

Reactivation of hepatitis B (HBV) during immunosuppressive treatments could present as serious clinical conditions such as fulminant hepatitis and liver failure[1]. It has been shown that many immunosuppressive treatments used in rheumatology practice may be associated with HBV reactivation. Anti-CD20 regimens [e.g. rituximab (RTX)][2], corticosteroids (CS)[3], methotrexate (MTX)[4] and tumor necrosis factor alpha inhibitors (TNFi)[1] could enhance the chance of HBV reactivation to varying degrees in hepatitis B surface antigen (HBsAg) positive patients. Despite the lack of consensus, current guidelines recommend screening patients for HBV with serum HBsAg and anti-HBc prior to immunosuppressive therapies[5].

The high risk of reactivation for HBsAg positive HBV cases and the necessity of having prophylaxis under immunosuppressive therapy have taken their place as very strong recommendations in the guidelines[6-8]. However, the evidence for HBsAg negative and anti HBc positive occult HBV cases that will receive TNFi is not so clear. Studies report a lower risk of reactivation (1.7-5%) in this group when compared to HBsAg positive patients[1,9]. It is therefore recommended that the decision between prophylactic antiviral therapies versus follow-up should include risk stratification according to immunosuppressive regimen that the patient is taking.

Hence, the aim of this retrospective cohort study was to determine HBV screening rates, the frequency of HBV reactivation rates and also the vaccination and prophylaxis rates in rheumatology patients under different immunosuppressive therapies.

MATERIALS AND METHODS

This study included 451 patients who were followed-up with rheumatologic diseases in rheumatology outpatient clinics in Mardin State Hospital and Bursa City Hospital. The data of patients were taken from the charts of the patients who were admitted to Rheumatology outpatient clinics in a time period of 3 months between October 2019 and January 2020 for Mardin State Hospital and 1 month in March 2020 for Bursa City Hospital retrospectively.

In the patient group, the demographic data, diagnosis, the medications [all the immunosuppressive agents as csDMARDs, CS, nonsteroid anti-inflammatory drugs (NSAIDs), bDMARDs] were all recorded.

Exclusion criteria for patient group were determined as,

1. Being younger than 18 years old,

2. Having previous diagnosis of malignancy, immunodeficiency syndromes, chronic infections as tuberculosis,

3. Having previous treatments for malignancy as cytotoxic therapies chemotherapy or radiotherapy,

4. Having signs and symptoms of rheumatologic diseases, but with diagnosis not yet clarified,

5. Having a diagnosis of a rheumatologic disease but no immunosuppressive therapy use.

The diagnosis of rheumatologic diseases and medications were recorded and categorized into two groups as bDMARDs and csDMARDs. All the TNFi, RTX, small molecules [tofacitinib (TOFA)], and IL-1 antagonists were categorized as bDMARDs. And, MTX, sulfasalazine (SLZ), azathioprine (AZA), hydroxychloroquine sulfate (OHQ), leflunomide (LEF), mycophenolate mophetil (MMF), and colchicine were categorized as the csDMARDs group. Also, the status of taking CSs and NSAIDs was recorded in both group of patients. If the patient was using a csDMARDs in addition to biologics, this patient was evaluated in the bDMARDs group.

At the inclusion visit, HBsAg, anti HBs, anti HBc-IgM and anti HBc-IgG, Anti HCV, HBV DNA, HCV RNA levels were all taken from the patients' charts, which were recorded at the initiation of immunosuppressive therapies and during the use of therapies. In addition, patients with disorders of liver function tests [aspartate aminotransferase (AST), alanine aminotransferase (ALT), albumin, alkaline phosphatase, gamma-glutamyl transferase, bilirubin levels] during the period of immunosuppressive therapies were noted with etiologies (drug induced, viral, toxic, etc.). Patients who received viral hepatitis prophylaxis during their follow-up and the agents they received were noted.

Viral hepatitis reactivation was defined as reverse seroconversion of HBsAg in HBsAg negative patients or a rise of serum HBV DNA level by one log or greater compared to the pre-exacerbation baseline period, or a new detection of HBV DNA in patients with previously undetectable HBV DNA in patients.

The study was performed according to the Declaration of Helsinki and Bursa City Hospital Ethics Board approved the study with approval number 2021-13/8, date: 14.07.2021.

Statistical Analyses

Data were statistically analysed with Statistical Package for the Social Science 13.0 (SPSS) program. Results were expressed as mean with standard deviation (SD) and median with minimum (min), maximum (max) values and interquartile range according to the distribution of the data. Baseline characteristics in terms of categorical variables were compared using the Mann-Whitney U test. Categorical variables were analyzed using the chi-square test. A 5% type-1-error level was used to infer statistical significance.

RESULTS

There were 451 patients from two centers from two different cities in Turkey [61.9% female, mean age 41.1 years, (SD: 13.78)]. The diagnosis of the patients was mainly rheumatoid arthritis and ankylosing spondylitis (Table 1).

There were two main groups of patients, as the patients in the cohort who were taking bDMARDs (n=348) and those who were taking csDMARDs (n=103).

The biological therapies were adalimumab (n=101), etanercept (n=54), certolizumab (n=47), infliximab (n=42), golimumab (n=41), TOFA, n=20, RTX, n=17, tocilizumab (n=11), secucinumab (n=7), Anakinra (n=3), canacinumab (n=3), abatacept (n=2). The majority of patients (n=277) who had bDMARDs were taking the first-line biologics, also 38 of them were taking second-line, 24 of them were taking third-line, 8 of them were taking fourth-line and 1 of them was taking the fifth-line biological therapy. Moreover, in the bDMARDs group, 58 (16.7%) patients were taking LEF, 46 (13.2%) patients were taking MTX, 43 (12.4%) patients were taking SLZ, 42 (12.1%) patients were taking OHQ, 21 (6%) patients were taking colchicine, 11 (3.2%) patients were taking AZA, and 5 (1.4%) patients were taking MMF; concomitant to bDMARDs. Totally 226 (64.9%) patients were using concomitant csDMARDs during biologic use.

In the csDMARDs group, 47 patients (45.6%) were taking MTX, 41 (39.8%) patients were taking OHQ, 23 (22.3%) were taking LEF, 17 (16.5%) patients were taking SLZ, 14 (13.6%) patients were taking colchicine, 11 (10.6%) were taking AZA, and 7 (6.8%) patients were taking MMF in different combinations.

Furthermore, 190 (42.1%) patients were taking CS (the mean dosage was 7.16 mg prednisone equivalent SD 4.80, min: 5 max: 25 mg) and 239 (53%) patients were taking NSAIDs in all bDMARDs and csDMARDs groups. One hundred and fourteen (32.8%) patients were exposed to CSs during bDMARDs use and 76 (73.8%) patients were exposed to CSs during only-csDMARDs use.

The data for viral hepatitis B for 20 patients were missing, all in the csDMARDs group. Also, viral hepatitis B serology tests were found to be incomplete in 51 (14.7%) patients in the bDMARDs group. In all of these patients, the missing test was determined as not checking the anti HBc-IgM and anti HBc-IgG, which were recommended by guidelines. In the csDMARDs group, viral hepatitis B serology was only evaluated with HBsAg and anti-HBs in 26 (%25.2) patients and only with HBsAg in 30 (%29.1) patients as simple screening (Table 2). Also, the data for viral hepatitis C (HCV) were missing in 23 (5.1%) of the patients, all in the csDMARDs group, with not checking anti-

Table 1. The rheumatologic diagnoses of the patients

Diagnosis	Patients (n)	Patients total (n, %)
AS	169	185 (41%)
AS/Behçet	4	
AS/Crohn	8	
AS/UC	1	
AS/Crohn/FMF	1	
AS/FMF	2	
RA	176	186 (41.2%)
RA/SLE	4	
RA/Scl	1	
RA/SjS	3	
RA/adult Still disease	2	
SLE	15	19 (3.3%)
Behçet	18	22 (4.9%)
Peripheral Spa	10	10 (2.2%)
FMF	6	9 (2%)
EGPA	1	1 (0.22%)
GPA	1	1 (0.22%)
PM/Scl	1	2 (0.44%)
PM/SjS	1	
PsA	13	13 (2.88%)
Scl	5	7 (1.55%)
SjS	2	6 (1.33%)
Adults Still disease	1	3 (0.66%)
TAK	6	6 (1.33%)
Total	451	

AS: Ankylosing spondylitis, RA: Rheumatoid arthritis, UC: Ulcerative colitis, FMF: Familial Mediterranean Fever, SLE: Systemic lupus erythematosus, Scl: Scleroderma, SjS: Sjögren's syndrome, Spa: Spondyloathritis, EGPA: Eosinophilic granulomatosis polyangiitis, GPA: Granulomatosis polyangiitis, PM: Polymyositis, PsA: Psoriatic arthritis, TAK: Takayasu arteritis

HCV. The test was evaluated as negative in all 428 patients who were tested or anti-HCV. Therefore, it was observed that HCV-RNA testing was not considered necessary in the entire patient group.

It was determined that HBV DNA follow-up was performed in 28 patients in the whole group. HBV DNA positivity was observed in only 4 of these patients, as not meeting the reactivation criteria.

The immunization rates for HBV in patients under bDMARDs were higher than patients under csDMARDs (p<0001). The rate of not being screened for HBV or being screened with simple tests for HBV (as checking only the HBsAg with/without anti-HBs) was detected higher in patients under csDMARDs than bDMARDs (p<0001) (Table 2). Patients under the bDMARDs group were detected as screened with detailed tests for HBV compared to the csDMARDs group (Table 2).

Antiviral prophylaxis for hepatitis B was given to 52 (11.4%) patients in total group with tenofovir (n=42), entecavir (n=7), and lamivudine (n=3). These patients were predominantly in the bDMARDs group (n=50). While 7 patients of the prophylaxis group consisted of HBsAg positive patients, all the remaining prophylaxis patients were detected in the HBsAg negative phase of chronic HBV infection.

The mean follow-up time was 27 months (min: 5 months, max: 58 months). During the follow-up of 451 patients, acute HBV infection was not observed in any of the patients. No hepatitis B reactivation was observed in the whole cohort. In the bDMARDs/TNFi group (non-RTX), there were 39 patients who did not receive prophylaxis despite having HBsAg negative phase of chronic HBV infection; no hepatitis B reactivation was also observed in this group.

One hundred twenty nine (28.6%) of the patients were evaluated as unvaccinated prior to immunosuppressive therapies. Recurrent HBV serology controls were performed in nearly half (n=75, 58.1%) of them during their follow-up and it was observed that all were still unvaccinated/non-immune.

Elevated liver enzymes (AST-ALT) were detected in 11 of the patients during the follow-up. It has been determined that toxic hepatitis due to drugs (4 isoniazid, 3 colchicine, 1 MMF), disease involvement in liver (1 myositis, 1 SLE), and primary biliary cirrhosis (1) were involved in the etiology.

DISCUSSION

This retrospective study showed that rheumatologists had satisfactory screening rates for HBV and HCV in patients prior to immunosuppressive therapies. No HBV reactivation was observed in the cohort, as a possible indicator of adequate screening and the appropriate use of prophylaxis. But also, the study showed that there was a significant deficiency in immunizing patients against HBV in follow-up.

Despite the lack of consensus, current guidelines recommend screening for HBV and HCV infection prior to all immunosuppressive therapy[5]. Guideline recommendations aside, real-life data in studies have actually shown that viral hepatitis screening is not optimal in immunosuppressive patients. There were two interview-based studies investigating rheumatologists' awareness of HBV and screening practices for HBV prior to immunosuppressive therapies. One of them detected that only 69% reported performing appropriate screening before bDMARDs[10]. In the other study, 93.8% of the physicians thought that screening should be performed before immunosuppressive therapies[11]. A study from Turkey showed

Table 2. Viral hepatitis B serology in patients in the bDMARDs and csDMARDs groups

Serology					bDMARDs (n, %)	csDMARDs (n, %)	p value
HBsAg	Anti-HBs	Anti-HBc-IgG	Anti-HBc-IgM				
(+)	(-)	(+)	(-)	Chronic HBV infection	6 (1.7%)	3 (2.9%)	0.43
(+)	(-)	(+)	(+)	Acute HBV infection	0 (0%)	0 (0%)	--
(-)	(-)	(+)	(-)	Resolved HBV infection	27 (7.7%)	4 (3.9%)	0.26
(-)	(+)	(+)	(-)	Natural immunity after exposure HBV	56 (16%)	2 (1.9%)	<0.0001
(-)	(-)	(-)	(-)	Not infected, no immunization	119 (34.2%)	10 (9.7%)	<0.0001
(-)	(+)	(-)	(-)	Immunization	89 (25.6%)	8 (7.8%)	<0.0001
(-)	(-)/(+)	Missing	Missing	Simple screening	23 (6.6%)	26 (25.2%)	<0.0001
(-)	Missing	Missing	Missing	Simple screening	28 (8%)	30 (29.1%)	<0.0001
Missing	Missing	Missing	Missing	No screening	0 (0%)	20 (19.4%)	<0.0001
					Total (n) 348	Total (n) 103	

bDMARDS: Biologic synthetic disease modifying anti rheumatic drugs, csDMARDs: Conventional synthetic disease modifying anti rheumatic drugs, HBV: Viral hepatitis B, HBsAg: Hepatitis B surface antigen, anti-HBs: Hepatitis B surface antibody, anti HBc-IgM/G: Hepatitis B core antibody Immunoglobulin M and G, n: Number

the overall HBV screening rate in patients before receiving TNFi as 82.3%, and this rate had an increasing trend during the years (64% in 2010, 87.4% in 2019)[12]. In a large cohort study from Germany, the HBV screening rate was found to be 94% in patients using bDMARDs, and it was considered successful[13]. In our cohort, the data for viral hepatitis B for 20 patients were missing, all in the csDMARDs group (4.4% of total patients). Viral hepatitis B serology scans were performed on all the patients in bDMARDs (100%). However, 107 (23.7%) of total patients were evaluated with incomplete examination as simple screening (Table 2). This screening rates of viral hepatitis serology was detected as successful in patients both in the bDMARDs and csDMARDs groups in this study.

The risk of reactivation of HBsAg-positive patients who are under immunosuppressive therapy has been known for long years. The guidelines of the American Association for the Study of Liver Diseases (AASLD), the European Association for the Study of Liver Diseases (EASL), and the Asian Pacific Association for the Study of Liver Diseases (APASL) all recommend prophylaxis in HBsAg positive patients under immunosuppressive therapy[5,8,14].

However, over time, it has been determined that besides HBsAg positive patients, those who are HBsAg negative but have positive antibodies against the core antigen (anti-HBc-IgM and IgG) carry the risk of reactivation under certain immunosuppressive therapies. These patients actually have chronic hepatitis B (CHB) with HBsAg seroclearance but they still carry HBV DNA material in the liver. They may or may not have antibodies to anti-HBs. The only positive serologic marker indicating previous HBV exposure could be having anti-HBc. The risk of reactivation differs with the type of immunosuppressive therapy in this group. Treatments such as RTX, CSs, TNFi, and MTX used in rheumatology practice are some immunosuppressive regimens that have been shown to increase the risk of HBV reactivation at different rates (>10%, 1-10%, 1%, <1%, respectively) in HBsAg negative phase CHB patients. The guidelines of AASLD, APASL, and EASL include different recommendations for this patient group, such as close monitoring, HBV DNA control or giving prophylaxis directly according to immunosuppressive drug regimen with weak evidence. For a patient with natural immunity from prior exposure to HBV (Table 2), the American College of Rheumatology guidelines strongly recommend that treatments should be the same as that of unexposed patients, as long as the patient's viral load is monitored regularly every 6-12 months[15,16].

In the follow-up of the patients in this study, the national viral hepatitis screening and treatment recommendations of the Turkish Society for Rheumatology were applied[17]. The need for antiviral prophylaxis was arranged according to the factors of the patients and the immunosuppressive therapy they received. There were 39 patients who did not receive prophylaxis despite having HBsAg negative phase of chronic HBV infection; no HBV reactivation was observed in this group of patients using TNFi. The study of Fidan et al.[12] supported this finding and showed that the risk of reactivation in occult HBV cases was very low (0.4%) in patients using TNFi. Similarly, Lee et al.[9] showed HBV occult carriers had HBV reactivation risk with a rate of 1.7% when treated with TNFi. This rate rises to 11.3-18.9% (reactivation according to virologic endpoints) and 41.5% (reactivation according to HBV DNA) in patients taking RTX in previous studies[18,19]. In our cohort, all the patients with occult HBV under RTX were detected as taking prophylaxis.

For this reason, appropriate risk stratification is needed for individual types of immunosuppressive therapies[20]. Since the seroprevalence of anti-HBc could be very high among HBV endemic regions (>40%)[21], it would not be cost effective to use HBV prophylaxis directly in all patients taking immunosuppressive therapies[20]. Some researchers state that the necessity of routine anti-HBc screening also needs more evidence in the patients who will use immunosuppressive therapies associated with a low risk of HBV reactivation[12]. Similarly, this study showed that in daily practice, rheumatologists only screen HBsAg and anti-HBs for HBV in patients under immunosuppressive treatments with a low risk of HBV reactivation (Table 2). The conditions of national health insurances can also be effective in adopting this approach by limiting the blood tests per visit. In this study, the higher vaccination rates and the higher screening rates with detailed tests in the bDMARDs group compared to the csDMARDs group showed that the physicians acted more cautiously, considering the bDMARDs group to be more risky for HBV (Table 2). Similarly, the screening rates for HCV were found to be higher in the bDMARDs group.

Another remarkable finding in this study was the low HBV vaccination rates of the patients. One hundred twenty nine (28.6%) of the patients were evaluated as never infected and unvaccinated prior to immunosuppressive therapies; also, nearly half of them were still non-immune for HBV during their follow-up. These data showed that rheumatologists had suboptimal HBV immunization rates in patients with rheumatologic diseases receiving immunosuppressive therapies. The frequency of recommendation of HBV vaccine to non-immune patients by physicians might be low, the efficacy of vaccines administered under immunosuppressive therapies might be weak, or vaccines might not be double dosed in this patient group as the guidelines suggested. These findings indicated that whatever the cause, insufficient attention was paid to immunizing patients against HBV in follow-up. In the literature, these are the first study notifying data on vaccination rates in the follow-up of the immunosuppressive patient group.

Study Limitations

As strength, this study was a cohort study based on real-life data. In the literature, it was observed that most of the studies investigating the approaches of physicians to HBV screening and treatment were interview-based studies. However, more detailed results can be obtained by keeping the number of participating rheumatologists and clinical centers larger. As limitations, in the study, the follow-up time was short and the design of the study was in a retrospective nature.

CONCLUSION

In conclusion, this study suggested that the screening rates of viral hepatitis serology were detected as satisfactory in patients under immunosuppressive therapies. Although the cohort included cases of occult hepatitis B using TNFi and not receiving prophylaxis, no HBV reactivation was observed in the entire group. Moreover, this study showed that there was a significant deficiency in vaccination against HBV in non-immune patients in follow-up.

Ethics

Ethics Committee Approval: The study was performed according to the Declaration of Helsinki and Bursa City Hospital Ethics Board approved the study with approval number 2021-13/8, date: 14.07.2021.

Informed Consent: Retrospective study.

Peer-review: Externally peer-reviewed.

Authorship Contributions

Surgical and Medical Practices: G.K., M.N.T., Concept: G.K., Design: G.K., Data Collection or Processing: G.K., M.N.T., Analysis or Interpretation: G.K., M.N.T., Literature Search: G.K., M.N.T., Writing: G.K.

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