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New onset liver test elevations with biological treatments in patients with rheumatological diseases

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Abstract

To identify the incidence and characteristics of liver enzyme elevations following initiation of biological treatments in patients with rheumatological diseases. Patients with rheumatological diseases taking biological treatments were analyzed retrospectively for new onset liver test abnormalities. Disease type, duration of treatment, concomitant medications, hepatitis b status and laboratory tests were recorded. Elevation of transaminases was defined as grade 1 if ALT elevation was 2–3 times the ULN, grade 2 if ALT ≥3xULN and grade 3 if ALT was ≥5xULN. RUCAM score was used to assess likelihood of causal association between liver toxicity and biological treatments. A total 418 patients were included. 46 (11%) patients had grade 2 ALT elevation. Mean treatment duration to ALT elevation from baseline was 200.5±255.4 and 67.3±54.0 days for patients with grade 2 and grade 3 ALT elevation, respectively (p:0.001). DMARDs use and the type of the biological agent used were not different for patient with grade 2 ALT elevation or not. 29 (6.9%) patients had RUCAM score of 3-5, thus possibly having DILI. No patient had RUCAM score of six or higher. Mild and transient enzyme elevations are relatively frequent with biological treatments. But, likelihood of causal association between liver toxicity and these therapies is usually low. Concurrent medications should be reviewed cautiously in each issue.

Keywords: Anti-TNF, biological agents, liver toxicity

Introduction

Several prescribed and herbal medications could be associated with drug-induced liver injury (DILI). DILI accounts for 10% of all acute hepatitis cases and is the leading cause of acute liver failure in USA [1,2]. Medications used in rheumatologic diseases could be related occasionally with liver test abnormalities. Non-steroidal anti-inflammatory drugs (NSAID) and methotrexate have been frequently used in rheumatological diseases and could result in significant hepatotoxic injury [3]. Over last decades, significant changes in the treatment of rheumatological diseases have occurred. Anti-tumor necrosis factor (TNF)-α agents and other biological agents have been increasingly used for the treatment of patients with rheumatic diseases. However, most of these agents have been reported to be associated to some extent with hepatotoxic injury [4,5]. Currently, five TNF-α antagonists have been approved for clinical use: infliximab (IFX), adalimumab (ADA), certolizumab pegol (CER), etanercept (ETA) and golimumab (GOL). Other biological agents with increasing use in rheumatological diseases include tofacitinib (JAK inhibitor), tocilizumab (humanized monoclonal antibody against interleukin (IL)-6 receptor), secukinumab (human monoclonal antibody against IL-17-A), abatacept (fusion protein composed of Fc region of Ig G1 fused to the extracellular domain of cytotoxic t-lymphocyte associated protein-4 (CTLA-4)) and ustekinumab (monoclonal antibody against IL-12 and IL-23). Increasing number of cases of liver injury with anti-TNF-α agents have been reported [6,7]. DILI is defined as alanine aminotransferase (ALT) >3× upper limit of normal (ULN) or an increase to >3× baseline if baseline was abnormal [8]. DILI secondary to biological agents may not be differentiated from other causes of abnormal liver tests in patients with rheumatological diseases duo to the frequent use of NSAII, methotrexate and other medications.

The aim of this study is to determine the frequency and nature of liver test abnormalities among patients with rheumatological diseases receiving biological agents and to define the most likely underlying etiology and associated patient-related factors in a single tertiary center.

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Material and Methods

This retrospective study included all consecutive patients treated with biological agents in Adana Baskent University Dr. Turgut Noyan Education and Research Center from January 2011 to June 2020. The study was approved by the Institutional Review Board of Adana Baskent University Dr. Turgut Noyan Education and Research Center. Patients having diagnosis of rheumatoid arthritis, psoriatic arthritis, ankylosing spondylitis or other spondyloarthropathies treated with at least one of biological agents including infliximab, adalimumab, etanercept, certolizumab pegol, golimumab, tocilizumab, tofacitinib, secukinumab, or abatacept and followed for at least six months were included. Comorbid diseases, alcohol use, disease duration, duration of treatment with biological agent and concomitant medications (including disease modifying drugs (DMARDs), isoniazid, steroids, NSAIDs) were recorded for all patients.

Laboratory parameters, including complete blood count, liver enzymes, hepatitis B and C serological tests (Hbsag, anti-hbs ab, anti hbc Ig G, anti-HCV) obtained on regular follow ups were recorded. Patients were grouped as uninfected (Hbsag: negative, antihbs: negative), Hbsag positive (Hbsag: positive) and anti hbc: positive/ Hbsag: negative. Basal and peak ALT levels were detected. Upper limit of normal for ALT levels were accepted as 33 units/L for males and 25 units/L for females [9]. Elevation of transaminases was defined as grade 1 if ALT elevation was 2–3 times the ULN, grade 2 if ALT elevation was equal or more than 3 times the ULN and grade 3 if ALT was ≥5xULN. Type and duration of biological agent and concomitant medication used at the time of peak ALT elevation were recorded separately. The Roussel Uclaf Causality Assessment Method (RUCAM) score includes clinical and pathological outcomes to define the likelihood that liver injury is caused by specific drug exposure [10]. RUCAM scoring was applied in all patients with abnormal liver tests (ALT>3xULN) to assess the likelihood of DILI. A score of 0 or lower excludes DILI and 1-2 means unlikely DILI. Whereas scores of 3-5, 6-8 and >8 for RUCAM point to possible, probable and highly probable DILI, respectively [10,11].

Exclusion criteria included age <18 years, non-compliance with treatment and regular follow-up, diagnosis of chronic liver disease including primary sclerosing cholangitis, cirrhosis or primary biliary cholangitis.

Statistical analysis

Statistical analysis was performed using SPSS software (version 23.0, IBM Corp., Armonk, NY, USA). Normally distributed continuous variables were described as means±standard deviations and compared by using the t-test. For comparison of categorical variables, Chi-squared test was used. Univariate logistic regression test was used to define risk factors for grade 1 and grade 2 enzyme elevations. Values of $p<0.05$ were considered indicative of statistical significance.

Results

From January 2011 to June 2020, 418 patients treated with biological agents and followed on Rheumatology Clinic of Adana Baskent University Dr. Turgut Noyan Education and Research Center were included. The mean age of patients was 49.7 ±13.4 years. 253 patients (60.5%) were female. Indications for therapy with biological agents were ankylosing spondylitis in 193 (46.2%), rheumatoid arthritis in 172 (41.1%), psoriatic arthritis in 35 (8.4%) and other spondyloarthropathies in 18 (4.3%) patients. Total of 354 patients (84.7%) were being treated with disease - modifying anti- rheumatic drugs (DMARDs) including methotrexate (MTX), sulfasalazine (SLZ), leflunomide (LEF), or hydroxychloroquine (HCQ) concurrently with biological agents. The mean treatment duration with biological agents was 66.1±29.3 months. Treatment modalities included anti-TNF treatments in 393 (94.0%) and other agents (including tocilizumab, tofacitinib, secukinumab or abatacept) in 25 (6%) patients. Demographic and laboratory findings of all patients are shown in table 1.

A total of 115 (27.5%) patients had ALT elevation of more than 2 times the ULN (grade 1), while ALT >3xULN (grade 2) and ALT>5x ULN (grade 3) were seen in 46 (11%) and 12 (2.9%) of all patients, respectively. Age, gender, disease type, disease age, DMARDs use, and type of the biological agent used were not different among patients with and without grade 2 ALT elevation ($p>0.05$). Compared to patients with normal ALT levels, basal ALT (p: 0.027) was higher and biological treatment duration (p 0.019) was longer among patients with grade 2 ALT elevation. INH use was also significantly more frequent among patients with ALT >3xULN (p:0.003). Four (3.7%) of 107 patients with Hbsag negativity and anti-hbc positivity had grade 2 ALT elevation, while 41 (13.3%) of 308 patients uninfected with hepatitis B had grade 2 ALT elevation (p:0.034). ALT elevation rate among uninfected and Hbsag positive patients were similar, while it was lower among hbsag: negative/anti-hbc: positive group. Anti-hbc positivity was not related with ALT elevation for cases taking biological treatment without pre-emptive anti-viral treatment. Table 2 shows demographics of patients with ALT>3xULN and ALT<3xULN.

132 patients had ultrasound examination which revealed normal findings in 47 patients, while mild and moderate to severe steatosis in 44 and 41 patients, respectively. Rate of grade 2 ALT elevation was similar between these groups ($p>0.05$). No patient had alkaline phosphatase elevation of more than 2 times the ULN or total bilirubin over 1.5mg/dl.

Univariate regression analysis identified INH treatment (p:0.002, OR=2.741), duration of biological treatment (p:0.021, OR=1.010) and basal ALT (p:0.003, OR=1.026) as risk factors for grade 2 hepatocellular toxicity (ALT >3x ULN) (Table 3).

Mean treatment duration to ALT elevation from baseline was 200.5±255.4 and 67.3±54.0 days for patients with grade 2 and grade 3 ALT elevation, respectively (p:0.001). RUCAM scores did not differ between these group of patients ($p>0.05$) (Table 4). No patient in cohort had RUCAM score of ≥6, meaningly no case of probable or highly probable of biological agent related DILI was detected. 17 of 46 patients with ALT >3xULN had RUCAM score of 1-2, thus having unlikely DILI. Remaining 29 (6.9%) patients had RUCAM score of 3-5, thus possibly having DILI. Only 4 patients had RUCAM score of five. In 7 out of 29 patients, anti-TNF treatment (1 infliximab, 3 etanercept, 2 adalimumab and 1 golimumab) was switched to an alternative biological agent. Remaining patients continued the biological treatment. Steroid treatment was not used in any patient with RUCAM score of ≥3.

Table 1. Demographics and laboratory tests of all patients

			All patients (n:418)
Age (years)*			49.7 ±13.4
Female	**n (%)**		253 (60.5)
Underlying disease	**n (%)**	AS	193 (46.2)
		RA	172 (41.1)
		PSA	35 (8.4)
		SPA	18 (4.3)
DMARDs	**n (%)**	Methotreate	155 (37.1)
		Leflunomide	75 (17.9)
		Sulfasalazine	81 (19.4)
		Hydroxychloroquine	62 (14.8)
Treatment	**n (%)**	Infliximab	42 (10)
		Adalimumab	155 (37.1)
		Etanercept	108 (25.8)
		Golimumab	50 (12)
		Certolizumab pegol	38 (9.1)
		Tocilizumab	18 (4.3)
		Secukinumab	3 (0.7)
		Tofacitinib	3 (0.7)
		Abatacept	1 (0.2)
Hepatitis B status	**n (%)**	Uninfected	308 (73.7)
		Hbsag (+)	3 (0.7)
		Hbsag (-), anti Hbc (+)	107 (25.6)
Anti-HCV positive			6 (1.4)
Isoniazid use			95 (22.7)
Basal ALT*			25.5 ±14.6
Peak ALT*			52.6± 47.0
ALP *			84.1 ±23.3
Total bilirubin*			0.57± 0.22
Abnormal ALT	**n (%)**	Grade 1 (> 2xULN)	115 (27.5)
		Grade 2 (> 3xULN)	46 (11)
		Grade 3 (> 5xULN)	12 (2.9)
Comorbidities	**n (%)**	Diabetes Mellitus	61 (14.6)
		Hypertension	73 (17.5)
		Hypothyroid	19 (4.5)
		Obesity	18 (4.3)
		Crohn's Disease	7 (1.7)
		Ulcerative Colitis	4 (0.96)

Abbreviations: ALT: Alanine aminotransferase, ULN: Upper limit of normal, HCV: Hepatitis C Virus, AS: Ankylosing spondylitis, RA: Rheumatoid arthritis, PSA: Psoriatic arthritis, SPA: Spondyloarthropathies, DMARD: Disease modifying drugs. *Mean ± Standard Deviation

Table 2. Characteristics of patients with and without liver test abnormality

		ALT>3xULN (n:46)	**ALT<3xULN (n: 372)**	**P**
Age *		49.1±12.3	49.8±13.5	
Female /Male		29/17	224/148	0.735
Duration of biological treatment (months)*		66.1±29.2	53.9±33.1	0.75
Time to onset (days)*		200.5±255.4	N/A	0.019
Disease age *		11.4±7.9	9.6±6.7	
Basal ALT*		32.2±22.1	24.6±13.3	0.098
Peak ALT*		143.41±91.23	41.44±18.09	0.027
RUCAM*		2.89±0.99	--	<0.0001
Disease	**n (%)**			
AS		19(41.3)	174(46.8)	0.571
RA		23(50)	149(40.1)	
PSA		3(6.5)	32(8.6)	
SPA		1(2.2)	17(4.6)	
DMARDs	**n (%)**	38(82.6)	316(84.9)	0.666
Methotrexate	**n (%)**	20(43.5)	135(36.3)	0.419
Leflunomide	**n (%)**	9(19.6)	66(17.7)	0.839
Sulfasalazine	**n (%)**	5(10.9)	76(20.4)	0.165
Hydroxychloroquine	**n (%)**	3(6.5)	59(15.9)	0.224
Isoniazid	**n (%)**	19(41.3)	76(20.4)	0.003
Hep B status				
Uninfected		41(89.1)	267(71.8)	0.034
Hbsag (+)		1(2.2)	8(2.1)	
Hbsag (-), anti Hbc (+)		4(8.7)	97(26.1)	
Peak biological agent	**n (%)**			
Infliximab		6(14.3)	36(85.7)	0.142
Adalimumab		16(10.3)	139(89.7)	
Etanercept		11(10.2)	97(89.8)	
Golimumab		4(%8)	46(92)	
Certolizumab pegol		4(10.5)	34(89.5)	
Tocilizumab		4(22.2)	14(77.8)	
Secukinumab		0(0)	3(100)	
Tofacitinib		0(0)	3(100)	
Abatacept		1(100)	0(0)	

Abbreviations: ALT: Alanine aminotransferase, ULN: Upper limit of normal, RUCAM: Roussel Uclaf Causality Assessment Method, AS: Ankylosing spondylitis, RA: Rheumatoid arthritis, PSA: Psoriatic arthritis, SPA: Spondyloarthropathies, DMARD: Disease modifying drugs. *Mean ± Standard Deviation

In 8 out of 12 patients with grade 3 ALT elevation, hepatocellular toxicity was associated with INH and with one exception, liver tests were normalized after the cessation of INH. In one patient therapy was changed from adalimumab to certolizumab pegol for full normalization of liver tests. NSAIDs were causative agents for liver toxicity for 2 other patients. Leflunomide and methotrexate were causative agents for remaining two patients. Liver tests were normalized on follow up for all those patients.

Table 3. Univariate analysis of risk factors for grade 1 and grade 2 liver enzyme elevations

		ALT>2x ULN (n: 115)		ALT>3x ULN (n: 46)	
		p	OR; 95% CI	p	OR; 95% CI
Age		0.390	0.993; 0.977-1.009	0.734	0.996; 0.974-1.019
Female /Male		0.930	0.980; 0.632-1.522	0.711	0.887; 0.471-1.672
Duration of biological treatment (months)		0.015	1.008; 1.002-1.014	0.021	1.010; 1.001-1.018
Time to onset (days)		0.154	1.005; 0.988-1.012	0.095	1.007; 0.999-1.016
Disease age		0.457	1.012; 0.981-1.043	0.101	1.033; 0.994-1.074
Basal ALT		0.001	1.036; 1.020-1.053	0.003	1.026; 1.009-1.043
Peak ALT		0.001	1.259; 1.186-1.337	0.001	1.203; 1.120-1.291
Disease	**n (%)**				
AS		0.708		0.581	
RA		0.434	1.510; 0.538-4.243	0.558	0.539; 0.068-4.276
PSA		0.644	1.208; 0.541-2.696	0.815	0.859; 0.240-3.071
SPA		0.306	1.273; 0.802-2.021	0.293	1.414; 0.741-2.697
DMARDs	**n (%)**	0.091	1.178; 0.911-3.469	0.678	0.842; 0.373-1.899
Methotrexate	**n (%)**	0.234	1.306; 0.841-2.026	0.342	1.350; 0.726-2.511
Leflunomide	**n (%)**	0.219	1.400; 0.818-2.395	0.761	1.128; 0.519-2.449
Sulfasalazine	**n (%)**	0.356	0.766; 0.435-1.349	0.129	0.475; 0.181-1.243
Hydroxychloroquine	**n (%)**	0.028	0.449; 0.220-0.917	0.098	0.363; 0.109-1.208
Isoniazid	**n (%)**	0.005	2.004; 1.234-3.254	0.002	2.741; 1.447-5.191
Hep B status	**n (%)**				
Uninfected		0.090		0.050	
Hbsag (+)		0.344	1.908; 0.501-7.266	0.848	0.814; 0.099-6.679
Hbsag (-), anti Hbc (+)		0.058	0.589; 0.341-1.018	0.014	0.269; 0.094-0.769
Peak biologic agent	**n (%)**				
Infliximab		0.811	0.821; 0162-4.152	0.399	0.567;0.151-.2120
Adalimumab		0.307	0.448; 0.096-2.092	0.102	0.391; 0.127-1.204
Etanercept		0.227	0.381; 0.080-1.820	0.112	0.386; 0.119-1.250
Golimumab		0.242	0.376; 0.073-1.938	0.094	0.296; 0.071-1.233
Certolizumab pegol		0.662	0.693; 0.134-3.575	0.212	0.400; 0.095-1.685
Tocilizumab		0.749	1.333; 0.230-7.743	0.849	0.120; 0.075-0.692

Abbreviations: ALT: Alanine aminotransferase, ULN: Upper limit of normal, RUCAM: Roussel Uclaf Causality Assessment Method, AS: Ankylosing spondylitis, RA: Rheumatoid arthritis, PSA: Psoriatic arthritis, SPA: Spondyloarthropathies, DMARD: Disease modifying drugs.

Table 4. Comparison of time to onset and RUCAM scores for gr 2 and 3 transaminase elevations

	ALT > 5x ULN (n:12)	ALT >3xULN (n:46)	p
Time to onset (Days)*	67.3± 54.0	200.5 ±255.4	0.001
RUCAM*	3.16± 1.11	2.79 ±0.94	0.269

Abbreviations:ALT: Alanine aminotransferase, ULN: Upper limit of normal, RUCAM: Roussel Uclaf Causality Assessment Method, *Mean ± Standard Deviation

Discussion

We investigated the incidence of liver test elevation among 418 patients under biological treatment due to rheumatological diseases. Grade 1 ALT elevation was relatively frequent, but grade 2 enzyme elevation was less common, seen in 46 (11%) of all our patients. Only 29 patients (6.9%) had RUCAM score of ≥3, with no patient having RUCAM score of ≥6. Thus, no patient in our cohort had probable and highly probable case of DILI associated with use of biological agent. The most common presentation of liver toxicity has been reported to be hepatocellular type [12]. Similarly, no patient in our study had ALP more than 2 times the ULN or total bilirubin level higher than 1.5 mg/dl.

In our study, 115 (27.5%) patients had ALT higher than 2 times the ULN. Brazdilova et al. reported grade 1 ALT elevation (1-3 x ULN) in 25.6 % of all patients undergoing anti-TNF treatment due to rheumatological diseases. ALT above 3xULN was reported only in 1.5% of all patients in that study [13]. As markedly different, ALT elevation of more than 3xULN was seen in 46 (11%) of our patients. Although in a different group of patients with inflammatory bowel disease (IBD), a prospective observational study by Koller et al. reported ALT elevation of less than 3× ULN in 26 (16%) patients under infliximab treatment [14]. Mild and transient enzyme elevation in this study was reported to be associated with higher BMI score, presence of hepatic steatosis, longer disease

duration, and infliximab monotherapy on multivariate analysis. In our study, biological treatment duration, INH use and basal ALT level were related with grade 2 liver enzyme elevation, while the type of treatment was not. In a report by Parisi et al, elevated liver enzymes were present in 39% of 176 IBD patients on infliximab. Similar with our study, enzyme elevation was associated with increased basal ALT (OR 3.854) and longer duration of infliximab treatment (OR 1.030) [15]. In contrast with our study, in a study with small number of patients, among patients with anti-TNF and immunomodulator use INH chemoprophylaxis was not defined as a strong risk factor for hepatotoxicity [16].

Mean duration of treatment to first ALT elevation was 200 days (28.5 weeks) that is similar to 29 weeks reported by Shelton et al. for IBD patients under TNF treatment [17]. In a report by Björnsson et al. mean time to ALT elevation was 14 weeks following anti-TNF treatment among patients mainly with rheumatologic diseases. Nine of 11 patients with anti-TNF related liver toxicity in this study were associated with infliximab use [18]. Infliximab was used in 42 (10%) of all cohort in our study. This low use of infliximab may explain the different mean time to ALT elevation in our study. In literature, infliximab is the most commonly reported anti-TNF to be associated with liver test abnormalities [17,18]. In contrast to literature, incidence of grade 2 ALT elevation did not differ according to the biological agent used in our study.

In a study by Shelton et al. among 1753 IBD patients treated with anti-TNF, 102 patients had ALT elevations and 48 (2.7%) of them were suspected to have anti-TNF-related liver enzyme elevation (RUCAM ≥3). Almost 50% of patients with ALT elevation had any other identifiable cause. Among those with RUCAM ≥3, 24 patients were possibly inked to anti TNF, whereas 4 and 20 patients were highly probably and probably linked to anti-TNF. Infliximab was used in 45 of those 48 patients [17]. In our study, 46 (11%) of all patients had ALT elevation of more than 3 times the ULN. But, only 29 patients had RUCAM score of 3-5, thus possibly having DILI associated with anti-TNF or other biological therapies, with no probable and highly probable case of DILI. Since it is the most frequently implicated drug with anti-TNF related liver toxicity, less frequent use of infliximab in our cohort may be an explanation for the absence of highly probably or probably link between liver toxicity and anti-TNF. Also, use of concurrent medications is more pronounced in rheumatological diseases than it is in IBD patients, especially for NSAID and DMARDs. Liver test abnormalities caused by those medications could make it difficult to establish a definite causality between biological agents and liver toxicity.

Anti-TNF users with HbsAg positivity were reported to have almost eight-fold higher likelihood of ALT elevation than uninfected patients [19]. In our study, Hbsag positivity was not associated with higher rate of ALT elevation. Compared to uninfected group, ALT elevation rate was even lower among hbsag: negative/anti-hbc: positive group (89.1% vs 8.7%, respectively).

There are some limitations of our study. Firstly, this is a retrospective study with relatively small number of patients. Due to the lack of some specific parameters, it was not possible to identify further risk factors for ALT elevation. Secondly, less than one third of all patients had radiological assessment. Thus, impact of fatty liver could not be defined clearly. Thirdly, there is no histopathological assessment for any patient. Thus, histological basis for the mild and transient ALT elevations which might be truly associated with biological treatments is missed.

Conclusion

In conclusion, mild to moderate ALT elevation is seen relatively frequently with use of biological treatments in rheumatological diseases. Most of the ALT elevations were not specifically related with anti-TNF or other biological agents and usually resolved on follow-up without requiring any switch in treatment. Further prospective and controlled studies are needed to identify risk factors in biological agent-related toxicity and safe borders to continue treatment in the case of liver toxicity.

Conflict of interests
The authors declare that there is no conflict of interest in the study.

Financial Disclosure
The authors declare that they have received no financial support for the study.

Ethical approval
The study was approved by the Institutional Review Board of Adana Baskent University Dr. Turgut Noyan Education and Research Center.

References

1. Ostapowicz G, Fontana RJ, Schiødt FV, et al. Results of a prospective study of acute liver failure at 17 tertiary care centers in the United States. Ann Intern Med. 2002;137:947-54.

2. Larson AM, Polson J, Fontana RJ, et al. Acetami¬nophen-induced acute liver failure: results of a United States multicenter, prospective study. Hepatology. 2005;42:1364-72.

3. Björnsson ES. Drug-induced liver injury: an overview over the most critical compounds. Arch Toxicol. 2015;89:327-34.

4. Björnsson ES, Bergmann OM, Björnsson HK,et al. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. Gastroenterol. 2013;144:1419-25.

5. Worland T, Chin KL, van Largenberg D, et al. Retrospective study of idiosyncratic drug-induced liver injury from infliximab in an inflammatory bowel disease cohort: the IDLE study. Ann Gastroenterol. 2020;33:162-9.

6. Ghabril M, Bonkovsky HL, Kum C, et al. Liver injury from tumor necrosis factor-αantagonists: analysis of thirty-four cases. Clin Gastroenterol Hepatol. 2013;11:558–64.

7. Rossi RE, Parisi I, Despott EJ, et al. Anti-tumour necrosis factor agent and liver injury: Literature review, recommendations for management. World J Gastroenterol. 2014; 20:17352–9

8. Fontana RJ, Watkins PB, Bonkovsky HL, et al; DILIN Study Group. Drug-Induced Liver Injury Network (DILIN) prospective study: rationale, design and conduct. Drug Saf. 2009; 32:55-68

9. Kwo PY, Cohen SM, Lim JK. ACG Clinical Guideline: Evaluation of abnormal liver chemistries. Am J Gastroenterol. 2017;112:18.

10. Danan G, Benichou C. Causality assessment of adverse reactions to drugs—I. A novel method based on the conclusions of international consensus meetings: application to drug-induced liver injuries. J Clin Epidemiol. 1993;46:1323–30.

11. Benichou C, Danan G, Flahault A. Causality assessment of adverse reactions to drugs—II. An original model for validation of drug causality assessment methods: case reports with positive rechallenge. J Clin Epidemiol. 1993;46:1331–3.

12. Lopetuso LR, Mocci G, Marzo M, et al. Harmful Effects and Potential Benefits of Anti-Tumor Necrosis Factor (TNF)-α on the Liver. Int J Mol Sci. 2018;19:2199.

13. Brazdilova K, Koller T, Killinger Z, Payer J. Prevalence and Risk Factors for Drug-Induced Liver Injury Among Patients With Rheumatic Diseases Treated With Biological Therapy: A Single-Center Experience. Physiol. Res. 2019; 68:S157-S63.

14. Koller T, Galambosova M, Filakovska S, et al. Drug-induced liver injury in inflammatory bowel disease: 1-year prospective observational study. World J Gastroenterol. 2017;23:4102–11.

15. Parisi I, O'Beirne J, Rossi RE, et al. Elevated liver enzymes in inflammatory bowel disease: the role and safety of infliximab. Eur J Gastroenterol Hepatol.2016;28:786-91

16. Shelton E, Chaudrey K, Sauk J, et al. New onset idiosyncratic liver enzyme elevations with biological therapy in inflammatory bowel disease. Aliment Pharmacol Ther. 2015;41:972–9.

17. Cansu DÜ, Güncan S, Bilge NŞY, et al. Does isoniazid chemoprophylaxis increase the frequency of hepatotoxicity in patients receiving anti-TNF-α agent with a disease-modifying antirheumatic drug? Eur J Rheumatol. 2014;1:62-6

18. Björnsson ES, Gunnarsson BI, Gröndal G, et al. Risk of Drug-Induced Liver Injury From Tumor Necrosis Factor Antagonists. Clin Gastroenterol Hepatol. 2015;13:602–8.

19. Chiu YM, Lai MS, Chan KA. Assessing risk of liver enzyme elevation in patients with immune-mediated diseases and different hepatitis B virus serostatus receiving anti-TNF agents: a nested case control study. Arthritis Res Ther. 2017;19:214.