Prevalence and Risk Factors for Drug-Induced Liver Injury Among Patients With Rheumatic Diseases Treated With Biological Therapy: A Single-Center Experience

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Summary

Drug-induced liver injury (DILI) is a common event in patients with rheumatic diseases (RD) on biological therapy (BT). We aimed at evaluating the prevalence and pattern of DILI. Consecutive RD patients treated with BT were followed for 6 months. ALT and ALP >the upper limit normal (ULN) and <to 3xULN defined injury Grade 1 and >3xULN injury Grade 2. 582 liver function tests (LFTs) in 199 patients were evaluated, median age 53y, 59.3 % females, RA in 108, AS 49, and PsA 42 patients. ALT Grade 1 elevation was observed in 25.6 %, transient in 18.6 %, persisting in 7 %, Grade 2 in 1.5 %, ALP Grade 1 in 3.5 %, transient in 2 %, persisting in 1.5 %. We report no case of ALP Grade 2 or Hy´s law (ALT>3xULN, bilirubin>2xULN). Patients with persisting ALT elevation had higher BMI (28.23 vs. 25.74, p=0.016), lower DAS28 (2.22 vs. 5.28, p=0.046). ALT Grade 1 injury was more frequent with solo tocilizumab compared with other agents (27.5 % vs. 13.6 %, p=0.01). DILI was frequent, in 18.6 % transient, in 7 % persisting, Grade 2 in 1.5 %, led to treatment alteration in 0.5 %, with higher prevalence on solo tocilizumab therapy. We report no new safety signals for BT in RD.

Key words

Drug-induced liver injury • Rheumatic diseases • Biological therapy

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Introduction and Aims

Drug-induced liver injury (DILI) is one of the most common and serious adverse drug reactions (Leise *et al.* 2014). It is the most common cause of acute liver failure in the USA and Europe and also a frequent differential diagnosis in patients with acute liver injury (Björnsson 2016). Liver injury has been reported from nearly all classes of prescription drugs including small chemical molecules, biological agents, but also traditional Chinese medicines, natural medicines, and herbal and dietary supplements. Nonsteroidal anti-inflammatory drugs (NSAIDs) and antirheumatic agents are among the more frequent causes of hepatotoxic injury (Björnsson 2015). Rheumatic diseases usually require long-term therapy with a single drug, but multiple agents are often required for disease control. Recently, medical therapy for rheumatic diseases is rapidly evolving. New molecules with different mechanisms of action are being developed and marketed. With the widespread use of these new products, clinicians caring for patients with rheumatic disease are challenged with their potential side-effects and toxicities (Anelli *et al.* 2012). Rare cases of DILI are usually not captured in clinical trials and occur only after the drug is used in real-life (Kaplowitz 2013). Therefore, the aim of our study was to evaluate liver injury in the cohort of real-life rheumatic disease patients treated with various biological agents as well as with traditional anti-rheumatic drugs. We aimed at evaluating the prevalence of liver injury, the pattern and risk factors as well as the evolution and clinical impact of potential toxicity.

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Patients and Methods

We included all consecutive patients from the Center for the biological treatment of rheumatic diseases of the teaching University Hospital during the period from 1st January 2015 to 1st June 2016. The inclusion criteria were 1) treatment with biological therapy for rheumatoid arthritis, ankylosing spondylitis or psoriatic arthritis at the center, 2) compliance with regular follow-up controls during the study period that included blood testing for LFTs at 3-month intervals. We included all eligible patients regardless of the treatment duration. Prior to initiation of the biologic therapy, all patients underwent evaluation for possible liver injury including viral hepatitis (negative HBs antigen, negative anti-HCV) and liver function tests (LFTs). LFTs had to be in the normal range prior to treatment start. Patients who were diagnosed with chronic LFTs elevation or chronic liver disease, patients with severe systemic disease such as chronic heart failure, chronic renal failure, pulmonary hypertension, obstructive pulmonary disease, systemic vasculitis, lupus erythematosus or active malignancies were excluded. Obesity or diabetes was not considered an exclusion criterion. Liver ultrasound or elastography was not systematically performed in all included patients.

Liver injury was monitored by measuring serum aminotransferase activities, alanine aminotransferase (ALT, hepatocellular injury), alkaline phosphatase (ALP, cholestatic injury), gamma glutamyl-transferase (GGT) and bilirubin. Mild liver injury (Grade 1) was defined as ALT, ALP or GGT elevation above the upper limit of the normal range (ULN) and inferior to three times the upper limit of normal (ULN). More severe injury (Grade 2) was defined as ALT elevation above 3 times the ULN, as defined by the Food and drug administration (FDA) or the European medicines agency (EMA). The evolution of liver injury was labeled as transient when ALT elevation was observed on 1 or 2 measurements. Persisting (chronic) elevation was diagnosed when ALT elevation was observed in all three measurements. The severity of the liver injury was also assessed by the prevalence of Hy´s law defined by ALT elevation of more than 3 times the ULN and bilirubin elevation superior to two times the ULN. The presence of Hy´s law signals the possibility of severe liver injury, acute liver failure or death (Kaplowitz 2013). We also recorded anthropometric variables, disease-specific variables such as activity index (Disease Activity Score, DAS28) and (Bath Ankylosing Spondylitis Disease Activity Index, BASDAI score) and all ongoing therapies among anti-rheumatic drugs and biological agents. The DAS 28 is a system developed and validated by the EULAR (European League Against Rheumatism) to measure the progress and improvement of rheumatoid arthritis, but it's used also in patients with psoriatic arthritis. It's a composite score derived from 4 of these measurements: the number of swollen joints, the number of tender joints, ESR (erythrocyte sedimentation rate) or CRP (C reactive protein), and a patient's global assessment of health. The BASDAI is a validated diagnostic test that allows determining the effectiveness of current drug therapy in patients with ankylosing spondylitis. It consists of a 0-10 scale measuring discomfort, pain, and fatigue.

Table 1. Summary statistics and characteristics of 199 patients with rheumatic diseases treated with biological therapy

	Median [IQR]/n (%)
Age	53.00 [24.00, 85.00]
Males (%)	81 (40.7)
Females (%)	118 (59.3)
BMI	26.03 [15.44, 42.52]
Ultrasound (n=24)	
Disease duration (years)	12.50 [2.00, 46.00]
Rheumatoid arthritis (%)	108 (54.3)
DAS 28 score	2.57 [0.63, 7.50]
Ankylosing spondylitis (%)	49 (24.6)
BASDAI score	1.40 [0.00, 8.90]
Psoriatic arthritis (%)	42 (21.1)
Ongoing treatment:	
Steroids	38 (19.1)
Non-steroidal anti-inflammatory	27 (13.6)
Methotrexate	87 (43.7)
Infliximab	2 (1.0)
Adalimumab	82 (41.2)
Adalimumab and methotrexate	40 (20.1)
Certolizumab	4 (2.0)
Etanercept	34 (17.1)
Etanercept and methotrexate	12 (6.0)
Golimumab	40 (20.1)
Golimumab and methotrexate	21 (10.6)
Tocilizumab	32 (16.1)
Tocilizumab and methotrexate	9 (4.5)

Data were assessed by the statistical software package MedCalc v.15.2, Belgium. Numerical variables were expressed as medians and interquartile range and proportions as numbers of cases and percentages. Liver enzyme activities were expressed as multiples of an upper limit of the normal range (xULN). Results were considered significant when *p* values were inferior to 0.05.

The study had an observational character with no protocol intervention and it was carried out in accordance with the proceedings of the Helsinki declaration. Data were anonymized according to our institutional guidelines and the study protocol was approved by our institutional ethics committee.

Table 2. Prevalence of all patterns of liver injury during 6 months of follow-up among 199 patients with rheumatic diseases treated with biological therapy

		N (%)
ALT above ULN (%)	*never*	148 (74.4)
	once	22 (11.1)
	twice	15 (7.5)
Transient ALT above ULN (%)		37 (18.6)
Persiting ALT above ULN (%)		14 (7.0)
ALT above 3xULN (%)		3 (1.5)
ALP above ULN (%)	*never*	192 (96.5)
	once	2 (1.0)
	twice	2 (1.0)
Transient ALP above ULN (%)		4 (2.0)
Persiting ALP above ULN (%)		3 (1.5)
ALP above 3xULN (%)		0 (0)
GGT above ULN (%)	*never*	159 (79.9)
	once	9 (4.5)
	twice	14 (7.0)
Transient GGT above ULN (%)		23 (11.6)
Persiting GGT above ULN (%)		17 (8.5)
GGT above 3xULN (%)		8 (4.0)

ULN - upper limit of normal, ALT - alanine aminotransferase, ALP - alkaline phosphatase, GGT - gamma glutamyl transpeptidase

Results

During the inclusion period, we included 199 patients with rheumatic diseases and during follow-up, we evaluated 582 aminotransferase measurements. Summary statistics and characteristics of the study cohort are displayed in Table 1. The median age was 53 years and 59.3 % of patients were females. The median disease duration was 12.5 years. 108 patients had rheumatoid arthritis (54.3 %), 49 had ankylosing spondylitis (24.6 %) and 42 had psoriatic arthritis (21.1 %). All patients were treated with biological therapy. In addition, 87 patients were treated with methotrexate (43.7 %), 27 patients with non-steroidal anti-inflammatory agents (13.6 %) and 38 patients with steroids (19.1 %).

The prevalence of liver injury in our study cohort is displayed in Table 2. ALT elevation above the ULN was observed in 51 patients (25.6 %). Mild transient ALT elevation was observed in 37 patients (18.6 %) and persisting (chronic) ALT elevation in 14 patients (7 %). ALT elevation above 3 times the ULN (Grade 2) was observed in 3 cases (1.5 %). One patient was treated with solo golimumab, one patient with golimumab and methotrexate (transient elevations) and one patient with etanercept and methotrexate (persisting elevation). In this late patient, the treatment with etanercept has been stopped leading to normalization of liver test abnormalities. ALP elevation was observed in 7 patients (3.5 %) and it was transient in 4 cases (2 %) and persisting in 3 cases (1.5 %). ALP elevation above three times the ULN has not been observed. GGT elevation above ULN was observed in 40 patients (20.1 %), it was transient in 23 cases (11.6 %) and persisting in 17 cases (8.5 %). GGT elevation above 3 times the ULN was observed in 8 patients (4 %).

Comparison of recorded variables between 14 patients with persisting ALT elevation above ULN and the remaining study cohort is displayed in Table 3. We found that patients with elevated ALT had higher BMI (median 28.23 vs. 25.74, p=0.016), lower DAS28 score (median 2.22 vs. 5.28, p=0.046) and there was a trend towards more frequent treatment with tocilizumab (35.7 % vs. 14.6 %, p=0.054).

Finally, we analyzed the prevalence of three most clinically relevant liver injury patterns (ALP above ULN, ALT above ULN, ALT above 3xULN) in Table 4 for six different biological agents used in our cohort: adalimumab, certolizumab, etanercept, golimumab, infliximab, and tocilizumab. We observed that the prevalence of ALT elevation above the ULN was more frequent among patients treated with tocilizumab (25 %) compared with other agents used in our cohort (13.6 %, p=0.01). In addition, by separately analyzing patients on solo tocilizumab therapy (n=23, 69 ALT measurements) and tocilizumab combined with methotrexate (n=9, 27 ALT measurements), only patients treated with tocilizumab alone had more frequent mild ALT elevations.

Table 3. Comparison of patients with and without persisting ALT elevation (6 months) among 199 patients on biological therapy

	no persiting ALT elevation n=185	persisting ALT elevation n=14	P-value
Age	53.00 [24.00, 85.00]	58.50 [27.00, 77.00]	0.705
Males (%)	73 (39.5)	8 (57.1)	0.26
Females (%)	112 (60.5)	6 (42.9)	
Body mass index	25.74 [15.44, 42.52]	28.23 [26.54, 38.97]	0.016
Disease duration	13.00 [2.00, 46.00]	10.00 [6.00, 31.00]	0.851
Reumathoid arthritis	101 (54.6)	7 (50.0)	0.786
DAS.28 score	2.58 [0.63, 7.50]	2.22 [0.77, 3.13]	0.046
Ankylosing spondylitis	47 (25.4)	2 (14.3)	0.524
BASDAI score	1.41 [0.00, 8.90]	1.15 [1.00, 1.30]	0.544
Psoriatic arthritis	37 (20.0)	5 (35.7)	0.179
Ongoing treatment:			
Steroids	35 (18.9)	3 (21.4)	0.733
Non steroidal anti-inflammatory drugs	27 (14.6)	0 (0.0)	0.224
Metothrexate	80 (43.2)	7 (50.0)	0.781
Infliximab	2 (1.1)	0 (0.0)	1
Adalimumab	76 (41.1)	6 (42.9)	1
Adalimumab and metothrexate			
Certolizumab	4 (2.2)	0 (0.0)	1
Etanercept	32 (17.3)	2 (14.3)	0.77
Etanercept and metothrexate	10 (5.4)	2 (14.3)	0.18
Golimumab	40 (21.6)	0 (0.0)	0.077
Golimumab and metothrexate	21 (11.4)	0 (0.0)	0.18
Tocilizumab	27 (14.6)	5 (35.7)	0.054
Tocilizumab and metothrexate	8 (4.3)	1 (7.1)	0.62

Table 4. Prevalence of liver injury according to different biological therapies among 582 ALT and ALP measurements in 199 patients with rheumatic diseases

		ADA	CZP	ETN	GOL	IFX	TOC	TOC alone	TOC and MTX
No.		246	12	102	120	6	96	69	27
ALP>ULN	*no*	243	12	99	115	6	92	65	27
(%)		(98.8)	(100.0)	(97.1)	(95.8)	(100.0)	(95.8)	(94.2)	(100)
	yes	3	0	3	5	0	4	4	0
		(1.2)	(0.0)	(2.9)	(4.2)	(0.0)	(4.2)	(5.8)	(0)
ALT>ULN	*no*	210	11	85	108	6	72	50	22
(%)		(85.4)	(91.7)	(83.3)	(90.0)	(100.0)	(75.0)	(72.5)	(81.5)
	yes	36	1	17	12	0	24	19	5
		(14.6)	(8.3)	(16.7)	(10.0)	(0.0)	(25.0)*	(27.5)*	(18.5)
ALT>3xULN	*no*	246	12	101	118	6	96	69	27
(%)		(100.0)	(100.0)	(99.0)	(98.3)	(100.0)	(100.0)	(100)	(100)
	yes	0	0	1	2	0	0	0	0
		(0.0)	(0.0)	(1.0)	(1.7)	(0.0)	(0.0)	(0)	(0)

*p<0.01, ADA-adalimumab, CZP-certolizumab pegol, ETN-etanercept, GOL-golimumab, IFX-infliximab, TOC-tocilizumab

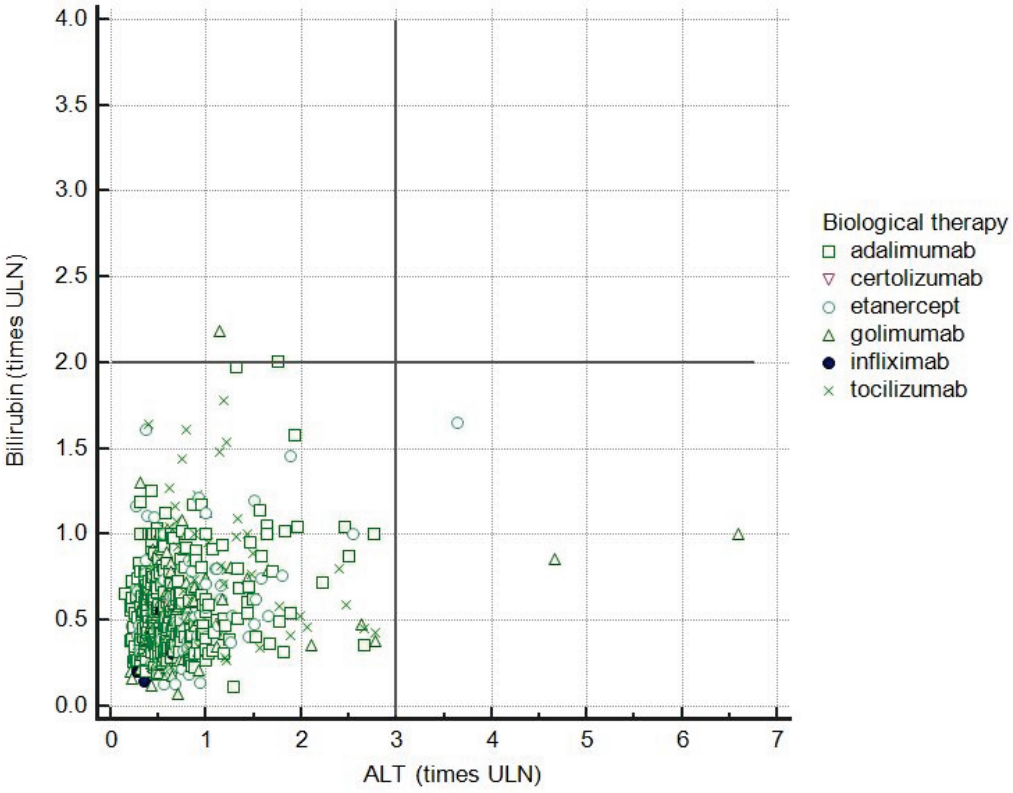

Fig. 1. Plot for ALT and Bilirubin (eDISH) reflecting the prevalence of liver injury among 199 rheumatic patients on biological therapy

During our study, the definition of Hy´s law has not been observed in any patient. ALT and bilirubin plot for all measurements in our study is displayed in Fig. 1. illustrating the observed patterns of liver injury.

Discussion

In our study, we evaluated liver injury in patients with rheumatic diseases treated with various biological therapies for a period of six months. The transient hepatocellular injury was observed in 18.6 % of cases, and persisting injury occurred in 7 % of cases. The cholestatic liver injury occurred transiently in 2 % of cases and persisted in 1.5 % of patients. Patients with persisting mild hepatocellular injury had a higher body mass index and lower DAS28. Therapy with solo tocilizumab compared with other biological agents more frequently caused a mild transient hepatocellular injury. The more severe hepatocellular injury occurred in 3 cases over 6 months (1.5 %) and led to discontinuation of etanercept in one patient with a favorable outcome.

In the clinical practice of biological therapy, potential side effect and toxicity occur frequently (Sokolove *et al.* 2010). Our study confirms that aminotransferase abnormalities are found more frequently in patients treated with biologics than in the general population (Liangpunsakul and Chalasani 2005). This particular group of therapeutic agents is known for inducing various types of autoimmune reactions in multiple organ systems (Wood and Caplan 2018). When confronted with the finding of mild liver injury, clinicians face a challenge. On one hand, one can assume that the liver injury is mostly mild and self-limited. It is frequently explained by causes similar to the general population such as liver steatosis (Koller *et al.* 2017) or non-hepatic origin and is unlikely caused by the administered therapy. However, newly introduced therapies with immunogenic potential do cause immune-mediated liver injury. This type of injury is frequently followed by the phase of immune tolerance with aminotransferase activities returning to normal levels (Kaplowitz 2013). On the other hand, any severe liver injury is often accompanied by a slow, but progressive rise in aminotransferase activities. Therefore, when following patients treated with biological therapy, there is still a need for serial aminotransferase monitoring for possible hepatotoxicity (Suk and Kim 2012). Markers predicting the immune-mediated liver injury are yet to come to clinical practice (Farghali *et al.* 2016). Any abnormalities persisting for more than 3 months or any progressive increase in aminotransferase levels above three times the ULN should alert the clinician to investigate the underlying cause and question the safety of the ongoing treatment. The finding, that patients with

persisting ALT elevation had lower disease activity scores appears independent on the BMI (analysis not shown). We might speculate for the reasons, however, low prevalence of the severe active RA and the apparent difference in group numbers might allow for a type 1 statistical error.

Biologics such as infliximab, have been reported as one of the most frequent hepatotoxins in the population study from Iceland and the molecule has been implicated in more than one hundred cases of liver injury (Bjornsson *et al.* 2013). Another frequently used agent adalimumab has also been reported as causing DILI with or without the typical signs of autoimmune hepatitis (Shelton *et al.* 2015). In clinical studies with golimumab therapy, liver enzyme elevations have been reported more frequent, but no severe cases of liver injury have been described (National Institutes of Health). Two of our three cases of more severe hepatocellular injury were treated with golimumab, but both were transient and due to small numbers of cases this finding cannot be interpreted as a signal for potential hepatotoxicity. Mild and transient liver test elevations have been reported in patients treated with etanercept, but they were less frequent than in infliximab-treated cases. In rare cases, etanercept has been reported causing clinically apparent autoimmune-like hepatitis syndrome (Girolomoni *et al.* 2012; National Institutes of Health). A single patient from our study cohort had persisting ALT elevation on treatment with etanercept and methotrexate and the clinician has decided to stop therapy due to liver injury as well as the secondary loss of response. Liver tests normalized after stopping the treatment and the patient is now treated with a different drug. Solo tocilizumab therapy in our study has been associated with more frequent aminotransferase elevations compared with other biological molecules. Of note, in patients treated with combination therapy with tocilizumab and methotrexate, the prevalence of liver injury was not different from other agents. We have recently reported a similar observation among patients with inflammatory bowel disease, that patients treated with solo immunosuppressive therapy with infliximab had the highest risk of liver injury (Koller *et al.* 2017). Thus, it appears that more severe immune suppression could hamper the development of immune-mediated liver injury. Clinical trials using tocilizumab have reported more frequent liver test abnormalities that have been mostly mild and transient (Genovese *et al.* 2013). However, there are some reports in the literature of a severe hepatocellular injury with one fatal case associated with this agent. Of note, clinicians in our center are monitoring liver test abnormalities in patients treated with tocilizumab and in cases of detected liver injury they are lowering the treatment dose (Genovese *et al.* 2017). Therefore, this strategy may explain our finding, that tocilizumab therapy caused only transient liver test abnormalities in all cases.

Our study has several limitations. First, to our study we included only cases with rheumatic diseases that were treated with biological therapy. Therefore, within our cohort of patients, we did not have a reference group to which we could compare the prevalence of liver injury. Second, we evaluated liver injury only during the six months of follow up, which could have hampered the detection of less frequent events. Third, we evaluated the prevalence of liver injury regardless of the treatment duration. It is known from previous studies, that liver injury tends to occur most frequently during the first three months after treatment initiation. In patients with a documented transient liver injury, we have no data on alcohol consumption or on the presence of fat in the liver during an ultrasound examination. These limitations could have slightly underestimated the true prevalence of liver injury. We might assume that liver steatosis could have explained the liver injury in patients with higher BMI in the group of persisting ALT elevation. Nevertheless, our reported prevalence is within the range that has been reported in clinical trials. Finally, other causes of liver injury in patients treated with immunosuppressive therapy such as reactivation of viral infections (CMV, VZV, etc.) could have been involved.

Conclusion

In a real-life cohort of 199 patients with rheumatic diseases treated with various biological therapies for 6 months, liver injury was frequent. Its duration was usually transient (18.6 %) and less frequently persisting (7 %), the severity rarely exceeding values above three times the ULN (1.5 %). The documented liver injury led to treatment alteration in only one patient (0.5 %). Among risk factors for persisting liver injury were higher body mass index and lower RA disease activity score (DAS28). Patients treated with solo tocilizumab had a higher chance of liver injury compared with another treatment regimen. Our study does not bring new safety signals for biological therapy, but it confirms the need for regular monitoring of liver function tests in these patients.

Conflict of Interest

There is no conflict of interest.

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