

World Journal of *Gastroenterology*

World J Gastroenterol 2017 June 14; 23(22): 3945-4134





EDITORIAL

- 3945 Bleeding with the artificial heart: Gastrointestinal hemorrhage in CF-LVAD patients

Gurvits GE, Fradkov E

REVIEW

- 3954 Role of non-steroidal anti-inflammatory drugs on intestinal permeability and nonalcoholic fatty liver disease

Utzeri E, Usai P

- 3964 Molecular mimicry in *Helicobacter pylori* infections

Chmiela M, Gonciarz W

- 3978 Gallbladder cancer epidemiology, pathogenesis and molecular genetics: Recent update

Sharma A, Sharma KL, Gupta A, Yadav A, Kumar A

ORIGINAL ARTICLE

Basic Study

- 3999 Serelaxin increases the antifibrotic action of rosiglitazone in a model of hepatic fibrosis

Bennett RG, Simpson RL, Hamel FG

- 4007 Bcl-2 degradation is an additional pro-apoptotic effect of polo-like kinase inhibition in cholangiocarcinoma cells

Sydor S, Jafoui S, Wingerter L, Swoboda S, Mertens JC, Gerken G, Canbay A, Paul A, Fingas CD

- 4016 Effect of *CXCR3/HO-1* genes modified bone marrow mesenchymal stem cells on small bowel transplant rejection

Yin ML, Song HL, Yang Y, Zheng WP, Liu T, Shen ZY

Case Control Study

- 4039 Systemic interleukin-9 in inflammatory bowel disease: Association with mucosal healing in ulcerative colitis

Matusiewicz M, Neubauer K, Bednarz-Misa I, Gorska S, Krzystek-Korpacka M

- 4047 Association of keratin 8/18 variants with non-alcoholic fatty liver disease and insulin resistance in Chinese patients: A case-control study

Li R, Liao XH, Ye JZ, Li MR, Wu YQ, Hu X, Zhong BH

Retrospective Study

- 4054** Barcelona Clinic Liver Cancer outperforms Hong Kong Liver Cancer staging of hepatocellular carcinoma in multiethnic Asians: Real-world perspective

Li JW, Goh BBG, Chang PE, Tan CK

Observational Study

- 4064** Single-operator cholangioscopy for biliary complications in liver transplant recipients

Hüsing-Kabar A, Heinzow HS, Schmidt HHJ, Stenger C, Gerth HU, Pohlen M, Thölking G, Wilms C, Kabar I

- 4072** Efficacy and safety of combined directly acting antivirals for treatment of Chinese chronic hepatitis C patients in a real-world setting

Chen JH, Zeng Z, Zhang XX, Zhang Y, Zhang RW, Wang S, Wu CH, Yu M, Liu D, Xi HL, Zhou YX, An YY, Xu XY

- 4080** Observation of the effect of targeted therapy of 64-slice spiral CT combined with cryoablation for liver cancer

Yan QH, Xu DG, Shen YF, Yuan DL, Bao JH, Li HB, Lv YG

Prospective Study

- 4090** Inflammatory bowel disease incidence in Czech children: A regional prospective study, 2000-2015

Schwarz J, Šykora J, Cvalínová D, Pomahačová R, Klečková J, Kryl M, Včelák P

- 4102** Drug-induced liver injury in inflammatory bowel disease: 1-year prospective observational study

Koller T, Galambosova M, Filakovska S, Kubincova M, Hlavaty T, Toth J, Krajcovicova A, Payer J

SYSTEMATIC REVIEWS

- 4112** Can fecal microbiota transplantation cure irritable bowel syndrome?

Halkjær SI, Boolsen AW, Günther S, Christensen AH, Petersen AM

CASE REPORT

- 4121** Application of novel magnified single balloon enteroscopy for a patient with Cronkhite-Canada syndrome

Murata M, Bamba S, Takahashi K, Imaeda H, Nishida A, Inatomi O, Tsujikawa T, Kushima R, Sugimoto M, Andoh A

- 4127** Synchronous triple occurrence of MALT lymphoma, schwannoma, and adenocarcinoma of the stomach

Choi KW, Joo M, Kim HS, Lee WY

LETTERS TO THE EDITOR

- 4132** Is tremor related to celiac disease?

Ameghino L, Rossi MD, Cerquetti D, Merello M

ABOUT COVER

Editorial board member of *World Journal of Gastroenterology*, Jun-Te Hsu, MD, Associate Professor, Surgeon, Surgical Oncologist, Department of Surgery, Chang Gung Memorial Hospital, Taoyuan County and Chang Gung Medicine Colledge, Tao Yuan 333, Taiwan

AIMS AND SCOPE

World Journal of Gastroenterology (*World J Gastroenterol*, *WJG*, print ISSN 1007-9327, online ISSN 2219-2840, DOI: 10.3748) is a peer-reviewed open access journal. *WJG* was established on October 1, 1995. It is published weekly on the 7th, 14th, 21st, and 28th each month. The *WJG* Editorial Board consists of 1375 experts in gastroenterology and hepatology from 68 countries.

The primary task of *WJG* is to rapidly publish high-quality original articles, reviews, and commentaries in the fields of gastroenterology, hepatology, gastrointestinal endoscopy, gastrointestinal surgery, hepatobiliary surgery, gastrointestinal oncology, gastrointestinal radiation oncology, gastrointestinal imaging, gastrointestinal interventional therapy, gastrointestinal infectious diseases, gastrointestinal pharmacology, gastrointestinal pathophysiology, gastrointestinal pathology, evidence-based medicine in gastroenterology, pancreatology, gastrointestinal laboratory medicine, gastrointestinal molecular biology, gastrointestinal immunology, gastrointestinal microbiology, gastrointestinal genetics, gastrointestinal translational medicine, gastrointestinal diagnostics, and gastrointestinal therapeutics. *WJG* is dedicated to become an influential and prestigious journal in gastroenterology and hepatology, to promote the development of above disciplines, and to improve the diagnostic and therapeutic skill and expertise of clinicians.

INDEXING/ABSTRACTING

World Journal of Gastroenterology (*WJG*) is now indexed in Current Contents®/Clinical Medicine, Science Citation Index Expanded (also known as SciSearch®), Journal Citation Reports®, Index Medicus, MEDLINE, PubMed, PubMed Central, Digital Object Identifier, and Directory of Open Access Journals. The 2015 edition of Journal Citation Reports® released by Thomson Reuters (ISI) cites the 2015 impact factor for *WJG* as 2.787 (5-year impact factor: 2.848), ranking *WJG* as 38 among 78 journals in gastroenterology and hepatology (quartile in category Q2).

FLYLEAF

I-IX Editorial Board

EDITORS FOR THIS ISSUE

Responsible Assistant Editor: *Xiang Li*
Responsible Electronic Editor: *Cai-Hong Wang*
Proofing Editor-in-Chief: *Lian-Sheng Ma*
Responsible Science Editor: *Yuan Qi*
Proofing Editorial Office Director: *Jin-Lei Wang*

NAME OF JOURNAL
World Journal of Gastroenterology

ISSN
 ISSN 1007-9327 (print)
 ISSN 2219-2840 (online)

LAUNCH DATE
 October 1, 1995

FREQUENCY
 Weekly

EDITORS-IN-CHIEF
Damian Garcia-Olmo, MD, PhD, Doctor, Professor, Surgeon, Department of Surgery, Universidad Autonoma de Madrid; Department of General Surgery, Fundacion Jimenez Diaz University Hospital, Madrid 28040, Spain

Stephen C Strom, PhD, Professor, Department of Laboratory Medicine, Division of Pathology, Karolinska Institutet, Stockholm 141-86, Sweden

Andrzej S Tarnawski, MD, PhD, DSc (Med), Professor of Medicine, Chief Gastroenterology, VA Long Beach Health Care System, University of California, Irvine, CA, 5901 E. Seventh Str., Long Beach,

CA 90822, United States

EDITORIAL BOARD MEMBERS
 All editorial board members resources online at <http://www.wjgnet.com/1007-9327/editorialboard.htm>

EDITORIAL OFFICE
 Jin-Lei Wang, Director
 Yuan Qi, Vice Director
 Ze-Mao Gong, Vice Director
World Journal of Gastroenterology
 Baishideng Publishing Group Inc
 7901 Stoneridge Drive, Suite 501,
 Pleasanton, CA 94588, USA
 Telephone: +1-925-2238242
 Fax: +1-925-2238243
 E-mail: editorialoffice@wjgnet.com
 Help Desk: <http://www.fpublishing.com/helpdesk>
<http://www.wjgnet.com>

PUBLISHER
 Baishideng Publishing Group Inc
 7901 Stoneridge Drive, Suite 501,
 Pleasanton, CA 94588, USA
 Telephone: +1-925-2238242
 Fax: +1-925-2238243
 E-mail: bpgoffice@wjgnet.com
 Help Desk: <http://www.fpublishing.com/helpdesk>

<http://www.wjgnet.com>

PUBLICATION DATE
 June 14, 2017

COPYRIGHT
 © 2017 Baishideng Publishing Group Inc. Articles published by this Open-Access journal are distributed under the terms of the Creative Commons Attribution Non-commercial License, which permits use, distribution, and reproduction in any medium, provided the original work is properly cited, the use is non commercial and is otherwise in compliance with the license.

SPECIAL STATEMENT
 All articles published in journals owned by the Baishideng Publishing Group (BPG) represent the views and opinions of their authors, and not the views, opinions or policies of the BPG, except where otherwise explicitly indicated.

INSTRUCTIONS TO AUTHORS
 Full instructions are available online at <http://www.wjgnet.com/bpg/gerinfo/204>

ONLINE SUBMISSION
<http://www.fpublishing.com>

Prospective Study

**Drug-induced liver injury in inflammatory bowel disease:
1-year prospective observational study**

Tomas Koller, Martina Galambosova, Simona Filakovska, Michaela Kubincova, Tibor Hlavaty, Jozef Toth, Anna Krajcovicova, Juraj Payer

Tomas Koller, Martina Galambosova, Simona Filakovska, Michaela Kubincova, Tibor Hlavaty, Jozef Toth, Anna Krajcovicova, Juraj Payer, 5th Department of Internal Medicine, Gastroenterology and Hepatology, Comenius University in Bratislava Faculty of Medicine, University Hospital Bratislava Ruzinov, 82606 Bratislava, Slovakia

Author contributions: Koller T drafted the manuscript, designed the protocol and performed data analysis; Galambosova M supervised and participated in data collection; Filakovska S participated in data collection; Kubincova M participated in data collection; Hlavaty T revised the protocol design, assisted with data analysis, participated in patient clinical management; Toth J participated in patient clinical management; Krajcovicova A participated in data collection and assisted at data analysis; Payer J suggested the subject of the study and participated at the discussion, approved the final manuscript.

Institutional review board statement: The study was reviewed and approved by the institutional ethics committee board of the University Hospital Bratislava Ruzinov of Slovakia.

Clinical trial registration statement: This study did not include any intervention or patient randomization, therefore clinical trial registration was not done.

Informed consent statement: All study participants, or their legal guardian, provided written informed consent prior to any diagnostic or therapeutic procedure. Informed consent for patient data collection was not required by the institutional ethics committee.

Conflict-of-interest statement: The authors of the manuscript having no conflicts of interest to disclose.

Data sharing statement: There is no additional data available.

Open-Access: This article is an open-access article which was selected by an in-house editor and fully peer-reviewed by external reviewers. It is distributed in accordance with the Creative Commons Attribution Non Commercial (CC BY-NC 4.0) license, which permits others to distribute, remix, adapt, build upon this work non-commercially, and license their derivative works on

different terms, provided the original work is properly cited and the use is non-commercial. See: <http://creativecommons.org/licenses/by-nc/4.0/>

Manuscript source: Invited manuscript

Correspondence to: Tomas Koller, MD, PhD, Associate Professor, 5th Department of Internal Medicine, Gastroenterology and Hepatology, Comenius University in Bratislava Faculty of Medicine, University Hospital Bratislava Ruzinov, Ruzinovska 6, 82606 Bratislava, Slovakia. tomas.koller@ru.unb.sk
Telephone: +42-190-5118692

Received: January 28, 2017

Peer-review started: February 8, 2017

First decision: March 16, 2017

Revised: March 29, 2017

Accepted: May 9, 2017

Article in press: May 9, 2017

Published online: June 14, 2017

Abstract**AIM**

To analyze 1-year liver injury burden in inflammatory bowel disease (IBD) patients.

METHODS

During a 6-mo inclusion period, consecutive IBD cases having a control visit at IBD center were included. Basic demographics, IBD phenotype and IBD treatment were recorded on entry. Aminotransferase (AT) activities of ALT, AST, ALP and gamma-glutamyl transpeptidase (GGT) were measured at baseline, 3 mo prior to study entry and prospectively every 3 mo for 1 year. Liver injury patterns were predefined as: Grade 1 in ALT 1-3 × upper limit of normal (ULN), grade 2 in ALT > 3 × ULN, hepatocellular injury in ALT > 2 × ULN, cholestatic injury in simultaneous GGT and ALP elevation > ULN.

Persisting injury was reported when AT elevations were found on > 1 measurement. Risk factors for the patterns of liver injury were identified among demographic parameters, disease phenotype and IBD treatment in univariate and multivariate analysis. Finally, implications for the change in IBD management were evaluated in cases with persisting hepatocellular or cholestatic injury.

RESULTS

Two hundred and fifty-one patients were included having 917 ALT and 895 ALP and GGT measurements. Over one year, grade 1 injury was found in 66 (26.3%), grade 2 in 5 (2%) and hepatocellular injury in 16 patients (6.4%). Persisting hepatocellular injury was found in 4 cases. Cholestasis appeared in 11 cases (4.4%) and persisted throughout the entire study period in 1 case. In multivariate analysis, hepatocellular injury was associated with BMI (OR = 1.13, 1.02-1.26), liver steatosis (OR = 10.61, 2.22-50.7), IBD duration (1.07, 1.00-1.15) and solo infliximab (OR = 4.57, 1.33-15.7). Cholestatic liver injury was associated with prior intestinal resection (OR = 32.7, 3.18-335), higher CRP (OR = 1.04, 1.00-1.08) and solo azathioprine (OR = 10.27, 1.46-72.3). In one case with transient hepatocellular injury azathioprine dose was decreased. In 4 cases with persisting hepatocellular injury, fatty liver or alcohol were most likely causes and IBD treatment was pursued without change. In the case with persisting cholestatic injury, no signs of portal hypertension were identified and treatment with infliximab continued.

CONCLUSION

Liver injury was frequent, mostly transient and rarely changed management. Infliximab or azathioprine were confirmed as its risk factors indicating the need for regular AT monitoring.

Key words: Drug-induced liver injury; Risk factors; Inflammatory bowel disease; Infliximab; Adalimumab; Azathioprine

© **The Author(s) 2017.** Published by Baishideng Publishing Group Inc. All rights reserved.

Core tip: We evaluated liver injury in consecutive inflammatory bowel disease (IBD) patients followed for one year in whom aminotransferase activities (AT) were measured at baseline and at 3 mo intervals. We found AT elevations frequently, but they were mostly mild and transient. Even persisting abnormalities had rarely an effect on IBD management. However, ALT elevations and cholestasis appeared more commonly among patients treated with infliximab (ALT) or azathioprine (cholestasis). This finding points to their potential for hepatotoxicity and the need for regular AT monitoring.

Koller T, Galambosova M, Filakovska S, Kubincova M, Hlavaty T, Toth J, Krajcovicova A, Payer J. Drug-induced liver injury in

inflammatory bowel disease: 1-year prospective observational study. *World J Gastroenterol* 2017; 23(22): 4102-4111 Available from: URL: <http://www.wjgnet.com/1007-9327/full/v23/i22/4102.htm> DOI: <http://dx.doi.org/10.3748/wjg.v23.i22.4102>

INTRODUCTION

Inflammatory bowel disease (IBD) is a chronic inflammatory condition of the digestive tract. Over past decades, significant changes in the treatment of this condition have occurred. Most patients are currently treated with long-term immunosuppression, which has been shown to be effective in improving patients' symptoms and quality of life^[1]. The treatment has a potential for various adverse events including a drug-induced liver injury (DILI). Recently, several reports have raised a concern that hepatotoxicity of IBD treatment might be underestimated. The DILI network has listed infliximab and azathioprine in category A, with more than one hundred well documented cases of hepatotoxicity^[2]. A population-based study from Iceland reported that azathioprine and infliximab were among five most common drugs causing liver injury^[3]. Furthermore, chronic drug induced liver injury is increasingly being recognized^[4]. Drug induced liver injury may range from mild aminotransferase elevations to symptomatic hepatitis or acute liver failure. Finding causes of mild or persisting aminotransferase (AT) elevations in immunosuppressed IBD patients is challenging. Apart from DILI, many other comorbid conditions and therapies could be involved^[5]. Analogically to other causes of liver injury, such abnormalities might indicate an ongoing liver injury^[6]. However, clinical relevance and evolution of these findings remain unclear. We are lacking studies from a real-life setting reporting on how often this potential risk actually interferes with IBD management.

We aimed to analyze a real-life burden of liver related adverse events in IBD patients over one year. First, we aimed to estimate the prevalence of liver injury among treated IBD patients. Second, to assess its prevalence according to IBD treatment. Third, to analyze evolution of liver injury and its independent risk factors. Fourth, to evaluate its implications on further IBD management.

MATERIALS AND METHODS

Study population

Our study was carried out in a single IBD center where we prospectively included all consecutive IBD patients having a control visit between January 2nd 2014 and June 30th 2014. Inclusion criteria for the study population were the diagnosis of ulcerative colitis or Crohn's disease and a control visit at the center during the inclusion period. All studied parameters

were prospectively entered into an electronic hospital database and patient folders according to the pre-defined protocol. At entry to the study, we recorded basic demographics (age, gender, body mass index), characteristics of IBD phenotype [IBD duration, IBD type, diagnosis of primary sclerosing cholangitis (PSC)], past surgeries (intestinal resections), current inflammatory activity (serum CRP and fecal calprotectin), quality of life (short IBDQ questionnaire) and current IBD therapy and dosing.

Patients with the history of known chronic liver disease other than PSC and patients with the history of known cirrhosis were not included in the study. Alcohol abuse was estimated during the baseline visit. In cases with significant AT elevations [> 3 times upper limit of normal (ULN)] it was also estimated in the process of evaluation for possible DILI. All patients were tested for HBs antigen and antibodies against HCV prior to any IBD treatment with negative results in all cases. Previous or incident infections with other hepatotropic viruses as well as other possible hepatotoxic drug were not assessed in the data analysis.

Liver injury

Serum activities of alanine aminotransferase (ALT), aspartate aminotransferase (AST), gamma-glutamyl transpeptidase (GGT), alkaline phosphatase (ALP) and serum bilirubin concentration were used as markers of liver injury as recommended by the regulatory authorities^[7]. Blood sampling for AT activities was carried out on entry to the study and was pre-planned at 3 mo intervals for up to 12 mo. We also recorded aminotransferase activities from electronic records 3 mo prior to the study entry. This allowed us to evaluate the evolution of AT elevations even in cases having abnormal baseline AT values. Overall, each patient had a baseline AT measurement, four prospective AT and bilirubin measurements and one retrospective AT measurement from electronic records.

Liver injury was graded as defined by the Common terminology criteria for adverse events v. 4.03^[8]. For hepatocellular injury enzymes ALT and AST, a grade 1 injury was defined as an increase in activity up to three times the upper limit of normal ($3 \times$ ULN), grade 2 injury as an increase superior to $3 \times$ ULN. We also evaluated a more conservative and clinically relevant ALT cut-off of $> 2 \times$ ULN further referred to as "hepatocellular injury". For cholestatic enzymes GGT and ALP, a grade 1 injury was defined as an increase in activity up to $2.5 \times$ ULN and Grade 2 injury as an increase superior to $2.5 \times$ ULN. Since GGT elevation is not considered a specific marker for liver injury, we used it in parallel with alkaline phosphatase. An event of cholestasis was defined as an increase in GGT and ALP $>$ ULN. An increase in bilirubin concentration was recorded when superior to $2 \times$ ULN ($> 34 \mu\text{mol/L}$). A subgroup patients ($n = 155$) had undergone abdominal ultrasound for the presence or absence of liver steatosis, but severity of liver

steatosis was not assessed. The following liver injury events were pre-defined: grade 1 and 2 ALT and AST increase, hepatocellular injury with ALT increase $> 2 \times$ ULN, grade 1 and 2 ALP increase, cholestasis and bilirubin increase $> 2 \times$ ULN.

We report the prevalence of liver injury by counting all particular events of an enzyme increase among all measurements of the enzyme. Second, we report the injury events separately for each of the following treatment groups: no immunosuppression, solo azathioprine, solo infliximab, solo adalimumab, azathioprine and infliximab, azathioprine and adalimumab. These treatment groups were defined according to the IBD treatment received at baseline. The prevalence of the liver event in the treatment group was compared to the prevalence of the same event in the entire study population. For graphical illustration of the findings we constructed an evaluation of drug induced serious hepatotoxicity (eDISH) plot^[9]. Third, an evolution of liver injury is reported by counting how many times a liver injury event was observed in patients (from once up to five times). Two patterns of evolution were pre-defined: a transient increase was defined as one grade 1 event, a persisting increase as two or more grade 1 events.

We assessed risk factors for the following events and patterns of liver injury: persisting grade 1 ALT and AST increase, hepatocellular injury with ALT increase $> 2 \times$ ULN and any event of cholestasis. Finally, all hepatocellular injury cases (ALT $> 2 \times$ ULN) were analyzed for further evolution and change of treatment.

All fasting blood samples were analyzed in a single local laboratory by the standard automated analyzers. All suspected DILI events were investigated for possible alternative causes of increased AT activities and were followed more closely.

Statistical analysis

Data were assessed by the statistical software package MedCalc v. 14, Ostende, Belgium. For normality testing we used Kolmogorov-Smirnov test and variables are expressed as a mean \pm SD, median and interquartile range or as a relative count and percentage. AT activities were expressed as multiples of an upper limit of normal. We used chi-square test to compare a relative proportion of an event in the treatment group with its proportion in the entire study population. Risk factors for liver injury events and patterns were identified using a logistic regression. All available parameters were assessed as independent variables and the liver injury event or pattern as the dependent variable. Results are given as odds ratios (OR) with 95% confidence intervals and *P* values. Risk factors were considered significant when *P* values were inferior to 0.05. All identified risk factors were entered into a stepwise multivariate logistic regression model to identify independently associated risk factors.

Table 1 Summary statistics table of the study group of 251 inflammatory bowel disease patients

<i>n</i> = 251	Median; IQR, <i>n</i> (%)
Age	39; 30.0-52.75
Female gender	129 (51.4)
Body mass index	24.298; 21.19-27.34
Crohn's disease	154 (61.4)
Ulcerative colitis	97 (38.6)
Inflammatory bowel disease duration (yr)	8 (5-13)
Primary sclerosing cholangitis	2 (0.8)
Prior intestinal resection	73 (29.4)
Short IBDQ questionnaire score	58 (50-64)
Fecal calprotectin on study entry (mg/g)	83.195 (23.45-331.8)
C-reactive protein on study entry (mg/L)	5 (2.4-8.2)
Inflammatory bowel disease therapy on entry	
Mesalamine	173 (69.5)
Antibiotics	17 (6.9)
No immunosuppression	66 (26.3)
Steroids	42 (16.9)
Azathioprine solo	47 (18.7)
anti TNF therapy (all)	138 (55)
anti TNF therapy solo	74 (29.5)
Infliximab solo	41 (16.3)
Adalimumab solo	33 (13.1)
Combination therapy (anti-TNF and azathioprine)	64 (25.5)
Days between 1 st and 5 th AT sampling	382 (353-439.8)
Liver steatosis on ultrasound (<i>n</i> = 155)	34 (21.9)

Ethical issues

Our study was non-interventional and was carried out in accordance with the Helsinki declaration. Data acquisition was approved by our University hospital ethics committee. Due to the noninterventional nature of our study, patients were exempted from signing an informed consent form.

RESULTS

We included 251 IBD patients fulfilling the inclusion criteria. Summary statistics of the entire study population is displayed in Table 1. One hundred and fifty-four cases had Crohn's disease and ninety-seven had ulcerative colitis. The prevalence of all predefined liver injury events is displayed in Table 2.

Hepatocellular injury

We assessed 917 ALT and AST measurements. Grade 1 ALT and AST elevation was observed in 112 and 55 measurements (12.2% and 6%). Hepatocellular injury with ALT superior to 2 × ULN was observed 26 times (2.84%), Grade 2 ALT and AST increase was observed 6 and 8 times (0.65 and 0.87%). We did not observe any grade 3 or 4 liver injury.

Cholestasis

We assessed 897 ALP and 895 GGT measurements. Grade 1 and 2 ALP elevation was observed in 34 and 0 measurements (3.79 and 0%). Cholestasis was observed 11 times (1.23%).

Table 2 Prevalence of liver injury events among all aminotransferase measurements in 251 inflammatory bowel disease patients over 1 year *n* (%)

Liver injury event	All measurements <i>n</i>	Abnormal Number of events
ALT increase Grade 1 (0-3 × ULN)	917	112 (12.21)
ALT increase > 2 × ULN (hepatocellular injury)	917	26 (2.84)
ALT increase Grade 2 (> 3 × ULN)	917	6 (0.65)
AST increase Grade 1 (0-3 × ULN)	917	55 (6.0)
AST increase Grade 2 (> 3 × ULN)	917	8 (0.87)
GGT increase Grade 1 (0-2.5 × ULN)	895	80 (8.94)
GGT increase Grade 2 (> 2.5 × ULN)	895	24 (2.68)
ALP increase Grade 1 (0-2.5 × ULN)	897	34 (3.79)
ALP increase Grade 2 (> 2.5 × ULN)	897	0 (0)
Cholestasis (parallel ALP and GGT elevation)	895	11 (1.23)
Total bilirubin > 2 × ULN	370	1 (0.27)

ULN: Upper limit of normal; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transpeptidase; ALP: Alkaline phosphatase.

Treatment

Among 251 study patients, 66 had no maintenance therapy, 47 were on solo azathioprine, 74 on solo anti TNF therapy (infliximab 41, adalimumab 33) and 64 had combination therapy of anti-TNF (infliximab 48, adalimumab 16) with azathioprine. Proportions of liver injury according to IBD treatment are displayed in Table 3. Grade 1 ALT increase was more common in patients treated with solo adalimumab (18.5% vs 12.2%) compared with the entire study population. In patients treated with solo infliximab: grade 2 ALT increase (2.5% vs 0.65%), hepatocellular injury with ALT > 2 × ULN (9.2% vs 2.84%) and grade 1 AST increase (12.3% vs 6.0%) were more common. The DISH plot showing ALT/total bilirubin and ALT/ALP relationship for all measurements and treatment groups is shown in Figures 1 and 2. Cholestasis was more common among patients treated with solo azathioprine (3.4% vs 1.23%). There were no differences among other treatment groups (combination therapy and no-immunosuppression) for other liver injury events.

Evolution and patterns of liver injury

ALT elevation was the most common liver injury event. Grade 1 increase was observed in 66 (26.3%) patients, it was unique in 38 patients and persisted in 28 cases (11.2%). Grade 2 increase was found in 5 cases, it was unique in 4 cases. Hepatocellular injury (ALT > 2 × ULN) was observed in 16 (6.3%) cases and was unique in 12 patients.

For AST, grade 1 increase was found in 34 (13.5%) cases, it was unique in 25 and persisted in 9 cases (3.6%). Grade 2 increase was observed in 6 cases, it was unique in 4 cases.

Table 3 Prevalence of liver injury events according to the inflammatory bowel disease treatment groups

Liver injury event	IBD treatment					
	Solo azathioprine		Solo adalimumab		Solo infliximab	
	All measurements	Abnormal	All measurements	Abnormal	All measurements	Abnormal
	<i>n</i>	<i>n</i> (%)	<i>n</i>	<i>n</i> (%)	<i>n</i>	<i>n</i> (%)
ALT increase Grade 1 (0-3 × ULN)	154	16 (10.4)	135	25 (18.5) ^a	163	26 (16)
ALT > 2 × ULN (hepatocellular injury)		3 (1.9)		2 (1.5)		15 (9.2) ^a
ALT increase Grade 2 (> 3 × ULN)		2 (1.3)		0 (0)		4 (2.5) ^a
AST increase Grade 1 (0-3 × ULN)	154	6 (3.9)	135	7 (5.2)	162	20 (12.3) ^a
AST increase Grade 2 (> 3 × ULN)		0 (0)		1 (0.1)		2 (1.2)
ALP increase Grade 1 (0-2.5 × ULN)	148	6 (4.1)	132	2 (1.5)	163	11 (6.7)
ALP increase Grade 2 (> 2.5 × ULN)		0 (0)		0 (0)		0 (0)
Cholestasis (parallel ALP and GGT > ULN)	146	5 (3.4) ^a	132	1 (0.1)	162	2 (1.2)
	Azathioprine + infliximab		Azathioprine + adalimumab		No immunosuppression	
	All measurements	Abnormal	All measurements	Abnormal	All measurements	Abnormal
	<i>n</i>	<i>n</i> (%)	<i>n</i>	<i>n</i> (%)	<i>n</i>	<i>n</i> (%)
ALT increase Grade 1 (0-3 × ULN)	199	15 (7.5)	59	8 (13.6)	207	22 (10.6)
ALT > 2 × ULN (hepatocellular injury)		2 (1)		1 (1.7)		3 (1.4)
ALT increase Grade 2 (> 3 × ULN)		0 (0)		0 (0)		0 (0)
AST increase Grade 1 (0-3 × ULN)	200	11 (5.5)	59	2 (3.4)	207	9 (4.3)
AST increase Grade 2 (> 3 × ULN)		1 (0.5)		2 (3.4)		2 (0.1)
ALP increase Grade 1 (0-2.5 × ULN)	195	0 (0)	58	3 (5.2)	201	12 (6)
ALP increase Grade 2 (> 2.5 × ULN)		0 (0)		0 (0)		0 (0)
Cholestasis (parallel ALP and GGT > ULN)	195	0 (0)	58	1 (1.7)	201	2 (1)

^a*P* < 0.05 for comparison with the prevalence of the liver injury event among all measurements (Table 2).

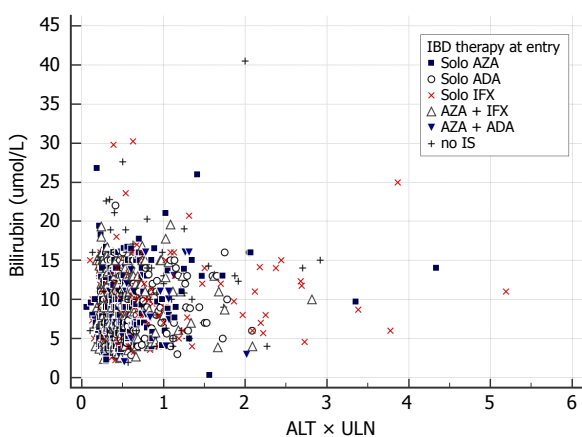


Figure 1 Serum alanine aminotransferase and bilirubin plot in 251 consecutive IBD patients (all measurements in all patients, values expressed in times the upper limit of normal. ADA: Adalimumab; AZA: Azathioprine; IFX: Infliximab; no-IS: No Immunosuppression).

For ALP, grade 1 increase was found in 19 (7.6%) patients, it was unique in 11 cases. We recorded no case of grade 2 ALP increase. Cholestasis was found in 11 (4.4%) cases, and was unique in 7 cases. Total bilirubin superior to 2 × ULN was observed once and it was not paralleled with AT elevation suggesting a Gilbert syndrome. Numbers of cases for each liver injury event and pattern of evolution are summarized Table 4.

Risk factors for liver injury

Univariate regression identified five risk factors for persisting grade 1 ALT increase: female gender (OR =

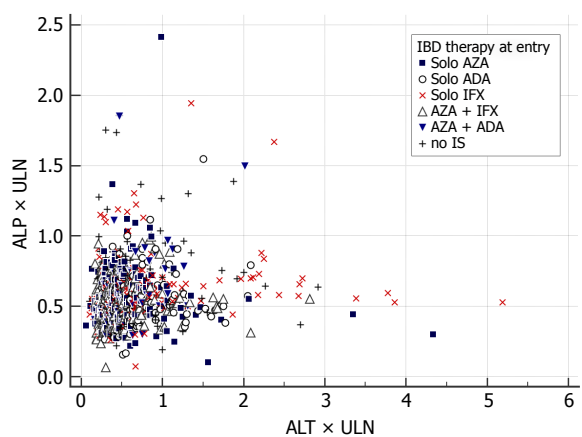


Figure 2 Serum alanine aminotransferase and alkaline phosphatase plot in 251 consecutive inflammatory bowel disease patients (all measurements in all patients, values expressed in times the upper limit of normal. ADA: Adalimumab; AZA: Azathioprine; IFX: Infliximab; no-IS: No immunosuppression).

0.22), body mass index (OR = 1.13), solo infliximab (OR = 2.8) and liver steatosis (OR = 7.77). For hepatocellular injury (ALT > 2 × ULN): body mass index (OR = 1.13), duration of IBD (OR = 1.08), solo infliximab (OR = 3.43) and liver steatosis (HR = 7.14). The exact same pattern of risk factors was observed for persisting AST increase. Finally, risk factors for cholestasis were prior intestinal resection (HR = 7.06), the level of CRP on entry (HR = 1.04) and solo azathioprine (HR = 3.93). IBD phenotype was not found to be a risk factor for any type of liver injury. Odds ratios for all demographic parameters, IBD

Table 4 Numbers of cases with liver injury events and patterns among 251 inflammatory bowel disease patients over 1 year *n* (%)

Liver injury event	Numbers of cases with liver injury events						
	No event	Any event	Transient		Persisting injury		
			1 event	2 events	3 events	4 events	5 events
ALT increase Grade 1 (0-3 × ULN)	185 (73.7)	66 (26.3)	38 (15.1)	16 (6.4)	6 (2.4)	6 (2.4)	0 (0)
ALT increase > 2 × ULN (hepatocellular injury)	235 (93.63)	16 (6.4)	12 (4.8)	1 (0.4)	1 (0.4)	1 (0.4)	1 (0.4)
ALT increase Grade 2 (> 3 × ULN)	246 (98.0)	5 (2)	4 (1.6)	1 (0.4)	0 (0)	0 (0)	0 (0)
AST increase Grade 1 (0-3 × ULN)	217 (86.45)	34 (13.5)	25 (10)	4 (1.6)	1 (0.4)	1 (0.4)	3 (1.2)
AST increase Grade 2 (> 3 × ULN)	245 (97.6)	6 (2.3)	4 (1.6)	2 (0.8)	0 (0)	0 (0)	0 (0)
ALP increase Grade 1 (0-2.5 × ULN)	232 (92.43)	19 (7.5)	11 (4.4)	3 (1.2)	4 (1.6)	0 (0)	1 (0.4)
ALP increase Grade 2 (> 2.5 × ULN)	251 (100)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)
Cholestasis (parallel ALP and GGT elevation)	240 (95.61)	11 (4.4)	7 (2.8)	2 (0.8)	1 (0.4)	0 (0)	1 (0.4)
Total bilirubin > 2 × ULN	250 (99.6)	1 (0.4)	1 (0.4)	0 (0)	0 (0)	0 (0)	0 (0)

ULN: Upper limit of normal; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase; GGT: Gamma-glutamyl transpeptidase; ALP: Alkaline phosphatase.

Table 5 Univariate analysis of risk factors for liver injury events and patterns among 251 inflammatory bowel disease patients

	Risk factors for selected liver injury events and patterns							
	Persisting ALT increase		ALT > 2 × ULN		Persisting AST increase		Cholestasis	
	OR; 95%CI	<i>P</i> value	OR; 95%CI	<i>P</i> value	OR; 95%CI	<i>P</i> value	OR; 95%CI	<i>P</i> value
Age ¹	1.01; 0.98-1.04	0.628	1.02; 0.98-1.05	0.317	1.03; 0.99-1.08	0.185	1.02; 0.98-1.06	0.300
Female gender	0.22; 0.87-0.57	0.002	0.55; 0.19-1.55	0.260	0.75; 0.20-2.86	0.672	2.62; 0.68-10.13	0.160
Body mass index ¹	1.13; 1.04-1.23	0.004	1.13; 1.03-1.23	0.011	1.18; 1.06-1.32	0.003	0.95; 0.82-1.08	0.413
Crohn's disease	2.03; 0.83-4.97	0.122	2.89; 0.80-10.41	0.105	1.27; 0.31-5.20	0.739	2.95; 0.62-13.94	0.173
Ulcerative colitis	0.49; 0.20-1.21	0.122	0.35; 0.10-1.25	0.105	0.79; 0.19-3.22	0.739	0.34; 0.07-1.60	0.173
Inflammatory bowel disease duration (yr) ¹	1.04; 0.98-1.09	0.180	1.08; 1.02-1.15	0.007	1.10; 1.03-1.18	0.006	1.04; 0.97-1.11	0.295
Prior intestinal resection	0.95; 0.40-2.28	0.915	1.10; 0.37-3.27	0.869	0.68; 0.14-3.33	0.631	7.06; 1.81-27.41	0.005
Short IBDQ questionnaire score ¹	1.00; 0.97-1.04	0.935	0.99; 0.95-1.04	0.703	0.99; 0.94-1.06	0.925	0.98; 0.93-1.04	0.545
Fecal calprotectin on study entry (mg/g) ¹	0.999; 0.99-1.00	0.909	1.00; 0.99-1.00	0.895	0.99; 0.99-1.00	0.424	1.00; 0.99-1.00	0.346
C-reactive protein on study entry (mg/L) ¹	0.98; 0.94-1.03	0.520	0.98; 0.93-1.04	0.590	1.00; 0.95-1.06	0.907	1.04; 1.01-1.07	0.024
Inflammatory bowel disease therapy on entry								
Mesalamine	0.64; 0.29-1.45	0.288	0.54; 0.19-1.51	0.241	0.34; 0.09-1.29	0.112	0.76; 0.22-2.67	0.667
No immunosuppression	0.58; 0.21-1.59	0.287	0.38; 0.08-1.73	0.211	0.34; 0.41-2.77	0.314	0.61; 0.13-2.9	0.535
Steroids	0.16; 0.02-1.22	0.078	0.69; 0.15-3.13	0.627	0.60; 0.07-4.96	0.640	1.90; 0.48-7.50	0.357
Azathioprine solo	0.49; 0.14-1.69	0.258	1.00; 0.27-3.67	0.998	0.53; 0.07-4.36	0.557	3.93; 1.15-13.47	0.030
Anti-TNF therapy solo	2.72; 1.22-6.03	0.014	2.56; 0.923-7.10	0.071	5.11; 1.24-21.05	0.024	0.89; 0.23-3.46	0.870
Infliximab solo	2.80; 1.18-6.80	0.020	3.43; 1.17-10.03	0.030	4.43; 1.14-17.28	0.032	1.15; 0.24-5.50	0.866
Adalimumab solo	1.51; 0.53-4.31	0.437	0.94; 0.20-4.33	0.937	1.94; 0.39-9.79	0.420	0.65; 0.08-5.25	0.686
Combination therapy (anti-TNF and azathioprine)	0.776; 0.3-2.01	0.601	0.66; 0.18-2.39	0.525	0.36; 0.04-2.90	0.330	0.28; 0.04-2.24	0.231
Liver steatosis on ultrasound (<i>n</i> = 155)	7.77; 3.03-19.9	< 0.0001	7.14; 2.15-23.59	0.001	6.78; 1.53-30.03	0.012	1.45; 0.27-7.83	0.666

¹Modeled as continuous variables. ULN: Upper limit of normal; ALT: Alanine aminotransferase; AST: Aspartate aminotransferase.

related phenotype, inflammatory activity, the quality of life and IBD treatment are displayed in Table 5.

Multivariate logistic regression identified the following independent risk factors for persisting grade 1 ALT increase: female gender (OR = 0.221; 95%CI: 0.07-0.67), BMI (OR = 1.15, 1.05-1.27), and liver steatosis (OR = 31.0, 6.76-142.1), for hepatocellular injury (ALT > 2 × ULN): IBD duration (OR = 1.07, 1.00-1.15), BMI (OR = 1.13, 1.02-1.26), solo infliximab (OR = 4.57, 1.33-15.7) and steatosis (OR = 10.61, 2.22-50.7), for cholestasis: prior IBD resection (OR = 32.7, 3.18-335); CRP (1.04, 1.00-1.08) and solo azathioprine (OR = 10.266, 1.46-72.3).

Implications for further management

Sixteen patients (6.3%) with observed hepatocellular

injury (ALT > 2 × ULN) were closely managed by a treating physician. ALT normalized in 12 cases with subsequent follow-up. In 4 cases, ALT elevation persisted. Analysis of possible causes of this persisting elevation identified other possible conditions: alcohol abuse in one case, type 2 diabetes with liver steatosis twice, obesity with liver steatosis once. Fifteen subjects had no change in IBD treatment, azathioprine dose was halved in one patient. Cholestasis was transient in 7 from 11 cases. One patient had persisting cholestasis at all measurements and was evaluated for possible NRH. Upper endoscopy and ultrasound did not suggest signs of portal hypertension and the patient continues the treatment with infliximab. We did not observe worsening of liver injury among subjects pursuing the treatment.

DISCUSSION

Our prospective study reports on the liver injury burden among treated IBD patients over one year. We found mild ALT elevation in 26.3% of patients, hepatocellular injury 6.4% and persisting elevation in 11.2% of patients. Events of hepatocellular injury were more common with higher BMI and steatosis, with longer duration of IBD and on treatment with solo infliximab. Cholestasis was observed in 4.4% of patients and was more common after intestinal resection, higher inflammatory activity at baseline and on therapy with solo azathioprine. Most events of liver injury were transient and rarely required any change in management.

Hepatocellular injury

Clinical interpretation of hepatocellular injury occurring in IBD patients remains a challenge. In most cases, competing etiologies do not allow identification of a single one. Alcohol abuse, fatty liver disease, de-novo viral infection, concomitant medication and comorbidities could all be involved. Specific etiological models such as RUCAM model^[10], might help in confirming or excluding DILI. However, AT abnormalities are frequently transient and stopping IBD therapy is not feasible at the moment of first appearance of liver injury. Therefore, this model does not help in cases with mild elevation. Moreover, it has been shown that several causes occurring in one patient might have a synergistic effect. Schröder *et al.*^[11] reported that patients with fatty liver were more susceptible to liver injury when treated with non-anti TNF immunosuppression. For now, it is not clear whether this finding also applies to anti-TNF therapy. In an observation study, Cappello *et al.*^[12] reported mild hepatocellular injury in 20.9% of 335 IBD patients. Liver injury was transient and most commonly due to fatty liver or DILI. Authors did not give details on IBD treatment and the most commonly observed pattern of injury was mild cholestasis. Parisi *et al.*^[13] report abnormal ALT in 39.2% and grade 2 increase in 7.9% of 176 patients treated with infliximab. In this study, authors identified several risk factors for liver injury: previous abnormal ALT suggesting a preexisting liver disease, immunomodulatory use and duration of infliximab therapy. Shelton *et al.*^[14] report a new transient increase in ALT $> 2 \times$ ULN following anti-TNF induction in 102 (6%) of 1753 patients. Liver injury could be linked to alternative etiologies in 54 of these cases (antibiotics, thiopurines, alcohol, fatty liver), leaving 48 (2.7%) directly linked to anti-TNF therapy. In 34 cases, ALT abnormalities were transient and anti-TNF therapy could continue. Fourteen patients with persisting abnormalities had to stop therapy. In our study, we included patients regardless of the timing of IBD induction and we did not exclude patients with fatty liver or preexisting ALT elevation. Nevertheless, our results appear consistent with previous reports

showing ALT elevations in roughly the same proportion of cases. It appears, that transient liver injury occurs during induction, but also during maintenance therapy with a thiopurine as well as anti-TNF^[13-15].

In our study, BMI, fatty liver, solo infliximab and longer duration of therapy have been identified as independent risk factors for hepatocellular injury. For BMI and fatty liver, the findings are consistent with the previous reports. However, ALT elevation was also more frequent among patients on solo infliximab compared to other treatment groups (adalimumab, azathioprine, combination therapy, no immunosuppression). This observation might be interpreted as a specific safety signal for solo infliximab therapy^[5,7]. It has been previously shown that severe liver injury occurs on the background of less severe ALT elevations occurring much more commonly. Björnsson *et al.*^[16] showed that solo infliximab therapy had higher risk of DILI compared to adalimumab or combination therapy. In theory, solo infliximab therapy could be more immunogenic than a combination therapy in triggering an immune response. Parisi *et al.*^[13] also found that immunomodulatory therapy increased the risk of infliximab induced liver injury. This might be explained by hepatotoxicity of the immunomodulatory therapy itself, but the true reason for this finding is unclear. Observed normalization of ALT in most cases does not appear to exclude drug-induced immune mediated injury. It might actually support it, since presumed induction of immune tolerance to the drug might lead to the resolution of liver injury. Normalization of ALT in cases of fatty liver without any intervention appears less likely. For now, there appears to be a background of common causes of hepatocellular injury (steatosis, obesity, diabetes, alcohol). In our study, it might be observed in patients with no immunosuppression. On top of this, there is likely a higher risk of the injury in cases with solo infliximab therapy. Concomitant immunomodulator and liver steatosis probably serve as modulators, but we might also anticipate other influencing factors: genetic, ethnic, co-treatment and its dosing, infliximab administration protocol *etc.* We also report that longer duration of IBD increases the risk of hepatocellular injury. Some studies have found a similar association with the duration of infliximab therapy.

In view of the observed safety signals and the fact that liver injury occurs at distinct time points, our results support the need for regular AT monitoring regardless of the treatment duration. There is apparently a growing need for predictive models being able to identify patients at risk for DILI^[17]. However, to date there are no clinically usable biomarkers that could preclude IBD patients from aminotransferase monitoring.

Cholestasis

Cholestasis, a parallel ALP and GGT elevation, was observed in 4.4% of patients. Cholestasis was

more frequently observed in cases treated with solo azathioprine compared with other treatment groups. Moreover, independent risk factors for cholestasis were solo azathioprine therapy, prior intestinal resection and higher CRP. Clinical interpretation of cholestasis in IBD patients should start with excluding possible biliary obstruction and the primary sclerosing cholangitis^[18]. In our cohort, two cases had diagnosed PSC, but none had cholestasis during the study period. Drug induced cholestatic liver injury has been described in IBD patients treated with azathioprine or less commonly by anti-TNF therapy^[19,20]. Symptomatic cholestatic hepatitis has been reported in patients on high-dose azathioprine^[21]. Milder liver injuries might also present as cholestasis. In fact, a very recent study shows that mild transient cholestasis is actually the most common pattern of azathioprine induced liver injury^[22]. Our findings are consistent with the report, since we found transient cholestasis in 7 of 11 cases. In contrast, persisting cholestasis during azathioprine therapy could be caused by PSC, IBD drugs and nodular regenerative hyperplasia (NRH). NRH is asymptomatic in most subjects and no specific NRH markers have been identified. The exact risk of this condition has not been accurately established^[23,24]. Nevertheless, thiopurine therapy, prior intestinal resection and male gender have been previously reported as risk factors for NRH^[25,26].

Another interesting finding of our study is that prior intestinal resection was an independent risk factor for cholestasis. Seventy-three patients in our study cohort had prior intestinal resection, 68 of whom had Crohn's disease. Azathioprine therapy was equally distributed between groups with or without resection, excluding the effect of the drug itself. It was therefore likely, that cholestasis was a consequence of shortening the terminal ileum. Extensive intestinal resection with intestinal failure have been shown to cause severe cholestasis^[27]. Moreover, terminal ileum resection in Crohn's disease decreases the amount of biliary acids reabsorbed into the enterohepatic pool^[28], causing diarrhea due to bile acid malabsorption. One proposed mechanism of this condition could be associated with cholestasis. Impaired bile acid reabsorption decreases farnesoid X receptor signaling (FXR) with decreased production of fibroblast growth factor 19 (FGF19). This might have an stimulatory effect on bile acid synthesis in the liver^[29]. Indeed, levels of FGF19 have been reported decreased in patients with diarrhea due to bile acid malabsorption^[30]. The role of FGF19 in cases with NRH remains unclear. Furthermore, cholestasis in patients with prior resection could also point to the NRH, as discussed above. For now, it appears that azathioprine treated patients are at risk for cholestatic hepatitis and NRH and should be monitored for liver adverse events while on treatment.

Our study has several strengths. We report a real-life burden of liver injury, not excluding patients with preexisting liver disease or other comorbidities. Our

study observed various well defined liver injury events, their severities and patterns. On entry to the study, the study cohort was well defined for IBD phenotype and IBD therapy. We also included patients not treated with immunosuppression. This enabled us to identify the background of liver injury in IBD and the comparison among treatment groups. Our study completes the mosaic of reports on the burden of liver injury in IBD patients coming from clinical trials, registries and cohort studies on azathioprine or infliximab induction.

There are several limitations of our study. The size our cohort was not designed to capture the prevalence of severe DILI. Not surprisingly, we have not observed a single case of severe liver injury. However, in accordance with previous reports, some of our results could be viewed as safety signals for solo infliximab or azathioprine. Our study cohort consisted of patients regardless of the treatment timing. Although most patients were on stable maintenance therapy, some patients could have induction treatment. Our treatment groups were assigned according to the treatment at baseline. Later changes in therapy due to treatment efficacy on IBD were possible, but were infrequent. Inclusion of one retrospective value of AT 3 mo prior to study entry was designed to minimize an effect of this change. Finally, cases with incident mild AT elevations were not investigated for other possible hepatotoxic drugs taken, nor changes in alcohol intake or infections with various hepatotropic viruses. By missing these factors, the real DILI prevalence could have been overestimated.

In conclusion, our study shows that aminotransferase abnormalities are common in IBD patients. They are caused by preexisting liver diseases as well as by the IBD treatment. We found no case of severe DILI, but we observed higher risk of hepatocellular injury in patients on solo infliximab and cholestasis in patients on solo azathioprine. These findings could be viewed as safety signals. The real burden of liver injury on IBD appeared low with most cases resolving spontaneously without any change in disease management. However, our findings point to the potential for hepatotoxicity indicating the need for regular aminotransferase monitoring.

COMMENTS

Background

There is a growing concern, that drug-induced liver injury of inflammatory bowel disease (IBD) therapies might be underestimated. Therefore the authors aimed to analyze a real-life burden of liver injury and its impact of IBD management in a prospective observation during 1 year.

Research frontiers

There are no valid predictive models or biomarkers which would allow us to predict liver injury in IBD treated patients. Therefore, all patients should be monitored for liver tests during treatment. Liver test monitoring during long-term therapy is costly and time consuming. The authors observation was designed to estimate the burden of liver injury and to identify its risk factors (from demographics, IBD phenotype and the particular treatment). Possibly, to

identify patients with high-risk of liver injury in which the liver test monitoring should be close. Or, to identify a low risk group in which monitoring would not be necessary. This observation study was the first step in this research project.

Innovations and breakthroughs

They showed that liver injury was common, but in the great majority of cases it was mild and did not require any change in IBD management. However, patients with longer IBD duration, on solo immunosuppressive therapy with infliximab or solo therapy with azathioprine had higher risk of liver injury. It appears therefore, that this group of patients would require regular monitoring of liver tests. These observations might lead in the future, to the development of a predictive model for liver injury in IBD.

Applications

For now, all patients on IBD therapy should be monitored. However, the risk is significantly higher in patients on solo immunosuppressive therapy, with prior intestinal resection and with longer IBD duration and these cases should be closely monitored for liver injury. In contrast, they have no arguments which would allow us to preclude other patients from liver test monitoring. Predictive models based on the current finding would probably allow us to identify low risk groups in the future.

Terminology

They use common terms and definitions. Hepatocellular injury was defined as ALT elevation superior to 2 x the upper limit of normal (ULN) and cholestasis as ALP and GGT elevation above the ULN.

Peer-review

The paper is well written and provides new insights about drug-induced liver injury occurrence and features in IBD patients.

REFERENCES

- Miehlsler W, Novacek G, Wenzl H, Vogelsang H, Knoflach P, Kaser A, Dejaco C, Petritsch W, Kapitan M, Maier H, Graninger W, Tilg H, Reinisch W. A decade of infliximab: The Austrian evidence based consensus on the safe use of infliximab in inflammatory bowel disease. *J Crohns Colitis* 2010; **4**: 221-256 [PMID: 21122513 DOI: 10.1016/j.crohns.2009.12.001]Available]
- Björnsson ES, Hoofnagle JH. Categorization of drugs implicated in causing liver injury: Critical assessment based on published case reports. *Hepatology* 2016; **63**: 590-603 [PMID: 26517184 DOI: 10.1002/hep.28323]
- Björnsson ES, Bergmann OM, Björnsson HK, Kvaran RB, Olafsson S. Incidence, presentation, and outcomes in patients with drug-induced liver injury in the general population of Iceland. *Gastroenterology* 2013; **144**: 1419-1425, 1425.e1-3; quiz e19-20 [PMID: 23419359 DOI: 10.1053/j.gastro.2013.02.006]
- Stine JG, Chalasani N. Chronic liver injury induced by drugs: a systematic review. *Liver Int* 2015; **35**: 2343-2353 [PMID: 26346512 DOI: 10.1111/liv.12958]
- Kaplowitz N. Drug-Induced Liver Injury. In: Drug-induced liver disease. Third edition Elsevier Inc, 2013: 3-14
- Kwo PY, Cohen SM, Lim JK. ACG Clinical Guideline: Evaluation of Abnormal Liver Chemistries. *Am J Gastroenterol* 2017; **112**: 18-35 [PMID: 27995906 DOI: 10.1038/ajg.2016.517]
- United States Department of Health and Human Services F. Guidance for Industry Drug-Induced Liver Injury: Premarketing Clinical Evaluation. *Drug Saf* 2009; **28**. Available from: URL: <https://www.fda.gov/downloads/Drugs/.../Guidances/UCM174090.pdf>
- Common Terminology Criteria for Adverse Events (CTCAE) 4.03. USDEPARTMENT Heal Hum Serv Natl Institutes Heal Natl Cancer Inst 2010. Available from: URL: https://evs.nci.nih.gov/fp1/CTCAE/CTCAE_4.03_2010-06-14_QuickReference_5x7.pdf
- Watkins PB, Desai M, Berkowitz SD, Peters G, Horsmans Y, Larrey D, Maddrey W. Evaluation of drug-induced serious hepatotoxicity (eDISH): application of this data organization approach to phase III clinical trials of rivaroxaban after total hip or knee replacement surgery. *Drug Saf* 2011; **34**: 243-252 [PMID: 21332248 DOI: 10.2165/11586600-000000000-00000]
- Lewis JH, Larrey D, Olsson R, Lee WM, Frison L, Keisu M. Utility of the Roussel Uclaf Causality Assessment Method (RUCAM) to analyze the hepatic findings in a clinical trial program: evaluation of the direct thrombin inhibitor ximelagatran. *Int J Clin Pharmacol Ther* 2008; **46**: 327-339 [PMID: 18793587]
- Schröder T, Schmidt KJ, Olsen V, Möller S, Mackenroth T, Sina C, Lehnert H, Fellermann K, Büning J. Liver steatosis is a risk factor for hepatotoxicity in patients with inflammatory bowel disease under immunosuppressive treatment. *Eur J Gastroenterol Hepatol* 2015; **27**: 698-704 [PMID: 25923946 DOI: 10.1097/MEG.0000000000000350]
- Cappello M, Randazzo C, Bravatà I, Licata A, Peralta S, Craxi A, Almasio PL. Liver Function Test Abnormalities in Patients with Inflammatory Bowel Diseases: A Hospital-based Survey. *Clin Med Insights Gastroenterol* 2014; **7**: 25-31 [PMID: 24966712 DOI: 10.4137/CGast.S13125.RECEIVED]
- Parisi I, O'Beirne J, Rossi RE, Tsochatzis E, Manousou P, Theocharidou E, Hamilton M, Murray C, Epstein O, Burroughs AK. Elevated liver enzymes in inflammatory bowel disease: the role and safety of infliximab. *Eur J Gastroenterol Hepatol* 2016; **28**: 786-791 [PMID: 27015138 DOI: 10.1097/MEG.0000000000000624]
- Shelton E, Chaudrey K, Sauk J, Khalili H, Masia R, Nguyen DD, Yajnik V, Ananthakrishnan AN. New onset idiosyncratic liver enzyme elevations with biological therapy in inflammatory bowel disease. *Aliment Pharmacol Ther* 2015; **41**: 972-979 [PMID: 25756190 DOI: 10.1111/apt.13159]
- Gisbert JP, González-Lama Y, Maté J. Thiopurine-induced liver injury in patients with inflammatory bowel disease: a systematic review. *Am J Gastroenterol* 2007; **102**: 1518-1527 [PMID: 17391318 DOI: 10.1111/j.1572-0241.2007.01187.x]
- Björnsson ES, Gunnarsson BI, Gröndal G, Jonasson JG, Einarsdottir R, Ludviksson BR, Gudbjörnsson B, Olafsson S. Risk of Drug-Induced Liver Injury From Tumor Necrosis Factor Antagonists. *Clin Gastroenterol Hepatol* 2014; Internet [DOI: 10.1016/j.cgh.2014.07.062]
- Chen M, Borlak J, Tong W. A Model to predict severity of drug-induced liver injury in humans. *Hepatology* 2016; **64**: 931-940 [PMID: 27302180 DOI: 10.1002/hep.28678]
- Yarur AJ, Czul F, Levy C. Hepatobiliary manifestations of inflammatory bowel disease. *Inflamm Bowel Dis* 2014; **20**: 1655-1667 [PMID: 24874461 DOI: 10.1097/MIB.0000000000000065]
- Gisbert JP, Chaparro M, Gomollón F. Common misconceptions about 5-aminosalicylates and thiopurines in inflammatory bowel disease. *World J Gastroenterol* 2011; **17**: 3467-3478 [PMID: 21941413 DOI: 10.3748/wjg.v17.i30.3467]
- Shaye OA, Yadegari M, Abreu MT, Poordad F, Simon K, Martin P, Papadakis KA, Ippoliti A, Vasiliauskas E, Tran TT. Hepatotoxicity of 6-mercaptopurine (6-MP) and Azathioprine (AZA) in adult IBD patients. *Am J Gastroenterol* 2007; **102**: 2488-2494 [PMID: 17764490 DOI: 10.1111/j.1572-0241.2007.01515.x]
- Chertoff J, Alam S, Black M, Elgandy IY. Azathioprine-induced hepatitis and cholestasis occurring 1 year after treatment. *BMJ Case Rep* 2014; **2014**: [PMID: 25471111 DOI: 10.1136/bcr-2014-206859]
- Björnsson ES, Gu J, Kleiner DE, Chalasani N, Hayashi PH, Hoofnagle JH. Azathioprine and 6-Mercaptopurine-induced Liver Injury: Clinical Features and Outcomes. *J Clin Gastroenterol* 2017; **51**: 63-69 [PMID: 27648552 DOI: 10.1097/MCG.0000000000000568]
- Jharap B, van Asseldonk DP, de Boer NK, Bedossa P, Diebold J, Jonker AM, Leteurtre E, Verheij J, Wendum D, Wrba F, Zondervan PE, Colombel JF, Reinisch W, Mulder CJ, Bloemena E, van Bodegraven AA. Diagnosing Nodular Regenerative Hyperplasia

- of the Liver Is Thwarted by Low Interobserver Agreement. *PLoS One* 2015; **10**: e0120299 [PMID: 26054009 DOI: 10.1371/journal.pone.0120299]
- 24 **Morris JM**, Oien KA, McMahon M, Forrest EH, Morris J, Stanley AJ, Campbell S. Nodular regenerative hyperplasia of the liver: survival and associated features in a UK case series. *Eur J Gastroenterol Hepatol* 2010; **22**: 1001-1005 [PMID: 20075739 DOI: 10.1097/MEG.0b013e3283360021]
- 25 **Musumba CO**. Review article: the association between nodular regenerative hyperplasia, inflammatory bowel disease and thiopurine therapy. *Aliment Pharmacol Ther* 2013; **38**: 1025-1037 [PMID: 24099468 DOI: 10.1111/apt.12490]
- 26 **Vernier-Massouille G**, Cosnes J, Lemann M, Marteau P, Reinisch W, Laharie D, Cadiot G, Bouhnik Y, De Vos M, Boureille A, Duclos B, Seksik P, Mary JY, Colombel JF. Nodular regenerative hyperplasia in patients with inflammatory bowel disease treated with azathioprine. *Gut* 2007; **56**: 1404-1409 [PMID: 17504943 DOI: 10.1136/gut.2006.114363]
- 27 **Mutanen A**, Lohi J, Heikkilä P, Koivusalo AI, Rintala RJ, Pakarinen MP. Persistent abnormal liver fibrosis after weaning off parenteral nutrition in pediatric intestinal failure. *Hepatology* 2013; **58**: 729-738 [PMID: 23460496 DOI: 10.1002/hep.26360]
- 28 **Nolan JD**, Johnston IM, Pattni SS, Dew T, Orchard TR, Walters JR. Diarrhea in Crohn's disease: investigating the role of the ileal hormone fibroblast growth factor 19. *J Crohns Colitis* 2015; **9**: 125-131 [PMID: 25518063 DOI: 10.1093/ecco-jcc/jju022]
- 29 **Walters JR**, Appleby RN. A variant of FGF19 for treatment of disorders of cholestasis and bile acid metabolism. *Ann Transl Med* 2015; **3**: S7 [PMID: 26046094 DOI: 10.3978/j.issn.2305-5839.2015.03.38]
- 30 **Pattni SS**, Brydon WG, Dew T, Johnston IM, Nolan JD, Srinivas M, Basumani P, Bardhan KD, Walters JR. Fibroblast growth factor 19 in patients with bile acid diarrhoea: a prospective comparison of FGF19 serum assay and SeHCAT retention. *Aliment Pharmacol Ther* 2013; **38**: 967-976 [PMID: 23981126 DOI: 10.1111/apt.12466]

P- Reviewer: Harmanci O, Pompili M, Lakatos PL **S- Editor:** Qi Y
L- Editor: A **E- Editor:** Wang CH





Published by **Baishideng Publishing Group Inc**
7901 Stoneridge Drive, Suite 501, Pleasanton, CA 94588, USA
Telephone: +1-925-223-8242
Fax: +1-925-223-8243
E-mail: bpgooffice@wjgnet.com
Help Desk: <http://www.f6publishing.com/helpdesk>
<http://www.wjgnet.com>



ISSN 1007-9327

