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Liver Injury From Tumor Necrosis Factor- α Antagonists: Analysis of Thirty-four Cases

MARWAN GHABRIL^{*}, HERBERT L. BONKOVSKY[‡], CLARISSA KUM[§], TIM DAVERN[§], PAUL H. HAYASHI^{||}, DAVID E. KLEINER[¶], JOSE SERRANO[¶], JIM ROCHON[#], ROBERT J. FONTANA^{**}, and MAURIZIO BONACINI[§] for the U.S. Drug-Induced Liver Injury Network

^{*}Department of Medicine, Indiana University School of Medicine, Indianapolis, Indiana [‡]Cannon Research Center, Department of Internal Medicine, and Liver-Biliary-Pancreatic Center, Carolinas Medical Center, Charlotte, North Carolina [§]Department of Transplantation, California Pacific Medical Center, San Francisco, California ^{||}Department of Internal Medicine, University of North Carolina at Chapel Hill, Chapel Hill, North Carolina [¶]Liver Disease Research Branch, National Institute of Diabetes and Digestive and Kidney Diseases, National Institutes of Health, Bethesda, Maryland [#]Duke Clinical Research Institute, Durham, North Carolina ^{**}Department of Internal Medicine, University of Michigan Medical Center, Ann Arbor, Michigan

Abstract

BACKGROUND & AIMS—Tumor necrosis factor (TNF)- α antagonists have been associated with drug-induced liver injury (DILI). We reviewed cases of DILI in the United States to identify those associated with use of TNF- α antagonists.

METHODS—We searched the U.S. DILI Network (DILIN) database, from 2003 to 2011, for cases associated with TNF- α antagonists. Mean Roussel-Uclaf Causality Assessment Method scores were calculated. A DILIN severity score was assigned according to a previously published scale, and we identified 6 subjects likely to have DILI associated with use of TNF- α antagonists. We also searched PubMed for articles that reported hepatotoxicity from TNF- α antagonists, identifying 28 additional cases suitable for analysis.

RESULTS—The drugs presumed to have caused DILI were infliximab (n = 26), etanercept (n = 4), and adalimumab (n = 4). The anti-TNF- α agent was the probable cause of 12 cases of DILI (35%), a very likely cause for 21 (62%), and a definite cause for 1 (3%). Median latency was 13 weeks (range, 2–104); however, 7 cases (20%) had latency periods longer than 24 weeks. Twenty-two of 33 subjects who underwent serologic analysis (67%) tested positive for anti-nuclear and/or smooth muscle antibodies. Of these 22, 17 underwent liver biopsy; 15 subjects had clear features of autoimmunity. The 22 subjects with autoimmune features had longer median latency (16 vs 10 weeks) and higher peak levels of alanine aminotransferase (784 vs 528 U/L) than the 12 without such features. There was 1 case of severe cholestasis. All but one subject improved after discontinuation of the implicated drug; 12 subjects received corticosteroid therapy. No deaths

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Address requests for reprints to: Maurizio Bonacini, MD, Department of Medicine, California Pacific Medical Center, 1580 Valencia Street, Suite 804, San Francisco, California 94110. bonacim@sutterhealth.org; fax: (415) 392-5632.

Supplementary Material

Note: To access the supplementary material accompanying this article, visit the online version of *Clinical Gastroenterology and Hepatology* at www.cghjournal.org, and at doi:10.1016/j.cgh.2012.12.025.

Conflicts of interest

The authors disclose no conflicts.

were attributed to liver injury, although one patient with preexistent cirrhosis required liver transplantation.

CONCLUSIONS—Acute liver injury caused by TNF- α antagonists may be a class effect because multiple agents in this category have been implicated. The most common presentation is an autoimmune phenotype with marked hepatocellular injury, but a mixed non-autoimmune pattern or predominant cholestasis also occurs. The prognosis is usually good after drug discontinuation, although some patients may benefit from a course of corticosteroids. ClinicalTrials.gov: Number, NCT00345930

Keywords

Drug-Induced Liver Injury; Tumor Necrosis Factor; TNF- α Antagonists; Hepatotoxicity; Autoimmunity

Biological response modifiers are prescribed to modify the body's response to inflammation, infection, and neoplasia. These compounds include interferons, interleukins, bone marrow colony-stimulating factors, and tumor necrosis factor (TNF)- α antagonists. All of the TNF- α antagonists have been associated with drug-induced liver injury (DILI).^{1,2} In addition, these agents carry specific warnings about the risk of reactivation of chronic hepatitis B.³

A Food and Drug Administration postmarketing surveillance program received more than 130 reports of liver injury resulting from either infliximab or etanercept treatment.⁴ The results were reported in Food and Drug Administration minutes, and although in many of these cases competing causes were identified, including viral reactivation, 7 of the reported cases were notable for their strong association with the TNF- α antagonist in question.⁴

Two cases of successful treatment with etanercept after a prior DILI episode attributed to infliximab have recently been reported, suggesting that cross-toxicity is not universal among the different TNF- α antagonists.^{5,6} However, it has been shown that several TNF- α antagonists have a similar ability to elicit the development of serologic markers of autoimmunity. These compounds have also been associated with reactivation of latent tuberculosis, hepatitis B, the development of lymphoma, demyelinating disease, seizures, aplastic anemia, and skin rash.³ Accordingly, some reported cases of TNF- α antagonist-induced liver injury exhibited autoimmune features on liver histology.⁶ This suggests the possibility that genetically susceptible individuals may generate an idiosyncratic immune response after inhibition of the TNF- α pathway.¹

In this report, we describe cases that are deemed to be 50% likely to represent bona fide TNF- α antagonist-associated hepatotoxicity. Six were enrolled in the ongoing U.S. Drug-Induced Liver Injury Network (DILIN) Prospective Registry Study.⁷ We also performed a detailed literature search and critically reviewed 34 additional published cases. Of those, 28 met criteria for inclusion. Herein we summarize the clinical and laboratory presentation as well as clinical outcome of these 34 subjects.

Methods

We searched the U.S. DILIN database (between 2003 and 2011) for instances of DILI associated with TNF- α antagonists that were scored probable (score 3) or higher likelihood on the following scale developed by the DILIN group: 1 = definite (>95% likelihood), 2 = highly likely (76%–95%), 3 = probable (51%–75%), 4 = possible (25%–50%), and 5 = unlikely (<25%).⁷ This means that we did not include cases of elevated liver test results associated with a TNF- α antagonist, which by consensus evaluation were found to be only possible or unlikely (ie, 50% likelihood of DILI). The Roussel-Uclaf Causality

Assessment Method (RUCAM)⁸ score was calculated according to published guidelines, and the mean score (from 3 reviewers) was calculated. Causality assessment by RUCAM scores is as follows: 0 or lower, relationship with the drug excluded; 1–2, unlikely; 3–5, possible; 6–8, probable; and >8, highly probable. A DILIN severity score was assigned according to a previously published scale from 1 (mild with bilirubin <2.5 mg%) to 5 (death or liver transplantation).⁷ Six subjects with a causality score of 1, 2, or 3 were identified, and demographics and descriptive statistics for them were summarized by the Duke Clinical Research Institute, the data coordinating center of the DILIN.

The authors had access to the study data and have reviewed and approved the final manuscript.

Search and Review of Literature

A detailed literature review was performed by using the PubMed database in April 2011 by using the search terms “hepatotoxicity,” “liver injury,” “tumor necrosis factor,” and the generic names of all commercially available TNF- α antagonists. All cases that were published as of December 2011 were reviewed by 2 of the authors by using a causality assessment method similar to that used in the DILIN Causality Committee meetings. However, instead of 1 principal investigator and 2 reviewers (not involved in the care of the subject), we used 2 DILIN reviewers (M.G., M.B.) who discussed the published cases, with assistance of a third reviewer (H.L.B.) in case of lack of consensus. However, the 2 reviewers came to a consensus in all literature cases and assigned each published case both a causality and a severity score in a fashion similar to and according to the DILIN protocol.^{1,2} Only those cases that were deemed at least a probable (score 3 or lower) on the DILIN causality scale were included in this report. Six published cases were excluded from the analysis because they were scored as only possible; thus, 28 cases are included in this report.^{9–13}

Autoimmunity was defined by the presence of antinuclear antibody (ANA) or smooth muscle antibody in a titer 1/80 (at the time of DILI onset) or, if available, liver histology consistent with autoimmune hepatitis (AIH). Liver biopsies obtained from the subjects in the DILIN registry were all interpreted by D.E.K. without knowledge of clinical or laboratory features.

Results

Drug-Induced Liver Injury Network Subjects

Selected demographic, clinical, and serum biochemical features of the 6 DILIN subjects with hepatotoxicity attributed to TNF- α antagonists are shown in Table 1. The median latency (duration of drug use before onset) was 16 weeks (range, 2–52 weeks). At presentation, half had jaundice, half had nausea, but only one had fever, and none had immunoallergic features of skin rash or eosinophilia. The hepatic injury pattern was predominantly hepatocellular; 4 patients developed jaundice, but only 1 had significantly impaired coagulation (international normalized ratio [INR], 3.5), and none developed ascites or other signs of hepatic failure. Five of the 6 patients were treated with corticosteroids. One patient had a protracted illness, but all ultimately recovered and could be withdrawn from corticosteroid therapy without recurrence. Clinical summary of a representative DILIN case is reported below, and those of the remaining cases are included in the Supplementary Materials.

Drug-Induced Liver Injury Network case report

Subject 1—A 28-year-old man with quiescent Crohn’s disease was started on infliximab (300 mg [5 mg/kg] intravenously monthly) for ankylosing spondylitis refractory to celecoxib. Four months before starting infliximab, serum enzymes were normal. Concomitant medications included fluoxetine, fluticasone, and omeprazole, and he reported no known drug allergies. After the fourth infusion, alanine aminotransferase (ALT) levels increased to 132 U/L, and total bilirubin was 0.8 mg/dL. In the week of his fifth infusion, ALT increased to 311 U/L, whereas alkaline phosphatase (Alk Phos) and bilirubin remained normal. Infliximab was stopped. He remained asymptomatic throughout, but ALT peaked at 1270 U/L. Serum ANA was initially negative, but 1 month later, it was positive in a titer of 1:160. Anti-smooth muscle antibody (ASMA) remained negative, and immunoglobulin (Ig) G levels were normal. Serum ALT fell to 198 U/L by 2 months after the last infusion but rose again to 1167 U/L, with a total bilirubin of 2.0 mg/dL (Figure 1 A1). Evaluation for hepatitis A, B, and C was negative, and hepatic computed tomography and ultrasound were normal. A liver biopsy obtained 3 months after the last infliximab infusion showed portal and lobular mixed inflammatory infiltrate with autoimmune features and no fibrosis (Figure 1 A2 and A3). Prednisone (50 mg/d) was started, and liver enzymes fell into the normal range within 2 months. Prednisone was tapered and stopped after 7 months. The serum ANA reverted to negative. He was placed on etanercept 11 months after his last dose of infliximab, and serum enzymes remained normal. The assigned DILIN causality score was 1 (definite), RUCAM 5 (possible), and severity score 1 (mild).

Comment—This subject developed progressively elevated serum aminotransferase levels after 5 doses of infliximab, but he remained asymptomatic and had only a mild increase in serum bilirubin. He was taking fluoxetine, fluticasone, and omeprazole at the time of onset, but these agents had been taken for more than a year and were continued. No other cause of liver disease was identified. Liver biopsy findings, ANA positivity, and response to prednisone suggested DILI with auto-immune features triggered by infliximab.

Literature Review

Twenty-eight additional published cases were evaluated, and the results are summarized together with the 6 DILIN cases in Tables 2 and 3. The most common underlying disease was psoriasis and/or psoriatic arthritis (13 cases, 8 women), followed by inflammatory bowel disease (12 cases, 7 women), rheumatoid arthritis (6 cases, all women), and ankylosing spondylitis (3 cases, 1 woman). The drug most commonly incriminated was infliximab (26 cases), followed by etanercept and adalimumab (4 each). No published cases were found linked to natalizumab, golimumab, or certolizumab. On the basis of the reports and causality assessment by 2 of the authors (M.G. and M.B.), 1 case was considered definite, 21 were considered very likely (causality score 2), and 12 cases were deemed probable (causality score 3). An alcohol use history was available in 21 cases. Alcohol was considered a possible competing cause in 3 cases, but the final causality assessment for the anti-TNF compound was very likely in 1 case and probable in the other 2.

Severity scores could be ascertained in 30 cases, and the reaction was rated as mild in 20, moderate in 8, and severe (including 1 liver transplant) in 2. Peak serum ALT ranged from 140–2250 U/L, and bilirubin ranged from normal–27.7 mg/dL. The presence or absence of autoimmune serologies or histologic features was reported in 33 cases; 22 (66%) had autoimmune serologic markers and/or histologic features at some point during the clinical course. Overall, the prognosis was good, although 1 patient with underlying cirrhosis required liver transplantation.¹⁴ Twelve subjects improved after discontinuation of the implicated drug and with the addition or increased dosage of oral or parenteral corticosteroid therapy. The remainder improved after discontinuation of the implicated drug. Several

patients tolerated treatment with etanercept without recurrence of liver injury after cessation of infliximab or adalimumab.^{5,6,9,15,16} Two did well with low-dose etanercept after DILI associated with full dose.^{11,12}

We compared 22 cases with autoimmune features (serology and/or histology) vs those without (Table 4). Those with auto-immune features had serum ANA titers ranging from 1:80 to 1:2560, and 17 subjects underwent liver biopsy that revealed autoimmune histopathologic features in 15. In contrast, among the 8 (of 12) patients without positive autoimmune serologies who underwent liver biopsy, none had clear-cut autoimmune features. Patients with autoimmune features tended to have longer latency and were more likely to have a hepatocellular pattern of serum enzyme elevations, with higher peak ALT and higher *R* values (Table 4).

Discussion

Increased levels of TNF- α have been described in numerous inflammatory and infectious conditions, including liver diseases, eg, alcoholic hepatitis. As a result, anti-TNF- α antibodies or other antagonists have been proposed as therapies for such liver diseases, because uncontrolled pilot studies have suggested beneficial effects.^{17,18} However, randomized, controlled trials have indicated that persons with alcoholic hepatitis treated with infliximab fared worse than untreated controls.^{17,18} Because TNF- α has beneficial as well as deleterious effects, down-regulation of its levels or activity needs to be carefully considered. In some patients treated with TNF- α blockers, acute liver injury has developed that may be severe and prolonged.² Of the TNF- α antagonists, infliximab-associated injury has been the best documented, most likely because of its earlier approval and more widespread clinical use. As of 2011, more than 1,500,000 persons had been exposed to infliximab alone.^{1,2} Fewer bona fide etanercept-induced hepatotoxicity case reports have been published. In fact, this drug has been successfully used after resolution of DILI caused by other TNF- α inhibitors^{5,6,9,15,16} (and DILIN subject 8). In all, a switch to an alternative TNF- α antagonist because of predominantly infliximab-associated DILI did not result in recurrent liver injury in 5 published cases.^{5,6,15,19,20}

A recent review of a national database reported that the risk of elevation of liver enzymes in patients with rheumatoid arthritis who were on TNF- α antagonists was low (ALT or aspartate aminotransferase [AST] elevation $>3\times$ upper limit of normal $<1\%$) and that etanercept was less likely to be associated with liver enzyme elevation as compared with infliximab or adalimumab.²¹ The fact that so few cases have been attributed to etanercept in psoriatic disease may be due to its more recent approval in 2004 and the smaller number of patients treated. Certolizumab (Cimzia) and golimumab (Symponi) are the newest drugs in the class. To our knowledge, DILI attributed to these 2 agents has not yet been reported, although both package inserts mention the risk of hepatitis B virus reactivation as well as idiosyncratic elevation of ALT, which are greater than in placebo. A systematic review of the use on anti-TNF agents in patients with chronic hepatitis C confirms the general impression that these agents are safe in the majority of patients, including those with underlying liver disease.²² An exception is that these agents can cause reactivation of hepatitis B.^{3,22}

Infliximab, etanercept, and adalimumab inhibit TNF- α signaling by directly binding soluble and membrane-bound TNF- α , and all contain, at least in part, a human IgG antibody component. Nevertheless, they differ in their molecular structures. Infliximab is a chimeric IgG1 monoclonal antibody, whereas etanercept is a fusion of recombinant soluble TNF- α receptor type 2 with an Fc domain of human IgG1, and adalimumab is a fully humanized IgG1 monoclonal antibody. In view of these differences, it is not surprising that in a few

cases, a lack of cross-toxicity between etanercept and infliximab has been noted.^{16,23} Each of these subjects had developed liver toxicity while using infliximab, recovered after cessation of infliximab, and did not exhibit any relapse in liver injury when later treated with etanercept. A similar case report has also recently been published that demonstrated successful treatment of psoriatic arthritis with etanercept after adalimumab hepatotoxicity.¹⁵ In addition, infliximab and etanercept have also been observed to elicit different effects on the humoral autoimmune response.²⁴ The frequent development of autoantibodies within 1 year of treatment has been reported in infliximab-treated patients, whereas in etanercept-treated patients, no significant variation of ANA or anti-DNA level was observed.²⁵ In contrast, all 4 etanercept cases in this report (2 from DILIN) developed serologic autoimmune markers, with ANA titers as high as 1:1280 and weakly positive serum antimitochondrial antibody in 1 case (Tables 2 and 3).

We used a causality assessment method similar to that used in the DILIN causality committee meetings, with 2 reviewers (M.G., M.B.) who discussed the published cases and came to a consensus. According to this process, 22 of 34 subjects (65%) were deemed definite or very likely and 12 (35%) probable.

Clinically, the most common presentation of anti-TNF hepatotoxicity is an acute hepatocellular injury ($R > 5$ in 75% of cases), occurring a median of 13 weeks after initiation of therapy; however, 7 of 34 cases had a latency greater than 6 months. Pure bland cholestasis was also observed in 1 case (DILIN subject 3). Laboratory data revealed that serum aminotransferases ranged from 140 to >2000 U/L and that bilirubin was significantly elevated (>3 mg/dL) in 10 of 27 patients (37%). Of note, reactivation of chronic hepatitis B, acute hepatitis B virus, hepatitis C virus, and hepatitis E virus infection were excluded in all of the DILIN cases. Autoimmune features (positive ANA and/or ASMA) were common, including some with classic histologic features of AIH.^{6,9,26–33}

Fortunately, the prognosis was usually good. The fact that in 6 cases (3 very likely and 3 probable), the autoantibodies decreased or disappeared with corticosteroid therapy suggests drug-induced rather than *de novo* idiopathic autoimmunity.³⁴ This autoimmune signature (either AIH on biopsy or ANA titers 1:80) was seen in 22 patients and occurred with infliximab, adalimumab, and etanercept treatment, supporting the concept that despite molecular structural differences, a class effect is present. The 12 cases lacking autoimmune features were also different, because their latency was significantly shorter (10 vs 16 weeks), and the peak serum ALT (median, 528 vs 784 U/L) and R values were lower than those cases with autoimmune features (Table 4). Prolonged cholestasis may also occur, as exemplified by DILIN subject 3.

The mechanism by which the TNF- α antagonists lead to DILI is unknown. Because the injury can occur after only one infusion, dose-dependent toxicity is unlikely, although patients in whom low dose etanercept was tolerated after developing DILI with full dose injection have been reported.^{11,12} Unpredictable idiosyncratic DILI seems most likely, because in this series no patients had clinical evidence of a rash or eosinophilia, and only one presented with fever. Nonetheless, the serologic and histopathologic studies with features of AIH strongly suggest that humoral and cell-mediated immune responses are important in the pathogenesis. Further studies are needed to ascertain whether genetic or other markers of the hepatotoxicity associated with TNF- α antagonists can be identified.

In summary, we have described 6 well-characterized cases of DILI in the setting of TNF- α antagonist therapy and also reviewed 28 additional published cases. The most common clinical presentation was that of an acute hepatocellular injury with autoimmune features, including histologic changes that are similar to spontaneous AIH. Additional presentations

include a milder mixed injury pattern with shorter latency and less commonly, a prolonged cholestatic injury pattern. The prognosis is generally favorable, and corticosteroids may be helpful in accelerating resolution in subjects with autoimmune features. Treatment with an alternative TNF- α antagonist after resolution of the liver injury appears to be well tolerated without recurrence.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Abbreviations used in this paper

AIH	autoimmune hepatitis
Alk Phos	alkaline phosphatase
ALT	alanine aminotransferase
ANA	antinuclear antibody
ASMA	anti-smooth muscle antibody
AST	aspartate aminotransferase
DILI	drug-induced liver injury
DILIN	U.S. Drug-Induced Liver Injury Network
Ig	immunoglobulin
INR	international normalized ratio
RUCAM	Roussel-Uclaf Causality Assessment Method
TNF-α	tumor necrosis factor- α

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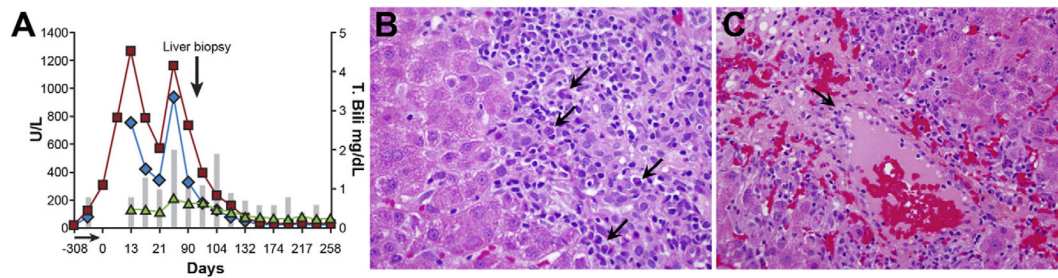


Figure 1.

DILIN subject 1. (A) Graphic summary of DILI caused by infliximab. *Left vertical axis*, serum enzymes (U/L); *right vertical axis*, serum total bilirubin (mg/dL); *horizontal axis*, time in days, with onset of DILI being day 0. *Blue diamonds*, serum AST; *red squares*, serum ALT; *green triangles*, serum Alk Phos; *gray columns*, serum total bilirubin; *horizontal red arrow*, duration of treatment with the anti-TNF-agent; *vertical blue arrow*, timing of liver biopsy. (B) Marked interface hepatitis with plasma cells (*arrows*) (H&E; original magnification, $\times 600$). (C) Zone 3 necrosis with inflammation and venulitis (*arrow*) (H&E; original magnification, $\times 400$).

Table 1

Presenting Clinical and Laboratory Features of 6 DILIN Subjects With Liver Injury Attributed to Anti-TNF- α Agents

Clinical parameter	Subjects with DILI caused by anti-TNF- α agents (n = 6)
Median age, y (25%–75%)	35 (33–38)
Female sex	5 (83%)
Body mass index (kg/m^2)	27 (20–44)
Latency (wks)	16 (2–52)
Peak ALT (U/L)	914 (384–1687)
Peak Alk Phos (U/L)	202 (83–1311)
Peak total bilirubin (mg/dL)	9.8 (1.5–34.2)
Peak INR	1.3 (1–3.5)
R value	10 (3–25)

R value, ratio of (serum ALT/upper limit of normal for ALT) divided by (Alk Phos/upper limit of normal for Alk Phos).

Table 2Summary of the 6 DILIN Cases and 28 Previously Published Cases of DILI Attributed to Anti-TNF- α Agents

Anti-TNF- α agent and DILIN case number or reference citation	Age (y), sex	Disease	Dose	Duration of therapy before onset of DILI (wks)
Infliximab DILIN 1	28, M	CD	5 mg/kg	20
Infliximab DILIN 2	54, F	PsA	5 mg/kg	12
Infliximab DILIN 3	35, F	CUC	5 mg/kg	2
Etanercept DILIN 4	34, F	Ps	50 mg	15
Etanercept DILIN 5	35, F	Ps	25 mg twice per week	16
Adalimumab DILIN 6	33, F	CD	40 mg	52
Infliximab ⁵	48, M	AS	5 mg/kg	14
Infliximab ⁶	48, M	AS	5 mg/kg	36
Infliximab ¹⁶	46, F	PsA	5 mg/kg	22
Infliximab ²⁸	22, F	Ps	5 mg/kg	6
Infliximab ³²	54, F	AS	5 mg/kg	12
Infliximab ³⁵	33, M	Ps	NA	20
Infliximab ³⁶	38, F	RA	3 mg/kg	38
Infliximab ³⁷	43, F	CD	5 mg/kg	4
Infliximab ³⁸	40, F	PsA	5 mg/kg	22
Infliximab ²³	64, M	Ps	5 mg/kg	3
Infliximab ³⁰	53, F	PsA	3 mg/kg	30
Infliximab ³³	36, F	RA	3 mg/kg	12
Infliximab ³⁹	34, F	CUC	5 mg/kg every 2 weeks	16
Infliximab ⁴⁰	28, M	CUC	5 mg/kg	1.5
Infliximab ¹⁴	39, F	RA	3 mg/kg	32
Infliximab, case 1 ⁴¹	37, M	Ps	5 mg/kg	12
Infliximab, case 2 ⁴¹	51, M	Ps	5 mg/kg	10
Infliximab ⁴²	60, M	CD	5 mg/kg	14
Infliximab ¹⁹	46, M	CD	5 mg/kg	6
Infliximab ⁴³	45, F	CD	5 mg/kg	7
Infliximab ⁴⁴	38, F	CD	5–10 mg/kg	104
Infliximab ²⁰	33, M	CD	NA	20
Infliximab ⁴⁵	58, F	CD	5 mg/kg	12
Etanercept ³¹	50, F	RA	25 mg twice per week	2
Etanercept ²⁹	9, F	JIA	0.4 mg/kg twice per week	40
Adalimumab ²⁷	36, F	PsA	40 mg every other week	12
Adalimumab ¹⁵	46, M	PsA	40 mg every other week	12
Adalimumab ²⁶	35, F	RA	NA	5

NOTE. Adalimumab was administered every other week. Infliximab was administered at 0, 2, and 6 weeks and every 8 weeks thereafter. Etanercept was administered weekly or twice weekly, as shown.

AS, ankylosing spondylitis; CD, Crohn's disease; CUC, chronic ulcerative colitis; JIA, juvenile inflammatory arthritis; NA, not available; Ps, psoriasis; PsA, psoriatic arthritis; RA, rheumatoid arthritis.

Table 3

Laboratory and Histologic Findings and Causality and Severity Assessment of the 6 DILIN Patients and 28 Published Case Reports of DILI Attributed to Anti-TNF- α Agents (Ordered by Cohort, Agent, and Causality Score)

Anti-TNF- α agent and DILIN case number or reference citation	Drugs taken concomitantly	R value at onset	Peak values for ALT (IU/L), total bilirubin (mg/dL)	Causality score	Severity score	Autoimmune markers	Liver biopsy features
Infliximab DILIN 1	None	25	1270, 2	1	1	ANA, 1:160	Portal and lobular mixed inflammation with autoimmune features
Infliximab DILIN 2	Methotrexate	5	287, 0.5	2	1	Negative	NA
Infliximab DILIN 3	None	3	640, 34.2	2	3	Negative	Bland cholestasis, worsened after 4–5 wks
Etanercept DILIN 4	NAbumetone	18	1687, 2.8	2	3, hospitalized	ANA 1:640, ASMA negative	AIH vs DILI
Etanercept DILIN 5	None	12	1188, 16.8	2	3	ANA 1:80, ASMA 1:20	AIH vs DILI vs viral hepatitis
Adalimumab DILIN 6	None	9	523, 18	3	4	Negative	NA
Infliximab ⁵	None	6	656, 0.61	2	1	Negative	NA
Infliximab ⁶	Methotrexate, phenylbutazone	NA	412, NA	2	3, hospitalized	ANA 1:160	Bridging necrosis with Kupffer cells
Infliximab ¹⁶	None	2,3 ^a	369, 1.5	2	1	Negative	NA
Infliximab ²⁸	None	NA	1663, NA	2	3, hospitalized	ANA 1:640	AIH
Infliximab ³²	None	4	621, 6.0	2	2	ANA 1:640, decreased with prednisone	AIH
Infliximab ³⁵	None	25	2132, 3.7	2	2	ANA negative to 1:320	NA
Infliximab ³⁶	Methotrexate	NA	234, normal	2	NA	Negative	Acute toxic hepatitis without methotrexate-related fibrosis
Infliximab ³⁷	None	20	1497, 0.6	2	1	Negative	NA
Infliximab ³⁸	Sertraline	—	536, NA	2	1	ANA 1:160–1:1280	Eosinophilia consistent with DILI
Infliximab ²³	Amlodipine, doxazosin	>5 ^a	569, NA	3	1	Negative	NA
Infliximab ³⁰	Methotrexate	NA	NA	3	3, hospitalized	ASMA 1:640 to negative with prednisone	AIH, 60% steatosis
Infliximab ³³	Minoocycline	NA	448, 16.6	3	2	1:640–1:160 with prednisone	AIH with bile duct damage and polymorphonuclear leukocytes
Infliximab ³⁹	Azathioprine	6	412, NA	3	NA	ANA 1:320	NA
Infliximab ⁴⁰	None	1.8	175, 7.5	3	2	Negative	NA

Anti-TNF- α agent number or reference citation	Drugs taken concomitantly	R value at onset	Peak values for ALT (IU/L), total bilirubin (mg/dL)	Causality score	Severity score	Autoimmune markers	Liver biopsy features
Infliximab ¹⁴	Leflunomide	NA	2250, 15.1	3	5, liver transplant	ANA negative to 1:640	NA
Infliximab, case 1 ⁴¹	None	10	1126, normal	2	NA	ANA 1:200	NA
Infliximab, case 2 ⁴¹	Alcohol	6	768, 3.1	3	2	ANA 1:2560, AMA 1:600	Overlap AIH/PBC
Infliximab ⁴²	NA	15	1307	2	NA	Positive ANA and anti-actin antibodies	Plasma cells and eosinophils
Infliximab ¹⁹	NA	6.5	528, normal	2	1	Negative	Converging necrosis
Infliximab ⁴³	NA	>5	18 \times ULN, normal	2	1	Negative	Centrilobular necrosis
Infliximab ⁴⁴	None	NA	191, normal	3	1	ANA 1:640	Interface hepatitis with plasma cells
Infliximab ²⁰	None	30	1227, normal	2	1	ANA 1:1280	Interface hepatitis with rosettes, plasma cells, bridging fibrosis
Infliximab ⁴⁵	Azathioprine	NA	140, normal	2	1	ANA 1:2560	Interface hepatitis with rosettes, plasma cells
Etanercept ³¹	None	5.2	800, 1.2	3	3, hospitalized	ANA 1:1280	c/w AIH
Etanercept ²⁹	NAproxen	17	354, 11.9	3	2	ANA 1:640	c/w AIH
Adalimumab ²⁷	Methotrexate	40	1265, 0.7	2	3, hospitalized	ANA 1:80 to negative with prednisone	AIH
Adalimumab ¹⁵	None	NA	252, NA	3	1	Negative	NA
Adalimumab ²⁶	NA	7	266, normal	2	1	ANA 1:80, ASMA 1:320	Mild/moderate inflammation

NOTE. R value scale: <2, cholestatic; 2–5, mixed; >5, hepatocellular injury pattern.

AMA, serum antimitochondrial antibody; c/w, consistent with; NA, no data available; PBC, primary biliary cirrhosis.

^a R value was calculated by using γ -glutamyltransferase.

Table 4

Comparison of Subjects With Autoimmune Features With Subjects Without

Clinical parameter	With autoimmune features (n = 22)	Without autoimmune features (n = 12)	P value
Latency (wk) ^a	16 (2–104)	10 (2–52)	.17
Peak ALT (U/L) ^a	784 (140–2250)	528 (175–2491)	.03
Peak bilirubin (mg/dL) ^a	2.4 (0.7–16.8)	1.0 (0.6–27.7)	.9
R value	13 (4–40)	6 (1.8–20)	.01

^aValues are described as medians and (ranges).