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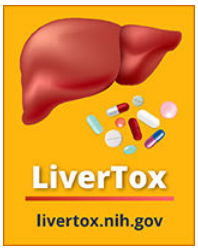

Autoimmune Hepatitis

Updated: May 4, 2019.

Description. Drug induced liver injury with autoimmune features (also called drug induced autoimmune hepatitis) is marked by acute or chronic liver injury accompanied by development of autoantibodies, a hepatocellular pattern of serum enzyme elevations, and liver biopsy features suggestive of idiopathic autoimmune hepatitis. Drug induced autoimmune hepatitis resembles idiopathic autoimmune hepatitis, but typically resolves completely once the medication is withdrawn, although recovery may be slow and lead to a limited course of corticosteroid therapy.

Latency to Onset. The time to onset of drug induced autoimmune hepatitis is usually more than 6 months and can be up to several years after initiation of therapy. In some situations, onset is more rapid and the clinical phenotype resembles acute hepatitis, but onset with appearance of autoantibodies is rare before 2 months.

Symptoms. The onset of drug induced autoimmune hepatitis is typically insidious, sometimes with extrahepatic manifestations such as rash or joint pains that precede symptoms of hepatic injury (fatigue, nausea, poor appetite). Jaundice arises late and may follow several months of nonspecific symptoms.

Serum Enzyme Elevations. Autoimmune hepatitis due to medications is typically manifested by moderate serum aminotransferase elevations (200 to 800 IU/L: 5 to 20 times ULN) with minimal increase in alkaline phosphatase levels (<230 U/L: <2 times ULN), suggestive of chronic rather than acute hepatitis. Serum autoantibodies are usually (but not invariably) present, including antinuclear (ANA), smooth muscle antibody (SMA) or antibody to liver-kidney microsomes (anti-LKM). Immunoglobulin levels and total globulins are often but not always raised. Medications that cause autoimmune hepatitis associated with chronic hepatitis can often also cause an acute viral hepatitis-like syndrome (minocycline, nitrofurantoin, methyldopa, hydralazine) and these two phenotypes may overlap. Recovery after stopping the medication in autoimmune hepatitis may be delayed and lead to use of corticosteroids, which typically results in prompt improvement. Autoantibody titers and immunoglobulin levels also decrease with recovery, but low levels of autoantibodies may persist long term. In most instances, drug induced autoimmune hepatitis ultimately resolves once the medication is stopped, although this may take 6 months or more; in some cases, however, particularly with biologic response modifiers (interferons, tumor necrosis factor antagonists), the autoimmune hepatitis appears to have been triggered rather than caused by the drug and can be self sustaining and require long term immunosuppressive therapy.

Drugs. Medications that typically cause autoimmune hepatitis include minocycline, nitrofurantoin, hydralazine, methyldopa, statins, fenofibrate, alpha and beta interferon, infliximab and etanercept. Individual case reports of an autoimmune hepatitis-like syndrome attributed to medications have implicated many other agents, including nonsteroidal antiinflammatory agents, azathioprine, and herbals. In addition, some medications induce autoantibodies even in the absence of hepatic injury (isoniazid, procainamide) and their presence during liver injury may be coincidental.

Criteria for Definition. There are no established diagnostic criteria for drug induced autoimmune hepatitis; however, based upon similarity to idiopathic autoimmune hepatitis the following are important elements in the diagnosis:

1. Time to onset of 2 months or more
2. Rash, arthralgias or extrahepatic manifestations
3. Hepatocellular pattern of serum enzyme elevations (R >5 at onset)
4. Presence of an autoantibody in titers of 1:80 or greater (ANA, SMA or anti-LKM)
5. Raised immunoglobulin (IgG >1800 mg/dL) or total globulin levels (>3.0 grams/dL)
6. Exposure to an agent that is typically associated with drug induced autoimmune hepatitis: nitrofurantoin, methyldopa, minocycline, hydralazine, alpha interferon, beta interferon, cholesterol lowering agents
7. Liver biopsy showing features of chronic hepatitis with interface hepatitis and prominence of plasma cells
8. Prompt response to corticosteroid therapy (decrease in ALT levels by half within 2 weeks)
9. Ultimate resolution upon stopping the medication (and corticosteroid therapy), although resolution may be slow and may call for corticosteroid therapy for several months.

Proof that a drug is the cause of an autoimmune hepatitis-like syndrome is sometimes difficult, particularly if the medication is not a common cause. Most diagnostic is a resolution of the syndrome with withdrawal of the agent. Improvements, however, often take several weeks to begin and the presence of features of autoimmunity often prompt treatment with corticosteroids, the usual therapy of idiopathic autoimmune hepatitis. While controlled trials of corticosteroid therapy have not been conducted in drug induced autoimmune hepatitis, case reports and small case series suggest that corticosteroids induce a prompt improvement in serum bilirubin and aminotransferase elevations. In this regard as well, drug induced resembles idiopathic autoimmune hepatitis.

Distinction between drug induced and idiopathic autoimmune hepatitis can also be made if corticosteroids can be withdrawn without a relapse in disease. Relapse upon withdrawal of immunosuppression is common with idiopathic but atypical of drug induced autoimmune hepatitis (at least if the course of corticosteroids was adequate). Also, typical of drug induced injury is disappearance of the autoantibodies with resolution. Spontaneous improvements can occur in idiopathic autoimmune hepatitis, but relapse is ultimately common, although sometimes months or years later. Once resolved, relapse of an autoimmune hepatitis initially triggered by a drug is unusual unless the drug is restarted.

Clinical Features and Course. Drug induced autoimmune hepatitis typically presents with the insidious onset of fatigue, weakness, nausea, poor appetite, right upper quadrant discomfort and jaundice or pruritus. The pattern of enzyme elevations is predominantly hepatocellular with prominent elevations in serum aminotransferase and modest increases in alkaline phosphatase levels. The severity of drug induced autoimmune hepatitis ranges widely from mild serum enzyme elevations with few if any symptoms, to symptomatic but anicteric hepatitis, to an acute or chronic hepatitis, to acute liver failure. If severe and prolonged injury occurs, evidence of hepatocellular dysfunction can arise including low serum albumin and prolongation of prothrombin time, and the injury can result in cirrhosis and end stage liver disease. In rare instances, the injury is acute and severe, leading rapidly to acute liver failure and death or need for liver transplantation.

Most characteristic of drug induced autoimmune hepatitis are the autoimmune features, including increases in serum immunoglobulins (particularly IgG) and autoantibodies. The most typical autoantibodies are directed at nuclear (ANA), smooth muscle (SMA) and liver-kidney microsomal antigens (anti-LKM). The pattern and specificity of these autoantibodies may provide a clue to the pathogenesis of the apparent autoimmune process induced by the medication, occasionally having specificity for a metabolic intermediate or drug-protein adduct such as antibody to altered P450 enzymes or anti-CYP 2D6. However, by far the most common autoantibodies found are nonspecific ANA reactivity or SMA with the typical anti-actin reactivity.

Drug induced autoimmune hepatitis typically arises 2 months to several years after starting the implicated medication and the clinical pattern of disease is more like chronic than acute liver injury. Patients may have extrahepatic manifestations of autoimmunity as well, such as arthralgias and skin rash or even other major organ involvement such as pneumonitis, nephritis or cerebritis. A history of other autoimmune diseases may be present but is not typical. Liver biopsy, if performed, usually shows elements that are typical of autoimmune hepatitis such as interface hepatitis with a lymphocytic or lymphoplasmocytic infiltrate and hepatic rosette formation. There may be variable degrees of fibrosis. In some instances, advanced fibrosis or even cirrhosis is present at the time of diagnosis, particularly if diagnosis and discontinuation of the medication is delayed.

Many of the agents that can induce autoimmune hepatitis can also induce other autoimmune conditions or symptoms such as a lupus-like syndrome (minocycline), pneumonitis (nitrofurantoin), hemolytic anemia (methyldopa) and acute thyroiditis (interferon alfa). Indeed, in these conditions there may be minor serum aminotransferase elevations indicative of a mild component of hepatic injury.

The important differential diagnosis for drug induced autoimmune hepatitis is, of course, spontaneous or idiopathic autoimmune hepatitis, a disease that can have spontaneous remissions and relapses, but that is typically severe and progressive without adequate immunosuppressive therapy. Some cases of drug induced autoimmune hepatitis do not resolve completely upon withdrawal of the medication, and some require long term immunosuppressive therapy and have had relapses (some severe) when corticosteroids were stopped. In these instances, it is not clear whether the autoimmune hepatitis-like syndrome was actually caused by the medication or was a co-incidence, arising spontaneously in a patient being treated long term with a common medication. An intermediate hypothesis is also possible, that the medication triggered the onset of autoimmune hepatitis in a susceptible patient that may have ultimately developed the disease, even without the medication. Often, this last possibility cannot be excluded. Spontaneous, idiopathic autoimmune hepatitis obviously has triggering factors for its onset and a medication or liver injury may be such a trigger. These issues call for careful clinical investigation of cases of autoimmune hepatitis associated with medications for genetic and environmental factors that might reveal the cause of this important syndrome.

Mechanism of Injury. The pathogenesis of autoimmune hepatitis due to medications is not clear. However, it is likely that hepatocytes, owing to their ability to metabolize drugs, can form drug-protein adducts which may be immunogenic. These newly formed antigens may, in turn, incite CD4+ and CD8+ cytotoxic lymphocyte and natural killer cell proliferative responses. The drug metabolizing enzymes (P450; CYP) are likely targets for neoantigen formation. Additionally, drugs may interact with T cell receptors to induce, and thus induce an immune response without forming cellular protein adducts.

There appears to be a genetic predisposition to autoimmune hepatitis from medications, and this may be the same genetic predisposition as for idiopathic autoimmune hepatitis. Indeed, in some instances, the hepatic injury from a medication appears to trigger autoimmune hepatitis and medications may be one of the environmental features that underlie the onset of this syndrome in susceptible patients. Genetic testing has shown that autoimmune hepatitis is closely linked to HLA types, in particular the extended haplotype of A3, B8, Dr3 and DrB03*0301 in Caucasians and northern Europeans with autoimmune hepatitis. This haplotype may also predispose to drug induced autoimmune hepatitis, although this has not been well defined.

Management. The most important element in management of drug induced autoimmune hepatitis is to recognize the possible role of the medication and discontinue it promptly. An adequate clinical and laboratory evaluation to assess the severity and characteristics of the injury is also important, as is testing for other possible causes. Liver biopsy is not necessary for diagnosis, but can be helpful and will provide information on the severity of the injury and the presence of any fibrosis.

Active therapy for autoimmune hepatitis using corticosteroids is often used in cases where a medication is thought to be the cause, although without controlled medical evidence for efficacy. Nevertheless, corticosteroid

therapy is appropriate if recovery does not start within 1 to 2 weeks of stopping the implicated agent or if there is any evidence of hepatic failure, such as prolongation of the prothrombin time, deepening jaundice, hepatic encephalopathy, serum hypoalbuminemia with edema or ascites. An appropriate regimen would be prednisone (or its equivalent) in doses of 20 to 60 mg daily, decreasing the dose rapidly upon evidence of improvement with the goal to discontinue therapy completely within 3 to 6 months. High dose corticosteroid therapy can have significant and even permanent side effects, so that use of lower initial doses (20 to 30 mg daily) is appropriate for cases without signs of hepatic failure. An important element in using corticosteroids is careful follow up for at least six months after they have been discontinued to document full recovery and the absence of relapse, which can be severe and even fatal in patients with spontaneous autoimmune hepatitis in whom corticosteroids are stopped early.

Representative Cases

Case 1. Chronic hepatitis-like syndrome caused by long term methyldopa therapy.

[DILIN Case: 104-0034]

A 25 year old woman developed signs and symptoms of chronic liver disease after 8 months of therapy with methyldopa. Methyldopa had been started in a dose of 250 mg twice daily during a pregnancy, but was then continued after she had a Caesarian section 3 months later. After being on methyldopa for 8 months, she had the insidious onset of nausea, dark urine, itching and jaundice. She was admitted to a local hospital and laboratory testing showed an ALT of 1292 U/L and bilirubin of 7.3 mg/dL. Tests for hepatitis A, B and C were negative. Both smooth muscle and antinuclear antibody were negative. CT scans and ultrasound of the liver were normal. A liver biopsy showed changes typical of chronic active hepatitis. Methyldopa was stopped, and she was placed on prednisone. Serum aminotransferase levels slowly improved. Six months later prednisone was stopped and, in follow up, her liver tests remained normal.

Key Points

Medication:	Methyldopa
Pattern:	Hepatocellular (R=21)
Severity:	3+ (jaundice, hospitalization)
Latency:	8 months
Recovery:	Complete after 6 month course of prednisone
Other medications:	Triamterene

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
Methyldopa Started During Pregnancy					
8 months	0	1292	126	10.3	Methyldopa stopped
	1 week	1053	101	19.3	
	2 weeks	1140	156	24.9	Prednisone started
9 months	4 weeks	362	169	11.9	
	6 weeks	88	102	3.0	
10 months	8 weeks	64	113	2.0	

Table continued from previous page.

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
11 months	3 months	80	61	1.0	Prednisone tapered
12 months	4 months	45	74	1.0	
14 months	6 months	29	69	0.5	Prednisone stopped
20 months	12 months	19	83	1.0	
Normal Values		**<60**	**<126**	**<1.2**	

Comment

This case represents a moderately severe example of autoimmune chronic hepatitis induced by methyldopa. Atypical was the lack of autoantibodies, but the clinical presentation, liver biopsy findings and response to corticosteroids provides convincing evidence for an autoimmune like reaction. The use of prednisone was justified based upon height of the bilirubin and ALT elevation. Importantly, once jaundice had resolved, the prednisone was withdrawn gradually, and in follow up, this patient was asymptomatic and had normal liver tests.

Case 2. Severe acute hepatitis with autoimmune features caused by minocycline.

(DILIN Case: 104-0061)

A 21 year old man was started on minocycline for acne and two months later developed fatigue, dark urine and weight loss and stopped therapy on his own. A week later he was admitted to the hospital because of jaundice. He denied a previous history of liver disease or risk factors for viral hepatitis. He drank alcohol rarely. Serum bilirubin was elevated as were serum aminotransferase levels. Tests for hepatitis A, B, and C and for infectious mononucleosis were negative. Autoantibody testing showed a positive antinuclear antibody (1:1280), but negative tests for smooth muscle and liver-kidney microsomal antibodies. A liver biopsy was done which showed changes suggestive of autoimmune hepatitis with marked activity. He was started on prednisone and rapidly improved. Therapy was gradually reduced and then discontinued several months later without relapse of symptoms or recurrence of laboratory abnormalities.

Key Points

Medication:	Minocycline (100 mg daily for 9 weeks)
Pattern:	Hepatocellular (R=6.3)
Severity:	3+ (jaundice, hospitalization)
Latency:	8 weeks
Recovery:	2 months on prednisone
Other medications:	None

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
10 weeks	1 week	1343	783	5.7	
11 weeks	2 weeks	1649	638	4.8	Liver biopsy
Prednisone (60 mg daily) started					

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Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
14 weeks	5 weeks	83	145	1.1	
Normal Values		**<35**	**<130**	**<1.2**	

Comment

Minocycline can cause either an acute or a chronic hepatitis, but both are characterized by a hepatocellular pattern of serum enzyme elevations, the presence of autoantibodies and a liver biopsy showing changes typical of autoimmune hepatitis. Spontaneous recovery with stopping minocycline is the rule, but recovery can be prolonged, and prednisone therapy may speed the process. Whether prednisone actually improves ultimate outcome has not been proven. Nevertheless, both drug induced and spontaneous autoimmune hepatitis can be severe and even fatal, and prednisone therapy may provide rapid relief. Most important, however, is to limit the dose and duration of therapy, carefully monitoring patients after stopping for evidence of recurrence.

Case 3. Severe autoimmune chronic hepatitis due to nitrofurantoin.

(DILIN Case: 101-0023)

An 84 year old woman was treated with nitrofurantoin 50 mg once daily for seven months. Because of recurrence of urinary tract infections, it was restarted one year later. After another 14 months of taking nitrofurantoin, she was found to have jaundice and peripheral edema. She was hospitalized for investigation. Serum aminotransferase, alkaline phosphatase, and bilirubin levels were elevated (Table). MRI suggested an infiltrating tumor in the liver, but endoscopic retrograde cholangiopancreatography was unrevealing and biopsy of the mass showed no evidence of tumor, but rather chronic inflammation and submassive hepatic necrosis. Tests for hepatitis A, B and C were negative. Antinuclear antibody and smooth muscle antibody titers were strongly positive. Symptoms of abnormal liver tests improved slowly after nitrofurantoin was stopped. At follow up 7 months later, the patient was asymptomatic, and liver enzyme levels were in reference range.

Key Points

Medication:	Nitrofurantoin
Pattern:	Chronic hepatitis, cholestatic pattern of enzymes (R=1.7)
Severity:	3+ (jaundice, hospitalization)
Latency:	3 years after starting (intermittent therapy)
Recovery:	Protracted but complete
Other medications:	Losartan, warfarin, atorvastatin, diltiazem

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
0		Nitrofurantoin started			
8 months		Nitrofurantoin stopped			
Pre-restarting		16			
Nitrofurantoin restarted					
7 months		52			
9 months		115			

Table continued from previous page.

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	Other
12 months		190	175	1.5	
13 months		197	359	3.8	Edema
14 months	0	307	503	5.0	Nitrofurantoin stopped
15 months	1 month	89	301	5.8	ANA 1:320
17 months	3 months	45	145	1.1	
21 months	7 months	39		0.9	
Normal Values		**<42**	**<130**	**<1.2**	

Comment

This elderly lady presented with a clinical picture suggestive of liver cancer after more than a year of intermittent therapy with nitrofurantoin. A liver biopsy demonstrated a histologic picture of severe chronic active hepatitis. Autoimmune markers were present. The resolution of the injury after withdrawal of drug supports the diagnosis of a drug induced chronic hepatitis with autoimmune features.

Case 4. Induction of autoimmune hepatitis by a course of peginterferon and ribavirin for chronic hepatitis C.

[NIH patient # G40]

A 52 year old woman with chronic hepatitis C developed sudden worsening of disease and jaundice 4 weeks after starting peginterferon therapy. She was known to have chronic hepatitis C for 12 years when she was found to have elevations in serum aminotransferase levels and antibody to hepatitis C in serum. She was largely asymptomatic and had no other medical problems. The source of hepatitis C was believed to be blood transfusions after Caesarian section 25 years previously. She had mild chronic hepatitis on liver biopsy and portal fibrosis (2+ fibrosis on a scale of 0 to 6+). HCV RNA levels ranged from 1 to 2 million IU/mL and genotype was 1b. She was started on peginterferon alfa-2a in a dose of 180 µg weekly and ribavirin (1200 mg daily) was added 4 weeks later. With therapy, her serum levels of HCV RNA fell rapidly (Table). Serum aminotransferase levels, however, started to rise and were above 1000 U/L by week four. By week five she was jaundiced and both peginterferon and ribavirin were stopped. Serum ANA was negative but SMA was weakly positive (1:40) and anti-LKM was present. IgM anti-HAV, anti-HBc and anti-HDV were negative. Ultrasound showed no evidence of biliary obstruction. Immunoglobin levels were elevated before therapy and had risen further (IgG 2130 to 2910 mg/dL). Jaundice worsened for a week and prednisone (20 mg daily) was started, whereupon both bilirubin and aminotransferase levels began to improve. Once ALT levels had returned to baseline, prednisone was gradually decreased and then stopped. However, serum ALT and immunoglobulin levels began to rise again and prednisone was reintroduced. After serum ALT levels had again fallen, the dose of prednisone was reduced and azathioprine was started (100 mg daily), ultimately allowing for discontinuation of prednisone. Serum aminotransferase levels remained normal on azathioprine alone but ANA became weakly positive. HLA typing showed A33, B42, 53 and DRB 3.

Key Points

Medication:	Peginterferon alfa-2a (180 µg/week)
Pattern:	Hepatocellular (R=20)
Severity:	3+ (jaundice requiring hospitalization and intervention)
Latency:	5 weeks to onset of jaundice

Table continued from previous page.

Recovery:	Incomplete, chronic autoimmune hepatitis requiring long term therapy
Other medications:	Ribavirin

Laboratory Values

Time After Stopping	Therapy	AST (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	HCV RNA (IU/mL)	Other
- 8 weeks		204	91	0.9	1,420,000	IgG 2130 mg/dL, ANA neg
- 4 weeks		185	83	0.7	2,890,000	
Peginterferon (180 ug/week) started						
0		203	92	0.4	2,130,000	
2 weeks	Peginterferon	329	102	0.4	587,000	
4 weeks	Peginterferon	1093	133	0.9	<100	
6 weeks	Peg & Rbv	1002	162	8.0	<10	IgG 2910, ANA neg, LKM pos
7 weeks	None	1206	147	15.8	<10	
Prednisone started (20 mg daily)						
8 weeks	Pred 20 mg	1110	136	5.3	<10	
10 weeks	Pred 20 mg	784	117	2.1	212,000	
5 months	Pred 10 mg	165	66	0.6		
9 months	Pred 5 mg	134	85	0.6	1,350,000	
Prednisone stopped						
18 months	None	216	98	0.4	3,645,000	
25 months	None	348	121	0.8	2,656,800	
Prednisone (20 mg daily) restarted with azathioprine						
29 months	Pred 20 & Az	54	100	0.8	7,452,000	
40 months	Pred 5 & Az	30	62	0.4		
Prednisone stopped and azathioprine continued (100 mg daily)						
4 years	Az 100	26	86	0.8	11,529,000	
5 years	Az 100	35	118	0.5	20,682,000	
Normal Values		**<42**	**<115**	**<1.2**		

Abbreviations: Peg, peginterferon; Rbv, ribavirin; Pred, prednisone; Az, azathioprine.

Comment

A patient with chronic hepatitis C and hyperglobulinemia developed worsening of serum aminotransferase levels and jaundice after 4 to 5 weeks of peginterferon therapy. Because of the autoimmune features and the lack of immediate improvement on stopping peginterferon, prednisone was started. Prednisone was gradually reduced in dose and discontinued 9 months later, but serum aminotransferase levels rose and hyperglobulinemia reappeared. Ultimately, the combination of prednisone and azathioprine led to control of the disease and normal serum aminotransferase levels. After a year of tapering doses of prednisone, it was stopped and she was maintained on azathioprine alone with normal serum aminotransferase levels despite high levels of HCV RNA. One interpretation of the events is that she had autoimmune hepatitis even before interferon therapy, and the HCV infection was benign and not the cause of the serum aminotransferase elevations. Peginterferon is known

to be immunomodulatory and capable of causing an exacerbation or flare of autoimmune conditions. The presence of a serious autoimmune disease is a relative contraindication to use of interferon.

Case 5. Autoimmune hepatitis arising during etanercept therapy.

[Modified from: Fathalla BM, Goldsmith DP, Pascasio JM, Baldridge A. Development of autoimmune hepatitis in a child with systemic-onset juvenile idiopathic arthritis during therapy with etanercept. J Clin Rheumatol 2008; 14: 297-8. PubMed Citation]

A 9 year old girl with juvenile idiopathic (rheumatoid) arthritis was treated with etanercept and hydroxychloroquine after she had failed to respond to a regimen of methotrexate, low dose prednisone and nonsteroidal antiinflammatory agents. Her dose of etanercept was increased to 50 mg weekly, which was followed by clinical improvement and allowed for lowering of the prednisone dose. Ten months after starting etanercept, she developed fatigue, abdominal discomfort and jaundice. Examination showed jaundice without fever, rash or signs of chronic liver disease. Laboratory results showed elevations in serum bilirubin (12 mg/dL) and aminotransferase levels (ALT 354 U/L, AST 486 U/L) with normal alkaline phosphatase. Tests for hepatitis A, B and C and Epstein-Barr virus were negative. Serum ANA was positive at 1:640 and SMA at 1:80, while antibodies to dsDNA and liver-kidney microsomal antigen were negative. Serum IgG levels were markedly increased (3637 mg/dL: normal <1600 mg/dL). Abdominal ultrasound was normal except for mild splenomegaly. A liver biopsy was consistent with autoimmune hepatitis with interface hepatitis and lobular necrosis with inflammation. Etanercept and hydroxychloroquine were discontinued and the dose of prednisone was increased to 2 mg/kg/day with the addition of azathioprine. Her jaundice resolved and serum aminotransferase levels fell into the normal range and autoantibodies became negative within 8 months of stopping etanercept.

Key Points

Medication:	Etanercept (50 mg once weekly)
Pattern:	Hepatocellular
Severity:	3+ (jaundice, hospitalization)
Latency:	10 months
Recovery:	Within 8 months (on prednisone)
Other medications:	Hydroxychloroquine, prednisone (5 mg daily), naproxen

Comment

A child with juvenile idiopathic arthritis (formerly known as juvenile rheumatoid arthritis) developed clinically apparent autoimmune hepatitis after 10 months of etanercept therapy. While it seems clear that the clinical syndrome was due to autoimmune hepatitis, it is not certain whether the hepatitis was caused by etanercept directly or was a preexisting diathesis that was triggered or merely worsened by the immunomodulatory therapy. The child improved upon stopping etanercept, but the improvement may have been due to the concurrent increase in prednisone dose and addition of azathioprine. Information on long term follow up and whether azathioprine or prednisone could be discontinued (or lowered to previous low levels) might help to resolve these issues. However, the majority of cases of autoimmune hepatitis associated with anti-TNF therapies (and other biologic agents such as the interferons) have appeared to be a triggering of autoimmune hepatitis in a susceptible patient, rather than the de novo induction of an autoimmune hepatitis-like liver injury that then resolves entirely with stopping therapy (as is typical of nitrofurantoin, minocycline or methyldopa). These different interpretations have important implications for the long term management of such patients; i.e., whether long term immune suppression will be required.

Case 6. Autoimmune hepatitis requiring long term immunosuppression arising during atorvastatin therapy.

[Modified from: Pelli N, Setti M, Ceppa P, Toncini C, Indiveri F. Autoimmune hepatitis revealed by atorvastatin. Eur J Gastroenterol Hepatol 2003; 15: 921-4. PubMed Citation]

A 65 year old woman developed fatigue and jaundice 3 months after starting atorvastatin (20 mg daily) for long standing hypercholesterolemia. She had a history of hypertension treated with doxazosin and hypercholesterolemia treated with pravastatin for 6 months, followed by fluvastatin for 3 years before being switched to atorvastatin. She had no history of liver disease or exposures to viral hepatitis and did not drink alcohol. On examination, she was jaundiced and had hepatomegaly but no fever, rash or signs of chronic liver disease. Laboratory tests showed a hepatocellular pattern of serum enzyme elevations and mild hyperbilirubinemia (Table). Tests for viral hepatitis were negative, but she had hyperglobulinemia with IgG 6.6 g/dL (normal <1.7) and high titers of both ANA and SMA (>1:1280). A liver biopsy showed chronic hepatitis and lobular collapse and mild fibrosis. She was started on prednisone with improvement in blood tests, but three months later she still had ALT elevations and autoantibody titers had not declined. A repeat liver biopsy showed early cirrhosis.

Key Points

Medication:	Atorvastatin (20 mg daily)
Pattern:	Hepatocellular (R=7.5)
Severity:	3+ (jaundice, hospitalization)
Latency:	3 months
Recovery:	Incomplete
Other medications:	Doxazosin

Laboratory Values

Time After Starting	Time After Stopping	ALT* (U/L)	Alk P (U/L)	Bilirubin* (mg/dL)	Other
12 weeks	0	510	481	3.0	Prothrombin index 17%
13 weeks	1 week	430		2.5	ANA >1:1280
14 weeks	2 weeks	280		4.4	First liver biopsy
15 weeks	3 weeks	220		5.6	
16 weeks	4 weeks	305		4.3	Prednisone started
18 weeks	6 weeks	210		2.6	
19 weeks	7 weeks	105		2.4	
5 months	3 months	80		1.5	ANA >1:1280
6 months	4 months	66	66	1.1	Second liver biopsy
Normal Values		**<40**	**<279**	**<1.2**	

* Values estimated from Figure 3. Bilirubin converted from µmol to mg/dL.

Comment

Jaundice and features of autoimmune hepatitis arose after 3 months of atorvastatin therapy in a patient who had been treated with other statins for more than 3 years. Liver tests improved minimally with stopping atorvastatin

and one month later prednisone was started, whereupon serum enzymes decreased from ~8 fold to ~twice normal. However, serum autoantibodies remained present in unchanging titers, and a repeat liver biopsy showed progression of fibrosis with nodularity and incomplete cirrhosis. In this case, atorvastatin appeared to trigger a self sustained autoimmune hepatitis. An alternative explanation is that atorvastatin was an innocent bystander and the development of autoimmune hepatitis was co-incidental and unrelated to the chronic statin therapy.

Selected References

Goldstein GB, Lam KC, Mistilis SP. Drug-induced active chronic hepatitis. Am J Dig Dis. 1973;18:177–84. PubMed PMID: 4688569.

(Among 21 cases of "active chronic hepatitis" presenting over a 1 year period, 9 were due to oxyphenisatin, 5 to methyldopa and 9 were idiopathic; methyldopa cases were all jaundiced and AST 200-600 U/L, latency averaged 15 months, all responded to corticosteroids; no mention of ANA).

Toghill PJ, Smith PG, Benton P, Brown RC, Matthews HL. Methyldopa liver damage. Br Med J. 1974;3:545–8. PubMed PMID: 4414663.

(Characterization of 20 cases of methyldopa induced liver injury: latency 2-32 weeks, most <6 weeks, all jaundiced, mostly hepatocellular or mixed, but two cholestatic, resolved with stopping; 2 chronic active hepatitis, 2 acute liver failure, 2 cirrhosis, severe recurrence with reexposure).

Neuberger J, Kenna JG, Nouri Aria K, Williams R. Antibody mediated hepatocyte injury in methyl dopa induced hepatotoxicity. Gut. 1985;26:1233–9. PubMed PMID: 3905530.

(9 cases of methyldopa hepatotoxicity: 5 with acute liver failure, 3 acute self limited hepatitis, 1 chronic active hepatitis; injury arose 7 weeks to 3 years after starting methyldopa).

Stricker BH, Blok AP, Claas FH, Van Parys GE. Desmet VJl. Hepatic injury associated with the use of nitrofurans: a clinicopathological study of 52 reported cases. Hepatology. 1988;8:599–606. PubMed PMID: 3371877.

(Analysis of 52 cases reported to a Central Registry in the Netherlands, 27 of which were considered at least "probable"; onset varied from less than a week to several years after starting nitrofurantoin; overall, 59% were jaundiced, 11% had rash and 20% eosinophilia, 2 were fatal, estimated to occur in 1:3000-1:5000 users; separated cases into "acute" vs "chronic" injury, chronic cases more likely to have ANA positivity and hepatocellular pattern of injury).

Adams LE, Hess EV. Drug-related lupus. Incidence, mechanisms and clinical implications. Drug Saf. 1991;6:431–49. PubMed PMID: 1793523.

(Review of drug related lupus-like syndrome, linked to more than 60 agents including isoniazid, hydralazine, chlorpromazine, methyldopa and procainamide; usually presents with arthralgias and fever and ANA positivity, usually occurring with long term use of the medication).

Papo T, Marcellin P, Bernuau J, Durand F, Poynard T, Benhamou JP. Autoimmune chronic hepatitis exacerbated by alpha-interferon. Ann Intern Med. 1992;116:51–3. PubMed PMID: 1727095.

(3 patients, one man and two women, 20, 40 and 42 years old, with autoimmune hepatitis [misdiagnosed initially as hepatitis C] had flares of hepatitis on interferon with onset of symptoms after 8, 4 and 4 weeks of treatment [bilirubin 15.5 mg/dL in one, but evidently normal in the others with peak ALT 1728, 378 and 456 U/L, autoantibodies present], improving with stopping interferon and adding prednisone; all 3 were anti-HCV negative by sensitive and specific assays).

Ganne-Carrié N, de Leusse A, Guettier C, Castera L, Levecq H, Bertrand HJ, Plumet Y, et al. Gastroenterol Clin Biol. 1998;22:525–9. [Autoimmune hepatitis induced by fibrates]. PubMed PMID: 9762291.

(Retrospective analysis of 5 patients [4 men, 1 woman] with chronic hepatitis due to fibrates identified between 1989-1996; ages 56-73 years, on fenofibrate [n=3] or ciprofibrate [n=2] for 5-36 months; 2 asymptomatic; none with immunoallergic features or eosinophilia, with bilirubin 0.6-36 mg/dL, ALT 4-26 times ULN; all had ANA 1:200-1:2560; liver biopsy showed active cirrhosis in 3 and chronic hepatitis with fibrosis in 2; hepatitis resolved spontaneously in 2 and 3 required corticosteroid therapy, in 2 of whom they could be stopped without relapse).

Elkayam O, Yaron M, Caspi D. Minocycline-induced autoimmune syndromes: an overview. Semin Arthritis Rheum. 1999;28:392–7. PubMed PMID: 10406406.

(Systematic review of literature on autoimmune syndromes from minocycline, 4 patterns: serum sickness, lupus-like syndrome, autoimmune hepatitis and vasculitis; usually presenting after 1-20 years, ANA common but so is pANCA, features may overlap, hepatitis most common: 66 cases reported).

Goldstein NS, Bayati N, Silverman AL, Gordon SC. Minocycline as a cause of drug-induced autoimmune hepatitis. Report of four cases and comparison with autoimmune hepatitis. Am J Clin Pathol. 2000;114:591–8. PubMed PMID: 11026106.

(Four cases of minocycline hepatitis and comparison to 10 spontaneous autoimmune hepatitis cases showed no distinguishing features except resolution with stopping drug; 16-52 year old women developed liver injury 4 months to 12 years after starting minocycline [bilirubin 0.4, 1.2, 6.5 and 7.3 mg/dL, ALT 137, 343, 700, and 1288 U/L, Alk P 49, 83, 138 and 253 U/L, all ANA positive], histology showed fibrosis in 2, all responded to prednisone with resolution persisting after stopping corticosteroids).

Alla V, Abraham J, Siddiqui J, Raina D, Wu GY, Chalasani NP, Bonkovsky HL. Autoimmune hepatitis triggered by statins. J Clin Gastroenterol. 2006;40:757–61. PubMed PMID: 16940892.

(Three cases of autoimmune hepatitis arising after simvastatin or atorvastatin therapy 6, 20 and 20 weeks after starting [bilirubin 11.3, 3.4 and 5.5 mg/dL, ALT 1749, 1170 and 155 U/L, Alk P of 228, 160, and 203 U/L, all being ANA or SMA positive in titers of 1:40 to 1:160], all responding to prednisone/azathioprine but remaining on long term therapy with azathioprine or mycophenylate alone).

Behrbolm J, Neid M, Stolzel U, Wittekind C, Hauss JP, Tillmann HL. Improvement of multiple sclerosis on tacrolimus plus mycophenolate mofetil after liver transplantation. Transplant Int. 2007;20:1077–9. PubMed PMID: 17937765.

(51 year old woman with multiple sclerosis developed jaundice 8 weeks after starting interferon beta [36.9 mg/dL, INR 1.7, ANA 1:160], progressing to liver failure and transplantation 3 days later; explant histology suggested autoimmune hepatitis).

Fathalla BM, Goldsmith DP, Pascasio JM, Baldridge A. Development of autoimmune hepatitis in a child with systemic-onset juvenile idiopathic arthritis during therapy with etanercept. J Clin Rheumatol. 2008;14:297–8. PubMed PMID: 18824922.

(9 year old girl with juvenile idiopathic [rheumatoid] arthritis developed abdominal pain and jaundice 10 months after starting etanercept [bilirubin 12.0 mg/dL, ALT 354 U/L, GGT 388 U/L, ANA 1:640, IgG 3637 mg/dL], stopping etanercept and starting prednisone and azathioprine led to resolution, normal liver tests and negative ANA: Case 5).

Goujon C, Dahel K, Bérd F, Guillot I, Gunera-Saad N, Nicolas JF. Autoimmune hepatitis in two psoriasis patients treated with infliximab. J Am Acad Dermatol. 2010;63:e43–4. PubMed PMID: 20633783.

(Two cases of autoimmune hepatitis during infliximab therapy, 37 and 51 year old men with psoriasis developed symptoms 4-6 weeks after a third infusion [bilirubin 0.8 and 3.2 mg/dL, ALT 1126 and 768 U/L, Alk P 181 and 391 U/L, ANA 1:200 and 1:2560], one resolving upon stopping and one after treatment with ursodiol, corticosteroids and azathioprine).

Björnsson E, Talwalkar J, Treeprasertsuk S, Kamath PS, Takahashi N, Sanderson S, Neuhauser M, Lindor K. Drug-induced autoimmune hepatitis: clinical characteristics and prognosis. Hepatology. 2010;51:2040–8. PubMed PMID: 20512992.

(Among 261 cases of autoimmune hepatitis seen at the Mayo Clinic between 1997 and 2007, 24 were attributed to drugs, 11 to minocylcine, 11 to nitrofurantoin and 2 to others; all responded to corticosteroid therapy and all who were withdrawn did not relapse).

Czaja AJ. Drug-induced autoimmune-like hepatitis. Dig Dis Sci. 2011;56:958–76. PubMed PMID: 21327704.

(Review of drug induced autoimmune hepatitis-like syndromes, most commonly caused by nitrofurantoin and minocycline, but also with hydralazine, methyldopa and more rarely with statins, fibrates, NSAIDs, various herbals and tumor necrosis factor antagonists).

Hepatic Histology in Autoimmune Hepatitis

[Under Construction]