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Alpha Interferon

Updated: May 4, 2018.

OVERVIEW

Introduction

Alpha interferon is a cytokine produced by the innate immune system in response to environmental exposures including viral infections. Alpha interferon in various formulations has been developed as therapy of several forms of cancer and viral infections, but its major use has been as therapy of chronic hepatitis C. Alpha interferon therapy can be associated with transient, mild-to-moderate serum aminotransferase elevations and it has been linked to induction of autoimmune conditions, including autoimmune hepatitis in susceptible persons.

Background

Alpha interferon (in"' ter feer' on) is a naturally occurring cytokine which is produced by cells of the innate immune system in reaction to viral infection or other environmental stresses. Alpha and beta interferon are considered type I interferons which share antiviral, immunomodulatory as well as antiproliferative effects. The pathways of induction and actions of alpha interferon are quite complex and the antiviral effects are due to induction of multiple intracellular genes. Overall, type I interferons produce an antiviral state inside of cells that decreases viral replication and protects against infection. There are at least 20 copies of the alpha interferon gene in the human genome and multiple formulations of standard recombinant interferon have been produced (alfa-2a, alfa-2b and alfa-con1 or "consensus" interferon). Furthermore, the interferon molecule can be pegylated which causes a prolongation of its half-life, allowing for once weekly as opposed to daily or every other day administration. Because interferon is a protein, it must be given parenterally (usually subcutaneously). Recombinant human interferons were approved for use in cancer in the 1980s, for hepatitis B in 1991 and for hepatitis C in 1992. Peginterferon became available in 2000 and has largely replaced the standard preparations. The typical dose of peginterferon alfa-2a is 180 µg once weekly for 24 or 48 weeks, and for peginterferon alfa-2b 1.5 µg/kg once weekly for 24 to 48 weeks. In chronic hepatitis C, peginterferon is usually given with ribavirin and, more recently, as triple therapy with a protease inhibitor, such as boceprevir, telaprevir, simiprevir or sofosbuvir. Ultimately, oral antiviral regimens are likely to replace peginterferon therapy in chronic hepatitis C. Standard interferon alfa is also approved for use in hairy cell leukemia, malignant melanoma, follicular lymphoma and AIDS-related Kaposi's sarcoma. Local injections of interferon are used to treat condylomata acuminata. Interferon has many side effects which often limit the dose and duration of therapy. The most common side effects include fatigue, muscle aches, headaches, depression, anxiety, bone marrow suppression and rash.

Hepatotoxicity

Therapy with interferon or peginterferon can be associated with transient and asymptomatic mild-to-moderate serum aminotransferase elevations in up to half of patients. Because the major use of peginterferon is for hepatitis C or in patients with cancer on multiple other medications, serum ALT elevations are often difficult to attribute to the therapy as opposed to the underlying disease. Importantly, however, 1% to 2% of persons receiving alpha interferon for 24 to 48 weeks develop an autoimmune condition, which can be autoimmune hepatitis characterized by development of marked serum aminotransferase activities and jaundice. This side effect usually arises within 1 to 2 months of starting therapy, but can arise later or even after therapy is completed (Case 1). The typical pattern of serum elevations is hepatocellular, and most but not all patients develop or have preexisting autoantibodies such as antinuclear antibody (ANA) or antibody to liver kidney microsomes (anti-LKM) in serum. Instances of primary biliary cirrhosis, sarcoidosis and hepatic granulomas have also been reported after interferon therapy. Finally, interferon therapy of hepatitis B can trigger an acute exacerbation of the hepatitis that is often associated with clearance of HBV DNA and HBeAg and may actually be a favorable prognostic sign suggesting a sustained response (Case 2).

Likelihood score: A (well known cause of clinically apparent liver injury).

Mechanism of Injury

Interferon has diverse effects on multiple cell types. The autoimmune hepatitis-like syndrome that has been attributed to interferon therapy appears to occur in patients who are predisposed to autoimmune diseases, and is probably due to the immunomodulatory effects of alpha interferon in increasing cell surface display of HLA antigens and in affecting CD4 and CD8+ T cell activity. Alpha interferon therapy can cause an acute exacerbation of autoimmune disease and some instances of an acute hepatitis-like syndrome developing on interferon therapy may represent an exacerbation of autoimmune hepatitis that coexisted with or was mistaken for chronic hepatitis B or C.

Outcome and Management

The serum aminotransferase abnormalities that arise during interferon therapy are usually asymptomatic and self-limited and rarely require dose modification. In contrast, the autoimmune hepatitis-like syndrome induced by interferon calls for prompt discontinuation of therapy. In most instances, the condition improves or resolves with stopping therapy, but instances of self-perpetuating autoimmune hepatic diseases (sarcoidosis, autoimmune hepatitis, primary biliary cirrhosis) have been reported. Patients with autoimmune hepatitis due to interferon may require corticosteroid or immunosuppressive therapy, which appears to ameliorate the course of injury and may be required long term. Several cases of acute liver failure and cases of chronic autoimmune hepatitis triggered by interferon therapy have been reported, but treatment has not been associated with chronic vanishing bile duct syndrome.

Related biological agents include beta interferon, gamma interferon, interleukin 2.

Agents active against hepatitis C include alpha interferon, peginterferon, boceprevir, ribavirin, simeprevir, sofosbuvir, telaprevir.

Drug Class: Antiviral Agents, Hepatitis C Agents

CASE REPORTS

Case 1. Induction of autoimmune hepatitis by a course of peginterferon and ribavirin for chronic hepatitis C.

[NIH Patient #P40]

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 HCV 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, HBsAg, 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 initially and later 50 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, B53 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
Recovery:	Incomplete, chronic autoimmune hepatitis requiring long term therapy
Other medications:	Ribavirin

Laboratory Values

Time After Starting	Therapy	ALT (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 µg/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	

Table continued from previous page.

Time After Starting	Therapy	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	HCV RNA (IU/mL)	Other
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 mo	Pred 10 mg	165	66	0.6		
9 mo	Pred 5 mg	134	85	0.6	1,350,000	
Prednisone stopped						
18 mo	None	216	98	0.4	3,645,000	
25 mo	None	348	121	0.8	2,656,800	
Prednisone (20 mg daily) restarted with azathioprine						
29 mo	Pred 20 & Az	54	100	0.8	7,452,000	
40 mo	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	
10 years	Az 50	38	47	0.4	28,300,000	
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 4-5 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 aminotransferases 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 2. Acute flare of hepatitis B during alpha interferon therapy.

[NIH Case #T37]

A 47 year old man with chronic hepatitis B was enrolled in a clinical trial of alpha interferon therapy in early 1989. He was known to have had HBsAg and HBeAg in serum for the previous 8 years and had persistent elevations in serum aminotransferase levels. He was symptomatic with mild fatigue with occasional periods of nausea, but denied dark urine, jaundice, itching, weight loss or abdominal swelling. Physical examination was unrevealing. A liver biopsy showed chronic hepatitis with marked activity (histology activity score=11 of a possible 18) and bridging hepatic fibrosis (Ishak fibrosis score 4 of a possible 6). He was started on interferon alfa-2b in a dose of 10 million units (MU) three times weekly. When he returned after 4 weeks of therapy, he

complained of fatigue, nausea and jaundice and serum bilirubin was 10.4 mg/dL. However, HBV DNA was no longer detectable (lower limit of detection was 160,000 copies/mL). The dose of interferon was decreased to 5 MU three times weekly. His symptoms resolved rapidly and, in follow up, serum bilirubin and aminotransferase levels fell into the normal range. He became HBeAg as well as HBsAg negative, but did not develop anti-HBs. During long term follow up, he remained HBsAg negative, with normal serum aminotransferase levels and no detectable HBV DNA.

Key Points

Medication:	Interferon alpha (10 MU three times weekly)
Pattern:	Hepatocellular
Severity:	2+ (jaundice and symptoms)
Latency:	4 weeks
Recovery:	12 weeks
Other medications:	None

Laboratory Values

Time After Starting	Time After Stopping	ALT (U/L)	Alk P (U/L)	Bilirubin (mg/dL)	HBV DNA (copies/mL)	Other
Pre		197	110	0.8	234,000	HBsAg positive
0		334	105	0.9	5,254,000	HBeAg positive
Interferon alfa-2b (10 MU thrice weekly) started						
4 weeks		1037	148	5.9	<160,000	
8 weeks		151	140	2.3	<160,000	HBeAg negative
12 weeks		93	119	1.7	<160,000	HBsAg negative
16 weeks	0	44	110	0.7		
Interferon alfa-2b stopped						
20 weeks	4 weeks	36	96	0.6		
24 weeks	8 weeks	25	93	0.7		
1 year	8 months	14	66	0.3	Undetectable	
5 years	5 years	13	112	0.7	None	HBsAg negative
Normal Values		**<42**	**<115**	**<1.2**		

Comment

A patient with HBeAg positive chronic hepatitis B developed an acute flare of disease and jaundice within 4 weeks of starting interferon alfa therapy. The flare was accompanied by a dramatic decrease in HBV DNA levels, followed by clearance of both HBeAg and HBsAg and resolution of the chronic hepatitis. Thus, the liver injury reflected clearance of hepatitis B virus rather than direct hepatotoxicity of interferon. An acute flare of hepatitis is often considered a favorable prognostic sign during the therapy of chronic hepatitis B presaging loss of HBeAg and, sometimes, loss of HBsAg as well. The initial HBV DNA testing was based upon a relatively insensitive method which had a lower limit of detection of 160,000 copies/mL. In follow up, polymerase chain reaction based assays for HBV DNA were used that had a lower limit of detection of 500 copies/mL.

PRODUCT INFORMATION

REPRESENTATIVE TRADE NAMES

Alpha Interferon – Avonex®

Peginterferon – Pegintron®

DRUG CLASS

Antiviral Agents

COMPLETE LABELING

Product labeling at DailyMed, National Library of Medicine, NIH

CHEMICAL FORMULAS AND STRUCTURES

DRUG	CAS REGISTRY NUMBER	MOLECULAR FORMULA	STRUCTURE
Alpha Interferon	76543-88-9	C860-H1353-N227-O255-S9	Not available
Peginterferon	215647-85-1	Unspecified	Not available

ANNOTATED BIBLIOGRAPHY

References updated: 04 May 2018

Zimmerman HJ. Antiviral agents. In, Zimmerman HJ. Hepatotoxicity: the adverse effects of drugs and other chemicals on the liver. 2nd ed. Philadelphia: Lippincott, 1999, pp. 621-3.

(Expert review of antiviral agents and liver injury published in 1999; mentions that the interferons can cause "dose-related hepatic injury in humans").

Núñez M. Hepatotoxicity of antiviral agents. In, Kaplowitz N, DeLeve LD, eds. Drug-induced liver disease. 3rd ed. Amsterdam: Elsevier, 2013, pp. 505-18.

(Review of hepatotoxicity of antiviral agents mentions the risk of decompensation in patients with pre-existing cirrhosis treated with interferon alfa).

Acosta EP, Flexner C. Antiviral agents (nonretroviral). In, Brunton LL, Chabner KA, Knollman KC, eds. Goodman & Gilman's the pharmacological basis of therapeutics. 12th ed. New York: McGraw-Hill, 2011, pp. 1591-1622.

(Textbook of pharmacology and therapeutics).

Jones GJ, Itri LM. Safety and tolerance of recombinant interferon alfa-2a(Roferon-A) in cancer patients. Cancer 1986; 57 (8 Suppl): 1709-15. PubMed PMID: 3948143.

(Pooled analysis on 1300 patients with cancer in clinical trials using varying doses [often high >12 MU] and regimens [daily or every other day] of alpha interferon reported elevations in ALT in 77%, Alk P in 48% and bilirubin in 31%, but these "were rarely severe or dose limiting" and no reports of hepatitis).

Quesada JR, Talpaz M, Rios A, Kurzrock R, Gutterman JU. Clinical toxicity of interferons in cancer patients: a review. J Clin Oncol. 1986; 4: 234-43. PubMed PMID: 2418169.

(Review of side effects of interferon, based partially on experience in treating 800 patients with cancer; ALT elevations occurred in 25-30% on standard and up to 80% with higher doses, peak AST values ranged from 50 to 300 U/L).

Vento S, Di Perri G, Garofano T, Cosco L, Concia E, Ferraro T, Bassetti D. Hazards of interferon therapy for HBV-seronegative chronic hepatitis. Lancet 1989; 2: 926. PubMed Citation

(Two patients, a 49 year old woman and a 17 year old man with chronic hepatitis C had an acute exacerbation of hepatitis during interferon alfa 2b therapy, with symptoms and jaundice arising at 4 and 6 weeks [bilirubin 7.4 and 13.7 mg/dL, ALT 1800 and 2125 U/L, ANA 1:160 and 1:80], both requiring prolonged prednisone therapy).

Mayet WJ, Hess G, Gerken G, Rossol S, Voth R, Manns M, Meyer zum Buschenfelde KH. Treatment of chronic type B hepatitis with recombinant alpha interferon induces autoantibodies nonspecific for autoimmune chronic hepatitis. Hepatology 1989; 10: 24-8. PubMed PMID: 2737600.

(Among 31 patients treated with interferon alfa for chronic hepatitis B, 27 [87%] developed at least one autoantibody, usually thyroid antibodies, ANA or SMA; none developed clinically apparent autoimmune disease).

Silva MO, Reddy KR, Jeffers LJ, Hill M, Schiff ER. Interferon-induced chronic active hepatitis? Gastroenterology 1991; 101: 840-2. PubMed PMID: 1860646.

(54 year old man with chronic hepatitis B and cirrhosis treated with interferon for 4 months became HBV DNA, HBeAg and HBsAg negative, but had persistence of ALT elevations, jaundice and ascites, improving somewhat with prednisone therapy).

Ruiz-Moreno M, Rua MJ, Carreno V, Quiroga JA, Manns M, Meyer zum Buschenfelde KH. Autoimmune chronic hepatitis type 2 manifested during interferon therapy. J Hepatol 1991; 12: 265-6. PubMed PMID: 1904895.

(16 year old girl with chronic hepatitis B developed rise in ALT levels after 2 months of interferon therapy, resolving with stopping but recurring with restarting, with rises in anti-LKM and need for prolonged prednisone therapy to control enzyme elevations).

Marcellin P, Colin F-F, Boyer N, Bernuau J, Degott C, Hirschauer C, Benhamou J-P. Fatal exacerbation of chronic hepatitis B induced by recombinant alpha-interferon. Lancet 1991; 338: 828. PubMed PMID: 1681203.

(62 year old man with hepatitis B and cirrhosis developed jaundice and ascites during clearance of HBV DNA, 9 weeks after starting interferon [bilirubin 20.5 mg/dL, ALT 2600 U/L], with progressive liver failure and death).

Durand JM, Kaplanski G, Portal I, Scheiner C, Berland Y, Soubeyrand J. Liver failure due to recombinant alpha interferon. Lancet 1991; 338: 1268-9. PubMed PMID: 1682660.

(60 year old man developed jaundice 9 months after starting interferon for leukemia [bilirubin 25.3 mg/dL, ALT 1268 U/L, Alk P 230 U/L, no autoantibodies], developing progressive hepatic failure and death).

Wandl UB, Kloke O, Niederle N. Liver failure due to recombinant alpha interferon for chronic myelogenous leukaemia. Lancet 1992; 339: 123-4. PubMed PMID: 1345846.

(43 year old woman developed jaundice 6 months after starting interferon for leukemia [bilirubin 14.8 mg/dL, ALT 705 U/L, Alk P 355 U/L, autoantibodies negative]; patient died of hepatic failure 6 weeks later, cirrhosis on autopsy).

Shindo M, Di Bisceglie AM, Hoofnagle JH. Acute exacerbation of liver disease during interferon alfa therapy for chronic hepatitis C. Gastroenterology 1992; 102 (4 Pt 1): 1406-8. PubMed PMID: 1551549.

(68 year man with chronic hepatitis C and cirrhosis and positive ANA [1:640] developed abdominal pain and jaundice during 2nd week of interferon therapy, improving with stopping and recurring with retreatment [bilirubin rising from 1.8 to 11.0 mg/dL, ALT 55 to 260 U/L, HCV RNA and ANA levels not changing], improving with prednisone therapy).

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, 40, 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).

Janssen HL, Brouwer JT, Nevens F, Sanchez-Tapias JM, Craxi A, Hadziyannis S. Fatal hepatic decompensation associated with interferon alfa. European concerted action on viral hepatitis (Eurohep). BMJ 1993; 306: 107-8. PubMed PMID: 8435602.

(Survey of European centers identified 9 of 2490 interferon treated patients who developed a severe and fatal worsening of hepatitis with therapy; all had cirrhosis; 7 had HBV, 1 HCV, 1 both; arising at 3-24 weeks on, or 3 and 16 weeks after therapy; with peak AST 9-500 U/L, bilirubin 3.1-40 mg/dL).

Lindahl K, Weiland O, Schvarcz R. [Report of a case: hepatic failure after treatment with interferon]. Lakartidningen. 1993; 90: 3075-6. Swedish. PubMed PMID: 8264269.

(22 year old man with diabetes and chronic hepatitis C with cirrhosis developed fatigue and jaundice 6 weeks after starting interferon [bilirubin rising from 0.6 to 26.8 mg/dL, ALT 120 to 1340 U/L and hyperglobulinemia without autoantibodies], progressing to multiorgan failure and death 8 weeks later).

van der Watt M, Lemmer E, Robson SC. Exacerbation of liver disease during interferon-alpha therapy for chronic hepatitis C. S Afr Med J 1994; 84 (8 Pt 1): 509. PubMed PMID: 7825090.

(3 cases, 37 year old woman, 12 year old boy and 50 year old man with chronic hepatitis C, 2 with ANA and/or SMA, who worsened on interferon therapy, patients appearing to have both autoimmune hepatitis and hepatitis C).

D'Amico E, Paroli M, Fratelli V, Palazzi C, Barnaba V, Callea F, Consoli G. Primary biliary cirrhosis induced by interferon-. therapy for hepatitis C virus infection. Dig Dis Sci 1995; 40: 2113-6. PubMed PMID: 7587775.

(55 year old woman with hepatitis C treated with interferon for 6 months, had relapse thereafter with rising Alk P and ALT and de novo development of AMA, biopsy showing probable primary biliary cirrhosis).

Propst A, Propst T, Dietze O, Kathrein H, Judmeier G, Vogel W. Development of granulomatous hepatitis during treatment with interferon-alpha 2b. Dig Dis Sci 1995; 40: 2117-8. PubMed PMID: 7587776.

(Two men, ages 31 and 23, had a rise in ALT after 3-4 months of interferon therapy of hepatitis found to have small, discrete granulomas with giant cells on liver biopsy, not seen before, ALT levels fell after stopping).

Todros L, Saracco G, Durazzo M, Abate ML, Touscoz G, Scaglione L, Verme G, et al. Efficacy and safety of interferon alfa therapy in chronic hepatitis C with autoantibodies to liver-kidney microsomes. Hepatology 1995; 22: 1374-8. PubMed PMID: 7590650.

(Among 12 patients with chronic hepatitis C and anti-LKM, the sustained response rate to interferon therapy was 25%, similar to the antibody negative group [19%]; one had flare at 3 months [ALT 426 U/L] without change in anti-LKM titers and resolving upon stopping).

Styrt B, Freiman JP. Hepatotoxicity of antiviral agents. Gastroenterol Clin North Am 1995; 24: 839-52. PubMed PMID: 8749901.

(Review of liver toxicity of antiviral agents; interferons can cause minor aminotransferase elevations in patients without hepatitis and can lead to flare of hepatitis B early in the course that can be life threatening in patients with advanced cirrhosis).

Garcia-Buey L, Garcia-Monzon C, Rodriguez S, Borque MJ, Garcia-Sanchez A, Iglesias R, De Castro M, et al. Latent autoimmune hepatitis triggered during interferon therapy in patients with chronic hepatitis C. Gastroenterology 1995; 108: 1770-7. PubMed PMID: 7768382.

(Among 144 patients with chronic hepatitis C treated with interferon, 7 women had a flare of liver enzymes on treatment [432-1500 U/L], mild bilirubin elevations [peak 2.4 mg/dL] and autoantibodies [anti-LKM in 3, ANA in 5], 5 responded to immunosuppressive therapy; frequently had autoimmune associated HLA types DR3 and DR4).

Fattovich G, Giustina G, Favarato S, Ruol A. A survey of adverse events in 11,241 patients with chronic viral hepatitis treated with alfa interferon. J Hepatol. 1996; 24: 38-47. PubMed PMID: 8834023.

(Retrospective survey of adverse effects among 11,241 patients with chronic viral hepatitis treated with interferon; 4 died of liver failure, 3 with preexisting cirrhosis, decompensation developing after 8-33 weeks; no mention of autoantibodies).

Maeda T, Onishi S, Muira T, Iwamura S, Tomita A, Saibara T, Yamamoto Y. Exacerbation of primary biliary cirrhosis during interferon-alfa2b therapy for chronic active hepatitis C. Dig Dis Sci 1996; 40: 1226-30. PubMed PMID: 7781437.

(60 year old woman with chronic hepatitis C [and AMA positivity when tested in retrospect] had improvements in ALT levels during interferon therapy, but rise in Alk P [120 to 210 U/L] and GGT [25 to 150 U/L] after 8 weeks, improving with stopping interferon and adding ursodiol; asymptomatic).

Hirashima N, Mizokami M, Orito E, Koide T, Itazu I, Kumada K, Sakakibara K, et al. Case report: development of hepatocellular carcinoma in a patient with chronic hepatitis C infection after a complete and sustained response to interferon-alpha. J Gastroenterol Hepatol 1996; 11: 955-8. PubMed PMID: 8912134.

(Patient with cirrhosis due to HCV infection had a sustained virological response to interferon therapy, but was found to have a 2.5 cm hepatocellular carcinoma one year later).

Cervoni JP, Degos F, Marcellin P, Erlinger S. Acute hepatitis induced by alpha-interferon, associated with viral clearance, in chronic hepatitis C. J Hepatol 1997; 27: 1113-6. PubMed PMID: 9453439.

(Among ~900 patients treated with interferon for chronic hepatitis C, one 38 year old man and one 54 year old woman developed symptoms with rise in ALT [652 and 1163 U/L] and bilirubin [19.3 and 2.1 mg/dL] 3 and 5 months after starting interferon alfa and resolving within 2 months of stopping, both patients had sustained loss of HCV RNA and no autoantibodies).

Veerabagu MP, Finkelstein SD, Rabinovitz M. Granulomatous hepatitis in a patient with chronic hepatitis C treated with interferon-alpha. Dig Dis Sci 1997; 42: 1445-8. PubMed PMID: 9246044.

(48 year old woman with chronic hepatitis C was found to have prominent granulomas on liver biopsy after 6 months of interferon therapy; granulomas were no longer present on repeat liver biopsy 6 months after stopping interferon).

Ryan BM, McDonald GS, Pilkington R, Kelleher D. The development of hepatic granulomas following interferon-alpha2b therapy for chronic hepatitis C infection. Eur J Gastroenterol Hepatol 1998; 10: 349-51. PubMed PMID: 9855053.

(Three patients, 2 women and one man, ages 41, 52 and 23 years, were found to have hepatic granulomas during or shortly after interferon therapy of hepatitis C; granulomas were not present before therapy and were absent in one patient on repeat biopsy 17 months later).

Crosignani A, Invernizzi P, Ferrari R, Manzin A, Bruno S, Zuin M, Bianchi FB, et al. Exacerbation of chronic hepatitis D during interferon alpha administration. Ital J Gastroenterol Hepatol 1999; 31: 66-9. PubMed PMID: 10091106.

(Among 7 patients with chronic hepatitis D treated with interferon, 2 developed sudden worsening of disease on therapy [bilirubin 20.4 mg/dL and 16.7 mg/dL, ALT >1000 U/L], and ascites, resolving 2 months after with stopping, both had antibody to basal cell layer [BCLA], which is common with HDV infection).

Lock G, Reng CM, Graeb C, Anthuber M, Wiedmann KH. Interferon-induced hepatic failure in a patient with hepatitis C. Am J Gastroenterol 1999; 94: 2570-1. PubMed PMID: 10484034.

(43 year old man with chronic hepatitis C developed rise in ALT [260 U/L] 4 weeks after starting interferon which resolved on stopping, but recurred with restarting with jaundice [bilirubin 10-27 mg/dL] and ALT elevation [1038 U/L] and progressing to acute liver failure and liver transplantation).

Kraus I, Vitezic D. Acute hepatitis induced by alpha-interferon in a patient with chronic hepatitis C. Can J Gastroenterol 2001; 15: 333-5. PubMed PMID: 11381301.

(33 year old man with chronic hepatitis C had virologic and biochemical response to interferon, but developed malaise and jaundice after 3 months [bilirubin 16.2 mg/dL, ALT 1075 U/L, Alk P 111 U/L], without autoantibodies, resolving with stopping therapy and had sustained loss of HCV RNA).

Fried M. Side effects of therapy of hepatitis C and their management. Hepatology 2002; 36 Suppl 1: S237-S244. PubMed PMID: 12407599.

(Review of side effects of interferon, peginterferon and ribavirin therapy; exacerbation of hepatitis is listed as an uncommon serious adverse event).

Leclerc S, Myers RP, Moussalli J, Herson S, Poynard T, Benveniste O. Sroidosis and interferon therapy: report of five cases and review of the literature. Eur J Intern Med 2003; 14: 237-43. PubMed PMID: 12919839.

(Analysis of 5 patients and 23 in literature who developed sarcoidosis [usually pulmonary and skin] on interferon therapy, onset after 1-16 [mean=4] months, all resolved but 5 required prednisone therapy, recurrence with restarting interferon in 5 patients).

Cholongitas E, Samonakis D, Patch D, Senzolo M, Burroughs AK, Quaglia A, Dhillon A. Induction of autoimmune hepatitis by pegylated interferon in a liver transplant patient with recurrent hepatitis C virus. Transplantation 2006; 81: 488-90. PubMed PMID: 16477242.

(52 year old man with liver transplant for hepatitis C had flare in disease 5 months after stopping peginterferon [ALT rising to 404 U/L and SMA titers increasing], biopsy showed changes suggestive of autoimmune hepatitis and prednisone therapy led to remission).

Kontorinis N, Agarwal K, Elhajj N, Fiel MI, Schiano TD. Pegylated interferon-induced immune-mediated hepatitis post-liver transplantation. Liver Transpl. 2006; 12: 827-30. PubMed PMID: 16628699.

(55 year old man with liver transplant for hepatitis C developed rising ALT levels, SMA positivity and biopsy appearance of autoimmune hepatitis on peginterferon therapy despite HCV RNA becoming negative; patient subsequently improved on azathioprine therapy).

Akay BN, Ekmekci P, Sanli H, Celik G, Bozdayi M. Cutaneous, pulmonary and hepatic sarcoidosis associated with autoimmune complications during interferon-alpha treatment for hepatitis C virus infection. J Eur Acad Dermatol Venereol 2006; 20: 442-5. PubMed PMID: 16643145.

(50 year old woman developed skin nodules after 8 months and hypothyroidism after 12 months of interferon therapy, with subsequent finding of cutaneous and pulmonary sarcoidosis and hepatic granulomas; skin lesions and chest x-ray abnormalities resolved spontaneously 12-18 months after stopping interferon).

Berardi S, Lodato F, Gramenzi A, D'Errico A, Lenzi M, Bontadini A, Morelli MC, et al. High incidence of allograft dysfunction in liver transplanted patients treated with pegylated-interferon alpha-2b and ribavirin for hepatitis C recurrence: possible de novo autoimmune hepatitis? Gut 2007; 56: 237-42. PubMed PMID: 16798778.

(Among 44 patients with liver transplant for hepatitis C treated with peginterferon for more than 6 months, 9 had abnormal liver tests despite virological response, some of whom appeared to have autoimmune hepatitis, ANA positive in 5, SMA in 2, AMA in 1; 5 subsequently appeared to improve with prednisone therapy).

Kogure T, Ueno Y, Fukushima K, Nagasaki F, Inoue J, Kakazu E, Matsuda Y, et al. Fulminant hepatic failure in a case of autoimmune hepatitis in hepatitis C during peg-interferon-alpha 2b plus ribavirin treatment. World J Gastroenterol 2007; 13: 4394-7. PubMed PMID: 17708618.

(27 year old woman with chronic hepatitis C developed rising ALT levels months after starting interferon [bilirubin rising from 0.6 to 5.5 mg/dL, ALT 47 to 280 U/L, Alk P 278 to 571 U/L, presence of ANA [1:160] and anti-LKM and raised IgG], subsequently developed signs of hepatic failure, but improved after stopping interferon and starting prednisone).

Soriano V, Miralles C, Berdú, Berdun MA, Losada E, Aguirrebenjoa K, Ocampo A, et al.; PRESCO Study Group. Premature treatment discontinuation in HIV/HCV-coinfected patients receiving pegylated interferon plus weight-based ribavirin. Antivir Ther 2007; 12: 469-76. PubMed PMID: 17668555.

(Among 389 patients with HIV-HCV coinfection treated with peginterferon and ribavirin in Spain, 45% stopped therapy early, 2 developed mitochondrial injury with pancreatitis and lactic acidosis [despite not using didanosine], resolving with stopping therapy).

Drugs for non-HIV viral infections. Treat Guidel Med Lett 2007; 5: 59-70. PubMed PMID: 17565338.

(Review of status of non-antiretroviral antiviral agents for prevention and treatment of herpes, varicella-zoster, cytomegalovirus, influenza A and B, and hepatitis B and C; no mention of liver related side effects for interferon or peginterferon).

Coriat R, Podevin P. Fulminant autoimmune hepatitis after successful interferon treatment in an HIV-HCV co-infected patient. Int J STD AIDS 2008; 19: 208-10. PubMed PMID: 18397566.

(48 year old woman with HIV-HCV coinfection developed ALT elevations [~300 U/L] 3 months after starting interferon despite sustained loss of HCV RNA; 4 months later, she developed jaundice and rising ALT with ANA and anti-LKM positivity and rapid progression to acute liver failure and death).

Fiel MI, Shukla D, Saraf N, Xu R, Schiano TD. Development of hepatic granulomas in patients receiving pegylated interferon therapy for recurrent hepatitis C virus post liver transplantation. Transpl Infect Dis 2008; 10: 184-9. PubMed PMID: 17916116.

(Analysis of liver biopsies done on 820 patients with chronic hepatitis C after liver transplantation; 14 [1.7%] had granulomas [usually small, only one found and lobular in location] in posttransplant, but not pretransplant liver, 9 had received peginterferon including 4 with a sustained response).

Loquai C, Nashan D, Hensen P, Luger TA, Grabbe S, Sunderkotter C, Schiller M. Safety of pegylated interferon-alpha-2a in adjuvant therapy of intermediate and high-risk melanomas. Eur J Dermatol 2008; 18: 29-35. PubMed PMID: 18086586.

(18 patients with metastatic melanoma received peginterferon adjuvant therapy for an average of 8 months; ALT elevations occurred in 72%, which were >5 times ULN in 11%, 1 requiring drug discontinuation).

Di Bisceglie AM, Shiffman ML, Everson GT, Lindsay KL, Everhart JE, Wright EC, Lee WM, et al.; HALT-C Trial Investigators. Prolonged therapy of advanced chronic hepatitis C with low-dose peginterferon. N Engl J Med 2008; 359: 2429-41. PubMed PMID: 19052125.

(Among 1050 adults with chronic hepatitis C who were nonresponders to a course of peginterferon and ribavirin and were then followed on no treatment or on low dose peginterferon alone for 3.5 years, there were no differences in rates of clinical outcomes between the two groups, but serum ALT levels were lower with peginterferon treatment and there was no evidence of hepatotoxicity).

Di Bisceglie AM, Stoddard AM, Dienstag JL, Shiffman ML, Seeff LB, Bonkovsky HL, Morishima C, et al.; HALT-C Trial Group. Excess mortality in patients with advanced chronic hepatitis C treated with long-term peginterferon. Hepatology 2011; 53: 1100-8. PubMed PMID: 21480316.

(Among 1050 adult nonresponders with chronic hepatitis C [Di Bisceglie 2008] who were followed on no treatment or treated for 3.5 years with low dose peginterferon, further follow up showed an excess mortality in peginterferon treated subjects [20% vs 15% at 7 years], but the difference was attributable to non-liver related causes).

Bruix J, Poynard T, Colombo M, Schiff E, Burak K, Heathcote EJ, Berg T, et al; EPIC3 Study Group. Maintenance therapy with peginterferon alfa-2b does not prevent hepatocellular carcinoma in cirrhotic patients with chronic hepatitis C. Gastroenterology 2011; 140: 1990-9. PubMed PMID: 21419770.

(Among 626 patients with chronic hepatitis C treated with low dose maintenance peginterferon or followed on no treatment for up to 5 years, there were no differences in time to first liver related complication, hepatocellular carcinoma or death while ALT elevations above 5 times baseline arose in 4 peginterferon treated vs 5 controls [1.3% vs 1.6%]).

Kowdley KV, Lawitz E, Crespo I, Hassanein T, Davis MN, DeMicco M, Bernstein DE, et al. Sofosbuvir with pegylated interferon alfa-2a and ribavirin for treatment-naïve patients with hepatitis C genotype-1 infection (ATOMIC): an open-label, randomised, multicentre phase 2 trial. Lancet 2013; 381 (9883): 2100-7. PubMed PMID: 23499440.

(Among 316 previously treated patients with chronic hepatitis C, genotypes 1, 4, 5 or 6, treated with 12 or 24 weeks with sofosbuvir, peginterferon and ribavirin, SVR rates were 87-89%, ALT elevations above 5 times ULN occurred in 4 patients [1%], and 1 patient developed an autoimmune hepatitis, but these abnormalities were attributed to peginterferon).

Lawitz E, Lalezari JP, Hassanein T, Kowdley KV, Poordad FF, Sheikh AM, Afdhal NH, et al. Sofosbuvir in combination with peginterferon alfa-2a and ribavirin for non-cirrhotic, treatment-naive patients with genotypes 1, 2, and 3 hepatitis C infection: a randomised, double-blind, phase 2 trial. Lancet Infect Dis 2013; 13: 401-8. *(* PubMed PMID: 23499158.

Among 122 previously untreated patients with chronic hepatitis C, genotypes 1, 2 or 3, who received sofosbuvir [200 or 400 mg daily] or placebo for 12 weeks combined with peginterferon and ribavirin for 12 to 28 weeks, SVR rates were 90-92% with sofosbuvir and 58% with placebo; ALT and AST elevations occurred in 5 patients on sofosbuvir within 4 weeks of starting therapy, remaining elevated during treatment and resolving once peginterferon was stopped).

Hézode C, Fontaine H, Dorival C, Larrey D, Zoulim F, Canva V, de Ledinghen V, et al.; CUPIC Study Group. Triple therapy in treatment-experienced patients with HCV-cirrhosis in a multicentre cohort of the French Early Access Programme(ANRS CO20-CUPIC) - NCT01514890. J Hepatol 2013; 59: 434-41. PubMed PMID: 23669289.

(Among 497 patients with chronic hepatitis C, genotype 1, and cirrhosis treated in a French early access program with 48 weeks of peginterferon and ribavirin with either boceprevir or telaprevir, serious adverse events occurred in 197 patients [40%], hepatic decompensation in 12 [2.4%], severe infection in 24 [4.8%], and 6 patients died [1.5%], the serious complications typically arising in the first 12 weeks of therapy).

Antiviral drugs. Treat Guidel Med Lett 2013; 11 (127): 19-30. PubMed PMID: 23459414.

(Review of status of antiviral agents for prevention and treatment of viral infections including hepatitis B and C; discussion of interferon as therapy of hepatitis B and the combination of peginterferon with ribavirin and a protease inhibitor [telaprevir or boceprevir], including side effects of serum aminotransferase elevations, autoantibody formation and induction of autoimmune chronic hepatitis).

Everson GT, Terrault NA, Lok AS, Rodrigo del R, Brown RS Jr, Saab S, Shiffman ML, et al; Adult-to-Adult Living Donor Liver Transplantation Cohort Study. A randomized controlled trial of pretransplant antiviral therapy to prevent recurrence of hepatitis C after liver transplantation. Hepatology 2013; 57: 1752-62. PubMed PMID: 22821361.

(Among 79 patients with advanced chronic hepatitis C awaiting liver transplantation who were treated with peginterferon and ribavirin or observed without treatment, 22% of treated subjects achieved a sustained virologic response, but side effects were frequent and sometimes severe, although rates of liver related adverse events were similar with vs without peginterferon treatment).

Muir AJ, Arora S, Everson G, Flisiak R, George J, Ghalib R, Gordon SC, et al; EMERGE study group. A randomized phase 2b study of peginterferon lambda-1a for the treatment of chronic HCV infection. J Hepatol 2014; 61: 1238-46. PubMed PMID: 25064437.

(Among 525 patients with chronic hepatitis C treated with 3 different doses of interferon lambda or standard doses of peginterferon alfa and ribavirin for 24 [genotypes 2 or 3] or 48 weeks [genotypes 1 or 4], response rates were similar in the four groups while ALT elevations above 5 times ULN occurred in 12% treated with peginterferon and 2-22% treated with interferon lambda).

Chalasani N, Bonkovsky HL, Fontana R, Lee W, Stolz A, Talwalkar J, Reddy KR, et al.; United States Drug Induced Liver Injury Network. Features and outcomes of 899 patients with drug-induced liver injury: The DILIN Prospective Study. Gastroenterology 2015; 148: 1340-52. PubMed PMID: 25754159.

(Among 899 cases of drug induced liver injury enrolled in a US prospective study between 2004 and 2013, 12 were attributed to antiviral agents, but all were antiretroviral agents and no case was attributed to interferon not to the oral direct acting agents used to treat hepatitis B and C).

Okajima A, Yamaguchi K, Taketani H, Hara T, Ishiba H, Seko Y, Nishimura T, et al. Drug-induced liver injury in a chronic hepatitis C patient treated by peginterferon, ribavirin and simeprevir. Hepatol Res 2015; 45: E156-60. PubMed PMID: 25581068.

(56 year old man with chronic hepatitis C and multiple nonresponses to therapy had a rapid virologic response to the combination of simeprevir, peginterferon and ribavirin, followed by a flare of disease at week 6 [bilirubin 1.2 mg/dL, ALT 796 U/L, Alk P 233 U/L, INR 0.8], which resolved rapidly with stopping all 3 drugs, the injury attributed to simeprevir).