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# Tolerability of Treatments for Viral Hepatitis

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## Contents



## Abstract

Interferon-α is the most widely used antiviral drug in chronic hepatitis B and C. Tolerability is usually good and serious adverse effects are rare. Most of the adverse effects are mild or transient and do not necessitate drug withdrawal. More than 90% of patients who are given interferon-α achieve 6 months to 1 year of treatment without serious adverse effects. The serious adverse effects usually occur in predisposed patients with pre-existing organ dysfunction. Nevertheless, careful selection of patients for therapy and observation during therapy are recommended.

Nucleoside analogues are promising drugs in the treatment of chronic hepatitis B through inhibition of viral DNA polymerase. Lamivudine has been licensed for use in this indication. Its tolerability is excellent even when used for periods of

1 year or more. The main concern is the relatively high incidence of viral resistance resulting in breakthrough during or relapse after therapy.

In the treatment of chronic hepatitis C, ribavirin, in combination with interferon-α is currently the reference therapy. The main adverse effect is haemolytic anaemia, which necessitates careful monitoring and adjustment of dosage in many cases. Recently, large trials showed the better efficacy of pegylated interferons as compared with standard interferon. The combination of pegylated interferon with ribavirin is under evaluation.

Chronic viral hepatitis is the main cause of liver disease and cirrhosis worldwide. Several viruses responsible for chronic hepatitis have been identified in the last 30 years. Numerous antiviral drugs have been tested for their ability to inhibit viral replication and decrease the activity of the liver disease in order to prevent the development of cirrhosis or hepatocellular carcinoma. However, the adverse effect profiles of these agents limit their use. Several excellent reviews have addressed these issues.[1-3]

This review will describe the tolerability of drugs used for the treatment of viral hepatitis. In the first part the adverse effects of interferon-α, the most widely used antiviral drug, will be reviewed. In the second part, the adverse effects of other immunomodulatory drugs and of the nucleoside analogues will be addressed.

## 1. Interferon-α

Interferon-α has been used since 1976 for the treatment of chronic hepatitis B.[4] Ten years later, a pilot study showed a beneficial effect in chronic 'non-A non-B' hepatitis[5] (later described as chronic hepatitis C). Interferon-α is the only known effective agent in chronic hepatitis D.[6] It is a potent antiviral agent with complex mechanisms of action that are not fully understood. As well as inducing 2′-5′ oligoadenylate synthetase, it also has immune effects. Which of its pleiotropic effects are responsible for its antiviral activity and which ones for its adverse effects is not known.

The extensive use of this drug led to numerous accounts of its adverse events.[1-3] A recent survey of 11 241 patients treated with interferon-α reported a 1.2% increase of severe adverse effects.[7] Psychiatric and autoimmune (mainly thyroiditis) complications were the most frequent and severe adverse effects observed in the various studies. Therefore, careful selection of patients for treatment, and appropriate follow-up is recommended.

### 1.1 General Manifestations

A flu-like syndrome occurs frequently at the initiation of interferon-α treatment. Fever, myalgias, arthralgias and headache occur in the hours following its injection, but their intensity diminishes as treatment is continued. Symptoms abate with oral administration of paracetamol.

Asthenia, weakness, anorexia, nausea and bodyweight loss may be sustained under treatment, leading to interferon dose reduction in 10 to 40% of the patients, or cessation of treatment in 5 to 10% of patients who are treated at dosages of 5 to 6 million units 3 times a week.[8,9]

### 1.2 Psychiatric, Neurological and Sensorial Manifestations

Depression is a common adverse effect of interferon-α therapy and 1 of the main causes for cessation of treatment. It may be observed in 14 to 39% of patients (being more frequent as treatment duration increases).[1] Severe depression which leads to suicide, has been reported in patients on interferon-α therapy[10,11] and antidepressant therapy has been advocated.[12] Rare psychiatric adverse effects such as delirium, psychotic manifestations and paranoid ideations have been described, especially in patients with pre-existing disorders.[13] These complications may be prevented by careful psychiatric assessment of the patient before therapy. Difficulty in concentrating, lack of motivation, sleep disturbance and perturbations of cognitive

functions have been described.[14] The frequency of anxiety or irritability can be as high as 35% in some studies.[15] Epileptic seizures and electroencephalographic changes have also been associated with interferon-α therapy.[16,17]

Severe neurological manifestations such as ataxia, encephalitis, peripheral neuropathy occur rarely and have been described only in patients with cancer receiving dosages above 50 million units interferon-α per day.[18] Regressive axonal polyneuropathy occurred in a patient who was treated for chronic hepatitis C.[19] Low dose interferon-α was suspected to have triggered a trigeminal sensory neuropathy.[20]

Ophthalmological manifestations such as retinal ischaemia with haemorrhage and cotton-wool spots[21] have been observed, as have cases of optical neuropathy, following interferon-α.[22,23] Before initiating interferon therapy, retinal examination should be performed in patients with preexisting optical disorders.

Auditory adverse events were observed in up to 45% of patients who received interferon-α (tinnitus, dizziness, vertigo and loss of hearing perception).[24]

### 1.3 Autoimmune Effects

Appearance of various autoantibodies such as antinuclear, antithyroid or anti-DNA have been frequently described at low dosages of interferon-α.[25,26] Hypothyroidism (3% of the treated patients) or hyperthyroidism (3% of the treated patients) are the most common autoimmune conditions observed.[27-29] In a prospective study, in 77 patients with chronic hepatitis C receiving interferon-α, 6.5% developed thyroid dysfunction (3.9% developed hyperthyroidism and 2.6% developed hypothyroidism).[30] In the majority of case reports, thyroid function usually recovers within a few months after interferon-α withdrawal; however, some patients may need hormonal therapy or carbimazole. The detection of antithyroid antimicrosomal autoantibodies before treatment is predictive of thyroid dysfunction during treatment;[28,30,31] therefore, assessment of these autoantibodies should be part of the pretherapeutic assessment. For early detection of thyroid dysfunction during treatment, the concentration of thyroid stimulating hormone should be measured every 3 months in patients without autoantibodies or monthly in patients with autoantibodies.

Development of diabetes mellitus was described during interferon-α therapy for chronic hepatitis B[32] and C.[33] Regression after the cessation of treatment is not constant.[32]

Several case reports have suggested that interferon-α may trigger myasthenia[34] or lupus-like syndrome.[35,36] Regression of clinical symptoms was observed in only 1 case after withdrawal of therapy.[35] Autoimmune liver diseases (primary biliary cirrhosis, autoimmune hepatitis) can be worsened during interferon-α treatment[37,38]

Type 2 autoimmune hepatitis must be excluded before initiating interferon-α treatment. This disease is difficult to distinguish from chronic hepatitis C because anti-LKM1 (liver kidney microsomal type 1) autoantibodies can be found in both diseases. In true autoimmune hepatitis (i.e. presence of anti-LKM1 antibodies and absence of anti-hepatitis C virus (HCV) antibodies), interferon-α treatment leads to exacerbation of the disease.[38-40] In chronic hepatitis C (defined by the presence of anti-HCV antibodies with detectable serum HCV RNA) anti-LKM1 autoantibodies may be found. Therefore, systematic detection of anti-LKM1 autoantibodies has to be performed before initiation of interferon-α therapy.

The therapeutic approach following detection of anti-LKM1 antibodies is controversial, since little clinical data are available. In our opinion, if anti-LKM1 are present at a high titre, corticosteroid rather than interferon therapy should be the first option.

Occurrence of Raynaud syndrome[41] and cryoglobulinaemia[42] have been described during interferon-α therapy as has worsening of cryoglobulinaemia.[43,44] Sarcoidosis may be another autoimmune complication of interferon-α therapy.[45] Pathogenesis of lichen planus is unknown but could be of autoimmune origin. That might explain

why interferon-α can reveal[46] or exacerbate[47] lichen planus.

### 1.4 Haematological Effects

Ten to 50% of interferon-α patients develop leuconeutropenia or thrombocytopenia during therapy.[1,48] Anaemia may be observed; however, it is rarely severe at the dose used to treat chronic viral hepatitis.[49,50] Bone marrow depression is transient and reversible after interferon-α withdrawal.[51] In some patients, immune mechanisms may induce haemolytic anaemia and thrombocytopenic purpura.[52,53] Under interferon-α therapy appearance of antibodies (antiphospholipids, antihaemophilic factor VIII) may interfere with normal coagulation.[54,55] A careful follow-up with monthly blood cell counts is recommended.

### 1.5 Dermatological Effects

Interferon-α therapy may be responsible for psoriasis,[56] with arthritis involvement[57] even at dosages normally used in treating chronic viral hepatitis.[58] Reducing the dose[59] or stopping treatment might be required to reduce the lesions.

Foliaceus pemphigus has been described after interferon-α therapy for chronic hepatitis C.[60] Other manifestations such as alopecia, pruritus, rashes and dryness have also been described.[1] Alopecia occurs frequently but is reversible after therapy cessation. Erythematous or ulcerative lesions at the injection point may be seen.

### 1.6 Metabolic Effects

The effect of interferon-α on lipid metabolism is controversial. Some authors have found a decrease in both high density and low density lipoprotein cholesterol.[61] Others did not find such disorders but reported an increase in triglycerides[62] which may lead to pancreatitis.

### 1.7 Pulmonary Effects

Interstitial pneumonia has been described[63] and may occur at the beginning of interferon-α therapy; however, it is reversible after cessation of therapy.

**Table I.** Minor or mild adverse effects of interferon-α

| | |
|---|---|
| Flu-like syndrome | Asthenia, myalgia, headache, arthralgia, chills, anorexia, fever, weakness, nausea |
| Neuropsychiatric | Difficulty concentrating, lack of motivation, sleep disturbance, perturbations of the cognitive functions, anxiety, irritability |
| Dermatological | Alopecia, pruritus, rashes, dryness, erythema and ulceration at the injection site |
| Digestive | Nausea, diarrhoea, abdominal pain |
| Laboratory | Decrease in red and white blood cell count, platelet count, increase in serum triglyceride and transaminases, proteinuria |

### 1.8 Digestive and Hepatic Effects

At the dose of interferon-α used in chronic viral hepatitis, one-third of patients may have mild or moderate gastrointestinal manifestations such as nausea, diarrhoea or abdominal pain.[64]

Interferon-α treatment can be associated with an increase in serum ALT. In chronic hepatitis B, cytolysis can lead to fatal hepatic decompensation in patients with cirrhosis.[65] This is related to an immune-mediated hepatocyte lysis reflected by an increase in serum ALT and frequently associated with hepatitis Be antigen seroconversion. It has to be distinguished from the usually mild ALT elevation that occurs as a direct result of interferon-α. This effect whose mechanisms are unknown may also be seen in interferon-α patients who do not have hepatitis.

In patients with chronic hepatitis B, the association of elevated ALT levels with decreasing serum HBV (hepatitis B virus) DNA is a substantial argument for seroconversion hepatitis. Finally, one should not forget that if anti-LKM1 or antiactine antibodies are present, exacerbation of an autoimmune hepatitis is possible with interferon-α treatment. Thus, monitoring of ALT is part of the follow-up to interferon-α treatment .

### 1.9 Renal Effects

Proteinuria and nephrotic syndrome have been described in patients treated with high dose

interferon-α for malignant diseases.[66] If glomerulonephritis occurs, it is difficult to assess the respective contributions of interferon-α therapy and the viral disease.

### 1.10 Cardiac Effects

The rare but severe cardiac adverse effects of interferon-α, observed at the doses used for chronic viral hepatitis, are rhythm disorders (atrial fibrillation, tachycardia),[67] ischaemic heart disease and atrioventricular block.[68] These complications are usually observed in patients with pre-existing cardiopathy. In such patients, interferon-α therapy should be given cautiously and carefully monitored. Electrocardiographic assessment should be systematic before initiation of therapy. Hypotension or hypertension may occur during the flu-like syndrome at the initiation of treatment.

### 1.11 Pregnancy

Interferon-α is contraindicated in pregnant women. Effective contraception is mandatory before starting treatment; however, no consequences of interferon-α treatment during pregnancy have been established, and the heavy molecular weight of interferon-α should in theory prevent transplacental passage[69]

**Table II.** Serious adverse effects of interferon-α

| | |
|---|---|
| Neuropsychiatric | Ataxia, encephalitis, peripheral neuropathy, epileptic seizure, trigeminal neuropathy, vertigo, loss of hearing, retinal ischaemia, retinal haemorrhages, cotton-wool spots, optical neuropathy, depression, suicide, delirium, psychotic manifestations |
| Autoimmune | Diabetes mellitus, autoimmune diseases, lichen planus |
| Haematological | Anaemia, leucopenia, bone marrow depression, thrombocytopenia |
| Dermatological | Psoriasis, foliaceus pemphigus |
| Pulmonary | Interstitial pneumonia |
| Hepatic | Hepatic failure, autoimmune hepatitis |
| Renal | Proteinuria, nephrotic syndrome |
| Transplanted patient | Rejection |
| Cardiac | Rhythm disorders (atrial fibrillation, tachycardia), atrioventricular block, hypotension or hypertension |

**Table III.** Life-threatening adverse effects of interferon-α

| | |
|---|---|
| Hepatic | Liver failure in cirrhosis or autoimmune hepatitis |
| Psychiatric | Suicide in depressed patients |
| Cardiac | Arrhythmia, sudden death, ischaemic heart disease |
| Haematological | Bone marrow suppression |

### 1.12 Patients with Transplants

The risk of rejection of transplanted organs is high during interferon-α therapy.[70,71] Preliminary studies suggest that the risk of rejection is lower when interferon-α is used in combination with ribavirin for the treatment of HCV recurrence in patients with liver transplants.

### 1.13 Summary

Interferon-α therapy is associated with numerous adverse effects. However, the most common (observed in up to 10% of the treated patients) adverse effects are minor or mild and do not require any dose modification (table I). More than 90% of patients can receive 6 months to 1 year of treatment without serious adverse effects. The risk of serious complications during interferon-α therapy is low (table II).

In the retrospective survey of 11 241 patients,[72] 0.04% of the patients had fatal complications related to therapy. The risk of life-threatening adverse effects is 0.07% (table III); serious adverse effects occurred in 1.2% of patients. A meta-analysis[73] showed a dose-dependent incidence of adverse effects (table IV). However, high doses (6 million units) compared with usual doses (3 millions units) do not lead to significantly more serious adverse effects (82 *vs* 73% in a recent study)[74]. Similarly, the nature of adverse events described with pegylated interferon-α is the same as nonpegylated interferon-α. The incidence of cutaneous lesions at the injection site and of neutropenia is slightly higher.

Serious adverse effects usually occur in predisposed patients with pre-existing organ dysfunction. Thus, candidates for interferon-α therapy should

**Table IV.** Meta-analysis of the most common adverse effects (%) according to the dose of interferon-α[73]

| | Flu-like | Depression | Alopecia | White blood cell decrease | Platelets decrease | Thyroid | Stopped therapy | Decreased therapy |
|---|---|---|---|---|---|---|---|---|
| 3 MU | 41 | 7 | 16 | 9 | 8 | 2 | 4 | 9 |
| >5 MU | 76 | 10 | 19 | 13 | 4 | 2 | 5 | 22 |

**MU** = million units.

be carefully assessed so that those with psychiatric, thyroid, cardiac or neurological contraindications are excluded (table V).

## 2. Other Cytokines and Immune Modifiers

### 2.1 Interleukin-2

This cytokine generates and regulates T cell responses. Its adverse effects are similar to the common adverse effects seen during interferon-α therapy: fever, asthenia, chills, myalgia and an influenza-like syndrome occur in a large proportion of patients.[75] Bronchospasm may be observed in predisposed patients.

### 2.2 Thymosin α-1, Thymopentin

Peptides of thymic origin have been shown to trigger maturational events in lymphocytes, to augment T cell function and induce the reconstitution of immune defects. Studies of thymosin α-1 in chronic hepatitis B and C (alone or in combination with interferon-α) show that there is discomfort at the site of injection and that mild fatigue occurs.[76-79] Thymopentin shows the same adverse effects and also mild dyspepsia and upper abdominal pain.[80]

## 3. Nucleoside Analogues

Nucleoside analogues have been shown to inhibit viral nucleic acid polymerases. Many of them were used in early trials but did not show a significant effect (aciclovir, azidothymidine).

Others were excluded from clinical use because of severe (adenine arabinoside, foscarnet) or fatal (fialuridine) toxicity. Others (ganciclovir) are difficult to use because of the need for infusion administration. More recently introduced nucleosides are widely used because of their good efficacy and safety profiles. Ribavirin is now the reference treatment for hepatitis C, in combination with interferon-α. Lamivudine has been recently registered for the treatment of chronic hepatitis B whilst others are currently under evaluation.

### 3.1 Ribavirin

Data from recent, large randomised controlled trials show that the combination of interferon-α with ribavirin is more effective than interferon-α alone in treating chronic hepatitis C with a 40% sustained response rate.[81-83] These results suggest that this drug combination is the treatment of choice in chronic hepatitis C. In practice, it is widely used.[84]

Ribavirin is contraindicated during pregnancy as teratogenic effects were described in animal studies.[85] The main adverse effect of ribavirin is haemolysis as a consequence of toxic accumulation inside red blood cells. A decrease in haemoglobin levels (2 g/dl on average) may be expected in 30% of patients.[81-88] Anaemia is more marked (haemoglobin less than 10 g/dl) in those patients who have relatively low haemoglobin levels before treatment (<13 g/dl in men and <12 g/dl in women) and occurs generally within the first weeks of therapy. Therefore, haemoglobin levels should be checked every week during the first month of treatment. The initial dosage (1000 to 1200 mg/day) must be decreased (400 to 600 mg/ day) if haemoglobin levels fall below 11 g/dl, then stopped if haemoglobin level does not stabilise.

Insomnia, anxiety, minor depressive symptoms have been reported. Ribavirin may cause moderate pruritus, rashes and alopecia.[89,90] Other minor effects such as hyperuricaemia, myalgia, asthenia and nausea may also occur.

In recent large randomised controlled trials, combination therapy of ribavirin with interferon-α did not significantly increase the frequency of adverse effects in selected patients compared with monotherapy with interferon-α.[81] However, in patients treated outside of protocols, the adverse effects of combination therapy should be carefully monitored, especially depression where there is a risk of suicide. Patients older than 50 years or with pre-existing cardiopathy may develop cardiac complications: a careful cardiac assessment is mandatory before treatment. In particular, because of anaemia, ribavirin may induce decompensation of coronary insufficiency.

### 3.2 Lamivudine

Lamivudine is a potent inhibitor of the HBV DNA polymerase. At a dosage of 100 mg/day for 1 year, it produces a sustained virological response in 20% of cases and is now widely used in the treatment of chronic hepatitis B.[91] This new nucleoside analogue does not pass mitochondrial membranes and therefore its toxicity is believed to be very mild.

Lamivudine administration is usually well tolerated and is associated with few adverse effects: dizziness, headache and muscle ache.[92] The main concern about lamivudine therapy is the occurrence of viral breakthrough during treatment and of relapse after withdrawal of treatment. Breakthrough with reappearance of serum HBV DNA during lamivudine administration is related to the occurrence of an HBV mutant resistant to lamivudine. It is observed in about 20% of patients after 1 year of therapy. The clinical significance and management of this breakthrough is not well defined. It has been suggested that continuation of lamivudine administration might decrease the severity of the breakthrough. Severe reactivation seems to be rare but may occur in cirrhotic patients.

In patients who have responded to lamivudine therapy, withdrawal of the drug frequently causes a relapse which may be severe in patients with cirrhosis. Mild adverse effects such as anaphylactoid reaction, angiodema and urticaria have been reported with lamivudine treatment.[93] Lamivudine may exacerbate peripheral neuropathy at higher dosages than those used for chronic hepatitis B infection (300 to 600mg daily).[94] With all nucleoside analogues, contraceptive treatment is needed since they can induce fetal abnormalities by interfering with DNA synthesis. However, studies are underway on the use of lamivudine during pregnancy in HIV infection to prevent vertical transmission of the virus.

**Table V.** Contraindications of interferon-α therapy

| | |
|---|---|
| Neurological | Ataxia, encephalitis, peripherical neuropathy, epileptic seizures |
| Psychiatric | Depression, delirium, psychotic ideation |
| Hepatic | Cirrhosis and autoimmune liver diseases |
| Autoimmune manifestations | Antithyroid autoantibodies, diabetes mellitus |
| Cardiac | Coronary artery disease, rhythm disorders (atrial fibrillation, tachycardia) and atrioventricular block |
| Ophthalmological | Retinal haemorrhages, cotton-wool spots, optical neuropathy |
| Other conditions | Patients with transplants, pregnancy |
| Laboratory | Thrombocytopenia, leucopenia, anaemia, high titers of autoantibodies |

### 3.3 Other Nucleoside Analogues

Many other nucleoside analogues have been evaluated for the treatment of chronic hepatitis B infection including famciclovir, adefovir dipivoxil and entecavir.

Trials of famciclovir have shown a significant but moderate antiviral effect with a poor sustained response.[95] Therefore, the development of the drug in this indication has been halted. Tolerance observed in trials was good with few and mild adverse effects. Anorexia, nausea, weakness, tiredness, diarrhoea and headache were relatively rare adverse effects.[96] A report of an acute necrotico-haemorrhagic pancreatitis after famciclovir administration in a patient with renal impairment[97] suggests that such adverse effects might happen if toxic metabolites accumulate in circumstances such as renal dysfunction.

Adefovir dipivoxil is currently being assessed in clinical trials. Preliminary studies indicate that

it is well tolerated at a dosage of 10 mg/day. Nephrotoxicity has been observed with a dosage equal or higher than 30 mg/day in patients with HIV infection. Phase II studies of entecavir have shown good tolerability. Phase III studies of these new nucleoside analogues will determine their efficacy and tolerability in patients with chronic hepatitis B.

## 4. Conclusion

Interferon-α is the most widely used antiviral drug in the treatment of chronic hepatitis B and C. Its tolerability is usually good and serious adverse effects are rare. Nevertheless, careful selection of patients for therapy is required as is monitoring during treatment.

In the treatment of chronic hepatitis C, ribavirin, in combination with interferon-α is currently the treatment of choice. Its main adverse effect, haemolytic anaemia, needs to be monitored and in many cases the dosage may need adjustment.

Nucleoside analogues are promising drugs in the treatment of chronic hepatitis B through inhibition of viral DNA polymerase. Lamivudine, recently registered, shows excellent tolerability even when used for periods of 1 year or more. The new nucleoside analogues, adefovir dipivoxil and entecavir, are being assessed in large phase III trials.

## References


1. Vial T, Descotes J. Clinical toxicity of the interferons. Drug Saf 1994; 10: 115-50
2. Renault PF, Hoofnagle JH. Side effects of alpha interferon. Semin Liver Dis 1990; 9: 273-7
3. Dusheiko G. Side effects of alpha interferon in chronic hepatitis C. Hepatology 1997; 26 Suppl. 1: 112S-21S
4. Greenberg HB, Pollard RB, Lutwick LI, et al. Effect of human leucocyte interferon on hepatitis B virus infection in patients with chronic active hepatitis. N Engl J Med 1976; 295: 517-22
5. Hoofnagle JH, Mullen KD, Jones DB, et al. Treatment of chronic hepatitis non-A, non-B with recombinant human interferon-alpha: a preliminary report. N Engl J Med 1986; 315: 1575-8
6. Farci P, Mandas A, Coiana A, et al. Treatment of chronic hepatitis D with interferon-alfa-2a. N Engl J Med 1994; 339: 88-94
7. Giustina G, Favarato S, Ruol A, et al. A survey of clinical toxicity of alfa interferon in 11 241 patients with chronic viral hepatitis. Ital J Gastroenterol 1994; 26: 203-4
8. Hoofnagle JH, Peters MG, Mullen KD, et al. Randomized, controlled trial of recombinant alpha-interferon in patients with chronic hepatitis B. Gastroenterology 1988; 95: 1318-25
9. Perrillo RP, Schiff ER, Davis GL, et al. A randomized, controlled trial of recombinant interferon alfa-2b alone and after prednisone withdrawal for the treatment of chronic hepatitis B. N Engl J Med 1990; 323: 295-301
10. Krogsgaard K, Marcellin P, Trépo C, et al. Presnidolone withdrawal therapy enhances the effect of human lymphoblastoid interferon in chronic hepatitis B. J Hepatol 1996; 25: 803-13
11. Janssen HLA, Brouwer JT, Van der Mast RC, et al. Suicide associated with alfa-interferon therapy for chronic viral hepatitis. J Hepatol 1994; 21: 241-3
12. Levenson JL, Fallon HJ. Fluoxetine treatment of depression caused by interferon alpha. Am J Gastroenterol 1993; 88: 760-1
13. Mc Donald EM, Mann AH, Thomas HC. Interferons as mediators of psychiatric morbidity: an investigation in a trial of recombinant alpha-interferon in hepatitis-B carriers. Lancet 1987; II: 1175-8
14. Adams F, Quesada JR, Gutterman JU. Neuropsychiatric manifestations of human leukocyte interferon therapy in patients with cancer. JAMA 1984; 252: 938-41
15. Renault PF, Hoofnagle JH, Park Y, et al. Psychiatric complications of long-term interferon alfa therapy. Arch Intern Med 1987; 147: 1577-80
16. Iaffaioli RV, Fiorenza L, D'Avino M, et al. Neurotoxic effects of long-term treatment with low-dose alpha 2B interferon. Curr Ther Res 1990; 48: 403-8
17. Janssen HLA, Berk L, Vermeulen M, et al. Seizures associated with low-dose alpha-interferon [letter]. Lancet 1990; 336: 1580
18. Smedley H, Katrak M, Sikora K, et al. Neurological effects of recombinant human interferon. BMJ 1983; 286: 262-4
19. Negoro K, Fukusako T, Morimatsu M, et al. Acute axonal polyneuropathy during interferon-alpha therapy for chronic hepatitis C. Muscle Nerve 1994; 17: 1351-2
20. Read SJ, Crawford DHG, Pender MP. Trigeminal sensory neuropathy induced by interferon-alpha [letter]. Aust N Z J Med 1995; 25: 54
21. Guyer DR, Tiedeman J, Yannuzzi LA, et al. Interferon-associated retinopathy. Arch Ophtalmol 1993; 11: 350-6
22. Yamada H, MizobuchiK, Isogai Y. Acute onset of ocular complications with interferon [letter]. Lancet 1994; 343: 914
23. Manesis EK, Petrou C, Brouzas C, et al. Optic tract neuropathy complicating low-dose interferon treatment. J Hepatol 1994; 21: 474-7
24. Kanda Y, Shigeno K, Kinoshita N, et al. Sudden hearing loss associated with interferon Lancet 1994; 343: 1134-5
25. Sarraco G, Touscoz A, Durazzo M, et al. Autoantibodies and response to α-interferon in patients with chronic viral hepatitis. J Hepatol 1990; 11: 339-43
26. Marcellin P, Benhamou JP. Autoimmune disorders associated with hepatitis C. In: Boyer JL, Ockner RK, editors. Progress in liver diseases (Vol. XIII). Philadelphia (PA): Saunders, 1995: 247-67
27. Lisker-Melman M, Di Bisciglie AM, Usala SJ, et al. Development of thyroid disease during therapy of chronic viral hepatitis with alpha interferon. Gastroenterology 1992; 102: 2155-60
28. Marcellin P, Pouteau M, Benhamou JP. Hepatitis C virus infection, alpha interferon therapy and thyroid dysfunction. J Hepatol 1995; 22: 364-9
29. Benelhadj S, Marcellin P, Castelnau C, et al. Incidence of dysthyroidism during interferon therapy in chronic hepatitis C. Horm Res 1997; 48: 209-14
30. Baudin E, Marcellin P, Pouteau M, et al. Reversibility of thyroid dysfunction induced by recombinant alpha interferon in chronic hepatitis C. Clin Endocrinol (Oxf) 1993; 39: 657-1
31. Watanabe U, Hashimoto E, Hishamitsu T, et al. The risk factors for development of thyroid disease during interferon-α ther-

apy for chronic hepatitis C. Am J Gastroenterol 1994; 89: 399-403
32. Waguri M, Hanafusata T, Itoh N, et al. Occurence of IDDM during interferon therapy for chronic viral hepatitis. Diabetes Res Clin Pract 1994; 23: 33-6
33. Fabris P, Betterle C, Floreani A, et al. Development of type 1 diabetes mellitus during interferon-a therapy for chronic HCV hepatitis [letter]. Lancet 1992; 340: 548
34. Quilichini R, Mazzerbo F, Baume D, et al. Myasthénie au cours d'un traitement par l'interféron alpha [letter]. Presse Med 1995; 45: 1178
35. Rönnblom LE, Alm GV, Oberg KE. Possible induction of systemic lupus erythematosus by interferon-alpha treatment in a patient with a malignant carcinoid tumor. J Intern Med 1990; 227: 207-10
36. Flores A, Oliv A, Feliu E, et al. Systemic lupus erythematosus following interferon therapy [letter]. Br J Rheumatol 1994; 33: 787
37. Shindo M, Di Bisciglie AM, Hoofnagle JH. Acute exacerbation of liver disease during interferon alfa therapy for chronic hepatitis C. Gastroenterology 1992; 102: 1406-8
38. Papo T, Marcellin P, Bernuau J, et al. Autoimmune chronic hepatitis exarcebated by alpha-interferon. Ann Intern Med 1992; 116: 51-3
39. Payen JL, Rabbia I, Combis JM, et al. Révélation d'une hépatite autoimmune par l'interféron. Gastroenterol Clin Biol 1993; 17: 404-5
40. Tran A, Beusnel C, Montoya ML, et al. Hépatite autoimmune de type 1 révélée par un traitement par interféron. Gastroentérol Clin Biol 1992; 16: 722-3
41. Arslan M, Ozyilkan E, Kayhan B, et al. Raynaud's phenomenon associated with alpha-interferon therapy [letter]. J Intern Med 1994; 235: 503
42. Roy V, Newland AC. Raynaud's phenomenon and cryoglobulinaemia associated with the use of recombinant human alpha-interferon. Lancet 1988; I: 944-5
43. Bojic I, Lilic D, Radojcic C, et al. Deterioration of mixed cryoglobulinaemie during treatment with interferon-alpha-2a. J Gastroenterol 1994; 29: 369-71
44. Harlé JR, Disdier J, Pelletier J, et al. Dramatic worsenning of hepatitis C virus -related cryoglobulinaemia subsequent to treatment with interferon alfa [letter]. JAMA 1995; 274: 126
45. Liozon E, Cransac M, Remenieras ML, et al. La sarcoïdose: une nouvelle complication de traitement par l'interféron alpha [letter]. Rev Med Interne 1993; 14: 1160
46. Perreard M, Constant T, Monges D, et al. Lichen plan cutanéo-muqueux induit par une deuxième cure d'interféron alpha à forte dose chez un malade atteint d'une hépatite virale C chronique [letter]. Gastroentérol Clin Biol 1994; 18: 1051
47. Protzer U, Oschendorf FR, Leopold-Oschendorf A, et al. Exacerbation of lichen planus during alfa-2a therapy for chronic active hepatitis C. Gastroenterology 1993; 104: 903-5
48. Poynard T, Bedossa P, Chevallier M, al. A comparison of three interferon alfa-2b regimens for the long term treatment of chronic non-A, non-B hepatitis. N Engl J Med 1995; 332: 1457-62
49. Shepherd PCA, Richards S, Allan NC. Severe cytopenias associated with the sequential use of busulphan and interferon-alpha in chronic myeloid leukaemia. Br J Haematol 1994; 86: 92-6
50. Talpaz M, Kantarjian H, Zurzrock R, et al. Bone marrow hypoplasia and aplasia complicating interferon therapy for chronic myelogenous leukaemia. Cancer 1992; 69: 410-9
51. Ernstoff MS, Kirkwood JM. Changes in the bone marrow of cancer patients treated with recombinant interferon alfa-2. Am J Med 1984; 76: 593-6
52. Mac Laughlin P, Talpaz M, Quasada JR, et al. Immune thrombocytopenia following alpha-interferon therapy in patients with cancer. JAMA 1985; 253: 1353-4
53. Barbolla L, Paniagua C, Outeirino J, et al. Haemolytic anemia to the alpha-interferon treatment: a proposed mechanism. Vox sang 1993; 65: 156-7
54. Becker JC, Winkler B, Klingert S, et al. Antiphospholipid syndrome associated with immunotherapy for patients with melanoma. Cancer 1994; 73: 1621-4
55. Stricker RB, Barlogie B, Kiprov DD. Acquired factor VIII inhibitor associated with chronic interferon-a therapy. J Rheumatol 1994; 21: 350-2
56. Quesada JR, Guterman JU. Psoriasis and alpha-interferon. Lancet 1986; I: 1466-8
57. Jucgla A, Marcoval J, Curco N, et al. Psoriasis with articular involvement induced by interferon alfa. Arch Dermatol 1991; 127: 910-1
58. Cervoni JP, Serfaty L, Picard O, et al. Le traitement des hépatites B et C par interféron alpha peut induire ou aggraver un psoriasis. Gastroenterol Clin Biol 1995; 19: 324-5
59. Funk J, Langeland T, Schrumpf E, et al. Psoriasis induced by interferon-alpha. Br J Dermatol 1991; 125: 463-5
60. Niizeki H, Inamoto N, Nakamura K, et al. A case of pemphigus foliaceus after interferon alpha-2a therapy. Dermatology 1994; 189 Suppl. 1: 129-30
61. Massaro ER, Borden EC, Hawkins MJ, et al. Effects of recombinant interferon-a2a treatment upon lipid concentration and lipoprotein composition. J Interferon Res 1986; 6: 665-72
62. Graessle P, Bonacini M, Chen S. Alpha-interferon and reversible hypertriglyceridemia. Ann Intern Med 1993; 118: 316-7
63. Moriya K, Yasuda K, Koike K, et al. Induction of interstitial pneumonitis during interferon treatment for chronic hepatitis C. J Gastroenterol 1994; 29: 514-7
64. Davis GL, Balart LA, Schiff ER, et al. Treatment of chronic hepatitis C with recombinant interferon alfa: a multicenter randomized controlled trial. N Engl J Med 1989; 321: 1501-6
65. Marcellin P, Colin JF, Boyer N, al. Fatal exacerbation of chronic hepatitis B induced by recombinant alpha-interferon [letter]. Lancet 1991; 338: 828
66. Quesada JR, Talpaz M, Rios A, et al. JU. Clinical toxicity of interferons in cancer patients: a review. J Clin Oncol 1986; 4: 234-43
67. Sonnenblick M, Rosin A. Cardiotoxicity of interferon: a review of 44 cases. Chest 1991; 99: 557-61
68. Mansat-Krzyzanowska E, Dréno B, Chiffoleau A, et al. Manifestations cardio-vasculaires associées à l'interféron α-2a. Ann Med Interne 1991; 142: 576-81
69. Waysbort A, Giroux M, Mansat V, et al. Experimental study of transplacental passage of alpha interferon by two assays techniques. Antimicrob Agents Chemother 1993; 37: 1232-7
70. Samuel D, Gigou M, Feray C, et al. Recombinant alpha interferon for hepatitis C on the graft in liver transplant patients [abstract]. Hepatology 1992; 16: 48A
71. Gadano AC, Mosnier JF, Durand F, et al. Alpha-interferon induced rejection of a HCV infected liver allograft tolerated with low dosage immunosuppressive regimen. Transplantation 1995; 59: 1627-9
72. Fattovich G, Giustina G, Favarato S, et al. A survey of adverse events in 11241 patients with chronic viral hepatitis treated with alfa interferon. J Hepatol 1996; 24: 38-47

73. Poynard T, Leroy V, Cohard M, et al. Metaanalysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. Hepatology 1996; 24: 778-89
74. Ouzan D, Babany G, Valla D, et al. Comparison of high initial and fixed dose regimens of interferon-alpha2a in chronic hepatitis C: a randomised controlled trial. J Viral Hepatitis 1998; 5: 53-59
75. Tilg H, Vogel W, Tratkiewicz J, et al. Pilot study of natural human interleukin-2 in patients with chronic hepatitis B. Immunomodulatory and antiviral effects. J Hepatol 1993; 19: 259-67
76. Mutchnick MG, Appelman HD, Chung HT, et al. Thymosin treatment of chronic hepatitis B: a placebo-controlled pilot trial. Hepatology 1991; 14: 409-15
77. Andreone P, Cursaro C, Gramenzi A, et al. A double-blind, placebo-controlled, pilot trial of thymosin alpha 1 for the treatment of chronic hepatitis C. Liver 1996; 16: 207-10
78. Andreone P, Cursaro C, Gramenzi A, et al. A randomized controlled trial of thymosin-a1 versus interferon alfa treatment in patients with hepatitis B e antigen antibody-and hepatitis B virus DNA-positive chronic hepatitis B. Hepatology 1996; 24: 774-7
79. Rasi G, Di Virgilio D, Mutchnick M G, et al. Combination thymosin $\alpha_1$ and lymphoblastoid interferon treatment in chronic hepatitis C. Gut 1996; 39: 679-83
80. Fattovich G, Giustina G, Alberti A, et al. A randomized controlled trial of thymopentin therapy in patients with chronic hepatitis B. J Hepatol 1994; 21: 361-6
81. Davis GL, Esteban-Mur R, Rustgi V, et al. Interferon alfa-2b alone or in combination with ribavirin for the treatment of relapse of chronic hepatitis C. N Engl J Med 1998; 339: 1493-9
82. McHutchison JG, Gordon SC, Schiff ER, et al. Interferon alfa-2b alone or in combination with ribavirin as initial treatment for chronic hepatitis C. N Engl J Med 1998; 339: 1485-92
83. Poynard T, Marcellin P, Lee SS, et al. Randomised trial of interferon $\alpha$2b plus ribarivin for 48 weeks or for 24 weeks versus interferon $\alpha$2b plus placebo for 48 weeks for treatment of chronic infection with hepatitis C virus. Lancet 1998; 352: 1426-32
84. International consensus conference on hepatitis C. Consensus statement. J Hepatol 1999; 30: 956-61
85. Johnson EM. The effects of ribavirin on development and reproduction: a critical review of published and unpublished studies in experimental animals. J Am Coll Toxicol 1990; 9: 551-61
86. Fried MW, Fong T-L, Swain M G, et al. Therapy of chronic hepatitis B with a 6-month course of ribavirin. J Hepatol 1994; 21: 145-50
87. Schalm SW, Hansen BE, Chemello L, et al. Ribavirin enhances the efficacy but not the adverse effects of interferon in chronic hepatitis C. J Hepatol 1997; 26: 961-6
88. Di Bisceglie AM, Shindo M, Fong TL, et al. A pilot study of ribavirin therapy for chronic hepatitis C. Hepatology 1992; 16: 649-54
89. Bodenheimer HC, Lindsay KL, Davis GL, et al. Tolerance and efficacy of oral ribavirin treatment of chronic hepatitis C: a multicenter study. Hepatology 1997; 26: 473-7
90. Bellobuono A, Mondazzi L, Tempini S, et al. Ribavirin and interferon-$\alpha$ combination therapy vs interferon-$\alpha$ alone in the retreatment of chronic hepatitis C: a randomized clinical trial. J Viral Hepat 1997; 4: 185-91
91. Zoulim F, Trépo C. Drug therapy for chronic hepatitis B: antiviral efficacy and influence of hepatitis B virus polymerase mutations on the outcome of therapy. J Hepatol 1998; 9: 151-68
92. Lai CL, Chien RN, Leung NWY, et al. A one-year trial of lamivudine for chronic hepatitis B. N Engl J Med 1998; 339: 61-8
93. Kainer MA, Mijch A. Anaphylactoid reaction, angioedema, and urticaria associated with lamivudine. Lancet 1996; 348: 1519
94. Cupler EJ, Dalakas M C. Exacerbation of peripheral neuropathy by lamivudine. Lancet 1995; 345: 460-1
95. de Man RA, Marcellin P, Habal F, et al. A randomized placebo-controlled study to evaluate the efficacy of 12-month famciclovir treatment in patients with chronic HBeAg-positive hepatitis B. Hepatology 2000; 32: 413-7
96. Cirelli R, Herne, K, Mc Crary M, et al. Famciclovir: review of clinical efficacy and safety. Antiviral Res 1996; 29: 141-51
97. Goffin E, Horsmans Y, Pirson Y, et al. Acute necrotico-hemorrhagic pancreatitis after famciclovir prescription. Transplantation 1995; 58: 1218-9

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