Interferon Alfa *(BAN, rINN)*

IFN-α; Interferón-α; Interferon-α; Interferón alfa; Interféron alfa; Interferon alpha; Interferoni alfa; Interferonialfa; Interferonum Alfa; Ro-22-8181 (interferon alfa-2a); Sch-30500 (interferon alfa-2b).

Интерферон Альфа

CAS — 74899-72-2 (interferon alfa); 76543-88-9 (interferon alfa-2a); 99210-65-8 (interferon alfa-2b); 118390-30-0 (interferon alfacon-1); 198153-51-4 (peginterferon alfa-2a); 215647-85-1 (peginterferon alfa-2b).

ATC — L03AB01 (natural); L03AB04 (2a); L03AB05 (2b); L03AB06 (n1); L03AB09 (alfacon-1); L03AB10 (peginterferon alfa-2b); L03AB11 (peginterferon alfa-2a).

ATC Vet — QL03AB01 (natural); QL03AB04 (2a); QL03AB05 (2b); QL03AB06 (n1); QL03AB09 (alfacon-1); QL03AB10 (peginterferon alfa-2b); QL03AB11 (peginterferon alfa-2a).

NOTE. Interferon alfa was previously known as leucocyte interferon or lymphoblastoid interferon.

Interferon alfa-2a, alfa-2b, alfa-n1, and alfa-n3 are *USAN*.

Interferon alfacon-1 (*BAN*, *USAN*, *rINN*) is a recombinant nonnaturally occurring alfa interferon. Peginterferon alfa-2a (*BAN*, *USAN*, *rINN*) and peginterferon alfa-2b (*BAN*, *rINN*) are interferons pegylated by conjugation with macrogols.

Pharmacopoeias. *Chin.* includes monographs for recombinant human alfa-2a and alfa-2b. *Eur.* (see p.vii) includes Interferon Alfa-2 Concentrated Solution.

Ph. Eur. 6.2 (Interferon Alfa-2 Concentrated Solution; Interferoni Alfa-2 Solutio Concentrata). It is produced by a method based on recombinant DNA technology using bacteria as host cells. It is a clear, colourless or slightly yellowish liquid. Store in airtight containers at a temperature of –20° or below. Protect from light.

Nomenclature. Interferon alfa may be derived from leucocytes or lymphoblasts, or produced by recombinant DNA technology. Sub-species of the human alfa gene may produce interferon alfa with protein variants or a mixture of proteins. The protein variants may be designated by a number (as in interferon alfa-2) which may be further qualified by a letter to indicate the amino-acid sequences at positions 23 and 34:

- interferon alfa-2a has lysine at 23 and histidine at 34
- interferon alfa-2b has arginine at 23 and histidine at 34
- interferon alfa-2c has arginine at both positions

In the case of a mixture of proteins an alphanumeric designation is given (as in interferon alfa-n1). Interferon alfacon-1 varies from interferon alfa-2 in 20 of 166 amino acids.

The name may be further elaborated on the label by approved sets of initials in parentheses to indicate the method of production: (rbe) indicates production from bacteria (*Escherichia coli*) genetically modified by recombinant DNA technology; (lns) indicates production from cultured lymphoblasts from the Namalwa cell line that have been stimulated by a Sendai virus; (bls) indicates production from leucocytes from human blood that have been stimulated by a Sendai virus.

References.

1. Finter NB. The naming of cats—and alpha-interferons. *Lancet* 1996; **348:** 348–9.

Adverse Effects and Treatment

The adverse effects of interferon are varied and the natural products appear to be less toxic than the pure synthetic compounds. The frequency and severity of adverse effects of peginterferon alfa appear to be similar to those for interferon alfa although dose-related neutropenia and thrombocytopenia and injection site reactions are more common. Clinical experience suggests that interferons beta and gamma have similar adverse effects.

Adverse effects are generally mild and reversible at doses less than 5 million international units/day. The majority of patients on interferon treatment have 'flu-like' symptoms such as loss of appetite, fever, chills, fatigue, headache, malaise, myalgia, arthralgia, and sweating. These symptoms tend to be dose-related, are most likely to occur at the start of treatment, and mostly respond to paracetamol (but for a possible interaction with paracetamol, see Interactions, below).

Other common adverse effects are alopecia, asthenia, weight loss, anxiety, depression, dermatitis, diarrhoea, irritability, nausea, nervousness, neutropenia, pruritus, sleep disturbances, taste alteration, and vomiting. Serious adverse effects reported include neuropsychiatric disorders (homicidal ideation, suicidal ideation, suicide attempt, and suicide) and neurological disturbances (confusion, coma, and seizures), severe bacterial infections (sepsis), bone marrow toxicity (cytopenia and rarely, aplastic anaemia), cardiovascular disorders (hypo- or hypertension, supraventricular arrhythmias and myocardial infarction), endocrine disorders (such as thyroid disorders and diabetes mellitus), pulmonary disorders (dyspnoea, pneumonia, bronchiolitis obliterans, interstitial pneumonitis and sarcoidosis), colitis (ulcerative and hemorrhagic or ischaemic colitis), pancreatitis, and ophthalmologic disorders (such as decrease or loss of vision, retinopathy including macular oedema and retinal thrombosis or haemorrhages, optic neuritis and papilloedema).

Hypersensitivity reactions, including anaphylaxis, have occurred, and interferon therapy may cause or exacerbate auto-immune disorders (such as idiopathic thrombocytopenic purpura, thrombotic thrombocytopenic purpura, psoriasis, SLE, rheumatoid arthritis, and interstitial nephritis).

Hypertriglyceridaemia, sometimes severe, has been seen. High doses may cause electrolyte disturbances including decreased calcium concentrations. There may be signs of altered liver function and hepatitis has been reported. Renal failure and nephrotic syndrome have also occurred. Interferons may impair fertility and menstrual irregularities have been reported, particularly with interferon beta. Subcutaneous injection may produce a reaction at the injection site, predominantly mild inflammation or erythema, but pain, hypersensitivity, and other non-specific reactions have been reported. The reaction is reported frequently with interferon beta, which can produce severe reactions including local necrosis.

Adverse effects of peginterferon alfa (alone or with ribavirin) reported in patients co-infected with hepatitis C virus and HIV, are similar to those reported in patients infected only with hepatitis C virus. Although haematological adverse effects such as neutropenia, thrombocytopenia, and anaemia occurred more often in co-infected patients, most patients could be managed by dose adjustments. Other adverse effects reported in co-infected patients given peginterferon and ribavirin include apathy, raised blood amylase, chapped lips, chromaturia, raised gamma-glutamyltransferase and hepatitis, influenza, lactic acidosis (including hyperlactacidaemia), lipodystrophy, mood alteration, pain in the pharynx, larynx, back, and limbs, pneumonia, and tinnitus. Peginterferon treatment was associated with decreases in CD4+ cell counts within the first 4 weeks that were reversible when the dose was reduced or stopped; no negative impact was noted on the control of HIV viraemia during treatment or follow-up.

Nasal dosage may produce mucosal irritation and damage.

◊ Reviews.

1. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10:** 115–50.
2. Pardo M, *et al.* Risks and benefits of interferon-α in the treatment of hepatitis. *Drug Safety* 1995; **13:** 304–16.
3. Kirkwood JM, *et al.* Mechanisms and management of toxicities associated with high-dose interferon alfa-2b therapy. *J Clin Oncol* 2002; **20:** 3703–18.
4. Sleijfer S, *et al.* Side effects of interferon-alpha therapy. *Pharm World Sci* 2005; **27:** 423–31.

Effects on the blood. Interferon alfa has myelosuppressive effects and the commonest haematological adverse effects associated with its use are dose-related leucopenia, neutropenia, and thrombocytopenia; anaemia is rarely reported. Other reported effects associated with interferon alfa include immune haemolytic anaemia[1] and immune thrombocytopenia.[2,3] Haemorrhage occurred in a patient with immune thrombocytopenic purpura treated with interferon alfa,[4] and it was thought prudent to use interferons with caution, if at all, in this condition.[3,4] Reports of clotting disorders are rare; bleeding associated with induction of factor VIII inhibitor has been seen in a patient given interferon alfa to enhance hydroxycarbamide therapy for chronic myeloid leukaemia.[5] Thrombosis associated with interferon alfa has also been reported.[6]

Restoration of bone-marrow function after marrow transplantation was delayed in 3 patients given a human interferon alfa preparation.[7] Laboratory results showed an inhibition of granulocyte colony growth by human leucocyte interferon alfa. It was considered that interferon alfa was contra-indicated in patients with severe bone-marrow insufficiency and should not be given to marrow transplant patients before the graft was fully functional. However, in another 5 patients recombinant interferon alfa did not affect bone marrow transplants, although 3 patients experienced fever and chills, 4 had more than a 60% reduction in absolute peripheral granulocyte counts, and 4 had a 37 to 80% reduction in absolute platelet counts.[8] Lymphocytes were increased in all patients; blood counts returned to normal when interferon therapy stopped. Interferon alfa produced a decline in CD4+ T-lymphocytes resulting in opportunistic infections in 2 HIV-positive patients being treated for chronic hepatitis C.[9]

1. Akard LP, *et al.* Alpha-interferon and immune hemolytic anemia. *Ann Intern Med* 1986; **105:** 306.
2. McLaughlin P, *et al.* Immune thrombocytopenia following α-interferon therapy in patients with cancer. *JAMA* 1985; **254:** 1353–4.
3. Färkkilä M, Iivanainen M. Thrombocytopenia and interferon. *BMJ* 1988; **296:** 642.
4. Matthey F, *et al.* Bleeding in immune thrombocytopenic purpura after alpha-interferon. *Lancet* 1990; **335:** 471–2.
5. English KE, *et al.* Acquired factor VIII inhibitor in a patient with chronic myelogenous leukaemia receiving interferon-alfa therapy. *Ann Pharmacother* 2000; **34:** 737–9.
6. Durand JM, *et al.* Thrombosis and recombinant interferon-α. *Am J Med* 1993; **95:** 115.
7. Nissen C, *et al.* Toxicity of human leucocyte interferon preparations in human bone-marrow cultures. *Lancet* 1977; **i:** 203–4.
8. Winston DJ, *et al.* Safety and tolerance of recombinant leukocyte A interferon in bone marrow transplant recipients. *Antimicrob Agents Chemother* 1983; **23:** 846–51.
9. Pesce A, *et al.* Opportunistic infections and CD4 lymphocytopenia with interferon treatment in HIV-1 infected patients. *Lancet* 1993; **341:** 1597.

Effects on the cardiovascular system. Hypotension or hypertension, tachycardia, and distal cyanosis are the most commonly reported cardiovascular adverse effects. Other reported cardiac complications include cardiac arrhythmias, atrioventricular block, symptoms of ischaemic heart disease, including myocardial infarction and sudden death, congestive heart failure, acute dyspnoea, pericardial effusion,[1,2] and cardiomyopathy.[1,3,4] Cardiac toxicity was not related to the daily or cumulative total dose, or duration of treatment and is usually reversible on stopping interferon treatment.[1]

Peripheral vascular complications such as Raynaud's syndrome[5-9] have been associated with interferon alfa therapy and other types of interferon.

1. Sonnenblick M, Rosin A. Cardiotoxicity of interferon. A review of 44 cases. *Chest* 1991; **99:** 557–61.
2. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10:** 115–50.
3. Angulo MP, *et al.* Reversible cardiomyopathy secondary to α-interferon in an infant. *Pediatr Cardiol* 1999; **20:** 293–4.
4. Kuwata A, *et al.* A case of reversible dilated cardiomyopathy after α-interferon therapy in a patient with renal cell carcinoma. *Am J Med Sci* 2002; **324:** 331–4.
5. Bachmeyer C, *et al.* Raynaud's phenomenon and digital necrosis induced by interferon-alpha. *Br J Dermatol* 1996; **135:** 481–3.
6. Linden D. Severe Raynaud's phenomenon associated with interferon-β treatment for multiple sclerosis. *Lancet* 1998; **352:** 878–9.
7. Kruit WH, *et al.* Interferon-α induced Raynaud's syndrome. *Ann Oncol* 2000; **11:** 1501–2.
8. Schapira D, *et al.* Interferon-induced Raynaud's syndrome. *Semin Arthritis Rheum* 2002; **32:** 157–62.
9. Iorio R, *et al.* Severe Raynaud's phenomenon with chronic hepatitis C disease treated with interferon. *Pediatr Infect Dis J* 2003; **22:** 195–7.

Effects on the endocrine system. Both hypothyroidism[1,2] and hyperthyroidism[2,3] have been associated with interferon alfa therapy. Thyroid disorders are usually minor and regress on stopping the interferon (with or without other specific treatment). However a case of long-lasting ophthalmopathy as a result of interferon alfa-induced Graves' disease has been reported in a patient being treated for hepatitis C.[4]

The development of type 1 diabetes has also been associated with interferon alfa therapy,[5-8] and exacerbation of existing type 2 diabetes has been reported.[9,10] Reversible hypopituitarism has been reported in patients receiving interferon alfa.[11,12] Recombinant interferon gamma was reported not to affect thyroid function.[13]

1. Fentiman IS, *et al.* Primary hypothyroidism associated with interferon therapy of breast cancer. *Lancet* 1985; **i:** 1166.
2. Burman P, *et al.* Autoimmune thyroid disease in interferon-treated patients. *Lancet* 1985; **ii:** 100–1.
3. Schultz M, *et al.* Induction of hyperthyroidism by interferon-α-2b. *Lancet* 1989; **i:** 1452.
4. Binaghi M, *et al.* Ophtalmopathie de Basedow sévère liée à l'interféron alpha. *J Fr Ophtalmol* 2002; **25:** 412–15.
5. Fabris P, *et al.* Development of type 1 diabetes mellitus during interferon alfa therapy for chronic HCV hepatitis. *Lancet* 1992; **340:** 548.
6. Guerci A-P, *et al.* Onset of insulin-dependent diabetes mellitus after interferon-alfa therapy for hairy cell leukaemia. *Lancet* 1994; **343:** 1167–8.
7. Gori A, *et al.* Reversible diabetes in patient with AIDS-related Kaposi's sarcoma treated with interferon α-2a. *Lancet* 1995; **345:** 1438–9.
8. Murakami M, *et al.* Diabetes mellitus and interferon-α therapy. *Ann Intern Med* 1995; **123:** 318.
9. Campbell S, *et al.* Rapidly reversible increase in insulin requirement with interferon. *BMJ* 1996; **313:** 92.
10. Lopes EPA, *et al.* Exacerbation of type 2 diabetes mellitus during interferon-alfa therapy for chronic hepatitis B. *Lancet* 1994; **343:** 244. Correction. *ibid.*: 680.
11. Sakane N, *et al.* Reversible hypopituitarism after interferon-alfa therapy. *Lancet* 1995; **345:** 1305.

12. Concha LB, *et al.* Interferon-induced hypopituitarism. *Am J Med* 2003; **114:** 161–3.
13. Bhakri H, *et al.* Recombinant gamma interferon and autoimmune thyroid disease. *Lancet* 1985; **ii:** 457.

Effects on the eyes. The most typical ocular adverse effect associated with interferon alfa treatment is retinopathy, which is characterised by cotton wool spots and superficial retinal haemorrhages. Reports of interferon-associated retinopathy have been reviewed.[1,2] Reduced vision or complete visual loss is rare or limited and is usually reversible after stopping treatment. In a study of 43 patients with chronic hepatitis given interferon alfa, retinopathy developed in 11 of 37 non-diabetic patients and in 3 of 6 diabetic patients after about 8 to 10 weeks of therapy.[3] None of the patients had had retinopathy before treatment; the condition was reversible in the non-diabetic patients on stopping therapy. Visual acuity remained unchanged. Subconjunctival haemorrhage occurred in a further 3 of the non-diabetic patients. Severe irreversible loss of vision has been reported in a non-diabetic patient given interferon alfa.[4] A prospective study[5] of 156 patients treated with interferon alfa or peginterferon alfa (with or without ribavirin) reported signs of retinopathy in 24% of the patients; 29 patients developed cotton-wool spots, 7 developed retinal haemorrhage, and 2 patients developed both lesions during treatment; none of the patients had retinopathy before starting treatment. The lesions remained asymptomatic and resolved in all the patients. Patient age above 45 years, hypertension, and the use of pegylated alpha-interferon were identified as risk factors for retinopathy. Neurovisual impairment was present in 31 patients before interferon treatment and in 74 patients during treatment. Another study[6] of 19 patients reported that 8 patients developed asymptomatic retinopathy while on treatment with interferon alfa (with or without ribavirin); patients who had previously failed to respond to interferon monotherapy seemed more likely to develop retinopathy when given combined therapy than patients who had responded and then relapsed. The changes were transient and sometimes disappeared while the patients were still on treatment. Retinopathy has been reported in patients being treated with interferon beta for the management of multiple sclerosis.[7,8] Symptoms also resolved after stopping treatment.

Pain in one eyeball leading to exophthalmos and complete visual loss has been reported in a patient given interferon alfa;[9] despite withdrawal of interferon and instigation of antibacterial and corticosteroid treatment, the eyeball subsequently ruptured necessitating ophthalmectomy. Other severe ocular effects reported during interferon alfa treatment include a disorder resembling Vogt-Koyanagi-Harada disease, central retinal vein occlusion, central retinal artery occlusion, and bilateral ischaemic optic neuropathy with severe visual impairment.[10]

1. Hayasaka S, *et al.* Interferon associated retinopathy. *Br J Ophthalmol* 1998; **82:** 323–5.
2. Savant V, Gillow T. Interferon-associated retinopathy. *Eye* 2003; **17:** 534–6.
3. Hayasaka S, *et al.* Retinopathy and subconjunctival haemorrhage in patients with chronic viral hepatitis receiving interferon alfa. *Br J Ophthalmol* 1995; **79:** 150–2.
4. Lohmann CP, *et al.* Severe loss of vision during adjuvant interferon alfa-2b treatment for malignant melanoma. *Lancet* 1999; **353:** 1326.
5. d'Alteroche L, *et al.* Ophthalmologic side effects during alpha-interferon therapy for viral hepatitis. *J Hepatol* 2006; **44:** 56–61.
6. Jain K, *et al.* Retinopathy in chronic hepatitis C patients during interferon treatment with ribavirin. *Br J Ophthalmol* 2001; **85:** 1171–3.
7. Saito H, *et al.* Retinopathy in a multiple sclerosis patient undergoing interferon-therapy. *Multiple Sclerosis* 2007; **13:** 939–40.
8. Longmuir R, *et al.* Cotton wool spots associated with interferon beta-1 alpha therapy. *Semin Ophthalmol* 2007; **22:** 49–53.
9. Yamada H, *et al.* Acute onset of ocular complications with interferon. *Lancet* 1994; **343:** 914.
10. Sène D, *et al.* Intraocular complications of IFN-alpha and ribavirin therapy in patients with chronic viral hepatitis C. *World J Gastroenterol* 2007; **13:** 3137–40.

Effects on the gastrointestinal tract. Mild and transient gastrointestinal adverse effects such as nausea, diarrhoea, vomiting, and anorexia occur in about 30 to 40% of patients being treated with interferon alfa. There have been reports[1-4] of the onset of coeliac disease during treatment of hepatitis C with interferon or peginterferon alfa, in some cases used with ribavirin. Symptoms generally resolved after interferon was stopped and a gluten-free diet started. A case[5] of eosinophilic enteritis has been reported in a patient, with no history of digestive disorders, after 12 weeks of recombinant interferon alfa-2b treatment; symptoms resolved after stopping interferon and on treatment with prednisolone. New[6,7] or exacerbated[8] cases of ulcerative colitis have been reported in patients on interferon or peginterferon alfa treatment (with or without ribavirin). Treatment with interferon was usually stopped[7,8] and symptoms tended to resolve or improve with appropriate therapy (such as mesalazine and/or corticosteroids).[6-8] Cases of ischaemic colitis associated with interferon or peginterferon alpha have been reported rarely.[9]

1. Bardella MT, *et al.* Celiac disease during interferon treatment. *Ann Intern Med* 1999; **131:** 157–8.
2. Cammarota G, *et al.* Onset of coeliac disease during treatment with interferon for chronic hepatitis C. *Lancet* 2000; **356:** 1494–5.
3. Bourlière M, *et al.* Onset of coeliac disease and interferon treatment. *Lancet* 2001; **357:** 803–4.
4. Martins EV, Gaburri AK. Celiac disease onset after pegylated interferon and ribavirin treatment of chronic hepatitis C. *Arq Gastroenterol* 2004; **41:** 132–3.
5. Kakumitsu S, *et al.* Eosinophilic enteritis observed during alpha-interferon therapy for chronic hepatitis C. *J Gastroenterol* 2000; **35:** 548–51.
6. Mavrogiannis C, *et al.* Ulcerative colitis associated with interferon treatment for chronic hepatitis C. *J Hepatol* 2001; **34:** 964–5.
7. Sprenger R, *et al.* Acute ulcerative colitis during successful interferon/ribavirin treatment for chronic hepatitis. *Gut* 2005; **54:** 438–9.
8. Watanabe T, *et al.* A case of exacerbation of ulcerative colitis induced by combination therapy with PEG-interferon alpha-2b and ribavirin. *Gut* 2006; **55:** 1682–3.
9. Leung Y, *et al.* Ischemic colitis during pegylated interferon-alpha and ribavirin therapy for chronic hepatitis C. *Can J Gastroenterol* 2006; **20:** 661–3.

Effects on the hair. Excessive temporary loss of telogen hair causing moderate and reversible alopecia occurs in about 7 to 30% of patients on interferon or peginterferon alfa treatment. Alopecia areata[1-3] and alopecia universalis[4,5] have occasionally been reported; complete regrowth of the hair usually occurs on completing interferon treatment.

A report of marked greying of the hair in a patient beginning after 5 months of treatment with interferon alfa for metastatic malignant melanoma; on completion of interferon therapy the hair regrowth returned to its normal colour.[6] Marked straightening of scalp and body hair has been reported in 2 patients after combined treatment with interferon alfa-2b or peginterferon alfa-2b and ribavirin for chronic hepatitis C.[7] In the first patient, there was also diffuse thinning of scalp hair, change in hair texture, increased greying of the hair, and eyebrow lengthening; the original curly hair began to regrow 6 months after stopping treatment, but the hair abnormalities recurred on rechallenge despite switching from interferon alfa-2b to peginterferon alfa-2b. In the second patient, treatment with peginterferon alfa-2b and ribavirin was associated with straightening of scalp hair, eyebrow hair, and pubic hair.[7] Lengthening and thickening of eyelashes has also been reported with interferon alfa therapy.[8,9] A case of eyelid and eyebrow trichomegaly has also been reported[10] in a patient treated with peginterferon alfa and ribavirin.

1. Radny P, *et al.* Alopecia areata induced by adjuvant treatment with alpha-interferon in malignant melanoma? *Dermatology* 2004; **209:** 249–50.
2. Agesta N, *et al.* Alopecia areata during interferon alpha-2b/ribavirin therapy. *Dermatology* 2002; **205:** 300–1.
3. Kernland KH, Hunziker T. Alopecia areata induced by interferon alpha? *Dermatology* 1999; **198:** 418–19.
4. Taliani G, *et al.* Reversible alopecia universalis during treatment with PEG-interferon and ribavirin for chronic hepatitis C. *J Chemother* 2005; **17:** 212–14.
5. Kartal ED, *et al.* Reversible alopecia universalis secondary to PEG-interferon alpha-2b and ribavirin combination therapy in a patient with chronic hepatitis C virus infection. *Eur J Gastroenterol Hepatol* 2007; **19:** 817–20.
6. Fleming CJ, MacKie RM. Alpha interferon-induced hair discolouration. *Br J Dermatol* 1996; **135:** 337–8.
7. Bessis D, *et al.* Straight hair associated with interferon-alfa plus ribavirin in hepatitis C infection. *Br J Dermatol* 2002; **147:** 392–3.
8. Hernández-Núñez A, *et al.* Trichomegaly following treatment with interferon alpha-2b. *Lancet* 2002; **359:** 1107.
9. Dikici B, *et al.* Interferon alpha and hypertrichosis of eyelashes. *Pediatr Infect Dis J* 2002; **21:** 448–9.
10. Howaizi M. Pegylated interferon-induced eyelid and eyebrow trichomegaly during chronic hepatitis C. *J Gastroenterol Hepatol* 2005; **20:** 1945–6.

Effects on hearing. Sensorineural hearing loss, mostly unilateral, has been rarely reported in patients treated with interferon or peginterferon. A prospective study[1] reported sensorineural hearing loss in 18 of 49 patients and tinnitus in 14 of 49 patients given interferons. The authors reported that effects were more common in those given interferon beta than in those given interferon alfa, and resolved in all patients on stopping therapy. A report[2] of 6 patients who experienced sudden hearing loss while on treatment with peginterferon alfa plus ribavirin found that hearing loss did not fully resolve after stopping treatment; but neither did it worsen in those who continued their treatment. A case report[3] of a patient who had acute sensorineural hearing loss 2 months after starting treatment with peginterferon alfa and ribavirin found that when treatment was re-started 4 months after stopping, the patient did not experience further hearing loss and hearing on the left-side was unaffected. In another case report[4] a patient who developed hearing loss 22 weeks after starting treatment with peginterferon alfa, continued with treatment and symptoms did not worsen. Hearing loss resolved within 2 weeks of stopping treatment.

1. Kanda Y, *et al.* Sudden hearing loss associated with interferon. *Lancet* 1994; **343:** 1134–5.
2. Formann E, *et al.* Sudden hearing loss in patients with chronic hepatitis C treated with pegylated interferon/ribavirin. *Am J Gastroenterol* 2004; **99:** 873–7.
3. Wong VK, *et al.* Acute sensorineural hearing loss associated with peginterferon and ribavirin combination therapy during hepatitis C treatment: outcome after resumption of therapy. *World J Gastroenterol* 2005; **11:** 5392–3.
4. Elloumi H, *et al.* Sudden hearing loss associated with peginterferon and ribavirin combination therapy during hepatitis C treatment. *World J Gastroenterol* 2007; **13:** 5411–12.

Effects on the kidneys. Renal adverse effects associated with interferon alfa are usually limited to mild, asymptomatic proteinuria and moderate increases in serum creatinine in 15 to 20% of patients. Dose-related asymptomatic proteinuria has been reported with interferon gamma treatment.[1] Acute renal failure and nephrotic syndrome associated with interferon alfa treatment is rare and has mostly been reported in patients with underlying renal disease, or malignancies,[2-5] and in those receiving high doses.[6] Cases have also been reported in patients receiving interferon or peginterferon alfa treatment for chronic hepatitis C.[7-9] Nephrotic syndrome has also occurred after use of interferon beta.[10-12] Renal dysfunction usually resolves after stopping treatment, but incomplete resolution and fatalities have been reported.[5,8]

1. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10:** 115–50.
2. Averbuch SD, *et al.* Acute interstitial nephritis with the nephrotic syndrome following recombinant leukocyte A interferon therapy for mycosis fungoides. *N Engl J Med* 1984; **310:** 32–5.
3. Selby P, *et al.* Nephrotic syndrome during treatment with interferon. *BMJ* 1985; **290:** 1180.
4. Herrman J, Gabriel F. Membranoproliferative glomerulonephritis in a patient with hairy-cell leukemia treated with alpha-II interferon. *N Engl J Med* 1987; **316:** 112–13.
5. Colovic M, *et al.* Interferon alpha sensitisation induced fatal renal insufficiency in a patient with chronic myeloid leukaemia: case report and review of literature. *J Clin Pathol* 2006; **59:** 879–81.
6. Kramer P, *et al.* Recombinant leucocyte interferon A induces steroid-resistant acute vascular rejection episodes in renal transplant recipients. *Lancet* 1984; **i:** 989–90.
7. Endo M, *et al.* Appearance of nephrotic syndrome following interferon-α therapy in a patient with hepatitis B virus and hepatitis C virus coinfection. *Am J Nephrol* 1998; **18:** 439–43.
8. Fisher ME, *et al.* A woman with chronic hepatitis C infection and nephrotic syndrome who developed multiple renal lesions after interferon alfa therapy. *Am J Kidney Dis* 2004; **44:** 567–73.
9. Couto CA, *et al.* Life-threatening thrombocytopenia and nephrotic syndrome due to focal segmental glomerulosclerosis associated with pegylated interferon alpha-2b and ribavirin treatment for hepatitis C. *Liver Int* 2006; **26:** 1294–7.
10. Nakao K, *et al.* Minimal change nephrotic syndrome developing during postoperative interferon-beta therapy for malignant melanoma. *Nephron* 2002; **90:** 498–500.
11. Auty A, Saleh A. Nephrotic syndrome in a multiple sclerosis patient treated with interferon beta 1a. *Can J Neurol Sci* 2005; **32:** 366–8.
12. Kumasaka R, *et al.* Nephrotic syndrome associated with interferon-beta-1b therapy for multiple sclerosis. *Clin Exp Nephrol* 2006; **10:** 222–5.

Effects on lipids. Cases[1-3] of reversible hypertriglyceridaemia (with or without elevation of total cholesterol level) have been reported in association with interferon alfa treatment. Hypertriglyceridaemia more often occurs with longer treatment durations and does not appear to be related to pre-existing cardiovascular disorders or baseline dyslipidaemia; frequency and severity are not dose dependent. Lifestyle modifications and drug treatment with a fibrate or statin are usually needed to reduce triglyceride levels. A small study[4] reported that taking omega-3 fatty acid supplements (3 g daily for 6 months) reduced serum triglyceride levels in patients on interferon alfa for the management of chronic hepatitis C.

1. Graessle D, *et al.* Alpha-interferon and reversible hypertriglyceridemia. *Ann Intern Med* 1993; **118:** 316–17.
2. Junghans V, Rünger TM. Hypertriglyceridaemia following adjuvant interferon-α treatment in two patients with malignant melanoma. *Br J Dermatol* 1999; **140:** 183–4.
3. Wong SF, *et al.* Management of hypertriglyceridemia in patients receiving interferon for malignant melanoma. *Ann Pharmacother* 2004; **38:** 1655–9.
4. Malaguarnera M, *et al.* Fish oil treatment of interferon-alpha-induced dyslipidaemia: study in patients with chronic hepatitis C. *BioDrugs* 1999; **11:** 285–91.

Effects on the liver. Mild hepatotoxicity with an asymptomatic and reversible rise in serum aminotransferases has been reported in about 25 to 30% of patients receiving interferon alfa; severe hepatotoxicity is rare[1] but cases of fatal liver failure have been reported,[2-5] sometimes due to severe exacerbation of chronic hepatitis B and/or C infection.[4,5] An analysis of the toxicity of adjuvant high-dose interferon alfa in 40 patients being treated for melanoma reported hepatotoxicity in 39 patients, with 26 patients experiencing grade 3 to 4 hepatotoxicity.[6] Cases[7,8] of peginterferon alfa-induced auto-immune hepatitis have been reported in patients receiving treatment for chronic hepatitis C.

Raised serum-alanine aminotransferase values have been reported in about 37% of patients given interferon beta therapy for the treatment of multiple sclerosis, with grade 3 to 4 hepatotoxicity being reported in about 1.4% of patients.[9]

1. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10:** 115–50.
2. Durand JM, *et al.* Liver failure due to recombinant alpha interferon. *Lancet* 1991; **338:** 1268–9.
3. Wandl UB, *et al.* Liver failure due to recombinant alpha interferon for chronic myelogenous leukaemia. *Lancet* 1992; **339:** 123–4.
4. Marcellin P, *et al.* Fatal exacerbation of chronic hepatitis B induced by recombinant alpha-interferon. *Lancet* 1991; **338:** 828.
5. Janssen HLA, *et al.* Fatal hepatic decompensation associated with interferon alfa. *BMJ* 1993; **306:** 107–8.
6. Jonasch E, *et al.* Adjuvant high-dose interferon alfa-2b in patients with high-risk melanoma. *Cancer J* 2000; **6:** 139–45.
7. Kogure T, *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.
8. Kontorinis N, *et al.* Pegylated interferon-induced immune-mediated hepatitis post-liver transplantation. *Liver Transpl* 2006; **12:** 827–30.
9. Byrnes V, *et al.* Drug induced liver injury secondary to interferon-beta (IFN-beta) in multiple sclerosis. *Ann Hepatol* 2006; **5:** 56–9.

Effects on the nervous system and mental state. Neurological adverse effects have been reported in association with interferon alfa treatment for chronic hepatitis C virus or for malignant diseases;[1-5] notably, an acute confusional state may develop rapidly after starting high-dose interferon alfa treatment and a depressive syndrome may develop more slowly over weeks to months of treatment. Less commonly a manic condition, usually characterised by extreme irritability and agitation but also occasionally by euphoria, may occur.

Acute interferon alfa-induced confusional states are typically characterised by disorientation, lethargy, difficulties with speaking and writing, parkinsonism, psychomotor retardation, psychotic symptoms (such as hallucinations), and somnolence.

Depression[5-9] occurs in about 16 to 58% of patients receiving interferon alfa. Patients considered to be at risk for developing depression are those with pre-existing symptoms of mood and anxiety disorders, those with a history of major depression, and those receiving higher doses of interferon alfa or on long treatment regimens. SSRIs have been used successfully to both treat patients with interferon-associated depression, thus allowing therapy to be continued,[10,11] and as pretreatment to prevent its occurrence.[12]

Should manic symptoms[13] occur, interferon alfa and antidepressant treatment should be stopped and a mood stabiliser given. Interferon alfa-induced mood disorders may also consist of an overlap between depressive and manic symptoms. A prospective study[14] of 93 patients treated with peginterferon alfa plus ribavirin for chronic hepatitis C reported that mood disorders occurred in 30 patients; 3 cases of mania, 15 cases of irritable hypomania, and 12 cases of mixed depressive states. The distinction between the 2 states is important in terms of management as depression-specific symptoms respond well to SSRIs, whereas antidepressants may worsen manic or hypomanic states.

Seizures[15-17] attributed to interferon alfa have been described.

Cases of neurological toxicity have been reported in patients receiving interferon beta,[1,18] although interferon beta is considered to be slightly less neurotoxic.

Chronic hepatitis C virus infection may be complicated by the development of systemic vasculitis caused by mixed cryoglobulinemia or of a non-cryoglobulinemic vasculitis resembling polyarteritis nodosa. Successful treatment of the hepatitis infection with interferon alfa usually results in the improvement of vasculitic symptoms, including neuropathy. However, vasculitis may also be precipitated or exacerbated by treatment with interferon (including peginterferon alfa)[19-21] resulting in development of vasculitic neuropathy; cases of apparently non-vasculitic peripheral neuropathy have also been reported.[20-22] Others[23] have reported no association between peginterferon alfa and peripheral neuropathy. In most cases symptoms improved on treatment with corticosteroids or spontaneously, but fatal exacerbations of vasculitis have occurred despite stopping the interferon treatment and giving immunosuppressants.[21]

1. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10:** 115–50.
2. Dieperink E, *et al.* Neuropsychiatric symptoms associated with hepatitis C and interferon alpha: A review. *Am J Psychiatry* 2000; **157:** 867–76.
3. Malek-Ahmadi P. Mood disorders associated with interferon treatment: theoretical and practical considerations. *Ann Pharmacother* 2001; **35:** 489–95.
4. Van Gool AR, *et al.* Neuropsychiatric side effects of interferon-alfa therapy. *Pharm World Sci* 2003; **25:** 11–20.
5. Raison CL, *et al.* Neuropsychiatric adverse effects of interferon-alpha: recognition and management. *CNS Drugs* 2005; **19:** 105–23.
6. Janssen HLA, *et al.* Suicide associated with alfa-interferon therapy for chronic viral hepatitis. *J Hepatol* 1994; **21:** 241–3.
7. Renault PF, *et al.* Psychiatric complications of long-term interferon alfa therapy. *Arch Intern Med* 1987; **147:** 1577–80.
8. Adverse Drug Reactions Advisory Committee (ADRAC). Depression with interferon. *Aust Adverse Drug React Bull* 1999; **18:** 6.
9. Capuron L, Ravaud A. Prediction of the depressive effects of interferon alfa therapy by the patient's initial affective state. *N Engl J Med* 1999; **340:** 1370.
10. Levenson JL, Fallon HJ. Fluoxetine treatment of depression caused by interferon-α. *Am J Gastroenterol* 1993; **88:** 760–1.
11. Schramm TM, *et al.* Sertraline treatment of interferon-alfa-induced depressive disorder. *Med J Aust* 2000; **173:** 359–61.
12. Musselman DL, *et al.* Paroxetine for the prevention of depression induced by high-dose interferon alfa. *N Engl J Med* 2001; **344:** 961–6.
13. Kingsley D. Interferon-alpha induced 'tertiary mania'. *Hosp Med* 1999; **60:** 381–2.
14. Constant A, *et al.* Mood alterations during interferon-alfa therapy in patients with chronic hepatitis C: evidence for an overlap between manic/hypomanic and depressive symptoms. *J Clin Psychiatry* 2005; **66:** 1050–7.
15. Janssen HLA, *et al.* Seizures associated with low-dose α-interferon. *Lancet* 1990; **336:** 1580.
16. Brouwers PJ, *et al.* Photosensitive seizures associated with interferon alpha-2a. *Ann Pharmacother* 1999; **33:** 113–14.
17. Ameen M, Russell-Jones R. Seizures associated with interferon-α treatment of cutaneous malignancies. *Br J Dermatol* 1999; **141:** 386–7.
18. Goeb JL, *et al.* Psychiatric side effects of interferon-beta in multiple sclerosis. *Eur Psychiatry* 2006; **21:** 186–93.
19. Batisse D, *et al.* Sustained exacerbation of cryoglobulinaemia-related vasculitis following treatment of hepatitis C with peginterferon alfa. *Eur J Gastroenterol Hepatol* 2004; **16:** 701–3.
20. Boonyapisit K, Katirji B. Severe exacerbation of hepatitis C-associated vasculitic neuropathy following treatment with interferon alpha: a case report and literature review. *Muscle Nerve* 2002; **25:** 909–13.
21. Beuthien W, *et al.* Vasculitic complications of interferon-alpha treatment for chronic hepatitis C virus infection: case report and review of the literature. *Clin Rheumatol* 2005; **24:** 507–15.
22. Gastineau DA, *et al.* Severe neuropathy associated with low-dose recombinant interferon-alpha. *Am J Med* 1989; **87:** 116.
23. Briani C, *et al.* Peripheral neurotoxicity of pegylated interferon alpha: a prospective study in patients with HCV. *Neurology* 2006; **67:** 781–5.

Effects on the oral mucosa. Painful oral ulcers, necessitating withdrawal of interferon alfa therapy, have occurred in a patient treated for chronic hepatitis.[1] Interferon alfa treatment has been reported to exacerbate pre-existing lichen planus associated with chronic hepatitis C.[2,3] New cases of oral lichen planus have been reported in patients receiving interferon alfa treatment for malignant diseases[4] and chronic hepatitis.[5]

1. Qaseem T, *et al.* A case report of painful oral ulcerations associated with the use of alpha interferon in a patient with chronic hepatitis due to non-A non-B non-C virus. *Mil Med* 1993; **158:** 126–7.
2. Areias J, *et al.* Lichen planus and chronic hepatitis C: exacerbation of the lichen under interferon-alpha-2a therapy. *Eur J Gastroenterol Hepatol* 1996; **8:** 825–8.
3. Nagao Y, *et al.* Exacerbation of oral erosive lichen planus by combination of interferon and ribavirin therapy for chronic hepatitis C. *Int J Mol Med* 2005; **15:** 237–41.
4. Kütting B, *et al.* Oropharyngeal lichen planus associated with interferon-α treatment for mycosis fungoides: a rare side-effect in the therapy of cutaneous lymphomas. *Br J Dermatol* 1997; **137:** 836–7.
5. Guijarro Guijarro B, *et al.* Aparición de un liquen plano erosivo durante el tratamiento con interferón alfa-2a por una hepatitis C crónica. *Med Oral* 2001; **6:** 358–63.

Effects on the respiratory system. Pulmonary adverse effects have occasionally been reported in association with interferon or peginterferon alfa treatment. A literature review[1] found that the most commonly reported adverse effect was interstitial pneumonitis, followed by a sarcoid-like reaction with non-caseating granuloma formation. Other, less commonly reported events were asthma exacerbation, pleural effusion, bronchiolitis obliterans with organizing pneumonia, and a case of fatal acute respiratory distress-like syndrome.

1. Midturi J, *et al.* Spectrum of pulmonary toxicity associated with the use of interferon therapy for hepatitis C: case report and review of the literature. *Clin Infect Dis* 2004; **39:** 1724–9.

Effects on skeletal muscle. Myalgia is one of the 'flu-like' symptoms frequently associated with interferons. Rhabdomyolysis[1-3] has occurred in patients being treated with interferon alfa and proved fatal when associated with multiple organ failure in a patient receiving adjuvant high-dose interferon alfa for multiple myeloma.[1] Rhabdomyolysis has also been reported in a patient receiving interferon beta for the treatment of multiple sclerosis.[4]

1. Reinhold U, *et al.* Fatal rhabdomyolysis and multiple organ failure associated with adjuvant high-dose interferon alfa in malignant melanoma. *Lancet* 1997; **349:** 540–1.
2. Gabrielli M, *et al.* Acute reversible rhabdomyolysis during interferon alpha2b therapy for hepatitis C. *Am J Gastroenterol* 2003; **98:** 940.
3. Ozdag F, *et al.* Acute rhabdomyolysis during the treatment of scleromyxedema with interferon alfa. *J Dermatolog Treat* 2001; **12:** 167–9.
4. Lünemann JD, *et al.* Rhabdomyolysis during interferon-beta 1a treatment. *J Neurol Neurosurg Psychiatry* 2002; **72:** 274. Correction. *ibid.*; **73;** 354.

Effects on the skin. Dermatological adverse effects such as dryness, erythema, rash, or urticaria, have been reported in about 5 to 12% of patients given interferon alfa; severe events occur rarely.[1] Exacerbation or development of psoriasis was reported in patients given recombinant interferon alfa[2-4] and peginterferon alfa.[5] However, no such effect was seen in 7 patients given interferon gamma.[6] Both vitiligo and psoriasis developed in a 10-year-old girl with chronic hepatitis B infection given interferon alfa; the skin conditions did not improve on stopping the interferon treatment.[7] A case[8] of vitiligo occurring during the third month of treatment for chronic hepatitis C with peginterferon alfa and ribavirin has been reported; the condition persisted after treatment with peginterferon was completed. Exacerbation of lichen planus has also been reported[9] during interferon alfa treatment (see also Effects on the Oral Mucosa, above). Cases of cutaneous sarcoidosis have been reported in patients with chronic hepatitis C being treated with interferon or pegylated interferon alfa plus ribavirin; skin lesions are usually benign and treatment with interferon alfa may sometimes be continued with resolution of the skin lesions occurring spontaneously or within a few months of completing treatment.[10,11] Cutaneous vascular lesions with punctate telangiectasias were noted in 18 of 44 patients treated with interferon alfa-2a; lesions did not appear at the injection site.[12] Severe necrotising cutaneous lesions were reported at injection sites in a patient given recombinant interferon beta-1b; the lesions healed when interferon alfa-n3 was substituted.[13] However, cutaneous necrosis has also been associated with interferon alfa[14,15] and peginterferon alfa.[16] Five cases[17] of a self-resolving cutaneous lesion at the injection site of interferon, mimicking lupus erythematosus, have been reported; 3 of them involved interferon alfa therapy for malignant melanoma and the other 2 patients were being given interferon beta for multiple sclerosis. Fatal paraneoplastic pemphigus developed in a patient given interferon alfa-2a.[18] Hyperpigmentation of the skin and tongue has been described[19] in 2 dark-skinned patients during treatment with interferon alfa and ribavirin.

1. Vial T, Descotes J. Clinical toxicity of the interferons. *Drug Safety* 1994; **10:** 115–50.
2. Quesada JR, Gutterman JU. Psoriasis and alpha-interferon. *Lancet* 1986; **i:** 1466–8.
3. Funk J, *et al.* Psoriasis induced by interferon-α. *Br J Dermatol* 1991; **125:** 463–5.
4. Taylor C, *et al.* Extensive psoriasis induced by interferon alfa treatment for chronic hepatitis C. *Postgrad Med J* 2000; **76:** 365–6.
5. Ketikoglou I, *et al.* Extensive psoriasis induced by pegylated interferon alpha-2b treatment for chronic hepatitis B. *Eur J Dermatol* 2005; **15:** 107–9.
6. Schulze H-J, Mahrle G. Gamma interferon and psoriasis. *Lancet* 1986; **ii:** 926–7.
7. Seçkin D, *et al.* Concomitant vitiligo and psoriasis in a patient treated with interferon alfa-2a for chronic hepatitis B infection. *Pediatr Dermatol* 2004; **21:** 577–9.
8. Tomasiewicz K, *et al.* Vitiligo associated with pegylated interferon and ribavirin treatment of patients with chronic hepatitis C: a case report. *Adv Therapy* 2006; **23:** 139–42.
9. Protzer U, *et al.* Exacerbation of lichen planus during interferon alfa-2a therapy for chronic active hepatitis C. *Gastroenterology* 1993; **104:** 903–5.
10. Eberlein-König B, *et al.* Cutaneous sarcoid foreign body granulomas developing in sites of previous skin injury after systemic interferon-alpha treatment for chronic hepatitis C. *Br J Dermatol* 1999; **140:** 370–2.
11. Hurst EA, Mauro T. Sarcoidosis associated with pegylated interferon alfa and ribavirin treatment for chronic hepatitis C: a case report and review of the literature. *Arch Dermatol* 2005; **141:** 865–8.
12. Dreno B, *et al.* Alpha-interferon therapy and cutaneous vascular lesions. *Ann Intern Med* 1989; **111:** 95–6.
13. Sheremata WA, *et al.* Severe necrotizing cutaneous lesions complicating treatment with interferon beta-1b. *N Engl J Med* 1995; **332:** 1584.
14. Shinohara K. More on interferon-induced cutaneous necrosis. *N Engl J Med* 1995; **333:** 1222.
15. Sasseville D, *et al.* Interferon-induced cutaneous necrosis. *J Cutan Med Surg* 1999; **3:** 320–3.
16. Bessis D, *et al.* Necrotizing cutaneous lesions complicating treatment with pegylated-interferon alfa in an HIV-infected patient. *Eur J Dermatol* 2002; **12:** 99–102.
17. Arrue I, *et al.* Lupus-like reaction to interferon at the injection site: report of five cases. *J Cutan Pathol* 2007; **34** (suppl 1): 18–21.
18. Kirsner RS, *et al.* Treatment with alpha interferon associated with the development of paraneoplastic pemphigus. *Br J Dermatol* 1995; **132:** 474–8.
19. Willems M, *et al.* Hyperpigmentation during interferon-alpha therapy for chronic hepatitis C virus infection. *Br J Dermatol* 2003; **149:** 390–4.

Shock. Fatal non-cardiogenic shock occurred after the third dose of interferon alfa-2b in a patient with malignant melanoma.[1] There were similarities to a fatal reaction reported in another patient with malignant melanoma (see under Effects on Skeletal Muscle, above).

1. Carson JJ, *et al.* Fatality and interferon α for malignant melanoma. *Lancet* 1998; **352:** 1443–4.

Precautions

Interferons should be used with caution or avoided altogether in patients with depression or psychiatric disorders, epilepsy or other CNS diseases, severe renal or hepatic impairment, chronic hepatitis with advanced, decompensated hepatic disease or cirrhosis of the liver, auto-immune hepatitis, cardiac disorders, myelosuppression, poorly controlled thyroid dysfunction, pulmonary disease, diabetes mellitus, auto-immune diseases, coagulation disorders, or a history of these conditions.

All patients receiving interferons should be closely monitored for any signs or symptoms of psychiatric disorders; if psychiatric symptoms continue or worsen, or suicidal ideation is identified, then interferon therapy should be stopped.

Interferon treatment is not advised for patients whose hypoglycaemia, hyperglycaemia and/or diabetes mellitus is not effectively controlled; patients who develop these conditions during treatment and cannot be controlled with medication should stop interferon treatment. Standard blood and biochemical laboratory tests (including thyroid function) should be done before starting treatment with interferon and then periodically during therapy. Interferon should be used with caution in patients also receiving other potentially myelosuppressive agents.

Assessment of cardiac function is advised before treatment is started in patients with pre-existing cardiac abnormalities and if there is any deterioration of cardiovascular status interferon should be suspended or stopped.

Hepatic and renal function should be monitored during treatment with interferons. Interferon treatment should

be stopped in patients who develop evidence of liver decompensation during treatment. Treatment should also be stopped in those patients who despite the dose of interferon being reduced still have progressive and clinically significant increases in serum-alanine aminotransferase.

Patients receiving interferons who have visual disturbances should undergo eye examination. A baseline ocular examination is recommended before treatment, and periodic eye examinations should be performed throughout treatment in patients predisposed to retinopathy, such as those with diabetes mellitus or hypertension; treatment should be stopped in patients who develop new or worsening ophthalmologic disorders.

Patients with psoriasis or sarcoidosis have been reported to experience exacerbations during interferon alfa therapy.

Patients should receive adequate fluids to maintain hydration during treatment with interferon alfa since hypotension related to fluid depletion has been seen in some patients.

Interferons may affect the ability to drive or operate machinery.

Antibodies may develop to exogenous interferon that reduce its activity.

Asthma. For a report of severe exacerbation of asthma in patients receiving interferon alfa, see Effects on the Respiratory System, above.

Breast feeding. The American Academy of Pediatrics[1] states that there have been no reports of any clinical effect on the infant associated with the use of interferon alfa by breast-feeding mothers, and that therefore it may be considered to be usually compatible with breast feeding. It has been suggested that interferons are too large in molecular weight to transfer into breast milk in clinically relevant amounts.[2]

1. American Academy of Pediatrics. The transfer of drugs and other chemicals into human milk. *Pediatrics* 2001; **108:** 776–89. Correction. *ibid.*; 1029. Also available at: http://aappolicy.aappublications.org/cgi/content/full/pediatrics%3b108/3/776 (accessed 12/06/08)
2. Kumar AR, *et al.* Transfer of interferon alfa into human breast milk. *J Hum Lact* 2000; **16:** 226–8.

Psychiatric disorders. For comment on the risk of mood disorders in patients with a history of such disorders, see Effects on the Nervous System and Mental State, above.

Interactions

Interactions involving interferons have not been fully evaluated, but it is known that they can inhibit hepatic oxidative metabolism via cytochrome P450 enzymes; the clinical relevance of this interaction is unclear and thus caution should be exercised during use with drugs metabolised in this way. Studies with peginterferon alfa showed increased activity of the cytochrome P450 isoenzymes CYP2C8/9 and CYP2D6; caution is advised when giving peginterferon alfa with drugs that are metabolised by these isoenzymes, such as warfarin, phenytoin, and flecainide. Interferon and peginterferon alfa have been shown to inhibit the metabolism of theophylline which is metabolised via the cytochrome P450 isoenzyme CYP1A2. Drugs likely to exacerbate the haematological effects of interferons, such as ribavirin and zidovudine, should also be used with caution. Interferons may also increase the neurotoxic and cardiotoxic effects of other drugs.

ACE inhibitors. For a report of possible synergistic haematological toxicity in patients receiving interferon alfa and ACE inhibitors, see p.1196.

Anticoagulants. For reference to potentiation of *acenocoumarol* or *warfarin* necessitating dosage reduction in patients also receiving interferon alfa, see p.1430.

Antineoplastics. For reduction in the area under the plasma concentration-time curve for *melphalan* in patients receiving interferon alfa, see p.742.

Antivirals. For a report of synergistic bone-marrow toxicity with interferon alfa and *zidovudine*, see p.915.

Paracetamol. Three patients had increases in liver enzyme values when given paracetamol 1 g two or three times daily on the same three days each week as interferon alfa; vinblastine was also given every third week.[1] Paracetamol has also been found to enhance the antiviral effect of interferon alfa in healthy subjects.[2]

1. Kellokumpu-Lehtinen P, *et al.* Hepatotoxicity of paracetamol in combination with interferon and vinblastine. *Lancet* 1989; **i:** 1143.
2. Hendrix CW, *et al.* Modulation of α-interferon's antiviral and clinical effects by aspirin, acetaminophen, and prednisone in healthy volunteers. *Antiviral Res* 1995; **28:** 121–31.

Thalidomide. For reports of toxicity associated with interferons and thalidomide, see p.2398.

Theophylline. For reference to reduced clearance of theophylline in patients receiving interferon alfa, see p.1144.

Antiviral Action

Interferons are naturally occurring proteins produced by eukaryotic cells in response to viral infection and other biological inducers that confer protection on uninfected cells of the same species. They are cytokines that affect many cell functions and have, in addition to their antiviral activity, antiproliferative and immunoregulatory properties. Three major classes have been identified: alfa, beta and gamma. Interferon alfa and beta are classified as Type I interferons and interferon gamma is a Type II interferon. These interferons have overlapping but clearly distinct biological activities; interferon gamma in particular is a potent macrophage-stimulating factor.

Interferons exert their biological effect by binding to specific receptors on the surface of human cells. After binding, a cascade of intracellular events, including the induction of certain enzymes, occurs. This process is thought to be responsible for the various cellular responses to interferon, including inhibition of virus replication in virus-infected cells, suppression of cell proliferation and such immunomodulating activities as enhancement of the phagocytic activity of macrophages and augmentation of the specific cytotoxicity of lymphocytes for target cells.

Pegylated interferons have similar, but possibly slightly weaker, actions to the native forms.

Studies have shown interferons to have benefit in infections with hepatitis B virus, hepatitis C virus, herpes simplex viruses, varicella-zoster virus, CMV, rhinoviruses, and papillomaviruses.

Pharmacokinetics

Interferons are not absorbed from the gastrointestinal tract. More than 80% of a subcutaneous or intramuscular dose of interferon alfa is absorbed. After intramuscular injection, interferon alfa produced by recombinant techniques and that from cultured leucocytes produce similar plasma concentrations although there is a large interindividual variation. Plasma concentrations are dose-related; and peak concentrations are usually reached within 4 to 8 hours returning to baseline by 16 to 24 hours. After intravenous doses, serum interferon levels decline at a slightly faster rate than after subcutaneous or intramuscular use and are undetectable 4 hours after infusion. After systemic use low levels of interferon are detected in respiratory secretions, CSF, eye, and brain. The elimination half-life of interferon alfa is about 2 to 7 hours after subcutaneous or intramuscular injections and 2 hours after intravenous infusion. Interferon alfa undergoes renal catabolism and negligible amounts of interferons are excreted in the urine; biliary excretion and liver metabolism are minor pathways of elimination.

The attachment of interferon to large inert macrogol (polyethylene glycol; PEG) molecules, termed pegylation, substantially reduces the rate of absorption and excretion of interferon and increases the plasma concentration. After a subcutaneous dose of peginterferon alfa-2b the maximum serum concentration is attained in about 15 to 44 hours and high concentrations are sustained for 48 to 72 hours; the mean elimination half-life is approximately 40 hours. The maximum serum concentration of peginterferon alfa-2a is attained about 72 to 96 hours after subcutaneous dosing and the mean terminal half-life is approximately 160 hours. The absolute bioavailability of peginterferon alfa-2a is 84% and is similar to that of unmodified interferon alfa-2a.

◊ Reviews.

1. Zeuzem S, *et al.* Pharmacokinetics of peginterferons. *Semin Liver Dis* 2003; **23** (suppl 1): 23–8.
2. Pedder SC. Pegylation of interferon alfa: structural and pharmacokinetic properties. *Semin Liver Dis* 2003; **23** (suppl 1): 19–22.
3. Caliceti P. Pharmacokinetics of pegylated interferons: what is misleading? *Dig Liver Dis* 2004; **36** (suppl 3): S334–9.

Uses and Administration

The interferons are cytokines that have a range of activities. In addition to their action against viruses they are active against malignant neoplasms and have an immunomodulating effect. Several alfa interferons are available: interferon alfa-2a (rbe), interferon alfa-2b (rbe), alfa-n3 (bls), alfacon-1 (rbe), and the pegylated interferons peginterferon alfa-2a (rbe) and peginterferon alfa-2b (rbe).

Alfa interferons are used in chronic hepatitis B (*alfa-2a and its pegylated form and alfa-2b*) and chronic hepatitis C (*alfa-2a and its pegylated form, alfa-2b and its pegylated form, and alfacon-1*); in several malignant neoplasms including AIDS-related Kaposi's sarcoma (*alfa-2a and alfa-2b*), hairy-cell leukaemia (*alfa-2a and alfa-2b*), chronic myeloid leukaemia (*alfa-2a and alfa-2b*), follicular lymphoma (*alfa-2a and alfa-2b*), cutaneous T-cell lymphoma (*alfa-2a*), carcinoid tumours (*alfa-2b*), melanoma (*alfa-2a and alfa-2b*), multiple myeloma (*alfa-2b*), and renal cell carcinoma (*alfa-2a*); and in condylomata acuminata (*alfa-2b and alfa-n3*).

ADMINISTRATION AND DOSAGE. Dosage regimens for alfa interferons are as follows:

- **Chronic active hepatitis B.** *Interferon alfa-2a* is given in a dose of 2.5 to 5 million units/m^2 three times weekly by subcutaneous injection for 4 to 6 months. *Peginterferon alfa-2a* is given in a dose of 180 micrograms once weekly subcutaneously for 48 weeks. *Interferon alfa-2b* is given in a dose of 5 to 10 million units three times weekly for 4 to 6 months, or 5 million units daily for 16 weeks, by subcutaneous or intramuscular injection.
- **Chronic hepatitis C.** *Interferon alfa-2a* is given in a dose of 3 to 4.5 million units three times weekly by subcutaneous injection for 6 months when it is used with ribavirin. In patients unable to tolerate ribavirin, interferon alfa-2a monotherapy is given either in an initial dose of 3 to 6 million units three times weekly for 6 months followed by 3 million units three times weekly for an additional 6 months, or in a dose of 3 million units three times weekly for 12 months, by subcutaneous injection. *Peginterferon alfa-2a* is given in a dose of 180 micrograms once weekly subcutaneously, with ribavirin or as monotherapy, for 24 to 48 weeks (depending on genotype). *Interferon alfa-2b* is given in a dose of 3 million units three times weekly for 6 to 12 months (depending on genotype) with ribavirin or, when given as monotherapy, for 6 to 18 months, or for up to 24 months (depending on genotype), by subcutaneous or intramuscular injection. *Peginterferon alfa-2b* is given subcutaneously in a dose of 1.5 micrograms/kg once weekly for 24 to 48 weeks with ribavirin, or in a dose of 0.5 or 1 microgram/kg once weekly for 24 to 48 weeks when given as monotherapy. *Interferon alfacon-1* is given in a dose of 9 micrograms three times weekly by subcutaneous injection for 24 weeks followed by 15 micrograms three times weekly for up to 48 weeks if necessary.
- **AIDS-related Kaposi's sarcoma.** *Interferon alfa-2a* is usually given in an escalating dose of 3 million units daily for 3 days, 9 million units daily for 3 days, 18 million units daily for 3 days, and 36 million units daily, if tolerated, on days 10 to 84, by subcutaneous injection; thereafter the maximum tolerated dose (up to 36 million units) may be given three times weekly. *Interferon alfa-2b* is given in a dose of 30 million units/m^2 three times weekly, by subcutaneous or intramuscular injection.
- **Hairy-cell leukaemia.** *Interferon alfa-2a* is given in an initial subcutaneous dose of 3 million units daily for 16 to 24 weeks, then the same dose three times weekly, by subcutaneous injection. Treatment has continued for up to 24 months. *Interferon alfa-2b* is given in a dose of 2 million units/m^2 three times weekly by subcutaneous or intramuscular injection for up to 6 months or more.

- **Chronic myeloid leukaemia.** *Interferon alfa-2a* is given by subcutaneous injection in an escalating dose of 3 million units daily for 3 days, 6 million units daily for 3 days, and 9 million units daily thereafter. Patients showing a response after 12 weeks should continue treatment until a complete haematological response is achieved or for a maximum of 18 months; those who achieve a complete haematological response should continue on 9 million units daily (or a minimum of 9 million units three times weekly) in order to achieve a cytogenetic response. *Interferon alfa-2b* is given in a dose of 4 to 5 million units/m^2 daily by subcutaneous injection, continuing at the maximum tolerated dose to maintain remission (usually 4 to 5 million units/m^2 daily).
- **Follicular lymphoma.** *Interferon alfa-2a* is given as an adjunct to chemotherapy in a dose of 6 million units/m^2 daily by subcutaneous injection on days 22 to 26 of each 28-day chemotherapy cycle. *Interferon alfa-2b* is given as an adjunct to chemotherapy in a dose of 5 million units three times weekly by subcutaneous injection for 18 months.
- **Cutaneous T-cell lymphoma.** *Interferon alfa-2a* is given by subcutaneous injection in an escalating dose of 3 million units daily for 3 days, then 9 million units daily for 3 days, and then 18 million units daily to complete 12 weeks of treatment. The maximum tolerated dose (up to 18 million units) is then given three times weekly for a minimum of 12 months in responding patients.
- **Carcinoid tumours.** *Interferon alfa-2b* is given in a dose of 3 to 9 million units (usually 5 million units) three times weekly by subcutaneous injection. In advanced disease, 5 million units may be given daily.
- **Melanoma.** *Interferon alfa-2a* is given in a dose of 3 million units three times weekly by subcutaneous injection for 18 months. Treatment should start no later than 6 weeks after surgery. *Interferon alfa-2b* is given in an initial dose of 20 million units/m^2 daily on 5 days each week for 4 weeks by intravenous infusion over 20 minutes, and then for maintenance 10 million units/m^2 three times weekly by subcutaneous injection for 48 weeks.
- **Multiple myeloma.** *Interferon alfa-2b* is given as maintenance treatment following chemotherapy induction at a dose of 3 million units/m^2 three times weekly by subcutaneous injection.
- **Renal cell carcinoma.** *Interferon alfa-2a* is given as an adjunct to cytotoxic chemotherapy in an escalating dose of 3 million units three times weekly for one week, then 9 million units three times weekly for one week, then 18 million units three times weekly thereafter for 3 to 12 months, by subcutaneous injection.
- **Condylomata acuminata.** *Interferon alfa-2b* is given in a dose of 1 million units injected into each lesion three times weekly for 3 weeks, and repeated after 12 to 16 weeks if necessary. No more than 5 lesions should be treated in each treatment course. *Interferon alfa-n3* is given in a dose of 0.25 million units per lesion twice weekly for up to 8 weeks, to a maximum of 2.5 million units in each session.

See below for further details of these as well as some other uses of alfa interferons.

◊ General reviews of interferons.

1. Volz MA, Kirkpatrick CH. Interferons 1992: how much of the promise has been realised? *Drugs* 1992; **43:** 285–94.
2. Dorr RT. Interferon-α malignant and viral diseases: a review. *Drugs* 1993; **45:** 177–211.
3. Haria M, Benfield P. Interferon-α-2a: a review of its pharmacological properties and therapeutic use in the management of viral hepatitis. *Drugs* 1995; **50:** 873–96.
4. Ruszczak Z, Schwartz RA. Interferons in dermatology: biology, pharmacology, and clinical applications. *Adv Dermatol* 1997; **13:** 235–88.
5. Edwards L. The interferons. *Dermatol Clin* 2001; **19:** 139–46, ix.
6. Moschos S, *et al.* Interferons in the treatment of solid tumors. *Cancer Treat Res* 2005; **126:** 207–41.
7. Pestka S. The interferons: 50 years after their discovery, there is much more to learn. *J Biol Chem* 2007; **282:** 20047–51.

Age-related macular degeneration. In age-related macular degeneration (senile macular degeneration), a common cause of visual impairment in the elderly, there is a gradual and progressive deterioration of central vision usually affecting both eyes (p.785). Although some encouraging preliminary results[1-4] have been obtained with interferon alfa, controlled data showed no benefit after treatment for one year.[5]

1. Fine SL, *et al.* Age-related macular degeneration. *N Engl J Med* 2000 **342:** 483–92.
2. Arnold JJ, Sarks SH. Extracts from "clinical evidence": age related macular degeneration. *BMJ* 2000 **321:** 741–4.
3. Comer GM, *et al.* Current and future treatment options for non-exudative and exudative age-related macular degeneration. *Drugs Aging* 2004 **21:** 967–92.
4. Sun JK, Miller JW. Medical treatment of choroidal neovascularization secondary to age-related macular degeneration. *Int Ophthalmol Clin* 2005 **45:** 115–32.
5. Pharmacological Therapy for Macular Degeneration Study Group. Interferon alfa-2a in ineffective for patients with choroidal neovascularization secondary to age-related macular degeneration: results of a prospective randomized placebo-controlled clinical trial. *Arch Ophthalmol* 1997; **115:** 865–72.

Angiomatous disease. Encouraging responses were reported in 4 of 5 children treated with interferon alfa-2a for various angiomatous diseases.[1] Regression of haemangioma size by more than 50% was achieved in 11 of 18 infants and children given interferon alfa-2a for 1 to 5 months,[2] and in 11 of 19 children treated for at least 4 months.[3] Interferon alfa-2b has also been found to cause regression of haemangioma in 27 of 38 children treated for at least 6 months.[4] In addition, there have been reports of the successful use of interferon alfa-2b to treat infantile giant cell angioblastoma[5] and pelvic metastases of adult haemangioendothelioma of the liver.[6]

The use of interferons as anti-angiogenic agents has been reviewed.[7]

1. White CW, *et al.* Treatment of childhood angiomatous diseases with recombinant interferon alfa-2a. *J Pediatr* 1991; **118:** 59–66.
2. Deb G, *et al.* Treatment of hemangiomas of infants and babies with interferon alfa-2a: preliminary results. *Int J Pediatr Hematol/Oncol* 1996; **3:** 109–13.
3. Greinwald JH, *et al.* An update on the treatment of hemangiomas in children with interferon alfa-2a. *Arch Otolaryngol Head Neck Surg* 1999; **125:** 21–7.
4. Garmendía G, *et al.* Regression of infancy hemangiomas with recombinant IFN-α 2b. *J Interferon Cytokine Res* 2001; **21:** 31–8.
5. Marler JJ, *et al.* Successful antiangiogenic therapy of giant cell angioblastoma with interferon alfa 2b: report of 2 cases. *Pediatrics* 2002; **109:** e37. Also available at: http://pediatrics.aappublications.org/cgi/content/full/109/2/e37 (accessed 12/06/08)
6. Kayler LK, *et al.* Epithelioid hemangioendothelioma of the liver disseminated to the peritoneum treated with liver transplantation and interferon alpha-2B. *Transplantation* 2002; **74:** 128–30.
7. Lindner DJ. Interferons as antiangiogenic agents. *Curr Oncol Rep* 2002; **4:** 510–14.

Behçet's syndrome. Behçet's syndrome (p.1499) is a systemic inflammatory disorder characterised by recurrent attacks of oral aphthous ulcers, genital ulcers, skin lesions, uveitis or other manifestations affecting the blood vessels, gastrointestinal tract, and respiratory and central nervous systems. Treatment is essentially symptomatic and empirical. A review of the literature[1] identified 338 patients who had been given interferon alfa (264 patients had received interferon alfa-2a and 74 interferon alfa-2b). Mucocutaneous symptoms improved in 86% of the patients; articular manifestations were present in 90 patients and 95% of them showed a partial or complete response to interferon alfa treatment. Ocular manifestations were present in 182 patients and 94% of them showed a partial or complete response to treatment. Higher doses were reported to be more effective than low-dose regimens. A review[2] on the management of Behçet's syndrome reported that treatment with interferon-alfa during an inflammatory attack improved the duration of and pain associated with oral aphthous ulcers; beneficial effects were also reported in patients with ocular manifestations. Randomised, controlled studies had shown that interferon alfa prevented recurrent attacks and it was considered to be effective in suppressing more severe systemic features, as well as mucocutaneous ones. Open studies with interferon alfa indicated that it might be of benefit in patients with disease resistant to conventional immunosuppressive treatments.

1. Kötter I, *et al.* The use of interferon alpha in Behçet disease: review of the literature. *Semin Arthritis Rheum* 2004; **33:** 320–35.
2. Gul A. Standard and novel therapeutic approaches to Behçet's disease. *Drugs* 2007; **67:** 2013–22.

Blood disorders. Interferon alfa may be used in the management of the myeloproliferative disorders such as *primary (essential) thrombocythaemia*[1-3] (p.654), *polycythaemia vera*,[1-4] (p.654) and *agnogenic myeloid metaplasia*.[2] Benefit has also been reported with interferon alfa in patients with HIV-associated thrombocytopenia,[5] although interferons have been reported to induce immune thrombocytopenia, and there has been a report of bleeding in a patient with idiopathic thrombocytopenic purpura (see Effects on the Blood under Adverse Effects, above).

In addition to case reports of interferon alfa producing improvements in patients with idiopathic *hypereosinophilic syndrome*[6-8] who had not responded to corticosteroids or hydroxycarbamide, studies have also shown beneficial responses to interferon alfa used alone[9] or with corticosteroids or hydroxycarbamide.[10,11]

See also under Malignant Neoplasms, below.

Paradoxically, interferon alfa has also been used with some success in patients with *thrombocytopenia* associated with hepatitis C.[12-14]

1. Elliott MA, Tefferi A. Interferon-alpha therapy in polycythemia vera and essential thrombocythemia. *Semin Thromb Hemost* 1997; **23:** 463–72.
2. Radin AI, *et al.* Eastern Cooperative Oncology Group. Phase II study of alpha2 interferon in the treatment of the chronic myeloproliferative disorders (E5487): a trial of the Eastern Cooperative Oncology Group. *Cancer* 2003; **98:** 100–109.
3. Jabbour E, *et al.* PEG-IFN-alpha-2b therapy in BCR-ABL-negative myeloproliferative disorders: final result of a phase 2 study. *Cancer* 2007; **110:** 2012–18.
4. Lengfelder E, *et al.*. Interferon alpha in the treatment of polycythemia vera. *Ann Hematol* 2000; **79:** 103–9.
5. Marroni M, *et al.* Interferon-α is effective in the treatment of HIV-1-related, severe, zidovudine-resistant thrombocytopenia. *Ann Intern Med* 1994; **121:** 423–9.
6. Zielinski RM, Lawrence WD. Interferon-α for the hypereosinophilic syndrome. *Ann Intern Med* 1990; **113:** 716–18.
7. Busch FW, *et al.* Alpha-interferon for the hypereosinophilic syndrome. *Ann Intern Med* 1991; **114:** 338–9.
8. Yoon T-Y, *et al.* Complete remission of hypereosinophilic syndrome after interferon-α therapy: report of a case and literature review. *J Dermatol* 2000; **27:** 110–15.
9. Butterfield JH, Gleich GJ. Interferon-α treatment of six patients with the idiopathic hypereosinophilic syndrome. *Ann Intern Med* 1994; **121:** 648–53.
10. Coutant G, *et al.* Traitement des syndromes hyperéosinophiliques à expression myeloproliferative par l'association hydroxyurée-interféron alpha. *Ann Med Interne (Paris)* 1993; **144:** 243–50.
11. Baratta L, *et al.* Favorable response to high-dose interferon-alpha in idiopathic hypereosinophilic syndrome with restrictive cardiomyopathy: case report and literature review. *Angiology* 2002; **53:** 465–70.
12. Uygun A, *et al.* Interferon treatment for thrombocytopenia associated with chronic HCV infection. *Int J Clin Pract* 2000; **54:** 683–4.
13. Rajan S, Liebman HA. Treatment of hepatitis C related thrombocytopenia with interferon alpha. *Am J Hematol* 2001; **68:** 202–9.
14. Benci A, *et al.* Thrombocytopenia in patients with HCV-positive chronic hepatitis: efficacy of leucocyte interferon-α treatment. *Int J Clin Pract* 2003; **57:** 17–19.

Churg-Strauss syndrome. For reports that interferon alfa may be beneficial in Churg-Strauss syndrome, see p.1501.

Hepatitis. Interferon alfa (including peginterferon alfa) is one of the main drugs used in the treatment of viral hepatitis B and C and chronic hepatitis B and C co-infection with HIV (p.851) and has been the subject of several general reviews.[1-3]

Interferon alfa was the first drug approved for the management of chronic **hepatitis B**. A meta-analysis[4] found that a significantly higher percentage of patients with chronic hepatitis B who were HBeAg-positive, and treated with interferon alfa for 3 to 6 months, became HbeAg-negative compared with the untreated control group. Interferon alfa was found to be most effective when it was used in patients with recently acquired hepatitis B infection, high pre-treatment ALT, and low hepatitis B DNA levels. Studies have suggested that subcutaneous peginterferon alfa is as effective or slightly more effective than interferon alfa given subcutaneously.[5] Results from various studies[6] have shown peginterferon alfa to be more effective than the antiviral lamivudine, in both HBeAg-positive[7] and HBeAg-negative patients with chronic hepatitis B,[8] when peginterferon alfa was given subcutaneously, once weekly for 48 weeks. However, the addition of lamivudine to peginterferon alfa did not significantly enhance efficacy.[8,9] Interferon alfa can produce benefit in some patients co-infected with chronic **hepatitis B and D**.[10] However, these co-infected patients are less responsive to interferon therapy than patients infected with hepatitis B virus alone. A study[10] with high-dose interferon alfa (9 million units) given 3 times a week for 48 weeks reported normalisation of ALT and inhibition of hepatitis D viral replication in 50% of the patients. However, relapse was common after treatment was stopped, although biochemical responses persisted for up to 4 years. Long-term follow-up of this same group of patients for 2 to 14 years revealed that high-dose interferon alfa may improve long-term outcome and patient survival.[11]

The first available treatment for **chronic hepatitis C** was interferon alfa-2b, and this was followed by interferon alfa-2a, given subcutaneously 3 times a week. A meta-analysis[12] of studies involving interferon treatment of hepatitis C suggested that treatment with interferon alfa 3 million units three times weekly for at least 12 months had the best risk-benefit ratio for patients with chronic hepatitis C. Studies[13,14] with once-weekly peginterferon alfa showed it to be more effective than interferon alfa given three times weekly in patients with chronic hepatitis C, including those with cirrhosis or extensive fibrosis.[15]

Combination therapy with interferon alfa and oral ribavirin for the treatment of chronic hepatitis C is more effective than either drug alone with sustained responses having been recorded, and is now generally considered to be the treatment of first choice.[16,17] A meta-analysis[18] of randomised studies has concluded that combination therapy is also more effective for chronic hepatitis C in patients who had failed to respond to interferon alone or to any other previous treatment. Studies[19,20] suggest that combination therapy with peginterferon alfa and ribavirin may be more effective and better tolerated than interferon alfa plus ribavirin. One study[19] with peginterferon alfa-2b or interferon alfa-2b and ribavirin showed a sustained virological response (SVR) of around 42% in patients with viral genotype 1, compared with about 80% in patients with genotypes 2 and 3. A review[21] of the use of peginterferon alfa with ribavirin has also concluded that this combination is superior to interferon alfa plus ribavirin or to peginterferon alfa alone. The British Society for Gastroenterology[22] and the American Association for the Study of Liver Diseases (AASLD)[23] recommend weekly subcutaneous peginterferon alfa with daily oral ribavirin as the first choice of treatment for chronic hepatitis C.

Guidelines for the management of **HIV and hepatitis B** co-infection have been developed by various expert groups.[24-26] In patients not requiring HIV therapy interferon alfa for 4 to 6 months

is considered suitable for non-cirrhotic HBeAg-positive patients, but limited evidence suggests that peginterferon alfa may be more effective.[24] Treatment of **HIV and hepatitis C** co-infected patients has been associated with a high rate of intolerance and a low rate of response. While combination therapy for hepatitis C is not as effective in co-infected patients as in those with hepatitis C alone, studies[27-29] have shown sustained virological responses with peginterferon alfa and ribavirin treatment in co-infected patients. Two studies[27,29] reported an SVR rate of 27% for patients given peginterferon alfa plus ribavirin as opposed to 12 to 20% in those treated with interferon alfa plus ribavirin. The APRICOT study group[28] reported an SVR rate of 40% for patients treated with peginterferon alfa plus ribavirin, compared with 20% for those given peginterferon alfa monotherapy and 12% for those given interferon alfa plus ribavirin. A much reduced rate of SVR to peginterferon alfa plus ribavirin therapy was found, however, in co-infected patients with hepatitis C virus genotype 1 (29%) compared with hepatitis C virus of genotypes 2 and 3 (62%) and further study is required to develop strategies for treating infection with genotype 1.[28,29] The British HIV Association guidelines[30] for the treatment and management of HIV and hepatitis C co-infection recommends combination therapy with peginterferon alfa and ribavirin for 48 weeks in patients with moderate liver disease and well controlled HIV disease. Similar recommendations have been made by the AASLD.[23] For further discussion on the management of chronic hepatitis B and C patients co-infected with HIV, see p.851.

Although antivirals are generally not required in **acute hepatitis**, treatment of acute hepatitis C with interferon alfa has been shown to produce more rapid resolution of viraemia[31] and may decrease the risk of chronic hepatitis developing.[32] Studies[33] with peginterferon alfa-2b, in a small number of patients with acute hepatitis C, have shown similar efficacy. The AASLD[23] recommends that either interferon or peginterferon alfa given for a period of at least 6 months should be considered for the treatment of acute hepatitis C if the infection persists 2 to 4 months after diagnosis. Similar views have been published by the Clinical Effectiveness Group of the British Association of Sexual Health and HIV[34] and by the Scottish Intercollegiate Guidelines Network.[35]

1. Plosker GL, Keating GM. Peginterferon-α-2a (40kD) plus ribavirin: a review of its use in hepatitis C virus and HIV co-infection. *Drugs* 2004; **64:** 2823–43.
2. Robins GW, *et al.* Peginterferon-α-2a (40kD): a review of its use in the management of patients with chronic hepatitis B. *Drugs* 2005; **65:** 809–25.
3. Keating GM, Plosker GL. Peginterferon α-2a (40KD) plus ribavirin: a review of its use in the management of patients with chronic hepatitis C and persistently 'normal' ALT levels. *Drugs* 2005; **65:** 521–36.
4. Wong DKH, *et al.* Effect of alpha-interferon treatment in patients with hepatitis B e antigen-positive chronic hepatitis B: a meta-analysis. *Ann Intern Med* 1993; **119:** 312–23.
5. Lok ASF, McMahon BJ. American Association for the Study of Liver Diseases. Chronic hepatitis B. *Hepatology* 2007; **45:** 507–39. Correction. *ibid.*; 1347. Also available at: http://www.aasld.org/practiceguidelines/Documents/Practice%20Guidelines/chronichepBcorrection.pdf (accessed 28/08/08)
6. Marcellin P, *et al.* Treatment of chronic hepatitis B. *J Viral Hepatitis* 2005; **12:** 333–45.
7. Lau GKK, *et al.* Peginterferon alfa-2a, lamivudine, and the combination for HBeAg-positive chronic hepatitis B. *N Engl J Med* 2005; **352:** 2682–95.
8. Marcellin P, *et al.* Peginterferon alfa-2a alone, lamivudine alone, and the two in combination in patients with HBeAg-negative chronic hepatitis B. *N Engl J Med* 2004; **351:** 1206–17.
9. Janssen HLA, *et al.* Pegylated interferon alfa-2b alone or in combination with lamivudine for HBeAg-positive chronic hepatitis B: a randomised trial. *Lancet* 2005; **365:** 123–9.
10. Farci P, *et al.* Treatment of chronic hepatitis D with interferon alfa-2a. *N Engl J Med* 1994; **330:** 88–94.
11. Farci P, *et al.* Long-term benefit of interferon α therapy of chronic hepatitis D: regression of advanced hepatic fibrosis. *Gastroenterology* 2004; **126:** 1740–9.
12. Poynard T, *et al.* Meta-analysis of interferon randomized trials in the treatment of viral hepatitis C: effects of dose and duration. *Hepatology* 1996; **24:** 778–89.
13. Zeuzem S, *et al.* Peginterferon alfa-2a in patients with chronic hepatitis C. *N Engl J Med* 2000; **343:** 1666–72.
14. Perry CM, Jarvis B. Peginterferon-α-2a (40 kD): a review of its use in the management of chronic hepatitis C. *Drugs* 2001; **61:** 2263–88.
15. Heathcote EJ, *et al.* Peginterferon alfa-2a in patients with chronic hepatitis C and cirrhosis. *N Engl J Med* 2000; **343:** 1673–80.
16. Scott LJ, Perry CM. Interferon-α-2b plus ribavirin: a review of its use in the management of chronic hepatitis C. *Drugs* 2002; **62:** 507–56.
17. Brok J, *et al.* Ribavirin plus interferon versus interferon for chronic hepatitis C. Available in The Cochrane Database of Systematic Reviews; Issue 2. Chichester: John Wiley; 2005 (accessed 13/06/08).
18. Cummings KJ, *et al.* Interferon and ribavirin vs interferon alone in the re-treatment of chronic hepatitis C previously nonresponsive to interferon: a meta-analysis of randomized trials. *JAMA* 2001; **285:** 193–9.
19. Manns MP, *et al.* Peginterferon alfa-2b plus ribavirin compared with interferon alfa-2b plus ribavirin for initial treatment of chronic hepatitis C: a randomised trial. *Lancet* 2001; **358:** 958–65.
20. Fried MW, *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection. *N Engl J Med* 2002; **347:** 975–82.
21. Keating GM, Curran MP. Peginterferon-α-2a (40kD) plus ribavirin: a review of its use in the management of chronic hepatitis C. *Drugs* 2003; **63:** 701–30.
22. Cramp M, Rosenberg W. British Society for Gastroenterology: guidance on the treatment of hepatitis C incorporating the use of pegylated interferons. 2003. Available at: http://www.bsg.org.uk/pdf_word_docs/pegylated_2003.doc (accessed 13/06/08)
23. Strader DB, *et al.*, American Association for the Study of Liver Diseases. Diagnosis, management, and treatment of hepatitis C. *Hepatology* 2004; **39:** 1147–71. Also available at: http://www.aasld.org/practiceguidelines/Documents/Practice%20Guidelines/hepatitisc.pdf (accessed 28/08/08)
24. Brook MG, *et al.* British HIV Association. BHIVA guidelines: HIV and chronic hepatitis: co-infection with HIV and hepatitis B virus infection. 2005. *HIV Med* 2005; **6** (suppl 2): 84–95. Also available at: http://www.bhiva.org/files/file1001581.pdf (accessed 13/06/08)
25. Soriano V, *et al.* Care of patients with chronic hepatitis B and HIV co-infection: recommendations from an HIV-HBV International Panel. *AIDS* 2005; **19:** 221–40. Correction. *ibid.*; 640.
26. Alberti A, *et al.* Short statement of the first European Consensus Conference on the treatment of chronic hepatitis B and C in HIV co-infected patients. *J Hepatol* 2005; **42:** 615–24. Correction. *ibid.*; **43:** 1098.
27. Carrat F, *et al.* Pegylated interferon alfa-2b vs standard interferon alfa-2b, plus ribavirin, for chronic hepatitis C in HIV-infected patients: a randomized controlled trial. *JAMA* 2004; **292:** 2839–48.
28. Torriani FJ, *et al.* Peginterferon alfa-2a plus ribavirin for chronic hepatitis C virus infection in HIV-infected patients. *N Engl J Med* 2004; **351:** 438–50.
29. Chung RT, *et al.* Peginterferon alfa-2a plus ribavirin versus interferon alfa-2a plus ribavirin for chronic hepatitis C in HIV-coinfected persons. *N Engl J Med* 2004; **351:** 451–9.
30. British HIV Association. BHIVA guidelines: HIV and chronic hepatitis: co-infection with HIV and hepatitis C virus infection. 2004. Available at: http://www.bhiva.org/files/file1001579.pdf (accessed 13/06/08)
31. Myers RP, *et al.* Interferon for acute hepatitis C. Available in The Cochrane Database of Systematic Reviews; Issue 4. Chichester: John Wiley; 2001 (accessed 13/06/08).
32. Jaeckel E, *et al.* Treatment of acute hepatitis C with interferon alfa-2b. *N Engl J Med* 2001; **345:** 1452–7.
33. Santantonio T, *et al.* Efficacy of a 24-week course of PEG-interferon α-2b monotherapy in patients with acute hepatitis C after failure of spontaneous clearance. *J Hepatol* 2005; **42:** 329–33.
34. Clinical Effectiveness Group (British Association of Sexual Health and HIV). United Kingdom national guideline on the management of the viral hepatitides A, B & C 2005 [under revision]. Available at: http://www.bashh.org/documents/117/117.pdf (accessed 28/08/08)
35. Scottish Intercollegiate Guidelines Network. Management of hepatitis C: a national clinical guideline (issued December 2006). Available at: http://www.sign.ac.uk/pdf/sign92.pdf (accessed 13/06/08)

Herpes simplex infections. Herpes simplex infections are commonly treated with aciclovir (see p.854), but beneficial responses to topical interferon alfa have been reported in genital herpes, although results are mixed.[1] Interferon alfa has also been reported to have benefit in the treatment of herpes keratitis. A systematic review[2] of interventions for herpes simplex epithelial keratitis found that interferon monotherapy had a slightly beneficial effect on dendritic epithelial keratitis, but no more than that of other antivirals and concluded that the use of an antiviral nucleoside with interferon seemed to speed healing.

1. Leung DT, Sacks SL. Current recommendations for the treatment of genital herpes. *Drugs* 2000; **60:** 1329–52.
2. Wilhelmus KR. Therapeutic interventions for herpes simplex virus epithelial keratitis. Available in The Cochrane Database of Systematic Reviews; Issue 1. Chichester: John Wiley; 2008 (accessed 13/06/08).

HIV infection and AIDS. Interferons have been tried with some success in the management of Kaposi's sarcoma and mycobacterial infections in patients with AIDS (see below and under Interferon Gamma, p.894, respectively).

Inflammatory bowel disease. Interferon alfa is one of many drugs that have been tried in inflammatory bowel disease (p.1697). A study[1] found that clinical remission was achieved in 26 of 28 patients with ulcerative colitis after 6 to 12 months of treatment with interferon alfa-2a. Partial remission was reported in 2 of 5 patients with Crohn's disease[2] given interferon alfa, but in another study in 12 patients[3] interferon alfa was of no benefit. Interferon beta has also been found to be of benefit for the treatment of ulcerative colitis unresponsive to corticosteroids.[4]

1. Sümer N, Palabiyikoğlu M. Induction of remission by interferon-α in patients with chronic active ulcerative colitis. *Eur J Gastroenterol Hepatol* 1995; **7:** 597–602.
2. Davidsen B, *et al.* Tolerability of interferon alpha-2b, a possible new treatment of active Crohn's disease. *Aliment Pharmacol Ther* 1995; **9:** 75–9.
3. Gasché C, *et al.* Prospective evaluation of interferon-α in treatment of chronic active Crohn's disease. *Dig Dis Sci* 1995; **40:** 800–4.
4. Musch E, *et al.* Induction and maintenance of clinical remission by interferon-β in patients with steroid-refractory active ulcerative colitis—an open long-term pilot trial. *Aliment Pharmacol Ther* 2002; **16:** 1233–9.

Kaposi's sarcoma. The various treatments used for Kaposi's sarcoma, including the role of HAART as first-line therapy in the AIDS-related form, are discussed on p.675. Interferon alfa has been used in AIDS-related Kaposi's sarcoma and in patients with the classical, nonepidemic form. In patients with AIDS-related Kaposi's sarcoma interferon alfa, either as monotherapy or with zidovudine, has shown benefit in HIV-positive patients provided they possess relatively elevated CD4+ T lymphocyte counts (greater than 150 cells/microlitre),[1] although other drugs have generally replaced interferon alfa as treatment for Kaposi's sarcoma.[2] Systemic and local therapy such as interferon alfa and chemotherapy may be combined with HAART.[3]

1. Jonasch E, Haluska FG. Interferon in oncological practice: review of interferon biology, clinical applications, and toxicities. *Oncologist* 2001; **6:** 34–55.
2. Krown SE. AIDS-associated Kaposi's sarcoma: is there still a role for interferon alfa? *Cytokine Growth Factor Rev* 2007; **18:** 395–402.
3. Aldenhoven M, *et al.* Therapeutic strategies for epidemic Kaposi's sarcoma. *Int J STD AIDS* 2006; 571–8.

Malignant neoplasms. Many reports have been published on the effects of interferons on various neoplasms; most have involved interferon alfa.

Interferons have become established in the treatment of a few malignant disorders, notably hairy-cell leukaemia (but see p.654), Kaposi's sarcoma (see above), and chronic myeloid leukaemia (p.653). Alfa interferons may improve the duration of remission in multiple myeloma,[1-4] but not necessarily survival.[2,5] Combination therapy including interferons has also been used in indolent low-grade non-Hodgkin's lymphoma (p.656) and interferon alfa has been used alone to maintain remission. In renal cell carcinoma (p.667) response to interferon alfa used with interleukin-2 has been promising, but toxicity high; interferon alfa alone produces very modest benefit.[6] Beneficial responses have also been reported in a number of other neoplasms including melanoma (p.673); carcinoid tumours[7] (p.643); myelodysplasia; cutaneous T cell lymphomas including mycosis fungoides (p.657); and in meningioma.[8,9] Interferons have been given locally as an adjunct to surgery for superficial bladder tumours (p.659) and intralesionally or perilesionally in basal cell carcinoma[10-12] and also for keloid scars.[13,14] Use of interferon alfa with fluorouracil has been tried in inoperable colorectal cancer but does not appear to be more beneficial than fluorouracil alone.[15] Interferon alfa given with zidovudine has produced encouraging results in adult T-cell leukaemia-lymphoma.[16] Peginterferon alfa has also been shown to be effective in the management of chronic myeloid leukaemia and solid tumours, including metastatic melanoma and renal cell carcinoma.[17]

1. Mandelli F, *et al.* Maintenance treatment with recombinant interferon alfa-2b in patients with multiple myeloma responding to conventional induction chemotherapy. *N Engl J Med* 1990; **322:** 1430–4.
2. Nordic Myeloma Study Group. Interferon-α2b added to melphalan-prednisone for initial and maintenance therapy in multiple myeloma: a randomized, controlled trial. *Ann Intern Med* 1996; **124:** 212–22.
3. Fritz E, Ludwig H. Interferon-α treatment in multiple myeloma: meta-analysis of 30 randomised trials among 3948 patients. *Ann Oncol* 2000; **11:** 1427–36.
4. Myeloma Trialists' Collaborative Group. Interferon as therapy for multiple myeloma: an individual patient data overview of 24 randomized trials and 4012 patients. *Br J Haematol* 2001; **113:** 1020–34.
5. Österborg A, *et al.* Natural interferon-α in combination with melphalan/prednisone versus melphalan/prednisone in the treatment of multiple myeloma stages II and III: a randomized study from the myeloma group of central Sweden. *Blood* 1993; **81:** 1428–34.
6. Medical Research Council Renal Cancer Collaborators. Interferon-α and survival in metastatic renal carcinoma: early results of a randomised controlled study. *Lancet* 1999; **353:** 14–17.
7. Kölby L, *et al.* Randomized clinical trial of the effect of interferon α on survival in patients with disseminated midgut carcinoid tumours. *Br J Surg* 2003; **90:** 687–93.
8. Wöber-Bingöl Ç, *et al.* Interferon-alfa-2b for meningioma. *Lancet* 1995; **345:** 331.
9. Kaba SE, *et al.* The treatment of recurrent unresectable and malignant meningiomas with interferon alpha-2B. *Neurosurgery* 1997; **40:** 271–5.
10. Kowalzick L, *et al.* Intralesional recombinant interferon beta-1a in the treatment of basal cell carcinoma: results of an open-label multicentre study. *Eur J Dermatol* 2002; **12:** 558–61.
11. Bostanci S, *et al.* Treatment of basal cell carcinoma located in the head and neck region with intralesional interferon alpha-2a: evaluation of long-term follow-up results. *Clin Drug Investig* 2005; **25:** 661–7.
12. Tucker SB, *et al.* Long-term follow-up of basal cell carcinomas treated with perilesional interferon alfa 2b as monotherapy. *J Am Acad Dermatol* 2006; **54:** 1033–8.
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14. Larrabee WF, *et al.* Intralesional interferon gamma treatment for keloids and hypertrophic scars. *Arch Otolaryngol Head Neck Surg* 1990; **116:** 1159–62.
15. Thirion P, *et al.* Alpha-interferon does not increase the efficacy of 5-fluorouracil in advanced colorectal cancer: Meta-analysis Group in Cancer. *Br J Cancer* 2001; **84:** 611–20.
16. Gill PS, *et al.* Treatment of adult T-cell leukemia-lymphoma with a combination of interferon alfa and zidovudine. *N Engl J Med* 1995; **332:** 1744–8.
17. Bukowski RM, *et al.* Treating cancer with PEG Intron: pharmacokinetic profile and dosing guidelines for an improved interferon-alpha-2b formulation. *Cancer* 2002; **95:** 389–96.

Mycobacterial infections. For the use of interferon alfa in mycobacterial infections, see Interferon Gamma, p.894.

Progressive multifocal leukoencephalopathy. Beneficial responses were reported in patients with HIV-associated progressive multifocal leukoencephalopathy (PML) after treatment with interferon alfa.[1] Daily intramuscular interferon alfa therapy for 2 weeks also resulted in some neurologic improvement in a patient identified as an asymptomatic human T-lymphotropic virus type I carrier, who developed PML and pneumocystis pneumonia.[2] However, in a retrospective analysis[3] of the relative value of HAART and interferon alfa in the treatment of PML associated with AIDS, prolonged survival associated with interferon alfa

was found to be not independent of the effects of HAART and it was concluded that interferon alfa provided no additional benefit.

1. Huang SS, *et al.* Survival prolongation in HIV-associated progressive multifocal leukoencephalopathy treated with alpha-interferon: an observational study. *J Neurovirol* 1998; **4:** 324–32.
2. Kimura A, *et al.* Progressive multifocal leukoencephalopathy in an HTLV-I carrier. *Clin Neurol Neurosurg* 2006; **108:** 768–71.
3. Geschwind MD, *et al.* The relative contributions of HAART and alpha-interferon for therapy of progressive multifocal leukoencephalopathy in AIDS. *J Neurovirol* 2001; **7:** 353–7.

Skin disorders. For the use of interferon alfa in skin disorders associated with raised IgE concentrations, see Interferon Gamma, p.894.

Warts. Various interferons have been tried by various routes in the treatment of anogenital warts (condylomata acuminata) (p.1584).

Intralesional injection has been used to ensure relatively high concentrations of interferon in the wart but the occurrence of systemic adverse effects shows that there is absorption from this site. Complete responses were reported[1] in 36% of patients given intralesional interferon alfa-2b compared with 17% given placebo, and a corresponding overall reduction in the affected area of 62.4% compared with 1.2% respectively. However, follow-up was not sufficiently long to comment on relapse rates. Another study[2] found similar responses using interferons alfa-2b, alfa-n1, or beta in patients with refractory warts, with complete responses in 47% of patients given intralesional interferons compared with 22% of patients given placebo. A study[3] evaluating two different doses of intralesional interferon beta given three times weekly for 3 weeks reported complete responses in 63% of lesions injected with 1 million units compared with 38% of lesions injected with 33 000 units. Good responses have also been reported in patients with both refractory and recurrent warts given intralesional interferon alfa-n3.[4] Relapses were delayed and fewer warts recurred in patients who had received interferon rather than placebo. Intralesional interferon alfa-2b used with podophyllum was more effective that podophyllum alone,[5] although about 66% of patients in each group subsequently relapsed. A systematic review concluded that based on limited available evidence intralesional interferons may have a therapeutic effect, but have no significant advantage over simpler and safer treatments.[6]

Topical application of interferon alfa has also been reported to be more effective than podophyllotoxin.[7,8] Interferon beta has also been applied topically after surgical removal of warts.[9]

Theoretically, *systemic* use should have advantages in controlling subclinical infections and reducing relapses. However, responses to subcutaneous interferon alfa have generally been disappointing[10-12] although responses comparable with cautierisation and a reduction in relapse rates with either subcutaneous or intramuscular interferon alfa-2b have been obtained.[13] Information on the use of systemic interferons as an adjunct to conventional therapy is scarce but a study in 97 patients[14] with recurrent warts found no difference in either response or relapse rates in patients given cryotherapy with subcutaneous interferon alfa or cryotherapy alone. A study comparing subcutaneous interferon alfa, beta, and gamma used with cryotherapy found no significant difference in response rate, although patients given interferon beta or gamma developed new warts at a lower frequency.[15]

Intralesional plus subcutaneous interferon alfa has also been tried in treatment of oral warts; 4 HIV-positive patients with recurrent oral warts that had failed to respond to surgery and other treatments responded to interferon alfa treatment.[16]

1. Eron LJ, *et al.* Interferon therapy for condylomata acuminata. *N Engl J Med* 1986; **315:** 1059–64.
2. Reichman RC, *et al.* Treatment of condyloma acuminatum with three different interferons administered intralesionally: a double-blind, placebo-controlled trial. *Ann Intern Med* 1988; **108:** 675–9.
3. Monsonego J, *et al.* Randomised double-blind trial of recombinant interferon-beta for condyloma acuminatum. *Genitourin Med* 1996; **72:** 111–14.
4. Friedman-Kien AE, *et al.* Natural interferon alfa for treatment of condylomata acuminata. *JAMA* 1988; **259:** 533–8.
5. Douglas JM, *et al.* A randomized trial of combination therapy with intralesional interferon α and podophyllin versus podophyllin alone for the therapy of anogenital warts. *J Infect Dis* 1990; **162:** 52–9.
6. Gibbs S, Harvey I. Topical treatments for cutaneous warts. Available in The Cochrane Database of Systematic Reviews; Issue 3. Chichester: John Wiley; 2006 (accessed 13/06/08).
7. Syed TA, *et al.* Human leukocyte interferon-alpha versus podophyllotoxin in cream for the treatment of genital warts in males: a placebo-controlled, double-blind, comparative study. *Dermatology* 1995; **191:** 129–32.
8. Syed TA, *et al.* Management of genital warts in women with human leukocyte interferon-α vs podophyllotoxin in cream: a placebo-controlled, double-blind, comparative study. *J Mol Med* 1995; **73:** 255–8.
9. Gross G, *et al.* Recombinant interferon beta gel as an adjuvant in the treatment of recurrent genital warts: results of a placebo-controlled double-blind study in 120 patients. *Dermatology* 1998; **196:** 330–4.
10. Reichman RC, *et al.* Treatment of condyloma acuminatum with three different interferon-α preparations administered parenterally: a double-blind, placebo-controlled trial. *J Infect Dis* 1990; **162:** 1270–6.
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12. Condylomata International Collaborative Study Group. Recurrent condylomata acuminata treated with recombinant interferon alpha-2a: a multicenter double-blind placebo-controlled clinical trial. *Acta Derm Venereol (Stockh)* 1993; **73:** 223–6.
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14. Eron LJ, *et al.* Recurrence of condylomata acuminata following cryotherapy is not prevented by systemically administered interferon. *Genitourin Med* 1993; **69:** 91–3.
15. Bonnez W, *et al.* A randomized, double-blind, placebo-controlled trial of systemically administered interferon-α, -β, or -γ in combination with cryotherapy for the treatment of condyloma acuminatum. *J Infect Dis* 1995; **171:** 1081–9.
16. Lozada-Nur F, *et al.* Use of intralesional interferon-alpha for the treatment of recalcitrant oral warts in patients with AIDS: a report of 4 cases. *Oral Surg Oral Med Oral Pathol Oral Radiol Endod* 2001; **92:** 617–22.

Preparations

Proprietary Preparations (details are given in Part 3)

Arg.: Avirostat; Bioferon; INF; Infostat; Inmutag†; Inter 2-B; Intron A Peg†; Intron A†; Pegasys; Roferon-A†; ***Austral.:*** Intron A; Pegasys; PegIntron; Roferon-A; ***Austria:*** IntronA; PegIntron; Roferon-A; ***Belg.:*** Infergen†; IntronA; Pegasys; PegIntron; Roferon-A; ***Braz.:*** Beferon; Blauferon; Intron A; Kinnoferon 2A; Pegasys; PegIntron; Roferon-A; ***Canad.:*** Infergen; Intron A; Pegasys; PegIntron†; Roferon-A†; Unitron PEG; ***Chile:*** Intermax-Alpha; Intron A†; IntronA; Pegasys; PegIntron; Roferon-A†; ***Cz.:*** Alfaferone; Infergen†; Interferon Alfanative†; Intron A; Pegasys; PegIntron; Roferon-A; Viraferon; ViraferonPeg; Wellferon†; ***Denm.:*** IntronA; Pegasys; PegIntron; Roceron-A†; ***Fin.:*** Finnferon-Alpha†; IntronA; Pegasys; PegIntron; Roferon-A; ***Fr.:*** Infergen; IntronA; Pegasys; Roferon-A; Viraferon; ViraferonPeg; ***Ger.:*** Inferax; IntronA; Pegasys; PegIntron; Roferon-A; ***Gr.:*** Infergen; IntronA; Pegasys; PegIntron; Roferon-A; ***Hong Kong:*** Intron A; Pegasys; PegIntron; Roferon-A; ***Hung.:*** Egiferon; Infergen†; Intron A; Pegasys; PegIntron; Roferon-A; ***India:*** Roferon-A; ***Indon.:*** Interferon Alfanative; IntronA; Kalferon; Pegasys; PegIntron; ***Irl.:*** IntronA; Pegasys; PegIntron†; Roferon-A; ViraferonPeg; ***Israel:*** Intron A; Pegasys; PegIntron; Roferon-A; ***Ital.:*** Alfaferone; Alfater; Biaferone; Cilferon-A†; Haimaferone†; Humoferon†; Infergen; IntronA; Isiferone†; Pegasys; PegIntron; Roferon-A; Wellferon†; ***Jpn:*** Canferon; OIF; Pegasys; Roferon-A; Sumiferon; ***Malaysia:*** Intron A; Pegasys; PegIntron; Roferon-A; ***Mex.:*** Alferon; Altemol†; Intron A; Lemeron; Pegasys; Pegtron; Proquiferon; Roferon-A; Urifron; Viraferon†; ***Neth.:*** Infergen; IntronA; Pegasys; PegIntron; Roferon-A; Viraferon; ViraferonPeg; ***Norw.:*** IntronA; Pegasys; PegIntron; Roceron; ***NZ:*** Intron A; Pegasys; PegIntron; Roferon-A; ***Philipp.:*** Intron A; Pegasys; PegIntron; Roferon-A; ***Pol.:*** Alfaferone; Intron A; Pegasys; PegIntron; Roferon-A; ***Port.:*** Intron A; Pegasys; PegIntron; Roferon-A; Viraferon; ViraferonPeg; ***Rus.:*** Interal; Pegasys (Пегасис); PegIntron (Пегинтрон); Realdiron (Реальдирон); Roferon-A (Роферон-А); Viferon (Виферон); Wellferon (Веллферон); ***S.Afr.:*** Intron A; Multiferon; Pegasys; PegIntron; Roferon-A; ***Singapore:*** Intron A; Pegasys; PegIntron; Roferon-A†; ***Spain:*** Intron A; Pegasys; PegIntron; Roferon-A; ***Swed.:*** IntronA; Multiferon; Pegasys; PegIntron; Roferon-A; ***Switz.:*** Intron A; Pegasys; PegIntron; Roferon-A; ***Thai.:*** Bioferon; Intron A; Pegasys; PegIntron; Roferon-A†; Wellferon†; ***Turk.:*** Intron A; Pegasys; PegIntron; Roferon-A; ***UK:*** IntronA; Pegasys; PegIntron; Roferon-A; Viraferon; ViraferonPeg; ***USA:*** Alferon N; Infergen; Intron A; Pegasys; PegIntron; Roferon-A†; ***Venez.:*** Intron; Intron A; Pegasys; PegIntron; Roferon-A.

Multi-ingredient: ***Arg.:*** Bioferon Hepakit; Pegatron†; Rebetron†; ***Austral.:*** Pegasys RBV; Pegatron; Rebetron; ***Canad.:*** Pegasys RBV; Pegetron; Rebetron†; ***Mex.:*** Hepatron C; Pegtron Cotronak Kit; ***NZ:*** Pegasys RBV; Pegatron; Rebetron; Roferon-A RBV; ***Philipp.:*** Pegasys RBV; ***S.Afr.:*** Rebetron†; ***Switz.:*** Intron A/Rebetol†; ***USA:*** Rebetron†.

Interferon Beta *(BAN, rINN)*

IFN-β; Interferón-β; Interferon-β; Interferón beta; Interféron bêta; Interferoni beta; Interferonum Beta; SH-Y-579A (interferon beta-1b).

Интерферон Бета

CAS — 74899-71-1 (interferon beta); 145258-61-3 (interferon beta-1a); 145155-23-3 (interferon beta-1b); 90598-63-3 (interferon beta-1b).

ATC — L03AB02 (natural); L03AB07 (1a); L03AB08 (1b).

ATC Vet — QL03AB02 (natural); QL03AB07 (1a); QL03AB08 (1b).

NOTE. Interferon beta was previously known as fibroblast interferon.

Interferon beta-1a and Interferon beta-1b are both *USAN*.

Nomenclature. Interferon beta may be derived from fibroblasts, or produced by recombinant DNA technology. Sub-species of the human beta gene produce interferon beta with protein variants designated by a number (as in interferon beta-1). Interferon beta-1 is further qualified by a letter to indicate the amino-acid sequences at positions 1 and 17, and to indicate whether or not glycosylation is present:

- interferon beta-1a has methionine at position 1 and cysteine at 17 and is glycosylated at position 80
- interferon beta-1b has serine at position 17 and is not glycosylated

The name may be further elaborated on the label by approved sets of initials in parentheses to indicate the method of production: (rch) indicates production from genetically engineered Chinese hamster ovary cells; (rbe) indicates production from bacteria (*Escherichia coli*) genetically modified by recombinant DNA technology.

Adverse Effects

As for interferons in general (see Interferon Alfa, p.885).

Severe local reactions at injection sites, including tissue necrosis, have been reported. Menstrual irregularities have been associated with interferon beta use. On injection, transient neurological symptoms that may mimic an exacerbation of multiple sclerosis have been reported. In addition transient episodes of hypertonia and/or severe muscular weakness may occur at any time during treatment.

◊ Reviews.

1. Bayas A, Rieckmann P. Managing the adverse effects of interferon-beta therapy in multiple sclerosis. *Drug Safety* 2000; **22:** 149–59.

Auto-immune disorders. Reversible subacute cutaneous lupus erythematosus[1] and SLE[2] have been reported in patients given interferon beta. A case[3] of lupus erythematosus profundus has been reported in a patient after 4 years of treatment with interferon beta-1b for multiple sclerosis; the neurological symptoms and subcutaneous nodules resolved after stopping treatment. There have been case reports of patients developing myasthenia gravis while receiving interferon beta; the patients responded to treatment with pyridostigmine.[4]

1. Nousari HC, *et al.* Subacute cutaneous lupus erythematosus associated with interferon beta-1a. *Lancet* 1998; **352:** 1825–6.
2. Crispín JC, Díaz-Jouanen E. Systemic lupus erythematosus induced by therapy with interferon-β in a patient with multiple sclerosis. *Lupus* 2005; **14:** 495–6.
3. Gono T, *et al.* Lupus erythematosus profundus (lupus panniculitis) induced by interferon-β in a multiple sclerosis patient. *J Clin Neurosci* 2007; **14:** 997–1000.
4. Dionisiotis J, *et al.* Development of myasthenia gravis in two patients with multiple sclerosis following interferon β treatment. *J Neurol Neurosurg Psychiatry* 2004; **75:** 1079.

Effects on the blood. Aplastic anaemia occurred[1] in a patient with multiple sclerosis after treatment with interferon beta-1a for about a year. The interferon was stopped and the patient had a good response to immunosuppressant treatment. The haematological effects of subcutaneous interferon beta-1a in multiple sclerosis patients have been reviewed.[2]

1. Aslam AK, Singh T. Aplastic anemia associated with interferon beta-1a. *Am J Ther* 2002; **9:** 522–3.
2. Rieckmann P, *et al.* Haematological effects of interferon-beta-1a (Rebif) therapy in multiple sclerosis. *Drug Safety* 2004; **27:** 745–56.

Effects on the cardiovascular system. Severe Raynaud's syndrome developed in a patient during treatment with interferon beta.[1] Symptoms subsided once interferon beta was stopped.

1. Linden D. Severe Raynaud's phenomenon associated with interferon-β treatment for multiple sclerosis. *Lancet* 1998; **352:** 878–9.

Effects on hearing. For a report of sensorineural hearing loss in patients receiving interferon beta, see Interferon Alfa, p.886.

Effects on the liver. Hepatotoxicity, sometimes severe and in rare cases fatal, has been reported with interferons and its association specifically with the use of interferon beta-1a in multiple sclerosis patients has been reviewed.[1]

1. Francis GS, *et al.* Hepatic reactions during treatment of multiple sclerosis with interferon-β-1a: incidence and clinical significance. *Drug Safety* 2003; **26:** 815–27.

Effects on the skin. Calcified subcutaneous nodules have been reported in a patient after 3 years of treatment with subcutaneous interferon beta-1a for the treatment of multiple sclerosis.[1] For a report of severe necrotising cutaneous lesions at injection sites in a patient receiving interferon beta, see Interferon Alfa, p.887. See also Auto-immune Disorders, above for a report of cutaneous lupus erythematosus associated with interferon beta.

1. Macbeth AE, *et al.* Calcified subcutaneous nodules: a long-term complication of interferon beta-1a therapy. *Br J Dermatol* 2007; **157:** 624–5.

Precautions

As for interferons in general (see Interferon Alfa, p.887).

Interferon beta in high doses is fetotoxic and abortifacient in *primates* and should be avoided during pregnancy.

Interactions

As for interferons in general (see Interferon Alfa, p.888).

Antiviral Action

As for interferons in general (see Interferon Alfa, p.888).

Pharmacokinetics

Interferons are not absorbed from the gastrointestinal tract. About 50% of a subcutaneous dose and 40% of an intramuscular dose of interferon beta is absorbed. For some formulations of interferon beta-1a, bioavailability and area under the plasma concentration-time