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 cauterisation 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.
11. Condylomata International Collaborative Study Group. Recurrent condylomata acuminata treated with recombinant interferon alfa-2a: a multicenter double-blind placebo-controlled clinical trial. *JAMA* 1991; **265:** 2684–7.
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.
13. Panici PB, *et al.* Randomized clinical trial comparing systemic interferon with diathermocoagulation in primary multiple and widespread anogenital condyloma. *Obstet Gynecol* 1989; **74:** 393–7.
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 (Вэллферон); ***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 curves are equivalent for subcutaneous and intramuscular dosage, but for others, intramuscular doses produce higher values than subcutaneous doses and subcutaneous doses therefore cannot be substituted for intramuscular doses. Peak serum concentrations of interferon beta-1a have been reported to occur 3 hours after subcutaneous injection and between 3 and 15 hours after intramuscular injection, and those for beta-1b have been reported to occur 1 to 8 hours after subcutaneous injection. The elimination half-life for intramuscular interferon beta-1a is about 10 hours. Interferon beta-1a is mainly metabolised and excreted by the liver and the kidneys.

Uses and Administration

Interferon beta is a cytokine with antiviral and immunomodulating activities. Two forms of interferon beta are available: interferon beta-1a and interferon beta-1b (see Nomenclature, above). Interferon beta is mainly used in the management of relapsing-remitting multiple sclerosis (below), although its mode of action is unclear. In the UK interferon beta-1b is also licensed for use in secondary progressive multiple sclerosis.

Interferon beta-1a is given in relapsing-remitting multiple sclerosis in a dose dependent upon the formulation used:

- *Avonex* (*Biogen*) is given in a dose of 6 million units (30 micrograms) once weekly by intramuscular injection.
- *Rebif* (*Serono*) is given in an escalating dose over 4 weeks, to 12 million units (44 micrograms) three times weekly by subcutaneous injection, or to 6 million units (22 micrograms) three times weekly by subcutaneous injection in patients unable to tolerate the higher dose.

Interferon beta-1b is given in both relapsing-remitting and in secondary progressive multiple sclerosis in an escalating dose over 3 to 6 weeks to a dose of 8 million units (250 micrograms) on alternate days by subcutaneous injection.

In the UK interferon beta-1a (*Avonex*) and interferon beta-1b are also indicated for the treatment of patients who have had a single demyelinating event with an active inflammatory process if it is sufficiently severe to warrant intravenous corticosteroids.

◊ Reviews.
1. Goodkin DE. Interferon beta-1b. *Lancet* 1994; **344:** 1057–60.
2. Etheridge LJ, *et al.* The use of interferon beta in relapsing-remitting multiple sclerosis. *Arch Dis Child* 2004; **89:** 789–91.
3. Markowitz CE. Interferon-beta: mechanism of action and dosing issues. *Neurology* 2007; **68** (suppl 4): S8–S11.

Guillain-Barré syndrome. Rapid improvement in motor function was reported during use of interferon beta-1a in a patient with Guillain-Barré syndrome associated with *Campylobacter jejuni* infection.[1] However, the relative contributions of interferon therapy and a course of plasma exchange that immediately preceded it could not be assessed.[2] Successful treatment of Guillain-Barré syndrome was reported in a patient after interferon beta-1a was added to treatment with intravenous immunoglobulin.[3] A small randomised, placebo-controlled pilot study[4] of subcutaneous interferon beta-1a or placebo, in addition to intravenous immunoglobulin, in patients with Guillain-Barré syndrome reported no significant difference in the rate of improvement.

1. Créange A, *et al.* Treatment of Guillain-Barré syndrome with interferon-β. *Lancet* 1998; **352:** 368.
2. Sawaya RA. Interferon beta for Guillain-Barré syndrome. *Lancet* 1998; **352:** 1550–1.
3. Schaller B, *et al.* Successful treatment of Guillain-Barré syndrome with combined administration of interferon-β-1a and intravenous immunoglobulin. *Eur Neurol* 2001; **46:** 167–8.
4. Pritchard J, *et al.* A randomized controlled trial of recombinant interferon-beta 1a in Guillain-Barré syndrome. *Neurology* 2003; **61:** 1282–4.

Multiple sclerosis. Multiple sclerosis (MS)[1-3] is a chronic inflammatory and demyelinating disease affecting the CNS. It is the most common disabling neurological disease among young adults and is most often diagnosed in those between the ages of 20 and 40, with women being almost twice as likely to develop it as men. Although the etiology and pathogenesis of MS is poorly understood, it is thought that the disease has an immunological basis and occurs in genetically susceptible individuals. MS is characterised by multiple areas of inflammation and demyelination; activated T-cells enter the CNS and produce an immune cascade resulting in localised loss of myelin, oligodendrocytes, and axons. The resulting lesions (plaques) accumulate over time, with impairment or less electrical transmission along the nerve fibres (axons).

Patients with MS commonly present with an individual mix of symptoms, which tend to progress over years to decades. The type and number of symptoms may vary according to the areas affected but typically include bowel and bladder dysfunction, changes in cognitive function, dizziness, depression, fatigue, difficulties with walking and balance, paraesthesias, pain, sexual dysfunction, spasticity, problems with speech and swallowing, tremor, and visual impairment, notably from optic neuritis. Most patients improve to some degree after the initial attack but the course and severity of the disease are unpredictable.

People with MS generally follow one of four clinical courses of disease, which in turn may be mild, moderate, or severe. In about 85% of patients the disease follows a relapsing-remitting course (RR-MS) in which there are recurrent exacerbations (flare-ups) followed by clinical improvement and relatively long periods of remission. After about 10 to 15 years up to 50% of patients develop progressive neurological deterioration, categorised as secondary progressive disease (SP-MS). However, about 15% of people with RR-MS will have a mild course with little or no disability after 15 years (benign MS). About 10 to 15% of patients present without relapses but have slow continuous deterioration, classified as primary progressive disease (PP-MS). In about 5% of patients the disease is described as progressive relapsing; people with this type of MS have steadily worsening disease from the onset but also have acute exacerbations.

Choice of treatment.

A wide range of drugs with immunological actions (disease-modifying drugs) have been tried in the treatment of MS itself with the aim of improving recovery from acute attacks, preventing or reducing further attacks (relapses), and halting the progressive stage of the disease. Different therapies are used for patients having acute attacks, for patients who have RR-MS, for patients who have the progressive subtypes, and for symptomatic management.

Corticosteroids are used for their immunomodulatory and anti-inflammatory effects in acute attacks (relapses). Corticosteroid therapy reduces the duration of the episode and accelerates recovery, but it is not known whether it alters the course of the disease in the long term.[4] The drug of choice is methylprednisolone; usually given intravenously in high doses (typically 1 g daily) for 3 to 5 days and sometimes followed by a tapering dose of oral prednisolone. Doses of up to 2 g daily have been tried.[5] In patients with acute optic neuritis (frequently the first manifestation of multiple sclerosis), methylprednisolone delayed the onset of other symptoms of multiple sclerosis,[6] although the effect was not sustained beyond 2 years.[7] Beneficial responses have also been reported with oral methylprednisolone at doses including 500 mg once daily for 5 days followed by a tapering dose over 10 days[8] and 48 mg once daily for 7 days followed by a tapering dose over 14 days.[9] A small clinical study indicated that the bioavailability attained after large doses of oral prednisone may be similar to that of high dose intravenous methylprednisolone.[10] In patients with PP-MS, the benefits of short-course methylprednisolone lasted no longer than 3 months[11] although, in patients with SP-MS, a preliminary study has suggested that progression may be delayed by intermittent high-dose methylprednisolone therapy.[12]

Interferon beta has become established for treatment of RR-MS selected patients, and is also used in SP-MS. Studies[13-15] in patients with active RR-MS have shown the efficacy of interferon *beta-1b* given subcutaneously and at different doses. Similar results in RR-MS have been obtained with interferon *beta-1a* given by either subcutaneous or intramuscular routes;[16-18] although comparative studies[19,20] have suggested that subcutaneous interferon beta-1a (44 micrograms given three times a week) is more effective than intramuscular interferon beta-1a (30 micrograms weekly). A prospective, randomised, multicentre study[21] comparing the different frequencies of dosing with interferon beta-1a and beta-1b concluded that high-dose interferon beta-1b given on alternate days was more effective in RR-MS than once-weekly interferon beta-1a. Studies[22-24] in patients presenting with a first demyelinating event (clinically isolated syndrome), or other manifestation of early disease, have shown that treatment with interferon beta may reduce the rate of progression to clinical MS, a view confirmed by a recent systematic review.[25] A 3-year follow-up analysis[26] of one study[24] found that early treatment with interferon beta-1b prevented the development of confirmed disability.

Concern has been expressed over the detection of neutralising antibodies against interferon in up to 46% of patients;[27-29] development of neutralising antibodies correlates with reduced treatment efficacy and the possibility for renewed disease activity. The development of neutralising antibodies is greater in patients treated with higher doses of interferon and in those treated with interferon beta-1b.[30]

Encouraging results have also been obtained with interferon beta-1b in patients with SP-MS,[31] but no effect has been found on disability progression from use of interferon beta-1a in SP-MS.[32,33]

Results of studies[34,35] with *glatiramer* in patients with RR-MS have shown that it can reduce the number of relapses and may produce some improvements in neurological disability. Follow-up of these patients for approximately 3 years continued to show a beneficial effect on disease relapse rate. MRI data supported the beneficial clinical results.[36] These benefits are produced in a different way from those gained with interferon beta leading to expectations of possible treatment with both drugs.

Natalizumab is a humanised monoclonal antibody that has been found to decrease the frequency of exacerbations in RR-MS. A 2-year randomised, placebo-controlled study[37] to assess the safety and efficacy of intravenous natalizumab reported a 68% likelihood of remaining relapse-free and a 83% reduction in the number of new or enlarging brain lesions on MRI; the cumulative probability of sustained disability progression was 17% in the natalizumab patient group compared to 29% in the placebo group. Another 2-year study[38] reported that natalizumab plus intramuscular interferon beta-1a was more effective than interferon beta-1a monotherapy. Patients receiving combination therapy were 55% less likely to relapse and had a 83% reduction in the number of new or enlarging brain lesions on MRI compared with monotherapy. A 23% probability of progression of disability was reported for the combination treatment group compared with 29% for interferon alone. Natalizumab has, however, been associated with an increased risk of progressive multifocal leukoencephalopathy and its use is therefore limited to patients with highly active RR-MS who have had an inadequate response to, or are unable to tolerate, other therapies.

Although some studies have shown modest benefits with *immunosuppressants*, the general conclusions of large controlled studies have tended to be that any slight benefits of existing therapies with immunosuppressants such as azathioprine, ciclosporin, cyclophosphamide, and methotrexate are outweighed by the toxicity of the doses required to have an effect.[39-46] However, a systematic review[47] concluded that azathioprine reduced the number of patients who had relapses and the number who progressed during the first 2 to 3 years of treatment. It considered that azathioprine might be given as an alternative to interferon beta for maintenance treatment for patients who frequently relapse and require corticosteroids. Long-term toxicity (including the risk of malignancy) may be related to cumulative doses above 600 g and treatment for longer than 10 years. Mitoxantrone (given by intravenous infusion) has been studied in patients with RR-, PR-, and SP-MS and found to be moderately effective in reducing disease progression and the frequency of relapses.[48,49] Its use may, however, be limited by dose-related cardiotoxicity and it is suggested that mitoxantrone be used to treat patients with rapidly progressive disease or those not responding to high-dose interferon. A review[50] of cladribine indicated that it reduced the number of enhancing lesions but also had significantly more adverse effects (including myelosuppression) than placebo. The authors suggested that cladribine might have a role in the treatment of refractory patients with SP-MS.

Other immunological approaches evaluated have included the use of monoclonal antibodies such as alemtuzumab, daclizumab, and rituximab, and immunosuppressants such as mycophenolate mofetil. HMG-CoA reductase inhibitors (statins) have immunomodulatory effects and a small study[51] reported that simvastatin significantly decreases the number and volume of new MRI lesions in patients with RR-MS.

A systematic review[52] on the use of intermittent intravenous normal immunoglobulins in patients with RR-MS concluded that there was a reduction in relapse rate and an increased time to relapse, but no evidence that immunoglobulin treatment reduces the progression of MS or reverses existing damage. Intravenous normal immunoglobulins are not effective in SP-MS.[53] Autologous haematopoietic stem cell transplantation has shown benefit in some patients with progressive MS.[54,55]

Guidelines for the management of multiple sclerosis have been produced in the UK,[56,57] the USA,[58] and other countries.[59,60]

Symptomatic treatment.

MS can produce a wide range of symptoms, many of which are manageable; symptomatic treatment is aimed at the management of spasticity, ataxia, tremor, paroxysmal symptoms, pain, fatigue, and bladder dysfunction. Baclofen, dantrolene, diazepam, and tizanidine are the usual drugs given for spasticity (see p.1887). There is also some anecdotal evidence to suggest that cannabis and individual cannabinoids, including synthetic cannabinoids such as nabilone, may improve pain and spasticity;[61] a review[62] considered evidence of effectiveness to be lacking. Patients with MS can suffer from a number of different types of pain, including pain from spasticity, and therapy must be individualised for each specific pain syndrome (see Choice of Analgesic, p.2). Pain, spasms, and spasticity have responded to gabapentin in preliminary studies.[63-68] A review has noted, however, that the absolute and comparative efficacy and tolerability of anti-spasticity drugs is poorly documented.[69] Paraesthesia and dysaesthesia, which can be common, may respond to tricyclic antidepressants or antiepileptics. Amantadine, modafinil, pemoline, and fampridine have all been investigated for the management of fatigue associated with MS.[70] Treatment of bladder dysfunction may include an alpha blocker such as phenoxybenzamine and appropriate parasympathomimetic or antimuscarinic (such as oxybutynin) therapy to control bladder contractions (see Urinary Incontinence and Retention, p.2180). Fampridine and amifampridine have been reported to produce beneficial symptomatic responses such as improvement in walking, dexterity, and vision, possibly as a result of potassium-channel blocking activity but a systematic review[71] was unable to come to a conclusion about safety and efficacy, noting that publication bias posed a problem.

Conventional treatments are only partially effective and may produce adverse effects, and many patients with MS try alternative therapies. The most common *dietary interventions* are supplementation with polyunsaturated fatty acids (such as omega-3 and omega-6 fatty acids, often as fish, evening primrose, or sunflower oils), allergen-free diets, vitamins, and micronutrients and antoxidants (such as selenium, ginkgo biloba extracts, and coenzyme Q10). A review of the relationship between these dietary interventions and MS concluded that there was insufficient evidence to determine their benefits or risks.[72] Polyunsaturated fatty acids seem to have no major effect on disease progression and recurrence of exacerbations over 2 years. Research into the value of vitamin D is ongoing after findings that higher levels of serum vitamin D are associated with a lower risk of MS.[73]

The use of *hyperbaric oxygen* therapy in MS was a matter of debate for many years. Some workers reported benefit, especially in bladder and bowel function or in cerebellar function whereas others were unable to substantiate any long-term benefit and reviews have concluded that there is no convincing evidence that hyperbaric oxygen therapy is useful.[74,75]

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Rheumatoid arthritis. Preliminary studies suggested that interferon beta might have a beneficial effect on rheumatoid arthritis,[1] the conventional management of which is described on p.11. However, a subsequent randomised, double-blind study[2] found that adding subcutaneous interferon beta to methotrexate treatment in patients with rheumatoid arthritis had no clinical or radiological benefit over adding placebo.

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Warts. For the use of interferon beta in the management of warts, see Interferon Alfa, p.891.

Preparations

Proprietary Preparations (details are given in Part 3)
Arg.: Avonex; Betaferon; Blastoferon; Rebif; ***Austral.:*** Avonex; Betaferon; Rebif; ***Austria:*** Avonex; Betaferon; Rebif; ***Belg.:*** Avonex; Betaferon; Rebif; ***Braz.:*** Avonex; Betaferon; Rebif; Serobif; ***Canad.:*** Avonex; Betaseron; Rebif; ***Chile:*** Avonex; Betaferon; Rebif†; ***Cz.:*** Avonex; Betaferon; Rebif; ***Denm.:*** Avonex; Betaferon; Rebif; ***Fin.:*** Avonex; Betaferon; Rebif; ***Fr.:*** Avonex; Betaferon; Rebif; ***Ger.:*** Avonex; Betaferon; Fiblaferon; Rebif; ***Gr.:*** Avonex; Betaferon; Rebif; ***Hong Kong:*** Betaferon; Rebif; ***Hung.:*** Avonex; Betaferon; Rebif; ***India:*** Betaferon; Rebif; ***Indon.:*** Rebif; ***Irl.:*** Avonex; Betaferon; Rebif; ***Israel:*** Avonex; Betaferon; Rebif; ***Ital.:*** Avonex; Betaferon; Betron R†; Rebif; Serobif; ***Jpn:*** Feron; ***Malaysia:*** Betaferon; Rebif; ***Mex.:*** Avonex; Betaferon; Rebif; Uribeta; ***Neth.:*** Avonex; Betaferon; Rebif; ***Norw.:*** Avonex; Betaferon; Rebif; ***NZ:*** Avonex; Betaferon; Rebif; ***Philipp.:*** Betaferon; Rebif; ***Pol.:*** Avonex†; Betaferon; Rebif; ***Port.:*** Avonex; Betaferon; Rebif; ***Rus.:*** Avonex (Авонекс); Betaferon (Бетаферон); Rebif (Ребиф); ***S.Afr.:*** Avonex; Betaferon; Rebif; ***Singapore:*** Betaferon; Rebif; ***Spain:*** Avonex; Betaferon; Rebif; ***Swed.:*** Avonex; Betaferon; Rebif; ***Switz.:*** Avonex; Betaferon; Rebif; ***Thai.:*** Betaferon; Rebif; ***Turk.:*** Avonex; Betaferon; Rebif; ***UK:*** Avonex; Betaferon; Rebif; ***USA:*** Avonex; Betaseron; Rebif; ***Venez.:*** Avonex; Rebif.

Interferon Gamma *(BAN, rINN)*

IFN-γ; Interferón-γ; Interferon-γ; Interféron gamma; Interferón gamma; Interferoni gamma; Interferonigamma; Interferonum Gamma.

Интерферон Гамма

CAS — 98059-18-8 (interferon gamma-1a); 98059-61-1 (interferon gamma-1b).

ATC — L03AB03.

ATC Vet — QL03AB03.

NOTE. Interferon gamma was previously known as immune interferon.

Interferon gamma-1b is *USAN* and was previously known as interferon gamma-2a.

Pharmacopoeias. *Eur.* (see p.vii) includes Interferon Gamma-1b Concentrated Solution.

Ph. Eur. 6.2 (Interferon Gamma-1b Concentrated Solution; Interferoni Gamma-1b Solutio Concentrata). It is a solution of the *N*-terminal methionyl form of interferon gamma. 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. The pH of the solution is 4.5 to 5.5. Store in airtight containers at a temperature of −70°. Protect from light.