Interferon-alpha in the management of patients with Behçet's disease

Behçet's disease is a multisystem vasculitis which often leads to serious complications. Current treatment is largely based on non-specific immunosuppression, but interferon-alpha may be able to induce disease remission. This article reviews what is known about interferon-alpha and its potential as a treatment for Behçet's disease.

Behçet's disease is a multisystem disorder, characterized by recurrent oral and genital ulcers and relapsing uveitis, as well as articular, neurological, vascular, intestinal and pulmonary manifestations. It is more common in young men and has its highest incidence in the Middle East, the Mediterranean basin and the Far East regions; it is rare in most developed countries.

The underlying pathological process is that of a systemic, immune-mediated occlusive vasculitis (George et al, 1997), but the aetiology remains unclear. However, current evidence suggests that genetic factors such as HLA-B51 predispose individuals to inflammation which is perpetuated by the adaptive immune response of T cells to infectious and/or auto-antigens has a role to play (Deuter et al, 2008). The clinical course of Behçet's disease is characterized by exacerbations and remissions of unpredictable duration and frequency (Evereklioglu, 2005).

Treatment is largely based on non-specific immunosuppression with drugs including systemic corticosteroids, colchicine, azathioprine, ciclosporin and methotrexate. Anti-inflammatory drugs including non-steroidal anti-inflammatory drugs (NSAIDs) may also prove useful. Drug combinations are preferred and many patients progress through various drug combinations with time, usually because of adverse effects. The prognosis of ocular involvement has improved with the advent of newer therapies but many patients still lose significant vision and serious neurological, vascular and gastrointestinal events are not uncommon (Evereklioglu, 2005).

Small case series have demonstrated the value of biological therapies such as interferon-α (IFN-α) and tumour necrosis factor-α (TNF-α) antagonists, particularly infliximab. Both agents have proved capable of rapidly inducing remission in active disease (Deuter et al, 2008), but the benefit of infliximab is usually temporary and infusions are required every 4–8 weeks to sustain remission (Imrie and Dick, 2007); very few cases have been described in which treatment could be stopped without relapses within a few months. In contrast, 50–60% of patients treated with IFN-α do not relapse within a year after cessation of therapy (Deuter et al, 2008).

Interferon alpha as a treatment option for Behçet's disease

Interferons are members of the cytokine family and have received attention because of their diverse effects, influencing both innate and adaptive immune responses (Baccala et al, 2005). They have well-documented efficacy in the treatment of haematological and solid tumours, viral hepatitis, and autoimmune diseases. IFN-α belongs to the type 1 interferon family and has at least 13 different isotypes. It can be produced by virtually all somatic cells after viral infection and is highly pleiotropic with antiviral, antiproliferative, antiangiogenetic and immunomodulatory properties (Pfeffer et al, 1998).

Recombinant leukocyte IFN-α was first used in Behçet's disease in 1986, based on the putative association between Behçet's disease and viral infection. Recent studies have focussed on IFN-α2a, either used alone or in association with steroids and/or immunosuppressive agents. Treatment modalities vary greatly, with doses ranging from 3 to 9 million units per injection, injections occurring from 3–7 times per week and duration of administration varying from 3–6 months. Antonelli et al (1991) suggested that a 6-month course is probably optimal, as no advantage is gained with longer therapy with respect to efficacy or duration of induced remission. Indeed, the risk of developing binding and neutralizing antibodies increases with longer treatment, possibly decreasing its beneficial effects. Recombinant IFN-α2a induces neutralizing antibodies in about 20% of patients, in contrast to only about 6% of those treated with recombinant IFN-α2b.

Overall, a meta-analysis of 144 Behçet's disease patients from 22 reports showed that despite different therapeutic regimens used in individual studies, overall efficacy of IFN-α therapy was 74% for mucocutaneous manifestations, 93% for arthritis and 95% for uveitis (Azizlerli et al, 1997). Maximum response was achieved about 2–

Mr David SF Yang *is Clinical Research Fellow,* **Mr Simon RJ Taylor** *is Honorary Clinical Lecturer and* **Professor Sue L Lightman** *is Professor of Clinical Ophthalmology, UCL Institute of Ophthalmology, Department of Clinical Ophthalmology, Moorfields Eye Hospital, London EC1V 2PD*

Correspondence to: Professor SL Lightman

4 months after starting IFN-α therapy. Intermediate to high IFN-α dosages were shown to be more effective than low-dose regimens, and long-term remissions were associated with higher IFN-α dosages, but not with an longer treatment period.

Clinical trials of interferon-alpha in Behçet's disease

Despite a lack of data from randomized controlled trials, the results of studies performed so far with IFN-α therapy have been promising, especially for those patients with disease resistant to conventional immunosuppressive treatments. In particular, the clinical efficacy of IFN-α in the treatment of Behçet's disease-associated uveoretinitis appears fairly convincing.

In one open-label, prospective series involving 50 Behçet's disease patients with sight-threatening refractory uveitis, a 92% response rate was demonstrated with recombinant human IFN-α2a at initial doses of six million units subcutaneously daily. Retinal infiltrates resolved after 2–3 weeks in all patients, macular oedema resolved, and visual acuity improved or remained stable in 97% of affected eyes (Kotter et al, 2004). The IFN-α dose was subsequently adjusted according to the clinical response, and was discontinued whenever possible. Importantly, 40% of patients remained in remission for a mean of 29.5 months after cessation of treatment. IFN-α treatment was also beneficial for extraocular problems including arthritis, genital ulcers, and cutaneous and gastrointestinal manifestations as well, but less so for oral ulcerations.

In a retrospective analysis carried out on 44 Behçet's disease patients with uveitis unresponsive to conventional immunosuppressants, IFN-α2a was given at an initial dose of 3–6 million units daily for a mean duration of 12.4 months and led to a partial or complete response in 91% of patients (Tugal-Tutkun et al, 2006a). Visual acuity significantly improved and this benefit was preserved in 95% of patients throughout follow up. Interestingly, patients who received IFN-α treatment at the time of a relapse did not respond differently compared with those whose treatment was started during remission. Another retrospective study by the same group found that treatment with IFN-α2a resulted in resolution of neovascularization of the optic disc, whether inflammation- or ischaemia-induced.

More recently, a retrospective study of 45 patients with severe refractory uveitis who were treated with IFN-α2a at a dose of 3–6 million units three times a week in combination with initial high doses of prednisolone also demonstrated impressive results, with uveitis being controlled in 82.6% of Behçet's disease patients and ten of 19 patients being able to stop IFN-α after a mean treatment period of 30.6 months. Of these ten patients, relapses occurred in four after discontinuation of IFN-α but reintroduction of IFN-α was effective in all cases (Bodaghi et al, 2007).

The beneficial effects of IFN-α for the non-ocular manifestations of Behçet's disease have also been demonstrated. A randomized, placebo-controlled, double-blind trial showed that both pain and duration of oral ulcers were reduced in 23 patients treated with IFN-α2a at a dosage of six million units subcutaneously three times a week for 3 months (Alpsoy et al, 2002). IFN-α decreased the frequency of both genital ulcers and papulopustular lesions. Additionally, in five of six patients, the severity and frequency of ocular attacks was noted to improve. However, all manifestations had the tendency to return to pre-treatment levels after cessation of therapy. In addition, the frequency and duration of arthritic attacks has been shown to decrease after treatment with IFN-α2b (Hamuryudan et al, 1994). Currently, there is little information concerning the efficacy of IFN-α therapy for involvement of the gastrointestinal tract, CNS and large vessels, although one small study demonstrated remission in nine out of ten patients with vascular disease and four of four with neurological disease.

One long-term retrospective analysis described experience of IFN-α treatment in seven paediatric Behçet's disease patients with severe uveitis (Guillaume-Czitrom et al, 2007). IFN-α2a was given at a dosage of 1.5 or 3 million units three times a week in children weighing 20–30 kg or 30–50 kg respectively. The treatment was combined with azathioprine for two of the children. The results were encouraging because of the rapid steroid-sparing effect in five patients, and sustained remission was achieved in four children. The results of the two studies suggest the combination of IFN-α and azathioprine might be an option in the management of severe refractory Behçet's disease uveitis.

The results of these trials are summarized in *Table 1*.

Alternatives to conventional subcutaneous interferon-alphas

The clinical use of recombinant IFN-α has been restricted because of its short circulating half-life, which makes frequent dosing over an extended period necessary. Polyethylene glycols (PEGs) are biologically inert molecules that can be attached to proteins to reduce their degradation; the molecular weight and conformation of PEG chains have an impact on the conjugate's properties. Two products are now in widespread clinical use. The 40 kDa PEG-IFN-α2a (F. Hoffmann-La Roche Ltd, Basel, Switzerland) is linked to a branch chain, 40 kDa PEG moiety and the 12 kDa PEG-IFN-α2b (Schering-Plough, Kenilworth, NJ, USA) consists of IFN-α2b linked to a linear PEG chain.

The two PEG-IFN-α drugs differ in the way that the PEG chain is cross-linked to the IFN-α. The PEG polymer in PEG-IFN-α2a is attached to a lysine residue within the IFN-α2a molecule via a hydrolytically stable amide bond and the PEG molecule in PEG-IFN-α2b is attached via a urethane bond. This urethane linkage is liable to hydrolysis and thus PEG-IFN-α2b is prob-

ably best regarded as a prodrug. Conventional IFN-α has an absorption half-life of 2.3 hours and 7–12 hours after subcutaneous administration conventional IFN-α reaches peak serum levels. It is rapidly eliminated with a clearance of 6000 ml/h and has an elimination half-life of 4–16 hours. There is almost no measurable IFN in the serum 24 hours after administration (Wills, 1990).

PEG-IFN-α2b has a relatively rapid absorption (absorption half life of 4.6 hours), a wide volume of distribution (approximately 0.99 litres/kg), and reduced clearance (725 ml/h), whereas the 40 kDa PEG-IFN-α2a is absorbed more slowly (absorption half life of 50 hours), has a more limited volume of distribution (8 litres, suggesting distribution predominantly into the intravascular compartment), and a noticeably diminished rate of clearance (60 ml/hour). PEG-IFN-α2b must be adjusted for body weight, but PEG-IFN-α2a can be given as a single fixed dose (Reddy, 2004). From the clinical experience, the relatively rapid absorption of PEG-IFN-α2b leads to swift onset of side effects and a fall in neutrophil and platelet counts could take place.

Biological effects and possible mechanisms of action

The mechanism of action of IFN-α in Behçet's disease patients is complex and multifactorial. IFN-α has been shown to decrease the number of circulating γδ T cells, yet increase the number of B cells, monocytes and neopterin serum levels (a marker for monocyte activation) (Treusch et al, 2004). Also, IFN-α has been observed to enhance human leukocyte antigen-1 (HLA-1) expression on peripheral monocytes from Behçet's disease patients (Piazzolla et al, 1996). As γδ T cells are able to prime downstream immune events, including the production of pathogenic TNF-α and T helper type 1 cytokines, it is conceivable that the disruption of γδ T cell-mediated immunostimulation is an important mechanism of action. The significance of the enhanced HLA-1 molecule expression induced by IFN-α is less apparent but this may facilitate foreign antigen processing and clearing while the disease is still active (Pipitone et al, 2006). The increase in B cells and monocytes under therapy may explain at least some of the side effects of IFN-α such as autoantibody production, autoimmune phenomena and fever (Treusch et al, 2004).

By interacting with the cytokine cascade, IFN-α has other anti-inflammatory properties which might partly account for its clinical efficacy, including its ability to inhibit IL-8 production by peripheral blood mononuclear cells and to induce the IL-1 receptor antagonist (Tilg et al, 1993). Evidence suggests that IFN-α may suppress TNF-α gene expression and protein synthesis in vitro or in vivo. IL-18 is a coinducer of IFN-γ, and IFN-α can induce the production of IL-18 binding protein and thus late IL-18 suppression (Kaser et al, 2002). It has previously been shown that IFN-α increases the frequency of IFN-γ producing CD4+ T cells, suggesting that it favours the expression of a Th1 phenotype (Brinkmann et al, 1993). IL-17 has been implicated as a pathological mediator of autoimmune disease and pretreatment with recombinant IFN-α inhibits peripheral blood mononuclear cells secretion of IL-17 and CD40L-induced pro-inflammatory cytokines IL-12p70 and IL-23 (Meyers et al, 2006).

Table 1. Significant clinical studies reporting the use of interferon-alpha in Behçet's disease

Reference	No. of patients on IFN	Type of IFN	Concurrent therapy	Manifestation(s) studied	Study design
Hamuryndan et al (1994)	20	α2b	Not reported	Mucocutaneous, joint	Open, self-controlled
Alpsoy et al (2002)	23	α2a	None	Mucocutaneous, joint, oral and genital ulcers, ocular	Randomized, placebo-controlled, double-blind
Hamuryndan et al (2002)	10	α2b	Azathioprine	Ocular	Open
Kotter et al (2004)	50	α2a	Prednisolone ≤ 10mg/day, immunosuppressives stopped	Ocular, joint, mucocutaneous, oral and genital ulcers, vascular, gastrointestinal	Open, non-randomized, uncontrolled, prospective
Calguneri et al (2003)	29	Not reported	Colchicine, benzathine penicillin (cyclophosphamide in one patient)	Ocular, joint, vascular, neurological	Open, prospective
Tugal-Tutkun et al (2006a)	44	α2a	Prednisolone ≤10 mg/day, immunosuppressives stopped	Ocular	Retrospective
Tugal-Tutkun et al (2006b)	26 (38 eyes)	α2a	Prednisolone ≤10 mg/day, immunosuppressives stopped	Ocular (neovascularization of the optic disc)	Retrospective
Bodaghi et al (2007)	45 (23 with Behçet's disease)	α2a	IV methylprednisolone then prednisolone 1 mg/kg/day	Ocular	Retrospective
Guillaume-Czitrom et al (2007)	7	α2a	Corticosteroids, azathioprine in two	Ocular	Retrospective

IFN = interferon; IV = intravenous

Furthermore, it has been found that IFN-α2a can influence the impaired intracellular IL-2 production in Behçet's disease by promoting Th1 differentiation which results in an increase of IL-2 up to normal levels. Studies demonstrate that IL-2, along with B7 costimulators, promotes the development of Treg cells or the apoptotic death of activated T cells (Abbas, 2003; Amberger et al, 2007). Other actions demonstrated by IFN-α involve the ability to suppress T cell binding to both unstimulated and IFN-γ-stimulated endothelial cells and to inhibit intercellular adhesion molecule-1 (ICAM-1) expression on endothelial cells stimulated by IFN-γ (Eguchi et al, 1992). The capacity of IFN-α to inhibit T cell adhesion to endothelial cells can conceivably impede with the transmigration of inflammatory cells and thus reduce tissue injury (Pipitone et al, 2006).

Side effects and contraindications

The side-effect profile of IFN-α is generally less severe than that of other systemic immunosuppressants. Common side effects of IFN-α include injection site reactions, flu-like symptoms (fever, headache, myalgia, arthralgia, sweating and fatigue), mild leukopenia and alopecia. The flu-like symptoms can be alleviated by concomitant administration of paracetamol and represent a good prognostic marker for a response to IFN-α treatment as this may indicate the absence of pre-existing anti-IFN-α autoantibodies (Mackensen et al, 2006; Deuter et al, 2008). Autoantibodies can be detectable 3–12 months after initiation of IFN-α therapy and their production or increase in titre has been observed in up to 50% of patients treated. Thyroid autoantibodies are reported to be the most frequent, but manifestations of overt autoimmune disease have been observed in only 1–2% of patients (Hauschild et al, 2008).

Depression and suicidal ideations can occur during therapy, independent of pre-existing psychiatric disease. Other neuropsychiatric side effects reported are sleep disturbances, irritability and rarely psychoses. An asymptomatic increase in liver enzymes is seen in as many as 15–30% of patients, especially ones who receive high-dose IFN-α. In case of a greater than five times elevation of liver enzymes, a therapy pause followed by a dose reduction is indicated (Hauschild et al, 2008).

IFN-associated retinopathy with features such as cotton wool spots, arteriolar occlusions, retinal oedema and haemorrhages has been described in hepatitis C and melanoma patients treated with high-dose IFN-α. Risk factors include arterial hypertension, diabetes mellitus and age above 45 years (Deuter et al, 2008; Hauschild et al, 2008). Gastrointestinal side effects such as dyspepsia, diarrhoea, loss of appetite and weight loss can occur, as can other less common side effects include thrombocytopenia, hypertriglyceridaemia, reduced libido, hypotension and cardiac disturbances (Hauschild et al, 2008).

The two IFN-α isotypes have a comparable adverse effect profile, although flu-like symptoms and mild leukopenia are more commonly reported with IFN-α2a regimens and mild alopecia more commonly with IFN-α2b treatment. Fortunately, nearly all of the side effects are temporary, dose-dependent and reversible, and discontinuation of IFN-α as a result of adverse effects is rare. Type 1 diabetes occasionally develops during IFN-α treatment. Interestingly, disorders such as systemic lupus erythematosus, sarcoidosis, rheumatoid arthritis, autoimmune hepatitis, epilepsy and psoriasis may present for the first time during IFN-α therapy. Unlike anti-TNF therapy, INF-α is not associated with an increased risk of infection (Imrie and Dick, 2007).

Conclusions

IFN-α shows promise when used to control inflammation in patients with Behçet's disease. The most impressive results have been achieved for severe and refractory ocular manifestations and the efficacy of the treatment might warrant its use earlier in the therapeutic process. However, owing to its relatively high cost, side-effect profile and limited long-term experience with IFN-α, its use is often reserved for disease resistant to traditional immunosuppressants. Longer follow-ups and adequately powered, randomized controlled studies are needed before drawing further conclusions about the use of IFN-α and its potential as a long-term disease-modifying agent. In addition, the optimum duration of IFN-α administration remains to be determined and the ideal treatment dosage at different stages of the disease needs to be established. **BJHM**

KEY POINTS

- Behçet's disease is a systemic vasculitis which can have serious ocular, neurological, vascular and gastrointestinal complications.
- Current treatment for Behçet's disease is largely based on non-specific immunosuppression.
- Small case series suggest that interferon-alpha may induce remission in a significant number of patients, especially for ocular disease.
- The side effects of interferon-alpha therapy are generally less severe than for other immunosuppressive agents.
- Further trials are needed to confirm the potential of interferon-alpha as a disease-modifying agent, and to determine the optimum dosing schedule and duration of treatment.

Conflict of interest: none.

Abbas AK (2003) The control of T cell activation vs. tolerance. *Autoimmun Rev* **2**(3): 115–18

Alpsoy E, Durusoy C, Yilmaz E, Ozgurel Y, Ermis O, Yazar S, Basaran E (2002) Interferon alfa-2a in the treatment of Behcet disease: a randomized placebo-controlled and double-blind study. *Arch Dermatol* **138**(4): 467–71

Amberger M, Groll S, Gunaydin I, Deuter C, Vonthein R, Kotter I (2007) Intracellular cytokine patterns in Behcet's disease in comparison to ankylosing spondylitis--influence of treatment with interferon-alpha2a. *Clin Exp Rheumatol* **25**(4 Suppl 45): S52–S57

Antonelli G, Currenti M, Turriziani O et al (1991) Neutralizing antibodies to interferon-alpha - relative frequency in patients

treated with different interferon preparations. *J Infect Dis* **163**: 882–5
Azizlerli G, Sarica R, Kose A et al (1997) The long-term treatment with interferon alpha-2a in Behcet's disease. In: Hamza M, ed. *Behcet's Disease.* Adhoua, Tunis: 453–5
Baccala R, Kono DH, Theofilopoulos AN (2005) Interferons as pathogenic effectors in autoimmunity. *Immunol Rev* **204:** 9–26
Bodaghi B, Gendron G, Wechsler B et al (2007) Efficacy of interferon alpha in the treatment of refractory and sight threatening uveitis: a retrospective monocentric study of 45 patients. *Br J Ophthalmol* **91**(3): 335–9
Brinkmann V, Geiger T, Alkan S, Heusser CH (1993) Interferon alpha increases the frequency of interferon gamma-producing human CD4+ T cells. *J Exp Med* **178**(5): 1655–63
Calguneri M, Ozturk MA, Ertenli I, Kiraz S, Apras S, Ozbalkan Z (2003) Effects of interferon alpha treatment on the clinical course of refractory Behcet's disease: an open study. *Ann Rheum Dis* **62**(5): 492–3
Deuter CM, Kotter I, Wallace GR, Murray PI, Stubiger N, Zierhut M (2008) Behcet's disease: ocular effects and treatment. *Prog Retin Eye Res* **27**(1): 111–36
Eguchi K, Kawakami A, Nakashima M et al (1992) Interferon-alpha and dexamethasone inhibit adhesion of T cells to endothelial cells and synovial cells. *Clin Exp Immunol* **88**(3): 448–54
Evereklioglu C (2005) Current concepts in the etiology and treatment of Behcet disease. *Surv Ophthalmol* **50**(4): 297–350
George RK, Chan CC, Whitcup SM, Nussenblatt RB (1997) Ocular immunopathology of Behcet's disease. *Surv Ophthalmol* **42**(2): 157–62
Guillaume-Czitrom S, Berger C, Pajot C, Bodaghi B, Wechsler B, Kone-Paut I (2007) Efficacy and safety of interferon-alpha in the treatment of corticodependent uveitis of paediatric Behcet's disease. *Rheumatology (Oxford)* **46**(10): 1570–3
Hamuryudan V, Moral F, Yurdakul S et al (1994) Systemic interferon alpha 2b treatment in Behcet's syndrome. *J Rheumatol* **21**(6): 1098–100
Hamuryudan V, Ozyazgan Y, Fresko Y, Mat C, Yurdakul S, Yazici H (2002) Interferon alfa combined with azathioprine for the uveitis of Behcet's disease: an open study. *Isr Med Assoc J* **4**(11 Suppl): 928–30
Hauschild A, Kahler KC, Schafer M, Fluck M (2008) Interdisciplinary management recommendations for toxicity associated with interferon-alfa therapy. *J Dtsch Dermatol Ges* [epub ahead of print 26 March]
Imrie FR, Dick AD (2007) Biologics in the treatment of uveitis. *Curr Opin Ophthalmol* **18**(6): 481–6
Kaser A, Novick D, Rubinstein M et al (2002) Interferon-alpha induces interleukin-18 binding protein in chronic hepatitis C patients. *Clin Exp Immunol* **129**(2): 332–8
Kotter I, Vonthein R, Zierhut M et al (2004) Differential efficacy of human recombinant interferon-alpha2a on ocular and extraocular manifestations of Behcet disease: results of an open 4-center trial. *Semin Arthritis Rheum* **33**(5): 311–19
Mackensen F, Max R, Becker MD (2006) Interferon therapy for ocular disease. *Curr Opin Ophthalmol* **17**(6): 567–73
Meyers JA, Mangini AJ, Nagai T, Roff CF, Sehy D, van Seventer GA, van Seventer JM (2006) Blockade of TLR9 agonist-induced type I interferons promotes inflammatory cytokine IFN-gamma and IL-17 secretion by activated human PBMC. *Cytokine* **35**(5-6): 235–46
Pfeffer LM, Dinarello CA, Herberman RB et al (1998) Biological properties of recombinant alpha-interferons: 40th anniversary of the discovery of interferons. *Cancer Res* **58**(12): 2489–99
Piazzolla G, Giannelli G, Antonelli G, Tortorella C, Jirillo E, Schiraldi O, Antonaci S (1996) Effects of interferon-alpha treatment on neutrophil oxidative metabolism, lymphocyte proliferation and monocyte HLA class I antigen expression in patients with chronic hepatitis C. *Immunopharmacol Immunotoxicol* **18**(4): 529–48
Pipitone N, Olivieri I, Cantini F, Triolo G, Salvarani C (2006) New approaches in the treatment of Adamantiades-Behcet's disease. *Curr Opin Rheumatol* **18**(1): 3–9
Reddy KR (2004) Development and pharmacokinetics and pharmacodynamics of pegylated interferon alfa-2a (40 kD). *Semin Liver Dis* **24:** 33–8
Tilg H, Mier JW, Vogel W et al (1993) Induction of circulating IL-1 receptor antagonist by IFN treatment. *J Immunol* **150**(10): 4687–92
Treusch M, Vonthein R, Baur M et al (2004) Influence of human recombinant interferon-alpha2a (rhIFN-alpha2a) on altered lymphocyte subpopulations and monocytes in Behcet's disease. *Rheumatology (Oxford)* **43**(10): 1275–82
Tugal-Tutkun I, Guney-Tefekli E, Urgancioglu M (2006a) Results of interferon-alfa therapy in patients with Behcet uveitis. *Graefes Arch Clin Exp Ophthalmol* **244**(12): 1692–5
Tugal-Tutkun I, Onal S, Altan-Yaycioglu R, Kir N, Urgancioglu M (2006b) Neovascularization of the optic disc in Behcet's disease. *Jpn J Ophthalmol* **50**(3): 256–65
Wills RJ (1990) Clinical pharmacokinetics of interferons. *Clin Pharmacokinet* **19**(5): 390–9