Interferon-beta for treatment of rheumatoid arthritis?

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Introduction
IFNs are a family of naturally secreted proteins with immunomodulatory functions. They enhance the ability of macrophages to destroy tumour cells, viruses and bacteria. The IFNs are divided into two types. Type 1 IFNs comprise IFN-α and IFN-β [1], and type 2 IFNs consist of IFN-γ alone. All type 1 IFNs probably originate from one common ancestral gene and are secreted in humans [2].

Under normal physiological conditions, type 1 IFNs are secreted endogenously by most human cells at low levels [3]. IFN-γ has a structure different from that of IFN-α and IFN-β, and acts through a unique receptor complex. IFN-β and IFN-γ appear to have opposing effects. IFN-γ promotes inflammatory responses whereas IFN-β has anti-inflammatory properties. IFN-γ can stimulate the production of chemokines, and is a powerful activator of mononuclear phagocytes, increasing their ability to destroy intracellular micro-organisms and tumour cells. Therefore, recombinant IFN-γ has been used clinically for the treatment of a variety of conditions, including chronic lymphocytic leukaemia, Hodgkin’s disease and other disorders. IFN-γ has also been tried in immune-mediated diseases such as rheumatoid arthritis (RA) and multiple sclerosis (MS). IFN-γ was used in a multicentre, randomized, double-blind trial in 197 patients with active RA [4], which compared recombinant IFN-γ and placebo subcutaneously for a period of 24 weeks. However, it appeared to have no more therapeutic value than placebo. In MS patients, IFN-γ provoked disease exacerbation [5].

In contrast, IFN-β given to MS patients during clinical trials has been shown to reduce the relapse rate, to decrease disease activity on magnetic resonance imaging scans, and to delay disability progression [6–10]. The exact mechanism of action of IFN-β therapy is not precisely known at present. However, it has been shown that IFN-β downregulates the proinflammatory cytokines IL-1β and tumour necrosis factor (TNF)-α in vitro, and it enhances IL-10 and IL-1 receptor antagonist production [11–13]. Other possible effects of IFN-β treatment include the following (Fig. 1) [14]: enhancement of T-cell cytotoxicity; regulation of antibody production; inhibition of T-cell proliferation and migration; enhancement of IL-2 production by Th1 cells; upregulation of transforming growth factor (TGF)-β, and TGF-β-receptor 2 expression on peripheral blood mononuclear cells; downregulation of major histocompatibility complex class II expression on virus-infected cells; and reduction of neovascularization and angiogenesis.

Review
Interferon-β for treatment of rheumatoid arthritis?
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Abstract
IFN-β treatment is emerging as a potentially effective form of therapy in various immune-mediated conditions. The present review addresses the possible role of IFN-β in immune-mediated diseases such as multiple sclerosis and rheumatoid arthritis. Several placebo-controlled trials are discussed, as are the available immunological data that are relevant to this field. Review of these data provides evidence that IFN-β has some beneficial therapeutic effect in patients with relapsing-remitting multiple sclerosis and might also have antirheumatic potential. This notion is supported by recent studies showing a critical role for IFN-β in bone homeostasis.

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Type 1 IFNs have also been found to be effective in antiangiogenic therapy for tumours such as haemangiommas [15,16] and Kaposi’s sarcoma [17]. The systemic administration of IFN-α and IFN-β can induce regression of vascularized tumours through a mechanism associated with endothelial cell damage, which leads to necrosis [18,19]. Two pathways of angiogenesis have recently been identified, based on their dependence on the related but distinct integrins αvβ3 and αvβ5. Basic fibroblast growth factor enhanced angiogenesis is dependent on integrin αvβ3, whereas vascular endothelial growth factor enhanced angiogenesis requires αvβ5. IFN-β has been shown to downregulate basic fibroblast growth factor at mRNA and protein levels [20].

Importantly, in that study the αvβ3 antagonist provided significant protection against the development of cartilage erosions.

The present review addresses the possible role of IFN-β in immune-mediated diseases such as MS and RA.

**Rationale for the use of IFN-β in multiple sclerosis**

Because IFNs possess antiviral properties, the rationale for the use of IFN-β in MS in the past was based on the belief that viruses may play a role in causing MS, as well as triggering relapses of disease. At present MS is considered an autoimmune disease, associated with immune activity directed against an antigen derived from the central nervous system (CNS). It is known that macrophages, which express major histocompatibility complex class II molecules, present non-self antigens to T-cell receptors on Th1 cells. These activated T cells increase the expression of adhesion molecules such as intercellular adhesion molecule (ICAM)-1 and vascular cell adhesion molecule (VCAM)-1 on blood–brain barrier (BBB) endothelial cells. By this mechanism activated T-cells can cross the BBB. The activated T cells then activate macrophages, which in turn produce TNF-α, nitric oxide, free radicals and proteases, causing myelin damage.

In experimental autoimmune encephalomyelitis (EAE; a well known animal model of MS) demyelination is associated with a Th1 response (IFN-γ, IL-2 and TNF-α produc-
tion), whereas Th2 cytokines (e.g. IL-4 and IL-10) tend to ameliorate the clinical signs of disease in mice and Lewis rats [25]. In MS, autoimmune T-cell responses to myelin antigens, particularly myelin basic protein, may contribute to the inflammatory processes in the CNS [26]. IFN-β has been shown to suppress myelin basic protein reactive T cells, to enhance the production of anti-inflammatory cytokines IL-4 and IL-10, and to decrease TNF-α and IFN-γ production [27–30]. Thus, IFN-β may induce immune deviation toward the production of Th2 cytokines, which may contribute to its therapeutic benefit in MS [27].

Extravasation of T cells across the BBB into the CNS is considered a major event in the pathogenesis of MS and EAE. In EAE, kinetic studies have demonstrated that antigen-specific T cells migrate to the CNS early in the immune response, which is followed by enhanced recruitment of a large number of non-antigen-specific T cells that traverse into the CNS parenchyma. The majority of these T cells are in an activated state [31]. Adhesion molecules on the BBB, such as ICAM-1 and VCAM-1, play important roles and may enhance T-cell trafficking into the CNS. The effect of IFN-β could be caused in part through affecting these adhesion molecules.

In EAE, expression of ICAM-1 and VCAM-1 correlates with disease phase, specifically upregulation during the initial phase and decreased expression during disease remission [32]. Calabresi et al. [33] found increased levels of soluble VCAM-1 in the sera of MS patients, which correlated with a decrease in the number of contrast-enhancing lesions on magnetic resonance imaging during IFN-β treatment. Because soluble VCAM-1 results from the cleavage of its bound form, increased serum levels of soluble VCAM-1 might reflect a decrease in VCAM-1 expression on endothelium in MS patients treated with IFN-β. This suggests that IFN-β may downregulate expression of adhesion molecules on the BBB, which inhibits T-cell trafficking into the CNS.

The effects of IFN-β on cytokine profile and cell trafficking in the MS models and patients described above have stimulated studies on its potential for treatment of RA patients.

### Innovative treatment of rheumatoid arthritis patients

RA is a chronic inflammatory disease that affects the synovial tissue in multiple joints. In most patients the disease leads to joint destruction and disability. Inflammation in RA is believed to be mediated by activation of T cells, leading to activation of macrophages and fibroblast-like synoviocytes. The latter produce a variety of proinflammatory cytokines, which results in proliferation of synovial tissue associated with destruction of cartilage and bone. Tissue destruction in RA is closely related to the production of matrix metalloproteinases (MMPs) and other proteinases, which are able to degrade collagen and proteoglycans. Macrophages play a central role in the amplification of stimulatory signals and tissue destruction. Macrophages are found in the synovial lining layer, where they may be involved in protection against infection. In RA they are activated and mediate inflammation by the production of cytokines such as TNF-α, IL-1β, IL-6, IL-12, IL-15, IL-18, platelet derived growth factor and TGF. These cytokines activate fibroblast-like synoviocytes, which maintain macrophage activation by secretion of granulocyte–macrophage colony-stimulating factor, IL-8 and other soluble mediators. Fibroblast-like synoviocytes and osteoclasts invade bone and cartilage, where chondrocytes are activated to produce further proinflammatory cytokines. It is believed that TNF-α is a key cytokine controlling the production of other proinflammatory cytokines.

As a consequence various anticytokine therapies for RA have been tried in the clinic. IL-1 and TNF-α are present in relatively high amounts in synovial fluid and synovial tissue of RA patients [34–36] and, as major contributors to the inflammatory and destructive manifestations of RA, they were the first cytokines to be targeted for treatment of RA. Although the natural inhibitors of IL-1 and TNF-α, namely IL-1 receptor antagonist and soluble TNF receptor, are present in rheumatoid synovium, there might not be enough to neutralize the proinflammatory actions of IL-1 and TNF-α. There appears to be an imbalance between proinflammatory and anti-inflammatory molecules in RA joints.

Following animal studies, two forms of TNF inhibitors have been used in clinical trials in RA: anti-TNF-α antibodies and soluble receptors, which bind with high affinity to TNF. A multicentre, placebo-controlled, double-blind trial in 73 patients was performed in 1994 [37]. Patients were followed over 4 weeks. A single infusion of TNF inhibitor induced significant improvement in arthritis activity. All other clinical trials performed with agents that block TNF-α revealed significant improvement in arthritis and protection against joint destruction [38–42].

The efficacy of recombinant human IL-1 receptor antagonist in RA patients was investigated in a 6-month, placebo-controlled, double-blind, randomized trial [43]. A group of 472 patients with active RA received daily, subcutaneous injections of placebo or one of three doses of recombinant human IL-1 receptor antagonist. After 6 months, the patients who received the highest dose of the active treatment exhibited significant clinical improvement, and X-ray films from those patients showed fewer bone erosions as compared with patients who received placebo.

Other therapeutic targets in RA include MMPs, to prevent the destruction of cartilage and bone. Collagenase (MMP-1), stromelysin-1 (MMP-3) and MMP-13 play important roles in RA [44–46]. Normal fibroblasts produce very
low levels of MMP-1 and MMP-3. However, levels increase markedly in response to a variety of stimuli, such as cytokines, crystals and phagocytosis of debris [44,47]. Increased amounts of MMPs are present in cartilage from patients with RA, and the level of enzyme activity correlates with the severity of the lesion. Similarly, synovial fluid from patients with RA exhibits an increase in MMP levels [48,49]. Natural inhibitors that are specific for MMPs exist; they are produced locally by chondrocytes and fibroblast-like synoviocytes, and are termed ‘tissue inhibitors of metalloproteinases’ (TIMPs). It is likely that joint destruction is in part due to a local imbalance between activated MMPs and TIMPs [44,50]. One study investigated intraperitoneal administration of TIMP-1 in the collagen-induced arthritis mouse model [51] and showed a significant reduction in the severity of disease as compared with untreated control animals. Several chemotherapeutic agents, antibiotics and synthetic peptides can inhibit the activity of MMPs. Despite promising preclinical data, MMP inhibitors have not been used extensively in the clinic [46]. Minocycline – an antibiotic that can inhibit MMP activity – has been evaluated in three well controlled trials in RA [52–54]. All trials assessed the animals injected with the IFN-β expressing fibroblasts before the onset of arthritis, and paw swelling, arthritic score and histological joint damage were assessed. The animals injected with the IFN-β expressing fibroblasts developed less severe disease as compared with the control group, and there was a significant decrease in paw swelling.

The effect of treatment on established disease has also been studied. A single intraperitoneal injection of IFN-β expressing fibroblasts was given in different dosages of cells after the onset of arthritis, again with significant improvement in clinical scores and decreased paw swelling as compared with untreated animals [56]. Histology revealed significant reductions in joint destruction in all groups of mice treated with IFN-β, indicating that constitutive expression of IFN-β has chondroprotective properties. In the same study, total level of type II collagen specific IgG and the levels of IgG1 and IgG2a were measured in order to investigate the effects of IFN-β treatment on the immune response to type II collagen. A modest decrease in total anticollagen IgG levels was observed. Anticollagen IgG2a (regarded as a marker for a Th1 response) was reduced, and there was an increase in IgG1 (regarded as a marker for a Th2 response). Taken together, an increase in the IgG1/IgG2a ratio was observed, which may indicate a modulation of a Th1 to a Th2 immune response. Furthermore, IFN-β could inhibit production of TNF-α, IL-12 and IFN-γ production in vitro in a dose-dependent manner. These effects were reversed by anti-IFN-β antibodies, giving further support to the hypothesis that IFN-β is able to downregulate Th1 responses.

A study in which mice with collagen-induced arthritis received daily intraperitoneal injections (up to 2.5 µg/mouse per day) of exogenous IFN-β yielded similar results [57]. A significant decrease in inflammation and, more importantly, a statistically significant decrease in cartilage and bone destruction were observed in the IFN-β treated group as compared with control mice. Of importance, the protection of joint integrity appeared to be the most important effect of IFN-β.

Consistent with these observations, Takayanagi et al. [58] recently demonstrated the critical role of IFN-β in bone homeostasis. Those investigators observed that mice lacking IFN-β exhibited severe osteopenia, probably by downregulating osteoclastogenesis. Bone-resorbing osteoclasts and bone-forming osteoblasts are essential to maintenance a balance between bone resorption and bone formation. When this balance is disrupted in favour of the osteoclasts, bone destruction (as observed in RA) may follow. Osteoclast numbers and activity are dependent on the balance between the osteoclast-promoting receptor activator of nuclear factor-κB ligand (RANKL) and osteoclast-inhibiting osteoprotegerin. In addition, there is a negative feedback mechanism by which osteoclasts can control their own differentiation. RANKL induces the expression of IFN-β in osteoclast precursor cells via the transcription factor c-Fos (an essential transcription factor for the formation of osteoclasts). IFN-β is then released from these cells, and binds to and activates its own cell surface receptor system on osteoclast precursors, leading to a decrease in c-Fos levels. Lack of c-Fos leads to inhibition of osteoclast differentiation [59]. Thus, the IFN-β regulatory mechanism is important to maintenance of bone homeostasis, supporting the view that IFN-β therapy may be used to inhibit bone destruction [58,59].

In addition to studies conducted in mouse models, IFN-β therapy has been evaluated in collagen-induced arthritis in...
rhesus monkeys [14]. The monkeys were susceptible to collagen type II induced arthritis because of lack of the major histocompatibility complex class I allele A-26. Three out of four monkeys had active polyarthritis at the time of treatment initiation. The fourth monkey was in a preclinical phase of the disease, as shown by elevation in serum acute phase reactants and synovial inflammation by arthroscopy. The monkeys were treated with a high dosage of 37 µg/kg mammalian cell-derived recombinant IFN-β subcutaneously each day for 1 week. Two monkeys with established arthritis exhibited clear clinical improvement after treatment, and the monkey with preclinical synovitis never developed signs of arthritis. During IFN-β treatment all four monkeys had a marked decrease in serum C-reactive protein levels. Thus, that study confirmed previous work in mouse collagen-induced arthritis indicating that continuous production of IFN-β by transfected cells or daily IFN-β injections has potential as an antirheumatic strategy.

IFN-β therapy in patients with arthritis

The preclinical studies encouraged us to perform an open phase I study in 12 patients with active RA [14]. They were treated with IFN-β subcutaneously three times a week, which is the schedule used in MS patients but differs from the treatment schedule used in the collagen-induced arthritis models described above. We chose not to use daily injections because it was anticipated that this would be less tolerable to the patients. Three different doses of IFN-β were used: 22 µg, 44 µg and 66 µg. Treatment was in general well tolerated. Although there was gradual and significant improvement in tender joint count, swollen joint count, patient’s assessment of pain, and patient’s and doctor’s global assessment, the effects appeared to be limited. Conceivably, the clinical effects could have been more pronounced after treatment with daily injections. It should be noted, however, that this uncontrolled pilot study was not designed to demonstrate a clinical effect.

Arthroscopy was performed in these patients and synovial biopsies were taken before study entry, after 1 month and after 3 months of IFN-β treatment [55]. A statistically significant reduction in the mean immunohistological scores for expression of IL-1β, IL-6, MMP-1 and TIMP was observed in synovial tissue from RA patients after IFN-β therapy, suggesting a biological effect of the treatment.

Another pilot study was recently performed [60]. Six children with juvenile rheumatoid arthritis were treated for 16 weeks with weekly intramuscular injections of 10 or 20 µg/m² IFN-β. All patients tolerated the treatment well and all six patients met criteria for a 30% response after treatment. Three of the six children even improved by at least 50%. It should be stressed, however, that this study was not placebo controlled.

There are two case reports claiming the development of RA after the onset of IFN-β treatment. One report describes a patient who developed a seropositive polyarthritis, which fulfilled the American College of Rheumatology criteria for RA, after 1.5 years of IFN-β treatment for MS [61]. In that case it appears that IFN-β was at least unable to prevent the onset of RA. Another case report describes a patient with the HLA-DRB1*0404 allele who developed a seronegative symmetric polyarthritis of the wrists and hand joints after 8 weeks of IFN-β treatment for MS [62]. Eight months after the IFN-β treatment ended, symptoms of arthritis subsided, with resolution of the synovitis. That patient did not fulfill the American College of Rheumatology criteria for RA. Taken together, these case reports show that IFN-β therapy does not prevent the development of arthritis in all patients.

Conclusion

In conclusion, IFN-β therapy has been shown to slow the progression of disability in patients with relapsing-remitting MS, and might also have antirheumatic potential. It remains to be shown whether these exciting biological effects can translate into clinically meaningful improvement if the cytokine is administered only three times weekly or if more continuous levels of IFN-β are required.

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