Interferon β for rheumatoid arthritis: new clothes for an old kid on the block

Margriet J Vervoordeldonk,^{1,2} Caroline J Aalbers,^{1,2}
Paul P Tak^{1,2}

The type I interferons (IFNs), IFN β and various IFN α s, are pleiotropic cytokines acting on a range of cell types and eliciting a diverse range of responses. For many years IFN β was thought to be a potential agent for the treatment of a variety of immune-mediated diseases. Clinical trials showing a beneficial effect of IFN β treatment on clinical and MRI measures in relapsing-remitting multiple sclerosis were published almost a decade ago.^{1,2} These publications have stimulated studies on its potential for the treatment of patients with rheumatoid arthritis (RA). IFN β has clear anti-inflammatory properties³ and plays an important role in bone homeostasis.⁴ Of special interest is the ability of IFN β to reduce the secretion of proinflammatory mediators such as interleukin (IL)6, tumour necrosis factor (TNF) α , matrix metalloproteinases (MMPs) and prostaglandin E2, which are key players in the pathogenesis of RA.^{5,6} In addition, IFN β has antiangiogenic properties,⁷ which could boost therapeutic effect in RA.⁸

The notion that IFN β treatment may reduce arthritis is supported by animal experiments. Several studies examining the effect of IFN β in collagen-induced arthritis (CIA) in mice have been published. In one study mice were given daily intraperitoneal injections with mouse IFN β ⁹ and in another study, mice were injected intraperitoneally with a single injection of fibroblasts expressing IFN β , resulting in continuous IFN β production.¹⁰ Both studies revealed a beneficial effect on arthritis activity and histological scores for inflammation. A similar effect was shown in CIA in rhesus monkeys that were treated daily for 7 days with recombinant human IFN β .¹¹ More recently, it has been shown that IFN β -deficient mice had prolonged CIA with a higher incidence

of arthritis compared to control mice,¹² supporting the evidence that IFN β has an anti-inflammatory effect.

Based on the favourable effects of daily treatment with relatively high dosages of IFN β in animal models of RA, we previously performed an open label phase I study in 12 patients with active RA who were treated with purified natural fibroblast IFN β ,¹¹ followed by a double-blind, placebo-controlled phase II trial that evaluated the efficacy of mammalian cell-derived recombinant IFN β 1a.¹³ In the first, open study there were trends towards clinical improvement, although there was no change in key synovial biomarkers.¹⁴ In the latter study 209 patients with RA who were on stable methotrexate received 2.2 or 44 μ g IFN β 1a, or placebo, subcutaneously three times weekly for a period of 24 weeks.¹⁵ It was felt that daily injections with higher dosages, comparable to those used in the animal models, would not be tolerated by the patients. This dosing regimen did not result in clinical improvement or protection against joint destruction,¹³ perhaps because higher and more constant levels of IFN β may be required to translate into clinical benefit.³

Novel approaches are under investigation using IFN β as a therapeutic agent. Two different strategies are being evaluated: (1) systemic combination therapy of low dosage IFN β treatment with inhibition of the I κ B kinase (IKK)-related kinase, IKK ϵ and (2) intra-articular gene therapy aimed at reaching relatively high levels of IFN β at the site of inflammation, thus limiting systemic side effects. The interesting study by Corr *et al* (see page 257) in this issue of the *Annals of the Rheumatic Diseases*¹⁵ examined the role of IKK ϵ in the K/BxN serum model of RA and its ability to improve the response to systemic IFN β therapy. IKK ϵ is constitutively expressed in synovial tissue of patients with RA and significantly higher levels of phosphorylated IKK ϵ were observed in RA synovium compared to osteoarthritis.¹⁶ IKK ϵ is an IKK-related

kinase with 30% homology to IKK1 and IKK2, and was first described as a lipopolysaccharide (LPS)-inducible kinase.¹⁷ Recent work has suggested that the primary role of IKK ϵ may be the phosphorylation of interferon regulatory factor 3 (IRF3),¹⁸ leading to the induction of type I interferons. In addition, IKK ϵ may induce the expression of several MMPs and chemokines, suggesting that IKK ϵ might be a good target to suppress synovial inflammation.¹⁹ Corr *et al* showed that either IKK ϵ deficiency or low dose IFN β treatment in wild type mice protects in part against inflammation in the passive serum transfer model of RA. There was a statistically significant decrease in arthritis activity in IFN β -treated mice and IFN α / β receptor-deficient mice had an accentuated course of arthritis, consistent with the studies evaluating the role of IFN β in arthritis discussed above. Of interest, the potential benefit of combination therapy was suggested by the observation that low dose IFN β treatment in IKK ϵ -deficient mice resulted in a further reduction of arthritis scores. This combination therapy could enhance efficacy and decrease the suppressive effects of IKK ϵ inhibition on host defence. Thus, combination therapy comprising low dose IFN β treatment and IKK ϵ inhibition may perhaps offer a new treatment option for patients with RA. An overview of the proposed mechanisms of action is shown in fig 1. The study by Corr *et al* does not only present very interesting scientific data on IFN-regulated mechanisms, but it also provides the rationale for more comprehensive preclinical studies on the effects of coadministration of IFN β with an IKK ϵ inhibitor. However, an important question will be if systematic treatment with even low dosages of IFN β will be tolerated by patients with RA. In our previous clinical trial we observed a trend towards increased injection site reactions (13%), flu-like symptoms (18%) and fever (6%) in the group that received very low IFN β dosages (2.2 μ g three times weekly) compared to matching placebo (3%, 12% and 0%, respectively).¹²

In light of the potential side effects of systemic treatment, an alternative might be the development of intra-articular treatment. We have previously hypothesised that continuous therapeutic levels of IFN β local at the site of inflammation may be required to induce clinical efficacy and to avoid systemic side effects.³ This could be achieved by local gene therapy of the inflamed joint. Recombinant adeno-associated (rAAV) vectors are currently

¹ Academic Medical Center, University of Amsterdam, Amsterdam, The Netherlands; ² Arthrogen BV, Amsterdam, The Netherlands

Correspondence to: Professor P P Tak, Division of Clinical Immunology and Rheumatology, F4-218, Academic Medical Center/University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, The Netherlands; p.p.tak@amc.uva.nl

Figure 1 Rationale for combination of IκB kinase (IKK)ε inhibition with interferon (IFN)β treatment. After activation of the appropriate receptor (eg, a Toll-like receptor) IKKε can phosphorylate interferon regulatory factor 3 (IRF3), leading to the production of IFNβ, matrix metalloproteinases (MMPs) and chemokines. The released IFNβ can bind to an IFNβ receptor on the same or a neighbouring cell and exerts its effect on the regulation of different proteins and factors. Upon inhibition of IKKε the production of IFNβ, MMPs and chemokines will be downregulated. The subsequent inhibition of IFNβ expression can be compensated for by administration of IFNβ protein or gene therapy with recombinant adenoassociated virus (rAAV) expressing IFNβ. The effects of IFNβ treatment could be enhanced by simultaneous inhibition of IKKε.

considered as the most optimal vectors for the treatment of immune-mediated inflammatory diseases, including RA, because of their high safety profile together with the capacity to confer long-term expression of therapeutic transgenes in a variety of tissues.²⁰ We have identified rAAV serotype 5 as the most efficient rAAV vector for transducing synovial tissue.^{21–22} After successful proof of concept studies, using an adenoviral vector (Ad),²³ we have investigated the potential of intra-articular IFNβ gene therapy using an rAAV5 vector expressing rat IFNβ in adjuvant-induced arthritis in rats.²⁴ Local delivery of Ad or rAAV5 vectors expressing rat IFNβ in the ankle joint after the onset of disease reduced paw swelling impressively in treated and untreated contralateral joints. Strikingly, IFNβ treatment also protected against bone erosions and cartilage degradation. Together, the results provide a strong rationale for IFNβ gene therapy as a novel therapeutic approach for arthritis. Recently, toxicity and biodistribution studies have been initiated evaluating the effects of an rAAV5 vector expressing human IFNβ. Conceivably, based on the results presented by Corr *et al*, the effects of this approach might be enhanced by simultaneous inhibition of IKKε, although this remains to be shown.

Taken together, recent studies have placed IFNβ back on the list of potential new therapies for RA aimed at targeting

synovial inflammation and joint destruction. Low dose IFNβ treatment combined with IKKε inhibition as well as intra-articular IFNβ gene therapy appear interesting options worth exploring for future clinical development.

Competing interests: All authors are affiliated with Arthrogen BV, a company developing adenoassociated virus based gene therapy for rheumatoid arthritis.

Accepted 23 September 2008

Ann Rheum Dis 2009;**68**:157–158.
doi:10.1136/ard.2008.097899

REFERENCES

- Li DK, Paty DW. Magnetic resonance imaging results of the PRISMS trial: a randomized, double-blind, placebo-controlled study of interferon-β1a in relapsing-remitting multiple sclerosis. Prevention of Relapses and Disability by Interferon-β1a Subcutaneously in Multiple Sclerosis. *Ann Neurol* 1999;**46**:197–206.
- PRISMS (Prevention of Relapses and Disability by Interferon-β1a Subcutaneously in Multiple Sclerosis) Study Group. Randomised double-blind placebo-controlled study of interferon β-1a in relapsing/remitting multiple sclerosis. *Lancet* 1998;**7**:1498–504.
- Tak PP. IFN-β in rheumatoid arthritis. *Front Biosci* 2004;**9**:342–7.
- Takayanagi H, Kim S, Matsuo K, Suzuki H, Suzuki T, Sato K, *et al*. RANKL maintains bone homeostasis through c-Fos-dependent induction of interferon-β. *Nature* 2002;**18**:744–9.
- Coclet-Nin J, Dayer JM, Burger D. Interferon-β not only inhibits interleukin-1β and tumor necrosis factor-α but stimulates interleukin-1 receptor antagonist production in human peripheral blood mononuclear cells. *Eur Cytokine Netw* 1997;**8**:345–9.
- Smeets TJ, Dayer JM, Kraan MC, Versendaal J, Chicheportiche R, Breedveld FC, *et al*. The effects of interferon-β treatment of synovial inflammation and

- expression of metalloproteinases in patients with rheumatoid arthritis. *Arthritis Rheum* 2000;**43**:270–4.
- McCarty MF, Bielenberg D, Donawho C, Bucana CD, Fidler IJ. Evidence for the causal role of endogenous interferon-α/β in the regulation of angiogenesis, tumorigenicity, and metastasis of cutaneous neoplasms. *Clin Exp Metastasis* 2002;**19**:609–15.
- Gerlag DM, Borges E, Tak PP, Ellerby HM, Bredesen DE, Pasqualini R, *et al*. Suppression of murine collagen-induced arthritis by targeted apoptosis of synovial neovasculation. *Arthritis Res* 2001;**3**:357–61.
- van Holten J, Reedquist K, Sattone-Roche P, Smeets TJ, Plater-Zyberk C, Vervoordeldonk MJ, *et al*. Treatment with recombinant interferon-β reduces inflammation and slows cartilage destruction in the collagen-induced arthritis model of rheumatoid arthritis. *Arthritis Res Ther* 2004;**6**:R239–49.
- Triantaphyllopoulos KA, Williams RO, Tair H, Chernajovsky Y. Amelioration of collagen-induced arthritis and suppression of interferon-γ, interleukin-12, and tumor necrosis factor α production by interferon-β gene therapy. *Arthritis Rheum* 1999;**42**:90–9.
- Tak PP, Hart BA, Kraan MC, Jonker M, Smeets TJ, Breedveld FC. The effects of interferon β treatment on arthritis. *Rheumatology (Oxford)* 1999;**38**:362–9.
- Treschow AP, Teige I, Nandakumar KS, Holmdahl R, Issazadeh-Navikas S. Stromal cells and osteoclasts are responsible for exacerbated collagen-induced arthritis in interferon-β-deficient mice. *Arthritis Rheum* 2005;**52**:3739–48.
- Van Holten J, Pavelka K, Vencovsky J, Stahl H, Rozman B, Genovese IM, *et al*. A multicentre, randomised, double blind, placebo controlled phase II study of subcutaneous interferon β-1a in the treatment of patients with active rheumatoid arthritis. *Ann Rheum Dis* 2005;**64**:64–9.
- Wijbrandts CA, Vergunst CE, MD, Haringman JJ, Gerlag DM, Smeets TJ, Tak PP. Absence of changes in the number of synovial sublining macrophages after ineffective treatment for rheumatoid arthritis: implications for use of synovial sublining macrophages as a biomarker. *Arthritis Rheum* 2007;**56**:3869–71.
- Corr M, Boyle DL, Ronacher L, Flores N, Firestein GS. Synergistic benefit in inflammatory arthritis by targeting IκBε and IFNβ. *Ann Rheum Dis* 2009;**68**:257–63.
- Aupperle KR, Bennett BL, Han Z, Boyle DL, Manning AM, Firestein GS. NF-κB regulation by I kappa B kinase-2 in rheumatoid arthritis synoviocytes. *J Immunol* 2001;**166**:2705–11.
- Shimada T, Kawai T, Takeda K, Matsumoto M, Inoue J, Tatsumi Y, *et al*. IKK-ι, a novel lipopolysaccharide-inducible kinase that is related to IκappaB kinases. *Int Immunol* 1999;**11**:1357–62.
- Fitzgerald KA, McWhirter SM, Faia KL, Rowe DC, Latz E, Golenbock DT, *et al*. IKKε and TBK1 are essential components of the IRF3 signaling pathway. *Nat Immunol* 2003;**4**:491–6.
- Sweeney SE, Mo L, Firestein GS. Antiviral gene expression in rheumatoid arthritis: role of IKKε and interferon regulatory factor 3. *Arthritis Rheum* 2007;**56**:743–52.
- Vervoordeldonk MJ, Adriaansen J, Fallaux FJ, Tak PP. Gene therapy for rheumatoid arthritis. *Anti-Inflamm Anti-Allerg Agents Med Chem* 2007;**6**:109–20.
- Adriaansen J, Tas SW, Klarenbeek PL, Bakker AC, Appariailly F, Firestein GS, *et al*. Enhanced gene transfer to arthritic joints using adeno-associated virus type 5: implications for intra-articular gene therapy. *Ann Rheum Dis* 2005;**64**:1677–84.
- Appariailly F, Khoury M, Vervoordeldonk MJ, Adriaansen J, Gicquel E, Perez N, *et al*. Adeno-associated virus pseudotype 5 vector improve gene transfer in arthritic joints. *Hum Gene Ther* 2005;**16**:426–34.
- Adriaansen J, Kuhlman RR, van Holten J, Kaynor C, Vervoordeldonk MJ, Tak PP. Intra-articular interferon-β gene therapy ameliorates adjuvant arthritis in rats. *Hum Gene Ther* 2006;**17**:985–96.
- Adriaansen J, Fallaux FJ, de Cortie CJ, Vervoordeldonk MJ, Tak PP. Local delivery of β interferon using an adeno-associated virus type 5 effectively inhibits adjuvant arthritis in rats. *J Gen Virol* 2007;**88**:1717–21.