Two injections of interferon-α could trigger the development of rheumatoid arthritis

Sirs,

Various autoimmune diseases including rheumatoid arthritis (RA) have been admittedly manifested after interferon (IFN)-α therapy against malignancies or viral hepatitis (1-3). The manifestation of RA from the therapy takes usually several months (4-7). Here we present a case of RA which has been precipitated after only 2 injections of IFN-α and discussed the significance of IFN-α as a trigger of immune abnormalities in the pathogenesis of RA.

Eighteen months earlier, a 50-year-old woman began to feel polyarthralgia in the metacarpal, proximal interphalangeal (PIP) and wrist joints and the serum rheumatoid factor (RF) was positive, although her symptoms were self-limiting. Three months before admission, because of the renal cell carcinoma, she was administered after nephrectomy with 3 x 10^6 units of IFN-α (Sumiferon, Sumitomo Pharmaceutics, Japan), followed by spike fever and polyarthralgia, and the former subsided with aspirin. Because polyarthralgia gradually worsened and morning stiffness of the fingers was noted after the second injection performed a week later, IFN-α was discontinued, and she was referred to our clinic. There were no abnormalities except for swelling of bilateral PIP and wrist joints. The erythrocyte sedimentation rate (ESR) was 38 mm/h and CRP was 1.0 mg/dl. The titer of the serum RF determined by RF-III ELISA kit (Eiken Chemical Co., Japan) was 30 IU/ml (N < 10 IU/ml) and increased to 56 IU/ml 2 weeks later. The serum anti-nuclear antibody and antibodies to various viruses including EB virus, hepatitis C virus or human T-cell leukemia virus-1 was negative. An X-ray of the hand disclosed no osteoporosis or bone erosions. Under the diagnosis of RA according to the criteria by American Rheumatism Association (8), bucillamine, an anti-rheumatic agent, was administered. Ten weeks later, polyarthralgia, swelling of the joints and morning stiffness became mild, as the titer of RF decreased to 7 to 19 IU/ml. There has been no recurrence of renal cell carcinoma for more than 9 months.

In this case, polyarthritis flared up, persisted for over 8 weeks with elevated RF titers after only 2 injections of IFN-α and became mild 10 weeks after discontinuation of IFN-α, while the effect of bucillamine was uncertain. On the other hand, her clinical course was not compatible with paraneoplastic syndrome or viral infections. Although coincidence of the manifestation of RA and IFN-α therapy could not be excluded, from difference of the clinical course between 15 months before and 9 months after the IFN-α therapy, it is likely that the administration of IFN-α might have triggered off the manifestation of RA.

IFN-α is known to activate macrophages to secrete tumor necrosis factor (TNF)-α or interleukin (IL)-1, and to show chemotactic activity for neutrophils. Furthermore, it has been reported that IFN-α up-regulates expression of major histocompatibility complex antigens on antigen-presenting cells (9). Among proinflammatory cytokines, TNF-α and IL-1 have been thought important because they induce production of other proinflammatory cytokines or prostaglandins, proliferation of fibroblasts or activation of osteoclasts, all of which are involved in the pathogenesis of RA. Therefore, chronic stimulation with IFN-α is likely to be associated with exacerbation of RA. In general, 3 to 10 x 10^6 units/day of IFN-α is administered daily or once a week for several months. Time to onset of different autoimmune diseases after initiation of the IFN-α therapy has varied from 3 to 5 months in RA (2,10). From this case, very minor doses of IFN-α could be enough to trigger a vicious cycle of immune abnormalities associated with the pathogenesis of RA. Particularly, when the patients have a history of rheumatoid arthritis or arthralgia, IFN-α should be used carefully under consideration of the manifestation of RA.

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No association of interleukin-4 gene polymorphisms in Chinese patients with rheumatoid arthritis in Taiwan

Sirs,

The genetic background of RA is still mostly unknown. Only a few cytokine gene polymorphisms (TNFα, IL-6, and IL-1α) have been studied. To date, genetic studies of multifactorial diseases have been difficult due to uncertainty surrounding the presence of a polygenic trait. In the present study, we chose 2 gene polymorphisms (IL-4 promoter and IL-4 intron 3) to screen candidate genes located outside the MHC. The gene for IL-4 has been mapped to the q am (q23-31) of chromosome 5 (1), in a cluster of cytokine genes (IL-3, IL-5, IL-9, IL-13, IL-15, GM-CSF, and interferon regulatory factor). The polymorphism is a C to T change at position –590 counting from the first ATG codon (2). The polymorphism is upstream of all the previously described control elements of IL-4. Another polymorphism has been located in the third intron, and is composed of a variable number of tandem repeats (VNTR) of a 70-bp sequence (3).

The purpose of this study was to examine whether Interleukin-4 gene polymorphism are markers of susceptibility of rheumatoid arthritis (RA) in Taiwan. The study included 104 patients with RA (4) and 103 unrelated, healthy individuals who were living in the middle of Taiwan were used as controls. From genomic DNA, 2 polymorphisms in genes for IL-4 (IL-4 intron 3 and IL-4 promoter) were typed. Allelic frequencies and carriage rates were compared be-

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Table I. Comparison of allelic frequency between rheumatoid arthritis (RA) patients and control subjects.

	Alleles frequency			Carriage rate		
	RA	Controls	P	RA	Controls	P
IL4 Intron 3						
RP1	173 (83.2)	165 (80.1)	NS	101 (97)	99 (96.1)	NS
RP2	34 (16.3)	41 (19.9)	NS	31 (29.8)	37 (35.9)	NS
RP0	1 (0.5)	0	NS	1 (0.9)	0	
IL-4 promoter						
C	30 (14.4)	44 (21.4)	NS	27 (26)	38 (35.8)	NS
T	178 (85.6)	162 (78.6)	NS	101 (97.1)	97 (94.2)	NS

*NS: not significant.

tween RA patients and control populations. As shown in table, no significant associations were observed in the distribution of genotypes, cytokine allele frequencies, and carriage rates between patients with RA and healthy controls. Furthermore, no statistical association in the distribution of IL-4 gene polymorphism frequency between RF positive and RF negative patients was observed.

In our present study, the distribution of IL-4 genotype at intron 3 (RP1/RP1 64.1%,RP1/RP2 32% and RP2/RP 23.9%) and promoter (C/C 5.8%, C/T 31.1%, and T/T 63.1%) in healthy Taiwanese subjects was different with data reported by Cantagrel et al. (5) in French Caucasian controls (intron 3 RP1/RP1 0%, RP1/RP2 17.9% and RP2/RP2 82.1% and promoter C/C 69.5%, C/T 30.5%, and T/T 0%, respectively). Recently, Cantagrel *et al*. demonstrated that the RP1 allele of the IL-4 gene was found a significantly higher frequency in French Caucasian RA patients compared with controls (5). In addition, the independent OR for IL-4 RP1 and IL-4 –590* T alleles in RA susceptibility were both much lower than the OR for carriage of both of these alleles together. While RA patients positive for the RP2 allele was found associated with less joint destruction in another report by Buchs *et al.* (6). In our present study, we did not observe any association in the distribution of IL-4 (intron 3 and promoter) genotypes, cytokine allele frequencies, and carriage rates between patients with RA and healthy controls. Although the frequency of the genotype of IL-4 promoter C/T in the RF positive patients was higher than that of the RF negative patients,the association did not reach significant difference.

In summary, the polymorphisms in the IL4 gene (intron 3 and promoter) studied here did not reveal any association with an increased risk of developing RA in Taiwan Chinese when compared with the control group. These results may be due to ethnic factors and will need further confirmation.

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Melatonin in rheumatoid arthritis: A disease-promoting and modulating hormone?

Sirs,

An altered functioning of the hypothalamic-pituitary-adrenal/gonadal axis seems to be an important factor in the perpetuation and circadian symptoms of rheumatoid arthritis (RA) (1). As a matter of fact, the clinical symptoms of RA show a circadian variation with joint stiffness and pain being more prominent in the early morning. Consistently, human pro-inflammatory cytokine production exhibits a diurnal rhythmicity with peak levels during the night and early morning at a time when plasma cortisol is lowest (2). The existence of a causal relationship between plasma cortisol and production of inflammatory cytokines is suggested by the finding that administration of cortisone acetate at physiological doses results in a corresponding reduction in pro-inflammatory cytokine production (2). An inappropriate low secretion of cortisol is a further typical feature of the inflammatory disease in patients with RA (1). Similarly, the secretion of adrenal androgens is significantly reduced (1).

However, cortisol may not be the only hormone affecting cytokine rhythms; a strong candidate is the pineal indoleamine melatonin, the circadian hormone “par excellence”, whose synthesis and secretion is regulated by the photoperiod with peak levels during the night,darkness hours (3). The circadian nocturnal release of melatonin has a profound influence on the internal environment of the organism with diverse physiological effects. Its main function seems to be that of synchronising the organism in the photoperiod and may play a role in reproduction, metabolism, seasonality, thermoregulation and immunity (4). In peripheral blood mononuclear cells, melatonin has been reported to stimulate the production of interleukin-2 interferon-gamma and interleukin-6 but not that of interleukin-4 (5). Physiologically, the nocturnal MLT peak has been associated with high IFN-γ/interleukin-10 ratio, i.e. the melatonin rhythm positively correlated with the rhythmicity of T-helper cell type 1/ T helper cell type 2 ratio (6). In ischaemic stroke patients an impaired nocturnal MLT excretion has been associated with impaired cell-mediated immunity and changes of lymphocyte subsets (7). Relevant to RA, melatonin can promote collagen-induced arthritis in mice (8) and stimulate primary cultures of synovial macrophages from RA patients to produce interleukin-12 as well as nitric oxide (9).