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IL-6 and some natural inhibitors of chronic human inflammation in RA and SLE

Sir,

The role of IL-6 in chronic inflammation is hotly debated (1). It is thought to be pro-inflammatory in some experimental models of arthritis (2) while in others it seems to be protective (3). One of the ways by which IL-6 may become protective is through the stimulation of the synthesis of some cytokine antagonists, among which TNF R type I (tumor necrosis factor soluble receptor type I-TNF RI) and IL-1 receptor antagonist (IL-1Ra) are thought to be acute phase reactants (4, 5). Since the role of IL-6 on APPs is one of the major biological actions of the cytokine, the possible inter-relationship between IL-6 and cytokine antagonists belonging to the acute phase proteins might be of considerable interest *in vivo*. We report here on the inter-relationships between IL-6 and natural inhibitors in two chronic diseases, rheumatoid arthritis (RA) and systemic lupus erythematosus (SLE), derived from data on serum circulating levels.

We followed 15 patients with rheumatoid arthritis (RA) longitudinally for a period of six months, seeing them at entry into the study, and at months 1, 3 and 6 (60 assays) and tested serum IL-6, TNF RI (p55), IL-1 receptor antagonist (IL-1 Ra) and several other parameters. We observed a strong correlation between IL-6 and TNF RI, as well as between IL-6 and CRP (C reactive protein) values. However, no such relationship was seen between IL-6 values and IL-1Ra levels (Fig. 1). Thus, in RA we observed that the higher the initial IL6 (interleukin 6) response, the stronger appeared to be the synthesis and shedding of soluble TNF RI, but not that of IL-1Ra.

On the other hand, the relationship between IL-6 levels and TNF RI was confirmed in another chronic inflammatory disease, SLE (28 samples: $R = 0.42$, $p < 0.04$). No relationship was found between IL-6 and IL-1Ra. In SLE high levels of IL-1Ra were seen (17 patients) while the IL-6 levels were half those usually found in RA (2).

Therefore certain natural inhibitors such as TNF RI seem to be strongly correlated with IL-6 in chronic human inflammatory disorders such as RA and SLE, while others such as IL1 Ra are not. This suggests that IL-6 may act as an inducer of the synthesis and shedding of TNF RI.

The available data *in vivo* suggest that IL-6 deserves a new look by those studying chronic inflammatory diseases, as a potential indirect antagonist of the tissue damage induced by TNFα through the synthesis and shedding of TNF RI.

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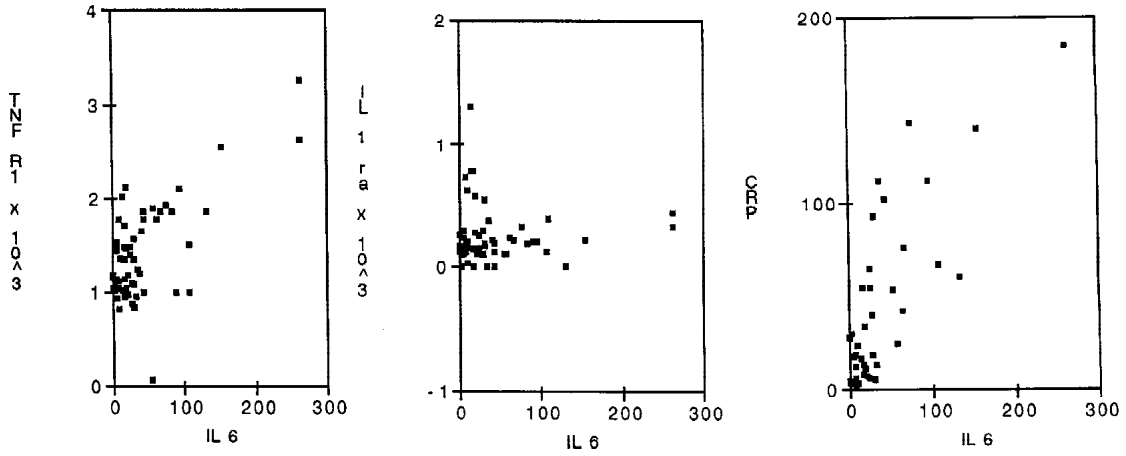

Fig. 1. Correlations over time between IL-6 (pg/ml) and TNF RI (pg/ml), IL-1 Ra (pg/ml), and CRP levels (mg/L) in rheumatoid arthritis.