Anti-Tumor Necrosis Factor Therapies Reduce Serum Macrophage Inflammatory Protein-1α in Ankylosing Spondylitis

To the Editor:

Chemokines orchestrate inflammatory status by stimulating the directional migration and activation of inflammatory cells. Synovial macrophages, lymphocytes, synoviocytes, and chondrocytes produce various chemokines, which are mainly stimulated by inflammatory cytokines in rheumatoid arthritis (RA)[1]. Although cytokines and chemokines are not fully characterized, tumor necrosis factor-α (TNF-α) is overexpressed in sacroiliac joints[2], and TNF-α blockade improves the outlook for spondyloarthropathies[3]. We evaluated serum concentrations of monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1α (MIP-1α) and the effects of anti-TNF therapies on chemokines in patients with RA and ankylosing spondylitis (AS).

Our study included 14 patients (8 RA, 6 AS) who were diagnosed according to established criteria and 13 healthy control subjects. Disease activities were determined. Nine patients received etanercept (25 mg twice in a week), and 5 patients received adalimumab (40 mg twice in a month).

Blood samples were drawn at Days 0, 1, and 60 from all patients and at Day 0 from the controls. Serum MCP-1 and MIP-1α levels were measured by ELISA (BioSource International, Camarillo, CA, USA). The minimum detectable concentrations of MCP-1 and MIP-1α were 5 and 2 pg/ml, respectively. Intra- and interassay variations were 3.6% and 7.4%, respectively, for MCP-1 and 5.5% and 6.8% for MIP-1α. Mann-Whitney U test and Wilcoxon's signed-rank test were used for statistical analysis.

MIP-1α levels were significantly higher in the RA and AS groups than in the control group although MCP-1 levels were not different among the groups (Table 1). MIP-1α level correlated with levels of erythrocyte sedimentation rate and C-reactive protein ($r = 0.860$, $p < 0.01$, and $r = 0.752$, $p < 0.05$, respectively) in RA patients and with MCP-1 level in controls ($r = 0.623$, $p < 0.05$). The anti-TNF therapies reduced Disease Activity Score-28 (5.2 ± 1.1 to 3.7 ± 0.5) and Bath AS Disease Activity Index (5.1 ± 1.1 to 2.9 ± 0.6) in RA and AS patients ($p < 0.05$ for both); and also reduced MIP-1α levels in AS patients, but not in RA; and they did not alter MCP-1 levels in either group.

Enhanced levels of MCP-1 have been reported in RA; however, anti-MCP-1 monoclonal antibody was not found to be clinically effective[4,5]. In our study, MCP-1 levels in RA and AS patients were similar to levels in controls, suggesting that MCP-1 may not play a significant role in the pathogenesis of these diseases. The reported MCP-1 levels have not been higher in AS, psoriatic arthritis (PsA), or reactive arthritis[6-8].

Abundant levels of MIP-1α have been found in patients with RA[9]; however, reported levels of MIP-1α have not been higher in AS, but have been higher in PsA[6,10]. In our study, levels of MIP-1α were higher in AS and in RA. Although histopathological data are limited for AS, there is synovitis, and subsequent pannus formation and granulation tissue in sacroiliitis[11]. Moreover, various inflammatory cells infiltrate synovial tissue, suggesting that they play important roles in AS[3]. In our study, increased MIP-1α levels in AS may support the pivotal role of MIP-1α in the pathogenesis of AS.

TNF-α stimulates MCP-1 production from synovial cells, and etanercept decreases the level of serum MCP-1 in RA[4]. Anti-TNF-α monoclonal antibody decreases synovial MCP-1 expression but not the production of other chemokines in RA[12]. Subsequent reports also documented that infliximab cannot alter serum MIP-1α levels in RA or AS[10,13]. Conversely, sTNFR:Fc/p80 decreased MIP-1α expression in experimentally induced autoimmune encephalomyelitis[14]. In our study, anti-TNF therapies decreased the level of MIP-1α in patients with AS.

We conclude MIP-1α may play a role in the pathogenesis of AS.

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Table 1. Serum MCP-1 and MIP-1α levels in patients treated with anti-TNF therapy vs controls.

	Controls, n = 13	RA, n = 8			AS, n = 6		
		Day 0	Day 1	Day 60	Day 0	Day 1	Day 60
MCP-1, pg/ml	85.9 ± 42.4	77.6 ± 37.1	59.3 ± 20.5	70.2 ± 27.8	118.6 ± 57.3	85.1 ± 43.2	127.4 ± 33.6
MIP-1α, pg/ml	8.1 ± 2.4	45.4 ± 61.4**	19.4 ± 24.1	9.3 ± 3.8	81.8 ± 104.6*	44.3 ± 59.7	32.7 ± 34.1†

* $p < 0.01$, ** $p < 0.05$ compared to controls. † $p < 0.05$ compared to Day 0. RA: rheumatoid arthritis; AS: ankylosing spondylitis; MCP: monocyte chemoattractant protein; MIP: macropage inflammatory protein.

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