

Anti-Tumor Necrosis Factor Therapies Reduce Serum Macrophage Inflammatory Protein-1 α 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 joints², and TNF- α blockade improves the outlook for spondyloarthropathies³. We evaluated serum concentrations of monocyte chemoattractant protein-1 (MCP-1) and macrophage inflammatory protein-1 α (MIP-1 α) 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-1 α levels were measured by ELISA (BioSource International, Camarillo, CA, USA). The minimum detectable concentrations of MCP-1 and MIP-1 α 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-1 α . Mann-Whitney U test and Wilcoxon's signed-rank test were used for statistical analysis.

MIP-1 α 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-1 α 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-1 α 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 arthritis⁶⁻⁸.

Abundant levels of MIP-1 α have been found in patients with RA⁹; however, reported levels of MIP-1 α have not been higher in AS, but have been higher in PsA^{6,10}. In our study, levels of MIP-1 α 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 sacroiliitis¹¹. Moreover, various inflammatory cells infiltrate synovial tissue, suggesting that they play important roles in AS³. In our study, increased MIP-1 α levels in AS may support the pivotal role of MIP-1 α in the pathogenesis of AS.

TNF- α stimulates MCP-1 production from synovial cells, and etaner-

cept decreases the level of serum MCP-1 in RA⁴. Anti-TNF- α monoclonal antibody decreases synovial MCP-1 expression but not the production of other chemokines in RA¹². Subsequent reports also documented that infliximab cannot alter serum MIP-1 α levels in RA or AS^{10,13}. Conversely, sTNFR:Fc/p80 decreased MIP-1 α expression in experimentally induced autoimmune encephalomyelitis¹⁴. In our study, anti-TNF therapies decreased the level of MIP-1 α in patients with AS.

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

HANDAN AKBULUT, MD, Associate Professor, Department of Immunology; SULEYMAN S. KOCA, MD, Associate Professor; METIN OZGEN, MD, Rheumatology Fellow; AHMET ISIK, MD, Professor, Department of Rheumatology, Faculty of Medicine, Firat University, 23119 – Elazig, Turkey. Address correspondence to Dr. Koca; E-mail: kocassk@yahoo.com

REFERENCES

- Iwamoto T, Okamoto H, Toyama Y, Momohara S. Molecular aspects of rheumatoid arthritis: chemokines in the joints of patients. *FEBS J* 2008;275:4448-55.
- François RJ, Neure L, Sieper J, Braun J. Immunohistological examination of open sacroiliac biopsies of patients with ankylosing spondylitis: detection of tumour necrosis factor alpha in two patients with early disease and transforming growth factor beta in three more advanced cases. *Ann Rheum Dis* 2006;65:713-20.
- Smith JA, Märker-Hermann E, Colbert RA. Pathogenesis of ankylosing spondylitis: current concepts. *Best Pract Res Clin Rheumatol* 2006;20:571-91.
- Kageyama Y, Kobayashi H, Kato N, Shimazu M. Etanercept reduces the serum levels of macrophage chemotactic protein-1 in patients with rheumatoid arthritis. *Mod Rheumatol* 2009;19:372-8.
- Haringman JJ, Gerlag DM, Smeets TJ, Baeten D, van den Bosch F, Bresnihan B, et al. A randomized controlled trial with an anti-CCL2 (anti-monocyte chemotactic protein 1) monoclonal antibody in patients with rheumatoid arthritis. *Arthritis Rheum* 2006;54:2387-92.
- Szodoray P, Alex P, Chappell-Woodward CM, Madland TM, Knowlton N, Dozmorov I, et al. Circulating cytokines in Norwegian patients with psoriatic arthritis determined by a multiplex cytokine array system. *Rheumatology* 2007;46:417-25.
- Choe JY, Lee MY, Rheem I, Rhee MY, Park SH, Kim SK. No differences of carotid intima-media thickness between young patients with ankylosing spondylitis and healthy controls. *Joint Bone Spine* 2008;75:548-53.
- Haringman JJ, Smeets TJ, Reinders-Blankert P, Tak PP. Chemokine and chemokine receptor expression in paired peripheral blood mononuclear cells and synovial tissue of patients with rheumatoid arthritis, osteoarthritis, and reactive arthritis. *Ann Rheum Dis* 2006;65:294-300.
- Koch AE, Kunkel SL, Harlow LA, Mazarakis DD, Haines GK, Burdick MD, et al. Macrophage inflammatory protein-1 alpha. A novel chemotactic cytokine for macrophages in rheumatoid arthritis. *J Clin Invest* 1994;93:921-8.

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

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

10. Duftner C, Dejaco C, Kullich W, Klauser A, Goldberger C, Falkenbach A, et al. Preferential type 1 chemokine receptors and cytokine production of CD28⁺ T cells in ankylosing spondylitis. *Ann Rheum Dis* 2006;65:647-53.
11. Francois RJ, Gardner DL, Degraeve EJ, Bywaters EG. Histopathologic evidence that sacroiliitis in ankylosing spondylitis is not merely enthesitis. *Arthritis Rheum* 2000;43:2011-24.
12. Taylor PC, Peters AM, Paleolog E, Chapman PT, Elliott MJ, McCloskey R, et al. Reduction of chemokine levels and leukocyte traffic to joints by tumor necrosis factor alpha blockade in patients with rheumatoid arthritis. *Arthritis Rheum* 2000;43:38-47.
13. Torikai E, Kageyama Y, Suzuki M, Ichikawa T, Nagano A. The effect of infliximab on chemokines in patients with rheumatoid arthritis. *Clin Rheumatol* 2007;26:1088-93.
14. Glabinski AR, Bielecki B, Kawczak JA, Tuohy VK, Selmaj K, Ransohoff RM. Treatment with soluble tumor necrosis factor receptor (sTNFR):Fc/p80 fusion protein ameliorates relapsing-remitting experimental autoimmune encephalomyelitis and decreases chemokine expression. *Autoimmunity* 2004; 37:465-71.

J Rheumatol 2010;37:5; doi:10.3899/jrheum.091469