ANTI-IL-6 receptor antibody therapy reduced serum matrix metalloproteinase-1 and -3 in rheumatoid arthritis

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Objective: Metalloproteinases (MMPs) are capable of degrading most of the proteoglycans and collagens of cartilage and bone, and considered playing important roles in destruction of joints of the patients with rheumatoid arthritis (RA). Recently, antibodies and receptor antagonists against inflammatory cytokines are reported to be effective as therapeutic agents for RA. We have shown that humanized anti-IL-6 receptor (IL-6R) antibody improves not only clinical symptoms but also laboratory abnormalities. To know whether anti-IL-6R antibody therapy influences MMPs and their inhibitors production, we measured MMPs and tissue inhibitors of metalloproteinase (TIMPs) in sera from RA patients treated with the humanized anti-IL6R antibody, MRA. We also examined synergistic effects of IL-6, TNFα and IL-1β on the production of MMPs and TIMPs from RA synovial cells in vitro.

Method: Eight patients with RA were analyzed for the serum MMP-1, -2, -3, -7, -8, -13 and TIMP-1, and -2 by the sandwich enzyme immunoassay systems before and 2 months after treatment with MRA (50 mg/body, I.V. infusion twice weekly). MMP-1, -3, and TIMP-1 in the culture supernatants of synovial cells treated by IL-6, TNFα and /or IL-1β was also examined.

Results: MRA treatment achieved ACR20% response in 7/8 patients and ACR50% in 4/8. Serum MMP-1, -3, and TIMP-1 levels of the patients before MRA therapy were significantly higher than normal individuals, and reduced by the MRA therapy. In vitro experiment revealed that IL-6 alone could not induce MMP-1 or MMP-3 production but augmented TNFα or IL-1β-induced production of MMP-1 and MMP-3 from synovial cells. Anti-IL-6R antibody inhibited the augmentation of MMP production by IL-6. Any of these cytokines could not induce TIMP-1 production, in vitro.

Conclusion: Anti-IL-6R antibody therapy may prevent the destruction of RA joints by reducing MMP-1 and -3 production.