Concomitant DMARD Therapies Increase Adalimumab Serum Concentrations in Patients With Rheumatic Diseases

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Patients with rheumatoid arthritis (RA) who are treated with adalimumab plus methotrexate (MTX) have higher serum trough levels of adalimumab and a better clinical response to therapy than patients treated with adalimumab alone [Pouw MF et al. *Ann Rheum Dis* 2013]. The Combination Therapy With Adalimumab in Subjects With Early Rheumatoid Arthritis trial [CONCERTO; Burmester G-R et al. *Ann Rheum Dis* 2014] showed that steady-state serum trough concentrations of adalimumab increased with increasing doses of MTX up to 10 mg/week. Charlotte Krieckaert, MD, PhD, Jan van Breemen Research Institute, Reade, The Netherlands, discussed the effect on adalimumab serum concentrations in patients with RA or psoriatic arthritis (PsA) taking concomitant MTX and concomitant disease-modifying antirheumatic drugs (DMARDs) other than MTX.

This observational study combined 2 cohorts of patients at Prof. Krieckaert's institution, a total of 375 patients including 272 with RA and 103 with PsA. All patients received adalimumab 40 mg subcutaneously every other week. Adalimumab serum trough concentrations were measured using enzyme-linked immunosorbent assay at 0, 4, 16, and 28 weeks of treatment. The statistical analysis used a general estimating equation; for patients discontinuing adalimumab (n=51) or receiving an increased dose of adalimumab (n=29) before 28 weeks of treatment, a last observation carried forward method was used. Patients were divided into 4 treatment groups: monotherapy with adalimumab (n=67), adalimumab plus MTX (n=224), adalimumab plus DMARDs other than MTX (n=26), and adalimumab plus MTX plus another DMARD (n=58). DMARDs other than MTX included leflunomide (n=15), hydroxycholoroquine (n=3), sulfasalazine (n=6), and combinations of these agents (n=2).

Adalimumab serum concentrations increased over the course of the study and reached steady state in the adalimumab monotherapy group by Week 4. Steady-state adalimumab concentrations were reached in the combination therapy groups by Week 16. Adalimumab concentrations were significantly increased in the presence of concomitant MTX ($p<0.001$), concomitant DMARDs plus MTX ($p<0.001$), and concomitant DMARDs other than MTX ($p=0.011$) compared with adalimumab monotherapy. There was no statistically significant difference in adalimumab concentrations between the group receiving DMARDs other than MTX and the groups receiving either MTX or MTX plus other DMARDs.

DMARDs other than MTX appear to increase serum trough concentrations of adalimumab. The highest adalimumab concentrations were observed in patients taking concomitant MTX with or without other DMARDs. The lowest adalimumab concentrations were seen in patients receiving adalimumab monotherapy.

There were only 26 patients in the group receiving DMARDs other than MTX, so results from this group should be interpreted with caution, particularly because there were several different DMARDs administered at different doses. The mechanism underlying the increase in adalimumab concentrations is not known. It could be due to suppression of antiadalimumab antibodies, although only 10% of patients in these cohorts developed anti-adalimumab antibodies. Higher adalimumab levels could also be the result of additional suppression of inflammation by the DMARDs other than MTX, with less available target resulting in more free circulating adalimumab. These possibilities could form the basis of further studies.

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