

Is attenuated COBRA treatment strategy (COBRA-light) non-inferior or not non-inferior than original COBRA strategy?

Sirs,

The treatment of rheumatoid arthritis (RA) patients with the combination of disease-modifying anti-rheumatic drugs (DMARDs) in the early phase of disease was a frequent practice. It was thought that combination treatment might provide better control of disease activity and radiographic progression as well. Actually, one of the most famous combinations, the COBRA (Combinatietherapie Bij Reumatoïde Artritis) therapy regimen, revealed that immediate combination of high-dose prednisolone (60 mg/day), methotrexate (MTX) and sulfasalazine (SSZ) may provide better disease control over SSZ alone (1). However, this regimen was not commonly used. In addition, recent systematic review showed that by using the tight control and treat-to-target strategies immediate combination of DMARDs may no longer have clinical and radiographic advantages over 'step-up' therapy. Because of these handicaps of the COBRA protocol, in a recent paper the efficacy of the COBRA-light regimen was evaluated (2). In contrast to original COBRA therapy (in which prednisolone started at 60 mg/day), COBRA-light protocol was started with prednisolone 30 mg/day and tapered to 7.5 mg/day in 9 weeks. However, total prednisolone dose was only marginally different between groups (2328 mg vs. 2013mg). The other major differences between originally proposed COBRA and the COBRA-light treatments are the up to date dosing of MTX (up to 25 mg/week in all patients) and exclusion of SSZ from the combination.

The authors tested the efficacy of COBRA-light regimen at 26 weeks by using a randomised controlled, non-inferiority trial design. They stated that the primary out-

come of this trial was the mean Δ DAS44 after 26 weeks. In this study the non-inferiority margin was set at a difference in change (Δ DAS44) of 0.5 points. However, the measurement error for DAS44 was known as 0.6 and the change of 1.2 was considered as a significant change (3). At week 26, the between-group difference regarding the change in DAS44 was reported as 0.33 (95% CI -0.03 to 0.68). The confidence interval for Δ DAS44 at 26 weeks includes the predefined non-inferiority boundaries, therefore this study failed to show the non-inferiority of COBRA-light protocol than original COBRA. If the DAS44 had been calculated by C-reactive protein this time Δ DAS44 would be 0.044 (95% CI -0.29 to 0.38) and it is less than the non-inferiority margin. However, it should be kept in mind that DAS-CRP was not the primary end-point reported for this study and this study was not powered to show for Δ DAS44-CRP. Despite these results, the conclusion of COBRA-light therapy as a feasible alternative to COBRA therapy in the first 6 months' might not be fully appropriate.

Moreover, in the most recent article reporting the one-year clinical and radiological outcomes of this trial (4), the authors used the statement 'COBRA-light was non-inferior to COBRA in clinical outcomes, safety and efficacy after 26 weeks of treatment'. Again we thought that this statement would not reflect the results of the primary outcome. Accordingly, the follow-up paper also showed that more COBRA-light patients (66%) needed to start etanercept than COBRA patients (57% and $p=0.04$) (4).

S. AKAR¹
M. TINAZLI²

¹Department of Internal Medicine,
Division of Rheumatology, Izmir Katip
Celebi University School of Medicine,
Izmir, Turkey;

²Department of Internal Medicine,
Near East University School of Medicine,
Lefkosa, North Cyprus.

Address correspondence to:

Servet Akar, MD,
Izmir Katip Celebi
University School of Medicine,
Department of Internal Medicine,
Division of Rheumatology,
Basinsitesi-Izmir, Turkey.
E-mail: servet.akar@gmail.com

Competing interests: none declared.

References

1. BOERS M, VERHOEVEN AC, MARKUSSE HM *et al.*: Randomised comparison of combined step-down prednisolone, methotrexate and sulphasalazine with sulphasalazine alone in early rheumatoid arthritis. *Lancet* 1997; 350: 309-18.
2. DEN UYL D, TER WEE M, BOERS M *et al.*: A non-inferiority trial of an attenuated combination strategy ('COBRA-light') compared to the original COBRA strategy: clinical results after 26 weeks. *Ann Rheum Dis* 2014; 73: 1071-8.
3. ANDERSON JK, ZIMMERMAN L, CAPLAN L, MICHAUD K: Measures of rheumatoid arthritis disease activity: Patient (PtGA) and Provider (PrGA) Global Assessment of Disease Activity, Disease Activity Score (DAS) and Disease Activity Score with 28-Joint Counts (DAS28), Simplified Disease Activity Index (SDAI), Clinical Disease Activity Index (CDAI), Patient Activity Score (PAS) and Patient Activity Score-II (PASII), Routine Assessment of Patient Index Data (RAPID), Rheumatoid Arthritis Disease Activity Index (RADAI) and Rheumatoid Arthritis Disease Activity Index-5 (RADAI-5), Chronic Arthritis Systemic Index (CASI), Patient-Based Disease Activity Score With ESR (PDAS1) and Patient-Based Disease Activity Score without ESR (PDAS2), and Mean Overall Index for Rheumatoid Arthritis (MOI-RA). *Arthritis Care Res (Hoboken)* 2011; 63 (Suppl. 11): S14-36.
4. TER WEE MM, DEN UYL D, BOERS M *et al.*: Intensive combination treatment regimens, including prednisolone, are effective in treating patients with early rheumatoid arthritis regardless of additional etanercept: 1-year results of the COBRA-light open-label, randomised, non-inferiority trial. *Ann Rheum Dis* 2014 May 12 [Epub ahead of print].