Severe Refractory Rheumatoid Arthritis Successfully Treated with Combination Rituximab and Anti-Tumor Necrosis Factor-α-Blocking Agents

To the Editor:

Despite the efficacy of anti-tumor necrosis factor-α (TNF-α) agents in rheumatoid arthritis (RA), about 30% of patients seem to have no response or no sustained response[1]. Other drugs such as rituximab have proven efficacy in refractory RA including in patients resistant to anti-TNF[2-5]. However, clinical experience shows that some patients may not respond to both therapies. We describe 2 patients with very severe refractory RA who failed to respond to anti-TNF or rituximab used alone, but who strikingly responded to the combination of rituximab and anti-TNF with sustained remission and good tolerance.

A 45-year-old woman was diagnosed with RA in 2003, with symmetric polyarthritis of the wrists, with antibodies positive for rheumatoid factor (RF) and anti-cyclic citrullinated protein (CCP) and increased C-reactive protein (68 mg/l). Initial radiographs were normal. Disease remained active despite conventional disease modifying antirheumatic drugs (DMARD) including methotrexate (MTX, 20 mg/week). She did not respond to adalimumab, even used once a week. At that time she presented a very pronounced alteration of health status, with generalized inflammation (CRP 292 mg/l). Other etiologies of systemic inflammation including infections and tumors were excluded. In March 2004, 2 infusions of rituximab 1 g on Days 1 and 15 were performed. Concomitant treatment consisted of MTX 20 mg/week and prednisolone 10 mg/day. A second cycle was performed in August 2004 (CRP 212 mg/l at time of infusion). In October 2004, the disease remained active; anti-TNF therapy was reinitiated, this time using etanercept 50 mg/week, leading to a 2-year remission. In November 2006, she developed a new flare. Etanercept was stopped and a third cycle of rituximab was administered. No clear response was observed and a fourth cycle of rituximab was performed in July 2007, but this time etanercept was reintroduced 2 weeks after the second infusion of rituximab. In September 2007, she was once again in remission with CRP 12 mg/l. She remains in remission in March 2009 with cycles of rituximab every 6 months and concomitant etanercept (Figure 1).

A 32-year-old man was diagnosed with RA in 1999, revealed by symmetric swelling of fingers, wrists, and knees. RF and anti-CCP antibodies were negative. Hand radiographs revealed small erosions of carpal bones. Initial treatments included sulfasalazine, prednisolone 10 mg/day, and MTX 10 mg/week that was stopped from March 2001 to May 2002 due to his wish to have a child. Inadequate response led to the introduction of etanercept in April 2004, with initial control of the disease. In November 2005 a new arthritic flare led to a switch to adalimumab 40 mg every 2 weeks. No improvement was obtained in February 2006. He preferred a switch back to etanercept despite the suggestion to start anti-CD20 therapy. In November 2006, after a total hip replacement, a first cycle of rituximab was performed. At the time of infusion, Disease Activity Score (DAS28) was 5.52 and CRP 125 mg/l. Four months later, no clinical or biological response had been obtained, and etanercept was reintroduced in April 2007, allowing remission (DAS = 2.21; CRP < 5 mg/l). A second cycle of rituximab was performed in October 2007 (DAS = 4.41 and CRP 32 mg/l). Since January 2008, he has been in remission (DAS = 2.46; CRP 4 mg/l), with rituximab cycles every 6 months and concomitant etanercept therapy. Changes in CRP values with time are shown in Figure 2.

Daily practice has shown that the management of aggressive and refractory forms of RA is difficult[5]. In our Patient 1, one may speculate that etanercept alone may have been effective, but the flare in November 2006 does not suggest this. Complete remission in RA is rarely obtained by the blockade of one pharmacologic pathway[6], which supports the concept of using MTX concomitantly with anti-TNF treatment. From a pharmacodynamic point of view, the combination of anti-TNF and CD20 B cell-blockade differs from any other previous combination therapy because of its selective action on both a cytokine pathway and lymphocyte inactivation, leading to a highly synergistic action. Due to the risk of infectious diseases, only very scarce data are available regarding combination of biologic agents. Trials investigating combinations of anti-TNF-α and anakinra[7] and anti-TNF and abatacept showed a higher risk of serious infections. In our 2 cases, we observed no complication after a followup of 4 years (Patient 1) and 18 months (Patient 2). It must be added that at the time of introduction of the combination, neither abatacept[8] nor tocilizumab[9] were available, and patients with such severe refractory RA could not ethically be enrolled in placebo clinical trials. Recently, a report on the combination of rituximab and etanercept also suggests its safety and efficacy in 8 patients with RA[10]. These results cannot support the generalization of this combination of biotherapy, but suggest its feasibility in the very rare cases of multidrug resistance in patients with severe RA.

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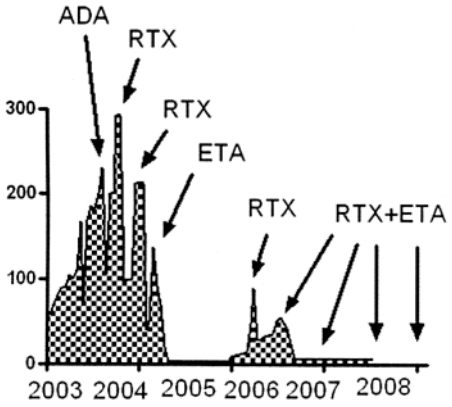

Figure 1. Patient 1: changes in CRP values (mg/l) from 2003 to 2008 and treatments with biologics, etanercept (ETA), adalimumab (ADA), and rituximab (RTX).

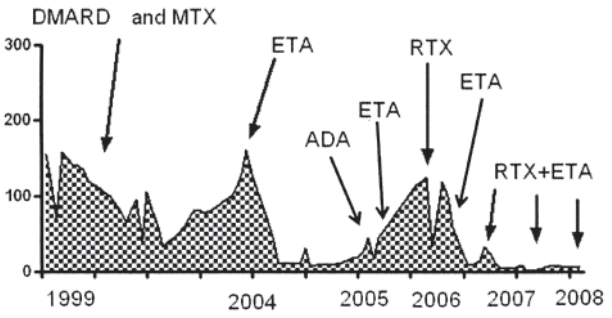

Figure 2. Patient 2: changes in CRP (mg/l) from 1999 to 2008 and treatments with DMARD and biologics, etanercept (ETA), adalimumab (ADA), and rituximab (RTX).

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J Rheumatol 2009;36:9; doi:10.3899/jrheum.090160