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

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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 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).


