Severe Parkinson’s disease in rheumatoid arthritis patient treated with infliximab

Sir, Infections are the most common adverse events associated with the use of tumour necrosis factor-α (TNF-α) inhibitors in rheumatoid arthritis (RA), and neurological complications are far less common. Nevertheless, the review of the Adverse Events Reporting System of the Food and Drug Administration (FDA) revealed a number of neurological events suggestive of demyelination that occurred during anti-TNF-α therapy [1]. Moreover, two studies on the use of TNF-α inhibitors in multiple sclerosis have been discontinued as exacerbations of neurological symptoms occurred in patients receiving study drugs [2].

We report on a 72-yr-old female patient with RA who developed severe Parkinson’s disease while treated with infliximab. Her arthritis started in 1997 with symmetric involvement of proximal interphalangeal joints and wrists and then progressed to symmetric polyarthritis involving most peripheral joints. The diagnosis of RA was made according to the clinical picture, presence of erosions on hand radiograms and positive rheumatoid factor, and a standard therapy with non-steroidal anti-inflammatory drugs, prednisone and methotrexate (12.5 mg/week) was introduced. As the disease progressed, anti-TNF-α treatment with infliximab (3 mg/kg i.v. every 8th week) was added. The arthritis improved rapidly after the first infusion of infliximab; by week 2, tender joint count and swollen joint count fell from 12 and 7 to 5 and 4, respectively, followed by a fall in the duration of morning stiffness, erythrocyte sedimentation rate and serum C-reactive protein. About 1 week later she noticed a sensation of stiffness different from that experienced from RA and a slight tremor of the right upper extremity. On her GP’s advice, she consulted a neurologist who diagnosed early-onset Parkinson’s disease (PD) and introduced low-dose l-dopa and benserazide, which were then gradually increased. The therapy for RA was continued and she was given a total of nine i.v. infliximab infusions over a 12-month treatment period. Although a full remission of arthritis was achieved, symptoms of PD progressed rapidly. One year after the first symptoms occurred, she suffered from severe generalized rigidity and tremor, was unable to walk and had difficulty in speaking, swallowing and even breathing deeply.

This case raises the question of whether RA treatment with infliximab may induce and/or accelerate PD in some (elderly?) patients. The data collected so far suggest that there is a link between the TNF family receptors and caspases in PD [3, 4] and that TNF-α may be toxic to mesencephalic dopamine neurons [5, 6]. Moreover, the frequency of the –1031C TNF-α gene allele, a high producer of TNF-α, was significantly increased in Japanese patients with early-onset PD compared with matched healthy controls [7]. In one study, cultures of dopaminergic cells exposed to both lipopolysaccharide (LPS) and neutralizing antibodies to TNF-α showed an attenuation of the LPS-induced cell loss by at least 50% [8]. Taken together, these data suggest that TNF-α blockade may be beneficial in patients with PD. One must be aware, however, that similar considerations gave rise to the studies on the use of TNF-α inhibitors in patients with multiple sclerosis, with known disappointing results.

Further surveillance is needed to better define risk factors associated with TNF-α blockade in RA. Special consideration should be given to patients with pre-existing neurological symptoms and to those who develop new neurological signs and symptoms on anti-TNF-α therapy.

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