

Guillain-Barré syndrome following adalimumab treatment

Sirs,

Tumour necrosis factor alpha (TNF- α) antagonist therapy has been associated with the onset of several demyelinating diseases of the central nervous system (CNS) and the peripheral nervous system (PNS), including Guillain-Barré syndrome (GBS), optic neuritis, chronic inflammatory demyelinating polyneuropathy, transverse myelitis and multiple sclerosis.

We report a patient with long-standing rheumatoid arthritis (RA), who developed GBS during adalimumab treatment after approximately seven years of anti-TNF- α therapy. The case has been reported to the Italian Pharmacovigilance System (registered as n. 140664).

In May 2000, a 57-year-old man was diagnosed with seronegative RA. After ineffective treatments, he started therapy with infliximab at 3mg/kg every 8 weeks in September 2003. The treatment was withdrawn after 15 months because of leukopenia. After a RA flare he started etanercept 50 mg/week in January 2005. The patient was admitted to our Rheumatology Department in April 2005 due to cutaneous vasculitis affecting the lower limbs. His medical history was uneventful except for arterial hypertension. Laboratory investigation showed an increased level of erythrocyte sedimentation rate (43 mm/h, n.v. <25); rheumatoid factor, tests for cryoglobulins, antinuclear antibodies and antiphospholipid antibodies were negative. Etanercept therapy was interrupted and steroid treatment was started. After four months, adalimumab at 40 mg every two weeks was initiated.

In January 2011 the patient was admitted to a Neurology Department because of mild weakness, paraesthesia and loss of cutaneous sensibility in the lower limbs with proximal progression. He reported a three-day history of malaise and cold. Physical examination revealed mild motor deficit and impairment of proprioceptive and exteroceptive sensibility in the lower limbs with distal involvement and paraparetic walking. A cervical and lumbar spine magnetic resonance imaging did not reveal any abnormality. The electromyogram showed a large reduction of motor and sensory nerve conduction velocities in the lower limbs with conduction blocks, without muscle involvement. Cutaneous sympathetic reflex responses latency was augmented and amplitude was reduced in the left lower limb. A lumbar puncture revealed a limpid and colourless cerebrospinal fluid with protein level of 0.36g/dl, glycochachia at 0.55g/dl, erythrocytes 8/mm³, leucocytes 1/mm³. Serum and cerebrospinal fluid dosage of anti-peripheral nerve autoantibodies was not performed.

A diagnosis of GBS was made and the patient was treated with a course of intrave-

nous immunoglobulin, physical therapy and neurological rehabilitation.

After five days the patient was discharged in good general condition. At present he remains off anti-TNF- α therapy.

Anti-TNF- α agents have been associated to the onset of GBS and its variant Miller Fisher syndrome (MFS) in the medical literature.

A search (1) in the US Food and Drug Administration's Adverse Events Reporting System database performed in September 2004 using the preferred terms "Guillain-Barré syndrome" and "Miller Fisher syndrome" from the Medical Dictionary for Regulatory Activities identified 15 patients diagnosed with GBS in temporal association with TNF- α antagonist therapy. Nine patients received infliximab, five received etanercept and one received adalimumab. Clinical and/or diagnostic information were not provided for 2 of these 15 patients. The authors described one additional patient who developed a progressively worsening, relapsing-remitting ataxia and dysarthria that evolved into the MFS over 6 months while he received three successive infusions of infliximab. The median age of these 14 patients was 56 years (range 34–81 years). Electrodiagnostic studies (9 patients) were compatible with a peripheral demyelinating process. The interval was 6 weeks to 2 years between the start of drug infusion and the onset of GBS. Reported antecedent events that may have played a role in the development of GBS included upper respiratory tract infections (3 patients), flu-like illness (2 patients), flu vaccine (1 patient) and fever of undetermined cause (2 patients).

We retrieved two additional cases of GBS during anti-TNF- α therapy in a 46-year-old woman with a 6-year history of seropositive RA after three infusions of infliximab (2) and in a 47-year-old woman affected by ankylosing spondylitis secondary to ulcerative colitis after her third dose of infliximab (3). MFS in a 77-year-old female patient with seropositive erosive RA has been reported after the second injection of adalimumab (4). An internet search from the Medicine and Healthcare products Regulatory Agency, UK spontaneous surveillance database revealed 2 suspected GBS cases following adalimumab, 6 following infliximab and 3 following etanercept (5).

We describe a primary myelinic form of GBS with secondary axonal involvement during long-term anti TNF- α therapy as documented by the conduction blocks and the prolonged motor latencies reported in the electroneurography examination. Although in our patient the exposure to TNF- α blockers before the onset of the neurological symptoms has been longer than that reported in the literature, we postulate an atypical immune response induced by adalimumab as a possible cause for the development of GBS triggered by an upper respiratory tract infection. The clinical expression of GBS in immunogenetically susceptible patients following

TNF- α antagonists treatment may have related to TNF- α immunoregulatory functions. The prolonged administration of TNF- α antagonists is thought to enhance autoimmune responses by altering antigen presenting cell function, potentiating T-cell receptor signalling and decreasing apoptosis of auto reactive T cells. TNF- α deficiency in the PNS compartment due to the access of systemically administered TNF- α antagonists could lead to failed regression of myelin-specific T cell reactivity and prolonged survival of activated T cells thus increasing the risk of developing or prolonging an immune-mediated neuropathy. Therefore, TNF- α antagonist therapy could promote the development of GBS by augmenting the number of activated peripheral T cells, or by disturbing the intrinsic balance of TNF- α and its receptors in the local PNS compartment (6).

Since 2004, the British Society of Rheumatology has recommended avoidance of TNF- α blockers in patients with pre-existing demyelinating disease and suggests withdrawal of therapy if demyelination occurs in patients without previous illnesses (7).

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