infections, primary lymphedema and sometimes disseminated HPV (human papillomavirus) skin infection [21,22]. Natalizumab inhibits the binding of \( \alpha_4 \beta_1 \) integrins to their receptors; \( \alpha_4 \beta_1 \) integrins are involved in the homing of CD4 T cells to target organs such as the lung. Therefore, natalizumab could have played a role in the development of MAC pneumonia through a local T-lymphocytic adaptive immune deficiency by preventing \( \alpha_4 \beta_1 \) integrin expressing-antigen specific Th1 CD4 T-cells from recirculating to the lung.

Disclosure of interest: the authors declare that they have no conflicts of interest concerning this article.

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Received 19 September 2013
Accepted 17 December 2013
Available online 16 April 2014

http://dx.doi.org/10.1016/j.jlpm.2013.12.012
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Peripheral neuropathy during Infliximab therapy for rheumatoid arthritis

Neuropathie périphérique durant un traitement par infliximab pour arthrite rhumatoïde

Infliximab is a tumor necrosis factor (TNF) alpha antagonist used successfully in the treatment of rheumatoid and seronegative rheumatoid arthritis.

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arthritis, Crohn’s disease, psoriasis, and severe cases of vasculitis. Main side effects of this drug are: hypersensitivity syndrome, infections, drug-induced lupus, retrobulbar optic neuritis. Central demyelinating diseases associated with TNF-alpha antagonist have been reported in many cases in the literature whereas axonal peripheral neuropathy has been reported only in isolated cases [1].

We report a case of peripheral axonal sensitive polyneuropathy induced by Infliximab.

Observation

A 61-year-old Mediterranean woman, with no previous neurological problems, had been suffering for a severe seropositive rheumatoid arthritis (RA) since 1983. Arthralgia was refractory to paracetamol, indomethacine and to methotrexate (12.5 mg weekly) taken since 2001. She was also properly followed and treated for diabetes mellitus since 1995 (glibenclamide 5 mg/day) and for hypertension since 2001 (nifedipine 40 mg/day). She had also an osteoporosis treated by calcium and ergocalciferol since 2000.

On the 18th of April 2006, because of increase of arthralgia, Infliximab was added to methotrexate: 3 mg/kg intravenously every 8 weeks. This dose was increased to 4.5 mg/kg at the 7th infusion on June 2007 in front of evolutionary RA (DAS 28 = 6.28). She had a good response to treatment with decrease of DAS 28 to 4.

On September 2007, 17 months after Infliximab initiation and few days after the 9th Infliximab infusion the patient developed bilateral paresthesia then burning pain of hands and essentially feet. This symptomatology persisted at the same intensity than worsened following the 10th infusion. She reported progressive numbness and paresthesia of both legs starting from the feet and slowly ascending to the knees, while her RA was on remission.

On January 2008, few days after the 11th infusion, burning pain became sleepless with loss of sensitivity in hands and feet. Neurological examination found ataxia patient with unstable standing and falls if eyes were closed and prominent loss of position sensibility in the toes. Electrophysiological studies identified severe axonal sensory polyneuropathy affecting the four limbs. Investigations for malignant, infectious or systemic etiology were negative. Evolution was spontaneously and progressively favorable. Three months after Infliximab withdrawal, the patient had completely recovered from peripheral neuropathy. Follow-up of 20 months after Infliximab withdrawal showed absence of recidive of paresthesia.

Discussion

Infliximab was currently licensed for Crohn’s disease and, in combination with methotrexate for the treatment of rheumatoid arthritis in patients with active disease when the response to disease-modifying drugs, including methotrexate, has been inadequate. In clinical trials infliximab produced significant improvements in all measures of rheumatic disease activity compared with placebo. Infliximab in combination with methotrexate was shown to be superior to methotrexate or Infliximab alone [2].

According to Begaud’s method of imputation [3], Infliximab was involved in the development of the above neurological complication with an imputation score of I1 (possible) resulting from the combination of both chronicologic score C1 and semilologic score S1. The chronicologic score was graded C1 on the basis of a compatible delay of 17 months between the initiation of Infliximab therapy and onset of neuropathy and a suggestive outcome characterized by a complete recovery within 3 months after Infliximab withdrawal. The semilologic score was graded S1 considering the negative investigations of malignant, infectious or systemic etiology. Diabetes was not involved because of favourable outcome.

Medication-induced neuropathies were observed in 2 to 4% of cases [4]. Some criteria have been established to recognize such association as:

- strong dose-response relation-ship;
- consistent manifestations;
- close proximity of symptoms to exposure;
- stabilization or improvement after drug cessation and exclusion of other causes.

Neurologic complications induced by TNF-alpha antagonist therapy include central neurological disorders, myasthenia gravis [5], and demyelinating neuropathy [6,7]. However few cases of axonal polyneuropathy have been reported in the rheumatology literature [8–10].

On 2006, Tektonidou et al. reported 2 cases of peripheral neuropathy that occurred in patients with rheumatoid arthritis receiving Infliximab treatment, one with multifocal motor neuropathy with conduction block and the second with axonal sensory polyneuropathy. In this case, polyneuropathy occurred in a 56-year-old female with a 5-year history of refractory RA to previous therapy with methotrexate and later leflunomide and prednisolone. Infliximab was started at 3 mg/kg dose with gradual improvement of her arthritis. First symptoms of neuropathy appeared one month after the third infusion and 10 months after Infliximab initiation therapy. Laboratory and immunological examinations and lumbar puncture findings were normal. Infliximab was discontinued and the patient received monthly gammaglobulin infusions with good response. Two months later, the patient was asymptomatic and nerve conduction tests were normal [1].

Three other cases with seropositive RA who developed neurological symptoms related to Infliximab therapy have been also described by Jarand et al. All had polyneuropathy with varying degrees of motor and sensory involvement associated with a very prominent motor axonal demyelination in the first patient. The second patient had very mild chronic sensory symptoms before taking Infliximab, therefore she developed...
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A more florid and severe neuropathy with the agent. Although she improved, she had ongoing impaired balance (ataxia). The dose was 3 mg/kg/day in all cases. Total exposure was respectively 1000 mg, 540 mg and 1400 mg. The delay was 8 months and 2 weeks in the first case and 4 months and 2 weeks in the second case. Evolution was favourable [11].

In the review article of Hamon et al. [12], they reported cases of neuropathy associated with infliximab use: 4 cases of motor neuropathy, one case of mononeuropathy associated to vasculitis, 10 cases of Guillain Barre syndrome and only one case of sensitive axonal polyneuropathy described first by Tektonidou et al. More recently in 2010, Faivre et al. described a case of axonal neuropathy with concomitant encephalopathy during TNF-alpha antagonist in a woman with Crohn’s disease. Nervology was appearing one week after the second infusion of 300 mg of Infliximab. Painless motor deficit was observed in all four limbs; 18 months later, neurologic symptoms were less severe [13].

The delay between the onset of Infliximab treatment and the beginning of paresis was 17 months in our case. It was 5 months in the case reported by Tektonidou [1]. In an observational study of 84 patients with established rheumatoid arthritis treated with Infliximab, only one case of paresis happened after 15 months of treatment and Infliximab was discontinued [14].

Recovery was obtained 3 months after Infliximab withdrawal and monthly gammaglobulin infusions. According to Stubgen et al., most neuropathies improve over a period of months by withdrawal of the TNF-alpha antagonist with or without additional immune-modulating treatment [6].

The pathogenesis of peripheral neuropathy during TNF-alpha antagonist therapy is not clearly understood. T-cell and humoral immune attack against peripheral nerve myelin, vasculitis-induced nerve ischemia, and inhibition of signaling support for axons are proposed mechanisms for TNF-alpha associated to neuropathies [6]. Autoimmune mechanism is also suggested in front of association of several autoimmune-like manifestations with Infliximab such as lupus like syndrome, cutaneous psoriasis, demyelination and leukocytoclastic vasculitis [1]. Otherwise, it has been reported [9] that treatment with Infliximab induces significant changes in electromyographic parameters in all patients. These changes remain in normal limits. This leads to suggest the presence of predisposing risk factors to develop neuropathy.

**Conclusion**

Although the use of Infliximab had led to improved outcomes in the treatment of refractory rheumatoid arthritis, this new therapeutic agent requires careful monitoring for neurological events. Studies with large series of patients are needed to establish if Infliximab increases the risk of peripheral neuropathies.

**Disclosure of interest:** The authors declare that they have no conflicts of interest concerning this article.

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Received 30 September 2013
Accepted 17 December 2013
Available online 16 April 2014

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