



Development of Amyotrophic Lateral Sclerosis during Ustekinumab use for Refractory Crohn's Disease

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Abstract

Ustekinumab, an interleukin 12/23 monoclonal antibody, has recently been approved for use in Crohn's Disease (CD). Safety data to date has been reassuring, however this is in the context of clinical trials and limited clinical experience in psoriasis, psoriatic arthritis and CD. We report the use of ustekinumab in a patient with CD who developed neurological symptoms concerning for amyotrophic lateral sclerosis soon after commencement. While no direct causative association can be drawn, this case emphasises the need for ongoing post-marketing surveillance with new therapies.

Case Presentation

A 59-year-old female presented with progressive neurological symptoms on the background of recent ustekinumab commencement for medically refractory Crohn's Disease (CD). Additional past medical history included prior pulmonary embolus, hypertension, fibromyalgia and osteoporosis. In addition to ustekinumab she was prescribed mesalazine, pantoprazole, topical fentanyl, mirtazapine, quetiapine, amlodipine, venlafaxine, loperamide and baclofen. She did not smoke or consume alcohol. She was previously employed as an accountant and she was married with two grown children. There was a family history of breast cancer, however there was no history of neurological disorders.

She was diagnosed with stenosing ileocolonic CD at age 27, and required an ileocolonic resection shortly after diagnosis. She had refractory disease with need for multiple courses of steroids, 5-ASA and azathioprine, all with limited benefit. Three years prior to the current presentation, she underwent further surgery for active ileal CD and an anastomotic stricture with the unexpected, additional finding intra-operatively, of a well-differentiated small bowel adenocarcinoma. Five cycles of de Gramont regime (fluorouracil and folinic acid) were administered, with no detection of malignant recurrence to date.

Following completion of chemotherapy, adalimumab was commenced for post-operative recurrence seen in the neoterminal ileum, however, was ceased after six months of therapy due to primary non-response with endoscopic evidence of on-going inflammation and obstructive symptoms. A further surgical resection was performed with the creation of a permanent ileostomy. Nine months later, endoscopic evidence of post-operative ileal recurrence prompted the use of ustekinumab which was not yet approved for CD in Canada at that time. Off-label use was therefore offered, with induction dosing comprising 270mg subcutaneously (SC) at Week 0, 180mg at Weeks 1 and 2, followed by maintenance schedule of 90mg SC every eight weeks.

Within two months of commencing ustekinumab, there was development of asymmetrical lower limb weakness, including the development of left foot drop, with progression over the following three months, limiting mobility to a wheelchair. Increasing bilateral upper limb weakness subsequently developed. There were no bulbar abnormalities reported. Clinical examination revealed upper and lower limb fasciculations, weakness, spasticity and hyperreflexia, suggestive of a combined upper and lower motor neurone disorder. Laboratory markers revealed mild anaemia with haemoglobin of 114g/L and C-reactive protein elevation of 4.5; remaining full blood count, electrolytes, renal function, liver function and Vitamin B12 level were normal. Serological testing for BK, JCV and HTLV 1 and 2 viruses was also negative. Magnetic resonance imaging of brain and spine, lumbar puncture and paraneoplastic antibodies were unremarkable. Nerve conduction studies of right peroneal nerve revealed low amplitude responses (ranging from 1.9 to 2.4mV) with adequate conduction velocities, however the degree of amplitude reduction was considered inconsistent with clinical weakness. Electromyography confirmed fasciculations in many muscle groups in all four extremities. Complex units were noted in the right and left gastrocnemius. Active denervation was

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seen in several paraspinal muscle segments. Neurological opinion was that of Amyotrophic Lateral Sclerosis (ALS), with the temporal onset of symptoms relative to ustekinumab commencement noted. Ustekinumab was ceased five months after commencement, however, the neurological symptoms have continued to progress, including the development of restrictive ventilator dysfunction, prompting recommendation for nocturnal noninvasive positive pressure ventilation.

Ustekinumab is a fully humanized monoclonal antibody with a mechanism of action of binding to the p40 subunit of unbound Interleukin (IL) 12 and 23, which in turn prevents IL-12/23 cytokines binding with the IL-12R β 1 receptor, thus reducing immune cell activation. Ustekinumab has proven efficacy in the treatment of psoriasis, psoriatic arthritis and CD [1-3]. To date there have been two published neurological events occurring in conjunction with ustekinumab use, one of demyelination and another of progressive

reversible progressive leukoencephalopathy (PML) [4,5]. There have been no preceding case reports of ALS onset following ustekinumab use. ALS occurs with an incidence of 1-2 in 10000 people, with 90% of cases considered sporadic and 10% familial [6]. The etiology is yet to be well-characterized, however is considered multifactorial with proposed roles of glutamate-induced excitotoxicity, oxidative stress, mitochondrial dysfunction, inflammation, protein mishandling and loss of neurotrophic factors.

In relation to the development of ALS in our reported case, the temporal onset of symptoms relative to ustekinumab commencement does raise the possibility of an association, however it is recognized it may be a mere coincidence. It is acknowledged that an anti-tumour necrosis factor agent had been received for a six-month period prior to ustekinumab commencement, however this had been ceased approximately one year prior to the development of neurological symptoms, while there had also been preceding chemotherapy. There has been documentation of neurological complications, in particular demyelinating disorders in association with anti-tumour necrosis factor agent use, while within another class of biologic agents used in CD, natalizumab, an anti-integrin antibody has been associated with neurological sequelae, specifically PML [7,8]. The recognition of the risk of PML associated with natalizumab resulted in withdrawal of this agent from the biologic armamentarium in CD, being a reminder of the need for vigilance for diseases that are rare, but serious that could be drug related.

As to a postulated mechanism to account for the development of ALS in the setting of ustekinumab, potential etiologies include reduction in immune surveillance and resultant triggers for excessive oxidative stress or excitotoxicity from what may have been otherwise benign antigens.

Ustekinumab has recently received approval for the indication to treat CD in Canada and the United States based on the results of the UNITI and UNITI-IM trials [3]. As a result, of the positive results in these trials, much greater use of this agent to treat CD is expected in the near future. While a direct biological correlation cannot be drawn between ustekinumab and onset of ALS, this case emphasizes the importance of post-marketing surveillance for a new therapeutic indication. Awareness of potential neurologic complications is essential should further cases come to light as clinicians gain experience with this agent for the treatment of CD.

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