Demyelination in a patient receiving ustekinumab for refractory Crohn’s disease

Dear Sir,

Ustekinumab is a monoclonal antibody targeting the common part of interleukins 12 and 23, which has proven its efficacy in Crohn’s disease and not in multiple sclerosis. Prevalence of autoimmune diseases including demyelinating disorders is increased in patients with inflammatory bowel disease (IBD) and cases of demyelination have been observed in patients receiving TNF- antagonist. We report here a case of demyelination in a patient with refractory Crohn’s disease treated by ustekinumab.

A refractory stenotic ileal Crohn’s disease was diagnosed in 1985 in a woman born in 1951. She experienced five small bowel resections from 1986 to 2004. Despite intensive medical treatments including azathioprine, methotrexate, infliximab, adalimumab and certolizumab, a sixth bowel resection was performed in 2009. On February 2010, she was enrolled in a randomized controlled trial comparing ustekinumab to placebo. After a primary response at week 6, she completed the placebo-controlled maintenance phase and was still responding at the end of the study period in October 2010. Since the end of the study, ustekinumab was continued as a compassionate drug, 90 mg every 12 weeks subcutaneously.

In early 2011, she developed progressive weakness of the left arm, followed several weeks later by the onset of pain and numbness of the same limb. The first neurological examination in 2012 disclosed gait ataxia, left hemiparesis (4/5 on Medical Research Council scale for muscle strength) and hypoesthesia of the left arm. A cerebral MRI revealed multiple white matter lesions on FLAIR imaging including periventricular and juxta-cortical regions (Fig. 1), while medullary MRI showed one gadolinium-enhancing cervical lesion. Cerebrospinal fluid analysis was normal without lymphocytic pleocytosis or intrathecal IgG synthesis. Taken together, clinical and paraclinical findings are compatible with a diagnosis of primary progressive multiple sclerosis according to the revised McDonald criteria.

In June 2012, she developed optic neuritis with a bilaterally delayed P100 on visual evoked potentials. Due to symptom severity and the lack of other therapeutic alternatives, a bolus of 1000 mg of methyl-prednisolone was given intravenously improving neurologic symptoms, and then administered monthly. In accordance with neurologists and the patient, ustekinumab was continued, achieving Crohn’s disease sustained clinical response until October 2013. The persistence of disabling neurologic symptoms (retro-ocular pain, ataxic gait and bilateral leg pain) and an

Figure 1  Brain MRI showing multiple white matter lesions on FLAIR imaging including periventricular and juxta-cortical regions.
increasing number of white matter lesions on MRI led to start mycophenolate mofetil in October 2013.

To our knowledge, we report here the first case of demyelination in a patient receiving ustekinumab for Crohn’s disease. As interleukins 12 and 23 may trigger autoimmune inflammation of the brain, the occurrence of demyelinating disease under anti-interleukin 12/23 treatment was unexpected and paradoxical. This observation calls for additional data to assess the safety of this agent in IBD.

Conflict of interest statements

Yaeesh Badat: none.
Wassilios G Meissner: none.
David Laharie: consulting and/or lecture fees from AbbVie, Ferring, Merck, Norgine, Takeda, Vifor.

References


Yaeesh Badat
CHU de Bordeaux, Hôpital Haut-Lévêque, Service d’Hépato-gastroentérologie, Univ. Bordeaux, Laboratoire de bactériologie, F-33000 Bordeaux, France

Wassilios G. Meissner
CHU de Bordeaux, Hôpital Pellegrin, Service de Neurologie, Univ. Bordeaux, Institut des Maladies Neurodégénératives, CNRS UMR 5293, F-33000 Bordeaux, France

David Laharie* CHU de Bordeaux, Hôpital Haut-Lévêque, Service d’Hépato-gastroentérologie, Univ. Bordeaux, Laboratoire de bactériologie, F-33000 Bordeaux, France
*Corresponding author at: Service d’Hépato-gastroentérologie, Hôpital Haut-Lévêque, CHU de Bordeaux, 33600 Pessac, France.
E-mail address: david.laharie@chu-bordeaux.fr.

6 February 2014