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LETTER TO THE EDITOR

Marginal zone lymphoma under anti-TNF treatment in Crohn disease☆

Linfoma no Hodgkin nodal de zona marginal bajo tratamiento anti-TNF en enfermedad de Crohn

Dear Editor,

Patients with Crohn's disease (CD) present an increased risk of developing non-Hodgkin's lymphoma (NHL) compared to the general population.[1] In the literature, most of the patients are on combination therapy with anti-TNF agents and thiopurines, without considering that the anti-TNF agents in monotherapy may be potential causative agents of NHL.

We present a female patient with CD and axial and peripheral spondyloarthritis treated with anti-TNF in monotherapy diagnosed with marginal zone NHL (MZL), and uncommon haematological condition,[2] and outline the safety of continuing anti-TNF versus switching the drug group while preserving efficacy.

Case report

Fifty-five-year-old female patient, smoker, with diarrhoea for 4 years who was diagnosed with ileal CD with an inflammatory pattern for which steroids were prescribed. Due to corticosteroid-dependence, azathioprine was started then discontinued due to pancreatitis. It was replaced with methotrexate. Given the persistent clinical and biological activity, treatment with adalimumab (ADA) was started in monotherapy. The symptoms resolved and the biological parameters of activity normalised.

After 29 months on ADA monotherapy, the patient presented with arthritis in the hands and tarsals, Achilles enthesitis and dactylitis. The lab tests showed CRP 20 mg/L. MTX was resumed then discontinued due to adverse effects. Prednisone 10 mg was also resumed. The ultrasound demonstrated radiologic inflammation (enthesitis and right Achilles tendinosis with associated bursitis and bilateral plantar fasciitis) and the pelvic CT scan showed bilateral sacroiliitis with no associated symptoms. After 5 years of monotherapy with ADA, a follow-up lab test showed an immunophenotype compatible with MZL (CD5−, CD20+, FMC7+) with scant peripheral blood expression and a chest-abdominal CT scan with no findings except for a thickened distal ileum, therefore it was decided not to start any treatment for the lymphoma. The anti-TNF was withdrawn by consensus after the NHL finding. Given the torpid course of the peripheral spondyloarthritis and seeking to maintain the CD remission while prioritising safety, ustekinumab (UST) was started with an intravenous induction dose of 6 mg/kg and a subcutaneous maintenance dose of 90 mg every 8 weeks. At present, 20 months after starting it, she continues treatment with UST at the same dose with persistent gastrointestinal clinical remission, but with joint symptoms (enthesitis and pain in the metatarsophalangeal joints). Haematologically, follow-up blood tests continued to no show progression of lymphocytosis. To date, no spontaneous resolutions of MZL have been reported.

Discussion

The risk of lymphomas in inflammatory bowel disease (IBD) is greater than in the general population because of the baseline disease and use of thiopurine immunomodulators and anti-TNF agents.[1] Furthermore, the regression of some cases of Hodgkin's lymphoma has been reported 3 months after discontinuing the anti-TNF agent.[3] In patients with IBD, we should consider the diagnosis of lymphoma at the onset of suggestive symptoms (nocturnal fever, toxic syndrome) and haematological dyscrasia on lab tests.[1] The established independent risk factors are being male, over 65 years, and being diagnosed with IBD at an early age.[1]

Our patient did not present any risk factors for lymphoma or any accompanying symptoms. Only a lymphocytic immunophenotype alteration was noticed, compatible in the context of a patient with MZL.[2]

Marginal zone lymphomas account for approximately 5%–15% of all NHLs in the Western world. The nodal subtype is the least common (10% of all cases), with an age-weighted reported incidence of 0.57/100,000 persons-year. The patients present disease localised to the peripheral lymph nodes (cervical and inguinal) with anaemia and thrombocytopenia in 25% and 10% of cases, respectively. The

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latest published guidelines suggest the possibility of a conservative approach in patients with a low tumour load and no B symptoms.[2] Unlike other NHL subtypes, such as MALT,[2] in MZL an increased incidence in patients with autoimmune diseases has not been reported.

Regarding the use of concomitant immunomodulators with anti-TNF, the patient only received a brief period of MTX, but with a total use of ADA until its withdrawal of 60 months, a drug that has not been demonstrated to increase the risk of cancer in monotherapy.[4] Thus, although the Pyramid register did not identify an increase in the risk of lymphoma, it is worth noting that the follow-up time, and therefore the exposure to ADA, was up to 6 years, but with an approximate mean of 3 years/patient, which may be sufficient for assessing the development of infections, but perhaps not for cancers.[4] The anti-TNF was withdrawn based on the risk of worsening her lymphoma. At that time, only conservative management was required. She continued to not develop B symptoms or any deterioration on the peripheral blood tests, and even the possibility of its regression was contemplated as has been reported with other types of lymphoma.[3] At present, there is no literature on starting another biologic in patients with active lymphoma. The ECCO guidelines recommend assessing the personal risk-benefit of each case.[1]

Since up to 25–40% of IBD patients experience associated extraintestinal manifestations, with the joints being the most common, the treatment objective must be control of both bowel and joint inflammation. Therefore, multidisciplinary management is essential. In the reported case, UST (anti-interleukin IL-12/23) was chosen for both its efficacy in intestinal CD as well as in the joints, as well as its safety profile regarding the onset of cancers. In fact, in the different clinical trials conducted with UST long-term psoriatic disease, the rates of newly diagnosed cancers are comparable to those of the placebo groups (0.3% and 0.4%, respectively) and no differences were observed regarding the expected rates in the general population as well. This trend seems similar in CD according to the recently published controlled studies as well as in the recently presented preliminary data (SUSTAIN study) in routine clinical practice.[5]

We consider this case an example of a potential comorbidity that may arise in routine clinical practice with IBD patients who require multidisciplinary management when making decisions, as well a personalised treatment to prioritise, in this case, safety.

Conflicts of interest

The authors declare the following conflicts of interest:

Carlos González-Muñoza: Norgine, Ferring, Janssen, Takeda.

Javier Briones and Hye Sang Park declare that they have no conflicts of interest.

Esther García-Planella: Abbvie, MSD, Janssen, Pfizer, Takeda, Faes, Ferring, Falk, Kern.

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