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Dear editor,

Our letter was modified following your comment, as you can see in the highlighted parts of the new following version:

- The follow up duration should be better defined: the mean follow up time was 16,9 years (ranging from less than 1 year to 42 years), as we collected data from our patients' registry; however, none of the patients underwent anti-TNF for more than 6 years.
- it is interesting to know if patients underwent routinary dermatological visits during follow up or not: our patients didn't undergo routinary dermatological visits.

- Some minor grammar errors should be revised (e.g line 27, line 52.): grammar errors were corrected.

Yours Sincerely,
Dott. Davide Giuseppe Ribaldone.

Risk of incident melanoma in patients with inflammatory disease treated with anti-TNF: the Turin experience.

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Key words: Inflammatory bowel disease, tumor necrosis factor, melanoma

Dear editor,

In a recent interesting letter, Bardazzi *et al.* reported their data on the association between the use of Anti-Tumor Necrosis Factor (anti-TNF)-α drugs and the onset of melanoma in patients with moderate to severe plaque psoriasis. They found one out of 214 patients with a diagnosis of melanoma, 33 months after the administration of etanercept.[1]

Anti-TNF are biological drugs widely used to treat severe intestinal, dermatological and rheumatological inflammatory disorders.[2] The inflammatory bowel diseases (IBD), characterized by chronic inflammation of the intestinal mucosa, are distinguished in two main phenotypes, Crohn's disease (CD) and ulcerative colitis (UC).[3] The pathogenesis of IBD remains to be elucidated. According to the 2017 updated ECCO guidelines, anti-TNF therapy is indicated as a second line therapy in steroid dependent/refractory UC and CD, either anti-TNF alone or combined with immunosuppressors, in thiopurines resistant UC and CD, in refractory proctitis and in perianal disease in CD. Moreover, biological treatment should also be administered in order to prevent CD recurrence after surgery and to maintain remission.[4] Since TNF-α induces necrotizing effect on tumor cell *in vitro*, its inhibition has been hypothesized to increase cancer risk. Actually, in IBD the overall cancer risk seems to be higher than in general population, especially for skin cancer (both melanoma and non-melanoma skin cancer) independently of the use of biological drugs. Some

authors argue that the risk of cutaneous malignant melanoma in IBD seems to be increased (1.32-fold) in those treated with anti-TNF agents.[5]

Recently, we evaluated the incidence of melanoma in a cohort of IBD patient undergoing anti-TNF agents. We collected data from our patients' registry and from our biobank database. All selected patients were outpatients followed at IBD ambulatory, Gastroenterology Unit, San Giovanni Antica Sede Hospital, Città della Salute e della Scienza of Turin, Italy. Eighty-two patients (44 male and 38 female) were included in the analysis: mean age was 54, ranging from 27 to 69; 10 patients were affected by UC, 69 by CD and 3 patients were diagnosed as having undetermined IBD. Mean time from diagnosis was 15 years (from 1 to 42 years) and 55 patients had developed complications of the illness (34 extra-intestinal complications and 21 intestinal complications). Moreover, 53 of the 82 patients included in our study had been treated with immunosuppressor before anti-TNF therapy. As anti-TNF therapy is concerned, our patients were treated with infliximab (IFX) or adalimumab (ADA); 22 patients were treated with biological therapy for less than one year, 20 for 1-2 years, 37 for more than 2 years and 3 patients had to stop biological drugs for adverse events (2 because of fever of unknown origin and one due to allergic reaction to IFX). Mean follow up time was 16,9 years (from less than 1 year to 42 years), although no patient underwent anti-TNF therapy for more than 6 years (mean time 3 years). None of the patients underwent routinary dermatological checkups during biological therapy.

Among our population, only one case of melanoma was detected: the patient was a 79-year-old man affected by UC, undergoing IFX (at a dose of 5mg/kg/8 weeks) in association with azathioprine (AZA) from 2 years when diagnosed with superficial spreading melanoma (Clark Level IV, with lymphatic metastasis). Thus, in our cohort the incidence of cutaneous melanoma was 1.2% (1/82), comparable to the incidence of this neoplasia in the general population (as current estimates indicate 2% of population will develop melanomas during lifetime).[5] Moreover, our patient was treated with immunosuppressive therapy together with anti-TNF at the time of diagnosis of skin melanoma and this could be a confounding factor. The main limit of our retrospective study

is the small number of patients, that does not allow to generalize our results. However, potential heterogeneity arising from this is limited by the fact that, in our outpatient clinic, all authors follow International Guidelines.[4] Furthermore, during the last 25 years, all consultations have been recorded in both a paper archive and a computerized data bank. In conclusion, in our experience does not seem to be a relationship between anti-TNF drugs and a higher risk of cutaneous melanoma, but studies with a larger population of IBD patients treated with anti-TNF should further investigate this issue.

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