

November 29, 2013

Dear Editor,

Please find enclosed the edited manuscript in Word format (file name: 7044-review.doc).

Title: TNF Inhibitors to Treat Ulcerative Colitis in a Metastatic Breast Cancer Patient

A case report and literature Review

Author: Ruwaida Ben Musa, Lydia Usha, John Hibbeln, Ece Mutlu

Name of Journal: *World Journal of Gastroenterology*

ESPS Manuscript NO: 7044

The manuscript has been improved according to the suggestions of reviewers:

- 1- Format has been updated
- 2- Revision has been made according to the suggestions of the reviewer

We thank the reviewer for his/her positive comments as follows:

“I think that the present study entitled “TNF Inhibitors to Treat Ulcerative Colitis in a Metastatic Breast Cancer Patient. A Case report and Literature Review” provides an interesting point to gastroenterologists.”

There was one major concern of the reviewer:

“Authors stated that ‘a TNF- α inhibitor acted in fact as an anti-neoplastic agent’ in page 8, line 20 to 21. This deception is a problem. The present report showed no evidence that adalimumab directly eliminated recurrent breast cancer. A series of combination chemotherapy achieved and eliminated recurrent breast cancer. Thus, it is not like that adalimumab deteriorates breast cancer, and that there is association between elimination of breast cancer adalimumab treatment. It is difficult and unnatural to think that adalimumab acts as an anti-neoplastic agent. Actually adalimumab has not currently been approved as an anti-neoplastic agent in the world wide. Please delete and improve the description that a TNF- α inhibitor acted in fact as an anti-neoplastic agent “

We thank the reviewer for this comment. With the two lines that were of concern to the reviewer in the discussion, our intent was certainly not to imply that adalimumab is an anti-neoplastic agent. As the reviewer correctly states, we are also aware that adalimumab has not been approved for such an indication.

However, the reason we wanted to point out that adalimumab may have contributed to tumor regression in our case report is the latest developments reported in the tumor immunology field, which are being regarded as the new “game-changing” frontier in cancer treatment. In fact, many basic science investigations for years in a variety of cancers have suggested that immune activation at the site of tumor can promote tumor persistence and metastasis. However, it has been difficult find immunotherapies that would work in the clinic until recently. Now, immune check point inhibitors such as anti-PD1, and PD-L1 antibodies are being investigated for treatment of metastatic cancers, and have achieved some of the most exciting results in patients with very large tumor burdens in metastatic melanoma, renal and squamous lung cancers, compared to traditional cancer chemotherapeutics, many of which simply target the proliferation of tumor cells. In the latest clinical trials in cancer, these immune check point inhibitors are being used in conjunction with standard therapy.

With this information in mind, we sought to draw parallels to our case: Our intention in the discussion was to simply point out the possibility that adalimumab may have contributed to tumor elimination in this patient, with breast cancer by affecting the local tumor environment and decreasing immune activation. We would like to respectfully point out to the reviewer that such an effect due to TNF inhibitors is not simply our own idea, but has led to the testing of etanercept (another TNF inhibitor) in three different clinical trials in cancer patients as a treatment of the cancer (references 31-33 of the manuscript). So, our speculation is also not without any basis. However, we also freely admit that the possibility that adalimumab helped eliminate cancer in our breast cancer patient is speculative: As the reviewer said, there is no evidence in the case we present or in the literature to this effect. On the other hand, it should be noted that we had taken care in the two sentences that the reviewer is commenting on, to highlight that this is indeed speculative by starting the sentences with “ we speculate”. We wanted to include such a speculation, partly because it may spark further evaluations on the role of TNF as a driver of the immune response to metastasis in breast cancer and other similar cancers.

Nevertheless, given the reviewer’s major concern, perhaps our speculative comment in the discussion has not resulted in our intended consequences. Therefore, as suggested by the reviewer we removed any sentences/phrases pertaining to adalimumab contributing to tumor elimination in the discussion section of the case report, and hope that this satisfies the reviewer’s major concern.

Thank you again for publishing our manuscript in the *World Journal of Gastroenterology*.

Sincerely,

A handwritten signature in black ink, appearing to read 'Ece Mutlu', with a stylized flourish at the end.

Ece A. Mutlu, MD, MS, MBA
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Director, Clinical Research
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