EJR European Journal of Rheumatology

DOI: 10.5152/eurjrheum.2022.21097

Case-based Review

Concurrent use of tumor necrosis factor inhibitor and tyrosine kinase inhibitor in ankylosing spondylitis and myeloid neoplasm

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Abstract

Biologic disease-modifying agents (bDMARDs) are highly effective in controlling the symptoms of autoimmune rheumatic diseases. The decision on whether to continue bDMARDs following a cancer diagnosis can be challenging for patients and physicians. Here, we describe a case of a middle-aged male with ankylosing spondylitis who was controlled on infliximab (IFX) and found to have a myeloid neoplasm with Platelet-Derived Growth Factor Receptor Beta rearrangement. The patient was started on a tyrosine kinase inhibitor imatinib. Given its significant positive effect on patient's quality of life, IFX was continued with a favorable outcome. This case highlights the importance of shared decision-making in balancing risks and benefits of immunosuppressants in appropriate cases of hematologic malignancy.

Keywords: Tumor necrosis factor inhibitor, tyrosine kinase inhibitor, ankylosing spondylitis, myeloid neoplasm with PDGFRB rearrangement, hematological malignancy

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Cite this article as: Gupta A, Afinogenova Y, Podoltsev NA, Danve A. Concurrent use of tumor necrosis factor inhibitor and tyrosine kinase inhibitor in ankylosing spondylitis and myeloid neoplasm. *Eur J Rheumatol*. 2022;9(4):215-216.

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Submitted: April 28, 2021
Accepted: May 5, 2021
Available Online Date: January 21, 2022

Introduction

Although biologic disease-modifying antirheumatic drugs (bDMARDs) are highly effective in autoimmune rheumatic diseases, a concern remains that bDMARDs may interfere with immune system's response to cancer.[1] The decision whether to continue bDMARDs following a new cancer diagnosis is challenging for physicians and patients. Traditionally, tumor necrosis factor inhibitors (TNFi's) are discontinued with diagnosis of hematological malignancy. Here, we present a patient with ankylosing spondylitis (AS) who was successfully continued on infliximab (IFX) despite a recent diagnosis of myeloid neoplasm with Platelet-Derived Growth Factor Receptor Beta (*PDGFRB*) rearrangement, which was concurrently treated with imatinib.

Case Presentation

A 67-year-old man was referred to rheumatology in January 2018 with longstanding back pain. He reported peripheral arthritis (knee) and arthralgias (shoulders). He did not have psoriasis, inflammatory bowel disease, uveitis, dactylitis, or enthesitis. He previously worked as a mechanic but developed difficulties with activities of daily living. Physical exam was notable for severely limited range of motion at cervical and lumbar spine and chronic warmth and mild joint effusion of the right knee. He had a positive HLA-B27 and elevated C-reactive protein of 36 mg L^{-1}. Pelvic X-ray showed fusion of bilateral sacroiliac joints. X-rays of the spine revealed extensive syndesmophytes in cervical, thoracic, and lumbar spine. He was diagnosed with AS. Due to previous gastrointestinal bleeding with NSAIDs, he was initiated on IFX 5 mg kg^{-1} every 6 weeks with dramatic symptom improvement and normalization of inflammatory markers.

Two years later, the patient was admitted with 2 weeks of fevers and fatigue. Lab tests revealed leukocytosis of 127,800 uL^{-1} with increased absolute neutrophil count of 52,400 uL^{-1}, left shift (18% metamyelocytes, 10% myelocytes, and 20% promyelocytes), absolute eosinophilia of 1,300 uL^{-1}, and monocytosis of 7,700 uL^{-1}. Platelets and hemoglobin were normal. Peripheral blood smear showed all stages of myeloid maturation. Blood flow cytometry demonstrated a myeloid left shift. Bone marrow aspiration and biopsy (BMB) was notable for hypercellular marrow for age (> 90%) with markedly increased left-shifted myelopoiesis. Fluorescence in situ hybridization (FISH) testing notable for negative BCR-ABL translocation showed a deletion of 5' PDGFRB gene in 68% of bone marrow cells. Comprehensive genomic profiling showed the presence of *TNIP1-PDGFRB* fusion and confirmed myeloid neoplasm with *PDGFRB*

rearrangement. Patient was started on a tyrosine kinase inhibitor (TKI) imatinib 400 mg daily, and IFX was discontinued. Leukocytosis normalized within 3 weeks. However, due to IFX discontinuation, he experienced remarkable worsening of spinal pain and stiffness leading the impaired activities of daily living and poor quality of life. After multidisciplinary meeting and shared decision-making, IFX was restarted after missing two infusions. At the third month, repeat BMB revealed hypercellular marrow (70%) with FISH demonstrating residual *PDGFRB* abnormality in only 2.5% of cells, close to the limit of detection. At 9-month follow-up, the patient continues to do well with no detection of *PDGFRB* abnormality in peripheral blood flow.

Discussion

It is difficult to ascertain the link between hematologic malignancy and biologics since autoimmune diseases increase baseline malignancy risk.[1,2] For instance, patients with RA have a 10-15% increased risk of cancer, notably lymphoma, compared to general population.[1] Using the Taiwan National Health Insurance Database, Chang et al.[3] found that male patients with AS had an increased risk of solid cancers and hematologic malignancy.

Interestingly, basic science data suggest that the ability of leukemic stem cells to persist even if there is a response to TKI therapy may be due to the stem cell-specific microenvironment.[4] TNFα levels and those cytokines downstream of TNFα have been shown to be elevated in patients with CML and induced in leukemic stem cells *in vitro*.[4,5] There are data to suggest that targeting TNFα in murine CML stem cell model may enhance TKI-induced reduction of clonogenic activity.[4] It is unclear if the same phenomenon may be observed in humans and may suggest a benefit of concurrent TNFi and TKI therapy that merits further investigation.

There is hesitation to continue bDMARD in patients with newly diagnosed malignancy. In a systematic review, Lopez-Olivo et al.[6] found no clear agreement on recommendations for bDMARD use in RA and cancer, which advise caution but not absolute contraindication. The further challenge in our case was that bDMARDs was the only effective treatment option in AS.

Our case is unique as it describes using a TKI and TNFα inhibition concurrently in a patient with myeloid neoplasm and AS with a favorable outcome. It demonstrates the importance of team-based care and shared decision-making, and emphasizes that continuation of TNFα inhibition in a carefully selected patient with rheumatic disease and particular types of hematologic neoplasms may be considered on a case-by-case basis.

Informed Consent: Written informed consent was obtained from the patient who participated in this study.

Main Points

- Continuing bDMARDs can be challenging, during a new cancer diagnosis for patients with autoimmune disease.
- Traditionally, tumor necrosis factor inhibitors (TNFi) are discontinued following a hematologic malignancy diagnosis.
- It is important to discuss with both the patient and hematologist about whether to consider TNFi in patients undergoing treatment for myeloid neoplasm.
- Patients can have a favorable outcome while on both tyrosine kinase inhibitor and TNFi for their autoimmune condition and myeloid neoplasm.

Peer-review: Externally peer-reviewed.

Author Contributions: Concept - A.G., Y.A.; Design - A.G., Y.A., A.D.; Data Collection and/or Processing - A.G., N.A.P., A.D.; Analysis and/or Interpretation - A.G., Y.A., N.A.P., A.D.; Literature Search - A.G., Y.A.; Writing Manuscript - A.G., Y.A., A.D.; Critical Review - Y.A., N.A.P., A.D.

Conflict of Interest: The authors have no conflicts of interest to declare.

Financial Disclosure: The authors declared that this study has received no financial support.

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