International Journal of Basic & Clinical Pharmacology
Modi K et al. Int J Basic Clin Pharmacol. 2022 Sep;11(5):477-479
http://www.ijbcp.com
pISSN 2319-2003 | eISSN 2279-0780

DOI: https://dx.doi.org/10.18203/2319-2003.ijbcp20222145

Case Report

Immunosuppressants in Behcet's disease: a boon or a bane?

Krishna Modi[1], Vipul Prajapati[1]*, Dhaiwat Shukla[2], Supriya D. Malhotra[1]

[1]Department of Pharmacology, Smt. NHL Municipal Medical College, Ahmedabad, Gujarat, India
[2]Department of Medicine, Vadilal Sarabhai General Hospital, Ahmedabad, Gujarat, India

Received: 14 July 2022
Accepted: 02 August 2021

***Correspondence:**
Dr. Vipul Prajapati,
Email: santabanta123456@gmail.com

ABSTRACT

Adalimumab is a disease-modifying antirheumatic drug and monoclonal antibody that works by antagonising tumour necrosis factor-alpha prescribed in many rheumatological conditions like Rheumatic arthritis, Ankylosing spondylitis and Behcet's disease. Serious side effects with this drug include heart and liver failure, nervous and blood disorders, allergic and immune system reactions and opportunistic infections. A 27-year-old female patient, known case of Behcet's disease presented to the hospital with complaints of fever, cough and breathlessness following administration of Adalimumab, six doses over three months. Chest X-ray and BAL-CBNAAT was suggestive of Tuberculosis. AKT was started and Adalimumab was suspended until patient recover.

Keywords: Adalimumab, TNFα inhibitors, Behcet's disease, Tuberculosis, Immunosuppression

INTRODUCTION

Bechet's disease (BD) is a multisystemic inflammatory disease of unknown aetiology. It is a tri-symptom complex manifested as recurrent oral aphthous ulcers, genital ulcers, and uveitis. The disease affects many organs and systems, causing mucocutaneous lesions, eye inflammation, musculoskeletal problems, and major vessel disease. There is cardiac, pulmonary, gastrointestinal and nervous system involvement. There is dysfunction of both innate and adaptive immune systems, resulting in an exaggerated response to viral or bacterial insults. Many drugs have been shown to be effective in various systemic manifestations of BD. Colchicine, azathioprine, cyclosporine, cyclophosphamide, methotrexate, chlorambucil, thalidomide, interferon alfa, and anti-TNF agents are most of them.[1]

The indications and use of antitumor necrosis factor therapy have expanded over time with the upcoming concept of top-down therapy, mucosal healing, and the improving economy of developing nations.[2] These drugs may modulate T cell number, function, or cytokine signalling important for the control of opportunistic infections like TB infection or the maintenance of granulomas, any of which may place patients at risk for reactivation of latent TB or acquisition of new infection.[3]

CASE REPORT

A 27-year-old female patient, known case of vascular (retinal and cutaneous) Behcet's disease since 3 years, was brought to a tertiary care hospital with complaint of fever not associated with chills or rigors, intermittent in nature, without diurnal variation and relieved by antipyretics along with complaint of cough without expectoration, breathlessness on exertion and loss of appetite since 10 days. She was treated empirically with injection piperacillin and clindamycin. Drug history comprises of taking 2 tablets of mycophenolate mofetil (MMF) 500 mg BD, tablet Prednisolone 25 mg OD, tablet Atorvastatin 10mg OD, tablet Rivaroxaban 2.5 mg BD, tablet Aspirin 150 mg BD since 1 year.

Patient has past history of vision loss in both eyes along with amputed left lower limb as a result of gangrene (complications of BD), complains of claudication pain in right lower limb with absent peripheral pulsations, frequent oral aphthous ulcers, genital ulcers and recurrent skin lesions. Patient was admitted and treated twice in the previous month for *Klebsiella* and *Pseudomonas* associated pneumonia respectively. Past history suggested that disease was not responding to mycophenolate mofetil, so tablet cyclosporin 50 mg BD was added for 15 days. Patient was prescribed tumour necrosis factor alpha (TNF-α) antibody adalimumab 40 mg subcutaneously every fortnight for 3 months. For screening of any active opportunistic infection before starting adalimumab, sputum smear for mycobacterium TB was tested and found negative. Bronchoscopy or BAL- CBNAAT was not done before starting the drug.

Patient had taken total six doses of Adalimumab 40mg in last three months, following which she demonstrated improvement in her symptoms of Behcet's disease. On admission, her vitals were: temperature: 99.2°F, pulse: 85/min, spO2: 98% on room air. Her investigations revealed as follows: Hb: 7.5g/dl (12-18), neutrophils: 92% (49-72), WBC: 6.39 Ku/l (5.2-12.4), platelets 39 kU/L (130-400), Serum LDH: 466U/l (100-250), CRP:188.51 mg/dl (0-5), serum ferritin: 629 ng/ml (10-282). Patient was positive for dengue IgM and was treated for the same. HRCT was done which was suggestive of active infective aetiology in form of multiple discrete and randomly distributed nodular infiltrates and bilateral pleural effusion (Figure 1).

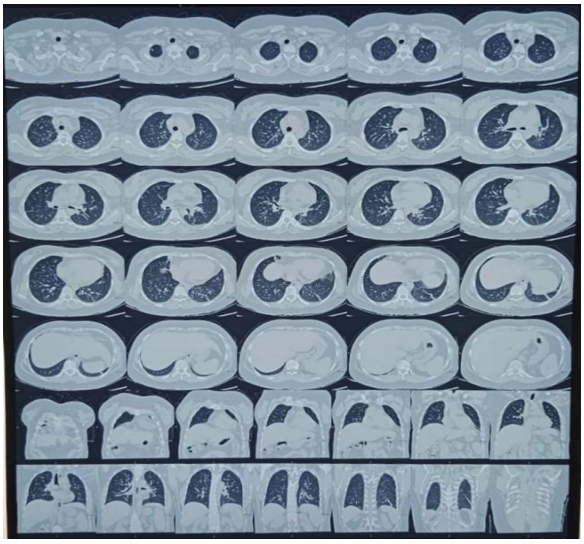

Figure 1: HRCT of lung suggestive of active infective aetiology in form of multiple discrete and randomly distributed nodular infiltrates and bilateral pleural effusion.

FNAC from the enlarged lymph nodes was insufficient and insignificant. Pulmonology refer was done and bronchoscopy was done which showed hyperaemic mucosa in left upper and lower lobe. BAL (Bronchoalveolar lavage) was sent. BAL culture sensitivity was insignificant for any infection. On chest Xray, blunting of right and left CP angle was there, suggestive of pleural effusion. Reticular opacities were noted in bilateral lung fields. Apical pleural thickening noted. Patient's BAL- CBNAAT came positive and patient was diagnosed with drug resistant Tuberculosis. Hence, AKT was started according to NTEP guidelines and patient was told to come for follow up after one month. Decision to withdraw Adalimumab was made till patient's complete recovery from tuberculosis is planned. This suspected ADR was reported as 'adalimumab induced tuberculosis' with unique ID number IN-IPC-300643261 under PvPI. As the reaction follows temporal relationship and it can also be explained by concomitant immunosuppressant drugs and steroids administered to the patient for long term, causality assessment of this ADR is "possible" by WHO-UMC criteria.

DISCUSSION

Behçet's disease (BD) is an inflammatory disease of unknown etiology, affecting many systems. There is a generalized derangement of the lymphocyte and neutrophils, which is characterized by elevated peripheral white blood cell count, activated monocytes, increased neutrophil motility with infiltration into the cutaneous and ocular lesions, and increased circulating proteins such as C3, C4, C5 and IgA. Active monocytes produce a number of proinflammatory cytokines, such as IL-1, IL-6, IL-8, TNF-α, and granulocyte-macrophage colony stimulating factor (GM-CSF), and these cytokines contribute to neutrophil activation by their augmented interactions with endothelial cells, causing tissue damage.[1,4] So, clinical manifestations include mucocutaneous lesions, eye inflammation, musculoskeletal problems, and major vessels, cardiac, pulmonary, gastrointestinal involvement as well as nervous system involvement. Commonly, males are affected by this disease, but conversely, in our case, female is affected. The average age at onset of BD is about 25 years.[1] International study group's classification criteria are widely used to establish the diagnosis of BD. According to these criteria, a diagnosis of BD requires recurrent oral aphthous ulcerations plus two of the following: genital ulcerations, skin lesions, eye lesions, or a positive pathergy test.[1] This criterion matches our case. Tumour necrosis factor (TNF), a major cytokine in BD, ''plays an important role in the pathogenesis'' of chronic inflammatory diseases. Hence, two types of anti-TNF therapies were created: monoclonal antibodies and soluble receptors. The medicines and healthcare products regulatory agency (MHRA) have approved three anti-TNF drugs, two are monoclonal antibodies namely Infliximab and Adalimumab, and one is a soluble receptor called etanercept.[5] Adalimumab is recommended at a dose of 40 mg subcutaneously every other week as prescribed in our case.[1] It is not surprising that there is a high incidence of infections seen as an adverse effect of patients being treated with anti-TNF drugs as they play

the ‘‘central role in the initial host response to infection’’. Hence, screening for latent or active TB prior to treatment is highly recommended.[5] In our case, since confirmatory tests for TB were not done earlier before administering Adalimumab, there is no evidence to prove that the infection was not latent. Many different types of infection have been reported such as, tuberculosis (TB), serious bacterial infections, listeriosis, atypical mycobacterial infections, histoplasmosis, coccidioidomycosis and pneumonia. Most of these infections are not serious and are resolved by antibiotic treatment or ‘‘temporarily stopping the drug”.[5] In our case, AKT is started in the patient to treat tuberculosis and adalimumab is withdrawn until the patient recovers from TB. Immunosuppression results from the use of these anti-inflammatory drugs mainly along with long term use of steroids. Review of the literature does not suggest noticeable increased risk of opportunistic infections or tuberculosis reactivation with the use of cyclosporin at 3-5 mg/kg/day doses or with more potent T-cell immunosuppressant MMF. Studies have shown that major reduction of dose did not seem necessary in case of mycobacterial infection.[6,7] Steroids act as “double edged sword” in case of tuberculosis. On one side, due to its anti-inflammatory property, steroids are given along with AKT to prevent exaggerated host immune response to tuberculous proteins whereas on the other side, high doses of steroids i.e., >20 mg/day for long duration i.e., >4 weeks can cause local lung immune defence defect leading to increased risk of tuberculosis because of reactivation of latent infection or relapse or acquiring new infection.[8] In our case, patient was taking prednisolone since long, which has played adjuvant role in weakening the immune response against infections. Immunocompromised patients with underlying diseases had an increased prevalence of primary pulmonary DR-TB. However, convincing data on DR-TB in immunocompromised patients with other diseases are lacking, previous studies have shown higher prevalence of primary- DR for the 1st line anti-TB agents occurs in these patients which is not the result of default, treatment failure or reactivation.[9] The TB risk was not influenced by other factors including age at anti TNF initiation, gender, duration of follow-up after anti-TNF. Of all the countries, which have used anti-TNF, India has the highest TB incidence (200/100,000).[2]

CONCLUSION

Actually, many of wheel chair bound patients are now walking due to these fancy drugs especially Adalimumab and Rituximab but at the same time it's causing this kind of infections and problems, so these drugs must be used cautiously and judiciously because severe opportunistic infections may cost lives of patients suffering from chronic rheumatological diseases. Proper screening and chemoprophylaxis of infections before starting such drugs is the main prerequisite to maintain benefit- risk ratio.

Funding: No funding sources
Conflict of interest: None declared
Ethical approval: Not required

REFERENCES

1. Akman-Demir G, Saip S, Siva A. Behcet’s disease. Curr Treat Neurol. 2011;13(3):290-310.
2. Kedia S, Mouli VP, Kamat N, Sankar J, Ananthakrishnan A, Makharia G, et al. Risk of tuberculosis in patients with inflammatory bowel disease on infliximab or adalimumab is dependent on the local disease burden of tuberculosis: a systematic review and meta-analysis. J Am College Gastroenterol. 2020;115(3):340-9.
3. Godfrey MS, Friedman LN. Tuberculosis and biologic therapies: anti-tumor necrosis factor-α and beyond. Clin Chest Med. 2019;40(4):721-39.
4. Türsen Ü. Pathophysiology of the Behcet's Disease. Pathol Res Int. 2012;2012:45-9.
5. Connor V. Anti-TNF therapies: a comprehensive analysis of adverse effects associated with immuno-suppression. Rheumatol Int. 2011;31(3):327-37.
6. Behnam SM, Behnam SE, Koo JY. Review of cyclosporine immunosuppressive safety data in dermatology patients after two decades of use. J Drugs Dermatol. 2005;4(2):189-94.
7. Vandermarliere A, Audenhove AV, Peetermans WE, Vanrenterghem Y, Maes B. Mycobacterial infection after renal transplantation in a Western population. Transplant Infect Dis. 2003;5(1):9-15.
8. Patil S, Jadhav A. Short course of high-dose steroids for anaphylaxis caused flare up of tuberculosis: a case report. J Translat Int Med. 2019;7(1):39-42.
9. Jiang JR, Yen SY, Wang JY. Increased prevalence of primary drug-resistant pulmonary tuberculosis in immunocompromised patients. Respirology. 2011;16(2):308-13.

Cite this article as: Modi K, Prajapati V, Shukla D, Malhotra SD. Immunosuppressants in Behcet’s disease: a boon or a bane? Int J Basic Clin Pharmacol 2022;11:477-9.