International Journal for Multidisciplinary Research (IJFMR)
E-ISSN: 2582-2160 ● Website: www.ijfmr.com ● Email: editor@ijfmr.com

Lupus Unmasked: The Infliximab Connection

Angelin Susan Varghese[1], Kavya Annie Rojin[2], Mathew Anil Chempakasseril[3], Vishnu S. Chandran[4], Sara Kurien Kodiattu[5]

[1]Pharm D Intern, Department of Clinical Pharmacy, Believers Church Medical College Hospital, Thiruvalla, Kerala, India
[2,3]Tutor, Department of Pharmacology, Believers Church Medical College Hospital, Thiruvalla, Kerala, India
[4]Head of Department & Associate Professor, Department of Rheumatology, Believers Church Medical College Hospital, Thiruvalla, Kerala, India
[5]Assistant Professor, Department of Pharmacology, Believers Church Medical College Hospital, Thiruvalla, Kerala, India

Abstract
Drug-induced lupus erythematosus (DILE) is an autoimmune phenomenon where the symptoms are similar to systemic lupus erythematosus (SLE) after exposure to certain drugs. While DILE tends to be less severe than SLE, the diagnosis can be challenging. Infliximab, a TNF-alpha inhibitor, is widely prescribed for autoimmune conditions such as Crohn's disease, rheumatoid arthritis, and ankylosing spondylitis. Although rare, Infliximab can cause Drug-Induced Lupus Erythematosus (DILE). This case report presents a 67-year-old male patient who developed this unconventional adverse drug reaction. It emphasizes the importance of vigilant monitoring, early detection, and prompt intervention to prevent long-term complications in patients receiving Infliximab treatment.

Keywords: Systemic Lupus Erythematosus, Infliximab, TNF-alpha Inhibitor, Rheumatoid arthritis, Adverse drug reaction, Drug Induced Lupus Erythematosus (DILE)

1. Introduction

Infliximab is a chimeral (made by fusing variable regions from one species like a mouse, with the constant regions from another species such as a human being) monoclonal antibody, a biological agent, approved by the US-FDA for treatment of refractory Crohn's disease, ulcerative colitis, ankylosing spondylitis, psoriasis and rheumatoid arthritis. It targets and inhibits tumor necrosis factor-alpha (TNF-alpha) which is a chemical messenger that induces inflammation. Adverse drug reactions (ADRs) associated with TNF-α inhibitors leading to drug discontinuation include opportunistic infections, hypersensitivity or skin reactions, cytopenia, heart failure, autoimmune hepatitis and transient vision loss due to optic neuritis and paradoxical reactions (Psoriasis or dermatitis).

Infliximab is generally well tolerated, but it has been linked to rare, yet serious, adverse drug reactions (ADRs), such as drug-induced lupus erythematosus (DILE) [1].

Drug-induced lupus erythematosus (DILE) is an autoimmune phenomenon where the symptoms mimics idiopathic systemic lupus erythematosus (SLE) which is triggered by long-term medication use like TNF-

alpha inhibitors, Hydralazine, etc. While DILE tends to be less severe than SLE, the diagnosis can be challenging. Unlike idiopathic SLE, DILE is milder, involving cutaneous, musculoskeletal, and serological abnormalities and rare organ involvement [2]. The common drugs causing systemic DILE include Hydralazine (high risk), Procainamide (high risk), Isoniazid (moderate risk), Minocycline (very low risk) and more recently reported TNF-α inhibitors [3].

2. Case History

Hereby discussing a case of a 67-year-old male patient who has been diagnosed with Seronegative Rheumatoid Arthritis (Rheumatoid factor and anti CCP negative) since 2012. Patient is also a known case of Hyperuricemia for 10 years (Tab. Febuxostat 40 mg OD), Systemic Hypertension for 1 year (Tab. Cilnidipine 10 mg HS), Type 2 Diabetes Mellitus for 1 year (Tab. Gliclazide 60 mg OD, Tab. Vildagliptin + Metformin 50/500 mg BD), Dyslipidemia for 1 year (Tab. Rosuvastatin 40 mg HS). Two years back, the patient had an episode of Ischemic heart disease with Single vessel involvement (Combination of Tab. Clopidogrel 75 mg and Aspirin 75 mg once in the night, Tab. Metoprolol 25 mg OD, Tab. Nitroglycerin 2.6 mg BD). He denies alcohol consumption, tobacco, or any substance abuse with no relevant family history.

In 2022, when the patient was non-compliant with his arthritis medication his symptoms worsened, so he was started on weekly Tab. Methotrexate 10 mg, twice weekly Tab. Folic acid 5 mg and Tab. Hydroxychloroquine 200 mg BD daily. Due to high disease activity, biological DMARDs were considered which was put on hold due to the positive Interferon Gamma Release Assay on 19th August 2022, Latent Tuberculosis diagnosis was made and started on Tab. Isoniazid 900 mg and Tab. Rifapentine 900 mg once a week for 3 months (completed in November 2022). Due to this latent TB treatment, Tab. Hydroxychloroquine was substituted with extended-release Tab. Tofacitinib 11 mg once at night in September 2022. While on Tofacitinib, he developed radiating chest pain in April 2023. A coronary angiogram showed evidence of single vessel involvement, hence started on dual antiplatelet therapy with a combination of Tab. Aspirin 75 mg and Tab. Clopidogrel 75 mg once at night, meanwhile Tab. Tofacitinib was switched to Inj. Infliximab in May 2023. During Infliximab therapy, patient developed migratory joint pain, mostly in the ankle joints and right shoulder joint, improving with oral Methylprednisolone and NSAIDs like Etoricoxib. ANA profile tested positive for ANA and Anti-dsDNA (393.34 IU/mL), Centromere B and DFS70. Anti-histone antibody tested negative, thereby reducing the likelihood of Isoniazid induced reaction. This suggested the onset of Infliximab-induced Lupus. Symptoms improved after discontinuation of Infliximab. Tab Methotrexate 10 mg once weekly, Tab. Methylprednisolone 8 mg thrice daily and Tab Etoricoxib 80 mg HS were continued. Since 2024, the patient is on Tab. Methotrexate, Tab. Sulfasalazine and Inj. Rituximab 1g completing two cycles till date with no further events.

3. Discussion

Infliximab, a TNF alpha inhibitor, is a disease modifying anti-rheumatoid arthritis drug, produced from murine myeloma cells. In rheumatoid arthritis pathogenesis, TNF plays a central role in the pro-inflammatory cytokine cascade by triggering the production of IL-1 and IL-6; recruits inflammatory cells into joints, stimulates the expression of adhesion mole-cules in the synovial endothelium and the secretion of matrix metalloproteinases by chon-drocytes and synovial fibroblasts and amplifies bone resorption by promoting osteoclast differentiation [4].

In this case, drug-induced lupus is attributed to Infliximab. Although its exact pathophysiol-ogy is unclear, several hypotheses exist. One hypothesis suggests cytokine shift, where the Th1 cytokine inhibition boosts Th2 cytokine action, causing B-cell proliferation, antibody production, and increased autoimmunity. Another involves reduced CD44 expression affect-ing the apoptosis and clearance of nuclear debris, promoting autoantibody production. Lastly, cytotoxic T-cells inhibition reduces autoantibody-producing B-cell elimination [5].

The temporal relationship between the drug administration and the onset of lupus-like mani-festation with elevated ANA and anti-ds DNA strongly suggests that it is infliximab induced lupus.

6% of all ADRs due to infliximab that has been reported globally are musculoskeletal and connective tissue disorders, of which 2050 cases (8%) are infliximab induced lupus as per Vigi access database [6]. Upon evaluation at our ADR Monitoring Centre, the causality was determined to be “Probable” using the WHO-UMC causality assessment scale. The type of ADR was classified as “TYPE B” according to the Rawlins-Thompson classification and was assessed as “Level 5” in terms of severity based on the Modified Hartwig’s scale. As per the WHO criteria, the seriousness of the reaction was categorized as "Other Medically Important." and the outcome of the reaction was "recovering." Additionally, according to the Schumock and Thornton scale, the ADR was deemed "Not Preventable". The Assessment of Causality and other attributes of the ADR was conducted using established scales and criteria to ensure comprehensive and standardized evaluation.

This case aligns with a study done by Sarzi-Puttini P et. al. where a patient on long-term Infliximab developed arthralgia, purple skin lesions and malar rash in the face and showed positive ANA and anti-ds DNA like that of SLE [7].

A study by Magno Pereira Vet. al. reported a similar case where a patient treated with infliximab for ulcerative proctitis developed malaise and polyarthralgia and tested positive for ANA, weak positive anti-dsDNA, positive anti-histones, indicative of infliximab-induced lupus. Symptoms resolved after the drug’s withdrawal [8].

Stopping Infliximab is the key to treating lupus-like manifestation. Prompt recognition and management is crucial.

Most patients do not experience severe complications of drug-induced lupus. Drug induced lupus erythematosus tends to have milder renal, or CNS involvement, vasculitis, leukopenia, and pericarditis are rare [2].

4. Conclusion

In conclusion, our exploration of Infliximab induced Lupus highlights a rare but clinically important ADR of TNF-α inhibitors, which requires careful monitoring in patients undergoing treatment for autoimmune conditions like Rheumatoid arthritis. Early detection of symptoms, like arthralgia, and laboratory changes like positive ANA and anti-dsDNA plays a pivotal role in the diagnosis and management of this rare ADR. Typically, instances resolve with drug withdrawal; however, some individuals may require corticosteroids or immunosuppressive medication for symptom control. Further research is needed to fully understand the etiopathogenesis of lupus induced by infliximab and identify potential risk factors to prevent and manage this condition effectively.

5. Declaration of Patient consent

The authors certify that they have obtained all appropriate patient consent forms. In the form, the patient

consented for his clinical information to be reported in the journal. The patient understands that his name and initials will not be published, and due efforts will be made to conceal his identity.

6. References

1. Ali Y, Shah S. Infliximab-induced systemic lupus erythematosus. Annals of internal medicine. 2002 Oct 1;137(7):625-6.
2. Cerqueira A, Seco T, Paiva D, Martins H, Cotter J. Isoniazid-induced lupus: when the cure can be lethal. Cureus. 2020 Mar 18;12(3).
3. He Y, Sawalha AH. Drug-induced lupus erythematosus: an update on drugs and mechanisms. Current opinion in rheumatology. 2018 Sep 1;30(5):490-7.
4. Perdriger A. Infliximab in the treatment of rheumatoid arthritis. Biologics: Targets and Therapy. 2009;3:183-91. doi: 10.2147/btt.s3099.
5. Almoallim H, Al-Ghamdi Y, Almaghrabi H, Alyasi O. Anti-tumor necrosis factor-α induced systemic lupus erythematosus. The open rheumatology journal. 2012;6:315.
6. Uppsala Monitoring Centre. Infliximab: Adverse Drug Reactions. Available from: https://www.vigiaccess.org/
7. Sarzi-Puttini P, Ardizzone S, Manzionna G, Atzeni F, Colombo E, Antivalle M, Car-rabba M, Bianchi-Porro G. Infliximab-induced lupus in Crohn's disease: a case re-port. Digestive and liver disease. 2003 Nov 1;35(11):814-7.
8. Magno Pereira V, Andrade C, Figueira R, Faria G, Jasmins L. Infliximab-induced lu-pus: a case report. GE-Portuguese Journal of Gastroenterology. 2017 Mar 10;24(2):84-8.