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Case Report

Tocilizumab induced immunosuppression in a case of adult-onset still's disease: are these newer biologics double edged sword?

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ABSTRACT

Adult-onset still's disease (AOSD) is a rare multisystemic inflammatory disorder of unknown etiology characterised by high spiking fever, evanescent skin rash, arthralgias, arthritis, neutrophilic leucocytosis. Initial treatment strategy includes use of hands-on drugs like non-steroidal anti-inflammatory drugs, low dose corticosteroids, conventional DMARDs. But as the disease progresses to severe form, targeted and biologic DMARDs could be the option for management. Interleukin-6 being one among the many cytokines involved in the pathogenesis of AOSD, has made itself a target for the treatment of refractory cases. Tocilizumab, a recombinant humanized anti IL-6 monoclonal antibody, is one such biologic drug available in the market that has proven its therapeutic efficacy in several clinical trials. We are presenting a case of 37-year-old female patient, known case of AOSD for 4 years. Patient was initially maintained on low dose corticosteroid and conventional DMARD like hydroxychloroquine and methotrexate. Flare ups of the disease warranted the use of tocilizumab and tofacitinib in this patient. After clinical as well as pathological improvement with tocilizumab 2 years before, signs of immunosuppression were observed when tocilizumab was reintroduced for the treatment. Patient suffered from acute pyelonephritis, septicemia, shock, oropharyngeal candidiasis and bronchitis which could be owned to immunosuppressive action of tocilizumab. One can reduce the chances of infection and other adverse effects by careful periodic monitoring of various laboratory parameters like total W.B.C., total platelet count and liver enzymes. Cautious selection of the patient is needed for the treatment with newer biologic agents.

Keywords: AOSD, Tocilizumab, Septicemia, Immunosuppression, Tofacitinib, Biologic DMARDs

INTRODUCTION

Adult-onset still's disease (AOSD) is a rare multisystemic disorder considered as a complex (multigenic) autoinflammatory syndrome characterized by fever, transient skin rash, arthritis, or arthralgia, increased neutrophils, hepatosplenomegaly, and lymphadenopathy.[1] The etiology is not clearly understood and with wide range of differential diagnosis available, it is difficult to diagnose AOSD.[2] Current treatment strategies comprise use of targeted synthetic DMARDs and biologic DMARDs for refractory cases of AOSD. These drugs can cause generalized immunosuppression which can be observed as increased frequency of infections, fungal opportunistic infections, and sepsis.[3] Elevated levels of transaminases and cholesterol can also be detected in patient receiving these drugs.

Here, we are presenting a case of AOSD, 37-year-old female patient who had a history of being treated with tab. Tofacitinib and inj. tocilizumab, admitted to tertiary care hospital with suspected ADR, septicaemia, shock, and pyelonephritis.

CASE REPORT

A 37-year-old female patient, known case of AOSD for 4 years was brought to a tertiary care hospital on 05/06/2022 with complaints of high-grade fever, generalized weakness, abdominal pain, vomiting, dehydration, and giddiness since 2 to 3 days.

Patient had been taking tab. methotrexate, tab. hydroxychloroquine, tab. prednisolone for last 4 years. Two years ago, patient had received 12 doses of IV tocilizumab. Subsequently, she was maintained on tab. tofacitinib 5 mg BD. Patient has a past history of flaring up of AOSD along with gastritis and *H. pylori* infection 3 months back. Tab. methotrexate, tab. hydroxychloroquine, tab. tofacitinib and tab. prednisolone were discontinued. Since then patient has been treated with inj. methotrexate 20 mg once weekly. One month before the admission she has received one dose of IV tocilizumab (560 mg).

Patient has drug allergy to aspirin and paracetamol.

On the day of admission, her vitals were: Temp. was normal, pulse-123/min, B.P.-82/44 mm Hg and oxygen saturation was 95% on room air.

Her lab investigations revealed haemoglobin-10.3 g/dl, total W.B.C-38020/cumm with neutrophils-93%, lymphocytes-03%, eosinophils-00%, monocytes-04%, basophils-0%, total platelet count-185000/cumm, S. creatinine-1.77 mg/dL, S. sodium-132.38 mEq/L, S. potassium-3.26 mEq/L, S. chloride-96.99 mEq/L, Procalcitonin-81.36 ng/ml, CRP-146.55 mg/L, S.G.P.T.-16 U/L, S.G.O.T.-56.71 U/L.

Urine analysis revealed presence of albumin, 8-10 pus cells and few granular casts. No organisms were isolated from urine culture.

X-ray chest PA view was normal.

USG whole abdomen showed "Raised cortical echo pattern of both kidneys with preserved cortico-medullary differentiation, suggesting possibility of renal parenchymal disease/ changes of pyelonephritis."

Table 1: Lab investigations of patient on follow up during admission.

Variables	Day 1	Day 4	Day 8
Total W.B.C. (cumm)	38020	9610	10780
S. creatinine (mg/dl)	1.77	1.38	0.72
CRP (mg/L)	146.55	102	40
K^+ (mEq/L)	3.26	3.91	4.35

Patient was treated with IV fluids, antacids, antiemetics and antibiotics. During the hospital stay, patient developed oral candida infection, which was treated with IV fluconazole and bronchitis, which was treated with IV antibiotic. Throat swab culture revealed presence of *Klebsiella pneumoniae*.

After 10 days of hospitalization, patient's S. creatinine level was within range, total WBC count was decreased, and fungal infection subsided. Subsequently patient was discharged. On discharge medication included tab. prednisolone 10 mg in morning and 5 mg in night and other supportive treatment.

The above case has been reported as 'tocilizumab induced septicaemia' under unique ID number IN-IPC-300641246 to Indian pharmacopoeia commission. As reaction follows temporal relationship and it can also be explained by other drugs, causality assessment of this ADR is "possible".

DISCUSSION

AOSD is a rare systemic inflammatory disorder characterized by inflammatory polyarthritis, daily fever, and a transient salmon pink maculopapular rash.[1] It has bimodal age distribution, the first peak between the ages of fifteen to twenty-five and the second between thirty-six to forty-six years of age. However, about three-quarters of the patients report the onset of disease between sixteen and thirty-five years of age.[2] In the case mentioned above, patient was diagnosed with the disease at age of 33 years.

The etiology of AOSD is still unknown but the hypothesis remains that AOSD is a reactive syndrome in which various infectious agents may act as triggers in genetically predisposed host.[2] Disease is very diverse, ranging from benign forms to severe life-threatening complications, as macrophage activation syndrome (MAS), requiring intensive immune modulation including biologic agents.

Mild cases of AOSD presenting with fever, rash, arthralgias or mild arthritis can be treated with non-steroidal anti-inflammatory drugs (NSAIDs) like aspirin, paracetamol, diclofenac, ibuprofen, and low dose corticosteroids like prednisolone.[2] In our case, the patient is allergic to aspirin and paracetamol.

Various conventional synthetic DMARDs (csDMARDs) have also been used, out of which Methotrexate (MTX) and cyclosporine are the most common. MTX is chiefly useful in steroid dependent AOSD patients and in cases where corticosteroids failed to control the disease.[1,4] Co-administration of corticosteroids and MTX is the most common treatment strategy accepted by clinicians for mild to moderate cases. Other agents such as leflunomide, tacrolimus, hydroxychloroquine sulphate, azathioprine, and cyclophosphamide have also been tried.[4] In the above-mentioned case, patient has been prescribed tab. methotrexate, tab. hydroxychloroquine and prednisolone.

Neutrophil and macrophage activation through IL-18 plays a major role in pathogenesis of AOSD. Moreover, elevated levels of Th-17 related cytokines like IL-6, IL-1, IL-21, and IL-23 have also been observed.[5] Thus, inhibiting these

cytokines is a rational approach in the treatment of AOSD. IL-1 inhibitors (Anakinra, Canakinumab), IL-6 inhibitors (Tocilizumab, sarilumab), IL-18 inhibitors (Tadekinig alfa), and TNF alfa inhibitors (Etanercept, infliximab) are some of the biologic DMARDs (bDMARDs) that have been tried for refractory cases of AOSD.[4]

In addition to bDMARDs, Jak inhibitors, are able to block the intracellular signalling of specific cytokines and are very effective for the treatment of RA in combination with MTX or monotherapy. IL-6 and IFN-γ can also be targets of Jak-1 and Jak-2 inhibitors. Jak inhibitors (Tofacitinib, Baricitinib) may be promising candidates for patients with an unfavourable response or adverse events to the currently available csDMARDs and bDMARDs.[4]

Infections such as tuberculosis, fungal opportunistic infections, and sepsis are among the most common adverse events observed in patients receiving bDMARDs, which can be attributed to the immunosuppressive action of these agents.[3] *Staphylococcal* cellulitis, acute pyelonephritis, and Sepsis are some of the reported adverse infectious events seen in patients receiving tocilizumab.[6] Other adverse effects include dyslipidaemia, neutropenia, thrombocytopenia, and enhanced levels of liver enzymes, gastrointestinal symptoms like nausea, abdominal pain, mouth ulceration, and gastritis can also be seen.[3,6]

The patient has a history of being treated with inj. tocilizumab and tab. tofacitinib. Tocilizumab can be associated with immunosuppression leading to septicemia and shock which is seen in this patient. Also, the patient encountered oropharyngeal candidiasis and bronchitis which can again be linked with the immunosuppressive effect of tocilizumab. Acute pyelonephritis seen in this patient can also be attributed to tocilizumab.

TOWARD (Tocilizumab in combination with traditional DMARD therapy) study was done in 2008 to examine the efficacy and safety of tocilizumab with other DMARDs in patients with rheumatoid arthritis (RA). They reported 5 serious infections in their trial: Acute pyelonephritis, *Staphylococcal* cellulitis, and sepsis in the tocilizumab group (Tocilizumab + DMARDs) and 2 cases of pneumonia in the control group (placebo + DMARDs).[7]

As per 'the British society for rheumatology biologic DMARD safety guidelines in inflammatory arthritis' and U.S. F.D.A. approved medication guide for usage of tocilizumab (ACTEMRA), such infections can be prevented by pre-treatment screening for infections as well as regular monitoring of total W.B.C. count while using these drugs.[8,9]

CONCLUSION

Despite the fact that treatment of autoimmune and autoinflammatory disease has been boosted with the availability of newer targeted biologic drugs, lack of safety reports as well as variation in individual responses to these drugs has made them difficult to use. Risk of infection is the most notable side effect associated with them. Periodic monitoring of total W.B.C. count, platelet count, and live enzymes is recommended. Reintroduction of tocilizumab carries the risk of development of macrophage activation syndrome, caution should be exercised while prescribing it. Physician should always keep in mind the risk benefit ratio of these drugs while using them, in context with the patient's clinical condition.

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