Tocilizumab for Refractory Adult-onset Still's Disease: Report of Three Cases

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ABSTRACT

OBJECTIVES. To present three cases of adult-onset still's disease (AOSD) who was initially refractory to corticosteroid therapy but were successfully treated with an interleukin-6 (IL-6) inhibitor, tocilizumab (TCZ).

BACKGROUND. Adult-onset Still's Disease (AOSD) is a systemic inflammatory disorder of unknown etiology characterized by quotidian fever, evanescent rash, and arthritis/arthralgia. The pro-inflammatory cytokine interleukin (IL) – 6 has been implicated in its pathogenesis.

CASE PRESENTATION. Three patients (40F, 37F, and 27M) presented with quotidian fever, evanescent maculopapular rash, arthritis, anemia, leukocytosis, elevated acute phase reactants and hyperferritinemia of 3 to 4 months duration. All were diagnosed AOSD by Yamaguchi criteria after extensive work up to exclude other diagnostic possibilities. Each patient received high dose corticosteroids and 2 patients also received methotrexate (MTX) with initial improvement of symptoms. However, there was recurrence and exacerbation of clinical symptoms on tapering of steroid doses. Each patient was then given TCZ at 8 mg/kg. Within a month of the initial dose of TCZ, there was dramatic clinical and laboratory improvement, enabling rapid steroid dose tapering.

CONCLUSION. This series substantiates the role of IL-6 in the pathomechanisms of AOSD and demonstrates use of TCZ in the management of AOSD refractory to corticosteroids.

Keywords: *Adult-onset Still's disease (AOSD), refractory, Interleukin-6 (IL 6), Tocilizumab (TCZ)*

INTRODUCTION

Adult-onset still's disease (AOSD) is an uncommon chronic systemic inflammatory disease of unknown etiology (1,2). It is characterized by quotidian fever, evanescent salmon-colored rash, and arthritis/arthralgia. It is a diagnosis of exclusion. In Europe, AOSD accounts for about 3-20% of patients with fever of unknown origin (FUO) (1,2). No laboratory test is specific for AOSD. Many clinicians used the Yamaguchi classification criteria in diagnosing AOSD. It has 96% sensitivity and 92% specificity.[1]

Many hypotheses have been proposed for the pathogenesis of AOSD. In a study by Chen et al., they showed predominance of T helper cell (Th1) cytokines in untreated patients with active AOSD (2). These Th1 cytokines include IL-2, IFN-γ and TNF-α which are implicated in AOSD. In another study by Chen et al., serum levels of pro-inflammatory cytokines IL-6, IL-8, IL-18 and TNF-α were elevated both in sera and pathological tissues of patients with AOSD.[2,5] These cytokines play a major role in AOSD. IL-6 in particular plays a crucial role in the pathogenesis of AOSD.[5,7] It is correlated with systemic symptoms such as fever, skin rash, and increased ferritin, serum CRP, and leukocyte levels. It is also associated with disease activity in AOSD. Hence, IL-6 inhibitors have been used in the management of AOSD.[4,5] An example of IL-6 inhibitor is tocilizumab (TCZ) which is a humanized monoclonal antibody that antagonizes IL-6 receptors.[5]

CASE PRESENTATION

Three patients (40F, 37F, and 27M) presented with quotidian fever, evanescent maculopapular rash, arthritis, anemia, leukocytosis, elevated acute phase reactants and hyperferritinemia of 3 to 4 months duration. Past medical history, personal/social history, and family history were all unremarkable. All were diagnosed AOSD by Yamaguchi criteria after extensive work up to exclude other diagnostic possibilities. Each patient received high dose corticosteroids and 2 patients also received methotrexate

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Table 1. Yamaguchi Classification Criteria for AOSD[1]

Major Criteria	Minor Criteria	Exclusion
Fever > 39ºC lasting 1 week or longer	Sore throat	Infections
Arthralgia or arthritis, lasting 2 weeks or longer	Recent development of significant lymphadenopathy	Malignancies
Typical rash	Hepatomegaly or splenomegaly	Other rheumatic disease
Leukocytosis > 10,000/mm^3 with > 80% PMNs	Abnormal liver function tests	
	Negative tests for antinuclear antibody (IF) and rheumatoid factor (IgM)	

Five or more criteria are required, of whom two or more must be major

Table 2. Summary of 3 AOSD cases

	40F	37F	27M
Yamaguchi Criteria fulfilled by patient	Fever≥39C for > 1 week (4 months) Arthralgia > 2 weeks Maculopapular salmon pink rash Leukocytosis ≥10,000 (-) RF, (-) ANA	Fever ≥39ºC for > 1 week (3 months) Arthralgia > 2 weeks Maculopapular salmon pink rash Leukocytosis ≥10,000 Abnormal aminotransferases (-) RF, (-) ANA Sore throat	Fever≥39C for > 1 week (3 months) Arthralgia > 2 weeks Maculopapular salmon pink rash Leukocytosis ≥10,000 Abnormal aminotransferases (-) RF, (-) ANA
Initial Treatment	Prednisone and Methotrexate	Methylprednisolone	Prednisone and Methotrexate
Tocilizumab	8 mg/kg	8 mg/kg	8 mg/kg
Improvement after Tocilizumab	Clinical Improvement Lysis of Fever Improvement in Anemia Decrease in Inflammatory Markers No recurrence of symptoms	Clinical Improvement Lysis of Fever Improvement in Anemia Decrease in Inflammatory Markers No recurrence of symptoms	Clinical Improvement Lysis of Fever Improvement in Anemia Decrease in Inflammatory Markers No recurrence of symptoms

(MTX) with initial improvement of symptoms. However, there was recurrence and exacerbation of clinical symptoms on tapering of steroid doses. Each patient was then given TCZ at 8 mg/kg. Within a month of the initial dose of TCZ, there was dramatic clinical and laboratory improvement, enabling rapid steroid dose tapering. One patient (40F) observed over 3 months remained in remission after a single dose of TCZ, another (27M) received a second dose of TCZ and stayed in remission on MTX alone over 12 months observation, and the third patient (37F) who refused steroids intermittently received 6 doses of TCZ over 24 months indicated by each AOSD flare. There were no adverse events with TCZ.

DISCUSSION

AOSD is a systemic inflammatory disease that is diagnosed by exclusion. It presents with prolonged high spiking fever/quotidian fever, rash, and arthritis or arthralgia. There is no specific laboratory test to diagnose with AOSD. The Yamaguchi classification criteria have been used by clinicians in aiding in the diagnosis of AOSD. In this report, we present three patients (40F, 37F, and 27M) presented with quotidian fever, evanescent maculopapular rash, arthritis, anemia, leukocytosis, elevated acute phase reactants and hyperferritinemia of 3 to 4 months duration. All three patients were diagnosed with AOSD after fulfilling the Yamaguchi criteria and other diagnostic possibilities were excluded.

The first line of treatment for AOSD is corticosteroids or non-steroidal anti-inflammatory drugs (NSAIDs).[1,2,7] Corticosteroids are usually required to induce remission of symptoms. Second-line of treatment for AOSD is immunosuppressives such as methotrexate, tacrolimus, and/or cyclosporine.[1,2,7] They act as steroid sparers. For AOSD refractory to corticosteroids, NSAIDs, or immunosuppressant biological drugs are the treatment of choice. Biologicals mostly used for AOSD are TNF-inhibitors, IL-1 inhibitors, and/or IL-6 inhibitors.[4,5]

The exact pathogenesis of AOSD is still unknown. Currently, AOSD patients are thought to have a dysregulated immune response and it is also hypothesized that there is alteration in cytokine production.[5,6] Both innate and adaptive immunity is hypothesized to be affected in AOSD. Pro-inflammatory cytokines such as IL-1, IL-6, and TNF-α play a major role in AOSD.[5] IL-6 in particular plays a crucial role in AOSD's pathogenesis and its serum levels correlate with the

severity of the disease. IL-6 levels are markedly elevated in patients with active AOSD.

Tocilizumab (TCZ), a humanized anti IL-6 receptor antibody, has shown promising results for management of AOSD.[5,6] It has been used for AOSD patients that are resistant to corticosteroids, methotrexate, or other biologic drugs. Several case reports have shown promising results of tocilizumab for AOSD. In a case report of Sakai et. al, they report two cases of AOSD who were successfully treated with TCZ.[5]. In a French study by Puechal, et.al, investigators reported 14 patients with refractory AOSD treated successfully with TCZ.[6] In most patients TCZ was administered at a dose of 8 mg/kg every 4 weeks intravenously and in most patients response to Tocilizumab was rapid and sustained. In this series, we reported three patients with refractory AOSD successfully treated with TCZ.

CONCLUSION

This series substantiates the role of IL-6 in the pathomechanisms of AOSD and demonstrates use of TCZ in the management of AOSD refractory to corticosteroids. TCZ may be effective for AOSD refractory to conventional treatment such as corticosteroids and immunosuppressants.

Patient Anonymity, Consent and Confidentiality

Written informed consent was obtained from the patients themselves for writing and publication of this case report. All personal information regarding the patient were kept in strict confidence and patient identifiers (such as name, geographical location, date of birth, contact number, etc.) were removed from the manuscript. Patients' anonymity and confidentiality were protected by non-disclosure of any personal information that will identify the individual when the study is published or presented. A breach of confidentiality may occur if the information is used in any other way.

Ethics Approval

There is no involvement of vulnerable persons in this report. Ethical principles set out in relevant guidelines (Declaration of Helsinki 2015) have been strictly followed. This has been approved by the Institutional Review Board of University of Santo Tomas Hospital, as required by the institution for presentation.

Conflict of interest

No potential conflict of interest relevant to this article was reported by the authors that may interfere with the presentation, review or publication of this case.

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