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Letter to the Editor

Long-Term Effect and Safety of Tocilizumab on Severe Adult-Onset Still's Disease Accompanied by Thrombotic Thrombocytopenic Purpura

Tatsuya Suwabe[1,2], Masayuki Yamanouchi[1,2], Yoshifumi Ubara[1,2], Naoki Sawa[1,2]

To the Editor,

Adult-onset Still's disease (AOSD) is a multi-systemic inflammatory disease usually treated with corticosteroids; however, patients with AOSD are often resistant to corticosteroid therapy. Although biological products have been recommended for corticosteroid-resistant AOSD,[1] their long-term effects and safety for patients with AOSD are unknown. We report a patient with severe AOSD who was successfully treated with tocilizumab for 14 years.

We previously reported a 69-year-old Japanese woman suffering from severe AOSD[2] who was refractory to intensive induction therapy including high-dose corticosteroid, cyclosporine A, and frequent plasma exchange. Ten days later, she developed thrombotic thrombocytopenic purpura (TTP) including thrombocytopenia, hemolytic anemia, acute renal failure, fever, and neuropsychiatric symptoms. She was in a fatal condition, and we started etanercept (a TNFα inhibitor [TNFαis]) as a salvage therapy. We selected etanercept because it might have a lower risk for serious infection than other drugs. Interleukin-1 (IL-1) inhibitor was not approved in Japan at the time. After the administration of etanercept (25 mg subcutaneous injection, twice/week), her condition improved dramatically and TTP and AOSD were completely controlled. However, after 4 months, symptoms of spike fever; skin rash; and elevated levels of serum ferritin, ALT, and LDH had gradually resumed, despite increasing the PSL dosage to 20 mg/day and the constant administration of etanercept. She was diagnosed with a relapse of AOSD. Etanercept was switched to tocilizumab (IL-6 inhibitor), and she achieved complete remission of AOSD. Subsequently, she continued to receive oral PSL 5 mg/day and cyclosporine A 75 mg/day plus tocilizumab 8 mg/kg (drip intravenous injection) every 4 weeks for 14 years. This controlled her AOSD completely. However, her consciousness disorder caused by multiple cerebral infarctions did not recover, and she remained in a vegetative state. She developed a urinary tract infection at 7 years and pneumonia at 8 years after starting tocilizumab; however, these were not severe, and she completely recovered. The administration of tocilizumab was suspended when she had serious infections. Symptoms related to AOSD relapses did not appear; therefore, it was considered that she had sustained remission. At 14 years after the onset of AOSD, she developed severe pneumonia and septic shock, which caused death at the age of 83 years.

Severe AOSD accompanied by TTP is often refractory; however, AOSD in this patient was well controlled by tocilizumab for 14 years. This patient eventually became refractory to etanercept, although it was effective for the first 6 months; however, tocilizumab had been effective for 14 years. Both TNF and IL-6 are key cytokines involved in the pathophysiology of AOSD; however, the retention rate of IL-6 inhibitors may be higher than that of TNFα inhibitors because IL-6 inhibitors reduce B cell activations and the immunogenicity of IL-6 inhibitors is low.[3,4] The frequency and severity of the adverse events of tocilizumab were similar to those of TNFα inhibitors.[5] Taken together, IL-6 inhibitors may be more suitable for the treatment of severe AOSD than TNFα inhibitors in terms of durability of effect and adverse events. In conclusion, tocilizumab is a safe and effective long-term therapeutic option for severe AOSD, despite the general condition of patients.

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ORCID iDs of the authors:
T.S. 0000-0003-0825-2512;
M.Y. XXX;
Y.U. XXX;
N.S. XXX

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[1] Department of Nephrology and Rheumatology, Toranomon Hospital Kajigaya, Kawasaki, Japan
[2] Okinaka Memorial Institute for Medical Research, Toranomon Hospital, Tokyo, Japan

Corresponding author:
Tatsuya Suwabe
E-mail: suwabetat@gmail.com

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