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Tocilizumab therapy for IL-6 increment in a patient with non-fatal severe fever with thrombocytopenia syndrome

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ABSTRACT

We report the administration of an anti-interleukin (IL)-6 antibody in a case of severe fever with thrombocytopenia syndrome (SFTS) with an increase in IL-6. On the day of admission, SFTS viral load and IL-6 concentration were 93 831 copies/ml and 5.4 pg/ml, respectively, and tocilizumab was administered. SFTS viral load decreased to 17 821.1 copies/ml on the 3rd day of admission, while IL-6 levels increased to 104.9 pg/ml; SFTS viral load and IL-6 levels had decreased to 2876.4 copies/ml and 48.2 pg/ml on 7th day of admission, respectively. The patient fully recovered no tocilizumab adverse events.

Introduction

Severe fever with thrombocytopenia syndrome (SFTS) is an emerging tick-borne disease caused by the *Dabie bandavirus* of the genus *Bandavirus* (formerly SFTS virus, SFTSV) in East Asia (Yu et al., 2011; Sizikova et al., 2022). The incidence of SFTS has been on the rise, and poses a threat to public health. SFTS has been reported to have a high case-fatality rate of more than 30%, and there are currently no effective treatments (Dualis et al., 2021). Therapeutic plasma exchange (TPE) is a therapeutic modality for rescue therapy in patients with fatal SFTS as it may remove cytokines and toxic mediators (Yoo et al., 2019). In a recent *in vitro* study, peramivir, nitazoxanide, and favipiravir were found to have inhibitory effects on SFTSV (Bang et al., 2022); however, these drugs have not yet undergone clinical trials to assess their safety and efficacy.

A high SFTS viral load and cytokine storm in patients with SFTS are associated with increased mortality (Nakamura et al., 2019). However, it is difficult to determine the SFTS viral load and cytokine levels in infected patients. The development of SFTS has been associated with the significant upregulation of pro-inflammatory cytokines, including high levels of interferon (IFN)-γ and interleukin (IL)-6 (Yoo et al., 2021). Nonetheless, anti-IL-6 antibodies significantly increased the survival of mice with SFTS (Bryden et al., 2022). Herein, we report for the first time, the early application of an anti-IL-6 antibody in a patient with SFTS.

Case presentation

A 77-year-old woman with SFTS, confirmed by real-time reverse transcription-polymerase chain reaction one-day prior to referral, was referred to the emergency department. The patient presented with nausea and vomiting for four days before the referral. The patient had hypertension, cerebral infarction, and thyroid cancer (Charlson Comorbidity Index score of 6). The patient resided in a rural area and had gone to gather bracken two weeks before admission. However, the patient had no recollection of any arthropod bites. On the day of admission, the patient had fever and general weakness. Physical examination did not reveal skin lesions from arthropod bites. The laboratory test results revealed the presence of neutropenia, thrombocytopenia, and increased liver enzymes (Supplementary Table). The sequential organ failure assessment (SOFA) score, which relates to sepsis-related organ failure, was five. A single dose of tocilizumab (480 mg, at a dose of 8 mg/kg of actual body weight) was administered as an intravenous infusion over one hour (Figure 1). The patient's symptoms improved on the 3rd day of admission. On the 5th day of admission, the patient's laboratory findings had improved (Supplementary Figure). On the 7th day of admission, the SOFA score was 1, and the patient was discharged without any complications.

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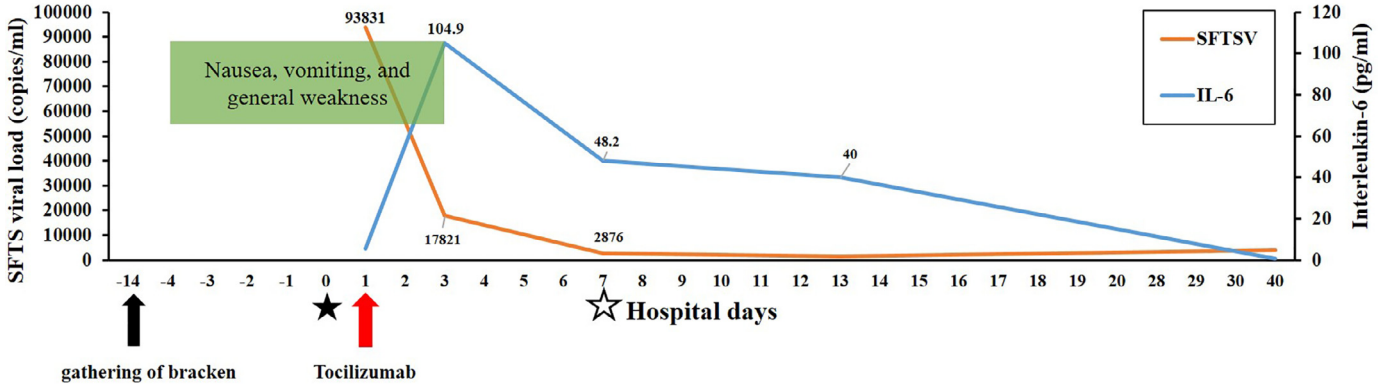

Admission days	1	3	7	13	41
SFTS viral load (copies/ml)	93,831	17821.1	2876.4	1620.6	4139.3
IL-6 (pg/ml)	5.4	4139.3	48.2	40.0	0.8

Figure 1. Dynamics of viral load and IL-6 levels following tocilizumab administration in a patient with SFTS
The green box indicate the duration of symptoms. The red arrow indicates that a single dose of tocilizumab (480 mg at a dose of 8 mg/kg of actual body weight) was administered as an intravenous infusion over one hour. The black asterisk indicates the patient's confirmed SFTS day, and the black line asterisk indicates the patient's discharged days. Severe fever with thrombocytopenia syndrome, SFTS; IL, interleukin

IL-6 levels and SFTS viral RNA load were determined according to the manufacturer's instructions (Supplementary Method). On admission, IL-6 levels and SFTS viral load were 5.4 pg/ml (≤7.0 pg/mL) and 93 831 copies/ml, respectively. IL-6 levels on the 3rd, 7th, 13th, and 41st days were 104.9, 48.2, 40.0, and 0.8 pg/ml, respectively, while SFTS viral load values were 17821.1, 2876.4, 1620.6, and 4139.3 copies/ml, respectively (Figure 1). The patient maintained a low SFTS viral load from the 41st day after admission, while IL-6 levels also remained low.

Discussion

We evaluated dynamic changes in SFTS viral load and IL-6 concentration to further understand the therapeutic effects of tocilizumab in this patient. In particular, fatal cases progress rapidly to multi-organ failure, a crucial period in exacerbation that typically occurs 7–13 days after onset of illness. It is known that excessive release of cytokines and chemokines (IFN-α, IL-10, IP-10, IFN-, IL-6, IL-8, MCP-1, MIP-1, and G-CSF) by activated immune cells and infected cells is involved in disease immunopathology (Kwon et al., 2021). Among 54 patients with SFTS in our previous study, average IL-6 levels of non-fatal and fatal cases were 10.8 (0.0–34.8) and 3151.2 (17.2–15 103.8) pg/ml (P<0.0001), respectively (Yoo et al., 2021). In another study performed in China, IL-6 levels were significantly higher in 11 severe cases than that in 48 non-severe cases, peaking at six and seven days after infection in non-severe and severe cases, respectively (Ding et al., 2014). IL-6 increased until the eighth day and was relatively stable in non-severe cases, but changed significantly in severe cases as the illness progressed. The initial plasma concentration of IL-6 in seven non-survivors, peaking after five days of hospitalization, was significantly higher than that in the 37 survivors [13.7 (12.2–53.8) vs. 112.8 (87.3–147.2), P<0.0001] (Kwon et al., 2021). The overproduction of IL-6 and IL-10 can lead to a cytokine storm, which is considered to contribute to the pathology of SFTS (Kwon et al., 2021).

Interleukin-6 is a key cytokine involved in the cytokine storm. It induces the production of cytokines and chemokines by endothelial and epithelial cells. Tocilizumab blocks IL-6 receptor activity and is approved by the US Food and Drug Administration for the treatment of rheumatoid arthritis. In addition, tocilizumab was found to improve outcomes and survival in patients with severe COVID-19 (The REMAP-CAP Investigators 2021). Furthermore, in 2022, it was recommended for the management of patients with severe COVID-19 in South Korea (Korean Society of Infectious Diseases 2022). In a recent SFTS animal study, the administration of an anti-IL-6 antibody, when disease progressed from mild to moderate, significantly increased the survival of the infected animals (Bryden et al., 2022). The above-mentioned studies support a therapeutic strategy of inhibiting IL-6 pathways in patients with SFTS.

Herein, we presumed that the patient was not a non-fatal case, because non-survivors have shown higher levels of SFTS viral loads than those observed for this patient. In addition, the peak of viral load in survivors was observed on the 1st and 2nd days of hospitalization, which then decreased over time. Kwon et al. reported that initial titer for median SFTSV viral RNA load in severe and non-severe cases was 6.28 log copies/μl (IQR, 4.67–6.94) and 2.59 log copies/μl (IQR, 1.78–3.68), respectively (Kwon et al., 2021). The patient's initial peak SFTS viral load was 93 831 copies/mL after two weeks of tick bite, while IL-6 levels peaked at 104.9 pg/mL. The patient's clinical course and laboratory findings after tocilizumab treatment showed a marked improvement. In addition, it might have been more effective to administer tocilizumab before attaining peak levels of the disease markers. The patient's levels of IL-6 peaked on admission day, and dramatically decreased after tocilizumab administration (Figure 1). The patient did not show any serious adverse events following tocilizumab administration. If the patient had undergone TPE, it could have depleted coagulation factors and immunoglobulins, induced hypocalcemia and metabolic alkalosis, and caused complications related to vascular catheterization. Additionally, TPE is more expensive than tocilizumab administration ($2500 vs. $500, respectively; Yoo et al., 2019). Therefore, tocilizumab, an IL-6 blocking agent, can be used as an affordable option for the treatment of patients with SFTS compared to TPE.

In conclusion, tocilizumab can be used to treat non-fatal SFTS in patients with no available treatment options and where TPE is not applicable. Further studies regarding its efficacy in a large sample size and fatal groups are warranted.

Funding source

None.

Ethical Approval statement

The study protocol was approved by the Institutional Review Board of Jeju National University Hospital (JNUH 2021-09-010-001) and informed consent was obtained from the participant.

Conflict of Interest

None of the authors have any conflicts of interest to declare in relation to this work.

Supplementary materials

Supplementary material associated with this article can be found, in the online version, at doi:10.1016/j.ijid.2022.06.058.

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