WORLD JOURNAL OF PHARMACEUTICAL RESEARCH
SJIF Impact Factor 8.084
Volume 12, Issue 22, 448-465. Review Article ISSN 2277– 7105

THERAPEUTIC INNOVATIONS IN SEVERE FEVER WITH THROMBOCYTOPENIA SYNDROME, EMPHASIZING THE EFFICACY OF FAVIPIRAVIR

Evander James Kamupini*, Priyanka Keshri

ITM University, Gwalior (MP).

Article Received on
27 Oct. 2023,

Revised on 17 Nov. 2023,
Accepted on 07 Dec. 2023

DOI: 10. 20959/wjpr202322-30574

***Corresponding Author**
Evander James Kamupini
B. Pharmacy, ITM University, Gwalior (MP).

ABSTRACT

Severe Fever with Thrombocytopenia Syndrome (SFTS) is an emergingtick- borne viral infection caused by the SFTS virus (SFTSV) belonging to the Bunyaviridae family (Xu B, 2011) (Yu XJ, 2011). This syndrome is characterized by severe fever, thrombocytopenia, leukocytopenia, and multi-organ dysfunction, with high morbidity and mortality rates. The limited understanding of SFTS pathogenesis has prompted the exploration of antiviral agents and therapeutic innovations to improve patient outcomes. Antiviral agents play a pivotal role in the management of SFTS, aiming to reduce viral replication and mitigate the severity of the disease. Favipiravir, a broad-spectrum antiviral drug, has demonstrated promising efficacy against various RNA viruses, including SFTSV. Clinical studies and case reports have explored the use of favipiravir in SFTS patients, revealing potential benefits in terms of symptom alleviation and improved clinical outcomes (Furuta Y, 2009). In addition to favipiravir, this review discusses other therapeutic innovations in the management of SFTS. These innovations encompass immune-based therapies, such as convalescent plasma therapy and interferon-alpha, as well as supportive measures aimed at mitigating the severe manifestations of the disease. Furthermore, the potential role of emerging technologies, including diagnostic advancements and digital health solutions, in early detection and management of SFTS is explored. As the understanding of SFTS continues to evolve, this abstract underscores the importance of ongoing research and collaboration to further delineate the optimal therapeutic strategies for this emerging infectious disease. The insights provided herein contribute to the broader discourse on SFTS management and offer a foundation for future investigations into novel treatment modalities.

KEYWORDS: Severe fever with thrombocytopenia, SFTS virus, Favipiravir (T-705), viral hemorrhagic fever, Ribavirin.

INTRODUCTION

Severe fever with thrombocytopenia syndrome (SFTS) is a viral hemorrhagic fever (VHF) that was first reported in China (Yu XJ, 2011) in 2009 and subsequently reported in South Korea (Kim KH, 2013), western Japan (Takahashi T, 2014), Missouri USA and Vietnam(Jc et al., 2021). The causative agent is a novel phlebovirus of the family Bunyaviridae named SFTS virus. SFTS is considered to be a disease similar to that of Crimean-Congo hemorrhagic fever (CCHF) in terms of its virus characteristics, disease manifestations, mode of virus transmission to humans, pathophysiology, and high case fatality rate (CFR). The syndrome poses a considerable challenge due to its high mortality rate (12% to 45%) and limited treatment options. The major clinical manifestations and laboratory findings of SFTS include fever, gastrointestinal symptoms, thrombocytopenia, leukopenia, and elevated serum hepatic enzyme levels. There is an urgent need for targeted treatment using antiviral agents, including antibodies against SFTSV, to minimize morbidity and mortality associated with Severe Fever with Thrombocytopenia Syndrome (SFTS). Given the absence of a vaccine at present, the identification of a potent anti-SFTSV drug is crucial for addressing the potential global spread of SFTS or similar diseases, particularly in the context of a pandemic.

Favipiravir (T-705) is a recently developed inhibitor of RNA-dependent RNA polymerase (RdRp) and was initially approved as an anti-influenza medication in Japan and is progressing through Phase 3 clinical trials in the USA. Several in vitro and animal studies have demonstrated the inhibitory effects of favipiravir on SFTSV, prompting clinical investigations to assess its safety and efficacy in human subjects. This review will critically analyze the existing literature on favipiravir, exploring its mechanism of action, pharmacokinetics, and the outcomes of clinical trials, shedding light on its role in the therapeutic armamentarium against SFTS. Beyond favipiravir, this article will delve into other promising therapeutic innovations in the realm of SFTS management. From immunomodulatory strategies to emerging antiviral agents. Ribavirin, which was suggested as a potential anti-SFTSV drug, was reported to be ineffective for improving the disease outcome in a retrospective study, or with limited efficacy when used early among patients with very low viremia(T.-I. M & M, 2020). As we navigate through the intricate landscape of SFTS therapeutics, this review aims to synthesize the latest evidence, discuss the potential

benefits and limitations of existing interventions, and highlight the directions for future research that will contribute to the evolving field of infectious disease management. Through a critical evaluation of antiviral agents, with a spotlight on favipiravir, and exploration of other therapeutic innovations, this article seeks to advance our understanding of SFTS treatment and inspire further investigation into novel approaches for combating this challenging infectious disease.

The looming threat

What makes SFTS a matter of critical concern is its capacity for outbreaks, high mortality rate, and the potential for widespread transmission. SFTS outbreaks have been recorded in several regions, and these incidents have often been associated with substantial morbidity and mortality, particularly among the elderly and immuno compromised individuals. While case fatality rates vary, they can reach as high as 30% or more in some outbreaks, making SFTS a considerable public health concern. The virus's broad geographical distribution, the presence of competent vectors (ticks), and the variety of animal hosts further exacerbate its threat potential.

Purpose and Scope of this review article

The purpose of this review article is to provide a comprehensive overview of SFTS as an emerging infectious disease. We aim to collate and synthesize the available knowledge on SFTS, encompassing its epidemiology, etiology, clinical presentation, diagnosis, treatment, and prevention strategies. By doing so, we seek to offer a holistic understanding of this syndrome to researchers, healthcare professionals, and public health authorities. Additionally, we highlight the importance of studying SFTS and maintaining vigilance in monitoring this emerging threat. The scope of this article includes a detailed exploration of the current state of research in the field and an emphasis on the ongoing studies that contribute to our evolving understanding of SFTS. As an emerging infectious disease, SFTS requires ongoing attention and research to combat its spread and mitigate its impact.

SFTSV Epidemiology and Transmission

SFTS has been documented in East Asia, spanning central and eastern China, rural areas of South Korea (Kim KH, 2013), and western Japan (Takahashi T, 2014). The identification of patients exhibiting high fever, gastrointestinal symptoms, thrombocytopenia, leukopenia, and multiple organ failure (MOF) between March and July 2009 led to a two-year epidemiological investigation in central and northeastern China (Jiangsu, Anhui, Hubei,

Henan, Shandong, and Liaoning), resulting in the identification of SFTSV in 2011. Japan reported its first confirmed SFTS case at the end of 2012, with subsequent epidemiological surveys from 2013 to 2017 revealing an average patient age of 74 years, primarily residing in eastern and southern Japan. South Korea reported 1,203 SFTS cases (including 231 fatalities) between 2013 and August 2020, with most cases occurring between April and November. SFTS cases have also emerged in Southeast Asia, including Vietnam, Pakistan, and Taiwan, in addition to the three East Asian countries mentioned earlier.

In Vietnam, Tran et al. conducted a retrospective analysis of serum samples from 80 patients with acute febrile illness, suggesting the potential presence of SFTSV in Vietnam(Xc et al., 2019). Conversely, SFTSV was confirmed in animals in Taiwan after human cases, providing stronger evidence of SFTS occurrence. In northwestern Missouri, United States, two patients with an SFTS-like illness were reported, and the newly discovered causative pathogen, the Heartland virus, was genetically closely related to SFTSV. Genetic analysis in China revealed three dominant genotypes (F, A, and D), while South Korea and Japan predominantly had genotype B. Yun et al. found that genotype B-2 strains in South Korea were associated with the highest mortality. The study also demonstrated varying clinical manifestations in a ferret model based on different SFTSV genotypes(Ct et al., 2016). Seroprevalence studies showed variations in SFTSV antibody prevalence among China, Korea, and Japan. China and Korea exhibited high seroprevalence, while Japan had a relatively low prevalence, possibly due to regional characteristics or differences in antibody detection methods(P et al., 2017).

SFTSV transmission involves various tick species, including Haemaphysalis longicornis, Amblyomma testudinarium, Ixodes nipponensis, and Rhipicephalus microplus is the principal vector, distributed in temperate regions of South Korea, Japan, China, and other areas(Xy et al., 2015). The virus is thought to circulate in a zoonotic cycle between ticks and vertebrates. Animals like cattle, goats, sheep, dogs, pigs, and chickens have been identified as hosts, and transmission from pets to humans has been reported. Additionally, infectious SFTSV has been detected in nasal discharge, saliva, urine, and body fluids, indicating potential routes of transmission, including aerosols and body fluids. Nosocomial transmission and the possibility of sexual transmission further highlight the importance of maintaining contact precautions during patient care.

Pathogenesis

The complete understanding of SFTS pathogenesis remains elusive, but it is closely linked to

a heightened viral load and inflammatory responses induced by various cytokines, including interleukin-1 receptor antagonist (IL-1RA), IL-6, IL-10, granulocyte colony-stimulating factor (G-CSF), and monocyte chemoattractant protein-1 (MCP-1). The glycoproteins of SFTSV facilitate receptor binding and viral entry into macrophages and dendritic cells, serving as targets for neutralizing humoral immunity. Natural killer cells exert immunoregulatory functions through cytokine production, with an increased proportion observed in the acute phase and severe SFTS cases, contributing to an upregulation of inflammatory cytokines and the onset of a cytokine storm (S. M, 2018).

Inflammatory cytokines play a pivotal role in viral disease pathogenesis, characterized by unbalanced profiles in three distinct patterns. Firstly, severe SFTS cases exhibit elevated levels of IL-1RA, IL-6, IL-10, G-CSF, and MCP-1, with a sharp increase in IL-10 levels during acute periods in both fatal and nonfatal cases. Secondly, the SFTSV nonstructural protein (SFTSV-NSs) acts as an interferon and NF-κB antagonist, inducing the expression of IL-10 to facilitate viral pathogenesis(Xu et al., 2011). Thirdly, levels of platelet-derived growth factor regulated upon activation, normally T-expressed, and presumably secreted (RANTES) are in low quantities that return to normal ranges during convalescence. Additionally, IL-1β, IL-8, and macrophage inflammatory proteins 1α and 1β levels increase in severe SFTS cases and in survivors during convalescence, correlating with viral load in the serum and playing a crucial role in SFTS pathogenesis.

These cytokine changes are associated with clinical features. MCP-1 is implicated in progressive renal failure, inflammation, and liver fibrosis, while IL-8 contributes to progressive renal failure and increased vascular permeability. Hemorrhagic fever symptoms in SFTS are attributed to TNF-α, causing vasodilation and heightened endothelial permeability. Thrombocytopenia results from phagocytosis of virus-bound platelets by splenic macrophages. SFTSV replication occurs in various cell types, with infected monocytes avoiding apoptosis, remaining intact, and spreading into the circulation via lymphatic drainage, causing viremia. SFTSV-infected cells in lymph nodes include macrophages and class-switched B cells with a plasma blast-like immunophenotype. Surviving patients exhibit hypermetabolism in regional lymph nodes and the spleen in fluorodeoxyglucose 18 positron emission tomography (18F-FDG PET) imaging, along with characteristic histologic findings of extensive necrosis and histiocytic proliferation in the lymph nodes.

Clinical characteristics of SFTS

Clinical manifestations

The incubation time from the infection to the disease onset was reported to be generally 7 to 14 days (about 2 weeks), with an average of 9 days. It was documented that the incubation period, measured from exposure to the onset of the disease, varied between 7- and 13 days (about 2 weeks) following contact with the deceased index patient of SFTS. The major clinical manifestations of SFTS are rapid onset of high fever, gastrointestinal tract symptoms, and hemorrhagic inclination. Those patients with hemorrhagic symptoms or deterioration in consciousness have poor prognoses and most patients show thrombocytopenia and leukopenia in their total blood cell counts. Recently a patient with hematemesis, was examined by gastrointestinal endoscopy to determine the cause of hemorrhage, and the results showed multiple ulcerative gastric lesions from which hemorrhagic oozing was occurring. The correlation between viremia levels and prognosis was examined by analyzing the association of viral copy numbers in blood specimens, determined through quantitative real-time reverse transcription PCR, with patient outcomes. It was demonstrated that statistically significant differences existed in the copy numbers between patients with fatal and non-fatal outcomes. The average viral copy number in patients who succumbed to the illness was greater than that in those who survived, indicating a higher mortality rate among patients with elevated copy numbers(Jc et al., 2021).

Pathophysiology

The first report of pathological findings from a patient who died of SFTS was documented and reported in Japan. Bone marrow aspiration was performed, in these patient and other patients in whom hemophagocytic lymph histiocytosis (HLH) with or without bone marrow cell dysplasia was present. The patient's right axillary lymph node on computed tomography imaging was enlarged to 3.5 x 2.0 cm. SFTSV-NP antigen was detected in the cytoplasm of blastic cells and in necrotic regions in the cortical area of the right axillary lymph node. Profound necrotizing lymphadenitis characterized by extensive necrosis, diminished small lymphocyte count, and intense infiltration of histiocytes, along with immunoblot observations, were noted in the swollen right axillary and right cervical lymph nodes. Gastric ulceration was also reported, and it was noted in the pyloric region, and hemorrhage was present in the colon and lung(S. M, 2018).

The organs in which SFTSV-NP antigen was detected by immunohistochemistry (IHC) in each of the examined patients are summarized in table 1.

Table 1: SFTSV antigen-positive organs detected in patients who underwent autopsy.

Organs tested	Patients					
	Patient 1-1	Patient 2-1	Patient 2-2[b]	Patient 3-1	Patient 4-1[b]	Patient 5-1
	Female in her 50s	Female, 83 years	Male, 88 years	Male, 82 years	Female, 86 years	Male, 53 years
	Takahashi et al., 2014	Hiraki et al., 2014	Hiraki et al., 2014	Uehara et al., 2016	Nakano et al., 2017	Kaneko et al., 2017
Central nervous system	NR	Negative	NR	Negative	NR	Positive
Midbrain						Positive
Pons						Positive
Medulla						Positive
Basal ganglia						Positive
Cerebellum						Positive
Cerebrum						Positive
Stomach	Negative	Negative	Positive	NR	NR	Positive
Ileum/Colon	Negative	NR	Positive	NR	NR	Positive
Appendix	NR	NR	Positive	NR	NR	NR
Pancreas	NR	Negative	Positive	NR	NR	Positive
Spleen	Positive	Negative	Positive	Positive	Positive	Positive
Heart	Negative	Negative	Positive	NR	NR	Positive
Lung	Negative	Negative	Positive	Negative	NR	Positive
Liver	Positive	Negative	Positive	Positive	Positive	Positive
Kidney	Negative	Negative	Positive	Negative	NR	Positive
Thyroid	NR	Negative	Positive	NR	NR	Positive
Adrenal glands	Positive	Negative	Positive	Positive	NR	NR
Uterus	NR	Negative	NR	NR	NR	NR
Ovaries	NR	Negative	NR	NR	NR	NR
Bladder	NR	Negative	Positive	NR	NR	NR
Tonsils	NR	Positive	NR	Negative	NR	NR
Bronchi	NR	Negative	Negative	Negative	NR	NR
Esophagus	Negative	Negative	Positive	NR	NR	NR
Bone marrow	Positive	Negative	NR	Positive	Positive	Positive
Pituitary gland	NR	Negative	NR	NR	NR	NR
Gallbladder	NR	NR	Positive	NR	NR	NR
Testes	NR	NR	Positive	NR	NR	NR
Lymph nodes	Positive	Positive	Positive	Positive	NR	NR
Axillary	Positive	NR	NR	NR	NR	NR
Cervical	Positive	NR	NR	NR	NR	NR
Diaphragmatic	Negative	Negative	Positive	NR	NR	NR
Paratracheal	NR	Negative	Positive	NR	NR	Positive
	NR	Negative	NR	Negative	NR	Positive
Inguinal (Left)	NR	Positive	NR	NR	NR	NR
Inguinal (Right)	NR	Negative	NR	NR	NR	NR
Abdominal	NR	Negative	NR	NR	NR	Positive
Paraaortic	NR	NR	Positive	Positive	NR	Positive

1. There appears to be two distribution patterns of the SFTSV antigen: “Entirely SFTSV antigen-positive type”, in which the SFTSV antigen was detected in most organs tested (Patients 2-2 and 5-1), and “Localized SFTSV antigen-positive type”, in which the SFTSV antigen was detected in limited organs tested (Patients 1-1 and 3-1).
2. SFTSV antigen was detected in one patient (Patient 5-1) with pathological lesions in the central nervous system (CNS).
3. Fungal infection was incidentally detected in the lower respiratory tract and lung of 2 patients (Patients 2-2 and 4-1).(S. M, 2018)

Cytokine storm was reported to be one of the major pathophysiological features in SFTS patients that cause the case fatality rate to be high. There have been reports in which the kinetics of cytokine and chemokines were studied in SFTS patients. Based on these reports, interleukin (IL)-6, IL-10, interferon (IFN)- g-induced protein (IP)-10, and IFN-gamma levels increased rapidly, in the early phase of the disease.

In the initial stage of the disease, there was a reported decrease in Regulated on Activation, Normal T-cell Expressed and Secreted (RANTES). Kwon et al. found a correlation between early-phase IP-10 levels and the SFTSV load, which has been linked to the prognosis of SFTS patients. This correlation between the IP-10 levels and the viremia levels was evaluated with only 10 patients, suggesting that further study is needed to address the connection. Ding

YP et al. studied the correlation between the cytokine and chemokine levels, platelet counts, and serum chemistry such as AST, LDH, and ALT in SFTS patients. The platelet count demonstrated a tendency to decrease in conjunction with lower levels of soluble CD40 ligand (sCD40L) and platelet-derived growth factor (PDGF) BB, as well as elevated levels of IL-10, soluble IL-2 receptor alpha (sIL-2RA), and IP-10. Additionally, there was a positive correlation observed between serum alanine aminotransferase (ALT) and aspartate aminotransferase (AST) levels and a cluster of cytokines or proteins, including IL-10, sIL-2RA, heat shock protein 70, IP-10, IL-4, IFN-g, and tissue plasminogen activator inhibitor (tPAI)-1. The serum CK level was positively associated with levels of IL-10, sIL-2RA, HSP70, IP-10, and IL-15. The lactate dehydrogenase (LDH) level was positively correlated with IL-10, sIL-2RA, HSP70, IP-10, IL-4, IFN-g and IL-15 levels. In contrast, negative connections existed between LDH and the cytokines soluble Fas ligand or sCD40L. The serum chemistry levels were found to have a correlation with both the SFTSV genome loads and the severity of the disease. These findings suggest that the intensity of the cytokine storm, specifically the severity of hemophagocytic lymphohistiocytosis (HLH), constitutes a significant pathophysiological factor influencing the severity of SFTS.

SFTS Treatment

Favipiravir

Favipiravir (T-705) is a pyrazine derivative and antiviral agent developed in Japan that has a broad spectrum of antiviral effects. Favipiravir inhibits the RNA polymerase of the influenza virus and those of various RNA viruses, such as bunyaviruses, arenaviruses, and the yellow fever virus. Several recent studies have reported the effects of favipiravir on SFTS and suggest that favipiravir has a stronger antiviral effect than ribavirin both in vitro and in vivo. In particular, Tani et al. and Baba et al. reported that favipiravir inhibited the replication of SFTSV in Vero cells, with an IC50 of 6 μM and a 50% effective concentration (EC50) of 25 μM. In addition, Tani et al. reported that the oral administration of favipiravir at dosages of 120 mg/(kg·day) and 200 mg/(kg·day) to interferon receptor 1 knockout mice infected with SFTSV was effective. Gowen et al. demonstrated that hamsters with stat2 knockout, hindering the initiation of the type I IFN response, exhibited responsiveness to oral favipiravir treatment at 300 mg/(kg·day). This treatment led to a reduction in both serum and tissue viral loads in hamsters infected with SFTSV(T. H et al., 2016).

In 2021, Suemori et al. documented a study involving 16 trials to assess the effectiveness and

safety of favipiravir. Out of 23 participants administered an oral loading dose of 1800 mg twice on the initial day, followed by a regimen of 800 mg twice a day for 7–14 days, the drug was well-tolerated. The 28-day mortality rate in this group was recorded at 17.3%. In addition, viral RNA was not detectable in surviving patients at a median of 8 days after favipiravir administration. As the study was a nonrandomized, uncontrolled, single-arm investigation, further randomized clinical trials are essential. Additionally, there is a need for animal models to evaluate the efficacy of antiviral agents, such as favipiravir and ribavirin, in the treatment of SFTSV infections(Ms et al., 2022). T-705 therapy evaluation to date, which was analyzed shows that T-705 had a significant effect on decreasing SFTS related CFR (9.0% vs. 20.0%), which corresponded to a 55.0% (95% CI 23.2%-66.8%) reduced OR of fatal within non-T-705 group(T. H et al., 2016).

Mechanism of T-705 against SFTSV in a mouse model

In a study investigating the mechanism of T-705 against SFTSV in an IFNAR−/− C57BL/6 mouse model, mice infected with SFTSV were treated with DMSO (vehicle), ribavirin (100 mg/kg/day), T-705 (150 mg/kg/day), or T-705 (300 mg/kg/day). The survival rates of T-705-treated mice were significantly higher than those treated with DMSO or ribavirin. The study further explored the mutagenesis mechanism of T-705 on RNA viruses in vivo, revealing reduced viral loads and enhanced virus mutation rates in serum samples of T-705-treated mice. The mutation rates increased with the duration of treatment, with 300 mg/kg/day showing higher accumulation compared to 150 mg/kg/day. While the mutagenesis mechanism of T-705 in treating SFTSV infection in a mouse model differs from the in vitro mechanism, which mainly induces transition mutations, these findings emphasize T-705's potential as an effective agent for inhibiting SFTSV replication in vivo by inducing viral lethal mutagenesis(L. H et al., 2021).

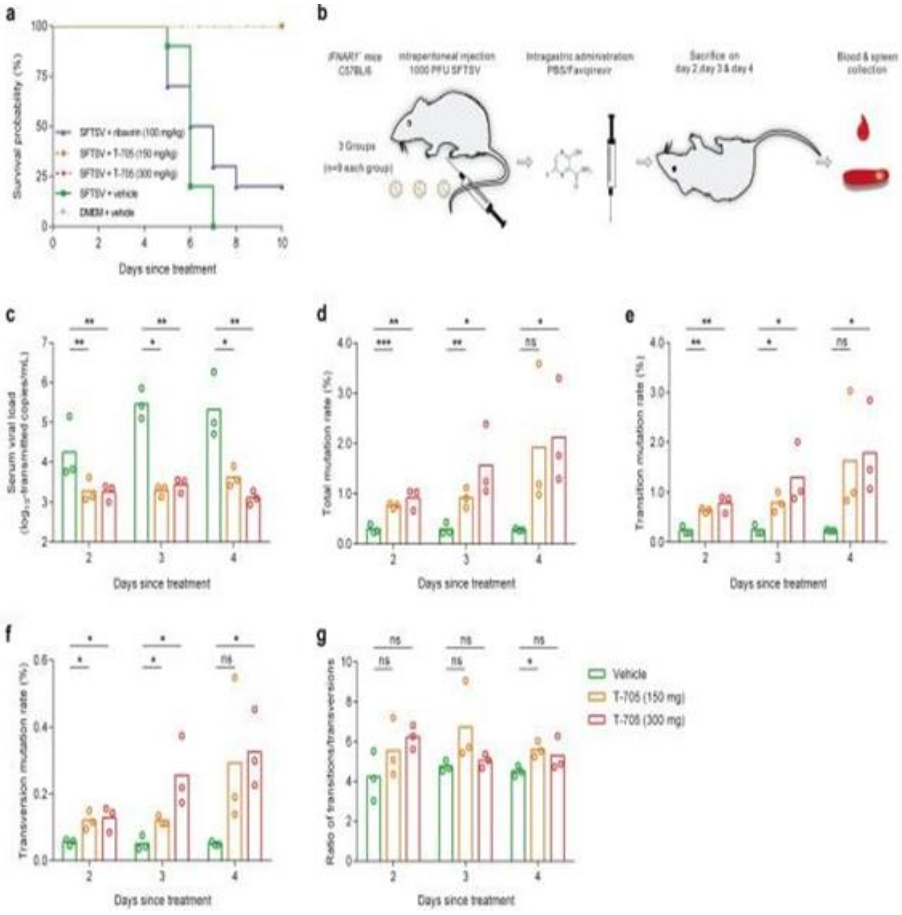

Fig. 1: The NGS and mutation analysis of SFTSV genome in serum samples collected from IFNAR−/− C57BL/6 mouse treated with or without T-705. a Kaplan–Meier curves for the T-705 treatment effect on the probability of survival in IFNAR−/− C57BL/6 mouse. IFNAR−/− C57BL mice were divided into five groups: SFTSV + vehicle group (five female and five male mice), SFTSV + T-705 group I (300 mg/kg/d, five female and five male mice), SFTSV + T-705 group II (150 mg/kg/d, five female and five male mice), SFTSV + ribavirin (100 mg/kg/d, five female and five male mice), and DMEM + T-705 group (300 mg/kg/d, three female and three male mice). b Flowchart of next-generation sequencing (NGS) of SFTSV genome in spleen and serum samples collected from IFNAR−/− C57BL/6 mouse. Three IFNAR−/− C57BL/6 mice from each group were sacrificed on days 2, 3, and 4 post infection, respectively. Serum and spleen samples were collected, and RNA was extracted for NGS analysis. Copy number of SFTSV genome in serum (c), the total mutation rates (d), transition mutation rates (e), transversion mutation rates (f), and ratios of transitions/transversions (g) were also calculated(L. H et al., 2021)

The study conducted NGS and mutation analysis of the SFTSV genome in serum samples

from IFNAR−/− C57BL/6 mice treated with or without T-705. The mice were divided into groups based on different treatments, including T-705, ribavirin, and control groups. Kaplan–Meier curves illustrated the T-705 treatment's impact on the probability of survival. The flowchart outlined the NGS process of SFTSV genome in spleen and serum samples from mice at various time points post-infection. Results included analysis of SFTSV genome copy number in serum, total mutation rates, transition and transversion mutation rates, and ratios of transitions/transversions.

In the clinical trial assessing T-705 treatment for SFTS patients, viral clearance, defined as the time to a first negative RT-PCR assay, was analyzed as a secondary outcome. The T-705-treated group exhibited a significantly shorter mean time to viral clearance (5.6 ± 2.1 days) compared to the control group (6.8 ± 2.8 days) (P = 0.012). This trend was consistent in patients with low or high baseline viral loads. Additionally, T-705 treatment was associated with a more rapid decrease in viral load, as evidenced by the generalized estimating equation (GEE) model (P = 0.024)(L. H et al., 2021). This association was also observed in patients with low-baseline viral loads, although data for patients with high-baseline viral loads were limited (K et al., 2021).

The antiviral mechanism of T-705 on SFTSV replication in human patients was investigated through NGS and mutation analyses on 74 longitudinally collected serum samples. The study involved 12 T-705-treated patients and 11 control patients. Before treatment, mutation rates were comparable between the groups. However, during the first week of treatment, the T-705-treated group exhibited significantly increased mutation rates compared to the control group, with notable differences observed at day 4. Survival patients in the T-705 group showed increased virus mutations, while fatal patients did not exhibit the same pattern. Patients without T-705 treatment showed no increase in virus mutations. The accumulating mutations correlated with the CT values of SFTSV, suggesting that T-705 reduces viral loads by inducing both transition and transversion mutations detrimental to viral proliferation. The mutagenesis pattern observed in SFTS patients resembled that seen in the mouse model, with no predominant pattern of transition or transversion mutations(L. H et al., 2021).

Favipiravir comparison to other treatments of SFTS

The antiviral agents that have been tested in animal models for an inhibitory effect on the replication of SFTSV in vitro and in vivo are ribavirin, favipiravir, antimalarial agent amodiaquine, and serum containing neutralizing antibody activity. Ribavirin was shown to

have an inhibitory effect on SFTSV replication in vitro and a partial effect in vivo. However, it has not been possible to demonstrate a beneficial effect of ribavirin in the treatment of hospitalized SFTS patients in PR China(B. M et al., 2017).

Table 2: Treatment effect on 30-day mortality in patients with SFTS.

Variables	Univariate			Multivariate		
	HR	95% CI	*p*-Value	aHR†	95% CI	*p*-Value
Prior antibiotic treatment	1.55	(0.76–3.16)	0.234	1.90	(0.75–4.81)	0.174
Ribavirin	1.61	(0.75–3.45)	0.217	1.06	(0.34–3.25)	0.923
Steroids	4.57	(1.96–10.66)	<0.001	3.31	(1·26–8.73)	0.016
IVIG	1.61	(0.74–3.51)	0.235	0.74	(0.32–1.72)	0.482
Plasmapheresis	2.19	(1.03–4.68)	0.043	1.40	(0.41–4.78)	0.593

Abbreviations: aHR, adjusted hazard ratio; CI, confidence interval; HR, hazard ratio; IVIG, intravenous immunoglobulin. † Adjusted variables: initial APCHE II score and symptom onset to admission within 7 days.

SFTS alternative treatments

Steroids

Severe cases of Severe Fever with Thrombocytopenia Syndrome (SFTS) often lead to rapid deterioration, with common causes of death including multiple organ failure (MOF), severe bleeding, and septic shock. A cytokine storm is identified as a key element in this pathogenic process. Clinicians consider steroids as a potential treatment option to suppress the immune system, akin to their role in treating severe cases of COVID-19 caused by the SARS-CoV-2 virus. Several case reports highlight successful treatment with a combination of steroids and intravenous immunoglobulin (IVIG) in South Korea and Japan. However, autopsy findings from patients treated with corticosteroids revealed marked fungal infections in the lungs, suggesting a potential risk of fungal infections associated with corticosteroid use. Studies indicate an increased occurrence of invasive aspergillosis in SFTS patients using corticosteroids, emphasizing the need for caution in steroid therapy. While one study demonstrated a significant difference in 30-day survival between steroid and nonsteroid groups in mild SFTS cases, caution is advised in severe cases, as steroid therapy within the first 5 days or in mild cases may increase complications and mortality risk.

Intravenous immunoglobulin

In the treatment of Severe Fever with Thrombocytopenia Syndrome (SFTS), Intravenous Immunoglobulin (IVIG) is considered significant. IVIG plays a crucial role in treating viral

diseases by activating complement, neutralizing viruses, promoting antibody-dependent cellular cytotoxicity, and facilitating opsonization. SFTS patients often exhibit decreased CD3 and CD4 T cell levels along with heightened natural killer T (NKT) cell activity, contributing to immunosuppression and a cytokine storm, characterized by elevated levels of IFN-γ, IL-10, and G-CSF. IVIG administration is believed to help reduce viral loads, restrain SFTSV spread, and effectively suppress the cytokine storm. Case reports have shown successful treatment of severe SFTS with IVIG, often in combination with other drugs. However, the specific impact of IVIG on SFTS remains unclear, and further research is needed to ascertain its effectiveness, considering the unique characteristics of SFTSV antibodies in the general population(S. M, 2018).

Plasma exchange or convalescent plasma

Cytokines like IL-1β, IL-8, macrophage inflammatory protein 1β, and IFN-γ are implicated in the progression and severity of Severe Fever with Thrombocytopenia Syndrome (SFTS). Plasma exchange is considered a potential therapy for cytokine removal in SFTS patients. Studies by Yoo et al. and Oh et al. observed improved clinical manifestations and laboratory findings in patients treated with plasma exchange compared to those who did not receive this treatment. Choi et al. explored convalescent plasma therapy as a follow-up for patients with no improvement after early plasma exchange, leading to decreased serum viral load and improved clinical outcomes. While these findings suggest a role for plasma exchange and convalescent plasma therapy in alleviating the cytokine storm during the early and late phases of SFTS, respectively, establishing them as standard treatments is challenging due to unclear inclusion criteria and variable therapeutic effects(S. M, 2018). Consequently, acknowledging these therapies as established strategies would require further randomized controlled studies.

Monoclonal antibodies

Monoclonal antibodies are emerging as novel therapeutic agents for Severe Fever with Thrombocytopenia Syndrome (SFTS) among various treatment options. Guo et al. demonstrated that monoclonal antibodies exhibit neutralizing activity against SFTSV infection in Vero cells by binding to a linear epitope in the ectodomain of the glycoprotein Gn. This neutralization occurs through the inhibition of viral cell attachment by blocking interactions between glycoprotein Gn and cellular receptors(Shimojima et al., 2022). Additionally, Kim et al. found that their specified antibody, reactive to the envelope glycoprotein Gn of SFTSV, protected 80% of mice and host cells, indicating the potential of

monoclonal antibodies as a promising therapeutic option against SFTS(Seo et al., 2021).

SUMMARY

SFTSV is present in the natural environment of PR China, DPRK, South Korea, and Japan, with documented cases of human-to-human transmission similar to CCHF infection. The significant case fatality rate of SFTS underscores the inherent risk in endemic regions. Emphasizing the pressing need for specific therapy and preventive measures against SFTS, including the development of antiviral agents and vaccines, is crucial. The key to mitigating morbidity and mortality in SFTS patients lies in advancing effective antiviral drug-based therapies and vaccines. At present, favipiravir emerges as a promising antiviral drug for SFTS, requiring further study with a focus on collaboration, not only domestically but also with the international community.

ACKNOWLEDGEMENT

I would like to express my gratitude to Mrs. Priyanka Keshri (Assistant Professor, School of Pharmacy, ITM University, Gwalior) for her invaluable assistance and supervision throughout the preparation of this review article. Her expertise, guidance, and unwavering support have played a pivotal role in shaping the content and ensuring the quality of this manuscript.

REFERENCES

1. Xu B, Liu L, Huang X, Ma H, Zhang Y, Du Y, et al. Metagenomic analysis of fever, thrombocytopenia and leukopenia syndrome (ftls) in henan province, China: discovery of a new bunyavirus. PLoS Pathog, 2011; 7: e1002369.
2. Yu XJ, Liang MF, Zhang SY, Liu Y, Li JD, Sun YL, et al. Fever with thrombocytopenia associated with a novel bunyavirus in China. N Engl J Med, 2011; 364: 1523e32.
3. Kim KH, Yi J, Kim G, Choi SJ, Jun KI, Kim NH, et al. Severe fever with thrombocytopenia syndrome, South Korea, 2012. Emerg Infect Dis, 2013; 19: 1892e4.
4. Takahashi T, Maeda K, Suzuki T, Ishido A, Shigeoka T, Tominaga T, et al. The first identification and retrospective study of severe fever with thrombocytopenia syndrome in Japan. J Infect Dis, 2014; 209: 816e27.
5. Kato H, Yamagishi T, Shimada T, Matsui T, Shimojima M, Saijo M, et al. Epidemiological and clinical features of severe fever with thrombocytopenia syndrome in Japan, 2013-2014. PLoS One, 2016; 11: e0165207.
6. Zhan J, Wang Q, Cheng J, Hu B, Li J, Zhan F, et al. Current status of severe fever with

thrombocytopenia syndrome in China. Virol Sin, 2017; 32: 51e62.

7. Choi SJ, Park SW, Bae IG, Kim SH, Ryu SY, Kim HA, et al. Severe fever with thrombocytopenia syndrome in South Korea, 2013-2015. PLoS Negl Trop Dis, 2016; 10: e0005264.
8. Furuta Y, Takahashi K, Shiraki K, Sakamoto K, Smee DF, Barnard DL, et al. T-705 (favipiravir) and related compounds: novel broad-spectrum inhibitors of RNA viral infections. Antivir Res, 2009; 82: 95e102.
9. Tani H, Fukuma A, Fukushi S, Taniguchi S, Yoshikawa T, Iwata-Yoshikawa N, et al. Efficacy of t-705 (favipiravir) in the treatment of infections with lethal severe fever with thrombocytopenia syndrome virus. MSphere, 2016; 1.
10. Gowen BB, Westover JB, Miao J, Van Wettere AJ, Rigas JD, Hickerson BT, et al. Modeling severe fever with thrombocytopenia syndrome virus infection in golden syrian hamsters: importance of stat2 in preventing disease and effective treatment with favipiravir. J Virol, 2017; 91.
11. Yun SM, Park SJ, Park SW, Choi W, Jeong HW, Choi YK, et al. Molecular genomic characterization of tick- and human-derived severe fever with thrombocytopenia syndrome virus isolates from South Korea. PLoS Negl Trop Dis, 2017; 11: e0005893.
12. Suh JH, Kim HC, Yun SM, Lim JW, Kim JH, Chong ST, et al. Detection of sfts virus in ixodes nipponensis and amblyomma testudinarium (ixodida: ixodidae) collected from reptiles in the Republic of Korea. J Med Entomol, 2016; 53: 584e90.
13. Li Z, Bao C, Hu J, Liu W, Wang X, Zhang L, et al. Ecology of the tick-borne phlebovirus causing severe fever with thrombocytopenia syndrome in an endemic area of China. PLoS Negl Trop Dis, 2016; 10: e0004574.
14. Luo LM, Zhao L, Wen HL, Zhang ZT, Liu JW, Fang LZ, et al. Haemaphysalis longicornis ticks as reservoir and vector of severe fever with thrombocytopenia syndrome virus in China. Emerg Infect Dis, 2015; 21: 1770e6.
15. Kitao A, Ieki R, Takatsu H, Tachibana Y, Nagae M, Hino T, et al. Severe fever with thrombocytopenia syndrome presenting as hemophagocytic syndrome: two case reports. SpringerPlus, 2016; 5: 361.
16. Chen H, Hu K, Zou J, Xiao J. A cluster of cases of human-to-human transmission caused by severe fever with thrombocytopenia syndrome bunyavirus. Int J Infect Dis, 2013; 17: e206e8.
17. Jiang XL, Zhang S, Jiang M, Bi ZQ, Liang MF, Ding SJ, et al. A cluster of person to-person transmission cases caused by SFTS virus in Penglai, China. Clin Microbiol Infect,

2015; 21: 274e9.

18. Kim WY, Choi W, Park SW, Wang EB, Lee WJ, Jee Y, et al. Nosocomial transmission of severe fever with thrombocytopenia syndrome in Korea. Clin Infect Dis, 2015; 60: 1681e3.
19. Liu Y, Li Q, Hu W, Wu J, Wang Y, Mei L, et al. Person-to-person transmission of severe fever with thrombocytopenia syndrome virus. Vector Borne Zoonotic Dis, 2012; 12: 156e60.
20. Tang X, Wu W, Wang H, Du Y, Liu L, Kang K, et al. Human-to-human transmission of severe fever with thrombocytopenia syndrome bunyavirus through contact with infectious blood. J Infect Dis, 2013; 207: 736e9.
21. Liu Q, He B, Huang SY, Wei F, Zhu XQ. Severe fever with thrombocytopenia syndrome, an emerging tick-borne zoonosis. Lancet Infect Dis, 2014; 14: 763e72.
22. Kaneyuki S, Yoshikawa T, Tani H, Fukushi S, Taniguchi S, Fukuma A, et al. Ulcerative lesions with hemorrhage in a patient with severe fever with thrombocytopenia syndrome observed via upper gastrointestinal endoscopy. Jpn J Infect Dis, 2016; 69: 525e7.
23. Yoshikawa T, Fukushi S, Tani H, Fukuma A, Taniguchi S, Toda S, et al. Sensitive and specific pcr systems for detection of both Chinese and Japanese severe fever with thrombocytopenia syndrome virus strains and prediction of patient survival based on viral load. J Clin Microbiol, 2014; 52: 3325e33.
24. Kaneko M, Shikata H, Matsukage S, Maruta M, Shinomiya H, Suzuki T, et al. A patient with severe fever with thrombocytopenia syndrome and hemophagocytic lymphohistiocytosis-associated involvement of the central nervous system. J Infect Chemother, 2017; 24: 292e7.
25. Hiraki T, Yoshimitsu M, Suzuki T, Goto Y, Higashi M, Yokoyama S, et al. Two autopsy cases of severe fever with thrombocytopenia syndrome (SFTS) in Japan: a pathognomonic histological feature and unique complication of SFTS. Pathol Int, 2014; 64: 569e75.
26. Nakano A, Ogawa H, Nakanishi Y, Fujita H, Mahara F, Shiogama K, et al. Hemophagocytic lymphohistiocytosis in a fatal case of severe fever with thrombocytopenia syndrome. Intern Med, 2017; 56: 1597e602.
27. Uehara N, Yano T, Ishihara A, Saijou M, Suzuki T. Fatal severe fever with thrombocytopenia syndrome: an autopsy case report. Intern Med, 2016; 55: 831e8.
28. Sun Y, Jin C, Zhan F, Wang X, Liang M, Zhang Q, et al. Host cytokine storm is associated with disease severity of severe fever with thrombocytopenia syndrome. J Infect

Dis, 2012; 206: 1085e94.

29. Kwon JS, Kim MC, Kim JY, Jeon NY, Ryu BH, Hong J, et al. Kinetics of viral load and cytokines in severe fever with thrombocytopenia syndrome. J Clin Virol, 2018; 101: 57e62.
30. Deng B, Zhang S, Geng Y, Zhang Y, Wang Y, Yao W, et al. Cytokine and chemokine levels in patients with severe fever with thrombocytopenia syndrome virus. PLoS One, 2012; 7: e41365.
31. Ding YP, Liang MF, Ye JB, Liu QH, Xiong CH, Long B, et al. Prognostic value of clinical and immunological markers in acute phase of sfts virus infection. Clin Microbiol Infect, 2014; 20: O870e8.
32. Liu MM, Lei XY, Yu H, Zhang JZ, Yu XJ. Correlation of cytokine level with the severity of severe fever with thrombocytopenia syndrome. Virol J, 2017; 14: 6.
33. Gai ZT, Zhang Y, Liang MF, Jin C, Zhang S, Zhu CB, et al. Clinical progress and risk factors for death in severe fever with thrombocytopenia syndrome patients. J Infect Dis, 2012; 206: 1095e102.
34. Shimojima M, Fukushi S, Tani H, Taniguchi S, Fukuma A, Saijo M. Combination effects of ribavirin and interferons on severe fever with thrombocytopenia syndrome virus infection. Virol J, 2015; 12: 181.
35. Shimojima M, Fukushi S, Tani H, Yoshikawa T, Fukuma A, Taniguchi S, et al. Effects of ribavirin on severe fever with thrombocytopenia syndrome virus in vitro. Jpn J Infect Dis, 2014; 67: 423e7.
36. Baba M, Toyama M, Sakakibara N, Okamoto M, Arima N, Saijo M. Establishment of an antiviral assay system and identification of severe fever with thrombocytopenia syndrome virus inhibitors. Antiviral Chem Chemother, 2017; 25: 83e9.
37. Shimada S, Posadas-Herrera G, Aoki K, Morita K, Hayasaka D. Therapeutic effect of post-exposure treatment with antiserum on severe fever with thrombocytopenia syndrome (sfts) in a mouse model of sfts virus infection.Virology, 2015; 482: 19e27.
38. Liu W, Lu QB, Cui N, Li H, Wang LY, Liu K, et al. Case-fatality ratio and effectiveness of ribavirin therapy among hospitalized patients in China who had severe fever with thrombocytopenia syndrome. Clin Infect Dis, 2013; 57: 1292e9.
39. Lu QB, Zhang SY, Cui N, Hu JG, Fan YD, Guo CT, et al. Common adverse events associated with ribavirin therapy for severe fever with thrombocytopenia syndrome. Antivir Res, 2015; 119: 19e22.
40. Spengler JR, Bente DA, Bray M, Burt F, Hewson R, Korukluoglu G, et al. Second

international conference on Crimean-Congo hemorrhagic fever. Antivir Res, 2018; 150: 137e47.

41. [Schram AM, Berliner N. How I treat hemophagocytic lymphohistiocytosis in the adult patient. Blood, 2015; 125: 2908e14.
42. Oh WS, Heo ST, Kim SH, Choi WJ, Han MG, Kim JY. Plasma exchange and ribavirin for rapidly progressive severe fever with thrombocytopenia syndrome. Int J Infect Dis, 2014; 18: 84e6.
43. Park I, Kim HI, Kwon KT. Two treatment cases of severe fever and thrombocytopenia syndrome with oral ribavirin and plasma exchange. Infect Che mother, 2017; 49: 72e7.
44. Yoo JR, Kim SH, Kim YR, Lee KH, Oh WS, Heo ST. Application of therapeutic plasma exchange in patients having severe fever with thrombocytopenia syndrome. Korean J Intern Med, 2017; 2016: 194.
45. Oh WS, Yoo JR, Kwon KT, Kim HI, Lee SJ, Jun JB, et al. Effect of early plasma exchange on survival in patients with severe fever with thrombocytopenia syndrome: a multicenter study. Yonsei Med J, 2017; 58: 867e71.
46. Oestereich L, Rieger T, Neumann M, Bernreuther C, Lehmann M, Krasemann S, et al. Evaluation of antiviral efficacy of ribavirin, arbidol, and T-705 (favipiravir) in a mouse model for Crimean-Congo hemorrhagic fever. PLoS Negl Trop Dis, 2014; 8: e2804.