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**Anti-inflammatory effect of recombinant thrombomodulin for fulminant hepatic failure**

Kurokohchi K *et al.* Recombinant TM for fulminant hepatic failure

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**Abstract**

Fulminant hepatic failure (FHF) is a critical illness that can be comorbid to primary liver damage. FHF shows a high mortality rate, and patients with FHF require intensive therapy including plasma apheresis. However, intensive care at the present is not enough to restore the severe liver damage or promote hepatocellular reproduction, and a standard therapy for the treatment of FHF has not been established. An 86-year-old female with FHF was admitted to our hospital. Her manifestation demonstrated a clinical situation of systemic inflammatory response syndrome (SIRS) and disseminated intravascular coagulation. A diagnosis of fulminant hepatitis was made according to the definition given in the American Association for the Study of Liver Diseases position paper. Her serum hepatocyte growth factor (HGF) level had increased to 11.84 ng/mL. The HGF level indicated massive liver damage as seen in FHF. Recombinant thrombomodulin (rTM) was administered daily from the admission day for 1 wk at 380 U/kg. The patient’s white blood cell and C-reactive protein responded to the rTM treatment within a few days. Not only the HGF level but also the PT recovered to the normal range. The levels of proinflammatory cytokines (tumor necrosis factor-α and interleukin-1β) were suppressed by the administration of rTM. The patient’s hepatic function such as PT and albumin completely recovered without plasma exchange. rTM may modulate the over-response of SIRS with the improvement of proinflammatory cytokines. The underlying mechanism is thought to be the inhibitory effect of rTM on high-mobility group box 1 (HMBG1). The pathogenesis of HMBG1 protein in fulminant hepatic failure has been already known. A novel favorable effect of rTM for SIRS would be promising for FHF, and the wide application of rTM for SIRS should be considered.

**Key words**: Fulminant hepatic failure; Thrombomodulin; Systemic inflammatory response syndrome; Disseminated intravascular coagulation; Hepatocyte growth factor

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**Core tip**:Fulminant hepatic failure (FHF) is a critical illness that can be comorbid to primary liver damage. However, no standard therapy for the treatment of FHF has been established. We experienced a fatal FHF case with systemic inflammatory response syndrome and followed by disseminated intravascular coagulopathy (DIC). We administered recombinant thrombomodulin (rTM) for the treatment of DIC, and which ameliorated all the lethal conditions; coagulopathy and inflammation. A monitoring of proinflammatory cytokines, hepatocyte growth factor and prothrombin time revealed the response of FHF to rTM. We hypothesized anti-inflammatory effect of rTM enhanced hepatocyte regeneration through inactivation of high-mobility group box 1.

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**INTRODUCTION**

Fulminant hepatic failure (FHF) is a critical illness that can be comorbid to primary liver damage[1]. FHF shows a high mortality rate, and patients with FHF require intensive therapy[2]. However, intensive care at the present is not enough to restore the severe liver damage or promote hepatocellular reproduction, and a standard therapy for the treatment of FHF has not been established[1]. FHF is produced from any background of liver injury such as those due to one or more drugs, autoimmune disorders, and acute or chronic viral infections[3]. Severe FHF is fatal, and the survival rate of FHF patients in the Japanese population has been estimated as 11.5%–24.4%[4]. Almost all patients with FHF are at risk of multi-organ failure. The only effective therapy for FHF is liver transplantation, but the indications for this are limited[2]. To rescue FHF patients, non-transplantation therapy, corticosteroids and plasma apheresis can be applied, but clinical evidence of the efficacy of these non-transplantation therapies is scarce. Several risk factors for fulminant hepatitis are known. FHF patients with systemic inflammatory response syndrome (SIRS) also show poor prognoses. The concomitance of any complication also significantly decreases the survival rate of FHF patients[2,4].

Thrombomodulin (TM) is a physiological anticoagulation factor that acts as a direct inactivator of thrombin and a suppressor of coagulation factors Va and VIIIa *via* activated protein C (APC)[5]. Recombinant thrombomodulin (rTM) was developed as a therapeutic agent for disseminated intravascular coagulation (DIC) syndrome, and it is widely used in a variety of clinical situations[6]. A loss or lack of TM disrupts the protein C anticoagulant pathway and causes thrombosis[7]. Some clinical situations associated with SIRS (including severe infection, sepsis, trauma and organ inflammation) may cause a decrease of TM, which is a substantial pathogenesis of DIC syndrome[8]. Additionally, a novel anti-inflammatory effect of TM and the APC pathway has been gradually unveiled[5], and the aggregated knowledge has established the dual mechanisms of TM in DIC and SIRS by the modulation of aberrant coagulopathy and the attenuation of inflammatory milieu. However, the anti-inflammatory effect of rTM in FHF has not been elucidated, and the greater involvement of rTM in SIRS, a nonspecific inflammatory disease, is not yet understood.

**CASE REPORT**

An 86-year-old female visited an outpatient clinic of our hospital due to increased fever, diarrhea and decreased blood pressure. Her laboratory data indicated intensely impaired liver function, bilirubinemia and renal dysfunction: aspartate transaminase 8929 U/L, alanine transaminase 5449 U/L, lactate dehydrogenase (LDH) 7248 U/L, total bilirubin (Tbil) 3.1 mg/dL, blood urea nitrogen (BUN) 34.8 mg/dL, Cr 1.9 mg/dL, PT 42%. She was diagnosed as having concomitant DIC based on the coagulation test: PT 63.5%, PT-INR 1.23, APTT 26.0 s, fibrinogen 273 mg/dL, FDP > 80 μg/dL and D-dimer > 5.00 μg/mL. She did not have a history of viral hepatitis or autoimmune liver disease such as primary biliary cirrhosis (PBC) or autoimmune hepatitis (AIH). The radiological findings on admission and on previous examinations revealed no fatty liver or splenomegaly. A diagnosis of fulminant hepatitis was made according to the definition given in the American Association for the Study of Liver Diseases (AASLD) position paper[2]. The cause of acute hepatic failure was not specified, but we suspected that the cause was associated with her treatment with a non-steroidal anti-inflammatory drug (NSAID), diclofenac suppository 25 mg/d, that was administered for lumbago starting 2 mo earlier[3].

On the day of the patient’s admission to our hospital, corticosteroid pulse therapy was initiated (500 mg/d, × 3 d). At the same time, we started the following biological agents derived from human blood in order to conserve the patient’s liver function. We transfused fresh frozen plasma (FFP) 2 units/d every day until her outcome (she died on the ninth day after her admission). We also administered rTM 380 U/kg/day for 6 d. An empirical treatment for infection was concomitantly driven by ceftriaxone (1 g × 1/d), cefozopran (1 g × 2/d), and cefoperazone/sulbactam (1 g × 2/d) appropriately dose-adjusted to the patient’s organ function (Figure 1). The clinical and laboratory alternation of the patient’s clinical course is illustrated in Figure 1, demonstrating a rapid decrease of liver function test values (GOT, GPT, LDH, ALP, and Tbil) immediately after the initiation of the treatment with rTM. The patient’s white blood cell and inflammatory reactive protein (C-reactive protein, CRP) gradually improved over the next few days. We also found her hepatocyte growth factor (HGF) and inflammatory or proinflammatory cytokines [tumor necrosis factor (TNF)-α and interleukin (IL)-1β] levels were all diminished after the initiation of the treatment with rTM (Figure 1).

Proteins reflecting the reproduction of liver cells such as PT and albumin were improved during the patient’s treatment, apparently responding to the rTM injection. Her hepatic function completely recovered without plasma exchange and without any interventional apheresis. The patient did not exhibit the development of hepatic encephalopathy (*e.g.*, confusion, stupor, and coma). Unfortunately, respiratory failure caused her death on day 9 after the initiation of treatment, but her hepatic failure was not a factor. An autopsy was not performed.

**DISCUSSION**

Severe FHF is fatal, and the only effective therapy for FHF is liver transplantation, but the indications for this are limited[2]. HGF was purified as a hepatocyte proliferation agent from patients with fulminant hepatitis; it promotes hepatocyte mitosis[9]. Substantial elevations of HGF in FHF patients have been observed in clinical settings[9]. It was hypothesized that external supplementations of an overdose of HGF may promote the regeneration of hepatocytes and modulate hepatic function[10], but recombinant HGF (rhHGF) administration failed to show efficacy as a treatment for FHF in a Phase I/II study setting[10]. These observations may indicate that an elevated plasma HGF level corresponds to hepatocyte breakage, explaining why no obvious efficacy of additional HGF treatment has been observed to date. In fact, it is known that the large-scale production of HGF occurs in the onset of fulminant hepatitis irrespective of causes of hepatitis such as drugs, viral infection and autoimmune-mediated causes[11].

HGF has also been investigated as a hepatocyte protective agent for the therapy of hepatitis[12]. However, many clinical observations showed that additional external HGF supplementation was not hepatotropic and did not induce the regeneration of hepatocytes or produce better outcomes in humans[10]. The up-regulation of HGF expression in injured liver is mediated by the pro-inflammatory cytokines IL-1, IL-6, IFN-γ and TNF-α[12]. We thus suggest that an increase in plasma HGF levels is a reflection of the degree of liver injury[12]. The dramatic improvement of our patient’s HGF level suggests that the rTM treatment attenuated her liver cell damage. This is substantiated based on the patient’s profile of pro-inflammatory cytokines TNF-α and IL-1β and during her rTM therapy.

The anti-inflammatory role of rTM has recently been highlighted in the field of clinical management for DIC[13]. The rTM correct coagulopathy through the inhibition of thrombin and the activation of protein C. The major pharmacological effect of rTM was demonstrated to be an enhanced physiological effect on APC[5]. Several research groups reported the anti-inflammatory effect of TM itself in the lectin-like domain, which can inactivate high-mobility group box 1 (HMGB1)[14], interfere with complement activation[15], and neutralize endotoxin[16]. HMGB1 is an inflammatory mediator that acts as a nuclear factor, and it is secreted by activated monocytes and macrophages[17]. Some clinical articles support the pathogenesis of HMGB1 protein in FHF[18]. We did not define an elevation of HMGB1 in our patient’s case, however, the rTM treatment may have suppressed the activation of HMGB1. Corticosteroid therapy can also modulate the inflammatory response[19]. An inhibitory effect of glucocorticoids on HMGB1-induced TNF-α production was observed in that report[19]. However, the effect is only for the reduction of extracellular HMGB1 expression. The effect of systemic corticosteroid treatment was confined to a reduction in extracellular HMGB1 expression, but not intracellular expression[20]. The inflammatory cellular responses downstream from HMGB1 are less understood[19]. Glucocorticoids inhibit HMGB1-induced TNF-α production in the pathway downstream from HMGB1. Some other pathway from HMGB1 are assumed. Moreover, HMGB1 is secreted mainly by monocytes and corticosteroid cannot adequately suppress activated monocytes[21]. Thus, some other pathway from HMGB1 are assumed. This mechanism can be specifically targeted to therapeutic advantage in sterile SIRS associated with HMGB1 elevation, refractory to corticosteroids[19,21].

Because our patient’s clinical status before her admission to our hospital was not fully evaluated, we categorized her case as fulminant hepatitis, subacute type[9] according to her medication history. Coagulopathy will occur generally in patients with FHF[2]. Beyond the anti-coagulant mechanism, however, the administration of rTM would be preferable to cure the inflammatory status, especially SIRS, possibly by inactivating HMBG1. rTM as a novel treatment for FHF could become promising when the inflammatory profile in FHF is identified, but the categorization of inflammation in FHF is not yet underway, to the best of our knowledge.

In the present case, both a variety of biomarkers reflecting hepatocellular damage (including GOT, GPT, LDH, and ALP) and inflammatory cytokines decreased very rapidly immediately after the administration of rTM. In cases of FHF, most liver cells are often necrotized at once by the intense immunological reaction, resulting in the decrease of GOT and GPT levels. In those cases, liver cells are not reproduced and the levels of PT and hepaplastin test do not recover. However, surprisingly, our patient’s decreased PT level was rapidly recovered (to over 100%) immediately after the administration of rTM. We have never experienced a case like this one in which the PT level was so remarkably recovered simply by the administration of FFP or a blood transfusion without plasma apheresis. Thus, rTM may play a critical role and become a new and effective therapeutic agent for the treatment of FHF and other disorders. Other organ failure with systemic or local inflammation may also be treatable with rTM[22]. We propose the necessity of confirming the effectiveness of rTM for the treatment of FHF in further studies.

**COMMENTS**

***Case characteristics***

An 86-year-old female came to an ambulatory care facility with fever, diarrhea and hypotension.

***Clinical diagnosis***

The patient showed dehydration diagnosed based on; fever, tachycardia and decreased blood pressure.

***Differential diagnosis***

The cause of dehydration was initially thought to be an infection.

***Laboratory diagnosis***

The patient’s laboratory tests showed severe liver dyfunction and renal dysfunction with coagulopathy: aspartate transaminase 8929 U/L, alanine transaminase 5449 U/L, lactate dehydrogenase 7248 U/L, total bilirubin 3.1 mg/dL, BUN 34.8 mg/dL, Cr 1.9 mg/dL, PT 42%.

***Imaging diagnosis***

Computed tomography imaging did not reveal hepatomegaly or splenomegaly, and did not detect an infection focus.

***Treatment***

We administered recombinant thrombomodulin (rTM), which ameliorated the coagulopathy and hepatic function.

***Related reports***

The potential role of rTM, the anti-inflammatory effect of which has been the focus in the clinical management of disseminated intravascular coagulopathy (DIC), is now being examined for the pathology of systemic inflammatory response syndrome (SIRS) including fulminant hepatic failure (FHF).

***Term explanation***

rTM is a novel product of human soluble thrombomodulin fragment that acts as a direct inactivator of thrombin and exert a powerful inhibitory effect on activated Factors V and VIII through activating protein C.

***Experiences and lessons***

This case suggested that rTM can be a promising agent to treat not only DIC but also any inflammatory pathogenesis including SIRS, as shown in this case of FHF. We hypothesized that the underlying mechanism is an inhibition of the high-mobility group box 1 (HMGB1) pathway, which is known to be elevated in the sera of patients with FHF.

***Peer-review***

The anti-inflammatory pharmacological effect of rTM has been attracting more attention for further clinical application to other pathological conditions. In the present case we observed the clinical effect of rTM in FHF with SIRS revealing the kinetics of growth factor (hepatocyte growth factor, HGF) and inflammatory/proinflammatory cytokines (tumor necrosis factor-α and interleukin-1β).

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**Figure 1 The clinical course of the patient, an 80-year-old Japanese female.** White blood cell (WBC) and C-reactive protein (CRP) recovered within a few days after the initiation of recombinant thrombomodulin (rTM) treatment. PT (indicated by a bar) rose to 100.8% from 54.4%. WBC, CRP, and transaminase (GOT and GPT) all recovered, corresponding to the rTM administration. Tbil: Total bilirubin; TNF: Tumor necrosis factor; IL: Interleukin.