Recombinant Human Thrombomodulin for Pneumonia-Induced Severe Acute Respiratory Distress Syndrome Complicated by Disseminated Intravascular Coagulation in Children: A feasibility study

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Abstract

Background Recombinant human soluble thrombomodulin (rTM) has been used to treat disseminated intravascular coagulation (DIC). Recent studies have shown the efficacy of rTM through its anti-inflammatory effects for treatment of adults with acute respiratory distress syndrome (ARDS). However, the safety and efficacy of rTM in children with severe ARDS complicated by DIC have not been reported. In this study, we investigated the feasibility of using rTM for the treatment of pneumonia-induced severe ARDS complicated by DIC in children.

Methods Six children (age: median 10 month-old) with pneumonia-induced severe ARDS complicated by DIC were enrolled in this feasibility study. rTM (380 U/kg) was administered for a maximum of 6 days, in addition to conventional therapies including cardiopulmonary support, antibiotics and/or antiviral drugs administration, steroid administration and intravenous immunoglobulin after diagnosis of severe ARDS complicated by DIC. After administration of rTM, we measured changes in the plasma TM concentration and evaluated the clinical course, status of DIC and ARDS, and other laboratory findings, including levels of cytokines, chemokines, and biomarkers.

Results In all six children, the plasma concentration of TM increased and DIC scores decreased after administration of rTM. Four of the six children recovered from the severe ARDS complicated by DIC after treatment in the pediatric intensive care unit, and were discharged from the hospital with no complications. In surviving children, levels of soluble receptors for advanced glycation end products, interleukin-6, interleukin-8 and monocyte chemoattractant protein-1 decreased after administration of rTM.

Conclusions The rTM administration is feasible as a therapeutic strategy for children over 2 months with pneumonia-induced severe ARDS complicated by DIC.

Background

Pneumonia is a leading infectious cause of hospitalizations and death among children globally [1]. Pneumonia can induce acute respiratory distress syndrome (ARDS) [2, 3], and disseminated intravascular coagulopathy (DIC) can develop in patients with severe ARDS [4]. Severe ARDS complicated by DIC is a life-threatening condition and is associated with a poor prognosis, indicating the need for early treatment [4].

Recombinant human soluble thrombomodulin (rTM) was primarily developed in Japan to treat DIC [5]. Based on its safety and efficacy, rTM is now administered to treat children with DIC [6, 7]. Recently, several clinical studies have been conducted to evaluate the efficacy of rTM as an adjunctive anti-inflammatory agent for various severe inflammatory conditions [8, 9]. Adjunctive rTM administration may be effective for ARDS complicated by DIC and sepsis in adult patients [9, 10]; however, the detailed clinical effects of rTM in children with severe ARDS complicated by DIC have not yet been clarified. This study aims to prospectively evaluate the feasibility of the use of rTM for the treatment of children with severe ARDS complicated by DIC. We examined not only the change of plasma levels of thrombomodulin

(TM) after rTM administration but also that of cytokines/chemokines and biomarkers which were associated with systemic inflammation and lung injury.

Methods

Patients and case definitions

This prospective feasibility study was carried out from January 2016 to May 2018 at the PICU in Vietnam National Children's Hospital, Hanoi, Vietnam. Children who met the following inclusion criteria within 72 hours of PICU admission were enrolled: (1) admission to the PICU with infectious pneumonia; (2) age of 1 month to 15 years; (3) DIC scores defined by the International Society of Thrombosis and Haemostasis (ISTH) ≥ 5 ; (4) $\text{PaO}_2/\text{FiO}_2$ ratio (P/F ratio) ≤ 100 mm Hg (based on the Berlin definition of 2012) [11]; (5) No severe left ventricular dysfunction; (6) Chest X-ray showing an abnormal shadow (consolidation, ground-glass opacity, or nodular shadow); and (7) Written informed consent prior to initiation of any study procedures, obtained from the patient's parents. Patients with severe renal dysfunction (creatinine clearance <10 mL/min) or bleeding symptoms, or those whom the treating doctor deemed ineligible for any reason, were excluded from this study.

rTM administration

Similarly to the administration of rTM to adults, rTM (380 U/kg) was administered for a maximum of 6 consecutive days via intravenous drip infusion for 30 minutes. All necessary treatments performed by PICU doctors were acceptable, except administration or co-administration of anticoagulants, thrombolytic agents, and platelet aggregation inhibitors. Blood samples were taken on the day of admission to the PICU (day X), before the first administration of rTM, and on α days after day X (day X+ α). Blood samples were used to evaluate plasma concentrations of TM, cytokines/chemokines, biomarkers, blood cell counts, blood chemistry and DIC scores. The rTM administration was discontinued in case that patients developed severe renal dysfunction or bleeding in vital organs. We observed the clinical time course including vital signs and physical examination findings, bleeding symptoms, P/F ratio, oxygenation index, ventilator settings, and radiographic findings.

Microbiological tests

Blood and tracheal lavage fluid (TLF) were collected on the day of admission to the PICU. Microbiological cultures were prepared according to standard microbiological procedures. To detect and differentiate up to 25 pathogenic microbial DNA types in blood samples, the LightCycler SeptiFast Test (Roche Diagnostics GmbH, Mannheim, Germany) was used [12]. Total nucleic acids from the TLF samples were extracted with a MagNA Pure LC total nucleic acid isolation kit using a Roche MagNA Pure LC instrument according to the manufacturer's instructions (Roche Diagnostics). The extracts were tested by multiplex real-time reverse transcriptase (rRT) polymerase chain reaction (PCR) (rRT-PCR) using the FTD

Respiratory Pathogens 33 Kit according to the manufacturer's instructions (Fast Track Diagnostics, Junglinster, Luxembourg) to screen 33 kinds of respiratory pathogens and by an in-house developed conventional single-target rRT-PCR and real-time PCR (rPCR) to detect genomes of cytomegalovirus (CMV), human immunodeficiency virus (HIV), and varicella zoster virus (VZV).

TM and biomarker assay

The plasma concentration of TM, soluble receptor of advanced glycation end products (sRAGE), pulmonary surfactant protein D (SP-D), angiopoietin-2 (Ang-2) and high-mobility group box 1 (HMGB-1) were measured using enzyme-linked immunosorbent assay (ELISA) kits and a microplate reader (Multiskan FC; Thermo Fisher Scientific K. K., Tokyo, Japan). ELISA kits for TM, sRAGE, SP-D and Ang-2 were purchased from R&D Systems (Tokyo, Japan) and for HMGB-1 from Shino-Test Corporation (Tokyo, Japan). All samples were run in duplicate and the average concentrations were used for statistical analysis.

Cytokine and chemokine assay

The levels of cytokines/chemokines in the plasma were measured using the Human Cytokine Magnetic 25-Plex Panel Kit (Invitrogen, Carlsbad, CA, USA) on a Magpix® system (Merck Vietnam Co., Ltd, Vietnam). All samples were run in duplicate and the average concentrations were used for statistical analysis.

Statistical analysis

DIC scores were shown as medians with the interquartile range (IQR), and the groups (day X and day X+6) were compared using the Wilcoxon signed rank test. $P < 0.05$ was considered statistically significant. Data were statistically analyzed using Prism 5.0 for Mac (GraphPad Software Inc., La Jolla, CA, USA) with a two-tailed hypothesis.

Results

Patients

Six children fulfilled the inclusion criteria of having severe ARDS and DIC. Although more than one virus genome was detected in each patient, the major causative pathogen of pneumonia in each case was estimated to be respiratory syncytial virus, tuberculosis, influenza A/H1N1pdm, *Pneumocystis jirovecii* / CMV, CMV and VZV, respectively (Table 1). No pathogenic microbial DNA was detected in blood samples, suggesting no bacteremia and fungemia. Case 3 (1y5M) and Case 4(3M) had past history of recurrent pneumonia. Case 4 was HIV positive. The other children had no significant past history.

Safety of rTM administration

Each patient except case 3 was administered rTM for 6 consecutive days after enrolment in this study. In case 3, rTM was discontinued on day X+3, because slightly bloody urine was detected after the fourth administration of rTM. The other cases showed no bleeding or other complications throughout the study. We did not find any adverse effects of rTM on liver or renal function during rTM administration (Table 2). We measured the plasma concentration of TM before rTM administration on day X and α days after administration (on day X+ α). On the days after rTM administration, the plasma concentration of TM increased in all patients (Figure 1). DIC scores decreased significantly after administration of rTM ($P < 0.05$) (Figure 2).

In cases 1, 3, and 4, the status of ARDS, including the P/F ratio and oxygenation index, improved and they were successfully extubated within a week after administration of rTM (Table 3). Case 2 required more time for improvement in the respiratory conditions due to tuberculous pneumonia, but this patient was later successfully extubated and survived [13]. Two patients, cases 5 and 6, died from their respiratory conditions that had not fully resolved (Table 3), although their DIC scores improved during administration of rTM. Case 5 developed severe hypoxia from respiratory failure occurred 7 days after completion of rTM administration (day X+12). In case 6, her respiratory status deteriorated after multiple drug-resistant *Acinetobacter baumannii* was cultured from TLF 5 days after completion of rTM administration.

Biomarkers and inflammatory cytokines / chemokines

Laboratory findings revealed that sRAGE, which is a biomarker of lung epithelial injury, decreased after administration of rTM in all 6 children (Figure 3). Plasma levels of interleukin (IL)-6 (Figure 4), and IL-8 (Figure 5) also decreased in all patients after administration of rTM, except in case 5. Monocyte chemoattractant protein-1 (MCP-1) is a member of the chemokine family, and regulates trafficking of monocytes from bone marrow to inflamed tissue in response to inflammatory signals [14]. Although plasma MCP-1 levels in the surviving children (except on day X+5 in case 4) decreased after rTM administration, those in the children who died increased (Figure 6). However, there was variability in changes in other biomarkers, such as HMGB-1 (Additional file 1), SP-D (Additional file 2) and Ang2 (Additional file 3), and cytokines/chemokines, such as interferon-gamma (IFN- γ) (Additional file 4), IL-10 (Additional file 5), and interferon- γ -inducible protein-10 (IP-10) (Additional file 6), among the patients.

Discussion

This prospective feasibility study showed that rTM administration increased the plasma concentration of TM and decreased DIC scores in children with severe ARDS complicated by DIC. In all six children, sRAGE decreased rapidly after rTM administration. In surviving children, levels of IL-6, IL-8 and MCP-1 decreased after administration of rTM. Our study suggests that the feasibility of administration of rTM for the treatment of children with ARDS complicated by DIC.

Previous studies in adults [15, 16] and children [6, 7] have shown the efficacy of rTM for DIC. We confirmed that rTM increased the plasma concentration of TM and DIC score decreased after rTM administration, consistent with previous studies. In adults, the effective concentration of rTM (TM alpha) is recommended to be more than 500 ng/mL at steady state [17]. Although few studies have focused on the plasma concentration of TM in children, Takeuchi et al. reported that the concentration of rTM (TM alpha) at steady state was 431 [278–727] ng/mL when the same dose of rTM as in our study was used in children with hematological malignancy and DIC [18]. In our study, after administration of rTM the median of peak concentration of TM was 475 [IQR 273–585] ng/mL. In children, a higher dose of rTM may be required to achieve a TM level higher than 500 ng/mL, and a higher concentration of TM may produce a better effect for not only the control of DIC but also of inflammation.

In patients who survived, the P/F ratio and oxygenation index improved after administration of rTM. Notably, sRAGE in all six children decreased after administration of rTM. sRAGE is a marker of lung epithelial injury [19], and has good diagnostic value for ARDS and is associated with the severity of lung injury, the degree of lung epithelial injury, impaired alveolar fluid clearance, and prognosis in ARDS [20, 21]. Based on these studies, administration of rTM may be related with improvement or attenuation of lung epithelial injury. However, respiratory conditions did not improve after rTM in the patients who died. Recently, Jabaudon et al. reported that a higher baseline level of sRAGE was associated with development of ARDS [22]. In this study, on day X (just before administration of rTM), the plasma concentrations of sRAGE in patients 5 and 6, who later died, were 4715 and 8501 pg/mL, respectively, whereas the median concentration of sRAGE in the patients who survived was 1817 [IQR 1437–1904] pg/mL. Thus, different degrees of damage in the lung epithelium in the patients who survived and those who did not survive may be involved in the different progress of ARDS and the subsequent outcomes.

In the patients who survived, rTM may have helped to improve the ARDS status via anti-inflammatory effects. Recently, the anti-inflammatory effects of rTM have been highlighted, and rTM may improve not only respiratory dysfunction but also mortality rates in patients with severe sepsis and DIC [8–10, 23]. We previously published case reports on 3 of the patients who survived (cases 1, 2, and 4) in this study [13, 24]. Interestingly, MCP–1, which is one of the chemokines, decreased in 3 of the 4 patients who survived, but not in the patients who died, after administration of rTM. A previous study reported that a higher serum MCP–1 level was associated with a 10-fold higher risk of death in ARDS [25]. In addition to sRAGE, these biomarkers may be useful for predicting the development of ARDS and outcomes. In contrast, there was variability in changes in other biomarkers, such as several inflammatory biomarkers (HMGB–1, SP-D, Ang2) and cytokines/chemokines (IFN- γ , IL–10, IP–10), which are associated with development of ARDS [26]. To determine the anti-inflammatory effects of rTM in patients with severe ARDS, further large studies with patients without rTM administration and with simultaneous measurement of multiple inflammatory biomarkers and cytokines/chemokines may be required.

Limitations

This study has several limitations. First, this feasibility study is not a randomized trial, and there were no control patients, who were treated without rTM. To validate the efficacy of rTM for children with severe ARDS complicated by DIC, a randomized controlled trial would be required. Second, we could not collect blood samples from the patients to evaluate the levels of biomarkers and cytokines/chemokines on the same days after administration of rTM because the children's conditions were different and the blood samples needed to be limited to avoid iatrogenic anemia.

Conclusion

In conclusion, we investigated the feasibility of rTM for the treatment of children with severe pneumonia-induced ARDS complicated by DIC. Our findings suggest that rTM improves DIC and may have beneficial effects in cases of pediatric ARDS via anti-inflammatory responses.

List Of Abbreviations

ARDS, acute respiratory distress syndrome; DIC, disseminated intravascular coagulation; OI, oxygenation index; PF ratio, $\text{PaO}_2/\text{FiO}_2$ ratio; RT-PCR, real-time polymerase chain reaction; rTM, recombinant human soluble thrombomodulin; HMGB-1, high mobility group box 1; sRAGE, soluble receptor for advanced glycation end products; PICU, pediatric intensive care unit; TLF, tracheal lavage fluid

Declarations

Ethics approval and consent to participate

This therapeutic protocol was approved by the biomedical research ethics committee of the National Hospital of Pediatrics Research Institute for Child Health (NHP-RICH, Hanoi, Vietnam) (reference number: NHP-RICH-15-008) and the ethical committee of the National Center for Global Health and Medicine (NCGM, Tokyo, Japan) (reference number: NCGM-G-001853-00).

The parents of all children provided written informed consent for participating to this study.

Consent to publish

The parents of all children provided written informed consent for the publication of this manuscript.

Availability of data and materials

The data supporting our findings can be found in the manuscript, tables and figures.

Competing interests

The authors state that they have no conflicts of interest.

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Authors' contributions

DTN, PHP, TAT, DMT and HTL performed medical treatment for patients. SK, NN, JT and NH participated in the conception of the treatment protocol, and drafted the manuscript. AA and TTBP performed rRT-PCR assays and analyzed biomarkers of ARDS. All authors have read and approved the final manuscript.

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Tables

Table 1. The characteristics of patients

	Gender	Age	PRISM III	Lowest P/F ratio	Maximum DIC score	Pathogen in TLF/NPA/blood on PICU admission	PICU admission day from the onset	LOS In PICU	LOS In Hospital	Outcome
Case 1	F	2M	10	36	7	RSV, CMV*	6	10	21	Alive
Case 2	F	2Y0M	3	35	6	TB, CMV*	20	32	33	Alive
Case 3	M	1Y0M	5	77	7	A/H1N1pdm, CMV*	8	13	27	Alive
Case 4	M	3M	10	69	6	PCP/CMV, HIV	9	8	34	Alive
Case 5	F	3M	10	68	5	CMV	8	17	17	Dead
Case 6	F	9Y0M	12	46	6	VZV, RV	12	14	14	Dead

PRISM; Pediatric risk score for mortality, P/F ratio; PaO₂/FiO₂ ratio, DIC; disseminated intravascular coagulopathy, TLF; tracheal lavage fluid, NPA; nasopharyngeal aspiration, RSV; Respiratory syncytial virus, CMV; cytomegalovirus, TB; tuberculous, A/H1N1pdm; Influenza A, subtype H1N1pdm, PCP; pneumocystis jiroveci, HIV; human immunodeficiency virus, VZV; varicella zoster virus, RV; Rhino virus, LOS; Length of stay.

CMV*; CMV latent infection

Table 2. Changes in biomarkers of liver function and renal function before and after recombinant thrombomodulin administration

Patient number	WBC (x 1000/ μ L)		Plt (x 1000/ μ L)		AST (U/L)		ALT (U/L)		BUN (mg/dL)		Creatinine (μ mol/L)	
	Normal range		Normal range		Normal range		Normal range		Normal range		Normal range	
	(4.5-10)		(150-450)		(5-40)		(7-56)		(7-20)		(50-110)	
	Day X	Day X+6	Day X	Day X+6	Day X	Day X+6	Day X	Day X+6	Day X	Day X+6	Day X	DayX+6
Patients who survived												
Case 1	19	12.4	42	89	65	49	106	27	7.4	13.6	35	36
Case 2	6.7	12.2	153	142	70	73	16	14	18	18	50	47
Case 3	12.1	5.9	98	143	234	142	41	32	15	48	63	161
Case 4	13.0	6.7	142	80	1757	102	874	84	7.5	12	48	46
Patients who died												
Case 5	11.5	25.2	27	23	288	39	10	23	4.5	20.3	39	52
Case 6	7.7	9.2	24	180	131	102	106	80	3.1	6.5	9	19

Table 3. Changes in PaO₂/FiO₂ ratio, oxygenation index and Body temperature before and after recombinant human thrombomodulin administration

Patient number	P/F ratio (mmHg)		Oxygenation Index		Extubation	Body temperature		
	Day X	Day X+6	Day X	Day X+6	(day)	Day X	Day X +6	
Patients who survived								
Case 1	100	extubated	15	extubated	Yes (day X+3)	37.0	37.0	
Case 2	35	50	61.5	20	Yes (day X+24)	38.2	39.7	
Case 3	93	244	21	4.7	Yes (day X+7)	38.5	37.0	
Case 4	82	extubated	24	extubated	Yes (day X+4)	37.3	36.8	
Patients who died								
Case 5	68	43	16	52	No	38.0	37.7	
Case 6	102	207	20	17	No	38.2	38.9	

ARDS; acute respiratory distress syndrome, P/F ratio; PaO₂/FiO₂ ratio, LOS; Length of stay

Figures

Figure 1

Changes in the plasma concentration of thrombomodulin before and after administration of recombinant human thrombomodulin (rTM). rTM administration increased the concentration of thrombomodulin in all patients.

Figure 2

Figure 2

Changes in DIC scores before and after administration of recombinant human thrombomodulin (rTM). Data were expressed as the median and interquartile range. rTM administration significantly decreased DIC scores.

Figure 3

Changes in soluble receptor of advanced glycation end products (sRAGE) before and after administration of recombinant human thrombomodulin (rTM). rTM administration decreased sRAGE.

Figure 4

Changes in interleukin-6 (IL-6) before and after administration of recombinant human thrombomodulin (rTM). rTM administration significantly decreased IL-6 in the patients except case 5.

Figure 5

Changes in interleukin-8 (IL-8) before and after administration of recombinant human thrombomodulin (rTM). rTM administration significantly decreased IL-8 in the patients except case 5.

Figure 6

Changes in Monocyte chemotactic protein-1 (MCP-1) before and after administration of recombinant human thrombomodulin (rTM). rTM administration decreased MCP-1 in 3 of the 4 patients who survived, but not in patients who died.

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