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Richi Kashyap
North Alabama Medical Center, Florence, AL, USA

Faiz Anwer
Associate Professor of Medicine Hematology, Oncology, Stem Cell Transplantation, Multiple Myeloma Program, Cleveland Clinic, Taussig Cancer Center, 10201 Carnegie Ave, Cleveland, OH 44195, USA, anwerf@ccf.org

Muhammad Areeb Iqbal
Allama Iqbal Medical College, Lahore, Pakistan

Farhan Khalid
Monmouth Medical Center, Long Branch, NJ, USA

Anam Khan
All India Institutes of Medical Sciences (AIIMS), New Delhi, India

See next page for additional authors

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Richi Kashyap, Faiz Anwer, Muhammad Areeb Iqbal, Farhan Khalid, Anam Khan, Muhammad Ashar Ali, Muhammad Yasir Anwar, Anamika Chaudhary, and Ali Jaan

REVIEW ARTICLE

Efficacy and Safety of Recombinant Thrombomodulin for the Prophylaxis of Veno-Occlusive Complication in Allogeneiccit Hematopoietic Stem Cell Transplantation: A Systematic Review and Meta-Analysis

Richi Kashyap [a], Faiz Anwer [b,*], Muhammad Areeb Iqbal [c], Farhan Khalid [d], Anam Khan [e], Muhammad Ashar Ali [f], Muhammad Yasir Anwar [f], Anamika Chaudhary [g], Ali Jaan [h]

[a] North Alabama Medical Center, Florence, AL, USA
[b] Associate Professor of Medicine Hematology, Oncology, Stem Cell Transplantation, Multiple Myeloma Program, Cleveland Clinic, Taussig Cancer Center, 10201 Carnegie Ave, Cleveland, OH 44195, USA
[c] Allama Iqbal Medical College, Lahore, Pakistan
[d] Monmouth Medical Center, Long Branch, NJ, USA
[e] All India Institutes of Medical Sciences (AIIMS), New Delhi, India
[f] King Edward Medical University, Lahore, Pakistan
[g] Sharda Medical College, Greater Noida, India
[h] Rochester General Hospital, Rochester, NY, USA

Abstract

Background: **Hepatic veno-occlusive disease (VOD), also termed as sinusoidal obstruction syndrome (SOS), is a lethal complication after hematopoietic stem cell transplantation (HSCT). Various factors put patients undergoing allogeneic HSCT at an increased risk for VOD. Thrombomodulin (TM) is an important factor which has a wide range of effects, including anticoagulant, anti-inflammatory, angiogenic, and protective effect, on endothelial cells. It plays a role in preventing excessive coagulation and thrombosis by binding with thrombin and inhibiting the coagulation cascade. There are a limited number of options for the prevention of this fatal complication. Recombinant thrombomodulin (rTM), an endothelial anticoagulant co-factor, as prophylactic therapy might be able to prevent veno-occlusive complications after stem cell transplantation.**

Methods: **A literature search was performed on PubMed, Embase, and Web of Science. We used the following Mesh terms and Emtree terms, "Hepatic Veno-Occlusive Diseases" OR "Sinusoidal Obstruction" OR "Stem Cell Transplantations" AND "Thrombomodulin" from the inception of data up to April 1, 2021. The PICO (Patient/Population, Intervention, Comparison and Outcomes) framework was used for the literature search.**

Results: **For the VOD incidence after HSCTstem cell transplantation, the result was in favor of rTM with a risk ratio (RR) of 0.53 (I^2 = 0%, 95% confidence interval [CI] = 0.32−0.89). The incidence of transplant-associated thrombotic microangiopathy (TA-TMA) after HSCT was reduced in rTM group. The RR for incidence of TA-TMA was 0.48 (I^2 = 62%, 95% CI = 0.20−1.17) favoring rTM. The RR for incidence of graft-versus-host disease (GvHD) was also lower in rTM group, 0.48 (I^2 = 64%, 95% CI = 0.32−0.72).**

Conclusion: **In our meta-analysis, we evaluate the efficacy and safety of rTM in the prevention of SOS after HSCT. According to our results, rTM use led to a significant reduction in SOS episodes, TA-TMA, and GvHD after HSCT.**

Keywords: Hematopoietic stem cell transplantation, Recombinant thrombomodulin, Sinusoidal obstruction syndrome, Veno-occlusive disease

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* Corresponding author.
E-mail address: anwerf@ccf.org (F. Anwer).

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1. Introduction

Hepatic veno-occlusive disease (VOD), also termed as sinusoidal obstruction syndrome (SOS), is a lethal complication seen after hematopoietic stem cell transplantation (HSCT). Conditioning regimens and immune system response lead to production of toxic metabolites which results in damage to sinusoidal endothelial cells [1]. Patients undergoing allogeneic stem cell transplantation (allo-HSCT) with the following risk factors are at increased risk for VOD/SOS: pre-existing hepatic disease, second myeloablative transplant, allogeneic transplant for leukemia beyond the second relapse, conditioning with busulfan-containing regimens, prior treatment with gemtuzumab ozogamicin, diagnosis of primary hemophagocytic lymphohistiocytosis, adrenoleukodystrophy, or osteopetrosis (1A, 2B) [2]. In a review by Dalle and Giralt [3], various risk factors contributing to the development of VOD/SOS were discussed; they indicated that understanding and identifying risk factors is critical for early initiation of prophylaxis or treatment for VOD/SOS to prevent morbidity and mortality. Incidence of VOD/SOS has been reported to be approximately 10–15% after myeloablative HSCT and 5% after reduced-intensity conditioning allo-HSCT [4,5]. The severe form of VOD/SOS is associated with a mortality rate of approximately 80% [6].

Activation of the coagulation cascade and endothelial injury in hepatic sinusoidal cells leads to sinusoidal obstruction and emboli formation. This process results in the development of clinical symptoms such as painful hepatomegaly, jaundice, fluid retention, and in severe cases, progressing to disseminated intravascular coagulation (DIC) with multiorgan involvement, which is fatal. VOD/SOS is diagnosed based on clinical symptoms using Seattle and Baltimore criteria [7,8]. However, not every episode of VOD/SOS seen fits these criteria. Late-onset VOD/SOS after 21 days post HSCT has also been described [9,10]. Cairo/Cooke criteria has been proposed for VOD/SOS diagnosis in adults and children [11]. There are a limited number of options for the prevention of this fatal complication. Recombinant thrombomodulin (rTM), an endothelial anticoagulant co-factor, might be able to help prevent veno-occlusive complications after stem cell transplantation [12,13].

TM is an important factor produced by endothelial cells; it plays a role in preventing excessive coagulation and thrombosis by binding with thrombin and inhibiting the coagulation cascade. Inactivation and neutralization of the high-mobility group box 1 (HMGB1) protein lead to anti-inflammatory action along with anticoagulation. HMGB1 is an important protein, which plays a role in the pathogenesis of DIC [14]. rTM is composed of the extracellular domain of thrombomodulin, and it binds with domains of TM on endothelial cells *in vivo*. Thrombin-rTM complex then cleaves factor VIIIa and Va and inhibits thrombin formation [15]. Across various trials, rTM therapy has been tried for the prevention of transplantation-associated coagulopathy (TAC) including VOD/SOS, thrombotic microangiopathy (TMA), and acute graft-versus-host disease (aGvHD) following HSCT [14].

The European Group for Blood and Marrow Transplantation (EBMT) has published the diagnostic and severity criteria recently [16]. EBMT continuously provides the practice guidelines for providing prophylactic, pre-emptive, and curative treatment for VOD/SOS based on efficacy established by various ongoing clinical trials [6].

Currently, treatment of VOD/SOS involves supportive care and defibrotide (DF) therapy. The approved dose by the FDA is 25 mg/kg/day for at least 21 days or till the symptoms associated with VOD/SOS have resolved [15].

Supportive care and intensive monitoring of the patient to recognize the development of VOD/SOS play an integral role in the management [16]. Prophylactic therapies to prevent development VOD/SOS have also been explored [6]. Although other drugs including heparin, ursodeoxycholic acid (UDCA), antithrombin, prostaglandin E1, pentoxifylline have been evaluated for possible VOD/SOS prophylaxis, none of them demonstrated significant efficacy to prevent the development of VOD/SOS [6]. In 2008, rTM was approved by the Japanese Ministry of Health, Labour and Welfare (JMHL&W) for DIC [12]. Through this systematic review and meta-analysis, we assess the efficacy and safety of rTM to prevent VOD/SOS.

2. Methods

This systematic review and meta-analysis were performed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement (Fig. 1).

2.1. Search strategy

A literature search was performed on PubMed, Embase, and Web of Science. We used the following Mesh terms and Emtree terms, "Hepatic Veno-Occlusive Diseases" OR "Sinusoidal Obstruction" OR "Stem Cell Transplantations" AND "Thrombomodulin" from the inception of data till April 01,

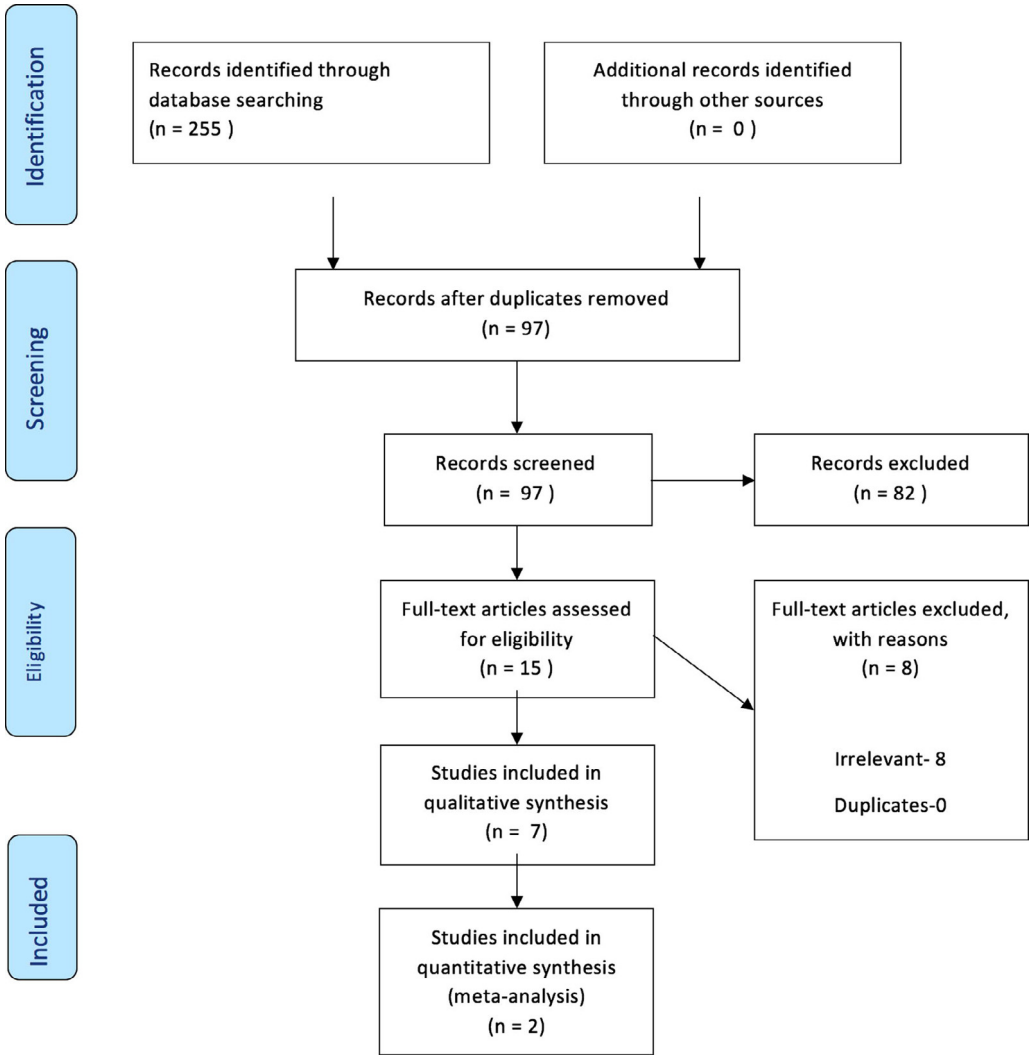

Fig. 1. Flow chart of literature search.

2021. The PICO (Patient/Population, Intervention, Comparison and Outcomes) framework [17] was used for the literature search (Supplementary Table S1).

2.2. Inclusion and exclusion criteria

Randomized clinical trials (RCTs), single-arm trials, and observational studies comparing the incidence of VOD/SOS, TMA, and aGvHD after rTM post HSCT were included. All case reports, case series, preclinical studies, review articles, meta-analysis, and trials irrelevant to the study question were excluded.

2.3. Study selection and data extraction

Four researchers (RK, MAA, and MYA, AC) independently reviewed the articles initially, and differences were addressed by two other researchers (FK and AK). We extracted data for author, year, characteristics of study (study design), baseline characteristics of participants (total number, age), and incidence of VOD/SOS, TMA, and aGvHD after HSCT.

2.4. Statistical analysis

The meta-analysis was conducted in R programming language using the "meta," "metaphor," and "dmetar" packages (version 3.3.0; R Foundation for Statistical Computing, Vienna, Austria). The inference was made based on the random-effects model. The meta-analysis of ratios was done using the Mantel–Haenszel method. All the meta-analyses used the DerSimonian–Laird estimator for between-study variance (tau squared), and if required, a continuity correction of 0.5 was used. Standard

errors and other calculations were done using a 95% confidence interval (CI). To assess heterogeneity, a sensitivity analysis was performed by omitting one study at a time. To assess the publication bias, a funnel plot was used. Egger's test was used to assess the funnel plot asymmetry, and a two-tailed p value of <0.05 was considered significant for asymmetry.

2.5. Risk of bias assessment

Cochrane collaboration's tool [18] was used to assess the risk of bias in RCTs, and the Newcastle–Ottawa scale [19] was used to assess the risk of bias in nonrandomized studies.

3. Results

A total of 255 articles were identified: 88 from PubMed, 71 from Embase, 91 from Web of Science, and five from Cochrane. A total of 158 articles were removed during deduplication, and 82 articles were removed based on exclusion criteria. Full lengths of seven studies were assessed in systematic review and two studies were selected for meta-analysis based on inclusion criteria. Nomura et al. [20] and Ishii et al. [21] divided participants into two groups: one group received rTM and the control group received heparin or no anticoagulation therapy. Other studies compared different treatment regimens; to maintain uniformity in studies to be included in meta-analysis, other studies were excluded. Yakushijin et al. [15] conducted a retrospective survey to study effects of DF and rTM for treatment of VOD/SOS after HSCT. Yamamoto et al. [12] studied the efficacy of rTM combined with UDCA and low-molecular-weight heparin (LMWH) as prophylactic agent against VOD/SOS. Inoue et al. [22] studied the efficacy of rTM for treatment of DIC and systematic inflammatory complications after HSCT, such as a GvHD and TMA. Fujiwara et al. [23] compared rTM with other therapies for treatment of transplant-associated thrombotic microangiopathy (TA-TMA) after HSCT. Ikezoe et al. [24] compared rTM versus LMWH and/or antithrombin concentrate for treatment of DIC after HSCT. Due to difference in treatment regimens and study population, these studies were excluded from meta-analysis.

The total number of patients tested in included studies was 494, 228 in rTM group and 266 in the control group (Tables 1 and 2).

3.1. Incidence of VOD

For the VOD/SOS incidence after stem cell transplantation, the result was in favor of rTM with

Table 1. Clinical outcomes Table 1 of rTM therapy in trials.

		Number of patient (Duration of treatment)	Dose	VOD	TMA	GVHD	S (Day 100)	Dead (Day 100)	A/E
Nomura et al. [20]	T	131 T(14 Days)	380 units/kg	7	10	27	55	20	
	C	169H or NO		15	40*	89*	44*	55*	
Yakushijin et al. [15]	T	41 (8 Days)	342 U/kg, 342–418 U/kg, > 418 U/kg	28			20		Gastrointestinal (grade 3, n = 2), bronchial (grade 3, n = 1), oral (grade 3, n = 1), intracranial (grade 4, n = 1) bleeding.
	DF	24		16			12		Gastrointestinal (grade 3) pulmonary (grade 4) bleeding, .
Yamamoto et al. [12]	T	8 T + U + H (13 Days)	380 U/kg	0					
	C	11U + H		3					
Inoue et al. [22]	T	10 T (8 Days)	380 U/kg				(Day 28) 8 5	(Day 28) 2 4	
	C	9 A/H							
Fujiwara et al. [13]	T	9 T (28 days)	380 U/kg CC > 10 ml/d, 130 U/kg CC < 10 ml/d			5	123.0 days	6	Minor bleed n = 2
	C	7 Other				4	45.5 days	7	
Ishii et al. [21]	T	97 T (10 Days)	380 u/kg	12	8	35			
	C	97H OR NO		24*	10*	60*			
Ikezoe et al. [24]	T	23 (18 T-4 Days + 5 (T + A-6 Days)	380 U/kg				19	3	Lung n = 1
	C	11H/7H + A					9*	8	Cerebral n = 1

Table 2. Characteristics of included studies.

Study	n (T/Other)	Male/Female	Diagnostic criteria (B/S)	Common underlying diseases	Type of transplant	Conditioning regimen	Immunosuppressive therapies/ GVHD prophylaxis
S. Nomura et al. [20]	300 (131 T/ 169H or NO)	172/128	National Institutes of Health consensus	AML n = 108 ALL n = 65 MDS n = 50 Other n = 77	155 BMT 64 PBST 81 CBT	Total body irradiation- 211 Non-total body irradiation-89	
K. Yakushijin et al. [15]	65 (41 T/ DF 24)	39/26 Overall 29/12 T	S 28/S + B 7/O6	AML n = 14 ALL n = 5 MDS n = 6 Lymphoma n = 9 CML/MPN n = 4 Other n = 3	Allogenic HSCT	MAC-45 RIC − 20	TAC-based 44 (T 26, DF 18) CSP-based 20 (T 14 DF 6)
Yamamoto et al. [12]	19 (8 T + U + L/11U + L)	11 and 8	modified Seattle	AML n = 8 ALL n = 3 NB n = 4 HLH n = 1 WAS n = 1 MDS n = 1 RMS n = 1	Allogenic HSCT 5 Auto/ 14 allogenic	RIC − 8 (rTM 5, control 3), MAC- 11 (rTM 3, control 8).	
Inoue, Y et al. [22]	(10 T/9 A/H)	9/3 T 4/5 A/H	Japanese Ministry of Health and Welfare diagnostic criteria for overt DIC. TMA, aGVHD, and engraftment syndrome were diagnosed and graded according to standard criteria and the definition	AA n = 0 AML n = 4 ALL n = 2 MDS n = 1 FL n = 4 DLBCL n = 0 HL n = 1 Others n = 0	Allogenic HSCT	MAC − 6 (T-3/C-3) RIC − 15 (T-9/ C- 6)	CsA/FK − 6/6 T 4/5 A/H
Fujiwara et al. [13]	16 (9 T/7 Other)	8/1 T 1/6O	TA-TMA was diagnosed based on the Blood and Marrow Transplant Clinical Network (BMT-CTN) criteria and/or the presence of pathologically confirmed intestinal transplant-associated microangiopathy (iTAM)	AML n = 1 MDS n = 0 ALL n = 1 CML BC n = 0 ML n = 5 ATL n = 2	PBSCT 5 BMT 4 Matched 1 One-locus mismatched 3 Two-locus mismatched 1 Haploidentical 4	MAC- 3 (T 1/ C 2) RIC- 13 (T 8/ C 5)	CsA/TAC + MTX − 5 T/5C Mpsl + TAC + ATG- 4 T/2C

(*continued on next page*)

Table 2. (continued)

Study	n (T/Other)	Male/Female	Diagnostic criteria (B/S)	Common underlying diseases	Type of transplant	Conditioning regimen	Immunosuppressive therapies/ GVHD prophylaxis
Ishii, K. et al. [21]	97 T/97H OR No	NA	NA	NA	Allogenic HSCT	There was no significant difference in the proportion of total body irradiation received as conditioning regimen between two groups characteristic.	
Ikezoe et al. [24]	23 (18 T + 5 (T + A)) 11 T or H 7 NO Th	14/9 T 10/8O	Seattle Criteria and TMA International Working Group Criteria	AML n = 6 ALL n = 5 CML BC n = 2 CML CP n = 2 MDS n = 3 ML n = 1 MF n = 1 ATL n = 3	rPBSCT 9 uBMT 12 rBMT 1 CBT 1 Matched 12 One-locus mismatched 7 Two-locus mismatched 4	MAC – 13 T 8/ C 5 RIC- 28 T 15/ C 13	CsA/TAC + MTX – 8 / 13 T 7/5C CsA/TAC + MMF – 1/1 T 2/1C CsA/TAC + steroid – 0/0 T 3/0C

T – Recombinant Thrombomodulin, H- Heparin, DF- Defibrotide, NO– No Therapy, O – Other Therapy, U- Ursodiol, L- Low Molecular Weight Heparin, A- Anti Thrombin III, BM – Bone Marrow, PB – Peripheral Blood, CB – Cord Blood, HSCT – Hematopoietic Stem Cell Transplantation, MAC myeloablative conditioning, RIC reduced-intensity conditioning, BU- busulfan CSP/CsA- cyclosporine A, FK/ TAC- tacrolimus, ATG-antithymocyte globulin MTX-methotrexate, MMF-mycophenolate mofetil

the risk ratio (RR) of 0.53 (I^2 = 0%, 95% CI = 0.32–0.89) (Fig. 2).

3.2. Incidence of TA-TMA

The incidence of TA-TMA after HSCT was reduced in rTM group. The RR for incidence of TA-TMA was 0.48 (I^2 = 62%, 95% CI = 0.20–1.17) favoring rTM (Fig. 3).

3.3. Incidence of GvHD

The RR for incidence of GvHD was also lower in rTM group, 0.48 (I^2 = 64%, 95% CI = 0.32–0.72; Fig. 4). In the study by Ishii et al. [21], anticoagulation therapy without rTM was found to be an independent risk factor for aGvHD ($p < .001$, odds ratio = 3.006) and VOD ($p = .015$, odds ratio = 2.65).

3.4. Survival rate after rTM therapy

Yakushijin et al. [15] compared rTM with DF and found similar complete remission (CR) rate and overall survival (OS) at Day 100 in both the groups. Use of rTM improved the survival rate of patients with DIC, diagnosed according to the criteria established by the JMHL&W, at Day 100 (83% vs. 50%, $p = .026$) and significantly prolonged the OS of these patients ($p = .044$). The Kaplan–Meier curves clearly showed the improved nonrelapse-related mortality of patients who received rTM after HSCT [24]. Mean DIC scores improved significantly with the use of rTM ($p = .003$; DIC withdrawal rate 91.7%) [22]. The mean peak plasminogen activator inhibitor-1 level was significantly lower in rTM group versus heparin and UDCA group ($p = .04$), and the mean peak activated protein C (APC) level was significantly higher in rTM group ($p = .01$) [12].

3.5. Adverse effects

No serious Grade 3 or 4 adverse events were reported by trials. Besides, no severe organ damage was reported in TM group by trials.

4. Discussion

DF, the only drug approved by FDA till now, is administered at a dose of 6.25 mg/kg intravenously four times daily in children and adults for the prevention of VOD/SOS. It displays anticoagulant effects by acting as an adenosine receptor agonist and leads to increased levels of endogenous prostaglandins, which further modulate thrombotic and

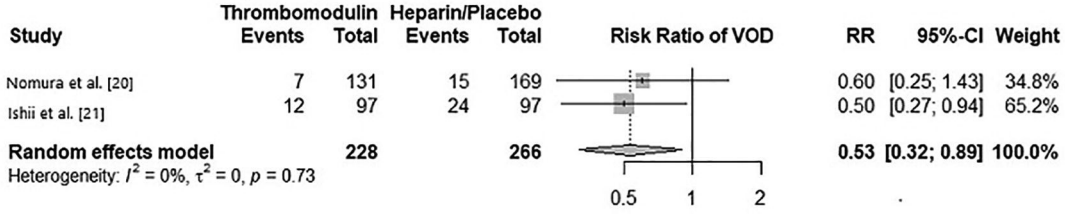

Fig. 2. Incidence of VOD. Note. CI = confidence interval; RR = risk ratio; VOD = veno-occlusive disease.

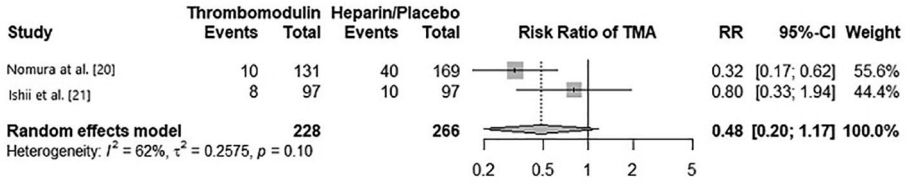

Fig. 3. Incidence of TA-TMA. Note. CI = confidence interval; RR = risk ratio; TA-TMA = transplant-associated thrombotic microangiopathy.

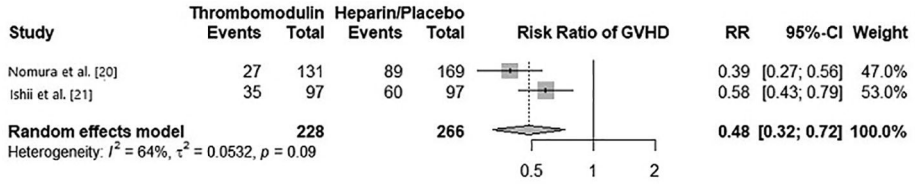

Fig. 4. Incidence of aGvHD. Note. aGvHD = acute graft-versus-host disease; CI = confidence interval; RR = risk ratio.

fibrinolytic pathways [25]. rTM has been reported to have prophylactic effect and reduce the incidence of VOD/SOS [26].

4.1. Other drugs

Among drugs being explored for the treatment of VOD/SOS, prostaglandin E1 (1B) and pentoxifylline (1A) are not recommended in the prophylaxis of VOD/SOS due to lack of efficacy and treatment-related toxicity. Due to the risk of increased toxicity, heparin (unfractionated and low molecular weight) is not suggested for use in the prophylaxis of VOD/SOS (2B). Antithrombin also failed to demonstrate efficacy in the prophylaxis of VOD/SOS (2B). UDCA has been suggested for use in the prophylaxis of VOD/SOS (2C) [2].

Although the JMHL&W approved rTM for treatment of DIC in Japan, it is not yet approved in other countries [12].

4.2. rTM as prophylactic therapy

In a study by Saito et al. [1], prophylactic rTM was administered along with the initiation of the conditioning regimen till 26 days after HSCT, for the prevention of VOD/SOS in patients with pre-existing severe hepatitis. While Nomura et al. [27] suggested that prophylactic rTM starting on Day 7, continued for 14 days after an HSCT, significantly reduced the levels of inflammatory markers, such as interleukin-6 (IL-6), compared with the patients treated only with prophylactic heparin therapy. Furthermore, it was reported that, as VOD/SOS was commonly diagnosed around Day 10 after HSCT, prophylactic rTM should be used from Days 7 to 13 (1 week). The rTM administration after HSCT reportedly led to suppression of increased serum intercellular adhesion molecule-1 (sICAM-1) and endothelial leukocyte adhesion molecule-1 (sELAM-1) levels [1,12].

4.3. Mild versus severe VOD/SOS

Yamamoto et al. [12] evaluated the role of rTM in mild versus severe VOD/SOS based on the EBMT criteria for diagnosing and grading the severity of VOD/SOS in children. Reportedly, the patient with mild VOD/SOS successfully improved with rTM (380 U/kg for 7 days), but those with severe VOD/SOS showed no improvement in SOS symptoms. Inagaki et al. [28] suggested that early identification of patients at high risk and early prophylactic treatment with rTM should be considered.

A nationwide survey was conducted by Yakushijin et al. [15] comparing DF and rTM use in the treatment of VOD/SOS in the Asian population. The CR rate and OS at Day 100 for rTM were almost equal to the values in DF group. In another study evaluating the use of rTM therapy in the pediatric population conducted in Japan, SOS was not seen in rTM group, but the patients with severe SOS failed to improve [12].

4.4. Dose of rTM

The recommended dose of rTM is 380 U/kg/day for the treatment of DIC in Japan. Yamamoto et al. [12] suggested that the optimal period of treatment might be from the start of the conditioning regimen until Day 30, and the adequate dose suggested was 380 U/kg/day. Further, the optimal dose required to prevent endothelial damage might be lower than 380 U/kg/day, but more trials are required to explore this. It was reported that the renal dysfunction might not affect rTM plasma concentration after repeated administration [29]. Patients with renal dysfunction were often treated with 130 U/kg/day of rTM, probably to prevent the occurrence of severe adverse events [15].

4.5. Risk factor interplay

Although the major mechanism responsible for VOD/SOS and aGvHD after HSCT involves endothelial insult due to various inflammatory mechanisms [12,13], Nomura et al. [14] found that soluble HLA-G (sHLA)-G levels were significantly elevated in patients who received rTM after HSCT. They reported that male sex, age, bone marrow transplantation, peripheral blood stem cell transplantation, cord blood transplantation, and IL-10 had no significant associations. These findings suggest the presence of some other additional mechanism unrelated to endothelial dysfunction through which rTM prevents GvHD. Downregulation of HMGB1 after rTM administration possibly led to increased levels of sHLA-G. HMGB1 is an inflammatory cytokine, which is responsible for cell damage [30].

In another trial by Nagasawa et al. [31], it was suggested that the immediate beneficial role of rTM was because of its function in the coagulation process rather than regulation of inflammatory mechanisms. GvHD (Grade $\geq$ 3), impairment of renal function, hyperbilirubinemia, intestinal bleeding, and severe thrombocytopenia were considered important factors related to transplant-associated mortality. Thrombocytopenic patients (<1.0 $\times$ 10^4/μL) and those refractory to platelet transfusion reportedly did not show any adverse effects, including deterioration of bleeding tendency, after rTM treatment. The trial concluded that the preventive usage of rTM could be considered in high-risk patients to achieve better outcomes. Moreover, other investigative trials have demonstrated that TM produced cytoprotective effects via both APC-dependent and APC-independent mechanisms.

4.6. Limitation

Trials included in this review were retrospective with a small sample size. Also, VOD/SOS was clinically diagnosed, and objective comparison between various studies could not be established. Further randomized large, prospective and blinded trials are required to determine the relationships between the effects of rTM and other major factors, which might be important determinants for changes in sHLA-G level. Prospective trials are required to determine the optimal dosing and duration of treatment.

5. Conclusion

In our meta-analysis, we evaluate the efficacy and safety of rTM in the prevention of VOD/SOS after HSCT. According to our results, rTM use may lead to a reduction in VOD/SOS episodes, TA-TMA, and GvHD after HSCT; however, further prospective randomized studies are warranted to evaluate the true efficacy of rTM in preventing VOD/SOS.

Conflicts of interest

FA has received honoraria from Incyte; Seattle Genetics for a consulting or advisory role; Seattle Genetics, Speakers' Bureau; research funding from InCyte Pharmaceutical; AbbVie Pharmaceuticals; Acetylon Pharmaceuticals; Astellas Pharma; Celgene; and Millennium Pharmaceuticals; and travel, accommodation, and expenses from Incyte; Seattle Genetics. The other authors declare no conflicts of interest.

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