Comparison of the efficacy and safety of caplacizumab versus placebo in thrombotic thrombocytopenic purpura: a meta-analysis and systematic review based on randomized controlled trials

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Background: We conducted this meta-analysis to investigate the efficacy and safety of caplacizumab in patients with thrombotic thrombocytopenic purpura (TTP). TTP is a potentially fatal disorder characterized by systemic microvascular thrombosis.

Methods: Randomized controlled trials (RCTs) were conducted from PubMed, Embase, Cochrane Library and Web of Science, China National Knowledge Infrastructure (CNKI), VIP and Wanfang databases. RCTs of caplacizumab treatment for TPP were mainly included. Data from eligible studies were extracted and analyzed using relative effect sizes versus placebo use. The Cochrane bias assessment tool was used to assess the risk of bias of included studies, and the assessment results were presented graphically in Revman5.3.

Results: Four RCTs with a total of 416 patients were included, all of which were of high quality. Caplacizumab was associated with improvements in platelet counts normalization time [weighted mean difference (WMD) −1.18, 95% confidence interval (CI): −2.55 to 0.19, I^2=69.9%, P=0.036], plasma exchange (PE) time (WMD −2.97, 95% CI: −4.44 to −1.50, I^2=8.2%, P=0.163) and hospital stay (WMD −2.88, 95% CI: −4.56 to −1.21, I^2=48.7%, P=0.036). In addition, the occurrence of adverse events was also investigated. The difference in mortality between the two groups was not statistically significant [relative risk (RR) 0.56, 95% CI: 0.18 to 1.72, I^2=22.7%, P=0.275], relapse (RR 0.68, 95% CI: 0.13 to 3.49, I^2=78.3%, P=0.01), or major thrombotic events (RR 1.01, 95% CI: 0.65 to 1.57, I^2=43.4%, P=0.151).

Conclusions: Caplacizumab shortens the platelet normalization time, PE time, and hospital stay in patients with TTP, and did not significantly increase the risk of adverse events. These results indicate that caplacizumab treatment provides significant benefits to patients with TTP. Even though this is evidence from RCTs, few original studies were included, so more multicenter RCTs are required.

Keywords: Caplacizumab; thrombotic thrombocytopenic purpura (TTP); meta-analysis

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Introduction

Thrombotic thrombocytopenic purpura (TTP) is a potentially fatal disorder characterized by systemic microvascular thrombosis (1). Based on its etiology, TTP can be divided into hereditary TTP and acquired TTP, and the latter can be further divided into idiopathic TTP and secondary TTP according to whether the etiology is clear. Thrombosis in patients with TTP is caused by platelet adhesion to the ultra-large von Willebrand factor (VWF) multimers, which is a result of ADAMTS13 (ADAM metallopeptidase with thrombospondin type 1 motif, 13) deficiency (2,3). TTP is a medical emergency. Following the introduction of plasma exchange (PE) in 1991, the mortality rate of TTP dropped from more than 90% to less than 20%. Subsequently, PE combined with corticosteroids became the standard treatment for TTP, and the survival rate of patients for the next two decades did not vary significantly (4).

Caplacizumab is a humanized bivalent single-domain nanobody that has been approved by the European Union and the U.S. Food and Drug Administration for the treatment of TTP in adults (5,6). It binds to the A1 domain of VWF and effectively inhibits the interaction with platelet GPIb-IX-V, thereby limiting platelet adhesion and microvascular thrombus formation (7). TITAN phase II studies evaluating the safety and efficacy of the drug, and HERCULES Phase III multi-center, randomized, double-blind trials noted fewer side effects and shorter hospital stays compared to the control group (8), but in other studies, the caplacizumab group had a higher incidence of bleeding (9-11).

Owing to its high price (12), In clinical trials, the use of caplacizumab is strictly controlled, adheres to strict dosing and withdrawal protocols, and is limited to use in trial hosting centers (9). Currently, there is a great controversy about the safety and efficacy of caplacizumab in the treatment of TPP, Therefore, we conducted this systematic review and meta-analysis of all available randomized controlled trials (RCTs) and summarized their results to evaluate the efficacy and safety of caplacizumab in patients with TTP. We strictly followed Population Intervention Comparison Outcome Study design (PICOS) principle to conduct this meta-analysis. We included patients diagnosed with TTP. The intervention in experimental group was caplacizumab, and placebo in control group. The main outcomes included days of PE, length of hospital stay, relapse, mortality, and major thrombotic events. Only RCTs were included for further analysis. We present the following article in accordance with the PRISMA reporting checklist (13) (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2847/rc).

Methods

Data source and searches

We performed a literature search of the PubMed, Web of Science, Cochrane Library, Embase, China National Knowledge Infrastructure (CNKI), VIP and Wanfang databases from the date of establishment of the database to March 5, 2022. We used medical subject headings plus free words as the retrieval method. Supplementary Data 1 (Table S1) displays the search strategy applied in this meta-analysis. In addition, we identified other studies by searching the reference sections of relevant articles and by corresponding with subject experts.

Inclusion and exclusion criteria

The inclusion criteria were as follows: (I) those >18 years old who meet the TPP diagnostic criteria; (II) the experimental group was treated with caplacizumab, and the control group was treated with blank control; (III) primary outcome measures were efficacy and safety; and (IV) RCT. The exclusion criteria were as follows: (I) *in vitro* and animal experiments; (II) studies involving too few samples (i.e., samples sizes of less than 10 cases in each group); and (III) grey journal literature.

Literature screening and data extraction

We imported the retrieved studies into EndNoteX9 software [Clarivate, Clarivate Analytics (UK) Limited, London, UK], and downloaded and read the full texts of the articles that met the inclusion/exclusion criteria. We developed a data extraction spreadsheet for this project, which included the following information: title, first author, year of publication, study type, author country, patient characteristics (age, gender, number of patients with ADAMTS13 activity <10%, platelet count at baseline), treatment conditions (experimental group dose, treatment period, follow-up period), and outcome indicators.

Two researchers (CB and CXX) independently conducted the literature screening and data extraction. Upon completion, the two researchers cross-examined each other, and a third researcher (XDQ) assisted in adjudicating

cases of disagreement.

Quality assessment

The quality of the resulting RCTS was assessed using the Cochrane Collaboration's risk of bias assessment tool, which assessed risk of bias for seven items from the following six aspects: (I) selection bias (random sequence generation, allocation concealment); and randomization; unspecified risk means randomization is mentioned but no specific method of randomization is stated; low risk refers to specific randomization and its specific method. (II) Performance bias (blinding of participants and personnel); high risk means that the implementation of blinding is not mentioned; unclear risk means that the implementation method of blinding is not specified; low risk means that the blinding method and specific implementation method are mentioned. (III) Detection bias (blind evaluation of results); low risk refers to blinding of outcome assessors, and high risk refers to no mention of blinding outcome assessors. (IV) Loss to follow-up and dropout bias (incomplete outcome data); low risk refers to the specific number and reasons for loss to follow-up and dropout reported in the article. High risk means that loss to follow-up and withdrawal are not mentioned in the article. (V) Reporting bias (selective reporting); low risk means that the outcome indicators are consistent with the observation indicators and include positive and negative results, and high risk refers to the observation indicators and outcome indicators inconsistent. (VI) Other biases; low risk values do not include other biases, and it is unclear whether other risks are included (14).

Outcomes measures

The primary outcome measure for this meta-analysis was platelet counts normalization time. Additional outcome measures included days of PE, length of hospital stay, relapse, mortality, and major thrombotic events.

Data synthesis and statistical analysis

Data were entered and analyzed using STATA software (StataCorp LLC 4905 Lakeway Drive College Station, Texas, USA). The weighted mean difference (WMD) was used for continuous outcomes (platelet count normalization time, days of PE, and length of hospital stay) to evaluate the differences between the caplacizumab and control groups in the included studies. The precision of the effect sizes was reported as 95% confidence intervals (CIs). A pooled estimate of the WMD was computed using the DerSimonian and Laird random-effects model (15). For dichotomous variables such as relapse, mortality, and major thrombotic events, relative risk (RR) values and corresponding 95% CIs were used.

Statistical heterogeneity between the studies was assessed using the Q and I^2 statistics. I^2>50% and P<0.1 indicated high heterogeneity, and the random-effects model was used. However, I^2<50% and P>0.1 indicated low heterogeneity, and a fixed-effects model was employed.

Results

Literature screening results

A total of 707 relevant studies were retrieved from the PubMed, Web of Science, Cochrane Library, Embase, CNKI, VIP, and Wanfang databases, and after preliminary screening, four RCTs were finally included in this meta-analysis. The literature screening process is shown in *Figure 1*.

Study characteristics

After step-by-step screening, four RCTs published between 2016 and 2021 with sample sizes ranging from 72 to 145, and a total of 416 participants (ages ranging from 3 to 93 years old) were eligible for inclusion in this meta-analysis (9-11,16). There were 228 patients in caplacizumab group and 188 in control group. All of the included RCTs enrolled patients who had reduced platelet counts, confirmed TTP, and had received PE. Of these, two were published in New England journals (10,11), and all four studies were RCTs. The characteristics of the included RCTs are shown in *Table 1*.

Three studies compared the study drug to a placebo (10,11,16), and the remaining study compared the patient characteristics and treatment outcomes between caplacizumab and historical standard of care regimens (9). Moreover, three studies examined the time to normalization of platelet counts (9-11), two studies investigated the PE days and length of hospital stay (9,11), three studies investigated relapse (10,11,16), and all studies examined TTP-related mortality and major thrombotic events. Among the four included studies, the study drug was administered as a fixed (10 mg dose) for 30 days in three studies (10,11,16) and 32 days in one study (9). The baseline characteristics of the treatment groups in the included RCTs were balanced.

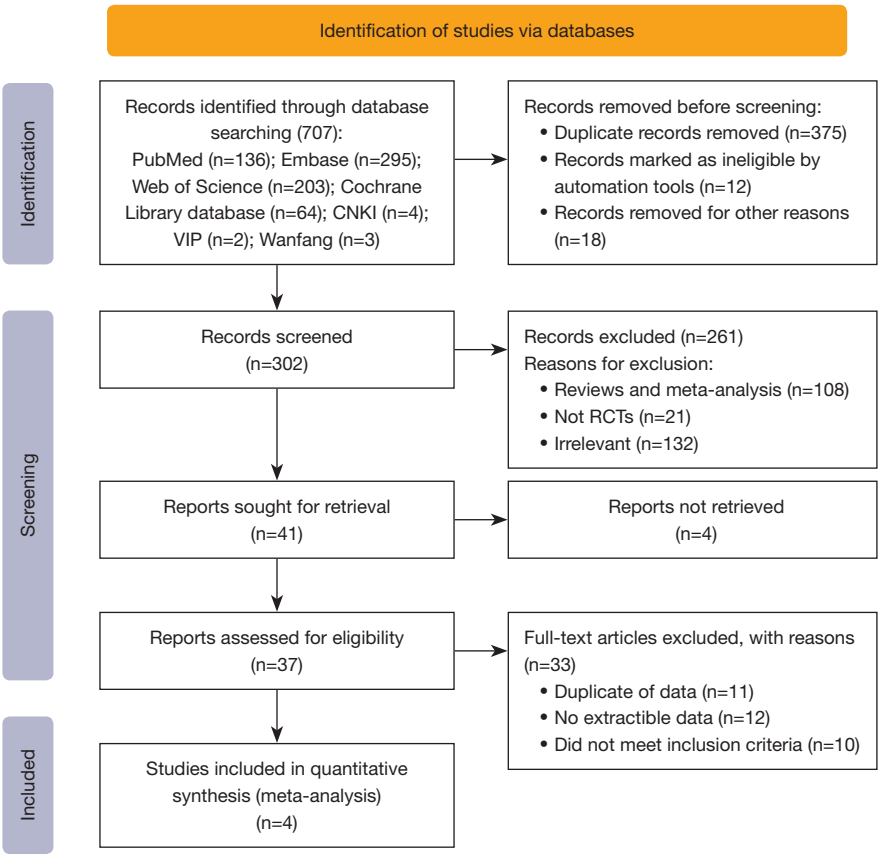

Figure 1 Literature selection flow chart. CNKI, China National Knowledge Infrastructure; RCT, randomized controlled trial.

Table 1 Characteristics of the studies included in the meta-analysis.

No.	Author	Year	Country	Sample size		Age (years), median [IQR]		(Female/male)		ADAMTS13 [%]		Platelet count $\times 10^9$/L, median [IQR]		Treatment (days)	Follow-up (days)
				I	C	I	C	I	C	I	C	I	C		
1	Scully M *et al.*	2019	UK	72	73	45 [18–77]	47 [21–79]	(49/68)	(51/70)	58 [81]	81 [89]	24 [3–119]	25 [9–133]	30	28
2	Dutt T *et al.*	2021	UK	85	39	46 [3–82]	45 [15–93]	(56/29)	(31/8)	84 [99]	39 [100]	13 [9–21]	10 [6–20]	32 [22–47]	80
3	Peyvandi F *et al.*	2016	UK	36	39	41 [19–72]	42 [21–67]	(24/12)	(20/19)	28 [78]	1.4±0.6	21.1 [20–70]	28 [5–84]	30	30
4	Peyvandi F *et al.*	2017	Italy	35	37	–	–	(49/68)	–	–	–	24 [3–119]	–	30	–

I, intervention group (caplacizumab + standardized treatment); C, control group (placebo + standardized treatment); UK, United Kingdom; ADAMTS13, the number of cases of ADAMTS13 activity <10%.

Quality assessment

The methodological quality of the included RCTs is summarized in *Figure 2*. All four studies reported acceptable methods of randomization (9-11,16). One study compared a historical control group with a treatment group for a specific period (9). Two studies described the blinding of patients and

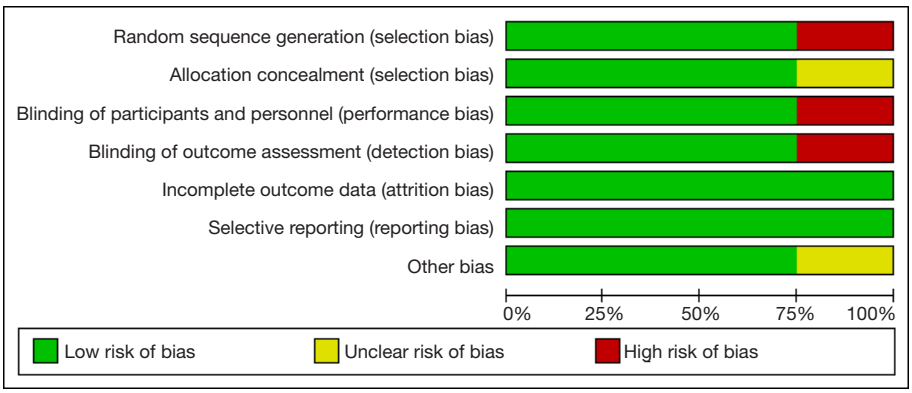

Figure 2 Risk of bias graph.

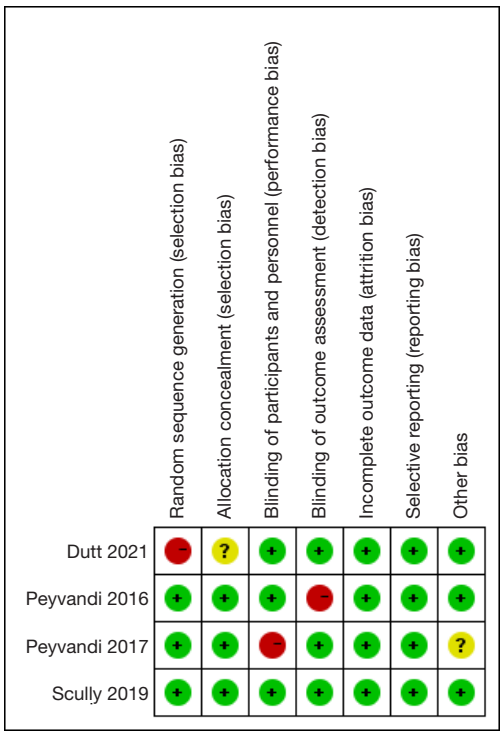

Figure 3 Risk of bias summary.

outcome assessors as single-blind (10,16). In all studies, the number of patients lost to follow-up was acceptable (<20%). Finally, one included RCT may have introduced reporting bias, as the statistics provided were unclear (16) (see *Figures 2,3*).

Meta-analysis

Platelet counts normalization time

Three studies examined the time to normalization of platelet counts (9-11). Normalization was defined as a platelet count of 150,000/mm or higher without PE following intravenous administration of the study drug. Caplacizumab appeared to be more effective than placebo in shortening the normalization time of platelet counts (WMD −1.18, 95% CI: −2.55 to 0.19, I^2=69.9%, P=0.036) (*Figure 4*).

Time of PE

Two studies investigated the PE time during trial treatment (9,11). The PE time appeared to be shorter in the caplacizumab group than in the control group (WMD −2.97, 95% CI: −4.44 to −1.50, I^2=8.2%), but the P value was close to the critical value (P=0.297) (*Figure 5*).

Hospital stay

Two studies reported the corresponding length of hospital stay (9,11). Caplacizumab treatment was significantly associated with a shorter hospital stay than placebo group (WMD −2.88, 95% CI: −4.56 to −1.21, I^2=48.7%, P=0.163) (*Figure 6*).

Mortality

All studies reported on all-cause mortality. There were only 12 deaths in the entire study population, including five patients in the caplacizumab group and seven patients in the control group. These results indicated that the difference in mortality between the two groups was not statistically significant (RR 0.56, 95% CI: 0.18 to 1.72, I^2=22.7%, P=0.275) (*Figure 7*).

Relapse

Three articles reported the relapse data. In these RCTs, relapse was defined as a new decrease in the platelet count

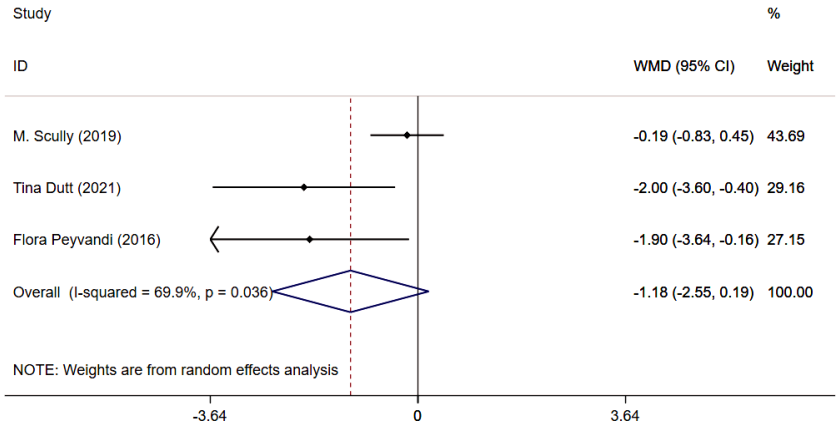

Figure 4 Forest plot showing WMD of platelet counts normalization time in the treatment of thrombotic thrombocytopenic purpura with caplacizumab. WMD, weighted mean difference.

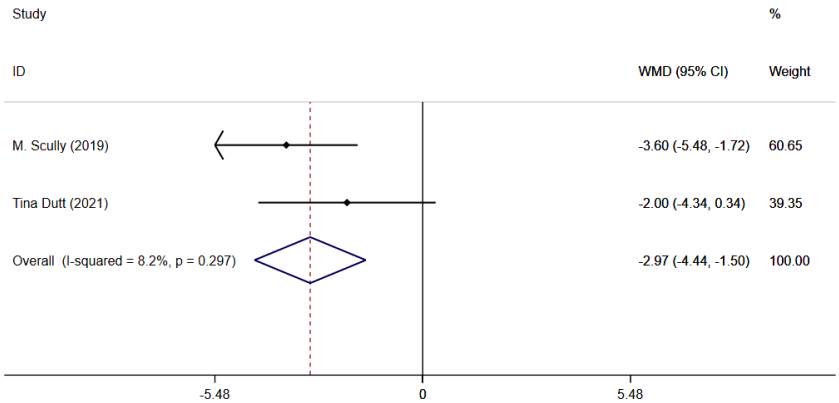

Figure 5 Forest plot showing WMD of plasma exchange time in the treatment of thrombotic thrombocytopenic purpura with caplacizumab. WMD, weighted mean difference.

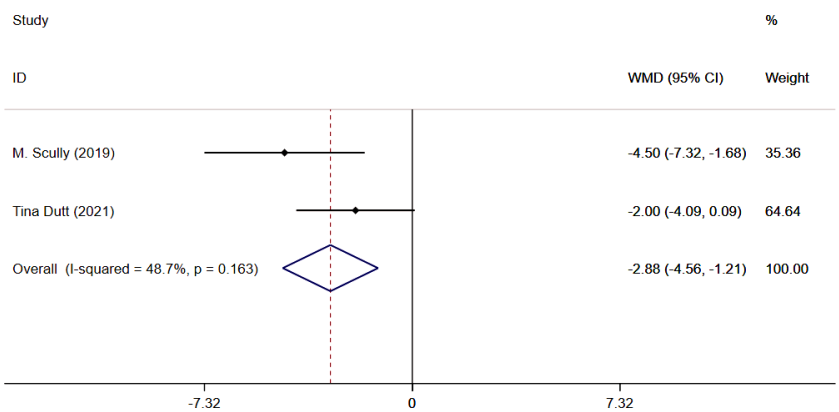

Figure 6 Forest plot showing WMD of hospital stay in the treatment of thrombotic thrombocytopenic purpura with caplacizumab. WMD, weighted mean difference.

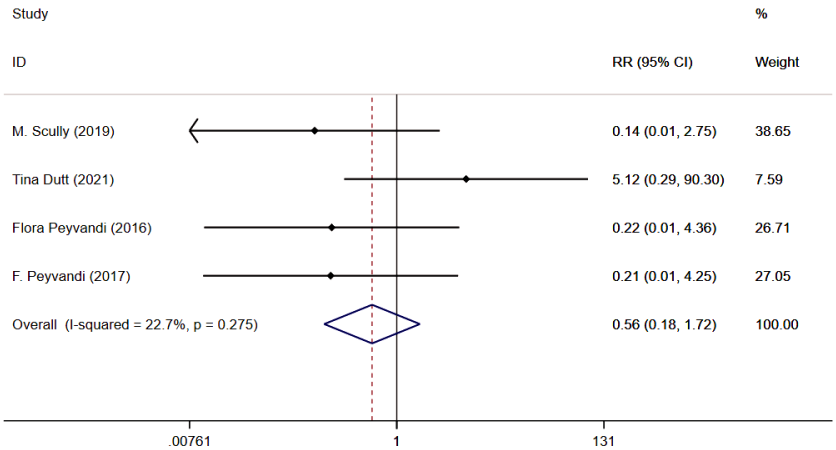

Figure 7 Forest plot showing risk ratio for mortality in the treatment of thrombotic thrombocytopenic purpura with caplacizumab.

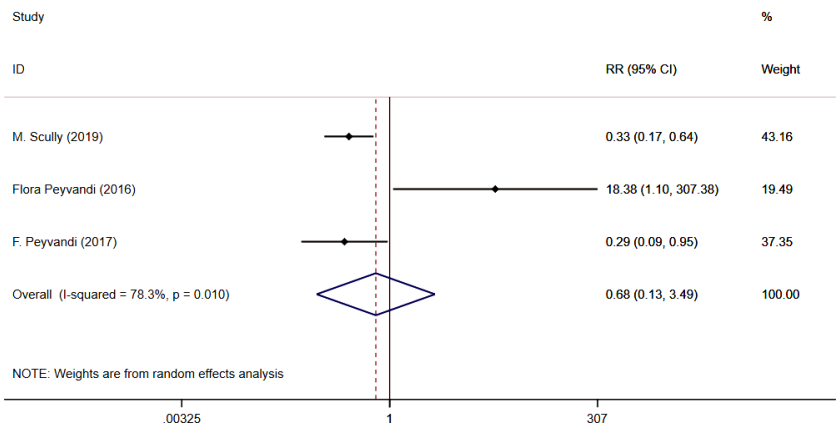

Figure 8 Forest plot showing risk ratio for relapse in the treatment of thrombotic thrombocytopenic purpura with caplacizumab.

after initial normalization of the platelet count in one study (11), a new episode of thrombocytopenia (where a new episode was defined as one that occurred more than 30 days after the last daily PE session) in another study (8), and as recurrence and worsening during treatment in the remaining study (16). The results of the combined data showed that there were no statistically significant differences between the caplacizumab and control groups (RR 0.68, 95% CI: 0.13 to 3.49, I^2=78.3%, P=0.01) (*Figure 8*).

Major thrombotic events

All four studies reported the incidence of major thromboembolic events. The results of the combined data showed that there were no significant statistical differences in the incidence of major thrombotic events between the caplacizumab and control groups (RR 1.01, 95% CI: 0.65 to 1.57, I^2=43.4%, P=0.151) (*Figure 9*).

Assessment of publication bias

Egger's chart was used to evaluate the publication offset of Major Thrombotic Events. It was found that P=0.037<0.05, indicating that there is a large possibility of publication bias (*Figure 10*).

Discussion

This meta-analysis evaluated the efficacy and safety of caplacizumab treatment in TTP patients. The results showed that in addition to reducing the time to normalization of platelet count in the treatment group, caplacizumab also reduced PE time and hospital stay. There were no statistically significant differences in TTP-related

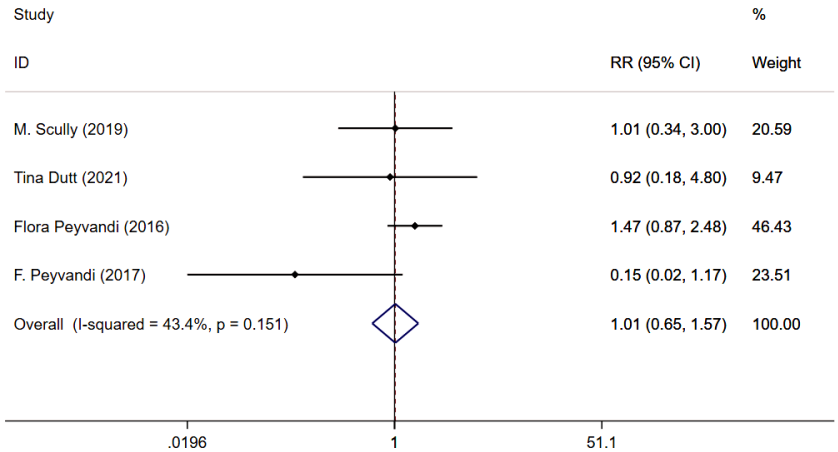

Figure 9 Forest plot showing risk ratio for major thrombotic events in the treatment of thrombotic thrombocytopenic purpura with caplacizumab.

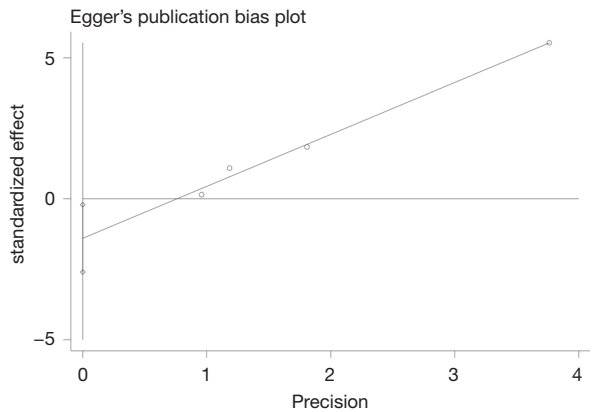

Figure 10 Publication offset of major thrombotic bias.

deaths, relapse, or major thrombotic events between the treatment and control groups.

TTP is a major clinical problem that severely affects the quality of life of patients (17) and can be fatal in severe cases. Although PE has markedly reduced the rate of early mortality and provided advantages in the emergency management of TTP, treatment outcomes have not changed significantly over the past two decades. Due to uncontrolled microvascular thrombosis, death occurs mainly in the acute phase, with a recently reported mortality rate of up to 20% (18).

Current treatments mainly involve PE combined with corticosteroids, but do not directly address microvascular thrombosis. PE and corticosteroids are not as effective at inhibiting autoantibodies, and as a result, TTP patients experience refractory TTP, exacerbation, and relapse (19). Therefore, new drug therapies are essential to improving the physical health and treatment of TTP patients. Rituximab (RTX), which inhibits the production of disease-related ADAMTS13 inhibitors by depleting B lymphocytes (20), was added to the standard regimen of TTP therapy in the mid-2000s. However, Parodi *et al.* (21) reported complications such as fever, itchy throat, nausea, arthralgia, and rash in patients receiving RTX, and Qu *et al.* (22) observed serum sickness in some pediatric patients receiving RTX. Furthermore, the optimal dosing regimen for the RTX infusion has not yet been established. Initially, most studies used four weekly infusions of 375 mg/m^2, but other studies have proposed four infusions of 375 mg/m^2 over a shorter period (days 1–4, 8–15) to improve bioavailability, since PE may eliminate RTX (23). However, more clinical trials are needed to validate the efficacy of this B cell-depleted anti-ADAMTS13 antibody-based immunomodulatory strategy.

In TTP, ADAMTS13 deficiency causes uncleaved oversized VWF multimers to bind to platelets, thereby inducing microthrombosis (24). Caplacizumab targets the A1 domain of VWF and blocks the adhesion to platelets (25), which is an important step in the formation of microthrombi. We expect caplacizumab to show good efficacy and benefits in TTP patients.

The TITAN study evaluated the safety and efficacy of caplacizumab in patients with an acute episode of TTP (10). It showed that caplacizumab use reduced the time to normalization of platelets (3.0 days; 95% CI: 2.7–3.9 days) relative to placebo use (4.9 days; 95% CI: 3.2–6.6 days). For patients who had previously undergone PE before enrollment

in the study, platelet normalization occurred at a median of 2.4 days (95% CI: 1.9–3.0 days) with caplacizumab, compared to 4.3 days (95% CI: 2.9–5.7 days) with placebo use. The investigators concluded that treatment with caplacizumab produced more rapid resolutions of acute episodes of TTP.

The TITAN study evaluated the safety and efficacy of caplacizumab in patients with an acute episode of TTP (10). It showed that caplacizumab use reduced the time to normalization of platelets (3.0 days; 95% CI, 2.7–3.9 days) relative to placebo use (4.9 days; 95% CI: 3.2–6.6 days). For patients who had previously undergone PE before enrollment in the study, platelet normalization occurred at a median of 2.4 days (95% CI: 1.9–3.0 days) with caplacizumab, compared to 4.3 days (95% CI: 2.9–5.7 days) with placebo use. It is concluded that the treatment of acute TTP with caplacizumab has a faster remission rate.

In the double-blind, randomized, placebo-controlled, multinational Phase 3 HERCULES trial investigating the efficacy of caplacizumab in patients with TTP (11), the time to normalization was shorter in the caplacizumab group than placebo group (2.69 *vs.* 2.88 days, P=0.01). Also, the caplacizumab group [12% (n=9)] had a lower proportion of patients with TTP recurrence throughout the trial than the placebo group [38% (n=28)]. Three patients in the placebo group developed refractory TTP (P=0.06). These RCTs demonstrate the positive effect of caplacizumab in TTP therapy.

However, the caplacizumab group [22% (n=8)] had a higher relapse rate than the placebo group (0%) in the TITAN study. ADAMTS13 activity remained below 10% in all patients who experienced relapse. It is thought that caplacizumab only delayed the time to relapse in patients with persistently low ADAMTS13 activity (26). It is therefore necessary to continuously track ADAMTS13 activity during the clinical treatment of TTP and adjust the duration of caplacizumab treatment accordingly (27). Moreover, as caplacizumab protects patients from exacerbations and refractoriness until ADAMTS13 improvement, we hypothesize that close monitoring of ADAMTS13 following platelet count recovery and PE cessation could identify the time-point at which ADAMTS13 improves (≥20%). This would facilitate cessation of caplacizumab, thereby avoiding prolonged and unnecessary exposure to the drug (8).

This study has the following advantages. Firstly, to our knowledge, this is the first meta-analysis of the efficacy and safety of caplacizumab in patients with TTP. Secondly, we included RCTs. However, our study has several limitations that should be noted. Firstly, even though we conducted a comprehensive and systematic literature search of the entire web, there were relatively few studies that met the inclusion criteria. Secondly, some of the included studies only recruited a small number of patients. Finally, the cost-effectiveness of caplacizumab, which is critical to decision-making, was not investigated.

Conclusions

Our meta-analysis showed that caplacizumab provided significant benefits in patients with TTP. In addition, patients receiving caplacizumab did not experience an increase in TTP-related death, re-examination, or major thrombotic events, and the proportion of refractory cases in the caplacizumab group was significantly lower than that in the control group. We concluded that caplacizumab is a safe and feasible treatment for newly diagnosed TTP patients and should be initiated as soon as possible. In the future, we look forward to more multi-center, high-quality, and larger-sample clinical studies to further validate our findings.

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Footnote

Reporting Checklist: The authors have completed the PRISMA reporting checklist. Available at https://atm.amegroups.com/article/view/10.21037/atm-22-2847/rc

Conflicts of Interest: All authors have completed the ICMJE uniform disclosure form (available at https://atm.amegroups.com/article/view/10.21037/atm-22-2847/coif). The authors have no conflicts of interest to declare.

Ethical Statement: The authors are accountable for all aspects of the work in ensuring that questions related to the accuracy or integrity of any part of the work are appropriately investigated and resolved.

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