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Real-World Evidence of Caplacizumab Use in the Management of Acute TTP

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Abstract:
The cornerstone of life-saving therapy in immune mediated thrombotic thrombocytopenic purpura (iTTP) has been plasma exchange (PEX) combined with immunomodulatory strategies. Caplacizumab, a novel anti-von Willebrand factor nanobody, trialled in two multicentre, randomised-placebo-controlled trials leading to EU and FDA approval, has been available in the UK through a patient-access scheme.

Data was collected retrospectively from 2018-2020 for 85 patients receiving caplacizumab, including 4 children, from 22 UK hospitals. Patient characteristics and outcomes in the real-world clinical setting were compared with caplacizumab trial endpoints and historical outcomes in the pre-caplacizumab era.

84/85 patients received steroid and rituximab alongside PEX; 26% required intubation. Median time to platelet count normalisation (3 days), duration of PEX (7 days) and hospital stay (12 days) was comparable with RCT data. Median duration of PEX and time from PEX initiation to platelet count normalisation was favourable compared with historical outcomes ($p<0.05$). TTP recurrence occurred in 5/85 patients; all with persistent ADAMTS13 activity <5iu/dL. Of 31 adverse events in 26 patients, 17/31 (55%) were bleeding episodes and 5/31 (16%) were thrombotic events (two unrelated to caplacizumab); mortality was 6% (5/85), with no deaths attributed to caplacizumab. In 4/5 deaths caplacizumab was introduced >48 hours after PEX initiation (3-21 days).

This real-world evidence represents the first and largest series of TTP patients receiving caplacizumab outside clinical trials, including paediatric patients. Representative of true clinical practice, the findings provide valuable information for clinicians treating TTP globally.

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Title

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Short title: Real-World Evidence of Caplacizumab in TTP

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Key Points

1. The UK real-world evidence of caplacizumab in iTTP represents the largest, international data collection outside clinical trials to date.

2. The UK real-world evidence of caplacizumab is comparable with RCT outcomes and includes paediatric patients.

Abstract

The cornerstone of life-saving therapy in immune mediated thrombotic thrombocytopenic purpura (iTTP) has been plasma exchange (PEX) combined with immunomodulatory strategies. Caplacizumab, a novel anti-von Willebrand factor nanobody, trialled in two multicentre, randomised-placebo-controlled trials leading to EU and FDA approval, has been available in the UK through a patient-access scheme.

Data was collected retrospectively from 2018-2020 for 85 patients receiving caplacizumab, including 4 children, from 22 UK hospitals. Patient characteristics and outcomes in the real-world clinical setting were compared with caplacizumab trial endpoints and historical outcomes in the pre-caplacizumab era.

84/85 patients received steroid and rituximab alongside PEX; 26% required intubation. Median time to platelet count normalisation (3 days), duration of PEX (7 days) and hospital stay (12 days) was comparable with RCT data. Median duration of PEX and time from PEX initiation to platelet count normalisation was favourable compared with historical outcomes ($p<0.05$). TTP recurrence occurred in 5/85 patients; all with persistent ADAMTS13 activity <5iu/dL. Of 31 adverse events in 26 patients, 17/31 (55%) were bleeding episodes and 5/31 (16%) were thrombotic events (two unrelated to caplacizumab); mortality was 6% (5/85), with no deaths attributed to caplacizumab. In 4/5 deaths caplacizumab was introduced >48 hours after PEX initiation (3-21 days).

This real-world evidence represents the first and largest series of TTP patients receiving caplacizumab outside clinical trials, including paediatric patients. Representative of true clinical practice, the findings provide valuable information for clinicians treating TTP globally.

Introduction

Thrombotic thrombocytopenic purpura (TTP) results from severe deficiency of von Willebrand cleaving protease, ADAMTS13. In immune-mediated TTP (iTTP) there are IgG autoantibodies against ADAMTS13[1]. Until recently, management of iTTP focused on the replacement of ADAMTS13 and the removal of autoantibodies using plasma exchange (PEX) and immunosuppression[2-4]. This approach has reduced the mortality of acute TTP from over 90% to around 10-20%[5].

Caplacizumab is a humanised, single-variable-domain nanobody targeting the A1 domain of von Willebrand factor (vWF)[6]. It has been developed for the treatment of iTTP and its novelty lies in its site of action, specifically inhibiting vWF-platelet interaction, thereby limiting platelet adhesion and microvascular thrombus formation[6,7].

In August 2018, caplacizumab was approved in the European Union (EU) for the treatment of iTTP following favourable results from phase II TITAN and phase III HERCULES clinical trials, studying a total of 220 adult patients with acute iTTP. Patients who received caplacizumab, in addition to standard care, demonstrated a significantly shorter time to platelet count normalisation ($p<0{\cdot}01$) and reduction in duration of PEX and overall hospital stay when compared with placebo[7,8]. There were no deaths reported in those patients receiving caplacizumab during an acute TTP episode.

The use of caplacizumab was highly controlled in the clinical trials, subject to adherence to strict protocols for drug administration and discontinuation and limited to use in the trial hosting centres. The unique value of real-world evidence lies in the inclusion of patients encountered in clinical practice where decisions are often influenced by everyday practice factors such as location, patient compliance, concomitant treatments and dynamic clinical factors such as refractory disease and relapse. Here we describe 85 patients with iTTP who received caplacizumab in the UK, following EU approval, through a patient access scheme. The objectives were to describe the iTTP patient population receiving caplacizumab in a real-world clinical setting, report their outcomes including

safety and tolerability and compare with trial and historical outcome data. To our knowledge, this is the largest cohort of TTP patients who have received caplacizumab outside of a clinical trial to be reported in the literature and includes the only case series in the paediatric age group to date.

Methods

An invitation to participate in real-world evidence data collection was sent to all UK TTP Registry collaborators indicating a final date for data submission. The data was retrospectively collected from consecutive, eligible patients' medical records from UK hospitals between May 2018 and January 2020. Inclusion criteria were patients of any age, who had received at least one dose of caplacizumab through the patient drug access scheme, following a confirmed diagnosis of acute TTP. There were no exclusion criteria. Patients received standard treatment, as per UK national guidance[2] and all patients included were recruited to the UK TTP Registry conferring consent, ethical approval and permissions for data collection. Sanofi confirmed the total number of patients for whom caplacizumab had been provided through the access scheme and had no other involvement in data collection or analysis.

Anonymised data were submitted by participating centres using password-protected, standardised databases requesting specific patient characteristics and outcome data. Relevant outcome parameters were identified ahead of data collection comparable with the caplacizumab randomised controlled trial (RCT) endpoints. These included patient demographics, ADAMTS13 serology, serological markers of organ injury, platelet count recovery, plasma exchange, TTP recurrences, bleeding/thromboembolic complications and mortality.

Characteristics and outcomes for patients receiving caplacizumab in the real-world setting were compared with outcome data from the Hercules phase III RCT[7] and a historical control group. The historical control group consisted of 39 consecutive cases from the UK TTP Registry 2014-2018 prior to, and outside of, the caplacizumab clinical trials. The standard of care for the historical control

group was as per UK national guidance[2] and included rituximab as a component of acute management.

For the real-world data collection, time to platelet count normalisation was defined in line with the HERCULES RCT as the time from the first intravenous administration of caplacizumab to the normalisation of platelet count (i.e. a platelet count of at least 150 $x10^9$/L, with discontinuation of plasma exchange within five days thereafter). Recurrence of TTP was defined as a new decrease in platelet count after initial normalisation, requiring plasma exchange therapy to be reinitiated. A recurrence within 30 days after completion of plasma exchange therapy was defined as an 'exacerbation', and a recurrence occurring more than 30 days after completion of plasma exchange therapy was defined as a 'relapse'. Refractory TTP refers to the progression of clinical symptoms or persistent thrombocytopenia despite plasma exchange.

Descriptive statistical analyses were used to summarise the data. Quantitative variables were presented using median, interquartile range (IQR) and categorical variables using counts and percentages. Between group comparisons were undertaken using Mann-Whitney U test for continuous data and Fisher's exact test for binary variables. The Kaplan-Meier estimator was used to calculate median follow-up time. All analysis were carried out using SPSS software (version 25).

Results

During the period May 2018 to January 2020 a total of 115 patients (110 adult and five paediatric) from 25 UK hospitals received caplacizumab through the free drug patient access scheme. Data was provided from 22 hospitals for 85/115 patients. Participation in data submission was voluntary and no data were received for the remaining 30/115 patients. Eighty-one patients were adult (≥18 years at the time of 1st dose of caplacizumab) and four were paediatric (<18 years). Using the Kaplan-Meier estimator (with those patients who died included as censored observations), the median

follow-up period (from date of initiation of caplacizumab to last documented clinical follow-up) was 80 days (IQR 59 - 166 days).

Patients receiving caplacizumab covered a wide geographical area of England, Scotland and Wales. The median number of cases treated per hospital was one. The highest number of cases treated in one centre was 30. In all paediatric cases, patient care was guided by an adult centre.

Patient Characteristics and Outcomes

Presenting parameters and concomitant treatments are summarised in Table 1; patient outcomes are presented in Table 2. All 85 patients had an ADAMTS13 activity at presentation of <20 iu/dL, with 99% of patients (84/85) having ADAMTS13 activity <10 iu/dL, confirming a clinical diagnosis of acute TTP.

Eighty five percent (72/85) of patients had a platelet count of <30 $x10^9$/L on admission, 76% (65/85) a raised troponin and 66% (56/85) neurological symptoms. Median presenting creatinine was 90 umol/L (IQR 71-135 umol/L) and median presenting troponin on admission was 98 ng/ml (IQR 31–317 ng/ml). Twenty seven percent (23/85) had multi-organ failure comprising raised troponin, acute kidney injury and neurological symptoms

Twenty six percent (22/85) of patients required intubation and ventilation either prior to transfer or following admission. The median duration of intubation was 4 days, (IQR 2 – 7 days) and in all cases the indication for intubation was neurological deterioration.

Time to initiate caplacizumab treatment

The median time taken for patients to receive the first dose of caplacizumab after initiation of PEX was two days (IQR 1–3 days), and 87% (74/85) of patients received caplacizumab within one week of starting plasma exchange (Figure 1A).

Median time to initiate caplacizumab was also compared for patients started on caplacizumab in the first 9 months of the data collection period (May 2018 until February 2019, n=24), with those who commenced in the second 9 months (March to December 2019, n=61), to evaluate any changes in familiarity and accessibility of the new therapy. The median time to initiate caplacizumab was 3 days (IQR 2–7 days) for patients commencing caplacizumab in the first 9 months compared with 1 day (IQR 0–3 days) for those commenced in the latter 9 months (p<0.001).

Time to platelet count normalisation, plasma exchange and hospital stay

Ninety five percent of patients achieved platelet normalisation in the caplacizumab cohort compared with 100% in the historical cohort (P=0.31). In the 4/85 patients receiving caplacizumab who did not normalise their platelet count (by 30 days, post-PEX discontinuation); one case was due to a concomitant diagnosis of ITP (immune thrombocytopenia) with a history of chronic low grade thrombocytopenia, one case normalised by day 43 and two cases had multiple organ failure resulting in death.

The median time from 1st PEX to platelet normalisation was 4 days (IQR 3-8 days) and 6 days (IQR 4-10 days), in the caplacizumab cohort and the historical cohort respectively (p=0.011). The median duration of plasma exchange was 7 days (IQR 5-14 days) and 9 days (IQR 8-16 days), respectively (p=0.007). This is the total number of days delivered and includes cases where PEX was tapered or reintroduced (4/85). In 26% of cases (22/85) PEX was continued despite normalisation of the platelet count for ≥48 hours.

Hospital length of stay was 12 days (IQR 8-24 days) and 14 days (IQR 9-17 days), in the caplacizumab cohort and the historical cohort respectively (P=0.62). Death occurred in 6% and 0%, respectively (p=0.32) (Table 3); however 10% of patients in the historical group required intubation compared to 26% of the caplacizumab group, suggesting a more severe disease phenotype in the latter.

Disease recurrence and ADAMTS13 activity recovery

Six percent (5/85) of patients in total were reported to have a TTP recurrence, of which 2/5 were classified as an exacerbation and 3/5 as relapse of TTP (Table S1). For this group, caplacizumab was commenced in all 5/5 cases within three days from commencing PEX and in all cases the time to platelet count normalisation was ≤7 days.

In both cases of exacerbation, caplacizumab was interrupted; one due to concurrent pulmonary embolism requiring anticoagulation and one due to patient non-compliance. In both cases, the ADAMTS13 activity was <5 iu/dl at the time of discontinuing plasma exchange.

For all patients, the median ADAMTS13 activity for specific time points were 12.4 iu/dL (IQR 0.0-57.9 iu/dL) at the time of final PEX, 49.3 iu/dL (IQR 16.3-72.7 iu/dL) at the time of caplacizumab discontinuation and 58.3 iu/dL (IQR 15.5-85.4 iu/dL) one week post caplacizumab discontinuation. All patients with recurrent TTP had ADAMTS13 activity <10iu/dL at time of final PEX (Figure 1C). In addition, for 4 out of 5 patients with recurrence, ADAMTS13 activity remained <5iu/dL at all 3 time points. Time to relapse after stopping caplacizumab was two, ten and fourteen days.

The duration of caplacizumab continuation post-PEX ranged from zero to 92 days (median of 28 days), with 32% (27/85) patients continuing caplacizumab beyond 30 days. Conversely, 55% of patients (47/85) discontinued caplacizumab ahead of the 30-day period; in almost half (23/47) of these cases, the ADAMTS13 was >30 iu/dL.

Safety data

Adverse events

There were 31 adverse event episodes reported in 26 patients. These were classified into bleeding or non-bleeding complications (Table 4).

Bleeding

Seventeen bleeding episodes were reported in the caplacizumab cohort compared with no reported bleeding episodes in the historical cohort. For the caplacizumab group, the most common bleeding complications were gum bleeding (6/17) and gastrointestinal bleeding (5/17). Six out of fifteen episodes resulted in interruption or discontinuation of caplacizumab. The two cases of intracranial bleeding were reported to be secondary haemorrhage following extensive cerebral infarction. One patient with intracranial bleeding died but death was determined by the treating physician to be non-attributable to caplacizumab; this complex case presented with dense hemiparesis following first PEX, with computed tomography (CT) brain imaging demonstrating acute infarct. Two doses caplacizumab were administered before the patient became drowsy and repeat CT imaging showed acute subarachnoid haemorrhage; consequently caplacizumab was not given for three days. The patient continued to deteriorate with drowsiness/agitation, and a further CT brain showed progressive infarction (a single further dose of caplacizumab was administered) and the patient did not survive. The second case with intracranial haemorrhage survived; the patient had caplacizumab interrupted for 48 hours following imaging suggesting secondary haemorrhage of a cerebral infarct, serial imaging showed no extension of the suspected haemorrhage prior to/following reintroduction of caplacizumab. The patient experienced no further intracranial bleeding complications whilst receiving caplacizumab. The gastrointestinal (GI) bleeding events included two upper GI and three lower GI complications. The lower GI events were minor bleeding events; small amount of PR bleeding with all patients remaining haemodynamically stable. The upper GI bleeding events included one minor upper GI bleed and one major bleeding event in a patient with a history of Barrett's oesophagus who experienced a drop in haemoglobin and haemodynamic instability with OGD features of oesophagitis/small ulcer. The patient was treated with high dose intravenous omeprazole and received 7 units of red cell transfusion in total; the patient improved over the subsequent five days.

Non-bleeding

In the caplacizumab group, there were fourteen episodes of complications other than bleeding, the most common of these was venous thromboembolism in 4/85 patients (compared with 2/39 patients in the historical group). Skin reaction/rashes related to caplacizumab injection and abnormal liver function tests were also reported. In 10/14 episodes, the complication resulted in interruption or discontinuation of caplacizumab; the decision to interrupt or stop therapy was based on the treating physician's judgement.

Mortality

Six percent (5/85) of patients died related to TTP, but unrelated to caplacizumab. All cases had poor prognostic markers at presentation and 4/5 patients required intubation (Table 5). Three of the five patients commenced caplacizumab >1 week after starting PEX (range 8 – 21 days). The time to initiate caplacizumab was significantly longer in those patients who died compared to those who survived (Figure 1B, p=0.007). Two of five patients did not normalise their platelet count with three patients taking ≥7 days (range 7 – 18 days). One patient experienced haemorrhagic transformation of a cerebral infarct whilst on caplacizumab. All deaths were thought by the treating clinician to result from complications of severe/refractory TTP.

Paediatric sub-group analysis

Four patients were <18 years of age at the time of administration of the 1st dose of caplacizumab (range 3 – 17 years). The dose of caplacizumab was modified according to weight and ADAMTS13 activity was <5 iu/dL in all cases at presentation with a detectable inhibitor (range 11 – >80 U/ml). One case experienced multi-organ failure and required intubation. All patients received steroid and rituximab; one patient also received mycophenolate mofetil (Table 6). The time between starting PEX and commencing caplacizumab ranged from 0-8 days. All patients normalised their platelet count. For three out of four patients, the time to platelet count normalisation was between 3-4 days; the remaining patient normalised their platelet count on day 25, having commenced caplacizumab

one day after PEX. Caplacizumab was continued post-PEX for a median duration of 30·5 days, with no reports of recurrence at a median follow-up of 92 days (IQR 61 – 130 days).

Discussion

It is widely acknowledged that there remains a gap in the current therapeutic armoury for acute TTP with regards to achieving a prompt and sustained normalisation of the platelet count, reducing ongoing microvascular thrombosis and preventing disease recurrence pending the action of immunomodulatory therapies. Presented is the largest collection of real-world evidence internationally describing the use of caplacizumab outside formal clinical trials, including paediatric cases uncaptured within TITAN or HERCULES[7].

Real-world evidence is crucial in rare disease. When evaluating the impact of new therapeutic molecules in the context of the natural course of the disease, it is valuable to consider complications associated with existing management. Severe treatment-related complications are relatively rare in acute TTP and in particular bleeding complication rates are low[9,10]. The mode of action of caplacizumab means that bleeding similar to a von Willebrand disease (vWD) phenotype may occur related to its efficacy at high shear blood flow rates where the A1 domain of vWF is exposed[11]. The historical control group demonstrated no further bleeding complications beyond cutaneous bleeding/bruising at presentation. For caplacizumab in the real-world setting, the primary bleeding event was gingival, similar to the pivotal trials[7,8]. Severe bleeding complications, however, were observed in 6% of patients, with two cases of intracranial haemorrhage, one case of severe GI bleeding, one haemarthrosis and one gingival bleeding requiring blood transfusion. In the two cases of intracranial bleeding, both occurred following an initial ischaemic insult; interruption of caplacizumab was followed by further serial infarction and secondary haemorrhage. Cases complicated by acute ischaemic stroke may represent a high risk group for intracranial bleeding complications and will require a case–by-case evaluation of the risk versus benefit of drug

initiation/continuation. Drug interruption acutely itself may be associated with progressive microvascular thrombosis and disease exacerbation.

A HERCULES post-hoc analysis reported fewer thromboembolic complications in caplacizumab treated patients[12]. Here, five episodes of VTE were reported and in four out of five cases caplacizumab was interrupted/discontinued to commence anticoagulation. In the UK, aspirin and low molecular weight heparin are typically introduced once the platelet count is greater than $50x10^9$/L, however, with concurrent caplacizumab therapy intuitive practice has been to withhold aspirin. Best practice regarding thromboprophylaxis or management of acute thrombosis remains unclear.

For rare conditions such as TTP, complex clinical trials often attract highly selected populations managed in environments with a capacity for strict adherence to study protocols. Further, it has been suggested that some patients with more severe disease have been under-represented in the clinical trials. Within this UK cohort patients demonstrated a severe disease phenotype, with a significant proportion demonstrating cardiac involvement and the need for assisted ventilation.

The median time to platelet count normalisation from initiation of caplacizumab was comparable with data from HERCULES and all surviving patients normalised their platelet count (with the exception of one patient with a known history of immune thrombocytopenia). Registry data from 2009 - 2018 reports 56% of patients receiving standard of care alone achieved a platelet count >150 $x10^9$/L within one week, compared with 88% of patients receiving caplacizumab[13]. It could be postulated that an increase in rituximab use may have a bearing on this result, however this has not been shown in previous rituximab studies[14].

A significant fall in median duration of PEX over time from fourteen to eight days is observed in registry data[13]. This is most likely due to earlier intervention with rituximab. Greater disease severity at presentation, including the need for intubation, may contribute to prolonged duration of PEX to

remission and the longer median duration of PEX seen within the caplacizumab cohort here of 7 days compared with 5.8 days in the HERCULES study[7]. Delayed initiation of caplacizumab, particularly in the initial months as Haematologists became familiar with the treatment, may also have played a role.

It remains unclear whether early introduction of caplacizumab may limit microthrombotic complications long-term. Acute neurological recovery was observed in around 60% of patients who received the drug, consistent with the proposed organ-protective properties of caplacizumab[8]. There are limited data on the recovery of organ damage in TTP, however longer-term neurological complications have become an increasingly recognised feature and a beneficial role of caplacizumab here is plausible[15-18].

The drug summary of product characteristics advises continuing caplacizumab for 30 days post-discontinuation of PEX and extension as required thereafter[19]. The UK TTP Forum have previously agreed that caplacizumab could be discontinued when the ADAMTS13 activity is >30 iu/dL, seven days from discontinuation of PEX and confirmed on repeat sampling. This may have influenced the observed rate of early discontinuation. Discontinuation of caplacizumab once the ADAMTS13 activity approaches >30 iu/dL could potentially limit drug exposure and further drug costs. If there is delayed recovery of ADAMTS13, there is an argument to continue the drug to avoid a recurrence. Literature suggests that exacerbations can occur in up to 50% of patients despite treatment[20-23]. Recurrent disease was seen here in 5/85 (6%) patients. Similar to HERCULES data, all patients experiencing a recurrence exhibited a persistently low ADAMTS13 activity[7]. This real-world data supports continuation of caplacizumab until an ADAMTS13 activity recovery in the region of 30 iu/dL is observed, recognising this may occur ahead of the advised 30 day drug administration period.

The 6% mortality observed in this cohort is lower than the reported national mortality and there has been little change in a mortality of 8-20% as a proportion of new diagnoses from the Office for National Statistics data 2003 - 2013. In a recent multi-centre retrospective study of patients with

iTTP, Colling *et al* found a mortality rate of 3.7% per acute TTP episode, acknowledging that the patients in their study had been managed in large academic centres potentially explaining the lower than usual mortality reported in the literature[10]. Here, five patients died whilst receiving caplacizumab, compared with zero in the caplacizumab arm of the HERCULES trial[7]. All of those who died in our cohort had poor prognostic markers and severe disease characteristics at presentation. The utility of caplacizumab outside of the acute presenting event is unknown. Therefore, the outcomes for these patients are likely linked to disease severity, rather than failure of caplacizumab. The time to initiate caplacizumab was significantly longer in those patients who died compared to those who survived (p=0·007) suggesting caplacizumab may be more effective as a component of acute therapy. In the trials, caplacizumab was initiated within 24 hours of the first PEX[7]. Logistical delays in obtaining caplacizumab in the absence of a previously established pathway may have contributed to the longer time taken to initiate therapy.

There are two case reports in the literature describing the use of caplacizumab in children <16 years of age, both immune-mediated; one in refractory disease, the other an acute episode of relapse. Both experienced platelet count normalisation by day three, with no reported adverse events or disease recurrence[24,25]. Within our paediatric group there were no reported adverse events including bleeding complications or mortality.

It is acknowledged that the data presented here are descriptive rather than the results of a randomised study. The validity of collection of real-world evidence was augmented by UK TTP registry data which provided existing confirmation of the natural history of the disease and management in the UK. Reproducibility was optimised through participation from multiple healthcare settings completing standardised electronic database entry increasing the uniformity and completeness of data. Although the demographics for the real-world group receiving caplacizumab and historical control group were well-matched, the limitations of using a historical unexposed

control group are acknowledged and due to the number of patients, matching of cases and controls could not be undertaken.

Conclusions

This real-world evidence from the largest series of TTP patients receiving caplacizumab, outside of the pivotal studies, provides confirmation of the therapeutic benefits of caplacizumab and its inherent bleeding risk. The severe disease phenotype of patients presenting with acute iTTP is described, alongside a reduced time to platelet count normalisation and duration of PEX in patients receiving caplacizumab, which is comparable with clinical trial data. The wide use of caplacizumab observed in the UK represents current clinical practice and important considerations when utilising caplacizumab as a component of standard care in acute TTP.

Authorship Contributions:

T.D, R.J.S: Joint 1st authors - literature search, study design, data collection, analysis and interpretation, figures, writing

M.Stubbs, J.Y - data collection and analysis, figures

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S.L - statistical analysis, interpretation and manuscript review

M.Scully: Last author - study design, data analysis and interpretation, writing

Conflict of Interest Disclosures:

T.D, M.Scully, R.G, J.J.V.V, W.T have received honoraria from Sanofi for attendance at advisory boards.

T.D and M.Scully have received speaker fees from Sanofi and Alexion.

The remaining authors declare no competing financial interests.

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Tables

Table 1. Characteristics at Presentation of Patients Receiving Caplacizumab

Baseline characteristics	Caplacizumab cohort (N=85)
Mean age in years (range)	46 (3 – 82)
Female sex, number (%)	56 (66)
Race, number (%)*	..
White	57 (67)
Black	16 (19)
Asian	6 (7)
Other	4 (5)
Median platelet count, x10^9/L (IQR)	13 (9 – 21)
Median cardiac troponin, ng/ml (IQR)†	98 (31 - 317)
Median serum creatinine (IQR)	90 (71 - 135)
Neurological symptoms at presentation, number (%)	56 (66)
ADAMTS13 activity, number (%)¥	..
<10iu/dL	84 (99)
≥10iu/dL	1 (1)
Detectable ADAMTS13 inhibitor, U/ml, number (%)**	68 (80)
Immunosuppressive/adjuvant therapy started during admission, number (%)	..
Glucocorticoids	84 (99)
Rituximab	84 (99)
Mycophenolate mofetil (MMF)	25 (29)
Bortezomib	5 (6)
Ofatumumab	2 (2)
Cyclophosphamide	1 (1)
N-Acetyl Cysteine	1 (1)
Intensive care intervention	..
Number of patients requiring intubation, number (%)	22 (26)
Duration of intubation, median days (IQR)	4 (2 - 7)

Table 1 Legend

* Race and ethnic group were determined by the Haematologist submitting data for each centre. Data on race were missing for N = 2.

† Median cardiac troponin on admission is based on N = 81 patients for whom the data were available. Data based on troponin T, the more commonly used cardiac enzyme in the Trusts submitting data.

¥ ADAMTS13, indicates a disintegrin and metalloproteinase with thrombospondin type 1 motif, member 13.

** ADAMTS13 inhibitor value on admission is based on N = 78 patients for whom the data were available**.** The NHS Trusts included in this study used differing assays for ADAMTS13 inhibitor; therefore the normal values for each laboratory were used to determine if the ADAMTS13 inhibitor was present/absent.

Table 2. Summary of Outcomes for Patients Receiving Caplacizumab for Immune-Mediated Thrombotic Thrombocytopenic Purpura (iTTP)

Patient outcomes	Caplacizumab cohort (N = 85)
Time to normalisation of platelet count, days§, median (IQR)	3 (2 - 4)
Total number of days of plasma exchange, median (IQR)	7 (5 - 14)
Numbers of days of caplacizumab, median (IQR)	32 (22 - 47)
Caplacizumab discontinued prior to 30 days, number (%)	47 (55)
Caplacizumab continued beyond 30 days, number (%)	27 (32)
Number of days of hospitalisation, median (IQR)⁋	12 (8 - 24)
Normalisation of neurological symptoms, number (%)≠	33 (61)
Normalisation of creatinine, number (%)€	18 (56)
Recurrence of TTP, number (%)‖	6 (7)
Exacerbation of TTP	2 (2)
Relapse of TTP	3 (4)
TTP related death, number (%)¥	5 (6)
Caplacizumab related death, number (%)	0 (0)

Table 2 Legend

§ Time to normalisation of platelet count was defined in line with the HERCULES study as the time from the first intravenous administration of caplacizumab administered to the normalisation of platelet count (i.e. a platelet count of at least 150 $x10^9$/L with discontinuation of plasma exchange within five days thereafter). Time to normalisation of platelet count based on N = 81/85 patients, N = 4/85 patients did not normalise their platelet count (by 30 days, post-PEX discontinuation); one case due to a concomitant diagnosis of ITP (immune thrombocytopenia) with a history of chronic low grade thrombocytopenia, one case which normalised by day 43 and two cases with multiple organ failure leading to death.

⁋ Based on N=81 patients, excluding n=4 who died prior to discharge from hospital.

≠ Based on available data for N = 54/55 patients who presented with neurological symptoms. The most common neurological symptoms on discharge were low mood and anxiety.

€ Based on available data for N = 32/35 patients who presented with acute kidney injury.

‖ Recurrence of TTP was defined as a new decrease in platelet count after initial normalisation of the platelet count, requiring plasma exchange therapy to be reinitiated. A recurrence within 30 days after completion of plasma exchange therapy was defined as an exacerbation, and a recurrence occurring more than 30 days after completion of plasma exchange therapy was defined as a relapse.

¥ The cause of death was determined by the Haematology clinician submitting the data, and in all cases the cause was felt to be secondary to severe and/or refractory TTP.

Table 3. Comparison of Presentation Characteristics and Outcomes in Caplacizumab Cohort versus a Pre-Caplacizumab Historical Control

Presentation characteristics & outcomes	Standard treatment cohort* (N=39)	Caplacizumab cohort (N=85)	P†
Mean age, years (range)	45 (15 – 93)	46 (3 – 82)	0·76
Female sex, number (%)	31 (80)	56 (66)	0·18
Median platelet count on admission, x10^9/L (IQR)	10 (6 - 20)	13 (9 - 21)	0.51
Raised cardiac troponin, number (%)	25 (64)	67·0 (79)	0·12
Raised serum creatinine, number (%)	10 (26)	35 (41)	0·080
Neurological symptoms at presentation, number (%)	29 (74)	56 (66)	0·74
ADAMTS13 activity <10 iu/dL, number (%)	39 (100)	84 (99)	>0.99
Patients achieving platelet count normalisation, number (%)	39 (100)	81 (95)	0.31
Time from 1st PEX to normalisation of platelet count, days, median (IQR)	6·0 (4 - 10)	4·0‖ (3 - 8)	0.011
Total number of days of plasma exchange, median (IQR)	9 (8 - 16)	7 (5 - 14)	0·0070
Adjuvant therapy with Rituximab, number (%)	34 (87)	84 (99)	>0.99
Number of patients requiring intubation, number (%)	4 (10)	22 (26)	0.060

Number of days of hospitalisation, median (IQR)	14 (9 - 17)	12 (8 - 24)	0·62
Patients with bleeding post admission (%)	0 (0)	15 (18)	0.0027
Patients with VTE during admission (%)	2 (5)	4 (5)	>0.99
TTP related death, number (%)	0 (0)	5 (6)	0.32

Table 3 Legend

* Standard treatment cohort is from N=39 consecutive cases from unpublished UK TTP Registry data from 2014 to 2018

† P values calculated using student t-test/chi squared for parametric data and Mann-Whitney U test for non-parametric data

‖ Based on N = 81/85 patients. Four of eighty-five patients did not normalise their platelet count (by 30 days, post-PEX discontinuation); one case due to a concomitant diagnosis of ITP (immune thrombocytopenia) with a history of chronic low grade thrombocytopenia, one case which normalised by day 43 and two cases with multiple organ failure leading to death.

Table 4. Summary of Adverse Events for Patients Receiving Caplacizumab

Episodes	Number of episodes†	Episodes with caplacizumab interruption	Major bleeding≠
	Bleeding		
Gum bleeding	6	1*	1
Epistaxis	1	0	0
Bruising	1	0	0
Haemarthrosis	1	1	1
Lower gastrointestinal bleeding	3	0	0
Upper gastrointestinal bleeding	2§	1	1
Intracranial bleeding	2‖	2	2
Traumatic	1	1☤	0
Total	17	6	5
	Non-bleeding		
Venous thromboembolism	5**	4µ	-
Injection site reaction/allergy	4	1	-
Skin rash	3	3‡	-
LFT derangements	1	1	-
Neutropenic fever¥	1	1	-
Total	14	10	

Table 4 Legend

† Some patients were reported to have more than one adverse event. There were 17 bleeding episodes in 15 patients and 14 non-bleeding episodes in 11 patients.

≠ Major bleeding was defined as per the International Society on Haemostasis and Thrombosis bleeding scale guideline. Major bleeding in non-surgical patients includes fatal bleeding and/or symptomatic bleeding in a critical area or organ (such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome) and/or bleeding causing a fall in haemoglobin level of 2 g/dL or more, or leading to transfusion of two or more units of whole blood or red cells.

* This case was associated with significant reduction in haemoglobin leading to drug interruption.

§ One case of severe upper gastrointestinal bleeding with subsequent drop in haemoglobin on background of Barrett's oesophagus, OGD showing small ulcer and oesophagitis. One case of minor upper GI bleed.

‖ One case of secondary haemorrhage of cerebral infarct, one case of intracranial haemorrhage following initial ischaemic insult. There were no cases of primary intracerebral haemorrhage whilst on caplacizumab.

𝛾 Post mechanical fall resulting in fractured neck of femur.

**Thrombotic episodes included: Left brachial and right internal jugular thrombosis (n=1), pulmonary embolism (n=4). These five episodes occurred in four patients. Two of these episodes occurred outside of the time the patient was being administered caplacizumab.

µ Caplacizumab was interrupted due to concerns managing bleeding risk on concurrent therapeutic anticoagulation in all cases.

‡ One case had concurrent thrombosis.

¥ Not listed on SmPC as a side effect.

Table 5. Summary of Mortality in Patients Receiving Caplacizumab

Summary of mortality					
Cases	**1**	**2**	**3**	**4**	**5**
Demographics					
Age, years	53	35	81	67	33
Sex	Female	Male	Female	Female	Male
Ethnicity	White/White British	Asian	White/White British	White/White British	White/White British
ADAMTS13 activity on admission, iu/dL	<5·0	0·0	<5·0	0·0	0·0
ADAMTS13 inhibitor on admission, U/mL	>100·0	>94·0	>100·0	37·0	92·0
Intubation during admission	Yes	Yes	Yes	No	Yes
Time from initiation of PEX to 1st dose caplacizumab, days	21	3	19	2	8
Total duration PEX, days	22	9	31	5	12
Total duration caplacizumab, days†	1	2	13	22	36
Outcomes					
Time to platelet count normalisation, days	18	N/A‡	N/A‡	7	9
Recovery of ADAMTS13 activity to >10% prior to death	No	No	Yes	No	No
Time from admission to death, days	22	10	36	29	15

Bleeding complications	No	Yes⁋	No	No	No
Cause of death**	Severe, progressive TTP	Refractory TTP	Concurrent mixed connective tissue disease and refractory TTP	TTP plus multiple co-morbidities, palliative management	Bowel ischaemia secondary to refractory TTP

Table 5 Legend

† The duration of caplacizumab was calculated from initiation and until death or discontinuation prior to death.

‡ Platelet count did not normalise prior to death

⁋ Case 2 suffered extensive cerebral infarct 24 hours after admission. Four days later the patient became drowsy with CT brain imaging showing subarachnoid haemorrhage leading to interruption of caplacizumab. Three days later there was further deterioration of GCS requiring intubation and repeat imaging. This showed multiple cerebral infarcts, deemed likely due to progressive TTP.

** Cause of death for each case was determined based on information provided by the Haematology clinician submitting data

Table 6. Characteristics and Outcomes for Paediatric* Patients Treated with Caplacizumab.

Cases	**1**	**2**	**3**	**4**
Demographics				
Age, years	12	17	3	13
Sex	Female	Female	Male	Male
Ethnicity	Black/Afro Caribbean	White/White British	Mixed	White/White British
ADAMTS13 inhibitor on admission, U/mL	11·0	30·0	56·0	>80·0
Platelet count on admission, x10^9/L	53	21	9	9
Troponin elevation on admission	No	No	Yes	No
Creatinine elevation on admission	No	No	Yes	No
Neurological symptoms on admission	No	Yes⁋	Yes⁋	No
Intubation during admission	No	No	Yes‡	No
Concurrent treatment	steroid, rituximab	steroid, rituximab	steroid, rituximab	steroid, rituximab, MMF
Time from initiation of PEX to 1st dose caplacizumab, days	0	8	1	7
Total duration of PEX, days	3	4	16	8
Total duration of caplacizumab, days	24	36	27	61
ADAMTS13 activity at discontinuation of caplacizumab, iu/dL	82·1	23·9	49·9	8·0
Outcomes				
Time to platelet count	3	4	25	3

normalisation, days				
Recurrence of TTP	No	No	No	No
Recovery of creatinine	N/A	N/A	Yes	N/A
Resolution of neurological symptoms	N/A	No**	Yes	N/A
Length of stay, days	10	14	28	13
Bleeding complications	No	No	No†	No
Outcome	Survived	Survived	Survived	Survived

Table 6 Legend

* The paediatric TTP cohort was defined as patients less than 18 years of age at the time of receiving the 1st dose of caplacizumab.

⁋ Neurological symptoms – Case 2: headaches, forgetfulness, limb weakness, paraesthesia; Case 3: agitation, encephalopathy.

‡ The indication for intubation was agitation and encephalopathy.

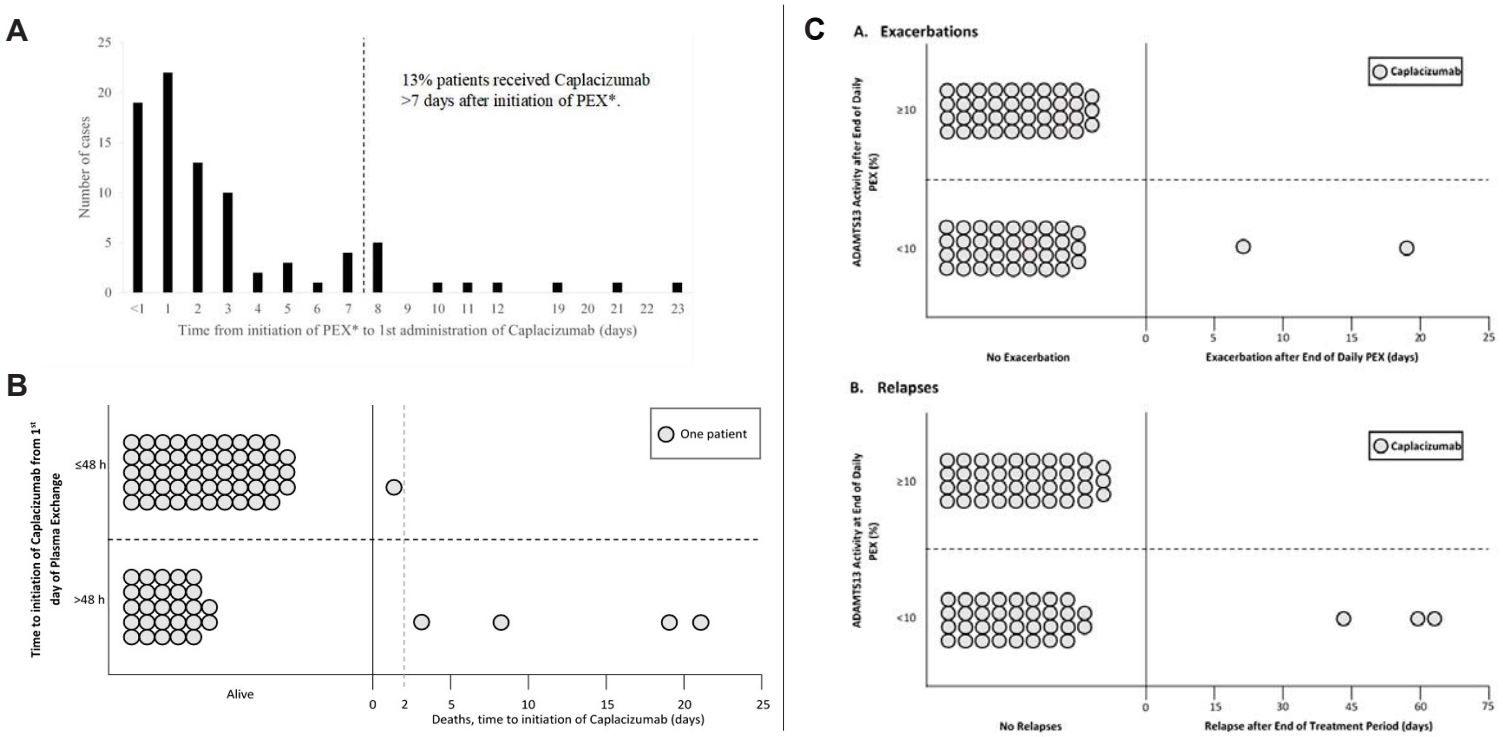
** Case 2 was reported to have residual anxiety and depression.

† Case 3 had caplacizumab interrupted as a precaution for 24 hours due to concerns of bleeding risk with removal of Vascath line. No bleeding occurred.

Figure Legends

Figure 1. (A) Time taken from initiation of plasma exchange therapy to the 1st dose of caplacizumab administered (days). <1 day refers to 1st administration of caplacizumab <24 hours following initiation of plasma exchange therapy. *PEX denotes plasma exchange therapy. **(B) Mortality according to caplacizumab initiation, ≤ 48 hours compared to > 48 hours**. Eighty percent of those who died had caplacizumab initiated more than 48 hours post-1st treatment with plasma exchange (PEX). **(C) Recurrence status according to the ADAMTS13 activity at completion of plasma exchange.** Panel A shows individual patient data on exacerbation status. ADAMST13 activity after end of daily PEX was available for 76 patients. Of these 37 (48·7%) had ADAMST13 activity of <10·0% (range <1·0-5.2%), where 2 patients exacerbated. The other 39 patients (51·3%) had ADAMST13 ≥10·0% (range 10.2-107.2%), without any exacerbations. Panel B shows individual patient data on relapse status. No patient with ADAMST13 activity ≥10·0% relapsed, while three patients of the 37 with ADAMST13 activity of <10·0% relapsed. Recurrences are termed exacerbations if they occur within 30 days of last plasma exchange (PEX) and relapses if they occur more than 30 days after last PEX.

Figure 1



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