Alternate-day dosing of caplacizumab for immune-mediated thrombotic thrombocytopenic purpura

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Abstract

Background: The anti-von Willebrand factor (VWF) nanobody caplacizumab directly prevents the fatal microthrombi formation in immune-mediated thrombotic thrombocytopenic purpura (iTTP), thereby adding a new therapeutic principle to the treatment of this disorder. However, real-world treatment modalities beyond clinical trials remain heterogeneous.

Methods: Here, we describe the risks and benefits of an alternate-day dosing regimen for caplacizumab by thoroughly analyzing the timing and outcome of this approach in a retrospective cohort of 25 iTTP patients treated with caplacizumab at seven different medical centers in Austria and Germany between 2018 and 2021.

Results: Alternate-day dosing of caplacizumab appeared feasible and led to persisting normal platelet counts in most patients. Five patients experienced iTTP exacerbations or relapses that led to the resumption of daily caplacizumab application. VWF activity
Immune-mediated thrombotic thrombocytopenic purpura (iTTP) is a rare but life-threatening autoimmune disease caused by autoantibodies against the von Willebrand-factor (VWF) cleaving metalloprotease ADAMTS13. Microthrombi formation triggered by the accumulation of uncleaved, ultralarge VWF multimers is the pathophysiological hallmark of iTTP, leading to subsequent organ ischemia. This microthrombi formation can directly be prevented by the anti-VWF nanobody caplacizumab, which inhibits the interaction between the A1 domain of VWF and the glycoprotein 1b-IX-V-receptor on platelets. Caplacizumab has found its way into the current standard of care and is added to therapeutic plasma exchange (PEX), steroids, and rituximab. Current labeling of caplacizumab follows the HERCULES study protocol and allows the extension of daily administration to a total of 58 days after cessation of PEX, in case of risk factors for recurrent iTTP (e.g., a persistent ADAMTS13 activity <10%). Recent real-world data demonstrated the therapeutic efficacy of caplacizumab, confirming a rapid normalization of the platelet count and a reduced need for PEX in selected cases, caplacizumab even allows a PEX-free management of iTTP.

Of note, in our Austrian-German cohort, we documented heterogeneous treatment modalities that occasionally deviated from the HERCULES study protocol, including the prolongation of caplacizumab treatment intervals. The published pharmacodynamic parameters of caplacizumab allow the extension of treatment intervals from daily to alternate-day dosing. Measurements of VWF antigen concentration and platelet binding capacity of VWF with ristocetin-induced platelet aggregation and ristocetin-cofactor assays in healthy volunteers and iTTP patients indicated a robust, caplacizumab-induced decrease in antigen levels and platelet-binding capacity that took up to seven days to be reversed after final dose administration.

Our study group reported the first use of an alternate-day dosing scheme for caplacizumab in selected iTTP patients. This modification of established protocols not only offers a cost-saving strategy limiting the economic burden associated with this novel drug but also most notably holds the potential for a more individualized therapy of iTTP patients. An alternate-day treatment regimen seems particularly beneficial for patients with a prolonged suppression of ADAMTS13 activity, multiple prior relapses, or those experiencing side effects. However, recommendations for the exact timing and duration of this treatment regimen are still missing, and data on potential complications and pitfalls have not been published so far. This article focuses on the risks and benefits of alternate-day caplacizumab therapy by analyzing the timing and outcome of this treatment approach in a retrospective cohort of 25 iTTP patients treated with caplacizumab.

This study was conducted as a retrospective observational study. Patients were identified from a real-world cohort of iTTP patients who received caplacizumab at seven different medical centers in Austria and Germany during the years 2018 to 2021. In total, 25 patients were identified who had periods in which caplacizumab was not given daily but every other day or every third day. A successful use of nondaily caplacizumab therapy (alternate-day or
>2 day dosing intervals) was defined as persisting normal platelet counts during nondaily treatment and the respective follow-up period. Exacerbations and relapses were defined as previously described.16,17 Time to normalization of platelet count was defined as time from initiation of caplacizumab treatment until the first day with a platelet count ≥150 \( \times 10^9/L \). ADAMTS13 activity and anti-ADAMTS13 antibodies were measured with different methods, as locally available (e.g., chromogenic ELISA techniques, FRET5-VWF73 assay, anti-ADAMTS13-IgG antibody ELISA, modified Bethesda assay). Measurements of VWF activity were performed with the INNOVANCE-VWF-AC reagent (Siemens Healthcare Diagnostics, Erlangen, Germany) on the BCS XP analyzing platform (Siemens Healthcare Diagnostics, Erlangen, Germany). Local standard methods were used to measure blood cell counts and serum chemistry. GraphPad Prism v8.0 was used for statistical analysis and compilation of graphs (GraphPad Software, San Diego, CA, USA).

### RESULTS

Key aspects of individual disease courses and treatment modalities are summarized in Figure 1. In addition, detailed clinical courses of all individual patients and treatment modalities, including platelet counts, lactate dehydrogenase (LDH) levels and ADAMTS13 activities are shown in Figure S1. Because there was no uniform algorithm for iTTP management and data were assessed retrospectively, this group of patients is heterogeneous. Decision on interval prolongation of caplacizumab application to every other day was made by the responsible physicians.

Baseline clinical features and relevant laboratory parameters at initial presentation are depicted in Table 1. Twenty-one patients were female and four were male, with a median age at diagnosis of 42 years (range 19–73 years) and a median body mass index of 28 kg/m\(^2\) (range 16–43 kg/m\(^2\)). A primary manifestation of iTTP was diagnosed in 17 patients whereas eight patients had a disease relapse. All patients presented with an initial ADAMTS13 activity <10% and median initial platelet count was 10 \( \times 10^9/L \) (range 4–112 \( \times 10^9/L \)). Fourteen of the reported 25 patients experienced a severe episode, based on organ damage markers and initial clinical presentation.

All patients were initially treated according to labeling with daily caplacizumab injections and additionally received rituximab and steroids. Four patients in this cohort (#9, #14, #15, #19) were treated without PEX, as reported before.9 A rapid rise in platelet count after initiation of caplacizumab therapy was observed in all patients with a median time to platelet count normalization (≥150 \( \times 10^9/L \)) of 3 days (range 2–7). LDH levels improved in parallel to platelet counts. Clinical and laboratory features at the time alternate-day dosing was initiated are summarized in Table 2. Median time of daily, post-PEX caplacizumab treatment until introduction of alternate-day dosing in this cohort was 11 days (range 1–230). Treatment with caplacizumab—daily and alternate-day dosing—generally followed an ADAMTS13 activity-guided approach.6 Median time to ADAMTS13 activity normalization was 43 days post-PEX (range 10–251). All 25 patients in this cohort received rituximab. Median time to first rituximab infusion after diagnosis was 4 days (range 1–53). Twelve of the 25 patients in this cohort received a frontline treatment with rituximab within 72 h after diagnosis. However, frontline rituximab therapy did apparently not lead to a faster recovery of ADAMTS13 activity compared with patients with a delayed first rituximab infusion. Median time to ADAMTS13 activity normalization was 41 days post-PEX (range 10–251) in patients with frontline rituximab and 43 days post-PEX (range 10–175) in patients with a delayed rituximab treatment, which was not significant in Wilcoxon rank-sum test (p = .5678).

Twenty patients on an alternate-day caplacizumab regimen showed persisting stable platelet counts without any signs of iTTP exacerbation or relapse (#1–#20). In nine of these 20 cases (#2, #5, #6 #8, #10, #11, #14, #18, #19), alternate-day therapy was implemented late in the disease course (after ≥30 days of daily post-PEX caplacizumab). In retrospect, all 9 of these patients had a prolonged time to recovery of ADAMTS13 activity (≥35 days post-PEX). The remaining 11 of these 20 patients were switched from daily to alternate-day dosing early in the disease course (within 17 days post-PEX). In 10 of the 11 cases (#1, #3, #4, #7, #9, #12, #13, #15–#17, #20), ADAMTS13 activity rapidly recovered to >10% within ≤25 days. Except for two patients (#6, #7), ADAMTS13 activity was <10% at the time of caplacizumab treatment interval prolongation.

Five of 25 patients in this cohort (#21–#25) experienced an iTTP exacerbation or relapse in association with alternate-day dosing, with platelet count decreasing to <150 \( \times 10^9/L \) (Figure 1, #21–#25 and Figure 2A–E). We observed three exacerbations (#21, #22, #25) that occurred after an initial clinical response within 30 days after cessation of PEX, and two relapses (#23, #24), that occurred after a clinical remission.17

One patient with an exacerbation (#21) was switched to an alternate-day regimen after only 2 days on daily caplacizumab post-PEX because platelet counts had already normalized (Figure 2A). However, after 8 days on alternate-day caplacizumab, a single missed dose led to a caplacizumab-free interval of 4 days, with platelet count decreasing to 17 \( \times 10^9/L \) and a concomitant rise in LDH level to 364 U/L. After resumption of alternate-day therapy, respective parameters rapidly normalized and were stable during 20 more days on alternate day caplacizumab. A similar exacerbation was observed in another patient (#22), with platelet count dropping to 49 \( \times 10^9/L \) 9 days after early termination of alternate-day dosing when ADAMTS13 activity was still <10% (Figure 2B). Daily caplacizumab was resumed, leading to normal platelet counts, and a second period (of 53 days) with alternate-day dosing resulted in sustained platelet counts ≥150 \( \times 10^9/L \). In a third patient with an exacerbation (#25), caplacizumab treatment was modified to alternate-day dosing after 5 consecutive days of daily application post-PEX when platelet count was stable at 413 \( \times 10^9/L \) (Figure 2C). In the following 5-day interval of alternate-day application, platelet count decreased to 38 \( \times 10^9/L \) with a mild rise in LDH levels. Daily caplacizumab application was immediately resumed, led to a normalization of platelet count within 5 days and was continued for 44 days. In retrospect,
time to recovery of ADAMTS13 activity to >10% in this patient was 60 days post-PEX.

Two patients experienced an iTTP relapse while on alternate-day caplacizumab (#23, #24). In one patient (#23), alternate-day dosing was introduced after 19 days of daily post-PEX caplacizumab (Figure 2D). In the following interval, platelet counts constantly decreased to $64 \times 10^9$/L after 14 days of alternate-day therapy, with a concomitant mild rise in LDH levels. Consequently, treating physicians resumed daily caplacizumab therapy, which again led to a sustained platelet count $\geq 150 \times 10^9$/L. A second attempt with alternate-day and later every-third-day caplacizumab dosing in the same patient was successful in remaining stable platelet counts. Interestingly, we identified another case (#24) with a similar disease course (Figure 2E). In this patient, alternate-day caplacizumab treatment was introduced after 11 days of daily post-PEX treatment. As in the previous case, platelet counts continuously decreased to a minimum of $44 \times 10^9$/L, again with a concomitant increase in LDH levels (to 540 U/L). Caplacizumab treatment was intensified to daily injections, which led to a rapid normalization of respective parameters. After 7 days of daily injections, caplacizumab treatment was again reduced to every other day and ultimately terminated after a second period with 25 days on alternate-day dosing. Of note, there were no
signs of inflammation in both patients with normal C-reactive protein and fibrinogen levels and no apparent trigger factors.

In all five patients, recurrence of laboratory features of thrombotic microangiopathy was at most accompanied by mild clinical symptoms only, and all instances were managed without hospital readmission, except for one exacerbation that occurred still during hospital treatment (#25). Of note, all five instances were managed solely by resumption or intensification of caplacizumab treatment (to daily dosing) and without resumption of PEX (Figure 2A-E). Four of these five patients were later again successfully treated with alternate-day dosing. In retrospect, we noted a prolonged time to recovery of ADAMTS13 activity (median 61 days post-PEX, range 24–119 days post-PEX) in these patients. Figure 3 illustrates the duration of daily caplacizumab treatment post-PEX until treatment was modified to alternate-day dosing in relation to time to ADAMTS13 activity normalization, distinguishing between patients with stable platelet counts and those with an exacerbation or relapse.

VWF activity, as a potential parameter to monitor efficacy of (alternate-day) caplacizumab therapy, was measured in 16 of 25 patients and showed sufficient suppression after 24 h (median 4%, range 2%–22%, lower limit of normal 50%), with a slight increase but still sufficient suppression after 48 h (median 7%, range 4%–77%), as illustrated in Figure 4. Five outlier patients with stable platelet counts showed an apparent increase in mean VWF activity after 48 h to levels between 26% and 38% VWF activity, respectively (Figure 4). At least in one case, this increase could be attributed to a single unsuccessful injection with an incomplete

### TABLE 1 Initial clinical features and laboratory parameters of iTTP patients with periods of nondaily caplacizumab treatment

| Parameter                                      | Median (Range) |
|------------------------------------------------|----------------|
| Age, y                                         | 42 (19–73)     |
| Female sex (n/total)                           | 21/25          |
| BMI, kg/m²                                      | 28 (16–43)     |
| First manifestation of iTTP (n/total)          | 17/25          |
| Initial platelet count, $\times 10^9$/L         | 10 (4–112)     |
| Initial LDH level, U/L                         | 994 (246–3077) |
| Initial hemoglobin, g/dL                       | 8.9 (6.8–15.1) |
| Initial creatinine, mg/dL                       | 1.08 (0.72–4.50) |
| Initial troponin >ULN (n/total)                | 11/25          |
| Glasgow Coma Scale (n/total)                   |                |
| 15                                             | 18/25          |
| <15                                            | 3/25           |
| Data missing                                   | 4/25           |
| ADAMTS13 activity <10% (n/total)               | 25/25          |
| ADAMTS13 antibody, U/L                         | 60.3 (15–99)   |

Abbreviations: BMI, body mass index; iTTP, immune-mediated thrombotic thrombocytopenic purpura; LDH, lactate dehydrogenase; ULN, upper limit of normal

### TABLE 2 Clinical and laboratory features at time alternate-day dosing of caplacizumab was introduced and follow-up data in patients with stable platelet counts during alternate-day dosing and patients with an iTTP exacerbation or relapse

| Parameter                                      | Stable platelet count (n = 20) | iTTP exacerbation or relapse (n = 5) |
|------------------------------------------------|-------------------------------|-------------------------------------|
| Days of PEX treatment                          | 3 (0–25)                      | 4 (2–9)                             |
| Days on steroid treatment                      | 18 (1–88)                     | 10 (2–26)                           |
| No of RTX infusions                            | 2 (0–4)                       | 2 (0–3)                             |
| Frontline RTX (within 72 h), n/total           | 12/20                         | 0/5                                 |
| Days from diagnosis to first RTX infusion      | 3 (1–53)                      | 6 (4–11)                            |
| Days since last RTX infusion                   | 9.5 (1–160)                   | 1 (1–7)                             |
| Days on daily caplacizumab post-PEX            | 17 (1–230)                    | 5 (1–19)                            |
| Time to platelet count normalization           | 3 (2–7)                       | 3 (2–4)                             |
| Days since platelet count normalization to alternate-day dosing | 15 (0–84)           | 4 (1–19)                            |
| ADAMTS13 activity <10%, n/total                | 18/20                         | 5/5                                 |
| ADAMTS13 Inhibitor, IU/mL                      | 28 (0–99)                     | 99 (68–99)                          |
| Platelet count, $\times 10^9$/L                | 292 (129–575)                 | 328 (103–413)                       |
| LDH level, U/L                                 | 228 (186–444)                 | 289 (239–323)                       |
| VWF activity trough level, 48 h postinjection (%) | 7 (4–77), n = 12              | 6.7 (4–18), n = 4                   |

Follow-up data

| Parameter                                      | Median (range) |
|------------------------------------------------|----------------|
| Days until recovery of ADAMTS13 activity >10% post-PEX | 35 (10–251) | 61 (24–119) |
| Total days on alternate-day dosing             | 16 (4–120) | 43 (4–56) |
| Total days on caplacizumab                     | 45 (8–251) | 62 (34–109) |
| Recovery of ADAMTS13 activity to >10% at time of caplacizumab treatment termination, n/total | 15/20 | 3/5 |

Note: Median (range).

Abbreviations: iTTP, immune-mediated thrombotic thrombocytopenic purpura; PEX, plasma exchange; RTX, rituximab.
FIGURE 2 iTTP patients with exacerbations (A, B, C) and relapses (D, E) during treatment with an alternate-day dosing regimen of caplacizumab. For simplicity, specific doses of RTX or PEX are not indicated. Gray areas represent duration of caplacizumab, with either daily application (q1), alternate-day dosing (q2), or application every third day (q3). All patients were treated with steroids (not shown here). Horizontal dashed lines indicate ADAMTS13 activity of 10%. Platelet counts are indicated by the blue line, ADAMTS13 activity is depicted in red circles with connecting line. LDH levels are indicated by the green line. CAP, caplacizumab; iTTP, immune-mediated thrombotic thrombocytopenic purpura; LDH, lactate dehydrogenase; PEX, days of plasma exchange treatment; RTX, rituximab treatment.
The higher VWF activity values after 48 h did not significantly correlate with age, sex, or body mass index. Of note, VWF activity after 24 and 48 h was measured in four patients with exacerbations or relapses but did not show any signs of impaired pharmacodynamics.

Because there was no uniform algorithm for iTTP management in this cohort, decision on frequency of laboratory testing was made by the treating physicians. Median number of analyses during alternate-day dosing was 1.5 per week (range 0.5–7 analyses per week) with a clear tendency toward more frequent monitoring in the early phase of alternate-day dosing (usually twice per week) followed by a slight reduction to usually once per week. In retrospect, the 25 patients in this cohort were treated with an alternate-day dosing regimen of caplacizumab for a total of 718 days, including 62 days of caplacizumab application only every third day. This corresponds to a total of 349 applied caplacizumab doses during this treatment period in contrast to 718 hypothetical doses of daily caplacizumab treatment. Based on the current market price (September 2021) for a single caplacizumab dose of 4396 € (7724 USD), this treatment modification led to cost savings of 1 622 124 € (2 850 156 USD) in this cohort. Median cost savings per patient was 43 960 € (77 240 USD) with a range of 8792 to 263 760 € (15 448–463 440 USD).

**4 | DISCUSSION**

Here, we analyze the clinical courses and treatment modalities of 25 iTTP patients treated with an alternate-day caplacizumab regimen in Austria and Germany between 2018 and 2021. The successful treatment modification in the majority of patients demonstrates the clinical feasibility of this treatment approach as the next step toward a more individualized treatment of iTTP patients.

In retrospect, successful alternate-day dosing of caplacizumab appears to depend on the timing of the treatment modification. A late conversion after ≥30 days post-PEX generally appeared safe in this cohort whereas stable platelet counts after an earlier modification were in retrospect mostly observed in cases with rapidly recovering ADAMTS13 activities (recovery shortly after treatment modification). Exacerbations or relapses in association with alternate-day dosing occurred solely in patients with a delayed recovery of ADAMTS13 activity (≥24 days post-PEX) and in whom alternate-day dosing was introduced or terminated early (≤19 days of daily caplacizumab post-PEX until treatment modification).

iTTP exacerbations were observed in three patients on alternate-day treatment, and—at least in two cases—could be attributed to a single missed dose or early termination of caplacizumab, respectively. In our view, these two exacerbations resemble cases in which daily caplacizumab treatment was terminated before recovery of ADAMTS13 activity, as previously published, and could have been prevented by continuous daily or probably even nondaily caplacizumab treatment. Nevertheless, these two cases demonstrate that patients need to be well-informed and highly compliant to reduce the risk of exacerbations because of missed doses while being on an alternate-day regimen.

A third exacerbation was observed after early treatment modification, with no apparent cause other than a potentially insufficient suppression of microthrombi formation by nondaily treatment in this early disease stage. Because the patient was still hospitalized when
the exacerbation occurred, a missed dose seems rather unlikely. In addition, there were no apparent trigger factors.

Two relapses occurred, with constant decreases in platelet count. Whether these relapses represent a serious disease activity that cannot be successfully inhibited by nondaily treatment remains a matter of speculation. The prompt and robust platelet response to reintensification of caplacizumab treatment to daily dosing in these patients argues in favor of this hypothesis. Taken together, these cases document a small, but notable risk of iTTP exacerbation or relapse in association with alternate-day dosing, especially after early treatment modification. All exacerbations and relapses could be managed solely by resumption or re-intensification of caplacizumab therapy.

Repeated measurements of VWF activity again confirm the published pharmacodynamic parameters of caplacizumab. On alternate-day dosing, regular determination of trough levels may
help to demonstrate successful suppression of VWF activity as part of a therapeutic drug monitoring. However, measurement of VWF activity did not help to identify patients at risk for exacerbations or relapses in association with an alternate-day dosing regimen. In the two relapsing patients, sufficient suppression of VWF activity was even documented on the day physicians noted the critical decrease in platelet count and decided to resume daily caplacizumab treatment. As a consequence, close monitoring of platelet counts and LDH levels is required on alternate-day dosing, and dynamics of VWF activity should have a limited influence on clinical decision making.

Based on these results, we have developed a guide for modification of caplacizumab treatment to an alternate-day dosing regimen (Figure 5). Treatment modifications should be made after thorough discussions with the patient. A later conversion to alternate-day therapy is preferred to avoid possible early exacerbations or relapses, especially in high-risk patients with persisting iTTP trigger factors. Introduction of alternate-day dosing may safely considered after 3 to 4 weeks of daily treatment, if ADAMTS13 activity remains <10%. In case of high-risk patients, (e.g., with persisting trigger factors or multiple prior relapses), daily caplacizumab therapy may be extended to 58 days or even beyond, and a conversion to alternate-day dosing may be postponed accordingly. Earlier treatment modifications may be safely considered in low-risk patients but require close monitoring of clinical and laboratory features for thrombotic microangiopathy, and patients should be highly compliant because missed doses may increase the risk for exacerbations or relapses.

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AUTHOR CONTRIBUTIONS
Lucas Kühne, Jessica Kaufeld, Linus A. Völker, Paul T. Brinkkoetter, and Paul Knöbl drafted the manuscript, calculated statistics, and prepared the figures. All authors were involved in patient management. All authors were involved in data collection and proofreading. The manuscript has been read and approved for submission to JTH by all authors.

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**SUPPORTING INFORMATION**

Additional supporting information may be found in the online version of the article at the publisher’s website.

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