Answering T.T.P.
Thrombotic Thrombocytopenic Purpura Foundation

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Dear TTP Treating Physician and Apheresis Nurses,

On behalf of Canadians diagnosed with acquired thrombotic thrombocytopenic purpura (aTTP), Answering TTP Foundation is writing to provide you an update with regard to our activities surrounding access to caplacizumab. First off, I'd like to confirm that Answering TTP Foundation is not influenced by Sanofi in any way. The only funds received from Sanofi include a sponsorship of $5,965 toward the 2019 annual fundraiser almost two years ago.

The purpose of this letter is to share some patient experiences with caplacizumab, to keep you informed of the activities and resources the Foundation has developed to support patients, and to gather information from you with regard to your experience with caplacizumab. **Please reply to contact@answeringttp.org with your thoughts, and advise if you've had experience treating patients with caplacizumab.** We look forward to your insights, as we move forward together on this important issue affecting TTP patients across the country.

In January 2021, Lorraine Wigston suffered a second relapse of TTP after contracting COVID-19 from her dying father who had tested negative days before. Despite receiving standard TTP treatment, Lorraine's case seriously worsened and she became very scared that maybe she would not dodge the bullet this time. Caplacizumab was added to her treatment regime and she was released from hospital two weeks later, requiring half the time in hospital as her first two TTP episodes. Lorraine is grateful to have been provided the opportunity to receive caplacizumab.

Answering TTP Foundation was devastated to learn that both CADTH and INESSS recommended that caplacizumab not be reimbursed for the treatment of adults with TTP. In response we have,

1. Written both CADTH evaluation bodies to express our disappointment and to identify gaps in their evaluation.
2. Written provincial Health Ministers.
3. Hosted a virtual educational Canadian TTP community meeting to outline the impact of not having access to caplacizumab in Canada.
4. Started a grassroots letter writing campaign engaging the TTP community and their network to use online templates to simplify writing their provincial Health Minister and MP.

Selena, a 19 year-old, had been in hospital for almost two weeks, and had suffered multiple strokes. Her case was grave. Then, she was given caplacizumab. Overnight she stabilized.

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Answering TTP Foundation is doing its part to empower the community. We understand that caplacizumab is our only immediate defence, and it works. Once administered, caplacizumab is proven to buy patients time by acting against these potentially life altering clots before they cause further damage. Caplacizumab can save these patients. Caplacizlumab shields patients from dangerous clots, to give these patients the time needed for standard therapies to work. Caplacizumab saves lives and prevents disability.

Answering TTP Foundation's Messaging. In the short-term, we hope to gain access to caplacizumab for refractory crisis, but in the future we hope that caplacizumab will be considered for all aTTP crises. Moreover, in the midst of a global pandemic when our healthcare system is stretched, the use of caplacizumab in the treatment of aTTP can alleviate some pressure by getting aTTP patients out of intensive care units, and out of the hospital much faster.

As TTP Treaters, you know that plasma exchange and immunosuppression therapy are the current standard treatment for aTTP, but this is not a targeted therapy, and is not without serious side-effects that are well documented. Most patients with aTTP require ICU admission, and nearly half of all Canadian respondents to our patient survey said that they spent more than three weeks, and up to 12+ weeks in hospital. Those are the patients who were lucky enough to survive.

Caplacizumab is the first new treatment developed for aTTP in the last 25 years. Peer nations have recognized its evidence-based utility by updating their international treatment guidelines to include the use of caplacizumab. For a country that pioneered TTP treatment by establishing the effectiveness of plasmapheresis,[1] Canada's unwillingness to adopt caplacizumab is causing undue suffering and death.

Answering TTP Foundation's Official Response to CADTH (CDEC)'s Published Reasons for the Recommendation

In the CDEC's recommendation report, it states, "*An important outcome identified by patients is a reduction in the risk and rate of experiencing relapses of aTTP. Unfortunately, the design and duration of HERCULES were insufficient to assess the effects of caplacizumab on the rate of relapse beyond the trial's duration.*" While CADTH is correct in its assertion that aTTP patients don't want to suffer a relapse, it is more accurate to focus on the word "risk". **We don't want a relapse to disable or kill us.** Patients need access to

Yhulan, a child and youth worker in Toronto, was rushed by ambulance to hospital with her 3rd TTP relapse in critical condition. She was intubated for a week in the ICU. Only after caplacizumab was added to her treatment regiment did her case turn around.

[1] Rock GA et al. Comparison of plasma exchange with plasma infusion in the treatment of thrombotic thrombocytopenic purpura. Canadian Apheresis Study Group. N Engl J Med. 1991 Aug 8;325(6):393-7.

caplacizumab because it is the first targeted treatment that addresses the formation of blood clots that are the cause of organ damage, and thus prevents many of the long-term disabilities and death associated with aTTP.

The CDEC report also states that it is not possible to determine the benefit of caplacizumab beyond the duration of the trials. Respectfully, this should not be a barrier to approval because caplacizumab is the only immediate defence available to prevent serious thromboembolic events. Caplacizumab protects patients while standard therapies are given the time required to take effect.

Moreover, organ damage from clots – especially brain damage – is cumulative. If for each relapse caplacizumab reduces the immediate damage, the cumulative beneficial effect of the drug compounds with each cycle of relapse. Caplacizumab is able to reduce the severe impacts of a relapse on organ damage, and we ask that CADTH consider the significant long-term benefit of reducing organ damage at each recurrence.

Additional Evidence

Two large real-world studies published since the original submission to CADTH confirm the utility of caplacizumab in improving response rate, time to platelet recovery, and reducing organ damage.[2,3] Caplacizumab has also shown to be efficacious in patients with aTTP who had a disease recurrence during double-blind treatment in the HERCULES trial and were switched to open label caplacizumab.[4] A retrospective study in 29 medical centres in Germany further confirmed the effectiveness of caplacizumab during acute disease management.[5]

CADTH's Drug Expert Committee report states that it is unclear if the effects of caplacizumab would be observed in Canadian practice due to the high percentage of patients who received rituximab in the HERCULES study. Further analysis of the HERCULES study data has been published that shows that treatment with caplacizumab improved outcomes in patients with aTTP, irrespective of the type of initial immunosuppressive therapy (i.e. with or without rituximab).[6]

These studies all support the use of caplacizumab in practice across a variety of real-world clinical settings and patient scenarios.

[2] Coppo P et al. A regimen with caplacizumab, immunosuppression and plasma exchange prevents unfavorable outcomes in immune-mediated TTP. Blood. 2020 Nov 4.
[3] Dutt T et al. Real-world evidence of caplacizumab use in the management of acute TTP. Blood. 2020 Nov 4.
[4] Knoebl P et al. Efficacy and safety of open-label caplacizumab in patients with exacerbations of acquired thrombotic thrombocytopenic purpura in the HERCULES study. Thromb Haemost. 2020;18:2,479-484.
[5] Völker LA et al. Real-world data confirm the effectiveness of caplacizumab in acquired thrombotic thrombocytopenic purpura. Blood Adv. 2020;4(13):3085-3092.

[6] Pavenski K et al. Efficacy of Caplacizumab in patients with aTTP in the HERCULES study according to initial immunosuppression regimen. Blood. 2019;134 (Supplement 1):2365.

Alignment with International Recommendations and Standards of Care

It is important to highlight that CADTH's recommendation differs from that of many of our peer nations. To date, caplacizumab has been approved for reimbursement for patients with aTTP in the United States, Austria, Belgium, Denmark, Netherlands, Finland, Italy, and the UK.

In their Technology Appraisal Guidance recommending caplacizumab with plasma exchange and immunosuppression, the National Institute for Health and Care Excellence (NICE) concluded that:

> "Standard care for an acute episode of acquired TTP includes plasma exchange and immunosuppressant medicines. Trial results show that, compared with standard care alone, caplacizumab plus standard care reduces:
>
> - the time it takes to bring platelet levels back to normal
> - the number of plasma exchange treatments needed
> - time in hospital and intensive care" [7]

Recent treatment guidelines published by the International Society on Thrombosis and Haemostasis, and by the multinational Nine-I Network recommend the use of caplacizumab in patients with aTTP.[8,9] Both multidisciplinary guideline panels based their recommendations on systematic reviews of the literature, and considered the quality of the studies, the consistency of the results, and directness of the evidence when making their recommendations.

Specifically, current clinical practice guidelines state:

> **"Caplacizumab must be used as a first-line therapy in severe TTP"** (Strength of recommendation: Strong) -*Expert Statement on the ICU Management of Patients with Thrombotic Thrombocytopenic Purpura.* [9]
>
> **"For patients with iTTP experiencing an acute event (first event or relapse), the panel suggests using caplacizumab over not using caplacizumab"** -*International Society on Thrombosis and Haemostasis Guidelines for Treatment of Thrombotic Thrombocytopenic Purpura.* [10]

CADTH's recommendation against the reimbursement of caplacizumab means that Canadian physicians are not able to provide the recommended evidence-based care for their patients consistent with international treatment guidelines.

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[7] National Institute for Health and Care Excellence (NICE). Caplacizumab with plasma exchange and immunosuppression for treating acute acquired thrombotic thrombocytopenic purpura. Technology appraisal guidance [TA667] 2020 Dec 16. Available from: www.nice.org.uk/guidance/ta667

[8] Azoulay E et al. Expert statement on the ICU management of patients with thrombotic thrombocytopenic purpura. Intensive Care Med 45. 2019, 1518–1539.

[9] Zheng XL et al. International Society on Thrombosis and Haemostasis (ISTH) guidelines for treatment of thrombotic thrombocytopenic purpura. J Thromb Haemost. 2020 Oct;18(10):2496-2502.

Special Considerations: COVID-19

From a larger health-system perspective, it is important to highlight caplacizumab's ability to reduce the time spent in ICUs, and lessen the overall length of hospital stay. With the COVID-19 pandemic, ICU beds are a critically stressed resource and caplacizumab can help reduce aTTP patients' use of limited resources.

Like COVID-19, aTTP patients cannot be re-scheduled, and they require immediate intensive use of hospital resources. In addition, the immune suppression of standard-of-care therapies puts aTTP patients at extremely high risk for catching COVID-19, further underscoring the need to discharge them from the ICU and the hospital as quickly as possible.

In January 2021, 35-year-old Stacy Kertzer's worst nightmare during the COVID-19 pandemic came true. Stacy was admitted to hospital with her second TTP relapse. For 11 days she did not improve despite standard treatment and remained at serious risk of major complications. Then, she says she was given a miracle in the form of caplacizumab. Incredibly, 4 days later she was well enough to be released from hospital.

3 ASKS of You

1. Please reply to contact@answeringttp.org with your perspective on this issue, and concerns with our approach. Please indicate if you have had personal experience treating TTP patient(s) with caplacizumab.
2. Please consider joining patients in writing your Provincial Health Minister and local elected provincial representative (MPP or MLA) to ask them to add caplacizumab to your province's formulary. Visit https://www.answeringttp.org/caplacizumab-letter-campaign to access our letter writing campaign. Share this link with your network to grow the campaign's impact.
3. Reach out to us at any time. We look forward to working with physicians on this issue.

Sincerely,

Sydney Kodatsky MBA, BSc.
Chair, Answering T.T.P. Foundation