Answering T.T.P.
Thrombotic Thrombocytopenic Purpura Foundation

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May 5, 2021

Minister of Health Honourable Lorne Kusugak
Department of Health - Government of Nunavut
Box 1000, Station 1000
Iqualuit NU X0A 0H0

Dear Minister Lorne Kusugak,

On behalf of Canadians diagnosed with acquired thrombotic thrombocytopenic purpura (aTTP), Answering TTP Foundation is writing to ask you to take life-saving action by adding caplacizumab to your provincial formulary, at least for those patients in Nunavut that are not responding to standard therapy, or are otherwise compromised by secondary disease or complications; less than 1 patient per year in your jurisdiction[A]. For these patients caplacizumab is undoubtedly life-saving. We expect that access to this subset of critical patients will further demonstrate the effectiveness of caplacizumab and its value for use in the entire aTTP community. Furthermore, 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.

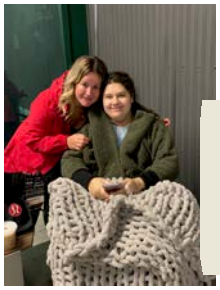
ATTP is an ultra-rare, life-threatening emergency that is rapidly fatal without immediate treatment. Even with prompt intervention, many patients face severe long-term consequences due to organ and brain damage from ongoing clotting because it takes time for standard treatments to take effect. TTP can strike people of all ages, but usually young women. Many of these young women have young families and promising careers. Immediate medical intervention is required. **For up to 20% of aTTP patients, the current therapy is insufficient and they die.**[1]

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 the 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.

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. Existing treatments are designed to control the

[1] 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.

underlying mechanism of disease, but require time to take effect, time that aTTP patients do not have. In aTTP, blood clots rapidly form in small blood vessels throughout the body and block the flow of oxygen-rich blood to the body's organs, including the brain, kidneys and heart. Caplacizumab prevents the formation of clots that cause organ damage, allowing patients to survive long enough for existing treatments to take effect. Caplacizumab saves lives and prevents disability.



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.

Not only does the standard therapy, of plasma exchange and immunosuppression, take time to work, but it is not a targeted therapy, and is not without serious side-effects. Caplacizumab not only acts to shield patients from clots while the standard therapy has time to work, but it has been proven to reduce the number of plasma exchange treatments required to bring a patient into remission. Plasma exchange is an arduous and time-consuming exchange of a patient's entire volume (or more) of blood plasma through an invasive central line that remains fixed for the duration of treatment. 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.

From the NEW ENGLAND JOURNAL OF MEDICINE. January 24, 2019

Among patients with TTP, treatment with caplacizumab was associated with faster normalization of the platelet count; a lower incidence of a composite of TTP related death, recurrence of TTP, or a thromboembolic event during the treatment period; and a lower rate of recurrence of TTP during the trial than placebo.

(Funded by Ablynx; HERCULES ClinicalTrials.gov number, NCT02553317)

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,[2] Canada's unwillingness to adopt caplacizumab is causing undue suffering and death.

Response to 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 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.

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.[3,4] 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.[5]

Yhulan Walters, 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.

[2] 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.
[3] Coppo P et al. A regimen with caplacizumab, immunosuppression and plasma exchange prevents unfavorable outcomes in immune-mediated TTP. Blood. 2020 Nov 4.
[4] Dutt T et al. Real-world evidence of caplacizumab use in the management of acute TTP. Blood. 2020 Nov 4.
[5] 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.

A retrospective study in 29 medical centres in Germany further confirmed the effectiveness of caplacizumab during acute disease management.[6]

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).[7]

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

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" [8]

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.[9,10] Both multidisciplinary guideline panels based their recommendations on systematic reviews of the

[6] Völker LA et al. Real-world data confirm the effectiveness of caplacizumab in acquired thrombotic thrombocytopenic purpura. Blood Adv. 2020;4(13):3085-3092.
[7] 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.
[8] 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
[9] Azoulay E et al. Expert statement on the ICU management of patients with thrombotic thrombocytopenic purpura. Intensive Care Med 45. 2019, 1518–1539.
[10] 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.

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]

Adding caplacizumab to the provincial formulary will mean that Canadian physicians would be able to provide the recommended evidence-based care for their patients consistent with international treatment guidelines.

Special Considerations: COVID-19

We strongly encourage you to immediately grant an emergency recommendation to add caplacizumab to the provincial formulary. 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 and suffering major complications including death. These are high risk patients who need to be discharged 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.

Conclusion

Given the body of clinical evidence showing that caplacizumab successfully addresses an important gap in care until existing therapeutics can take effect, we at Answering TTP respectfully request that you add caplacizumab to the provincial formulary.

Sincerely;

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

CC: Suzanne McGurn – CADTH
Jennifer Berry - Assistant Deputy Minister of Operations

ENDNOTE A: Calculation of refractory aTTP cases by province/territory. See data sources below.

Metric	Value	Source
Population by province	*38,048,738*	*Q1 2021 Statistics Canada. Table 17-10-0009-01 Population estimates, quarterly. DOI: https://doi.org/10.25318/1710000901-eng*
Rate of aTTP per million	*4*	*Estimates 3-4 per million as per Answering TTP website.* per year
Rate of refractory cases	*20%*	*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.*

		aTTP Cases per year	
Region	**Population**	***Total***	***Refractory***
Canada	**38,048,738**	**190**	**38**
Newfoundland and Labrador	520,438	3	**1**
Prince Edward Island	159,819	1	**0**
Nova Scotia	979,449	5	**1**
New Brunswick	782,078	4	**1**
Quebec	8,575,944	43	**9**
Ontario	14,755,211	74	**15**
Manitoba	1,380,935	7	**1**
Saskatchewan	1,178,832	6	**1**
Alberta	4,436,258	22	**4**
British Columbia	5,153,039	26	**5**
Yukon	42,192	0	**0**
Northwest Territories	45,136	0	**0**
Nunavut	39,407	0	**0**