Platelet Disorder Support Association
Empowering ITP Patients

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Dear CADTH/ACMTS,

Thank you for sending this proposed project scope to the Platelet Disorder Support Association (PDSA) for comment. PDSA-Canada is proud to have a voice in this. As you know, we are committed to ensuring our patient population, in Canada and elsewhere in the world, has access to appropriate medical care and we are dedicated to enhancing the lives of people with ITP and other platelet disorders through education, advocacy, research, and support.

We are thrilled that CADTH is taking an interest in looking further into ITP drug access in Canada. Considering the potential for severe health-related consequences and high medical costs for ITP treatment, it is concerning that current clinical guidelines and evidence are not reflected in Canadian drug plans. Especially for rituximab. It is used off label for ITP but there are years' worth of published evidence of its effectiveness among ITP patients yet it is only approved for lymphoma.

Before we address the questions within the project proposal you have asked us to provide feedback on, we would like to recommend that this project include pediatric ITP patients in addition to adult ITP patients. *It is not clear to us why this is only for adults.* Pediatric ITP patients (especially with chronic disease) have even less treatment options available to them and some do require treatment to manage bleeding symptoms and prevent additional bleeding events. When taking into account chronic ITP among children and adolescence, the overall incidence is 0.2-0.7 per 10,000 per year (children) and 0.4-0.5 per 10,000 per year (adolescence) (Matzdorff et al., 2018).

There are a few things to enhance your background and rationale.

1. ITP is not always reported to be more commonly seen in women. In fact, a prestigious European ITP guideline reported in the epidemiology section that globally, ITP in children affects males more than females and that in adults, there are more males over the age of 60 years with ITP than women. Gender really is irrelevant for the purpose of this project (Matzdorff et al., 2018).
2. The updated ASH guidelines https://ashpublications.org/bloodadvances/article/3/23/3829/429213/American-Society-of-Hematology-2019-guidelines-for recommend treatment for children too if ITP persists beyond three months and they have bleeding beyond petechia and bruising.

The 'watch and see' approach for children is for those who do not have extremely low levels with serious bleeding. In fact, in the International Consensus report https://www.pdsa.org/images/InternationalConsensusReport2019.pdfit is reviewed that multiple studies support the use of TPO-RAs in children with persistent-chronic ITP demonstrating a good response in the reduction of bleeding frequency in absence of side effects in the majority of patients.

3. While the American guidelines do not provide recommendations on " azathioprine (Imuran), cyclosporine (Sandimmune), mycophenolate mofetil (MMF) (Cellcept), dapsone, danazol, or vincristine " there are many studies supporting their use as a monotherapy and combination therapy. In fact, at the 2020 virtual ASH meeting, Dr Bradbury (https://ash.confex.com/ash/2020/webprogram/Paper143563.html) presented data from the FLIGHT trial showing the effectiveness using MMF in combination with steroids to treat ITP patients.

4. In addition to the availability of romiplostim (Nplate) and eltrombopag (Revolade) there is now avatrombopag (Doptelet) and fostamatinib (Tavalisse). Tavalisse is a syk inhibitor while the others are TPO-RAs. In clinical trials currently there are a number of therapies that will likely be available for ITP patients within the next few years including BTK inhibitors and another monoclonal antibody treatment, Sutimlimab. Canada needs to position itself to be current, and in line with professional management guidelines for the safety of ITP patients. *Appendix one is a compilation of patient stories we previously submitted to the Ontario provincial government highlighting the need for urgent drug reform policies in Canada.*

5. Professional guidelines are limited for various reasons. ITP is a rare disorder, there are little randomized control trials. ASH (2019) updated guidelines for ITP state:

"Limitations of these guidelines

The limitations of these guidelines are inherent in the low or very low certainty in the evidence identified for many of the questions. The contribution of indirect evidence is specified for each recommendation. For some recommendations, which related to relatively common clinical questions, there was very little or no published direct or relevant indirect evidence, and the guideline panel was surveyed to provide unpublished collective data on which decisions could then be based. However, interpretation of the survey data was limited by recall bias, determination of individual provider practice compared with center-wide practice, and the fact that hematologists are generally consulted only after the decision for admission has been made by another provider. This process is explicitly identified for relevant recommendations. Additionally, these guidelines focus on the clinical and management aspects of ITP and do not address the pathophysiologic aspects of the disease. *These guidelines are also limited by not being inclusive of all possible clinical scenarios.* The panel prioritized questions for which there is clinical uncertainty or where it was felt there might be new information to guide decision-making. Identification of the specific population then informed the literature search. *For these reasons, these guidelines do not address the diagnosis of ITP, management of patients with severe or life-threatening bleeding, ITP in pregnancy, and treatments available after 2017. Some of these clinical scenarios were addressed in the 2011 guidelines and have been carried forward.* Furthermore, the guidelines relied on dichotomous comparisons that may not reflect clinical practice in which >2 treatment options may be considered at a given time."

PART ONE

Our responses to CADTH's policy questions:

1. Which treatment(s) is (are) most appropriate for adults with chronic immune thrombocytopenia after a trial of first line treatments?

Yes, these therapies are appropriate for patients with ITP. We are not familiar with the use of biosimilars, so we cannot comment on that.

As an organization, we have supported many adult ITP patients (and children) around the world who have reported using one or more therapies beyond traditional first-line therapies at any given time, including: rituximab (Rituxan), eltrombopag (Revolade), romiplostim (Nplate), and fostamatinib (Tavalisse – however this is used for ADULT chronic ITP when there is a lack of significant response to other TPO-RA agents). There are therapies that are not on the list that many ITP patients report using in various situations, such as mycophenolate mofetil (MMF) (Cellcept), dapsone, danazol. When to use is often dependent on the patient and their treatment response and disease symptoms. Sometimes they are used in combination with other treatments for a synergistic effect. For instance, using eltrombopag and dapsone or MMF and steroids as examples.

While Table 2 lists the drugs available in Canada relevant to this CADTH project, there are other therapies outlined above that are helpful to ITP patients, and there will likely be new therapies in the next five years. ITP is extremely heterogenous in treatment response and disease course. Thus, no two patients will respond in the same way to a particular drug. Currently, there is no way to predict who will respond to a particular therapy vs who will not. So to force patients to trial drugs in a step-approach manner, some patients may pass away before the most appropriate therapy is tried. The decision for which therapy to try should be made on an individual basis, between a hematologist and the patient (or parent, if the ITP patients is a child). This is also reflected in the updated guidelines.

2. Should splenectomy be required prior to accessing a TPO-RA or rituximab?

NO.

As an organization, we work with ITP experts across the globe. We do not believe that a splenectomy should be forced prior to accessing second-line therapy options. Professional guidelines in North American and Internationally also support this.

In today's time, splenectomy is offered if there is a lack of significant response to second-line therapies, or if the patient selects this method of treatment. Some patients select splenectomy because they cannot afford the cost of second-line therapies since they currently are not covered in Canada, including by many insurance companies. Splenectomy can be a good therapeutic choice for some patients with ITP however the long-term consequences are life-long. There is also a 1% fatality risk and a 10% complication risk immediately following the surgery. A patient should not have to risk their life to access safer therapies, increase their risk for dementia and heart attacks from blood clots, take up a surgeon's time and require a hospital bed for recovering, deal with living without a spleen forever, just to access safer therapies. It just doesn't make sense. Especially since a significant number of ITP patients fail to respond to splenectomy, or relapse a few years following the procedure. For adult patients who have bleeding manifestations beyond petechia and bruising and/or low platelet counts below 30,000, first line therapies only function as a band-aide solution. If a patient responds, even if only for a few days, they cannot access second-line

therapy through the federal or provincial system. Second-line therapies are not just for refractory patients. They are not designed to be used long term. Steroids and other first line therapies have only been used long-term because in past there was a lack of other alternatives. However over the last ten years, that is no longer the case and CADTH should take this opportunity to make ITP drug access better in Canada.

Long term use of first line therapies such as corticosteroids cause long-term health risks and reduce quality of life substantially, and IVIG is extremely expensive and in short supply. With TPO-RAs available, that produce minimal side-effects, it is important to recognize these can be used long term and should be available to patients who meet criteria for their use. *Patients want treatments that won't cause them to go into financial debt, that have minimal side effects, that work long term, reduce their fatigue, and are convenient. Most patients would choose to take a medication over an infusion for many hours (IVIG for instance). And the cost of IVIG is high.*

Current ITP drug coverage in Canada potentially violates the principles of 'accessibility' and 'comprehensiveness' under the Canada Health Act (R.S.C., 1985, c C-6: Section (9), (12) – 2 April 2020. Sections (9) and (12) cover accessibility and comprehensiveness of coverage for services felt 'medically necessary' to maintain health, prevent disease, and diagnosis and treat and injury, illness, or disability. This seems to apply to ITP patients who are forced to deal with toxic side effects that wear off quickly and have to live in fear of bleeding and possibly dying.

PART TWO

In addition to your proposed research questions, consider incorporating these additional elements into the analysis:

- Health related quality of life (HRQoL) – the decision to treat in adults is not only based on bleeding, and platelet counts, but also on quality of life. Work to reduce overall lifetime costs but also improve the QoL by relieving corporal symptoms, and by removing barriers that may exist obtaining employment or education while undergoing extended treatment.
- What offers best potential for remission, as well as disease progression to a chronic form or more severe bleeding risk
- Appreciate that ITP studies have limitations such as reduced sample size (rare disease) and disease course is variable among all ITP patients.
- Overall cost on health care system – need for multiple platelet counts, hospital visits to check platelet counts, rescue treatments, hospitalization for rescue therapy (such as IVIG), adverse event treatment and/or additional medications used to prevent such reactions (combination vs monotherapy)
- Workforce cost and direct costs for patients– need to appreciate not only cost on health care system, but of adults taking time off, losing their job due to frequent appointments and mental/physical symptoms of ITP such as fatigue, cost of therapies (many private companies if they cover a second line therapy will only cover 80% so the patient is responsible for 20% of the cost and over time that can be very expensive and out of reach for many patients). For adolescence who just finish school and do not have a high paying job, they may lose their access to a second line therapy once they are taken off their parents insurance (between age 18-25). Many cannot afford to pay for treatments privately due to high education costs. For many, their second line therapy is preventing a serious bleeding event.

Efficacy and cost-benefit analysis papers: **This is not a comprehensive list at all.** Just a few we wanted to pass along. There is a lack of published studies comparing the benefits of using one therapy over another.

- If you visit our website, https://www.pdsa.org/healthcare-professionals-researchers/hcp-resources.html, you will find helpful information for your analysis on treatments, ITP, and QoL. Particularly on i-WISh publications focusing on ITP and quality of life:
https://ashpublications.org/blood/article/134/Supplement_1/1097/426878/Physicians-and-Patients-Perspectives-on-Treatments
https://ashpublications.org/blood/article/134/Supplement_1/1076/426661/The-Burden-of-Disease-and-IMPACT-of-Immune
https://ashpublications.org/blood/article/132/Supplement%201/4804/262467/Results-from-the-ITP-World-IMPACT-Survey-I-WISh

- "Conclusion: Based on these results, the addition of rituximab (sequences 2–3) results in lower treatment costs and greater efficacy compared to that of standard treatment for ITP in adults. According to the study results, if rituximab is reimbursed for the treatment ITP in Japan, medical expenses will be reduced." https://www.ncbi.nlm.nih.gov/pmc/articles/PMC4307915/
- "Our meta-analysis results indicated that TPO-RAs significantly increased the rates of R or DR and reduced the incidences of any or severe bleeding events in persistent and chronic primary ITP patients compared with control subjects. Moreover, our results indicated that TPO-RAs significantly decreased the need for rescue medications and increased the numbers of patients who were able to reduce or discontinue concurrent ITP therapies. The incidence of AEs in the TPO-RA-treated groups was similar to that in the placebo groups, and there was a decreasing trend in the incidence of severe AEs in ITP patients receiving TPO-RAs compared with control subjects".
https://www.ncbi.nlm.nih.gov/pmc/articles/PMC5171907/

(See next page for what PDSA submitted previously to the Ontario Provincial Government – includes patient stories and *why funding for second line treatment is essential.* One patient story involves a 10 year old boy who passed away who may not of had he had access to second line therapy.

Sincerely,

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Platelet Disorder Support Association

Jennifer DiRaimo
Research Program Manager
Platelet Disorder Support Association

Enclosed: Call for Action to MOH