CADTH
ACMTS

Proposed Project Scope

Treatment of adult patients with chronic immune thrombocytopenia after failure of first line therapies

January 6, 2020
For stakeholder feedback

BACKGROUND AND RATIONALE

Immune thrombocytopenia (ITP) is a disorder characterized by low platelets and an increase in bleeding risk due to increased platelet destruction and impaired platelet production.[1] It was previously called idiopathic thrombocytopenic purpura; however, it is no longer considered an idiopathic disease, and some patients may not have purpura (skin hemorrhage).[1] ITP falls into three disease groups: newly diagnosed ITP (0 to 3 months), persistent ITP (3 to 12 months), and chronic ITP.[2] Chronic ITP is defined as ongoing, active disease at 12-month follow-up.[3]

The cause of ITP is unknown; there may be genetic and/ or environmental risk factors (such as infections with Helicobacter pylori, hepatitis C virus and human immunodeficiency virus).[1] A family history of thrombocytopenia is seen in 2% of children and 3% of adults.[3]

ITP has an incidence of 5/ 100,000 to 10/ 100,000 children per year and 3.3/ 100,000 adults per year. [3] It is more commonly seen in women than men, with a predominance of 2:1.[3] At diagnosis, 90% of children and 69% of adults will have bleeding symptoms.[3] The bleeding will be severe (e.g., bleeding in the gastrointestinal tract or in the brain) in 20% of children and in approximately 10% of adults.[1,3] Current data show that the mean platelet count at presentation is 18.1 x 10^9 /L for children and 25.4 x 10^9 /L in adults.[3] More than 30% of adults and approximately 4% of children will present with one or more comorbid conditions.[3]

Spontaneous remission is seen in 70% and 45% of children and adults, respectively, at 6 months, and in 71% and 49% of children and adults, respectively, at 12 months.[3] Among those with chronic ITP, 28% of children and 30% of adults achieve remission at 24 months.[3]

The American Society of Hematology 2019 Guidelines for Immune Thrombocytopenia[4] recommend a short course of corticosteroids as first line treatment in newly diagnosed adult patients with a platelet count of <30 x 10^9 /L and no or minor mucocutanenous bleeding. In adult patients with ITP for three to 12 months (persistent ITP), who are corticosteroid-dependent or who are unresponsive to corticosteroids, the guidelines recommend treating with a thrombopoietin receptor agonist (TPO-RA) (romiplostim, eltrombopag) or rituximab. For these same types of patients, with ITP for greater than 12 months (chronic ITP), the guidelines recommend one of three treatment modalities (romiplostim, eltrombopag, rituximab, or splenectomy). The choice of treatment will depend on patient preferences, whether they prefer a durable response, avoid long-term medication, or avoid surgery. These recommendations are all based on evidence of low to very low quality.[4] Refractory ITP is characterized by a non-response to splenectomy or relapse after surgery, with high risk of bleeding for which continued treatment is required.[5]

The American guidelines' authors do not provide recommendations regarding azathioprine, cyclophosphamide, cyclosporine, danazol, dapsone mycophenolate mofetil, and the vinca alkaloids given the current evidence (studies' small sample size and heterogeneous patient population).[4]

An update to the International Consensus Report on the Investigation and Management of Primary Immune Thrombocytopenia was published in 2019.[6] For newly diagnosed adult patients, it is suggested to administer a short course of corticosteroids. Those who are unresponsive, or with a contraindication to corticosteroids, may use IVIG or anti-D immunoglobulin. TPO-RAs and rituximab are not recommended as initial treatments. Recommended subsequent treatments include: eltrombopag, avatrombopag, romiplostim, fostamatinib, rituximab, or surgery

(splenectomy to be performed 12 to 24 months from diagnosis) for which, the panel states, there is robust evidence.[6]

With the availability of romiplostim and eltrombopag, there has been a decline in the use of splenectomy.

The F/P/T public drug plans are interested in knowing the place in therapy of available treatments for adults with chronic immune thrombocytopenia who have already received first-line therapies (i.e., steroids and/or IVIG). They would also like to know if TPO-RAs or rituximab should be reimbursed without requiring a splenectomy.

Table I: Policy Questions

1. Which treatment(s) is (are) most appropriate for adults with chronic immune thrombocytopenia after a trial of first line treatments?
2. Should splenectomy be required prior to accessing a TPO-RA or rituximab?

Table II describes the drugs available in Canada that are relevant to this CADTH project.

Table II: Drug Availability

Drug	Brand Name	Manufacturer (NOC)	Indication	Availability and Administration
Thrombopoietin receptor agonists (TPO-RAs)				
Eltrombopag	Revolade	Novartis Pharmaceuticals Canada Inc (April 2011)	For the treatment of chronic immune thrombocytopenia to increase platelet counts in adult and pediatric patients one year and older who have had an insufficient response to corticosteroids or immunoglobulins	12.5 mg, 25 mg, 50 mg, and 75 mg oral tablets The recommended initial dose is 50 mg once daily for adults and children 6 years and older, and 25 mg once daily for patients with Asian ancestry and children aged one to less than six years. Monitoring and dosing adjustments based on platelet counts are described in the product monograph as well as criteria for discontinuation. The maximum daily dose is 75 mg
Romiplostim	Nplate	Amgen Canada Inc (April 2009)	To increase the platelet levels in adult patients with chronic immune (idiopathic) thrombocytopenic purpura who are nonsplenectomized and have had an inadequate response or are intolerant to corticosteroids and/ or immunoglobulins; who are splenectomized and have had an inadequate response to splenectomy	250 mcg/ 0.5 mL vial and 500 mcg/ 1 mL vial Initial dose is 1 mcg/ kg based on body weight, administered once weekly as a subcutaneous injection. The product monograph further stipulates criteria for treatment discontinuation and dose adjustments to reach a platelet count of equal or greater than

				50 x 10^9/ L. The maximum weekly dose is 10 mcg/ kg
Spleen tyrosine kinase (SYK) inhibitor				
Fostamatinib	Tavalisse	Rigel Pharmaceuticals Inc. (December 2020)	To treat adult patients with chronic immune thrombocytopenia who are refractory to other treatments	100 mg and 150 mg oral tablets 100 mg taken orally twice daily. After a month, if platelet count has not increased to at least 50 x 109/L, increase dose to 150 mg twice daily.
Monoclonal antibody (anti-CD20)				
Rituximab and biosimilars	Rituxan	Hoffman-La Roche Ltd	NA	Intravenous: 10 mg/mL single use vials of 10 mL or 50 mL Subcutaneous: 120mg/ mL single use vials of 15 mL or 20 mL Dose for ITP: 375 mg /m^2 intravenous infusion once a week for four weeks (4 total doses; Days 1, 8, 15, and 22). Low dose for ITP: 100 mg intravenous infusion once a week for four weeks (4 total doses; Days 1, 8, 15, and 22).
	Riximyo	Sandoz Canada Inc		
	Ruxience	Pfizer Canada ULC		
	Truxima	Celltrion Healthcare Co Ltd		

NA = not applicable; NOC = notice of compliance

PROJECT DESCRIPTION

The PICO statement (population, interventions, comparators, and outcomes) and research questions are described in Table IV and Table V.

Table IV: Selection Criteria

Population	▪ Adult patients with ongoing, active chronic immune thrombocytopenia (> 12 months) who have failed first-line treatments
Interventions	▪ Rituximab ▪ Rituximab biosimilars ▪ Eltrombopag ▪ Romiplostim ▪ Fostamatinib
Comparators	▪ Rituximab ▪ Rituxmab biosimilars ▪ Rituximab low dose ▪ Eltrombopag ▪ Romiplostim ▪ Fostamatinib ▪ IVIG

	▪ Immunosuppressants (e.g., azathioprine, cyclosporine, cyclophosphamide, mycophenolate mofetil, danazol, dapsone) ▪ Splenectomy
Outcomes	▪ Bleeding symptoms ▪ Platelet response ▪ Time to platelet response ▪ Need for rescue medication ▪ Need for surgery ▪ Fatigue ▪ Menorrhagia ▪ Emergency room visits ▪ Hospitalization ▪ Health-related quality of life ▪ Harms

Table V: Research Questions

1. What are the efficacy and safety of therapies in adult patients with chronic immune thrombocytopenia who have failed fist line treatments?
2. What are the efficacy and safety of splenectomy compared with TPO-RAs or rituximab in adult patients with chronic immune thrombocytopenia?
3. What is the cost-effectiveness of therapies in adult patients with chronic immune thrombocytopenia who have failed fist line treatments?
4. What is the cost-effectiveness of splenectomy compared with TPO-RAs or rituximab in adult patients with chronic immune thrombocytopenia?

KEY PROJECT AND PROTOCOL COMPONENTS

To address the questions described above, this health technology assessment project may include the following key components:

- A systematic review of the evidence on clinical efficacy and effectiveness. Statistical pooling of the clinical data, in the form of a meta-analysis or a network meta-analysis, will be considered if data are amenable to such types of analysis.
    - Study design to be considered:
        - Randomized clinical trials
- Cost-effectiveness analysis
    - Key features:
        - Review of published economic analyses
        - Economic model
        - Cost-utility analysis (preferred design).
- Budget impact analysis (if the clinical data are not amenable to a cost-effectiveness analysis).
- Depending on the outcomes of the health technology assessment, other CADTH work may be considered to assist with policy and implementation.

STATUS OF THE DOCUMENT

This proposed project scope is posted for 10 business days for stakeholder feedback. The feedback will be considered as the project plan is finalized. A list of included studies and a project protocol may be posted on CADTH's website if required.

REFERENCES

1. Swinkels M, Rijkers M, Voorberg J, Vidarsson G, Leebeek FWG, Jansen AJG. Emerging Concepts in Immune Thrombocytopenia. *Frontiers in immunology.* 2018;9:880.
2. Cooper N. State of the art - how I manage immune thrombocytopenia. *British journal of haematology*. 2017;177(1):39-54.
3. Despotovic JM, Grimes AB. Pediatric ITP: is it different from adult ITP? *Hematology American Society of Hematology Education Program.* 2018;2018(1):405-411.
4. Neunert C, Terrell DR, Arnold DM, et al. American Society of Hematology 2019 guidelines for immune thrombocytopenia. *Blood advances.* 2019;3(23):3829-3866.
5. Onisâi M, Vlădăreanu AM, Spînu A, Găman M, Bumbea H. Idiopathic thrombocytopenic purpura (ITP) - new era for an old disease. *Rom J Intern Med.* 2019;57(4):273-283.
6. Provan D, Arnold DM, Bussel JB, et al. Updated international consensus report on the investigation and management of primary immune thrombocytopenia. *Blood advances.* 2019;3(22):3780-3817.