CADTH

CADTH Reference List

Treatment of Pediatric Patients With Immune Thrombocytopenia

September 2022

Summary of Abstracts

CADTH

Authors: Weiyi Xie, Hannah Loshak

Cite As: *Treatment of Pediatric Patients With Immune Thrombocytopenia*. (CADTH reference list). Ottawa: CADTH; 2022 Sep.

About CADTH: CADTH is an independent, not-for-profit organization responsible for providing Canada's health care decision-makers with objective evidence to help make informed decisions about the optimal use of drugs, medical devices, diagnostics, and procedures in our health care system.

Funding: CADTH receives funding from Canada's federal, provincial, and territorial governments, with the exception of Quebec.

Questions or requests for information about this report can be directed to **requests@cadth.ca**

CADTH

Key Message

CADTH found 7 systematic reviews and 14 randomized controlled trials about the potential clinical benefits and harms of interventions used in children with immune thrombocytopenia.

Research Question

What literature describes the potential clinical benefits and harms of interventions used in children with immune thrombocytopenia?

Methods

Literature Search Methods

A limited literature search was conducted by an information specialist on key resources including Medline, the Cochrane Database of Systematic Reviews, the International HTA Database, the websites of Canadian and major international health technology agencies, as well as a focused internet search. The search strategy comprised both controlled vocabulary, such as the National Library of Medicine's MeSH (Medical Subject Headings), and keywords. The main search concepts were immune thrombocytopenia and pediatrics. CADTH-developed search filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses, indirect treatment comparisons, randomized controlled trials, controlled clinical trials, or guidelines. Where possible, retrieval was limited to the human population. The search was completed on August 2, 2022, and limited to English-language documents published since January 1, 2012. Internet links were provided, where available

Selection Criteria

One reviewer screened literature search results (titles and abstracts) and selected publications according to the inclusion criteria presented in Table 1. Full texts of study publications were not reviewed.

Results

Twenty-one relevant references were identified for this report.[1-21] Seven systematic reviews[1-7] (5 with meta-analyses[1-5]) and 14 randomized controlled trials[8-21] were identified regarding the potential clinical benefits and harms of interventions used in children with immune thrombocytopenia. No relevant health technology assessments were identified.

Additional references of potential interest that did not meet the inclusion criteria are provided in Appendix 1.

Table 1: Selection Criteria

Criteria	Description
Population	Pediatric patients (≤ 18 years) with ongoing, active immune thrombocytopenia
Concept	Pharmacological interventions (e.g., thrombopoietin receptor agonists [i.e., eltrombopag, romiplostim] alone or combined with an immunosuppressant, dapsone, rituximab [including biosimilars]), and surgical intervention (e.g., splenectomy)
Type of information	Descriptions of potential clinical benefits (e.g., platelet response, bleeding events, use of rescue medication, hospitalization, emergency department visits, treatment-free remission, health-related quality of life, reduction or discontinuation of corticosteroids, mortality) and harms (e.g., adverse events, serious adverse events, withdrawal due to adverse events, death)
Study designs	Health technology assessments, systematic reviews, randomized controlled trials

Overall Summary of Findings

Seven systematic reviews[1-7] (5 with meta-analyses[1-5]) and 14 randomized controlled trials[8-21] were identified regarding the potential clinical benefits and harms of interventions used in children with immune thrombocytopenia. The included studies examined the effect of various treatments for children with different types of immune thrombocytopenia. A detailed summary of study characteristics for the included systematic reviews and randomized controlled trials can be found in Table 2.

Three systematic reviews[1,3,7] examined rituximab as an intervention but varied on comparators of interest. Two systematic reviews[5,6] compared the benefits and harms of romiplostim, eltrombopag, and placebo. Liogar et al. (2020) compared IV immunoglobulins (IVIG) to anti-D immunoglobulin (anti-D).[4] Additionally, Acero-Garces et al. (2020) evaluated the effects of anti-D, IVIG, corticosteroids, methylprednisolone, and prednisone.[2]

The identified randomized controlled trials varied in interventions of interest, including anti-D,[13,15,19,20] IVIG,[8,11-13,19,20] dexamethasone,[9] cyclosporine,[10] prednisone,[9] methylprednisone,[8,20] sirolimus,[10] romiplostim,[14,16,21] and eltrombog.[17,18] Six randomized controlled trials[11,14,16-18,21] compared interventions to placebo or no treatment, whereas the 8 randomized controlled trials[8-10,12,13,15,19,20] compared interventions to other pharmacological treatments.

Table 2: Summary of Included Systematic Reviews and Randomized Controlled Trials

Study citation	Study design	Population	Intervention(s)	Comparator(s)	List of outcomes
Systematic reviews					
Ayad et al. (2022)[1]	SR	Children with ITP	Rituximab	TPO-RAs	AEs, need for rescue therapy, durability of treatment effect, and overall platelet response

Study citation	Study design	Population	Intervention(s)	Comparator(s)	List of outcomes
Acero-Garces et al. (2020)[2]	SR with 12 clinical trials	Children with newly diagnosed primary ITP	Anti-D, corticosteroids, methylprednisolone, and prednisone, each at varying doses	Anti-D, corticosteroids, methylprednisolone, and prednisone, each at varying doses	AEs, PC, and response rates
Qu et al. (2020)[3]	SR with 5 NRSs	Children with ITP; N = 100	Rituximab	Splenectomy	Adverse drug reaction and response rates
Lioger et al. (2019)[4]	SR with 11 RCTs	Children with ITP; N = 558	IVIG	Anti-D	Bleeding, hemolysis, infusion reactions, and response rates
Tumaini et al. (2019)[5]	SR with 5 RCTs	Children aged 1 to 17 years with chronic ITP; N = 261	Romiplostim and Eltrombopag	Romiplostim, eltrombopag, and placebo	AEs and efficacy
Zhang et al. (2017)[6]	SR with 5 RCTs	Children with ITP; N = 261	Romiplostim and Eltrombopag	Romiplostim, eltrombopag, and placebo	AEs, SAEs, clinically significant bleeding, response rates, overall bleeding events, and use of rescue medication
Liang et al. (2012)[7]	SR with 18 NRSs	Children with primary ITP; N = 323 Children with secondary ITP; N = 29	Rituximab	NR	AEs, death, and response rates
Randomized controlled trials					
Carcao et al. (2020)[8]	Randomized, double-blinded trial	Children aged 1 to 17 years with primary ITP; N = 32	Combination of IV methylprednisolone with IVIG	IVIG and placebo	IVIG-related headaches, PCs, and severe bleeding or unexpected severe AEs
Ma et al. (2020)[9]	Randomized single-centre study	Children with previously untreated primary ITP; N = 211	High-dose dexamethasone	Prednisone	Bleeding score improvement, bleeding events, response rates, Cushing disease, glucocorticoid-related adverse effects, infection, remission, and weight gain
Mousavi-Hasanzadeh et al. (2020)[10]	Randomized blinded trial	Children aged over 5 years old with chronic ITP; N = 67	Sirolimus	Cyclosporine	PC, response rates, and safety profile

Study citation	Study design	Population	Intervention(s)	Comparator(s)	List of outcomes
Heitink-Polle et al. (2018)[11]	Multicenter randomized trial	Children aged 3 months to 16 years with newly diagnosed ITP; N = 206	Single infusion of IVIG	No treatment	Bleeding, development of chronic ITP, response rates, and PCs
Elalfy et al. (2017)[12]	Randomized multicenter, open-label study	Children aged 1 to 18 years with newly diagnosed ITP; N = 72	Mini-pool IVIG	Single IVIG	Adverse drug reactions, response rates, and median time to response
Eghbali et al. (2016)[13]	Randomized, open-label, single-centre clinical trial	Children aged 1 to 15 years with acute and chronic ITP; N = 60	IVIG	Anti-D	Hemoglobin concentration, PCs, response rates, response time, and AEs
Mathias et al. (2016)[14]	Phase III, randomized, double-blind, placebo-controlled study	Children aged < 18 years with ITP ≥ 6 months; N = 62	Romiplostim	Placebo	HRQoL and parental burden
Swain et al. (2016)[15]	RCT	Children aged 4 to 14 years with newly diagnosed ITP; N = 164	Anti-D 75 mcg/kg	Anti-D 50 mcg/kg	Response rates, hemolysis, median time to response, and PC
Tarantino et al. (2016)[16]	Phase III randomized, double-blind, placebo-controlled study	Children aged 1 to 17 years with chronic ITP; N = 62	Romiplostim	Placebo	Durable platelet response and SAEs
Bussel et al. (2015)[17]	Three-part, randomized, multicentre, placebo-controlled study	Children aged 1 to 17 years with persistent or chronic ITP; N = 67	Eltrombopag	Placebo	AEs, PC, and SAEs
Grainger et al. (2015)[18]	Two-part, randomized, multicentre, placebo-controlled study	Children aged 1 to 17 years with chronic ITP; N = 92	Eltrombopag	Placebo	AEs, bleeding, PC, response rates, and SAEs
Alioglu et al. (2013)[19]	RCT	Children aged 1 to 18 years with newly diagnosed acute ITP; N = 78	Anti-D IVIG 50 mcg/kg or 75 mcg/kg	IVIG 2g/kg	AEs, bleeding, PC, response rates, and SAEs
Celik et al. (2013)[20]	RCT	Rh-positive children with newly diagnosed ITP; N = 60	Anti-D, IVIG, and methylprednisolone	Anti-D, IVIG, and methylprednisolone	Chronic ITP, PCs, hemoglobin and hematocrit levels

Study citation	Study design	Population	Intervention(s)	Comparator(s)	List of outcomes
Klaassen et al. (2012)[21]	Multicenter, randomized, double-blind, placebo-controlled phase I and II treatment study	Children aged 1 to 18 years with chronic ITP; N = 22	Romiplostim	Placebo	HRQoL and parental burden

AE = adverse event; anti-D = anti-D immunoglobulin; HRQoL = health-related quality of life; ITP = immune thrombocytopenia; IVIG = IV immunoglobulins; NR = not reported; NRS = non-randomized study; PC = platelet count, RCT = randomized controlled trial; SAE = serious adverse event; SR = systematic review; TPO-RAs = thrombopoietin receptor agonists.

References

Health Technology Assessments

No literature identified.

Systematic Reviews

1. Ayad N, Grace RF, Al-Samkari H. Thrombopoietin receptor agonists and rituximab for treatment of pediatric immune thrombocytopenia: a systematic review and meta-analysis of prospective clinical trials. *Pediatr Blood Cancer*. 2022;69(3):e29447. PubMed
2. Acero-Garces DO, Garcia-Perdomo HA. First line treatments for newly diagnosed primary immune thrombocytopenia in children: a systematic review and network meta-analysis. *Curr Pediatr Rev*. 2020;16(1):61-70. PubMed
3. Qu M, Zhou J, Yang SJ, Zhou ZP. Efficacy and safety of rituximab for minors with immune thrombocytopenia: a systematic review and meta-analysis. *J Int Med Res*. 2020;48(10):300060520962348. PubMed
4. Lioger B, Maillot F, Ternant D, Passot C, Paintaud G, Bejan-Angoulvant T. Efficacy and safety of anti-D immunoglobulins versus intravenous immunoglobulins for immune thrombocytopenia in children: systematic review and meta-analysis of randomized controlled trials. *J Pediatr*. 2019;204:225-233.e228. PubMed
5. Tumaini Massaro J, Chen Y, Ke Z. Efficacy and safety of thrombopoietin receptor agonists in children with chronic immune thrombocytopenic purpura: meta-analysis. *Platelets*. 2019;30(7):828-835. PubMed
6. Zhang J, Liang Y, Ai Y, Xie J, Li Y, Zheng W. Thrombopoietin-receptor agonists for children with immune thrombocytopenia: a systematic review. *Expert Opin Pharmacother*. 2017;18(15):1543-1551. PubMed
7. Liang Y, Zhang L, Gao J, Hu D, Ai Y. Rituximab for children with immune thrombocytopenia: a systematic review. *PLoS ONE*. 2012;7(5):e36698. PubMed

Randomized Controlled Trials

8. Carcao M, Silva M, David M, et al. IVMP+IVIG raises platelet counts faster than IVIG alone: results of a randomized, blinded trial in childhood ITP. *Blood Adv*. 2020;4(7):1492-1500. PubMed
9. Ma J, Fu L, Chen Z, Gu H, Ma J, Wu R. High-dose dexamethasone as a replacement for traditional prednisone as the first-line treatment in children with previously untreated primary immune thrombocytopenia: a prospective, randomized single-center study. *Int J Hematol*. 2020;112(6):773-779. PubMed
10. Mousavi-Hasanzadeh M, Bagheri B, Mehrabi S, Eghbali A, Eghbali A. Sirolimus versus cyclosporine for the treatment of pediatric chronic immune thrombocytopenia: a randomized blinded trial. *Int Immunopharmacol*. 2020;88:106895. PubMed
11. Heitink-Polle KMJ, Uiterwaal C, Porcelijn L, et al. Intravenous immunoglobulin vs observation in childhood immune thrombocytopenia: a randomized controlled trial. *Blood*. 2018;132(9):883-891. PubMed
12. Elalfy M, Reda M, Elghamry I, et al. A randomized multicenter study: safety and efficacy of mini-pool intravenous immunoglobulin versus standard immunoglobulin in children aged 1-18 years with immune thrombocytopenia. *Transfusion*. 2017;57(12):3019-3025. PubMed
13. Eghbali A, Azadmanesh P, Bagheri B, Taherahmadi H, Sadeghi Sedeh B. Comparison between IV immune globulin (IVIG) and anti-D globulin for treatment of immune thrombocytopenia: a randomized open-label study. *Fundam Clin Pharmacol*. 2016;30(4):385-389. PubMed
14. Mathias SD, Li X, Eisen M, Carpenter N, Crosby RD, Blanchette VS. A phase 3, randomized, double-blind, placebo-controlled study to determine the effect of romiplostim on health-related quality of life in children with primary immune thrombocytopenia and associated burden in their parents. *Pediatr Blood Cancer*. 2016;63(7):1232-1237. PubMed
15. Swain TR, Jena RK, Swain KP. High dose intravenous anti-D immune globulin is more effective and safe in Indian paediatric patients of immune thrombocytopenic purpura. *J Clin Diagn Res*. 2016;10(12):FC12-FC15. PubMed
16. Tarantino MD, Bussel JB, Blanchette VS, et al. Romiplostim in children with immune thrombocytopenia: a phase 3, randomised, double-blind, placebo-controlled study. *Lancet*. 2016;388(10039):45-54. PubMed
17. Bussel JB, de Miguel PG, Despotovic JM, et al. Eltrombopag for the treatment of children with persistent and chronic immune thrombocytopenia (PETIT): a randomised, multicentre, placebo-controlled study. *Lancet Haematol*. 2015;2(8):e315-325. PubMed
18. Grainger JD, Locatelli F, Chotsampancharoen T, et al. Eltrombopag for children with chronic immune thrombocytopenia (PETIT2): a randomised, multicentre, placebo-controlled trial. *Lancet*. 2015;386(10004):1649-1658. PubMed
19. Alioglu B, Ercan S, Tapci AE, Zengin T, Yazarli E, Dallar Y. A comparison of intravenous immunoglobulin (2 g/kg totally) and single doses of anti-D immunoglobulin at 50 µg/kg, 75 µg/kg in newly diagnosed children with idiopathic thrombocytopenic purpura: Ankara hospital experience. *Blood Coagul Fibrinolysis*. 2013;24(5):505-509. PubMed
20. Celik M, Bulbul A, Aydogan G, et al. Comparison of anti-D immunoglobulin, methylprednisolone, or intravenous immunoglobulin therapy in newly diagnosed pediatric immune thrombocytopenic purpura. *J Thromb Thrombolysis*. 2013;35(2):228-233. PubMed
21. Klaassen RJ, Mathias SD, Buchanan G, et al. Pilot study of the effect of romiplostim on child health-related quality of life (HRQoL) and parental burden in immune thrombocytopenia (ITP). *Pediatr Blood Cancer*. 2012;58(3):395-398. PubMed

Appendix 1: References of Potential Interest

Previous CADTH Report

Hui D, Barbara A, McGill SC. Guidelines for pediatric immune thrombocytopenia. (CADTH health technology review). *Can J Health Technol*. 2022;2(6). Available from: https://canjhealthtechnol.ca/index.php/cjht/article/view/rc1426/721. Accessed 2022 Aug 5.

Systematic Reviews

Alternative Population — Not Specific to Pediatric Populations

Kolanis S, Vasileiou E, Hatzipantelis E, Economou M, Tragiannidis A. Safety and efficacy of eltrombopag in children and adults with immune thrombocytopenia: a systematic review and meta-analysis. *Cardiovasc Hematol Agents Med Chem*. 2021;19(1):83-92. PubMed

Owattanapanich W, Wongprasert C, Rotchanapanya W, Owattanapanich N, Ruchutrakool T. Comparison of the long-term remission of rituximab and conventional treatment for acquired thrombotic thrombocytopenic purpura: a systematic review and meta-analysis. *Clin Appl Thromb Hemost*. 2019;25:1076029618825309. PubMed

Mithoowani S, Gregory-Miller K, Goy J, et al. High-dose dexamethasone compared with prednisone for previously untreated primary immune thrombocytopenia: a systematic review and meta-analysis. *Lancet Haematol*. 2016;3(10):e489-e496. PubMed

Randomized Controlled Trials

Unclear Population — Population Age Not Specified

Zhou H, Xu M, Qin P, et al. A multicenter randomized open-label study of rituximab plus rhTPO vs rituximab in corticosteroid-resistant or relapsed ITP. *Blood*. 2015;125(10):1541-1547. PubMed

Kuter DJ, Mathias SD, Rummel M, et al. Health-related quality of life in nonsplenectomized immune thrombocytopenia patients receiving romiplostim or medical standard of care. *Am J Hematol*. 2012;87(5):558-561. PubMed

Wang S, Yang R, Zou P, et al. *A multicenter randomized controlled trial of recombinant human thrombopoietin treatment in patients.*

Review Articles

Kim TO, Despotovic JM. Pediatric immune thrombocytopenia (ITP) treatment. *Ann Blood.* 2021;6(4). Available from: https://aob.amegroups.com/article/view/6316/pdf. Accessed 2022 Aug 5.

Xu JY, Wang Y, Wu Y, Gu JW. Safety and efficacy of eltrombopag in the treatment of children with immune thrombocytopenia: a meta analysis. *Zhongguo Dangdai Erke Zazhi*. 2021;23(9):944-950. PubMed

Al-Samkari H, Grace RF, Kuter DJ. The role of romiplostim for pediatric patients with immune thrombocytopenia. *Ther Adv Hematol.* 2020;11:2040620720912992. PubMed

Guo JC, Zheng Y, Chen HT, et al. Efficacy and safety of thrombopoietin receptor agonists in children with chronic immune thrombocytopenia: a meta-analysis. *Oncotarget*. 2018;9(6):7112-7125. PubMed

Li H, Yang H, Liu WJ. Efficacy of romiplostim in the treatment of ITP in children: a meta-analysis. *Eur Rev Med Pharmacol Sci*. 2018;22(18):6162-6169. PubMed

Elgebaly AS, Ashal GE, Elfil M, Menshawy A. Tolerability and efficacy of eltrombopag in chronic immune thrombocytopenia: meta-analysis of randomized controlled trials. *Clin Appl Thromb Hemost*. 2017;23(8):928-937. PubMed

Burness CB, Keating GM, Garnock-Jones KP. Eltrombopag: a review in paediatric chronic immune thrombocytopenia. *Drugs*. 2016;76(8):869-878. PubMed