Evidence Development and Standards Branch at Health Quality Ontario

Special Report

October 2014

Intravenous Immune Globulin (IVIG) for Treatment of Primary Immune Thrombocytopenia (ITP)

K McMartin

Context

Primary immune thrombocytopenia (ITP) is defined as a platelet count less than 100 x 10^9/L in the absence of other causes or disorders that may be associated with thrombocytopenia. Treatments for ITP aim to decrease autoantibody production or interfere with platelet destruction. The overall goal of treatment is to achieve platelet counts that are sufficient for hemostasis—not necessarily normal counts. Conventional treatments include corticosteroids, intravenous immune globulin (IVIG), rhesus immune globulin (for rhesus blood group–positive individuals), immune-suppressant medications, cytotoxic agents, and splenectomy. Corticosteroids are generally considered to be first-line treatment for ITP. The addition of IVIG is usually reserved for treatment of severe ITP associated with mucosal or more substantial bleeding.

Research Question

What is the effectiveness of IVIG plus corticosteroids versus corticosteroids alone for the treatment of ITP in newly diagnosed asymptomatic patients?

Conclusion

No randomized controlled trials, observational studies, systematic reviews or meta-analyses met the inclusion criteria. The American Society of Hematology provided evidence-based recommendations using the GRADE system in areas where evidence existed.

Methodology

Research questions are developed by Choosing Wisely Canada, in consultation with experts, end users, and/or applicants in the topic area. Evidence Development and Standards then produces one of two types of rapid reviews, or a special report to answer the research question. A rapid review of Systematic Reviews is conducted when a systematic literature search identifies relevant systematic reviews, health technology assessments, or meta-analyses that meet the inclusion criteria specified in the methods section. A rapid review of primary studies is conducted when none of the aforementioned study designs are available. On occasion, a special report may be provided that does not strictly follow the rapid review methodology set out by HQO. These reports are completed in a 2- to 8-week time frame. For more detail on rapid review methodology, please visit the Health Quality Ontario website at: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations/rapid-reviews

Context

Choosing Wisely Canada is a national campaign that aims to help physicians and patients engage in informative conversations about tests, treatments, and procedures, and help physicians and patients make smart and effective choices to ensure high-quality care. It will support physicians as they work with patients to ensure they not only get the care they need, but avoid tests, treatments, and procedures that have no value and could cause them harm.

As part of this campaign, Health Quality Ontario (HQO) has developed rigorous, evidence-based reviews of tests, treatments, and/or procedures that may be overused. Choosing Wisely Canada has made recommendations based on the evidence provided by HQO. These recommendations are available on the Choosing Wisely Canada website.

Objective of Review

The objective of this review was to determine the effectiveness of intravenous immune globulin (IVIG) plus corticosteroids versus corticosteroids alone for the treatment of primary immune thrombocytopenia (ITP) in newly diagnosed asymptomatic patients.

Clinical Need and Target Population

Description of Disease/Condition

Primary ITP is defined as a platelet count less than 100 x 10^9/L in the absence of other causes or disorders that may be associated with thrombocytopenia. (1) Immune thrombocytopenia manifests as a bleeding tendency, easy bruising, or extravasation of blood from capillaries into skin and mucous membranes. Although most cases of ITP are mild and self-limited, intracranial hemorrhage may occur when the platelet count drops below 10 x 10^9/L. (2)

Prevalence and Incidence

The prevalence of adult ITP is approximately 23 per 100,000 population. (2) The estimated incidence of ITP is 3.3 per 100,000 adults per year. (3)

Technology/Technique

Treatment is rarely indicated in patients with platelet counts above 50 x 10^9/L in the absence of the following: bleeding due to platelet dysfunction or another hemostatic defect, trauma, surgery, clearly identified comorbidities for bleeding, mandated anticoagulation therapy or a profession or lifestyle that predisposes the person to trauma. (4)

Treatments for ITP aim to decrease autoantibody production or interfere with platelet destruction. The overall goal of treatment is to achieve platelet counts that are sufficient for hemostasis—not necessarily normal counts. (2) Conventional treatments include corticosteroids, IVIG, rhesus immune globulin (for rhesus blood group–positive individuals), immune-suppressant medications, cytotoxic agents, and splenectomy. (2) Randomized controlled trial (RCT) data are available for some new ITP treatments (e.g., romiplostim, eltrombopag), but only a very limited number of RCTs have been conducted in adults using traditional therapies. (4)

Corticosteroids are generally considered to be first-line treatment for ITP. The addition of IVIG is usually reserved for treatment of severe ITP associated with mucosal or more substantial bleeding. (2)

Question, Methods, and Findings

Research Question

What is the effectiveness of IVIG plus corticosteroids versus corticosteroids alone for the treatment of ITP in newly diagnosed asymptomatic patients?

Methods

See Appendix 1 for a detailed description of the search strategy, including terms and results.

Inclusion Criteria

- English-language full-text publications
- published between January 1, 2004, and July 28, 2014
- RCTs, observational studies, systematic reviews, meta-analyses
- adult patients newly diagnosed with ITP who are asymptomatic

Exclusion Criteria

- pediatric patients
- geriatric patients
- adults with symptomatic ITP requiring emergent treatment
- adults with chronic ITP

Outcomes of Interest

- bleeding
- adverse events

Findings

The database search yielded 1,211 citations published between January 1, 2004, and July 28, 2014 (with duplicates removed). Articles were excluded based on information in the title and abstract. The full texts of potentially relevant articles were obtained for further assessment.

No RCTs, observational studies, systematic reviews, or meta-analyses met the inclusion criteria.

In the absence of studies meeting the inclusion criteria, the American Society of Hematology (ASH) 2011 evidence-based practice guidelines for ITP were examined. (1) The ASH provided evidence-based recommendations using the Grading of Recommendations Assessment, Development, and Evaluation (GRADE) system in areas where evidence existed. (5)

Treatment of Newly Diagnosed Adult ITP

- Treatment should be administered for newly diagnosed patients with a platelet count < 30 x 10^9/L (GRADE 2C).

First-Line Treatment of Adult ITP

- Longer courses of corticosteroids are preferred over shorter courses of corticosteroids or IVIG as first-line treatment (GRADE 2B).
- IVIG should be used with corticosteroids when a more rapid increase in platelet count is required (GRADE 2B).
- Either IVIG or anti-D (in appropriate patients) should be used as a first-line treatment if corticosteroids are contraindicated (GRADE 2C).
- If IVIG is used, the dose should initially be 2 g/kg as a 1-time dose. This dosage may be repeated if necessary (GRADE 2B).

Conclusions

No RCTs, observational studies, systematic reviews or meta-analyses met the inclusion criteria. The American Society of Hematology provided evidence-based recommendations using the GRADE system in areas where evidence existed.

Acknowledgements

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Appendices

Appendix 1: Research Methods

Literature Search Strategy

A literature search was performed on July 28, 2014, using Ovid MEDLINE, Ovid MEDLINE In-Process and Other Non-Indexed Citations, Ovid Embase, EBSCO Cumulative Index to Nursing & Allied Health Literature (CINAHL), and EBM Reviews, for studies published from January 1, 2004, to July 28, 2014. Abstracts were reviewed by a single reviewer and, for those studies meeting the eligibility criteria, full-text articles were obtained. Reference lists were also examined for any additional relevant studies not identified through the search.

Search Results

Search date: July 28, 2014
Databases searched: Ovid MEDLINE, Ovid MEDLINE In-Process, Embase and All EBM Databases (see below)
Database: EBM Reviews - Cochrane Database of Systematic Reviews <2005 to June 2014>, EBM Reviews - ACP Journal Club <1991 to July 2014>, EBM Reviews - Database of Abstracts of Reviews of Effects <2nd Quarter 2014>, EBM Reviews - Cochrane Central Register of Controlled Trials <June 2014>, EBM Reviews - Cochrane Methodology Register <3rd Quarter 2012>, EBM Reviews - Health Technology Assessment <2nd Quarter 2014>, EBM Reviews - NHS Economic Evaluation Database <2nd Quarter 2014>, Embase <1980 to 2014 Week 30>, Ovid MEDLINE(R) <1946 to July Week 3 2014>, Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations <July 25, 2014>
Search Strategy:

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1 Purpura, Thrombocytopenic, Idiopathic/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed (4679)
2 idiopathic thrombocytopenic purpura/ use emez (8830)
3 (((immune or autoimmun* or idiopathic or purpura* or primary) adj2 thrombocytopeni*) or ITP or werlhof* disease*).ti,ab. (34062)
4 or/1-3 (37016)
5 Immunoglobulins, Intravenous/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed (10371)
6 exp immunoglobulin/ use emez (343249)
7 exp intravenous drug administration/ use emez (307075)
8 and/6-7 (9323)
9 immunoglobulin/iv use emez (21272)
10 ((intravenous adj immunoglobulin*) or IVIG or sandoglobulin or (intravenous adj immune adj globulin*) or gamimmune or gamimune or endobulin or venoglobulini or immunoglobulins iv or iveegam or gammagard or gammonativ or venoglobulin or intraglobin or (intravenous adj antibod*) or globulin-n or venoglobulin i or alphaglobin or privigen or flebogamma dif or intravenous ig or gamunex or modified immune globulin or globulinn).mp. (29380)
11 or/5,8-10 (54958)
12 4 and 11 (4786)
13 exp Adrenal Cortex Hormones/ use mesz,acp,cctr,coch,clcmr,dare,clhta,cleed (356013)
14 exp corticosteroid/ use emez (685699)
15 (corticosteroid* or corticoid* or (adren* adj (cortex or cortical) adj (hormone* or steroid*)) or adrenocorticosteroid or dermocorticosteroid or cortical steroid or cortico steroid or ((adrenal or adrenocortical) adj (steroid* or hormone*))).mp. (363861)
16 or/13-15 (1105530)
17 12 and 16 (2567)
18 limit 17 to (english language and yr="2004 -Current") [Limit not valid in CDSR,ACP Journal Club,DARE,CLCMR; records were retained] (1393)
19 remove duplicates from 18 (1211)

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Conflict of Interest Statement

All authors in the Evidence Development and Standards branch at Health Quality Ontario are impartial. There are no competing interests or conflicts of interest to declare.

Disclaimer

This report is the work of the Evidence Development and Standards branch at Health Quality Ontario and is developed from analysis, interpretation, and comparison of published scientific research. It also incorporates, when available, Ontario data and information provided by experts. This report may not reflect all the available scientific research and is not intended as an exhaustive analysis. The analysis may not have captured every relevant publication and relevant scientific findings may have been reported since completion of the review. Health Quality Ontario assumes no responsibility for omissions or incomplete analysis resulting from its reports. This report is current as of the date of the literature search specified in the Research Methods section. This report may be superseded by an updated publication on the same topic. Please check the Health Quality Ontario website for a list of all publications: http://www.hqontario.ca/evidence/publications-and-ohtac-recommendations.

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Health Quality Ontario is an arms-length agency of the Ontario government. It is a partner and leader in transforming Ontario's health care system so that it can deliver a better experience of care, better outcomes for Ontarians, and better value for money.

Health Quality Ontario strives to promote health care that is supported by the best available scientific evidence. The Evidence Development and Standards branch works with expert advisory panels, clinical experts, scientific collaborators, and field evaluation partners to conduct evidence-based reviews that evaluate the effectiveness and cost-effectiveness of health interventions in Ontario.

Based on the evidence provided by Evidence Development and Standards and its partners, the Ontario Health Technology Advisory Committee—a standing advisory subcommittee of the Health Quality Ontario Board—makes recommendations about the uptake, diffusion, distribution, or removal of health interventions to Ontario's Ministry of Health and Long-Term Care, clinicians, health system leaders, and policy-makers.

Health Quality Ontario's research is published as part of the *Ontario Health Technology Assessment Series*, which is indexed in MEDLINE/PubMed, Excerpta Medica/Embase, and the Centre for Reviews and Dissemination database. Corresponding Ontario Health Technology Advisory Committee recommendations and other associated reports are also published on the Health Quality Ontario website. Visit http://www.hqontario.ca for more information.

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To create its CWC reports, the Evidence Development and Standards branch and its research partners review the available scientific literature, making every effort to consider all relevant national and international research and solicit any necessary supplemental information.

In addition, Evidence Development and Standards collects and analyzes information about how a health intervention fits within current practice and existing treatment alternatives. Details about the diffusion of the intervention into current health care practices in Ontario add an important dimension to the review. Information concerning the health benefits, economic and human resources, and ethical, regulatory, social, and legal issues relating to the intervention may be included to assist in making timely and relevant decisions to optimize patient outcomes.

Health Quality Ontario
130 Bloor Street West, 10th Floor
Toronto, Ontario
M5S 1N5
Tel: 416-323-6868
Toll Free: 1-866-623-6868
Fax: 416-323-9261
Email: EvidenceInfo@hqontario.ca
www.hqontario.ca