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CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Off-Label Use of Intravenous Immunoglobulin for Hematological Conditions: Clinical Effectiveness

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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.

Research Question

What is the clinical effectiveness of the off-label use of intravenous or subcutaneous immunoglobulin for the treatment of hematological conditions?

Key Findings

Three systematic reviews (one with meta-analyses), four randomized controlled trials, and four non-randomized studies were identified regarding the clinical effectiveness of the off-label use of intravenous or subcutaneous immunoglobulin for the treatment of hematological conditions.

Methods

This report makes use of a literature search developed for a previous CADTH report. The original literature search was conducted in November 2009 on key resources including PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases, Canadian and major international health technology agencies, as well as a focused Internet search. Methodological filters were applied to limit retrieval health technology assessments, systematic reviews, and meta-analyses, randomized controlled trials, and non-randomized studies. Where possible, retrieval was limited to the human population. The initial search was also limited to English-language documents published between January 1, 2004 and November 24, 2009. For the current report, database searches were rerun on October 11, 2017 to capture any articles published since the initial search date. The search of major health technology agencies was also updated to include documents published since November 2009.

Selection Criteria

One reviewer screened citations and selected studies based on the inclusion criteria presented in Table 1.

Table 1: Selection Criteria

Population	Patients any age with hematological conditions that are not approved indications for IVIG, including but not limited to: • Acquired hemophilia • Acquired von Willebrand Disease • Alloimmune thrombocytopenia • Aplastic anemia • Autoimmune hemolytic anemia • Autoimmune neutropenia • Erythroid aplasia • Evans syndrome • Hemolytic disease of the fetus and newborn • Hemolytic uremic syndrome • Hyperhemolysis after transfusion • Low platelet counts in adult patients with HIV • Post-transfusion purpura • POEMS syndrome
Intervention	Human IVIG or SCIG products, including but not limited to those available in Canada, alone or in combination with corticosteroids or other immunomodulation therapies
Comparators	Treatment as usual; Placebo; No treatment
Outcomes	Clinical benefits and harms
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, non-randomized studies

Results

Rapid Response reports are organized so that the higher quality evidence is presented first. Therefore, health technology assessment reports, systematic reviews, and meta-analyses are presented first. These are followed by randomized controlled trials and non-randomized studies.

Three systematic reviews (one with meta-analyses), four randomized controlled trials, and four non-randomized studies were identified regarding the clinical effectiveness of the off-label use of intravenous or subcutaneous immunoglobulin for the treatment of hematological conditions. No relevant health technology assessments were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

Three systematic reviews[1-3] (one with meta-analyses[2]), four randomized controlled trials,[4-7] and four non-randomized studies[8-11] were identified regarding the clinical effectiveness of the off-label use of intravenous or subcutaneous immunoglobulin for the treatment of hematological conditions. Detailed study characteristics are provided in Table 2.

Three hematological conditions that are not approved indications for IVIG were investigated in the literature.[1-11] These were fetal or neonatal alloimmune thrombocytopenia,[1,3,9] hemolytic disease of the fetus and newborn,[2,4-7,10-11] and autoimmune hemolytic anemia.[8] Three studies reported a benefit with IVIG therapy in treating either alloimmune thrombocytopenia[1] or hemolytic disease of the fetus and newborn.[6,10] These results were inconsistent in eight studies, where the authors suggested that IVIG therapy either did not provide clinical benefit or was associated with an increase in adverse events for the treatment of fetal or neonatal alloimmune thrombocytopenia,[3,9] hemolytic disease of the fetus and newborn,[2,4-5,7,11] or autoimmune hemolytic anemia.[8]

Table 2: Summary of Included Studies on the Clinical Effectiveness of the Off-label Use of Intravenous or Subcutaneous Immunoglobulin for the Treatment of Hematological Conditions

First Author, Year	Study Characteristics	Intervention	Comparator	Outcomes	Conclusions
Systematic Reviews and Meta-Analyses					
Winkelhorst, 2017[1]	• Four RCTs and 22 NRS included • Pregnant mothers who have had a previous neonate with FNAIT • N = NR	• Antenatal treatment strategies for FNAIT (including maternal IVIG, with or without corticosteroid therapy)	• Not specified in abstract	• Intracranial hemorrhage • Complication rate • Adverse events	• The authors concluded that weekly IVIG (with or without corticosteroids) should be administered a for the first-line management of FNAIT
Louis, 2014[2]	• MA performed • 12 RCTs and qRCTs included • Neonates with isoimmune haemolytic disease • N = 813	• IVIG	• Placebo or controls	• Rate of exchange transfusions	• Studies with a low risk of bias indicated no benefit of IVIG in preventing exchange transfusions • Studies with a high risk of bias reported a potential benefit to IVIG in reducing the rate of exchange transfusions • The authors concluded that the evidence was inconclusive
Rayment, 2011[3]	• Four RCTs included • Pregnant women at risk for FNAIT • N = 206	• Antenatal interventions for FNAIT (including IVIG)	• No treatment • Interventions compared to each other (including the corticosteroid prednisone)	• Fetal and neonatal hemorrhage and death	• One included trial compared IVIG versus prednisone. The results indicated that there was no significant difference in the treatment arms for predefined outcomes
Randomized Controlled Trials					
van Klink, 2016[4]	• Children with rhesus hemolytic	• IVIG	• Placebo	• Cerebral palsy • Severe cognitive	• There was no observed difference in the rate of

First Author, Year	Study Characteristics	Intervention	Comparator	Outcomes	Conclusions
	disease of the fetus and newborn • N = 66			and/or motor developmental delay • Bilateral deafness or blindness	neurodevelopmental impairment between the IVIG and the placebo group
Santos, 2013[5]	• Newborns with rhesus hemolytic disease • N = 92	• IVIG in the presence of high-intensity phototherapy	• Placebo	• Rate of exchange transfusions • Phototherapy time • Peak bilirubin • Length of hospital stay • Adverse events	• IVIG was not effective in preventing the need for exchange transfusion in neonates with rhesus hemolytic disease • Groups did not significantly differ in phototherapy time, peak bilirubin, or length of hospital stay • No adverse events resulting from IVIG treatment were reported
Elalfy, 2011[6]	• Neonates with Rh incompatibility unmodified by antenatal treatment and not eligible for early exchange transfusion • N = 90	• IVIG (at either 0.5 and 1 g/kg)	• "Conventional method"	• Rate of exchange transfusion • Mean bilirubin levels • Duration of phototherapy • Length of hospital stay	*"We conclude that IVIG administration at 12 h was effective in the treatment of severe Rh HDN; the low-dose IVIG (0.5 g/kg) was as effective as high dose (1 g/kg) in reducing the duration of phototherapy and hospital stay, but less effective in avoiding exchange transfusion."*[6]
Smits-Wintjens, 2011[7]	• Neonates with rhesus hemolytic disease • N = 80	• IVIG	Placebo	• Rate of exchange transfusions • Number of exchange transfusions per patient • Duration of phototherapy • Maximum bilirubin levels • Proportion of neonates who required top-up red-cell transfusions	• The authors concluded that prophylactic IVIG does not reduce the need for exchange transfusion or the rates of other adverse neonatal outcomes in neonates with rhesus hemolytic disease
Non-Randomized Studies					
Fan, 2018[8]	• Retrospective analysis • Children diagnosed with	• IVIG treatment	• Non-IVIG treatment	• Duration of therapy • Relapse rate	• The results suggested no difference in duration of therapy or relapse rate between IVIG and non-

First Author, Year	Study Characteristics	Intervention	Comparator	Outcomes	Conclusions
	autoimmune hemolytic anemia • N = 68				IVIG treatment groups
Bakchoul, 2014[9]	• Study design not clear from the abstract • Infants born with severe NAIT • N = 17	• IVIG and random-donor platelet transfusions	• Random-donor platelet transfusions alone • Matched HPA-1bb platelets alone	• Post-transfusion platelet count • Major bleeding events • Intracranial hemorrhage • Total platelet transfusion requirements	• IVIG did not have a positive effect in reducing total platelet transfusions required or increase the post-transfusion platelet count • The authors concluded that transfusion of random donor platelets alone was effective for the treatment of newborns with severe NAIT
Corvaglia, 2012[10]	• Retrospective chart review of two cohorts • Newborns with rhesus hemolytic disease • N = 88	• IVIG	• No IVIG	• Length of phototherapy • Number of exchange transfusions • IVIG infusions, • Intrauterine and top-up red blood cell transfusions • Need and permanence of umbilical venous catheter • Length of hospital stay • Treatment-related adverse events	*"IVIG appear as an effective alternative to [exchange transfusions], reducing the risk of neurological impairment and complications related to [exchange transfusions]. However, side effects of IVIG treatment (higher need of top-up transfusions and longer hospital stay) should be taken into account and the risk of [necrotizing enterocolitis] should be carefully monitored during treatment."*[10]
Figueras-Aloy, 2010[11]	• An observational, retrospective study • Newborns with severe isoimmune hemolytic jaundice caused by Rh and ABO incompatibility • N = 492	• IVIG treatment	• Non-IVIG treatment	• Rate of necrotizing enterocolitis	• The use of high-dose IVIG in newborns with severe isoimmune hemolytic jaundice was associated with a higher incidence of necrotizing enterocolitis

Abbreviations: FNAIT = fetal or neonatal alloimmune thrombocytopenia; HDN = hemolytic disease of newborn; HPA-1 = human platelet antigen 1; IVIG = intravenous immunoglobulin; MA = meta-analysis; NAIT = neonatal alloimmune thrombocytopenia; NR = not reported; NRS = non-randomized study; qRCT = quasi-randomized controlled trial; RCT = randomized controlled trial; SR = systematic review.

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-Analyses

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Randomized Controlled Trials

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Non-Randomized Studies

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Appendix — Further Information

Previous CADTH Reports

12. Management and patient safety of IVIG administration: a review of clinical practice guidelines [Internet]. Ottawa (ON): CADTH; 2011 [cited 2017 Oct 23]. Available from: https://www.cadth.ca/sites/default/files/pdf/htis/march-2011/L0245_IVIG_Administration_final.pdf

13. Intravenous immunoglobulin: evidence for clinical effectiveness of off-label use [Internet]. Ottawa (ON): CADTH; 2009 [cited 2017 Oct 23]. Available from: https://www.cadth.ca/sites/default/files/pdf/htis-L1/J0342%20Intravenous%20Immunoglobulin%20final.pdf

14. Polyclonal intravenous immunoglobulin in patients with immune thrombocytopenic purpura: clinical systematic review [Internet]. Ottawa (ON): CADTH; 2008 [cited 2017 Oct 23]. Available from: https://www.cadth.ca/sites/default/files/pdf/298A_Polyclonal-Intravenous-Immunoglobulin_tr_e.pdf

Systematic Reviews and Meta-Analyses

Alternative Comparator – Comparison with IVIG Treatment Strategies

15. Buehler AM, Flato UP, Ferri CP, Fernandes JG. Is there evidence for recommending specific intravenous immunoglobulin formulations? A systematic review of head-to-head randomized controlled trials. Eur J Pharmacol. 2015 Jan 15;747:96-104. PubMed: PM25496751

Randomized Controlled Trials

Alternative Comparator – Comparison with IVIG Treatment Strategies

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Alternative Intervention – IVIG Combination Therapy

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Non-Randomized Studies

Alternative Comparator – Comparison with IVIG Treatment Strategies

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Case Reports

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No Comparator

23. Van Der Lugt NM, Kamphuis MM, Paridaans NP, Figee A, Oepkes D, Walther FJ, et al. Neonatal outcome in alloimmune thrombocytopenia after maternal treatment with intravenous immunoglobulin. Blood Transfus. 2015 Jan;13(1):66-71. Available from: http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4317092 PubMed: PM24960663

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Review Articles

25. Winkelhorst D, Oepkes D, Lopriore E. Fetal and neonatal alloimmune thrombocytopenia: evidence based antenatal and postnatal management strategies. Expert Rev Hematol. 2017 Aug;10(8):729-37. PubMed: PM28644735

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http://www.transfusionontario.org/media/IVIG%20Toolkit_COM_2012.pdf