

CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Off-Label Use of Intravenous Immunoglobulin for Solid Organ Transplant Rejection, Paraneoplastic Disorders, or Recurrent Miscarriage: 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 Questions

What is the clinical effectiveness of the off-label use of intravenous immunoglobulin for the treatment of solid organ transplant rejection, paraneoplastic disorders, or recurrent miscarriage?

Key Findings

Five systematic reviews, three randomized controlled trials, and nine non-randomized studies were identified regarding the off-label use of intravenous immunoglobulin for the treatment of solid organ transplant rejection, paraneoplastic disorders, or recurrent miscarriage.

Methods

A limited literature search was conducted 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 to health technology assessments, systematic reviews, meta-analyses, randomized controlled trials, and non-randomized studies. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2012 and October 26, 2017. Internet links were provided, where available.

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 the following conditions that are not approved indications for IVIG: <ul style="list-style-type: none"> • Acute rejection and antibody-mediated rejection resistant to steroids after solid organ transplantation • Paraneoplastic disorders (non-neurology-related) • Recurrent miscarriage
Intervention	Human IVIG or SCIG products, including but not limited to those available in Canada, alone or in combination with corticosteroids or other immunomodulation therapy.
Comparator	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.

Five systematic reviews, three randomized controlled trials, and nine non-randomized studies were identified regarding the off-label use of intravenous immunoglobulin for the treatment of solid organ transplant rejection, paraneoplastic disorders, or recurrent miscarriage. No relevant health technology assessments were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

One systematic review¹ examined the use of intravenous immunoglobulin (IVIG) for the management of paraneoplastic dermatomyositis but did not report any results in the abstract. Four systematic reviews,²⁻⁵ three randomized controlled trials,⁶⁻⁸ five prospective observational studies,⁹⁻¹³ and four retrospective non-randomized studies¹⁴⁻¹⁷ were identified examining the use of IVIG for recurrent miscarriage. The results of the studies were varied and are presented in further detail in Table 2. No studies examining acute rejection and antibody-mediated rejection resistant to steroids after solid organ transplantation were identified.

Table 2: Summary of Included Studies

First Author, Year	Indication	Population	Results	Authors' Conclusions
Systematic Reviews				
Zerdes (2017) ¹	Paraneoplastic dermatomyositis	Not specified in the abstract	Not reported in the abstract	The authors indicated that IVIG might be a treatment alternative for patients resistant to steroids.
Mekinian (2016) ²	Recurrent miscarriage and implantation failures	Women who had experienced ≥ 3 miscarriages	Patients treated with TNF-alpha antagonists + low-dose aspirin, heparin and IVIG had live births of 71% vs 19% with aspirin + heparin	No specific conclusion regarding IVIG was presented in the abstract.
Wang (2016) ³	Unexplained recurrent spontaneous abortion	Not specified in the abstract	More live births were reported with IVIG than placebo, but the difference was not significant	The authors concluded that IVIG may be a beneficial treatment option but there is not enough evidence to support a definitive conclusion.

First Author, Year	Indication	Population	Results	Authors' Conclusions
Egerup (2015) ⁴	Recurrent miscarriage	Not specified in the abstract	<ul style="list-style-type: none"> No significant difference in live births was found between IVIG, placebo, or usual care The risk of AEs appeared to increase with IVIG vs placebo 	The authors concluded that they could not recommend IVIG for recurrent miscarriage.
Wong (2014) ⁹	Recurrent miscarriage	Not specified in the abstract	There was no significant difference in live births between IVIG and control groups	The authors concluded that IVIG was not beneficial in improving live birth rate.
Randomized Controlled Trials				
Meng (2016) ⁵	Unexplained recurrent spontaneous abortion	Not specified in the abstract	There were no significant differences in successful pregnancy between the IVIG and intralipid groups	The authors concluded that intralipid may be used as an alternative to IVIG for unexplained recurrent spontaneous abortion.
Christiansen (2015) ⁷	Secondary recurrent miscarriage	Women with unexplained secondary recurrent miscarriage and ≥ 4 miscarriages	<ul style="list-style-type: none"> Live birth rates were not significantly different between IVIG and placebo groups Median gestational length was higher for IVIG but mean birthweight was not significantly increased 	The authors concluded IVIG could not be recommended for the treatment of secondary recurrent miscarriage.
Nazari (2015) ⁶	Recurrent abortion with unknown etiology	Not specified in the abstract	There was no significant difference in live births or abortion in the IVIG vs the enoxaparin + aspirin group	The authors concluded that the lower cost combination of enoxaparin + aspirin may be an appropriate substitution for IVIG in these patients.
Prospective Observational Studies				
Ahmadi (2017) ⁹	Recurrent miscarriage	Pregnant women with recurrent miscarriage	<ul style="list-style-type: none"> Th17 cells were down-regulated and Treg cells were up-regulated significantly in the IVIG group vs placebo Live births were not significantly different between groups 	The authors concluded that IVIG used for women with recurrent miscarriage influences the Th17/Treg ratio in peripheral blood.

First Author, Year	Indication	Population	Results	Authors' Conclusions
Manfredi (2015) ¹⁰	Recurrent spontaneous abortions	Women with IgG subclass deficiency	Successful pregnancy rate was >90% in the IgG group treated with IVIG	The authors concluded that IVIG was the only successful treatment for these patients. Identifying patients with IgG deficiencies may help target patients who will benefit from IVIG.
Yamada (2015) ¹¹	Recurrent miscarriage	Women who had experienced ≥ 6 miscarriages	<ul style="list-style-type: none"> • Live birth rate was 30.8% • Rate of reduction of NK cell activity was greater in the group with successful pregnancies 	The authors did not provide an overall conclusion regarding IVIG in the abstract.
Ramos-Medina (2014) ¹²	Recurrent reproductive failure	Women with recurrent reproductive failure with NK or NKT-like expansion	Live birth rate was significantly improved in the IVIG group vs no treatment group (96.3% vs 30.6%)	The authors concluded that clinical pregnancy and live birth rates were improved with IVIG in these patients.
Moraru (2012) ¹⁵	Recurrent reproductive failure	Women with recurrent reproductive failure and expanded CD56(+) cells	<ul style="list-style-type: none"> • Pregnancy and live birth rates were significantly greater in the IVIG vs those without. • After 3 cycles of IVIG, NK cell percentages decreased significantly 	The authors concluded that IVIG was safe and effective for these women.
Retrospective Observational Studies				
Lee (2016) ¹⁴	Recurrent pregnancy loss	Women who had experienced ≥ 2 miscarriages, with or without cellular immune abnormality	<ul style="list-style-type: none"> • No significant difference in live birth rates in women with or without cellular immune abnormality • No significant difference in success rates between groups with cellular immune abnormality 	The authors concluded that IVIG was likely to be clinically effective for women with cellular immune abnormality and recurrent pregnancy loss.
Cohen (2015) ^{1b}	Recurrent miscarriage	Women who had experienced recurrent miscarriage (average = 5) and elevated NK cells	<ul style="list-style-type: none"> • 86.7% of women became pregnant • 82.0% had a live birth 	The authors concluded that low-dose IVIG therapy was effective for women with immunologic abortion and elevated NK cells.

First Author, Year	Indication	Population	Results	Authors' Conclusions
Nyborg (2014) ¹⁰	Recurrent miscarriage and implantation failure	Women who had experienced ≥ 3 consecutive pregnancy losses after ART	<ul style="list-style-type: none"> 36.5% of patients had a live birth after first ET with IVIG + prednisone Cumulative live-birth rate was 61.5% 	The authors concluded that IVIG + prednisone was a promising treatment for these women but further placebo controlled trials were required.
Coulam (2012) ¹¹	Reproductive failure	Women who had experienced reproductive failure with elevated NK cells	No difference was observed between IVIG and intralipid for women with recurrent implantation failure and elevated NK cell activity	

AE = adverse events; ART = assisted reproductive technology; IVIG = intravenous immunoglobulin; NK = natural killer; NKT = natural killer T; vs = versus

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

Prospective Observational Studies

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Appendix — Further Information

Previous CADTH Reports

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Randomized Controlled Trials – Steroid Resistance not Specified in Abstract

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Non-Randomized Studies – Steroid Resistance not Specified in Abstract

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