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CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Off-Label Use of Intravenous Immunoglobulin for Autoimmune or Inflammatory Conditions: Clinical Effectiveness

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Acknowledgments:

Research Question

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

Key Findings

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

Methods

A limited literature search was conducted on key resources PubMed, The Cochrane Library, University of York Centre for Reviews and Dissemination (CRD) databases and a focused Internet search. Methodological filters were applied to limit retrieval to health technology assessments, systematic reviews, meta-analyses and randomized controlled trials. A focused search for non-randomized studies was conducted. For this search, main concepts appeared in title or subject heading and a non-randomized studies filter was applied. Both searches were limited to English language documents published between November 2009 and October 18, 2017.

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 autoimmune or inflammatory conditions that are not approved indications for IVIG, including but not limited to: • Antineutrophil cytoplasmic antibody-positive vasculitis • Catastrophic antiphospholipid syndrome • Kawasaki disease • Polymyositis • Rheumatoid arthritis • Still's disease • Systemic juvenile idiopathic arthritis • Systemic lupus erythematosus • Systemic vasculitis • Wegener's granulomatosis
Intervention	Human IVIG or SCIG products, 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.

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

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

Fourteen systematic reviews[1-14] (three with meta-analyses[2,8,14]), four randomized controlled trials,[15-18] and seven non-randomized studies[19-25] were identified regarding the clinical effectiveness of the off-label use of intravenous or subcutaneous immunoglobulin for the treatment of autoimmune or inflammatory conditions. Detailed study characteristics are provided in Table 2.

The literature investigated the effectiveness of IVIG in fourteen autoimmune or inflammatory conditions that are not approved indications for IVIG.[1-25] These were pediatric

autoimmune neuropsychiatric disorders associated with streptococcal infections,[1,16] myasthenia gravis,[2,11] acute rheumatic fever,[3,10] Sydenham's chorea,[4,18] autoimmune encephalitis,[5] dermatomyositis,[6,12-13,17,24-25] polymyositis,[6,12-13,17,21] systemic lupus erythematosus,[7,8] Wegener's granulomatosis,[9] Lambert-Eaton myasthenic syndrome,[14] bullous pemphigoid,[15] Kawasaki disease,[19,22] autoimmune congenital heart block,[20] and antiphospholipid syndrome.[20,23] Fifteen studies suggested IVIG provided benefit alone or as an adjuvant treatment for patients with autoimmune or inflammatory conditions that are not approved indications for IVIG.[1,5-8,12-15,18,20,22-25] Nine studies reported that IVIG therapy was either ineffective or that there was insufficient data to draw a conclusion from.[2-3,9-11,16-17,19,21] The findings of one study were unavailable as the authors did not report any results in the abstract.[4]

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

First Author, Year	Study Characteristics	Intervention	Comparator	Outcomes	Conclusions
Systematic Reviews and Meta-Analyses					
Farhood, 2016[1]	• 11 studies included (1 RCT and 1 retrospective study on IVIG) • Children with PANDAS • N=NR	• Tonsillectomy • Antibiotic treatment • IVIG • Psychiatric medications or therapy	• Not specified in abstract	• Not specified in abstract	*"Studies support the use of IVIG, however more investigation is needed prior to widespread adoption of this treatment given its potential risks."*[1]
Ortiz-Salas, 2016[2]	• MA performed • 24 RCTs and analytical observational studies included • Any patient with Guillain-Barre syndrome or MG • N=NR	• IVIG	• PE	• Safety • Length of hospital stay • Duration of ventilator support	• The authors concluded that no evidence was found to suggest IVIG or PE differed in their efficacy or safety • In addition, no statistically significant differences were observed for length of hospital stay or duration of ventilator support
Cilliers, 2015[3]	• 8 RCTs included • Adults and children with acute rheumatic fever • N=996	• Anti-inflammatory agents (including IVIG)	• Placebo or controls • No treatment • Anti-inflammatory agents versus one another	• Cardiac disease one year after treatment • Adverse events	*"Little evidence of benefit was found when corticosteroids or intravenous immunoglobulins were used to reduce the risk of heart valve lesions in patients with acute rheumatic fever."*[3]
Mohammad, 2015[4]	• Number and type of studies included not	• IVIG	• Not specified in abstract	• Clinical recovery • Morbidity	• Not specified in abstract

First Author, Year	Study Characteristics	Intervention	Comparator	Outcomes	Conclusions
	specified in abstract • Patients with acute Sydenham's chorea • N=NR				
Nosadini, 2015[5]	• Number and type of studies included not specified in abstract • Patients with autoimmune encephalitis • N=NR	• Immune therapy (including IVIG)	• Not specified in abstract	• Not specified in abstract	*"There are common therapeutic themes emerging. Firstly, patients given immune therapy do better and relapse less than patients given no treatment. Secondly, patients given early treatment do better. And thirdly, when patients fail first-line therapy, second-line therapy improves outcomes and reduces relapses. Given the retrospective uncontrolled data, the literature has inherent bias, including severity and reporting bias."*[5]
Vermaak, 2015[6]	• 12 studies included • Adults with DM or PM • N=NR	• Immunotherapy (including IVIG)	• Not specified in abstract	• Muscle strength after 6 months • IMACS definition of improvement • Patient and physician global scores • Physical function • Muscle enzymes	• Patients with DM or PM treated with IVIG demonstrated improved outcomes • Additional high-quality RCTs are required to establish which treatments are most likely to benefit patients
Man, 2014[7]	• Number and type of studies included not specified in abstract • Patients with systemic lupus erythematosus • N=NR	• Treatment options for the neuro-ophthalmologic manifestations of systemic lupus erythematosus (including IVIG)	• Not specified in abstract	• Not specified in abstract	• IVIG can be considered for the treatment of glucocorticoid-dependent or refractory cases of neuro-ophthalmologic manifestations in systemic lupus erythematosus
Sakthiswary, 2014[8]	• MA performed • 13 studies included (3 RCTs and 10	• IVIG	• Not specified in abstract	• Disease activity scores • Steroid dose • Complement	• IVIG was effective in reducing disease activity scores and improving complement levels

First Author, Year	Study Characteristics	Intervention	Comparator	Outcomes	Conclusions
	observational studies) • Adults with systemic lupus erythematosus • N=NR			levels • Autoantibodies • Renal function	• According to the authors, the review was limited by well-designed controlled trials with adequate sample size
Fortin, 2013[9]	• 1 RCT included • Adults with Wegener's granulomatosis • N=34	• IVIG with azathioprine and prednisolone	• Placebo with azathioprine and prednisolone	• Mortality • Adverse events • Time to relapse • Open-label rescue therapy • Infection rate • Disease activity score	*"There is insufficient evidence from one RCT that Ivig adjuvant therapy provides a therapeutic advantage compared with the combination of steroids and immunosuppressants for patients with WG."*[9]
Cilliers, 2012[10]	• 8 RCTs included • Adults and children with acute rheumatic fever • N=996	• Anti-inflammatory agents (including IVIG)	• Placebo or controls • No treatment • Anti-inflammatory agents versus one another	• Cardiac disease one year after treatment • Adverse events	*"There is little evidence of benefit from using corticosteroids or intravenous immunoglobulins to reduce the risk of heart valve lesions in patients with acute rheumatic fever. The antiquity of most of the trials restricted adequate statistical analysis of the data and acceptable assessment of clinical outcomes by current standards. Additionally there was substantial risk of bias, so results should be viewed with caution."*[10]
Gajdos, 2012[11]	• 7 RCTs included • Patients with chronic MG • N=450	• IVIG	• No treatment • Placebo • Methylprednisolone • PE	• Quantitative MG score • Myasthenic muscle score • Adverse events	• Individual studies varied in their conclusions. Some studies reported a benefit to IVIG therapy while other did not • The authors concluded there was insufficient evidence from RCTs to determine the efficacy of IVIG in chronic MG
Gordon, 2012[12]	• 10 RCTs or qRCTs included • Patients with DM or PM • N=258	• Immunotherapy (including IVIG)	• Placebo • Immuno-suppressant regimes versus one another	• Function or disability scale • IMACS definition of improvement • Number of relapses and time to relapse • Remission and	• The only included RCT on IVIG reported statistically significant improvement in scores of muscle strength over placebo • There is a lack of high quality RCTs that assess the clinical effectiveness

First Author, Year	Study Characteristics	Intervention	Comparator	Outcomes	Conclusions
				time-to-remission • Cumulative corticosteroid dose • Serious adverse effects	of immunosuppressants in inflammatory myositis
Wang, 2012[13]	• 14 studies included (2 RCTs, 9 prospective open studies, and 3 retrospective studies) • Adults with DM or PM • N=308	• IVIG (with or without corticosteroid)	• Placebo	• Muscle strength • Serum creatine kinase level • Adverse events • Corticosteroid dose required for maintenance	• IVIG was effective in the treatment of adult patients with PM or DM • Adverse events resulting from IVIG treatment were generally well tolerable
Keogh, 2011[14]	• MA performed • 4 controlled trials included (3 cross-over trials and 1 parallel group) • Adults and children with Lambert-Eaton myasthenic syndrome • N=308	• 3,4-diaminopyridine • IVIG	• Placebo	• Muscle strength score • Myometric limb strength • Resting compound muscle action potential	• IVIG showed a beneficial effect on myometric limb strength versus placebo • No significant improvement in the mean resting compound muscle action potential amplitude was observed
Randomized Controlled Trials					
Amagai, 2017[15]	• Patients with bullous pemphigoid • N=56	• IVIG	• Placebo	• Disease activity score • Anti-BP180 antibody titer • Safety	• IVIG had a beneficial effect on the disease activity score for patients with bullous pemphigoid who are resistant to steroid therapy
Williams, 2016[16]	• Children with PANDAS and moderate to severe OCD • N=35	• IVIG	• Placebo	• Children's Yale-Brown Obsessive Compulsive Scale • Clinical Global Impressions-Improvement rating	• IVIG failed to show superiority over placebo • IVIG was safe and well tolerated • Further future investigations are warranted
Miyasaka, 2012[17]	• Patients with PM or DM resistant to corticosteroids • N=26	• IVIG (drug code GB-0998)	• Placebo	• Manual muscle test score • Serum creatine kinase level • Activities of daily living score	• No significant differences between treatment groups were observed

First Author, Year	Study Characteristics	Intervention	Comparator	Outcomes	Conclusions
Walker, 2012[18]	• Children with Sydenham's choreas • N=20	• IVIG and standard management	• Standard management alone	• Not specified in abstract	*"All three outcome measurement tools found improved outcomes in the group that received intravenous immunoglobulin."*[18]
Non-Randomized Studies					
Lin, 2015[19]	• Retrospective study • Patients with Kawasaki disease • N=1,073	• Therapy for Kawasaki disease (including IVIG)	• Therapy for Kawasaki disease	• Acute coronary severities • Survival free of coronary aneurysm persistence and ischaemia	*"Although IVIG use improves the initial severity of coronary lesions, it does not further modify the long-term fate of coronary aneurysms."*[19]
Ruffatti, 2015[20]	• Prospective cohort study • Pregnant women with high-risk APS • Patients with autoimmune CHB • N=56	• In APS patients: PE plus IVIG • In CHB patients : PE combined with IVIG and steroids	• In APS patients : PE or IA plus IVIG • IN CHB patients: steroids alone	• Efficacy • Safety • Maternal features • Pregnancy outcome • Side effects	• The authors concluded that PE or IA along with IVIG and conventional therapy could be valuable for treating pregnant APS women • Patients with autoimmune CHB treated with the combined therapy (PE with IVIG and steroids) showed improved outcomes versus treatment with steroids alone
Liew, 2014[21]	• Retrospective analysis • Children and adolescents with juvenile MG • N=54	• IVIG	• PLEX	• Improvement in objective physical examination findings • Patients' reported improvement in symptoms and functional abilities	*"This study provides class III evidence that PLEX and IVIG both have high response rates as maintenance therapies and are reasonable therapeutic options for juvenile MG. Plasmapheresis may have a more consistent response rate than IVIG in this setting."*[21]
Kobayashi, 2013[22]	• Retrospective review • Patients with Kawasaki disease who failed to respond to initial IVIG • N=359	• IVIG	• Prednisolone • IVIG and prednisolone	• Failing to respond to first-line rescue therapy • Coronary artery abnormalities	• IVIG and prednisolone in combination was more promising than either drug alone in the treatment of IVIG nonresponders
Tenti, 2013[23]	• Prospective study • Adults with APS	• IVIG plus conventional	• Conventional therapy alone	• Occurrence of thromboembolic	• The addition of IVIG to conventional therapy was

First Author, Year	Study Characteristics	Intervention	Comparator	Outcomes	Conclusions
	• N=14	therapy		events • Number of anti-phospholipid antibodies	effective in preventing the occurrence of thromboembolic events • Additional research using larger sample sizes is required to fully understand the role of IVIG for the treatment of patients with APS
Kampylafka, 2012[24]	• Retrospective study • Adults with DM • N=42	• IVIG plus conventional therapy	• Conventional therapy	• Muscular remission rate • Muscular and cutaneous involvement • Number of muscular relapses	• The authors concluded that IVIG may improve the short-term prognosis of DM patients • IVIG treated patients had significantly better muscular and cutaneous involvement scores (compared to their pre-treatment scores)
Lam, 2011[25]	• Retrospective cohort study • Patients with juvenile DM • N=78	• Treatment with IVIG	• Treatment without IVIG	• Muscle strength • Photosensitivity • Time to quiescence • Disease activity	*"This study, involving the largest [juvenile] DM cohort receiving Ivig to date, applied bias-reduction methods and demonstrated Ivig efficacy in controlling [juvenile] DM disease activity, particularly for [corticosteroid resistant] patients."*[25]

APS = antiphospholipid syndrome; CHB = congenital heart block; DM = dermatomyositis; IA = immunoadsorption; IMACS = International Myositis Assessment and Clinical Studies Group; IVIG = intravenous immunoglobulin; MA = meta-analysis; MG = myasthenia gravis; NR = not reported; OCD = obsessive-compulsive disorder; PANDAS = pediatric autoimmune neuropsychiatric disorders associated with streptococcal infections; PE = plasma exchange; PLEX = plasmapheresis; PM = polymyositis; 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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Appendix — Further Information

Previous CADTH Reports

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Alternative Comparator – Comparison of IVIG Treatment Strategies

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