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CADTH RAPID RESPONSE REPORT: SUMMARY OF ABSTRACTS

Off-Label Use of Intravenous Immunoglobulin for Dermatological 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 dermatological conditions?

Key Findings

Twenty-one systematic reviews and meta-analyses and five randomized controlled trials were identified regarding the clinical effectiveness of the off-label use of intravenous or subcutaneous immunoglobulin for the treatment of dermatological conditions.

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 and randomized controlled trials. Where possible, retrieval was limited to the human population. The search was also limited to English language documents published between January 1, 2009 and October 24, 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 dermatological conditions that are not approved indications for IVIG, including but not limited to: • Atopic dermatitis/eczema • Autoimmune bullous diseases • Dermatomyositis/Polymyositis • Pemphigus • Pyoderma gangrenosum • Stevens-Johnson syndrome • Systemic sclerosis/scleroderma • Toxic epidermal necrolysis • Urticaria
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.
Comparator	Treatment as usual, placebo, no treatment
Outcomes	Clinical benefits and harms
Study Designs	Health technology assessments, systematic reviews, meta-analyses, randomized controlled trials

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.

Twenty-one systematic reviews and meta-analyses and five randomized controlled trials were identified regarding the clinical effectiveness of the off-label use of intravenous or subcutaneous immunoglobulin for the treatment of dermatological conditions. No relevant health technology assessments were identified.

Additional references of potential interest are provided in the appendix.

Overall Summary of Findings

Twenty-one systematic reviews and meta-analyses[1-21] and five randomized controlled trials[22-26] were identified regarding the clinical effectiveness of the off-label use of intravenous or subcutaneous immunoglobulin for the treatment of dermatological conditions. The dermatological conditions that were studied included necrobiotic xanthogranuloma,[1] paraneoplastic dermatomyositis,[2] Stevens-Johnson syndrome and toxic epidermal necrolysis,[3,6,7,9,18,20,21] drug rash with eosinophilia and systemic symptoms,[4] pemphigus,[5,8,11,12,14,15,22,26] *Mycoplasma pneumoniae*-associated mucocutaneous disease,[10] dermatomyositis and polymyositis,[13,17,19,24] Wegener's granulomatosis,[16] skin sclerosis in diffuse cutaneous systemic sclerosis,[23] and moderate to severe childhood atopic dermatitis.[25] The results of the studies varied in reference to the effectiveness of intravenous immunoglobulin for these conditions. Further details are provided in Table 2.

Table 2: Summary of Included Studies

First Author, Year	Indication	Population	Results	Authors' Conclusions
Systematic Reviews				
Miguel (2017)[1]	Necrobiotic xanthogranuloma	Not specified in the abstract	NR in the abstract	High-dose IVIG was specified as one treatment option identified in the review but not results or conclusions were provided in the abstract.
Zerdes (2017)[2]	Paraneoplastic dermatomyositis	Not specified in the abstract	NR in the abstract	IVIG may be a viable alternative treatment for cases resistant to prednisone.
Zimmermann (2017)[3]	SJS/TEN	Not specified in the abstract	NR in the abstract	There were no beneficial findings identified regarding the use of IVIG for SJS/TEN.

Table 2: Summary of Included Studies

First Author, Year	Indication	Population	Results	Authors' Conclusions
Bommersbach (2016)[4]	DRESS	Not specified in the abstract	NR in the abstract	IVIG may be a promising management option for DRESS.
Cholera (2016)[b]	Pemphigus vulgaris	Not specified in the abstract	NR in the abstract	IVIG was reported in the literature as a treatment option for patients who did not respond to standard treatment.
Huang (2016)[b]	TEN	Not specified in the abstract	• Overall mortality = 24.2% • Overall mortality of adults treated with high-dose IVIG = 11.7%	The authors concluded the evidence did not support the use of IVIG, including high-dose, for the treatment of TEN.
Ye (2016)[f]	SJS/TEN	Not specified in the abstract	• Corticosteroid IVIG combination significantly reduced recovery time compared with corticosteroid alone • Beneficial effects were greater for those treated with high-dose IVIG • IVIG use was associated with a decrease in mortality	The authors concluded that the combination of IVIG and corticosteroid may reduce recovery time for SJS/TEN.
Atzmony (2015)[8]	Pemphigus vulgaris and pemphigus foliaceus	Not specified in the abstract	• Adjuvants, including IVIG, were found to decrease the risk of relapse. • Different adjuvants were pooled in the analysis	The authors concluded that adjuvant therapies, including IVIG, may have a role in treating pemphigus.
Barron (2015)[9]	SJS/TEN	Not specified in the abstract	• "Meta-regression demonstrated a strong inverse correlation between IVIG dosage and SMRs."	The authors concluded that IVIG at doses ≥2 g/kg may significantly reduce mortality in these patients.

Table 2: Summary of Included Studies

First Author, Year	Indication	Population	Results	Authors' Conclusions
			• SMRs did not differ significantly between studies	
Canavan (2015)[10]	Mycoplasma pneumoniae-associated mucocutaneous disease	All ages	NR in the abstract	IVIG was identified from the literature as a treatment option.
McMillan (2015)[11]	Pemphigus vulgaris	Not specified in the abstract	NR in the abstract	IVIG was identified from the literature as a treatment option.
Taylor (2015)[12]	Mucous membrane pemphigoid	Not specified in the abstract	NR in the abstract	The authors identified IVIG as a promising intervention for mucous membrane pemphigoid.
Vermaak (2015)[13]	Dermatomyositis and polymyositis	Not specified in the abstract	NR in the abstract	The authors concluded that no specific treatment could be recommended based on the results of the review; however, IVIG was identified as one treatment with improved outcomes.
Zhao (2015)[14]	Pemphigus vulgaris	Not specified in the abstract	NR in the abstract	The authors concluded that the available evidence was incomplete and inconclusive. IVIG appeared to be a promising treatment but requires further study for confirmation.
Atzmony (2014)[15]	Pemphigus vulgaris and pemphigus foliaceus	Not specified in the abstract	IVIG had more favourable short-term efficacy versus placeb0	Further study is required before treatment recommendations can be made.
Fortin (2013)[16]	Wegener's granulomatosis	Not specified in the abstract	No significant difference was reported in mortality, serious	The authors concluded there was not sufficient evidence to recommend

Table 2: Summary of Included Studies

First Author, Year	Indication	Population	Results	Authors' Conclusions
			adverse events, time to relapse, open-label rescue therapy, and infection rates between IVIG and placebo as adjuvant treatment.	IVIG as adjuvant treatment.
Gordon (2012)[17]	Dermatomyositis and polymyositis	Not specified in the abstract	Significant improvement was reported in muscle strength scores over 3 months in the IVIG group,	The authors concluded that the review highlighted the need for RCTs to assess the efficacy of treatments.
Huang (2012)[18]	TEN	All ages	• Overall mortality of patients treated with IVIG = 19.9% • Treatment with high-dose IVIG resulted in significantly lower mortality than low-dose IVIG • Pediatric patients had significantly lower mortality than adults	The authors concluded that the evidence did not support the clinical benefit of IVIG.
Wang (2012)[19]	Polymyositis or dermatomyositis	Adult patients	IVIG + corticosteroid significantly improved muscle strength and decreased serum creatine kinase versus placebo	The authors concluded that IVIG was an effective and relatively safe treatment for patients with polymyositis or dermatomyositis
Del Pozzo-Magana (2011)[20]	SJS/TEN	Children	IVIG + steroids • had similar results as dressing and support treatment alone • longer time to achieve remission • associated with more complications and deaths	The authors concluded that IVIG + steroids improved outcomes but the results were variable between the identified studies.
Roujeau (2011)[21]	SJS/TEN	Not specified in the abstract	Pooled mortality ratio = 0.82	The authors concluded that neither corticosteroids nor IVIG

Table 2: Summary of Included Studies

First Author, Year	Indication	Population	Results	Authors' Conclusions
				resulted in any important reduction in the risk of mortality.
Randomized Controlled Trials				
Amagai (2017)[22]	Bullous pemphigoid	Patients who failed prednisolone Age not specified in the abstract	• DAS15 was 12.5 points lower in the IVIG group versus placebo	The authors concluded that IVIG was therapeutically beneficial for patients with bullous pemphigoid who were resistant to steroids.
Takehara (2013)[23]	Skin sclerosis in diffuse cutaneous systemic sclerosis	Not specified in the abstract	There was no significant difference observed in MRSS between IVIG and placebo groups	The authors indicated that the primary endpoint was not met but they still considered that repeated IVIG may be effective for skin sclerosis in diffuse cutaneous systemic sclerosis.
Miyasaka (2012)[24]	Polymyositis and dermatomyositis resistant to corticosteroids	Not specified in the abstract	Significant improvements in manual muscle test score, serum creatine kinase level, and activities of daily living score were observed in both groups	The authors concluded that IVIG therapy with polyethylene glycol-treated human IgG could be used with the same precautions as other IVIG therapy.
Jee (2011)[25]	Moderate to severe childhood atopic dermatitis	Children	Disease severity index was significantly reduced in the IVIG group at 3 months	The authors concluded that IVIG may improve symptoms at 3 months of use but the improvement may not be sustained beyond 6 months.
Amagai (2009)[26]	Pemphigus vulgaris or pemphigus foliaceus	Patients who failed prednisolone Age not specified in the abstract	• Disease activity and enzyme-linked immunosorbent assay scores were significantly lower in the high-dose IVIG	The authors concluded that high-dose IVIG was effective and safe for patients with pemphigus who were resistant to steroid treatment.

Table 2: Summary of Included Studies

First Author, Year	Indication	Population	Results	Authors' Conclusions
			group • There was no difference in safety between 400mg/kg, 200 mg/kg or placebo doses	

DAS15 = disease activity score on day 15DRESS = drug rash with eosinophilia and systemic symptoms; IVIG = intravenous immunoglobulin; MRSS = modified Rodnan skin thickness score; NR = not reported; SJS = Stevens-Johnson syndrome; SMR = standardized mortality ratio; TEN = toxic epidermal necrolysis

References Summarized

Health Technology Assessments

No literature identified.

Systematic Reviews and Meta-analyses

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Appendix — Further Information

Systematic Reviews of Case Studies or Case Series

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Case Studies and Case Series

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