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SUMMARY WITH CRITICAL APPRAISAL

Off-Label Use of Intravenous Immunoglobulin for Dermatological Conditions: A Review of 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.

Context and Policy Issues

Immunoglobulin (also referred to as immune globulin or gamma globulin) is a sterile, purified blood product pooled from the plasma of thousands of healthy donors.[1-3] Immunoglobulin may be used as a replacement therapy for patients with primary or secondary antibody deficiency,[4] as an immunomodulatory agent,[5] or for treatment or prophylaxis of systemic inflammation.[4,5] Immunoglobulin contains Aβ-antibodies, which help patients regain normal immunoregulation and immune homeostasis,[3,6] and immunoglobulin may be administered as intravenous immunoglobulin (IVIG) or as subcutaneous immunoglobulin (SCIG).

In Canada, various preparations of immunoglobulin are approved specifically for use in patients with one or more of the following six conditions: primary immune deficiency, immune thrombocytopenic purpura, secondary immune deficiency states, chronic inflammatory demyelinating polyneuropathy, Guillain-Barré Syndrome, and multifocal motor neuropathy.[7] The products approved for use in Canada are Flebogamma, Octagam and WinRho SDF.[7] Others approved for marketing are Atgam, Cytogam, Gammagard, Gamunex, Hepagam B, Igivnex, Panzyga, Privigen, and Varizig.[8]

In recent years, IVIG has increasingly been considered for or used off-label for other conditions with variable etiology and the mechanism of action for IVIG in each treatment is not yet clearly understood. In 2017, a CADTH Rapid Response report[9] reviewed the off-label use of IVIG for Alzheimer's disease, drug-resistant epilepsy, influenza, sepsis or septic shock syndrome, and for adverse effects of allogeneic bone marrow or stem cell transplantation. Off-label IVIG has been added to the treatment of dermatological conditions such as atopic dermatitis/eczema, autoimmune bullous diseases, dermatomyositis/polymyositis, pemphigus, pyoderma gangrenosum, Stevens-Johnson syndrome, systemic sclerosis/scleroderma, toxic epidermal necrolysis, and urticaria, especially when the conditions were refractory to conventional corticosteroid therapy.[10,11]

Atopic dermatitis is a chronic pruritic inflammatory skin disease that occurs most frequently in children, affecting approximately 5 to 20 percent of children worldwide and approximately 11 percent in the US population.[12] Dermatomyositis and polymyositis are idiopathic inflammatory myopathies, characterized by the shared features of proximal skeletal muscle weakness and by evidence of muscle inflammation; cardiac involvement can happen and may be expressed as changes in cardiac enzymes such as creatine kinase; the combined incidence of dermatomyositis and polymyositis has been estimated at 2 per 100,000 annually in the general population.[13] Pemphigus or bullous pemphigoid is defined as a group of life-threatening blistering disorders characterized by acantholysis (loss of keratinocyte to keratinocyte adhesion) that results in the formation of intraepithelial blisters in mucous membranes and skin.[14,15] Pyoderma gangrenosum is a neutrophilic dermatosis that presents as an inflammatory and ulcerative disorder of the skin; it is a rare disorder with an estimated incidence of 3 to 10 cases per million people worldwide per year.[16] Stevens-Johnson syndrome and toxic epidermal necrolysis are severe mucocutaneous adverse reactions, most commonly triggered by medications, characterized by fever and extensive necrosis and detachment of the epidermis, with an overall mortality rate

approximately 25 percent.[17] Scleroderma may be a clinical feature of limited anatomic extent affecting only the skin and subjacent tissues, or it may be associated with systemic involvement scleroderma is used to describe the presence of thickened, hardened skin. The prevalence rates of scleroderma-like conditions range from 4 to 489 cases per million individuals in the US.[18] Chronic urticaria is defined by the presence of urticaria (hives) for a duration of longer than six weeks; it affects up to 1 percent of the general population in the United States.[19]

This Rapid Response report aims to review the comparative effectiveness of IVIG and SCIG for off-label use for dermatological conditions, and is complementary to the 2017 CADTH Rapid Response, Summary of Abstracts report: "Off-Label Use of Intravenous Immunoglobulin for Dermatological Conditions: Clinical Effectiveness".[20]

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

The literature search identified evidence regarding the comparative clinical effectiveness of IVIG versus supportive care, corticosteroid treatment, or placebo, on dermatological conditions such as Stevens-Johnson Syndrome (SJS), toxic epidermal necrolysis (TEN), polymyositis (PM), dermatomyositis (DM), bullous pemphigoid (BP), and systemic sclerosis (SS). In general, evidence on IVIG use for dermatological conditions is scarce and based mainly on reviews of non-randomized studies and small-sized RCTs. The results should be interpreted with caution given the strength of the evidence and the heterogeneity among the included studies.

For patients with SJS and/or TEN, treatment with IVIG - alone or combined with corticosteroids did not have survival benefit compared to no-IVIG treatment, but there may be a positive correlation between high IVIG dosage and clinical benefits such as mortality rate and recovery time. Pediatric patients treated with IVIG seemed to have lower mortality than adults. For PM and/or DM, IVIG combined with corticosteroid improved muscle strength and improved biochemical profile compared to placebo or corticosteroid alone, while IVIG alone did not seem to have any impact compared to placebo. For BP, there was a statistically significant decrease in the time required until treatment reduction in the IVIG group compared to the placebo group. For SJS/TEN, PM/DM and BP, treatment with IVIG was based on one course of treatment. For SS, there was no statistically significant difference in skin thickness between the IVIG group and the placebo group after one course of treatment, while the difference was statistically significant in favour of IVIG after two courses of treatment.

No study involving subcutaneous immunoglobulin met the inclusion criteria for this report

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, 2012 and October 24, 2017. Internet links were provided, where available.

Rapid Response reports are organized so that the evidence for each research question is presented separately.

Selection Criteria and Methods

One reviewer screened citations and selected studies. In the first level of screening, titles and abstracts were reviewed and potentially relevant articles were retrieved and assessed for inclusion. The final selection of full-text articles was 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	Heath technology assessments (HTAs), systematic reviews (SRs) and meta-analyses (MAs), randomized controlled trials (RCTs)

Exclusion Criteria

Articles were excluded if they did not meet the selection criteria outlined in Table 1, they were duplicate publications, or were published prior to 2012. SRs that included only one trial (which was not an RCT or was published before 2012) were excluded.

Critical Appraisal of Individual Studies

The included systematic reviews and clinical trials were critically appraised using AMSTAR II,[21] and Downs and Black[22] instruments, respectively. Summary scores were not calculated for the included studies; rather, a review of the strengths and limitations of each included study were described.

Summary of Evidence

Quantity of Research Available

A total of 552 citations were identified in the literature search. Following screening of titles and abstracts, 528 citations were excluded and 24 potentially relevant reports from the electronic search were retrieved for full-text review. No potentially relevant publications were retrieved from the grey literature search. Of these potentially relevant articles, 16 publications were excluded for various reasons, while eight publications met the inclusion criteria and were included in this report. Appendix 1 presents the PRISMA flowchart of the study selection.

Summary of Study Characteristics

A detailed summary of the included studies is provided in Appendix 2.

Study Design

Four SRs with meta-analysis,[23-26] one narrative SR,[27] and three RCTs[28-30] were included in the review. One SR performed literature search up to 2012 and included ten relevant non-RCTs (total 96 studies on all interventions),[23] one SR performed literature search up to 2011 and included 13 non-RCTs,[24] one SR performed literature search up to 2015 and included 26 non-RCTs,[25] one SR performed literature search up to 2011 and included 17 non-RCTs,[26] and one SR performed literature search up to 2011 and included 12 non-RCTs and two RCTs.[27]

Country of Origin

One SR was conducted in Germany,[23] one SR in the US,[24] two SRs in China,[25,27] and one SR in Taiwan.[26] All three RCTs were conducted in Japan.[28-30]

Patient Population

Four SRs included patients with STS and/or TEN,[23-26] and one SR included patients with PM and/or DM.[27] One RCT included patients with BP,[28] one RCT included patients with SS,[29] and one RCT included patients with PM and/or DM.[30] All included SRs included patients of any age (number of patients not specified). One SR had subgroup analysis for pediatric and adult patients (number of patients not specified).[26] All included RCTs included patients with any age, and included 56 patients,[28] 62 patients,[29] and 26 patients.[30]

Interventions and Comparators

Two SRs compared IVIG to supportive care,[23,26] one SR compared IVIG + corticosteroids to corticosteroids alone,[25] one SR compared IVIG to no IVIG,[24] and one SR compared IVIG to placebo and corticosteroids alone.[27] All three RCTs compared IVIG to placebo.[28-30] All included SRs and clinical trials had patients on one course of IVIG treatment, except one RCT[29] having data on patients with one and two courses of IVIG treatment. No study involving subcutaneous immunoglobulin met the inclusion criteria for this report

Outcomes

One SR reported risk of death,[23] one SR reported risk of death and correlation between IVIG dosage and death rate,[24] one SR reported risk of death, recovery time and length of hospital stay,[25] one SR reported risk of death with subgroup analyses for high vs low IVIG dosage and for children vs adults.[26] All three SRs above that reported risk of death are on

patients with STS and/or TEN. One SR reported muscle strength improvement, serum creatine kinase level reduction, corticosteroid dose reduction, and adverse events.[27] One RCT reported Disease Activity Score (DAS), time to treatment reduction, costicosteroids use and anti-BP180 antibody titers,[28] one RCT reported Modified Rodnan skin thickness score (MRSS) and adverse reactions,[29] and one RCT reported manual muscle test score (MMT), serum creatine kinase levels, activities of daily living score (ADL), length of hospital stay, and time to normalization of serum creatine kinase level.[30]

Summary of Critical Appraisal

Details of the strengths and limitations of the included studies are summarized in Appendix 3.

The included SRs[23-27] provided an a priori design and performed a systematic literature search. Procedures for the independent duplicate selection and data extraction of studies were in place, a list of included studies and characteristics were provided. Quality assessment of the included studies was performed and used in formulating conclusions in two SRs,[23,27] and not performed in the remaining three.[24-26]. Publication bias was assessed in three SRs,[23-25] and not assessed in the remaining two.[26,27] All five SRs did not included a list of excluded studies.[23-27] The SRs were based mainly on non-RCTs which may be a source of bias.

The included clinical trials[28-30] are RCTs, patient and assessors were blinded to treatment assignment, the hypotheses were clearly described, the method of selection from the source population and representation were described, losses to follow-up were reported, main outcomes, interventions, patient characteristics, and main findings were clearly described, and estimates of random variability and actual probability values were provided. Two trials did not perform a power calculation to detect a clinically important effect.[29,30] One trial performed power calculation[28] but there was over 20% drop-out rate, leading to a sample size of completed patients that could not have an 80% power to detect a clinically important effect.

Summary of Findings

Details of the findings of the included studies are provided in Appendix 4.

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

Stevens-Johnson Syndrome and/or toxic epidermal necrolysis (SJS/TEN)

Four SRs with meta-analysis evaluated the effectiveness of IVIG for patients with SJS and/or TEN.[23-26] In general, IVIG alone or combined with corticosteroid did not have a survival benefit compared to no-IVIG treatment, but a positive correlation between IVIG dosage and clinical benefit was found.

The authors of one SR[23] found no statistically significant difference in survival benefit between IVIG and supportive care; they concluded that no beneficial findings were observed. The authors of a second SR[24] also found that survival benefit was not statistically significant between the no-IVIG group and patients on IVIG (alone or combined with corticosteroid treatment). Subgroup analyses showed there was a correlation between IVIG dosage and survival benefit, with the IVIG ≥2 grams (g)/kilogram (kg)/day group

showing a statistically decreased mortality rate compared to no-IVIG use. The authors concluded that IVIG at high dosage appeared to significantly reduce mortality. One SR[25] found IVIG combined with a corticosteroid did not statistically impact survival as compared to corticosteroid treatment alone, but reduced the length of hospital stay and the time required for recovery, with the impact being more profound when IVIG ≥ 2 g/kg/day was used or when just TEN was considered. The authors concluded that IVIG combined with corticosteroid treatment could reduce recovery time while its impact on mortality was insignificant. One SR[26] found that IVIG did not impact survival benefit compared to supportive care, but subgroup analyses showed that IVIG ≥ 2 g/kg/day had significantly more impact on mortality rate than lower IVIG dosage, and IVIG-treated children had lower mortality rate than IVIG-treated adults. The authors concluded that children treated with IVIG may have good prognosis, and high-dose IVIG tended to improve mortality.

Polymyositis and/or dermatomyositis (PM/DM)

One narrative SR[27] and one RCT[30] examined the clinical effectiveness and efficacy of IVIG for patients with PM and/or DM. In general, IVIG combined with corticosteroid trereatment had some clinical benefits compared to placebo or corticosteroid alone, while IVIG alone did not seem to have any clinical impact compared to placebo.

The authors of the SR[27] found that IVIG combined with corticosteroid treatment improved muscle strength and decreased serum creatine kinase level compared to placebo, and reduced the time to muscle recovery, improved muscle strength, decreased serum creatine kinase level, and decreased the dose of concomitant corticosteroid when compared to corticosteroid alone. It is noteworthy that the evidence was from one RCT for each comparison. The authors concluded that IVIG may be a good choice in patients with PM/DM refractory to corticosteroid monotherapy

The RCT[30] found that IVIG 400 milligrams (mg)/kg/day did not have a statistically significant impact on muscle strength, serum creatine kinase levels, and daily activity score compared to placebo for patients with PM/DM refractory to corticosteroid treatment. IVIG, however, significantly reduced the time until normalization of serum creatine kinase and the length of hospital stay. The authors concluded that IVIG was not associated with any significant difference between the groups.

Bullous pemphigoid (BP)

One RCT[28] evaluated the comparative efficacy of IVIG 400 mg/kg/day in patients with BP refractory to corticosteroid treatment. There was no statistically significant difference in daily activity score on day 15 between the IVIG and placebo groups. Over an observation period of 57 days, there was a statistically significant decrease in the time required until treatment reduction in the IVIG group compared to the placebo group, while there was no difference in antibody titers or adverse reactions between the groups. The authors concluded that IVIG provided a beneficial therapeutic outcome for patients with BP who were resistant to corticosteroid treatment.

Systemic sclerosis

One RCT[29] examined the efficacy of IVIG 400 mg/kg/day in patients with diffuse cutaneous systemic sclerosis. After one course of treatment, there was no statistically significant difference in skin thickness between the IVIG group and the placebo group, while after two courses of treatment the difference was statistically significant in favour of IVIG. More patients in the IVIG group had adverse reactions than in the placebo group. The authors concluded that repeated administration of IVIG may be effective for skin sclerosis in diffuse cutaneous systemic sclerosis.

Limitations

Evidence on IVIG use for the identified dermatological conditions was scarce and based mainly on reviews of poorly controlled non-randomized observational studies which are prone to bias due to inherent limitations of the study design, and from small RCTs which may lack the power to detect clinically important effects. The majority of the included studies were retrospective which presents a source of recall bias. There is no study conducted in a Canadian setting.

The variability in IVIG dosage in the intervention arms, together with variability of concomitant corticosteroid use, and the different measures of supportive care in the comparator arm also make it difficult to make strong conclusions.

Conclusions and Implications for Decision or Policy Making

For patients with SJS and/or TEN, treatment with IVIG, alone or combined with a corticosteroid, did not provide survival benefit compared to no-IVIG treatment, but there may be a positive correlation between high IVIG dosage and clinical benefits such as lower mortality rate and recovery time. Pediatric patients treated with IVIG seemed to have lower mortality than adults. For PM and/or DM, IVIG combined with corticosteroid treatment improved muscle strength and decreased serum creatine kinase compared to placebo or corticosteroid alone, while IVIG alone did not seem to differ from placebo. For BP, there was a statistically significant decrease in the time required until treatment reduction in the IVIG group compared to the placebo group. For SS, there was no statistically significant difference in skin thickness between the IVIG group and the placebo group after one course of treatment, while the difference was statistically significant in favour of IVIG after two courses of treatment. No study involving subcutaneous immunoglobulin met the inclusion criteria for this report.

Evidence on IVIG use for off-label dermatological conditions is scarce and based mainly on reviews of non-randomized studies and small-size RCTs. Further, there was variability in IVIG dosages, the concomitant use of corticosteroid treatment, and differing definitions of supportive care used as a comparator, making it difficult to draw firm conclusions regarding the effectiveness of IVIG for these off-label indications. Larger, high quality RCTs are needed to further elucidate the effectiveness of IVIG in treating Canadian patients with dermatological conditions.

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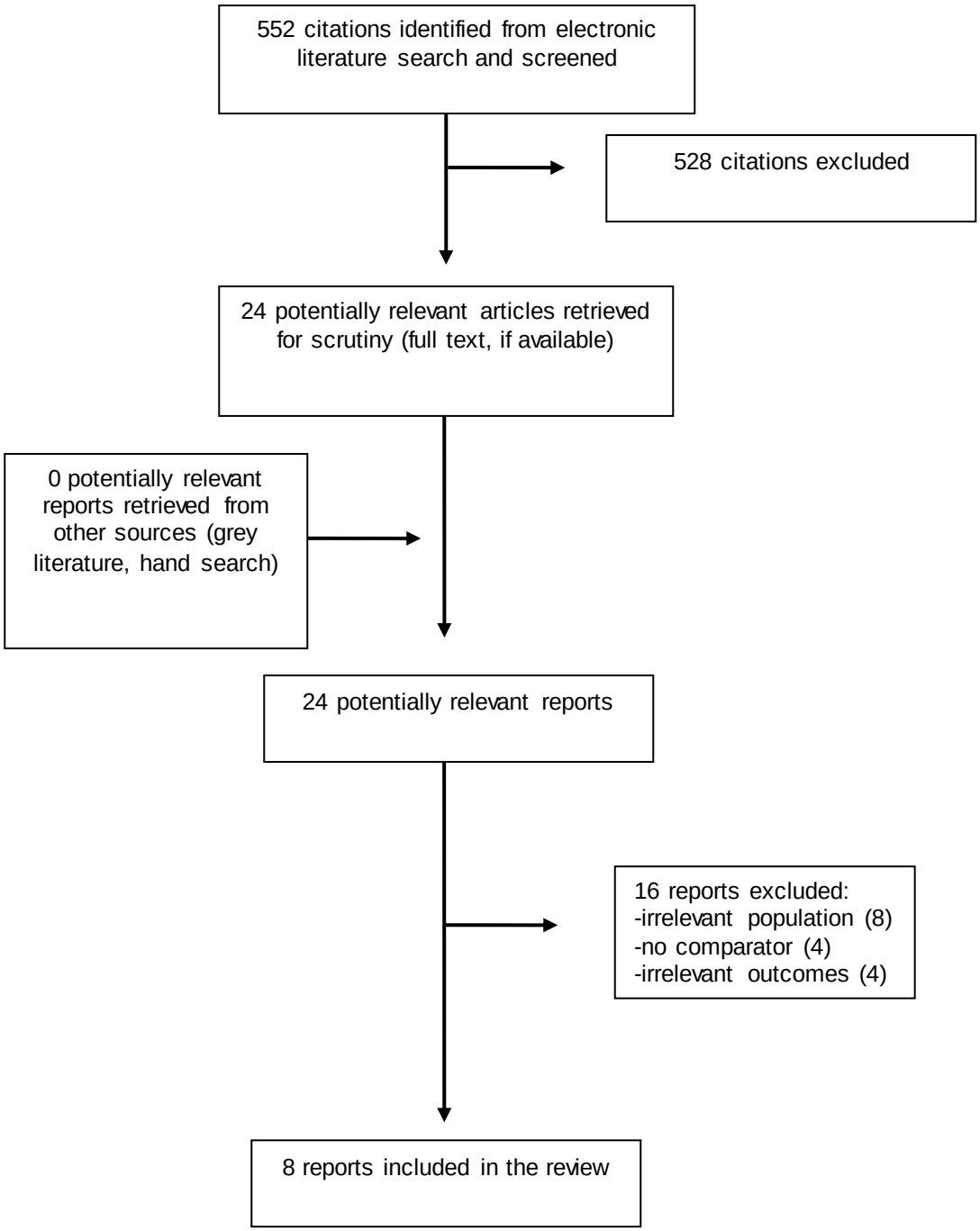
Appendix 1: Selection of Included Studies



Appendix 2: Characteristics of Included Publications

Table 2: Characteristics of Included Systematic Reviews

First author, Year, Country	Objectives Literature Search Strategy	Inclusion Criteria	Exclusion Criteria	Number of Studies Outcomes
Stevens-Johnson Syndrome and/or Toxic Epidermal Necrolysis				
Zimmermann,[23] 2017, Germany	*"To provide an overview on possible immunomodulating treatments for SJS/TEN and estimate their effects on mortality compared with supportive care"* (p 514) *"literature search was performed in December 2012 for articles published in MEDLINE, MEDLINE Daily, MEDLINE Inprocess,Web of Science, EMBASE, Scopus, and the Cochrane Library (Central) from January 1990, through December 2012, and updated in December 2015, in the English, French, Spanish, and German languages looking for treatment proposals for SJS/TEN"* (p 514)	*"Studies were assessed according to the following eligibility criteria (eMethods 2 in the Supplement): (1) clearly described type of study, (2) diagnostic accuracy of SJS/TEN, (3) sufficient description of treatment, (4) information on mortality, and (5) at least 5 participants per study"* (p 515)	Studies not fulfilling inclusion criteria	10 non RCTs on IVIG (96 studies on various immunomodulating treatments) Survival benefit (risk of death)
Barron,[24] 2015, US	*"This systematic review evaluates the existing literature to determine if IVIG impacts the standardized mortality rate (SMR) in patients with SJS or TEN"* (p 108) *"The MEDLINE database was searched for the period 1966–2011 for pertinent Studies"* (p 108)	*"To be eligible for inclusion, studies were required to: (i) refer to patients (adults or children) whose diagnosis met the established criteria for SJS or TEN as determined by a physician; (ii) include an identified group of patients who received IVIG as part of their therapeutic regimen; (iii) refer to disease severity in patients treated with IVIG using the SCORTEN system, and (iv) include a minimum of five patients"* (p 108)	Studies not fulfilling inclusion criteria	13 non RCTs Survival benefit (risk of death) Correlation between IVIG dosage and death rate
Ye,[25] 2016, China	*"We conducted a comprehensive meta-analysis through combining the published eligible studies to evaluate the effectiveness of IVIG on SJS and TEN treatment"* (p 1) *"Literature search was conducted on PubMed, Web of Science, Cochrane Library, China Biology Medicine (CBM) disc, WanFang*	*"case-control studies that explored the effect of IVIG on the improvements of SJS/TEN patients were selected. Since most of these studies recruited individuals treated with the combination of IVIG and corticosteroid as case group and steroid applied cases as*	Studies not fulfilling inclusion criteria	26 non RCTs Survival benefit (risk of death) Recovery time (reduction in medication use time) Length of hospital stay

First author, Year, Country	Objectives Literature Search Strategy	Inclusion Criteria	Exclusion Criteria	Number of Studies Outcomes
	Database (Chinese) and Chinese National Knowledge Infrastructure (CNKI). The following key words or their equivalent Chinese terms were used to find all relative records: Stevens-Johnson syndrome, SJS, toxic epidermal necrolysis, TEN, immunoglobulin, intravenous immunoglobulin and IVIG. The period of literature search was from 1966 to Oct 2015" (p 1)	*control group, only this kind of studies were selected"* (p 3)		
Huang,[26] 2012, Taiwan	*"To provide a meta-analysis evidence-based examination of IVIg efficacy against TEN"* (p 424) *"We searched PubMed, MEDLINE, EmBase and the Cochrane Library (including The Cochrane Database of Systematic Reviews, The Database of Abstracts of Reviews of Effects, The Cochrane Controlled Trials Register and The Health Technology Assessment Databases) from inception to 31 July 2011"* (p 425)	*"in the absence of RCTs, we included observational studies (controlled and noncontrolled) with at least eight patients with SJS-TEN overlap or TEN receiving IVIg treatment"* (p 425)	Studies not fulfilling inclusion criteria *"Review articles, case reports and correspondence or letters to the editor were excluded"* (p 425)	17 non-RCTs Survival benefit (risk of death)
Polymyositis and/or dermatomyositis				
Wang,[27] 2012, China	*"The objectives of this study are to review and summarize published information on the use, effectiveness, and adverse effects of intravenous immunoglobulin (IVIG) in patients with polymyositis (PM) or dermatomyositis (DM)"* (p 801) *"We conducted a systematic literature review by searching the MEDLINE database… Studies published inclusive of January 1985~May 2011 were selected" (p 802)*	*"A study was defined as relevant if it examined the efficacy of IVIG in PM/DM patients"* (p 802)	*"Case reports and articles that primarily involved animal studies were excluded from the review. A study was also excluded if the patients were mainly children"* (p 802)	14 studies (2 RCTs, 12 non RCTs) Effectiveness (muscle strength improvement, serum creatine kinase level reduction, corticosteroid dose reduction) Adverse events

IVIG = intravenous immunoglobulins; RCT = randomized controlled trial; SJS = Stevens-Johnson Syndrome; TEN = toxic epidermal necrolysis

Table 3: Characteristics of Included Clinical Studies

First Author, Year, Country	Study Design Objectives	Intervention Comparators	Patients	Main Study Outcomes
Amagai,[28] 2017, Japan	*"A multicenter, randomized, placebo-controlled, double-blind trial was conducted to investigate the therapeutic effect of high-dose intravenous immunoglobulin (IVIG; 400 mg/kg/day for 5 days) in BP patients who showed no symptomatic improvement with prednisolone (≥0.4 mg/kg/day) administered"* (p 77)	IVIG 400mg/kg/day for 5 consecutive days Placebo	Patients with corticosteroid-refractory bullous pemphigoid (29 IVIG, 27 placebo) Mean age 64.0 IVIG, 66.3 placebo	Disease activity score on day 15 (DAS15) Over time up to 57 days - DAS - Time to treatment reduction (length of time until symptoms were improved and the evaluator determined that a reduction in treatment was required) - Corticosteroids use - Anti-BP180 antibody titers
Takehara,[29] 2013, Japan	RCT and readmission observational study *"This paper aims to investigate the efficacy of intravenous immunoglobulin (IVIG) for skin sclerosis in diffuse cutaneous systemic sclerosis (dcSSc) by a randomised, double-blind, placebo-controlled, multicentre trial (DBT) with subsequent long-term observational and readministration studies"* (p S-151)	IVIG 400mg/kg/day for 5 consecutive days Placebo	Patients with diffuse cutaneous systemic sclerosis (31 IVIG, 31 placebo) Mean age 54.3 IVIG, 53.8 placebo	Modified Rodnan skin thickness score (MRSS) (normal score = 0; range 1 to 3/area; maximum 21/total 17 areas) Adverse drug reactions
Miyakasa,[30] 2012, Japan	RCT *"we present the results of a double-blind, placebo controlled,*	IVIG 400mg/kg/day for 5 consecutive days Placebo	Patients with corticosteroid-refractory PM and DM (16 PM, 10 DM)	Manual muscle test score (MMT) (normal score 90 points; abnormal when ≤80 points) Serum creatine kinase levels

First Author, Year, Country	Study Design Objectives	Intervention Comparators	Patients	Main Study Outcomes
	crossover study designed to evaluate the efficacy and safety of polyethylene glycol-treated human IgG (GB-0998) in patients with corticosteroid-resistant PM or DM" (p 383)		Mean age 50.6 IVIG, 48.1 placebo years	Activities of daily living score (ADL) (normal score 45 points) Time to discharge (length of hospital stay) Time to normalization of serum creatine kinase level

BP = bullous pemphigoid; DM = dermatomyositis; IVIG = immunoglobulins; kg = kilogram; mg = milligram; PM = polymyositis; RCT = randomized controlled trial

Appendix 3: Critical Appraisal of Included Publications

Table 4: Strengths and Limitations of Systematic Reviews and Meta-Analyses using AMSTAR II[21]

Strengths	Limitations
Zimmermann[23]	
• a priori design provided • independent studies selection and data extraction procedure in place • comprehensive literature search performed • list of included studies, studies characteristics provided • quality assessment of included studies provided and used in formulating conclusions • assessment of publication bias performed • conflict of interest stated	• list of excluded studies not provided • heterogeneity across trials in IVIG dosage, concomitant use, measures in control arm
Barron[24]	
• a priori design provided • independent studies selection and data extraction procedure in place • comprehensive literature search performed • list of included studies, studies characteristics provided • assessment of publication bias performed • conflict of interest stated	• list of excluded studies not provided • heterogeneity across trials in IVIG dosage, concomitant use, measures in control arm • quality assessment of included studies not provided
Ye[25]	
• a priori design provided • independent studies selection and data extraction procedure in place • comprehensive literature search performed • list of included studies, studies characteristics provided • assessment of publication bias performed • conflict of interest stated	• list of excluded studies not provided • heterogeneity across trials in IVIG dosage, concomitant use, measures in control arm • quality assessment of included studies not provided
Huang[26]	
• a priori design provided • independent studies selection and data extraction procedure in place • comprehensive literature search performed • list of included studies, studies characteristics provided • conflict of interest stated	• assessment of publication bias not performed • list of excluded studies not provided • heterogeneity across trials in IVIG dosage, concomitant use, measures in control arm • quality assessment of included studies not provided
Wang[27]	
• a priori design provided • independent studies selection and data extraction procedure in place • comprehensive literature search performed • quality assessment of included studies provided and used in formulating conclusions • list of included studies, studies characteristics provided • conflict of interest stated	• review presented narratively • assessment of publication bias not performed • list of excluded studies not provided

Table 5: Strengths and Limitations of Randomized Controlled Trials using Downs and Black[22]

Strengths	Limitations
Amagai[28]	
• randomized controlled trial • patient and assessor blinded to patient treatment assignment. • hypothesis clearly described • method of selection from source population and representation described • loss to follow-up reported • main outcomes, interventions, patient characteristics, and main findings clearly described • power calculation to detect a clinically important effect performed • estimates of random variability and actual probability values provided	• More than 20% dropped out rate, leading to a sample size of completed patients that may not have an 80% power to detect a clinically important effect
Takehara[29]	
• randomized controlled trial • patient and assessor blinded to patient treatment assignment. • hypothesis clearly described • method of selection from source population and representation described • loss to follow-up reported • main outcomes, interventions, patient characteristics, and main findings clearly described • estimates of random variability and actual probability values provided	• study did not perform power calculation to detect a clinically important effect
Miyasaka[30]	
• randomized controlled trial • patient and assessor blinded to patient treatment assignment. • hypothesis clearly described • method of selection from source population and representation described • loss to follow-up reported • main outcomes, interventions, patient characteristics, and main findings clearly described • estimates of random variability and actual probability values provided	• study did not perform power calculation to detect a clinically important effect

Appendix 4: Main Study Findings and Author's Conclusions

Table 6: Summary of Findings of Included Studies

Main Study Findings	Author's Conclusion
Stevens-Johnson Syndrome and/or Toxic Epidermal Necrolysis	
Zimmermann[23] (systematic review)	
IVIG vs supportive care *Risk of death* (data from 10 studies) OR 0.99 (95% CI, 0.64 to 1.54) *P* = 0.77	No beneficial findings were observed for IVIG treatment as compared to supportive care
Barron[24] (systematic review)	
IVIG vs no-IVIG *Risk of death* (data from 8 studies) SMR -0.322 (95% CI, -0.766 to 0.122) *P* = 0.155 Subgroup analysis: With studies with IVIG dose ≥2g/kg, difference was statistically significant (p = 0.028) When patients were treated with IVIG alone SMR -0.262 (95% CI, -0.957 to 0.432) *P* = 0.459 When patients were treated with IVIG plus corticosteroids SMR -0.363 (95% CI, -0.941 to 0.215) *P* = 0.218 *Correlation between IVIG dosage and SMR* Slope -0.59 (95% CI, -0.14 to -1.03) *P* = 0.009 (strong inverse correlation)	*"Intravenous IG at dosages of ≥2 g/kg appears to significantly decrease mortality in patients with SJS or TEN"* (p 108)
Ye[25] (systematic review)	
IVIG + costicosteroids vs corticosteroids alone *Recovery time* (data from 13 studies) WMD -1.63 days (95% CI, -0.83 to -2.43) *P* < 0.001 Subgroup analysis: When patients are Asians WMD -2.19 days (95% CI, -1.41 to -2.97) *P* < 0.001 When the condition is TEN WMD -2.56 days (95% CI, -0.35 to -4.77) *P* = 0.023 When high dose IVIG was used (≥2g/kg) WMD -1.78 days (95% CI, -0.42 to -3.14) *P* = 0.010 *Length of hospital stay* (data from 14 studies) WMD -3.19 days (95% CI, -0.08 to -6.30) *P* = 0.045 *Risk of death* (data from 17 studies) SMR 0.84 (95% CI, 0.66 to 1.08) *P* = 0.178	*"Our current meta-analysis suggests that IVIG combined with corticosteroid could reduce recovery time for SJS and TEN. This effect is greater among Asian patients. Whereas, its impact on reducing mortality is not significant"* (p 1)
Huang[20] (systematic review)	
IVIG vs supportive care	*"Although high-dose IVIg exhibited a trend towards improved*

Main Study Findings	Author's Conclusion
Risk of death (data from 6 studies) OR 1.00 (95% CI, 0.58 to 1.75) *P* = 0.99 Subgroup analysis When high dose IVIG was used (≥2g/kg) OR 0.63 (95% CI, 0.27 to 1.44) *P* = 0.27 *Mortality rate* (data from 15 studies): 19.9% Subgroup analysis High dose IVIG vs low dose IVIG (<2g/kg) (adults) 18.9% vs 50% *P* = 0.022 Children vs adults 0% vs 21.6% *P* = 0.001	*mortality and children treated with IVIg had a good prognosis, the evidence does not support a clinical benefit of IVIg. Randomized controlled trials are necessary*" (p 424)
Polymyositis and/or Dermatomyositis	
Wang[27] (systematic review)	
Compared to placebo IVIG combined with corticosteroid improved muscle strength and decreased serum creatine kinase level (data from one RCT; *P* < 0.018) *Compared to corticosteroid alone* IVIG combined with corticosteroid reduced the time to muscle recovery, improved muscle strength, decreased serum creatine kinase level, and decreased the dose of concomitant corticosteroid (data from one RCT; *P* < 0.05)	*"IVIG is effective in the treatment of adult patients with PM/DM and appears to be relatively well tolerated and safe. IVIG may be a good choice especially in patients with refractory, flare-up, rapidly progressive, or severe PM/DM, and can be tried in patients with a contraindication for corticosteroid"* (p 801)
Miyasaka[30] (randomized clinical trial)	
IVIG vs placebo (difference of mean ; 95% CI) MMT (muscle strength) 1.9 (-4.8 to 8.5) *Creatine kinase levels* 0.1029 (-0.8382 to 1.0439) ADL (daily living activities) 3.3 (-1.8 to 8.3) *Length of hospital stay* IVIG 11.5 days Placebo 41.5 days *P* value not reported *Time to normalization of creatine kinase level* IVIG 22.0 days Placebo 57.5 days *P* = 0.0301	*"comparison of the GB-0998 group with the placebo group did not show any significant difference between the groups"* (p 382)
Bullous Pemphygoid	
Amagai[28] (randomized clinical trial)	
IVIG vs placebo (mean, SD)	"*IVIG provides a beneficial therapeutic outcome for patients with BP who are resistant to steroid therapy"* (p 77)

Main Study Findings	Author's Conclusion
Changes in DAS15 IVIG 19.8 ± 22.2 Placebo 32.3 ± 31.5 *P* = 0.089 Significant decrease in time to treatment reduction in IVIG group compared to placebo group (*P* = 0.010) No significant difference between the 2 groups in antibody titers *Adverse drug reactions* (% of patients) IVIG 37.9% Placebo 18.5% *P* = 0.143	
Diffuse Cutaneous Systemic Sclerosis	
Takehara[29] (randomized clinical trial)	
Changes in MRSS compared to baseline (mean units ± SD) At 12 weeks after 1 course of treatment IVIG -3.3 ± 4.2 Placebo -4.2 ± 4.6 *P* value not provided *Adverse drug reactions* (% of patients) IVIG 32.3% Placebo 12.5% At 60 weeks after 2 courses of treatment (readmission for non-responders) IVIG -8.3 ± 1.0 After 1 course of treatment for the previous group with placebo: --4.1 ± 1.1 *P* = 0.0040	*"No significant difference was noted in the primary endpoint, MRSS change, between IVIG and P groups, but significant improvements in the MRSS were noted in the GG group over those in the PG group in the readministration study, suggesting that the efficacy of a single course of administration is insufficient for patients with this disease requiring IVIG, but readministration (multiple courses) may decrease MRSS"* (p S-154)

95% CI = 95% confidence interval; ADL = activities daily living scale; DAS15 = daily activity score at day 15; g = gram; GG = IVIG to IVIG; IVIG = intravenous immunoglobulin ; kg = kilogram; MMT = manual muscle test score; MRSS = modified Rodnan skin thickness score; OR = odds ratio; PG = placebo to IVIG; RCT = randomized controlled trial; SD = standard deviation; SJS = Stevens-Johnson Syndrome; SMR = standardized mortality ratio; TEN = toxic epidermal necrolysis; WMD = w eighted mean difference