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Drug Class Literature Scan: Immunoglobulins

Date of Review: October 2024

Date of Last Review: August 2020
Literature Search: 06/01/20 – 05/23/24

Current Status of PDL Class:
See **Appendix 1**.

Plain Language Summary:

- Immunoglobulins (Ig) are medicines used to:
  - help fight infections in people with immune systems that don't work normally or
  - treat muscle weakness in conditions caused when the immune system attacks parts of the body.
- Conditions for which Ig has been studied include:
  - chronic inflammatory demyelinating polyradiculoneuropathy (CIDP), a disease caused when the body's immune system damages nerves leading to muscle weakness and numbness of the arms and legs
  - Kawasaki disease, a disease that can cause heart and blood vessel damage, mostly in children younger than 5 years old
  - viral myocarditis, a disease that causes swelling and irritation of the heart muscle and decreases the heart's ability to pump blood
  - multifocal motor neuropathy (MMN), a disease that causes weakness in the arms and legs that worsens over time
  - dermatomyositis, a disease that causes muscle weakness and skin problems.
- Studies show that immunoglobulins:
  - improve weakness in people that have CIDP,
  - work better than aspirin to reduce the swelling in the walls of small blood vessels, which is called coronary artery abnormalities (CAA) in people with Kawasaki disease,
  - may improve survival in people who have viral myocarditis, but additional studies are needed to confirm these findings,
  - may keep muscles strong in people that have multifocal motor neuropathy, and
  - reduce disease activity in people who have dermatomyositis.
- The American College of Rheumatology recommends Ig for people with a lung disease that is associated with a disease called Systematic Autoimmune Rheumatic Diseases (SARDs). Depending on the type of lung disease, Ig may be recommended as initial treatment or after other types of medicine have been tried.
- Based on this information, we do not recommend any changes to the Ig preferred drug list for the Oregon Health Plan fee-for-service program.

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Conclusions:

- A literature search of Ig products ending in May of 2024 identified 4 new systematic reviews and meta-analyses, one new guideline, 3 new indications, 5 new formulations, and one new randomized controlled trial (RCT).
- The use of intravenous immunoglobulins (IVIg) for CIDP was evaluated in a 2024 Cochrane review. There is evidence that IVIg is more effective than placebo for improving disability within 6 weeks of starting treatment, with a number needed to benefit (NNTB) of 4 (high quality of evidence).[1]
- A Cochrane review evaluating the use of IVIg in patients with Kawasaki disease found moderate quality of evidence that the use of IVIg was more effective for reducing the incidence of CAAs compared to aspirin (ASA).[2] Comparisons of high-dose IVIg (over 1600 mg/kg total) reduced CAAs compared to low-dose (less than 1000 mg/kg total IVIg) and medium-dose (1000 to 1600 mg/kg IVIg) (moderate quality evidence). [2]
- A 2020 Cochrane review found very low quality evidence that IVIg may improve survival, compared to placebo, in adults and children with presumed viral myocarditis; however, results were not statistically significant.[3]
- A Cochrane review on the use of Ig for multifocal motor neuropathy (MMN) was published in 2022.[4] Compared to placebo, IVIg may improve disability and strength but evidence was of low quality.[4] The use of subcutaneous immunoglobulin (SCIg) for MMN was of very low quality and additional evidence is needed for this route of administration.[4]
- Guidance from the American College of Rheumatology was published in 2023 for interstitial lung disease (ILD) associated with Systematic Autoimmune Rheumatic Diseases (SARDs).[5] In those patients with idiopathic inflammatory myopathies (IMM-ILD) and mixed connective tissue disorders (MCTD-ILD) that have progressive disease despite first-line ILD treatment, IVIg is *conditionally* recommended.[5] In patients with rapidly progressive ILD, IVIg is conditionally recommended as a first-line treatment option.[5]
- There are 3 new Ig indications and 5 new formulations approved since the last Pharmacy and Therapeutics Committee review. There was no comparative evidence to suggest improved efficacy or safety of the new formulations compared with previously approved formulations.
- One new study compared Octagam® to placebo in adult patients (n=95) with dermatomyositis.[6] Octagam demonstrated reduced disease activity more than placebo based on a 35% reduction in Total Improvement Scores (TIS), which measures myositis activity over time.[6]
- There is no new evidence that prompts changes to current policy. There is no evidence of clinical differences in efficacy or safety between Ig products.

Recommendations:

- No changes to the preferred drug list (PDL) are recommended based on the review of the evidence.
- Implement prior authorization (PA) criteria for non-preferred pharmacy claims to support off-label use of Ig for evidence supported diagnoses through the pharmacy benefit.
- After evaluation of costs in executive session, HIZENTRA, PRIVIGEN, and GAMMAGARD liquid were made preferred. GAMMUNEX was made non-preferred. All other products without a PDL status were made non-preferred.

Summary of Prior Reviews and Current Policy

- A literature review conducted for a drug use evaluation (DUE) in August of 2020 found no evidence of differences in safety or efficacy of Ig products. Immunoglobulin products differ in manufacturing processes, such as stabilizing and preservative agents, but products are not usually differentiated in the clinical setting by these small differences.
- Immunoglobulins are commonly used for many off-label indications, despite a lack of high-quality evidence. There is low quality evidence for some off-label indications that suggest efficacy but most off-label indications have not been extensively studied.

- The current PA criteria authorizes use of Ig products for approved FDA indications that are billed through pharmacy claims. Medical claims do not have to be reviewed for FDA approved indications.
- The preferred Ig product is Gamunex-C. There is no pathway for coverage of non-preferred Ig therapies for off-label indications. The status of Ig products on the Preferred Drug List is presented in **Appendix 1.**
- In quarter one of 2024 there were 3 claims for the preferred product billed by medical, 5 claims for non-preferred products billed by the pharmacy and 37 claims for non-preferred products billed as medical claims.

Methods:

A Medline literature search for new systematic reviews and RCTs assessing clinically relevant outcomes to active controls, or placebo if needed, was conducted. A summary of the clinical trials is available in **Appendix 2** with abstracts presented in **Appendix 3**. The Medline search strategy used for this literature scan is available in **Appendix 4**, which includes dates, search terms and limits used. The OHSU Drug Effectiveness Review Project, Agency for Healthcare Research and Quality (AHRQ), National Institute for Health and Clinical Excellence (NICE), Department of Veterans Affairs, the Oregon Mental Health Clinical Advisory Group (MHCAG), the Scottish Intercollegiate Guidelines Network (SIGN), and the Canadian Agency for Drugs and Technologies in Health (CADTH) resources were manually searched for high quality and relevant systematic reviews. When necessary, systematic reviews are critically appraised for quality using the AMSTAR tool and clinical practice guidelines using the AGREE tool. The FDA website was searched for new drug approvals, indications, and pertinent safety alerts.

The primary focus of the evidence is on high quality systematic reviews and evidence-based guidelines. Randomized controlled trials will be emphasized if evidence is lacking or insufficient from those preferred sources.

New Systematic Reviews:

<u>Intravenous Immunoglobulin for Chronic Inflammatory Demyelinating Polyradiculoneuropathy</u>

A 2024 Cochrane review evaluated the use of IVIg for management of CIDP.[1] Chronic inflammatory demyelinating polyradiculoneuropathy is a weakness and numbness of the limbs that can be progressive or relapsing and lasts over 2 months. The pathophysiology of CIDP includes multifocal demyelination, mononuclear cells in close proximity to demyelinated axons, remyelination, fibre loss and 'onion bulbs'. The literature was searched from 2013 to March 2023 for relevant RCTs.[1] Included studies compared IVIg to plasma exchange, corticosteroids (e.g., prednisolone and IV methylprednisolone [IVMP]) or placebo. Nine trials were identified which included a total of 372 participants. Patients were a mean age of 45 to 60 years. Males represented 50% to 86% of the total study population.[1] The most common loading dose of IVIg was 2 g/kg bodyweight for 2-5 days and maintenance doses ranged from 1-2 g/kg bodyweight every 3-4 weeks.[1] One study using oral prednisolone as the comparator, gave participants a taper from 60 mg to 10 mg daily for 6 weeks and one study dosed prednisolone at 0.8 mg/kg tapered over 6 months. The primary outcome was significant improvement in disability within 6 weeks of starting treatment. The overall risk of bias was considered low for the included studies.

Outcomes assessing efficacy were based off of 3 disability scales: the Inflammatory Neuropathy Cause and Treatment (INCAT) disability score, the modified Rankin scale and the Overall Neuropathy Limitation Scale (ONLS). The INCAT score ranges from 0-10 with lower scores indicating normal movement and 10 unable to make purposeful movements with arms and/or legs.[7] Patients are considered responders if they have at least a 1-point decrease in their INCAT score. The modified Rankin scale is used to determine disability with scores ranging from 0-6, higher scores indicate more disability. Significant improvement is a reduction of at least 1 point. The ONLS is a validated scale measuring upper and lower limb functions with scores ranging from 0-5 on the upper limbs and 0-7 on the lower limbs.[8] Higher scores indicate greater disability.

There was insufficient evidence to compare IVIg to plasma exchange. Results for other comparisons are presented in **Table 1.**[1] All studies took place in tertiary care centers, which may limit applicability to outpatient fee-for-service (FFS) patients. Additionally, studies used different measurement scales to evaluate outcomes limiting comparisons between treatments.

Table 1. IVIg compared to Placebo for the Treatment of Chronic Inflammatory Demyelinating Polyradiculoneuropathy[1]

Outcome	Result	Quality of Evidence	Comments
IVIg vs. Placebo			
Significant improvement in disability within 6 weeks (5 studies) Follow up: 2-6 weeks	RR 2.40 (95% CI, 1.72 to 3.36) NNTB of 4	High	Magnitude of efficacy is hard to determine due to the use of different measurement scales to assess disability improvement
Change in mean disability score on Rankin scale* (3 studies) Follow-up: 2-6 weeks	MD -0.26 points (95% CI, -0.48 to -0.05)	High	IVIg resulted in improved disability compared to placebo
Change in mean disability score at 24 weeks or later (assessed with the INCAT score†) (1 study) Follow-up: 24 weeks	MD 0.80 points (95% CI, 0.23 to 1.37)	Moderate	IVIg resulted in improved disability compared to placebo
Serious adverse events (3 studies)	RR 0.82 (95% CI, 0.36 to 1.87)	Moderate	No significant difference in adverse events between groups
IVIg vs. Prednisolone (1 study)			
Change in mean disability score within 6 weeks (assessed with the INCAT score†) Follow-up: 4 weeks	RR 0.91 (95% CI, 0.50 to 1.68)	Moderate	No significant difference in disability improvement between groups
Change in mean disability score on Rankin scale* Follow-up: 4 weeks	MD 0.21 points (95% CI, -0.19 to 0.61)	Moderate	No significant difference in disability improvement between groups
Serious adverse events	RR 0.45 (95% CI, 0.04 to 4.69)	Moderate	No significant difference between groups
IVIg vs. Methylprednisolone (1 study)			

Significant improvement in disability within 6 weeks (assessed with the ONLS disability score‡) Follow up: 2 weeks	RR 1.46 (95% CI, 0.40 to 5.38)	Moderate	Methylprednisolone improved disability more than IVIg
Change in mean disability score on Rankin scale* Follow-up: 2 weeks	MD 0.24 points (95% CI, -0.15 to 0.63)	Moderate	No significant difference between groups
Change in mean disability score at 24 weeks or later (assessed with the ONLS score‡)	MD 0.03 points (95% CI, -0.91 to 0.97)	Moderate	No significant difference between groups
Serious adverse events	RR 4.40 (95% CI, 0.22 to 86.78)	Moderate	Wide confidence intervals suggest imprecision in the estimate and lowers confidence in the results
Key: * Rankin scale ranges 0-6 with lower scores indicating less disability; † INCAT disability score ranges from 0-10 with lower scores indicating less disability, ‡ The ONLS score is a disability score ranging from 0-12 with lower scores indicating less disability Abbreviations: CI = confidence intervals; INCAT = Inflammatory Neuropathy Cause and Treatment; IVIg = intravenous immunoglobulin; MD = mean difference; NNTB = number needed to benefit; ONLS = Overall Neuropathy Limitation Scale; RR = relative risk			

Intravenous Immunoglobulin for the Treatment of Kawasaki Disease

In a 2023 Cochrane review, the use of IVIg for Kawasaki disease to prevent cardiac consequences was evaluated.[2] The literature was searched up to April 2022. Treatments used for initial or refractory Kawasaki disease were included. Intravenous immunoglobulins were compared to aspirin, different doses of IVIg, infliximab or corticosteroids (e.g., methylprednisolone).[2] Thirty-one studies were identified and enrolled patients from 2 months to 14 years of age (n=4609). Sixty-three percent of study participants were male. Doses of IVIg ranged from 50 mg/kg/day to 2 g/kg/day. Doses were given as a single infusion or daily infusions up to 5 days.[2] Concomitant aspirin was given to most patients. The primary outcomes were the incidence of CAAs and adverse effects of treatment.

Table 2. Efficacy of IVIg for the Treatment of Kawasaki Disease[2]

Outcomes	Relative Effect	Strength of Evidence	Comments
IVIg vs. ASA for primary treatment			
Incidence of CAAs	OR 0.60 (95% CI, 0.41 to 0.87)	Moderate	Less incidence of CAA was demonstrated with treatment with IVIg compared to ASA
Duration of fever	4 days less (5.06 to 2.93 lower) in those treated with IVIg	Moderate	Duration of fever was reduced in patients treated with IVIg compared to ASA
Need for additional treatment (up to 30 to 60 days)	OR 0.27 (95% CI, 0.05 to 1.57)	Low	No difference was found between groups
Adverse events	OR 0.57 (95% CI, 0.17 to 1.89)	Very low	Little or no difference between groups
IVIg high-dose regimens (over 1600 mg/kg total) vs. low-dose (less than 1000 mg/kg total IVIg) and medium-dose (1000 to 1600 mg/kg IVIg) for primary treatment			

Incidence of CAAs	OR 0.60 (95% CI, 0.40 to 0.89)	Moderate	Likely that high dose IVIg reduced CAAs compared to low or medium doses
Duration of fever	Reduced 0.71 days (95% CI, -1.36 to -0.06) in patients treated with high dose IVIg compared to low or medium dose IVIG	Low	There may be a slight benefit in fever reduction in patients treated with high dose IVIg
Need for additional treatment	OR 0.29 (95% CI, 0.10 to 0.88)	Low	Slightly less need for additional treatment for those treated with high dose IVIg
Length of hospital stay	Reduced 0.24 days (95% CI, 0.78 to 0.3) in high-dose IVIG regimens	Low	A difference of 0.24 days is unlikely to be clinically significant
Mortality	Relative effect could not be estimated	Moderate	One trial reported one death in the high dose regimen group. The other 7 studies did not report mortality data.
Adverse Events	OR 1.11 (95% CI, 0.52 to 2.37)	Low	There was no difference between groups.
IVIg vs. Prednisolone for primary treatment			
Incidence of CAAs	OR 0.60 (95% CI, 0.24 to 1.48)	Very low	Only 2 RCTs available for analysis making evidence unclear
Adverse Events	OR 4.18 (95% CI, 0.19 to 89.48)	Low	No difference in adverse events were detected; however, results favored IVIg. Wide confidence intervals suggest imprecision in the estimate and lowers confidence in the results
Abbreviations: ASA = aspirin; CAA = coronary artery abnormality; CI = confidence interval; IVIg = intravenous immunoglobulin; NA = not applicable; OR = odds ratio; RCT = randomized controlled trial.			

<u>Intravenous Immunoglobulin for Presumed Viral Myocarditis in Children and Adults</u>

In 2020 Cochrane performed a systematic review and meta-analysis on the use of IVIg for presumed viral myocarditis.[3] Literature was searched till July 2019 and updated a previous Cochrane review. Two new trials were identified and combined with the existing evidence. The overall risk of bias was unclear in both adult trials and low the pediatric trial.[3] The primary outcome was event-free or overall survival of adults and children with presumed viral myocarditis. An event was defined as death, requirement for cardiac transplant, or placement of a left ventricular assist device.

The quality of evidence was considered very low for the adult trials. Event-free survival (median follow-up of 23 months) was higher in those treated with IVIg compared to placebo (RR 1.76; 95% CI, 0.48 to 6.40) and risk of death (overall survival) was higher with IVIg compared to placebo (RR 0.91; 95% CI, 0.23 to 3.62), but not statistically different for both comparisons.[3]

The trial enrolling pediatric patients (n=86) had low risk of bias, but evidence was considered very low quality. Overall survival at 6 months between IVIg and placebo was uncertain (RR 0.48; 95% CI, 0.20 to 1.15).[3]

Evidence for use of IVIg in presumed viral myocarditis is very low and conclusions of efficacy are uncertain.

Immunoglobulin for Multifocal Motor Neuropathy

Multifocal motor neuropathy is a rare disorder causing weakness in one or more limbs that is progressive and has minimal treatment options. A 2022 Cochrane review evaluated the use of IVIg and SCIg for people with MMN.[4] Studies were evaluated from a literature search ending in April 2021. Of the 6 studies identified, 5 compared IVIg to placebo and one study compared IVIg to SCIg. Outcomes of interest included disability, muscle strength or electrophysiological conduction block (partial motor conduction block is often present in patients with MMN).

IVIg as induction therapy, compared to placebo, may improve disability based on low quality evidence (RR 3.00; 95% CI, 0.89 to 10.12; p=0.08; follow-up 2 to 6 weeks after last treatment); however, results are not statistically signficant.[4] Muscle strength may also improve with IVIg compared to placebo (RR 11.00; 95% CI, 2.86 to 42.25); however, wide confidence intervals suggest additional data is needed to confirm benefit. As maintenance therapy, withdrawing IVIg led to increased disability (determined by study authors) when compared to placebo (RR 2.43; 95% CI, 1.13 to 5.24) and deterioration in muscle strength (RR 0.20; 95% CI, 0.07 to 0.54) (moderate quality evidence for both outcomes).[4] Results for adverse events were uncertain and conclusions could not be drawn.

Evidence for use of SCIg in MMN was considered very low quality and consisted of 1 trial comparing IVIg to SCIg. Results were uncertain for the comparative efficacy of IVIg to SCIg as maintenance therapy as only one trial was available for analysis and it did not measure disability and evidence for muscle strength was uncertain (standardized mean difference [SMD] 0.08; 95% CI, -0.84 to 1.00; 9 people).

After review, 16 systematic reviews were excluded due to poor quality, wrong study design of included trials (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical).[9–15, 16–24]

New Guidelines:

High Quality Guidelines:

American College of Rheumatology – Treatment for Interstitial Lung Disease in Adults

In 2023 the ACR provided guidelines for ILD treatment associated with Systematic Autoimmune Rheumatic Diseases (SARDs).[5] Patients at highest risk of ILD are those with the following: systemic sclerosis (SSc), rheumatoid arthritis (RA), idiopathic inflammatory myopathies (IIM), mixed connective tissue disorders (MCTD) and Sjogren's Disease (SjD).[5] The literature was searched and evaluated using the Grading of Recommendations Assessment, Development and Evaluation (GRADE) methodology. Exact search history was not described. Conflicts of interest (COIs) were recorded and 51% of the authors had to be free from COIs.

Treatment recommendations were provided for first-line treatment of ILD, treatment of progressive ILD despite first-line treatment, and treatment of Rapidly Progressive ILD (RP-ILD).[5] The evidence for the use of IVIg in most people with ILD is mixed. The ACR *conditionally* recommends that IVIg not be used in those with SARD-ILD as a first-line treatment. In those patients with IMM-ILD and MCTD-ILD that have progressive disease despite first-line ILD treatment, IVIg is *conditionally* recommended. In patients with SARD with rapidly progressive ILD, IVIg is conditionally recommended as a first-line treatment option.[5]

After review, 5 guidelines were excluded due to poor quality.[25–29]

New Formulations/Indications:

New Indications:

HYQVIA (Immune Globulin Infusion 10%): In January of 2024 Hyqvia®, for subcutaneous administration, was approved by the FDA for primary immunodeficiency (PI) in adults and pediatric patients 2 years of age and older.[30] Evidence for approval was based on a prospective, open-label, non-controlled, multicenter trial. Patients (n=89) were a median age of 35 years and 90.8% identified as Caucasian. One cohort of patients were treated intravenously for 3 months and then subcutaneously each week at 137% of the intravenous dose for one year before trial entry.[30] The second cohort was treated with Hyqvia® intravenously for 3 months and then immediately enrolled in the trial. Once in the trial, patients were administered subcutaneous infusions over 10 minutes of Hyqvia® at 108% of the intravenous dose. All patients received a minimum of 12 doses, at 3- or 4-week dose intervals. Median treatment duration was 91 days. The primary outcome was rate of infections. Patients experienced infections as an annual mean rate of infections per patient per year of 2.97 (95% CI 2.51 to 3.47).[30]

GAMMAGARD LIQUID (Immune globulin infusion 10%): Gammagard® liquid, for intravenous and subcutaneous administration, was approved for the additional indication of CIDP in January of 2024 to improve neuromuscular disability and impairment in adult patients.[31] Approval was based on an open-label, single-arm, multi-center study in 18 patients. Patients were treated with a maintenance dose every 3 weeks for 6 months, initiated at 2 g/kg, which could be adjusted based on investigator's discretion. The primary outcome was responder rate (e.g., improvement in functional disability, indicated by at least a 1-point decrease in the adjusted Inflammatory Neuropathy Cause and Treatment [INCAT] disability score) at 6 months. Patients treated with Gammagard® had a responder rate of 94.4% (95% CI, 74.2% to 99.0%).[31]

BIVIGAM (Immune globulin intravenous – 10% liquid): Bivigam® received an approval for a new indication for the treatment of adults and pediatric patients 2 years of age and older with PI.[32] Approval was based on an open-label, single-arm, multi-center study in adult (n=53) and pediatric patients (n=9) who were already receiving a stable dose of IVIg for least 3 months at a dose of 300 to 800 mg/kg.[32] Bivigam® was given every 3- 4 weeks for approximately a year, depending on prior dosing intervals. The most common indication was for variable immunodeficiency. The primary outcome was prevention of serious bacterial infections (e.g., less than 1 case of bacterial pneumonia, bacteremia/septicemia, osteomyelitis/septic arthritis, visceral abscess, and bacterial meningitis per year). There were 2 cases of bacterial infection with an event rate per person per year of 0.03.[32]

New Formulations:

ALYGLO (immune globulin intravenous – 10% liquid): In December 2023, a new formulation of immune globulin was approved for the treatment of PI in adults.[33] Patients enrolled in the study ranged from 17 to 70 years with a mean age of 49.6 years. Study patients were receiving stable doses of 300 to 900 mg/kg of IVIg replacement therapy prior to enrollment. Study doses were given every 21 to 28 days for 12 months. The primary outcome, annualized rate of severe bacterial infections, occurred at a rate of 0.03 acute infections per person per year which met the predefined success rate of less than one acute serious bacterial infection per subject per year.[33]

CUTAQUIG (Immune globulin subcutaneous, human – hipp, 16.5% solution): A new immunoglobulin formulation was approved in December 2018 for the treatment of PI in adults and pediatric patients 2 years of age and older.[34] A prospective, open-label, single-arm, multi-center study was conducted in 75 patients. The mean

age was 47.5 years (range 2 to 73 years).[34] A 12-week wash in (availability of Ig trough levels)/wash-out period was followed by a 12-month treatment period in which efficacy was evaluated. Patients received a mean dose of 174 mg/kg in a weekly SC infusion. The primary outcome was severe bacterial infection, which occurred at an annual rate (number of severe bacterial infections per subject year) of 0.13 for adults and pediatrics, for a total annual rate of 0.06.[34]

ASCENIV (immune globulin intravenous, human – sira): Asceniv® is a 10% liquid for intravenous injection indicated for the treatment of PI in adults and adolescents (ages 12 to 17 years) and was approved in April 2019.[35] Evidence for approval came from a single-arm, multicenter trial in patients (n=59) already receiving regular IVIg replacement therapy of doses consisting of 300 and 800 mg/kg for at least 3 months. Asceniv® is given every 3-4 weeks for 12 months. Patients were a mean age of 42 years (3 to 74 years), and 93% identified as Caucasian, 5% as Hispanic and 2% as African American. The primary outcome, severe bacterial infection, did not occur in any patients with a mean rate of 0 infections per year. Rate of infections was 3.4 (infections/total person-years).[35]

PANZYGA (immune globulin intravenous, human – ifas): In August 2018, a new formulation was approved for the treatment of PI in patients 2 years of age and older, chronic immune thrombocytopenia (ITP) in adults, and CIDP in adults.[36] Approval for PI was based on a single, open-label, single-arm, multicenter study (n=51). Participants were between the ages of 2-65 years with a mean age of 26.8 years. Panzyga® was administered at 200-800 mg/kg/min IV every 3-4 weeks. The primary endpoint was number of episodes of serious bacterial infections (e.g., pneumonia, bacteremia or sepsis, osteomyelitis/septic arthritis, visceral abscesses, or bacterial meningitis) per patient per year, which occurred at a rate of 0.8 (4 infections over 50.2 patient-years).[36]

For the indication of ITP in adults, Panzyga® was studied in a single, open-label, single-arm, multicenter study (n=40) in participants 18 to 72 years of age (median age 32 years). Panzyga® was dosed as 2 g/kg/day IV, divided into 2 daily doses, given on 2 consecutive days. The primary outcome was response rate, which was defined as percentage of subjects with an increase in platelet count to at least 50 x 10^9/L within the first 7 days after the first infusion.[36] Twenty-nine participants were considered responders (81%; 95% CI, 64% to 92%).[36]

Evidence for the approval for the use of Panzyga® for CIDP in adults was based on double-blind, randomized, multi-center, dose-comparison study enrolling 142 participants. Eligible participants were 18 to 83 years of age with CIDP who deteriorated in the wash-out phase. Participants received 7 maintenance infusions at 3-week intervals during the 24-week dose-evaluation phase.[36] Participants received a Panzyga® loading dose of 2 g/kg and then one of three dosing regimens: 0.5 g/kg, 0.1 g/kg or 2.0 g/kg. The primary outcome was the percent of responders in the 1.0 g/kg Panzyga® group, defined as a decrease in 1 point in the adjusted 10-point INCAT disability score at week 24 relative to baseline. Fifty-five participants were considered responders compared to 14 patients considered non-responders (79.71%; 95% CI, 68.8-87.5).[36] Patients treated with Panzyga® 1.0 g/kg demonstrated non-statistically different changes in INCAT scores compared to patients treated with 0.5 g/kg (OR 0.5; 95% CI; 0.2–1.2) or 2.0 g/kg (OR 2.7; 95% CI, 0.7–10.2).[37]

XEMBIFY (immune globulin subcutaneous, human – klhw): A 20% immune globulin solution for subcutaneous injection was approved in July 2019 for the treatment of PI in patients 2 years and older.[38] The main North American study used for approval of Xembify® was an open-label, single-arm, multi-center clinical trial conducted in 53 adult and pediatric patients. The median dose was 171 mg/kg/week. The primary outcome was annualized serious bacterial infection at 6 months. The annual rate of severe bacterial infections was 0.05 per subject year (95% CI, 0.02 to 0.10; 1 event in 20 patient-years).[38]

New FDA Safety Alerts:
None identified.

Randomized Controlled Trials:
A total of 274 citations were manually reviewed from the initial literature search. After further review, 273 citations were excluded because of wrong study design (e.g., observational), comparator (e.g., no control or placebo-controlled), or outcome studied (e.g., non-clinical). The remaining trial is summarized in the table below. The full abstract is included in **Appendix 2**.

Table 3. Description of Randomized Comparative Clinical Trials.

Study	Comparison	Population	Primary Outcome	Results	Notes/Limitations
Aggarwal, et al[6] DB, PC, RCT	1.IVIg (Octagam 10%) 2.0 g/kg every 4 weeks vs. 2. Placebo every 4 weeks (16 weeks)	Adult patients with dermatomyositis (n=95)	Response (defined as a Total Improvement Score* [TIS] of at least 20 – indicating minimal improvement‡) at week 16	1. IVIg: 37 (79%) 2. Placebo: 21 (44%) TD 35% (95% CI, 17 to 53) P<0.001 ARR 35%/NNT 3	IVIg reduced disease activity more than placebo based on one short term, small study.

Abbreviations: ARR = absolute risk reduction; DB = double-blind; IVIg = intravenous immune globulin; NNT = number needed to treat; PC = placebo controlled; RCT = randomized controlled trial; TD = treatment difference
Key: * Total Improvement Score (TIS) is a composite score reflecting the change in a core set of six measures of myositis activity over time, with scores ranging from 0-100; higher scores indicate greater improvement; ‡ A change of 20 in the TIS indicates at least minimum improvement.

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31. GAMMAGARD LIQUID (Immune Globulin Infusion [Human], 10% solution, for Intravenous and Subcutaneous administration) [prescribing information]. Lexington, Massachusetts; Takeda Pharmaceuticals U.S.A., Inc. January 2024.

32. BIVIGAM (immune Globulin Intravenous - Human, 10% liquid) [prescribing information]. Boca Raton, FL; ADMA Biologics, Inc. December 2023.

33. ALYGLO (Immune Globulin Intravenous, human - stwk) [prescribing information]. Teaneck, New Jersey; GC Biopharma USA, Inc. December 2023.

34. CUTAQUIG (Immune Globulin Subcutaneous [Human] - hipp) [prescribing information]. New York, New York; Pfizer Labs. October 2021.

35. ASCENIV (Immune Globulin Intravenous - human - sira). Boca Raton, Florida; ADMA Biologics. August 2019.

36. PANZYGA (Immune Globulin Intravenous, human - ifas) [prescribing information]. Paramus, New Jersey; Octapharma USA, Inc. January 2021.

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38. XEMBIFY (Immune Globulin Subcutaneous, human - klhw) [prescribing information]. Research Park, North Carolina; Grifols Therapeutics LLC. July 2019.

Appendix 1: Current Preferred Drug List

Generic	Brand	Generic	Form	Route	PDL
immune globul G/gly/IgA avg 46	GAMUNEX-C	immune globul G/gly/IgA avg 46	VIAL	Injection	Y
IgG/hyaluronidase,recombinant	HYQVIA	IgG/hyaluronidase,recombinant	VIAL	Subcutaneous	N
imm glob G (IgG)/sorb/IgA 0-50	FLEBOGAMMA DIF	imm glob G (IgG)/sorb/IgA 0-50	VIAL	Intravenous	N
immun glob G(IgG)/gly/IgA ov50	GAMMAGARD LIQUID	immun glob G(IgG)/gly/IgA ov50	VIAL	Injection	N
immun glob G(IgG)/gly/IgA ov50	BIVIGAM	immun glob G(IgG)/gly/IgA ov50	VIAL	Intravenous	N
immun glob G(IgG)/gly/IgA ov50	CUVITRU	immun glob G(IgG)/gly/IgA ov50	VIAL	Subcutaneous	N
immun glob G(IgG)/gly/IgA ov50	HYQVIA IG COMPONENT	immun glob G(IgG)/gly/IgA ov50	VIAL	Subcutaneous	N
immun glob G(IgG)/pro/IgA 0-50	HIZENTRA	immun glob G(IgG)/pro/IgA 0-50	SYRINGE	Subcutaneous	N
immun glob G(IgG)/pro/IgA 0-50	PRIVIGEN	immun glob G(IgG)/pro/IgA 0-50	VIAL	Intravenous	N
immun glob G(IgG)/pro/IgA 0-50	HIZENTRA	immun glob G(IgG)/pro/IgA 0-50	VIAL	Subcutaneous	N
immun glob G(IgG)-ifas/glycine	PANZYGA	immun glob G(IgG)-ifas/glycine	VIAL	Intravenous	N
immun globG(IgG)/malt/IgA ov50	OCTAGAM	immun globG(IgG)/malt/IgA ov50	VIAL	Intravenous	N
immune globul G/gly/IgA avg 46	GAMMAKED	immune globul G/gly/IgA avg 46	VIAL	Injection	N
immune globulin,gamma(IgG)	CARIMUNE	immune globulin,gamma(IgG)	VIAL	Intravenous	N
immune globulin,gamma(IgG)klhw	XEMBIFY	immune globulin,gamma(IgG)klhw	VIAL	Subcutaneous	N
immune globulin,gamma(IgG)slra	ASCENIV	immune globulin,gamma(IgG)slra	VIAL	Intravenous	N
immun glob G(IgG)/gly/IgA 0-50	GAMMAPLEX	immun glob G(IgG)/gly/IgA 0-50	VIAL	Intravenous	
immun glob G(IgG)-hipp/maltose	CUTAQUIG	immun glob G(IgG)-hipp/maltose	VIAL	Subcutaneous	
immun glob G/gly/gluc/IgA 0-50	GAMMAGARD S-D	immun glob G/gly/gluc/IgA 0-50	VIAL	Intravenous	
immun glob G/sorb/gly/IgA 0-50	GAMMAPLEX	immun glob G/sorb/gly/IgA 0-50	VIAL	Intravenous	
immun globG(IgG)/malt/IgA ov50	OCTAGAM	immun globG(IgG)/malt/IgA ov50	VIAL	Intravenous	
immune globul G (IgG)/glycine	GAMASTAN	immune globul G (IgG)/glycine	VIAL	Intramuscular	
immune globulin,gamma(IgG)	GAMMAR-P I.V.	immune globulin,gamma(IgG)	VIAL	Intravenous	
immune globulin,gamma(IgG)	IMMUNE GLOBULIN	immune globulin,gamma(IgG)	VIAL	Intravenous	
immune globulin,gamma(IgG)	SANDOGLOBULIN	immune globulin,gamma(IgG)	VIAL	Intravenous	

Appendix 2: Abstracts of Comparative Clinical Trials

Trial of Intravenous Immune Globulin in Dermatomyositis

Aggarwal R, Charles-Schoeman C, Schessl J, Bata-Csörgő Z, Dimachkie MM, Griger Z, Moiseev S, Oddis C, Schiopu E, Vencovský J, Beckmann I, Clodi E, Bugrova O, Dankó K, Ernste F, Goyal NA, Heuer M, Hudson M, Hussain YM, Karam C, Magnolo N, Nelson R, Pozur N, Prystupa L, Sárdy M, Valenzuela G, van der Kooi AJ, Vu T, Worm M, Levine T; ProDERM Trial Group.

Background: Intravenous immune globulin (IVIG) for the treatment of dermatomyositis has not been extensively evaluated.
Methods: We conducted a randomized, placebo-controlled trial involving patients with active dermatomyositis. The patients were assigned in a 1:1 ratio to receive IVIG at a dose of 2.0 g per kilogram of body weight or placebo every 4 weeks for 16 weeks. The patients who received placebo and those without confirmed clinical deterioration while receiving IVIG could enter an open-label extension phase for another 24 weeks. The primary end point was a response, defined as a Total Improvement Score (TIS) of at least 20 (indicating at least minimal improvement) at week 16 and no confirmed deterioration up to week 16. The TIS is a weighted composite score reflecting the change in a core set of six measures of myositis activity over time; scores range from 0 to 100, with higher scores indicating greater improvement. Key secondary end points included at least moderate improvement (TIS ≥40) and major improvement (TIS ≥60), and change in score on the Cutaneous Dermatomyositis Disease Area and Severity Index.

Results: A total of 95 patients underwent randomization: 47 patients were assigned to the IVIG group, and 48 to the placebo group. At 16 weeks, 79% of the patients in the IVIG group (37 of 47) and 44% of those in the placebo group (21 of 48) had a TIS of at least 20 (difference, 35 percentage points; 95% confidence interval, 17 to 53; P<0.001). The results with respect to the secondary end points, including at least moderate improvement and major improvement, were generally in the same direction as the results of the primary end-point analysis, except for the change in creatine kinase level (an individual core measure of the TIS), which did not differ meaningfully between the two groups. Over 40 weeks, 282 treatment-related adverse events occurred in the IVIG group, including headache (in 42% of patients), pyrexia (in 19%), and nausea (in 16%). A total of 9 serious adverse events that were considered to be related to IVIG occurred, including 6 thromboembolic events.

Conclusions: In this 16-week trial involving adults with dermatomyositis, the percentage of patients with a response of at least minimal improvement based on a composite score of disease activity was significantly greater among those who received IVIG than among those who received placebo. IVIG was associated with adverse events, including thromboembolism. (Funded by Octapharma Pharmaceuticals; ProDERM ClinicalTrials.gov number, [6]).

Appendix 3: Medline Search Strategy

Database(s): **Ovid MEDLINE(R) ALL** 1946 to May 16, 2024
Search Strategy:

#	Searches	Results
1	immunoglobulins.mp. or Immunoglobulins/	86982
2	intravenous immunoglobulins.mp. or Immunoglobulins, Intravenous/	17696
3	1 or 2	86982
4	limit 3 to (english language and humans and yr="2020 -Current")	5852
5	limit 4 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	274
6	immunoglobulins.mp. or Immunoglobulins/	86982
7	intravenous immunoglobulins.mp. or Immunoglobulins, Intravenous/	17696
8	subcutaneous immunoglobulins.mp.	86
9	6 or 7 or 8	86982
10	limit 9 to (english language and humans and yr="2020 -Current")	5852
11	limit 10 to (clinical trial, phase iii or guideline or meta analysis or practice guideline or "systematic review")	274

Appendix 4: Key Inclusion Criteria

Population	Patients with an indication for IVIG or SCIG
Intervention	Intravenous or subcutaneous immunoglobulins
Comparator	Placebo or active treatment
Outcomes	Infection rate, platelet counts, decrease in symptoms (i.e., neuropathy, disability, myositis activity), hospitalizations, mortality
Setting	Outpatient