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Drug Use Evaluation: Immune Globulins

Purpose of the Review:

- Immune globulin (IgG) formulations appear on the top physician assisted drug (PAD) report due to high utilization. Immune globulins are used for many off-label uses without the support of high-quality evidence. This evaluation will determine the number of IgG claims that are used for an approved Food and Drug Administration (FDA) indication or off-label usage. If they are used for an off-label diagnosis, the indication and the evidence supporting that indication will be evaluated.

Research Questions:

- How many IgG claims in the fee-for-service (FFS) population are used for an FDA-approved diagnosis?

Conclusions:

- There were 30 unique patients with a PAD or point of sale pharmacy claim for a drug in the IgG preferred drug list (PDL) class from January 1, 2018 to December 31, 2018. Of those, 17 patients (56.6%) had a claim for an FDA approved indication, 9 (30%) patients with claims for an off-label diagnosis, and 4 (13.3%) patients with no known diagnosis associated with the claim.
- Claims for an FDA-approved indication accounted for 56 claims (54.4%) and 12 (11.7%) claim were for an off-label indication, 35 (34%) of claims were not associated with any indication.
- Immune globulin use in patients with a transplant indication accounted for the largest number of off-label use with 4 patients and 6 claims.
- Ten percent of patients (n=3) had IgG claims for the preferred treatment, GAMUNEX-C (2 patients with an approved indication and 1 patient with an off-label diagnosis).
- Over half of IgG claims are prescribed in concordance with FDA labeling. There are no strong trends in the data that suggest policy changes are necessary at this time.

Recommendations:

- Recommend reanalyzing off-label use annually to inform future restrictions within the class.

Background

There are several types of intravenous IgG (IVIG) formulations, 5 exclusively subcutaneous IgG (SCIG) products, and 1 intramuscular IgG product. Several IVIG products may also be administered subcutaneously. Immune globulin replacement has demonstrated efficacy in multiple outcomes, such as disease improvement, increased functionality, and reduced incidence of infection (**Table 1**).[2] Previous reviews have found no evidence to suggest efficacy differences between IVIG formulations. Products containing high amounts of IgA are associated with a higher number of adverse events, specifically anaphylaxis. Products with a sucrose stabilizer were associated with higher rates of osmotic renal injury than products using a non-sucrose stabilizer. There are not currently any sucrose-based products available in the United States. There is no evidence to suggest efficacy or safety differences between IVIG and SCIG products. Immune

globulins are also commonly used for off-label indications, as monotherapy or in combination with other agents or therapies (e.g., plasma exchange), which is substantiated by limited evidence for certain disease states or insufficient evidence of efficacy for other indications (**Table 2**). A 2014 drug utilization review found that 73% of patients in the Oregon Medicaid fee-for-service (FFS) population had an FDA-approved indication and 24% had an indication supported by efficacy data, suggesting appropriate use of IgG. GAMMAGARD (IgG [Human] 10%) and OCTAGAM (IgG [Human] 5%) were identified in the top 50 FFS PAD medical claims in the second quarter of 2019.

Table 1. FDA-Approved Indications for Immune Globulin Products[2]

Indication
• Primary immunodeficiency
• Immune thrombocytopenia purpura (ITP)
• Multifocal motor neuropathy (MMN)
• B-cell chronic lymphocytic leukemia (CLL)
• Kawasaki syndrome
• Chronic inflammatory demyelinating polyneuropathy (CIDP)

Table 2. Off-label uses for Immune Globulin Products[2,3]

Diagnosis
• Multiple Sclerosis (MS)
• Systemic lupus erythematosus
• Scleroderma
• Myocarditis
• Guillain-Barré syndrome
• Sjogren syndrome
• Dermatomyositis
• Myasthenia gravis (MG)
• Autoimmune thrombocytopenia in pregnancy
• Dermatological auto-immune diseases
• Toxic epidermal necrolysis (TEN) / Stevens-Johnson syndrome (SJS)

A recent Drug Effectiveness Review Project (DERP) review of off-label IgG use in treatment of autoimmune disorders did not find high-quality clinical evidence supporting efficacy for off-label indications.[2] A systematic review of the literature identified 10 trials of IVIG in patients with multiple sclerosis (MS), myasthenia gravis (MG), chronic inflammatory demyelinating polyneuropathy (CIDP) and Guillain-Barré syndrome (**Table 3**). No evidence was found for the use of SCIG. The trials were found to be of poor or fair methodological quality. The original report is available to Oregon Pharmacy and Therapeutics Committee members upon request.

Table 3. Findings from DERP for the Off-Label Use of Immune Globulins

Indication	Findings
Multiple Sclerosis (relapsing-remitting and acute relapse)	- IVIG reduced yearly exacerbation rate (0.59 events per year) compared to placebo (1.61 events per year) (p=0.001) in one trial - Study of IVIG infusion, given every 4-weeks, was not found to be more effective than placebo in the number of relapse-free participants - Combination IVIG and methylprednisolone was not more effective than methylprednisolone alone in preventing relapse
Myasthenia Gravis	- No significant differences were found between IVIG and plasma exchange in the degree of disability
Chronic Inflammatory Demyelinating Polyneuropathy (CIDP)	- One small (n=27) study found Gammagard and Kiovig (not available in the US) IVIG to have similar efficacy based on the Overall Disability Sum Score
Guillain-Barré Syndrome*	- A single administration study of IVIG and plasma exchange demonstrated similar findings on a validated functional scale - Plasma exchange followed by IVIG had similar efficacy as plasma exchange or IVIG alone based on functional disability

Abbreviations: IVIG – intravenous immunoglobulin
Key: * Not approved for Guillain-Barré Syndrome in the United States

Off-label IgG use was the focus of several Canadian Agency for Drugs and Technology in Health (CADTH) evidence reviews.[3–8,,9] There was no evidence to support the use of IgG for some indications, and mixed or limited evidence for their use in other indications (**Table 3**). Evidence for some indications lacked precision, requiring additional studies to clarify effect. The authors concluded that there was limited evidence to support off-label use of IgG in autoimmune diseases.

Table 3. CADTH Evidence for Off-label Use of Immune Globulin Products[3-7]

Condition	Indication with No Supporting Evidence for Use	Indication for which the Efficacy Evidence is Limited* or May or May not Provide Benefit
Neurological	• Alzheimer disease • Encephalitis • Post-polio Syndrome	• Pediatric Guillain-Barré Syndrome*ł • Multiple sclerosis* • Epilepsy • Myasthenia Gravis • Chronic inflammatory demyelinating polyneuropathy
Hematological	• Aplastic anemia • Autoimmune neutropenia • Hyperhemolysis after transfusion • Acquired Hemophilia	• Blood conditions affecting the fetus or newborn*
Autoimmune or Inflammatory	• Dermatomyositis • Myasthenia Gravis • Polymyositis • Kawasaki disease • Sydenham chorea • Acute rheumatic fever cardiac complications	• Systemic lupus erythematosus* • Cardiac outcomes in infants of mothers with antiphospholipid syndrome during pregnancy*

Dermatological	• Stevens-Johnson syndrome – survival benefit	• Stevens-Johnson syndrome – decreased recovery time with high dose* • Bullous pemphigoid* • Polymyositis* • Dermatomyositis*
Recurrent Spontaneous Abortion	• No effect on obstetrical, perinatal, and neonatal outcomes	• Improved live-birth rates in some studies
Solid Organ Transplant Rejection (chronic, antibody mediated rejection)	• No benefit on renal transplant outcomes when given with rituximab	• Improved renal transplant outcomes versus methylprednisolone*

Key: ł Health Canada considers adult Guillain-Barré syndrome as an "on-label" use

Cochrane systematic reviews have not found evidence to support the use of off-label IgG for the following indications: encephalitis[10], epilepsy[11], presumed viral myocarditis in children and adults[12], and suspected or proven infection in neonates. However, IVIG reduced recovery time to a similar extent as plasma exchange (PLEX) in patients with severe forms of Gullain-Barré syndrome (mean difference 0.02; 95% CI, 0.25 to 0.20; moderate strength evidence).[13]

Guidance from the European Academy of Dermatology and Venereology support the use of IVIG in patients with toxic epidermal necrolysis (TEN) despite lack of high-quality evidence due to the severity and rarity of the condition.[14] Additional indications for IVIG recommended by the guidelines are: severe forms of dermatomyositis, severe autoimmune blistering diseases, severe systemic vasculitic syndromes, severe forms of lupus erythematodes, and scleromyxedema. Recommendations were based on consensus of expert opinion and authors had conflicts of interest. Guidance was included due to lack of other sources of high-quality evidence.

<u>American Society of Hematology – 2011 Evidence-based Guidelines for Immune Thrombocytopenia</u>

The American Society of Hematology (ASH) offers guidance on the treatment of immune thrombocytopenia (ITP) in pregnant adults.[1] This guideline is included due to the high number claims in OHP FFS population for off-label use of IgG in patients with ITP in pregnancy. There is insufficient evidence on the management of ITP in pregnant adults. The expert consensus is to treat pregnant adult patients in the same manner as non-pregnant adults. The ASH strongly recommends corticosteroids or IVIG for treatment of ITP in pregnancy based on low quality evidence.[1]

Methods:

Patients of any age were included if they had a paid FFS PAD or pharmacy POS claim for an IgG in the Immune Globulin preferred drug list (PDL) class from January 1, 2018 to December 31, 2018. Diagnoses for FDA-approved and off-label conditions (as defined in **Table 4**) were identified based on the diagnosis submitted on the claim within the study period for patients with an IgG claim. If patients have claims with multiple diagnoses, they may be counted more than once. Claims were classified as new start (no claims for IgG 6 months prior to start of study period) or continuous therapy (any IgG claim 6 months prior to start of study period or multiple claims within the reporting period). Patient demographic data were collected based on the reference claim (the first paid claim for IgG) for the reporting period.

Patients were excluded if they had Medicare crossover claims for an IgG product indicating Medicare Part B coverage.

Table 4. Diagnosis codes of Disease States of Interest

Diagnosis Code (ICD-10)	Disease State
FDA Approved Diagnosis	
D84.9, D80.2, D80.3, D80.4	Primary immunodeficiency, immunoglobulin deficiency
D69.3, D69.4, D69.5, D69.6	Immune thrombocytopenia purpura (ITP)
M30.3	Kawasaki syndrome
G61.82	Multifocal motor neuropathy (MMN)
C91.1, C91.10, C91.11, C91.12	B-cell chronic lymphocytic leukemia (CLL)
G61.81	Chronic inflammatory demyelinating polyneuropathy (CIDP)
Off-label Diagnosis	
G70, G70.0, G70.00, G70.01	Myasthenia gravis (MG)
O99.119	ITP in pregnancy
G35	Multiple sclerosis
M32	Systemic lupus erythematosus
L94, L94.1, M34	Scleroderma
A38.1, A39.52, B26.82, B33.22, B58.81, D86.85, I01.2, I09.0, I40, I41, I51.4, J10.82, J11.82	Myocarditis
G61.0, G65.0	Guillain-Barré syndrome
M35.0	Sjogren syndrome
M33.10	Dermatomyositis
L12.0, L12.3, Q81, L10, L01, H35.06, L95, M05.2	Dermatological auto-immune diseases
L51.2, L51.3, L51.1, L51.3	Toxic epidermal necrolysis (TEN)/ Stevens-Johnson syndrome (SJS)

Results:

The search found 30 patients with claims (4 point of sale [pharmacy] claims and 26 physician administered) for an IgG product in the designated time period. Mean patient age was 24 years, 60% were female, and 63% were white (**Table 4**). Seventy percent of patients were administered IgG in the outpatient hospital setting. Sixty-three percent were new starts and 37% had prior use of IgG. Immune globulin use in distinct patients for an FDA-approved indication was documented in 17 (56.6%) patients, 9 patients (30%) used IgG for an off-label indication, and 4 patients (13.3%) used IgG without a noted diagnosis (**Table 5**). Primary immunodeficiency accounted for 40% of the FDA-approved uses. Solid organ transplant (13.3%) was the most common diagnosis for patients with off-label use. Claims for patients with an FDA-approved diagnosis accounted for 54.4% of all claims in the study period and off-label use accounted for 11.7% of claims. Four patients, all with point of sale claims, had an unknown diagnose and accounted for 34% of all claims in the study period (**Table 5**). Immune globulin utilization was divided between 7 different agents, with GAMMAGARD, FLEBOGAMMA and PRIVIGEN the most commonly prescribed (**Table 6**). There was no utilization for BIVIGAM, CUTAQUIG, CUVITRA, GAMMAKED, GAMMAPLEX, and PANZYGA.

Table 4. Demographics

	Number of Patients (N=30)	Percent
Mean Age: 24 years		
Female	18	60%
Race		
• White	19	63.3%
• Unknown	9	30.0%
• Other	2	6.6%
IgG Product		
• Gammagard liquid (IV or SC)	10	33.3%
• Privigen (IV)	5	16.7%
• Flebogamma (IV)	5	16.7%
• Octagam (IV)	4	13.3%
• Gamunex-C (IV or SC)	3	10.0%
• Hizentra (SC)	2	6.7%
• Hyqvia (SC)	1	3.3%
Prior IgG Use		
• New Start	19	63.3%
• History of IgG	11	36.7%
Indication		
• FDA Approved	17	56.6%
• Off-label use	9	30.0%
• None	4	13.3%
Setting based on claim type*		
- Hospital (Outpatient PAD)	21	70.0%
- Clinic (Professional PAD)	5	16.7%
- Pharmacy POS	4	13.3%

* Patients may be counted more than once if they had claims in multiple settings or claims for multiple diagnoses.

Table 5. Summary of Immune Globulin Use by Diagnosis

Indication	Number of Patients # (%)	Number of Claims	Evidence for Use
Any FDA-approved indication	17 (56.6%)	56 (54.4%)	
Immune thrombocytopenia purpura (ITP)	4 (13.3%)	50	Approved indication
Chronic inflammatory demyelinating polyneuropathy (CIDP)	1 (3.3%)	1	Approved indication
Primary immunodeficiency	12 (40%)	5	Approved indication

Off-label Indication	9 (30.0%)	12 (11.7%)	
Myasthenia gravis (MG)	1 (3.3%)	2	May provide benefit
Transplant	4 (13.3%)	6	Limited evidence of benefit
Asthma	1 (3.3%)	1	Insufficient evidence
Degenerative disease of the nervous system	1 (3.3%)	1	Insufficient evidence
Juvenile dermatomyositits	2 (6.6%)	2	Insufficient evidence
Unknown	4 (13.3%)	35 (34%)	

Table 6. Claims for Immune Globulins According to Diagnosis

	FLEBOGAMMA	GAMMAGARD	GAMUNEX-C	HIZENTRA	HYQVIA	OCTAGAM	PRIVIGEN
Any FDA-approved indication							
Immune thrombocytopenia purpura (ITP)	1	3	1				
Chronic inflammatory demyelinating polyneuropathy (CIDP)		1					
Primary immunodeficiency	13	19	1			16	1
Off-label Indication							
Myasthenia gravis (MG)						2	
Transplant		3	2				1
Asthma						1	
Degenerative disease of the nervous system							1
Juvenile dermatomyositits							2
Unknown		3		29	2		

Table 7. Provider Information for Immune Globulin Claims*

Provider	Number of Patients # (%)	Number of Claims # (%)
Hematology and Oncology	9 (23%)	47 (46.5%)
Pulmonology	1 (2.6%)	3 (3%)
Rheumatology	1 (2.6%)	2 (2%)
Internal Medicine/Family Medicine	1 (2.6%)	1 (1%)
Nurse Practitioner	1 (2.6%)	1 (1%)
Hospital listed as provider	26 (66.7%)	47 (46.5%)

* Patient counts are not unique, as some patients fall under multiple providers

Conclusions:
Fifty-seven percent of IgG claims were used for an FDA-approved indication. Off-label use of IgG accounted for about 30% of claims for the designated time period. Patients with an IgG claim without a diagnosis were point of sale claims, which can be a limitation in obtaining a diagnosis. There is no discernable trend in prescriber type or type of IgG prescribed. Requiring a diagnosis be applied to IgG claims would inform if administration is used for an appropriate indication. Additional data would help to inform policy decisions in the future.

Limitations:
Inherent limitations to Medicaid claims data:

- Diagnostic accuracy: Diagnoses data based on claims may be inaccurate or incomplete. Diagnoses must be submitted for PAD claims, but are not associated with POS pharmacy claims; therefore, it is difficult to determine the intended indication of the drug.
- Provider Specialty: Information on provider specialty may be inaccurate, out-of-date, or incomplete for some providers. Prescribers with multiple specialties or designation may not be identified.
- Days of coverage: Estimated number of covered days attempts to approximate the frequency which a patient takes a prescription, but accuracy of this method has not been validated, covered days may not accurately correlate to actual medication adherence, and patients may not always be categorized appropriately.
- No diagnosis: It is difficult to draw conclusions of appropriate utilization when 34% of patients with an IgG claim had no associated diagnosis.

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