CLINICAL PROFILES IN **PRIMARY IMMUNODEFICIENCY DISEASE (PIDD)***

ASCENIV™

IMMUNE GLOBULIN INTRAVENOUS (HUMAN) — slra 10% LIQUID

* Cases are hypothetical. Images and descriptions are for illustrative purposes only.

Indication

ASCENIV (immune globulin intravenous, human-slra) is a 10% immune globulin liquid for intravenous injection, indicated for the treatment of primary humoral immunodeficiency (PI) in adults and adolescents (12 to 17 years of age). PI includes, but is not limited to, the humoral immune defect in congenital agammaglobulinemia, common variable immunodeficiency (CVID), X linked agammaglobulinemia, Wiskott-Aldrich syndrome, and severe combined immunodeficiencies (SCID).

Important Safety Information for ASCENIV™

WARNING: THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE

Thrombosis may occur with immune globulin (IGIV) products, including ASCENIV. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling central vascular catheters, hyperviscosity, and cardiovascular risk factors. Thrombosis may occur in the absence of known risk factors.

Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with the administration of Immune Globulin Intravenous (Human) (IGIV) products in predisposed patients.

Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. ASCENIV does not contain sucrose.

For patients at risk of thrombosis, renal dysfunction or renal failure, administer ASCENIV at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

Please see additional Important Safety Information throughout and accompanying full Prescribing Information, including Boxed WARNING.

IS YOUR PATIENT WITH PIDD APPROPRIATE FOR TREATMENT WITH ASCENIV™?

PATIENTS WITH A HISTORY OF RESPIRATORY INFECTION MAY BE AT INCREASED RISK.[1]
WHAT IS YOUR TREATMENT APPROACH FOR THESE PATIENTS?

Annabelle S.

Age 19
Gender Female
Occupation College student
Hobbies Environmental science

CONDITION

Common variable immunodeficiency (CVID) requiring hospitalizations due to recurrent bacterial infection in lower respiratory tract

CHIEF COMPLAINT/ PRESENTATION

- High fever
- Fatigue, general weakness
- Rapid, shallow, irregular breathing

PATIENT HISTORY

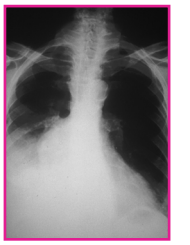
- At age 5 years, low serum Ig was documented but no intervention
- Initiated standard IVIG therapy at age 7
- Hospitalized twice in 24 months for pneumonia, with average of length of 7 days
- Recurrent otitis media, sinusitis, and two hospitalized episodes of pneumonia over the course of three years

PHYSICAL EXAM

- Temperature: 102°F
- HR: 136 bpm
- BP: 96/70
- RR: 30 breaths/minute
- O_2 saturation: 90% on room air
- Crepitation heard in right lung base

LABS/ IMAGING

- Pan culture of sera and nasopharyngeal swab
- WBC: 12.4 x 103/uL
- IgG: 0.55 g/L (range 7.51 – 15.60)
- Radiograph reveals asymmetric opacities and fluid on right middle lobe



Source: https://www.medicalimages.com/stock-photo-chest-x-ray-frontal-view-showing-pneumonia-in-the-base-of-the-right-lung-in-a-female-patient-image9258622.html

Kara W.

Age 35
Gender Female
Married
Occupation Yoga instructor
Hobbies Outdoors and hiking

CONDITION

PIDD and history of recurrent respiratory infection

CHIEF COMPLAINT/ PRESENTATION

- Periods of fatigue
- Recurrent viral infections and bronchiectasis
- Fever, cough, dehydration, and poor appetite
- Respiratory distress/difficulty breathing

PATIENT HISTORY

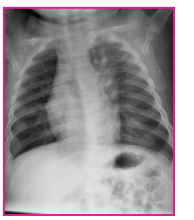
- Admitted to ICU for acute LRTI and received broad-spectrum prophylactic antibiotics and standard IVIG
- Culture positive for RSV
- After 10 days in the ICU, the patient developed severe hypoxemia and respiratory acidosis, requiring mechanical ventilation

PHYSICAL EXAM

- Temperature: 103.1°F
- HR: 120 bpm
- BP: 90/60
- RR: 30 breaths/minute
- O_2 saturation: 87% room air
- $PaCO_2$: 35 mmHg

LABS/ IMAGING

- WBC: 11.2 x 103/uL
- IgG: 0.374 g/L
- Radiograph reveals asymmetric, bilateral patchy opacities



Source: https://www.medicalimages.com/stock-photo-x-ray-of-the-chest-frontal-view-showing-a-respiratory-syncytial-virus-rsv-infection-in-a-five-image15698468.html

Important Safety Information for ASCENIV

Adverse Reactions

The most common adverse reactions to ASCENIV (≥5% of study subjects) were headache, sinusitis, diarrhea, gastroenteritis viral, nasopharyngitis, upper respiratory tract infection, bronchitis, and nausea.

You are encouraged to report side effects of prescription drugs to ADMA Biologics @ 1-800-458-4244 or the FDA. Visit www.fda.gov/MedWatch or call 1-800-FDA-1088.

Richard A.

Age 54
Gender Male
Occupation Computer engineer
Married
Hobbies Loves his fantasy football league

CONDITION

Diagnosed with PIDD in young adulthood; history of bronchiectasis and recurrent respiratory tract infections

CHIEF COMPLAINT/ PRESENTATION

- Respiratory distress: difficulty breathing; persistent productive cough
- Referred to regional hospital for a surgical consultation for a lobectomy following a diagnosis of bronchiectasis
- Confirmed bronchiectasis; continued deterioration in pulmonary function measured by PFTs
- Admitted and placed on broad-spectrum antibiotics
- Hospital-acquired pneumonia from *Streptococcus pneumoniae*

PATIENT HISTORY

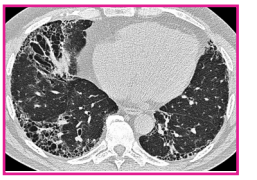
- Recurrent URTIs and LRTIs
- Recurrent seasonal bacterial infections despite IVIG dose increases and prophylactic antibiotics
- Hospitalized with pneumonia twice in the past 4 years; discharged on prophylaxis for gram-negative pulmonary infection antibiotics and standard IVIG
- Development of hypotension and respiratory failure; placed on NRB at 15 LPM

PHYSICAL EXAM

- Temperature: 99.2°F
- HR: 110 bpm
- BP: 135/108
- RR: 25 breaths/minute
- O_2 saturation: 92% room air
- PaO_2: 70 mmHg

LABS/ IMAGING

- Pan culture of sera negative, sputum nasopharyngeal swab, and stool
- WBC: 11.11 x 10^3/uL – 81.3% lymphocytes
- Protein electrophoresis: decreased gamma fraction confirmed by analysis of immunoglobulins
- IgG: 0.68 g/L (range 7.51 – 15.60)
- Chest CT scan revealed interstitial pneumonia with bronchiectasis
- Nodular lesions with surrounding density and thickened widened bronchioli
- Enlarged axillary, mediastinal and hilar lymphadenopathies



Source: https://www.medicalimages.com/stock-photo-pulmonary-fibrosis-ct-scan-image23352710.html

Benjamin T.

Age 66
Gender Male
Divorced
Occupation Retired
Hobbies Fishing with his two boys

CONDITION

PIDD since young adulthood; bronchiectasis and recurrent respiratory tract infections

CHIEF COMPLAINT/ PRESENTATION

- Fever
- Respiratory distress

PATIENT HISTORY

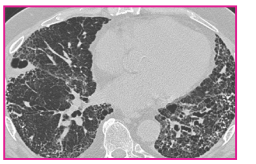
- 20-yr history of hypogammaglobulinemia
- Receiving standard IVIG prophylactic
- Recurrent bacterial and viral infections despite IVIG dose increases and prophylactic antibiotics
- Hospitalized twice over last year, received broad-spectrum antibiotics

PHYSICAL EXAM

- Body temperature: 102.2°F
- HR: 125 bpm
- BP: 90/65
- RR: 30 breaths/minute
- O_2 saturation: 88%
- PaO_2: 65 mmHg

LABS/ IMAGING

- Chest CT scan revealed interstitial pneumonia with bronchiectasis, consistent with pneumonia of unknown etiology
- On Day 3, all cultures were negative except NP swab, which was positive for RSV



Source: Darel Heitkamp, MD. - https://commons.wikimedia.org/w/index.php?curid=31127997

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- **Renal dysfunction, acute renal failure, osmotic nephrosis, and death may occur with the administration of Immune Globulin Intravenous (Human) (IGIV) products in predisposed patients.**
- **Renal dysfunction and acute renal failure occur more commonly in patients receiving IGIV products containing sucrose. ASCENIV does not contain sucrose.**
- **For patients at risk of thrombosis, renal dysfunction or renal failure, administer ASCENIV at the minimum dose and infusion rate practicable. Ensure adequate hydration in patients before administration. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.**

Contraindications

ASCENIV is contraindicated in:

- Patients who have had an anaphylactic or severe systemic reaction to the administration of human immune globulin.
- IgA-deficiency patients with antibodies to IgA and a history of hypersensitivity.

Warnings and Precautions

Severe hypersensitivity reactions may occur with IGIV products, including ASCENIV. In case of hypersensitivity, discontinue ASCENIV infusion immediately and institute appropriate treatment. Patients with known antibodies to IgA may have a greater risk of developing potentially severe hypersensitivity and anaphylactic reactions.

Thrombosis may occur following treatment with immunoglobulin products and in the absence of known risk factors. Consider baseline assessment of blood viscosity in patients at risk for hyperviscosity and ensure adequate hydration before administration. For patients at risk of thrombosis, administer ASCENIV at the minimum dose and infusion rate practicable. Monitor for signs and symptoms of thrombosis and assess blood viscosity in patients at risk for hyperviscosity.

Acute renal dysfunction/failure, osmotic nephrosis, and death may occur upon use of human IGIV products. Ensure that patients are not volume depleted before administering ASCENIV. Periodic monitoring of renal function and urine output is particularly important in patients judged to be at increased risk of developing acute renal failure. Assess renal function, including measurement of blood urea nitrogen (BUN) and serum creatinine, before the initial infusion of ASCENIV and at appropriate intervals thereafter. Discontinue ASCENIV if renal function deteriorates. In at risk patients, administer ASCENIV at the minimum infusion rate practicable.

Hyperproteinemia, increased serum viscosity, and hyponatremia or pseudohyponatremia may occur in patients receiving IGIV treatment, including ASCENIV. It is critical to clinically distinguish true hyponatremia from a pseudohyponatremia that is associated with or causally related to hyperproteinemia. Treatment aimed at decreasing serum free water in patients with pseudohyponatremia may lead to volume depletion, a further increase in serum viscosity, and a possible predisposition to thrombotic events.

Aseptic meningitis syndrome (AMS) may occur with IGIV treatments, including ASCENIV. AMS usually begins within several hours to 2 days following IGIV treatment. AMS may occur more frequently in association with high doses (2 g/kg) and/or rapid infusion of IGIV. Conduct a thorough neurological examination on patients exhibiting signs and symptoms of AMS, including cerebrospinal fluid (CSF) studies, to rule out other causes of meningitis.

IGIV products, including ASCENIV, may contain blood group antibodies that can act as hemolysins and induce in vivo coating of red blood cells (RBCs) with immunoglobulin, causing a positive direct antiglobulin reaction and hemolysis. Monitor patients for clinical signs and symptoms of hemolysis, including appropriate confirmatory laboratory testing.

Non-cardiogenic pulmonary edema may occur with IV administered IG. Monitor patients for pulmonary adverse reactions. If suspected, perform appropriate tests for presence of anti-neutrophil in both product and patient serum. May be managed using oxygen therapy with adequate ventilatory support.

Because ASCENIV is made from human blood, it may carry a risk of transmitting infectious agents, e.g., viruses, the variant Creutzfeldt-Jakob disease (vCJD) and theoretically, the Creutzfeldt-Jakob disease (CJD) agent. All infections suspected by a physician to possibly have been transmitted by this product should be reported to ADMA Biologics at **(1-800-458-4244)**.

After infusion of immunoglobulin, the transitory rise of the various passively transferred antibodies in the patient's blood may yield positive serological testing results, with the potential for misleading interpretation. Passive transmission of antibodies to erythrocyte antigens (e.g., A, B, and D) may cause a positive direct or indirect antiglobulin (Coombs') test.

Adverse Reactions

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Reference: 1. Jolles S. Subclinical infection and dosing in primary immunodeficiencies.Clin Exp Immunol. 2014;178(suppl 1):67-69.

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ADMA BIOLOGICS

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