Octagam [Immune Globulin Intravenous, (Human)], 10% Liquid Preparation

Presented by: Dr. Rohit Aggarwal, MD, MS
Professor of Medicine
Medical Director, Arthritis and Autoimmunity Center
Co-Director, Myositis Center
Department of Medicine/Division of Rheumatology
University of Pittsburgh
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Disclosures

- This study was sponsored by Octapharma Pharmazeutika Produktionsgesellschaft m.b.H., Vienna, Austria
- Advisory Board: Mallinckrodt, Orphazyme, Octapharma, CSL Behring
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- Research Grant: Mallinckrodt, Bristol Myers Squibb, Pfizer, Genentech, Q32, EMD Serono

Please see Boxed Warning on slide 4 and Highlights of Prescribing Information shown at the end of this presentation
Octagam 10% is available in the US

- Octagam 10% is an immune globulin intravenous (human) liquid preparation indicated for the treatment of chronic immune thrombocytopenia purpura (ITP) in adults and for the treatment of dermatomyositis (DM) in adults.

Please see Boxed Warning on slide 4 and Highlights of Prescribing Information shown at the end of this presentation.
Boxed Warning for Octagam 10%

Warnings, contraindications, and precautions

Octagam 10% [Immune Globulin Intravenous (Human)]
liquid solution for intravenous administration
Initial U.S. Approval: 2014

WARNING
THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE
See full prescribing information for complete boxed warning

- Thrombosis may occur with immune globulin intravenous (IGIV) products, including Octagam 10%. Risk factors may include: advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogens, indwelling vascular catheters, hyperviscosity, and cardiovascular risk factors.
- Renal dysfunction, acute renal failure, osmotic nephropathy, 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. Octagam 10% does not contain sucrose.
- For patients at risk of thrombosis, renal dysfunction or renal failure, administer Octagam 10% at the minimum 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

- History of anaphylactic or severe systemic reactions to human immunoglobulin (4)
- IgA deficient patients with antibodies against IgA and a history of hypersensitivity (4)

WARNINGS AND PRECAUTIONS

- IgA-deficient patients with antibodies against IgA are at greater risk of developing severe hypersensitivity and anaphylactic reactions to Octagam 10%. Epinephrine should be available immediately to treat any severe acute hypersensitivity reactions (5.1).
- Monitor renal function, including blood urea nitrogen and serum creatinine, and urine output in patients at risk of developing acute renal failure (5.2).
- Falsely elevated blood glucose readings may occur during and after the infusion of Octagam 10% with testing by some glucometers and test strip systems (5.3).
- Hyperproteinemia, increased serum osmolarity and hyponatremia may occur in patients receiving Octagam 10% (5.4).
- Hemolysis that is either intravascular or due to enhanced red blood cell sequestration can develop subsequent to Octagam 10% treatments. Risk factors for hemolysis include high doses and non-O-blood group. Closely monitor patients for hemolysis and hemolytic anemia (5.6).
- Aseptic Meningitis Syndrome may occur in patients receiving Octagam 10%, especially with high doses or rapid infusion (5.7).
- Monitor patients for pulmonary adverse reactions (transfusion-related acute lung injury (TRALI)) (5.8).
- Octagam 10% is made from human plasma and may contain infectious agents, e.g. viruses and, theoretically, the Creutzfeldt-Jakob disease agent (5.9).

Please see Highlights of Prescribing Information shown at the end of this presentation
Dermatomyositis (DM)  
A disease with many faces

- Type of idiopathic inflammatory myopathy (IIM) characterized by inflammatory changes of the muscles and skin

- Typical Features →
  - Symmetric proximal muscle weakness
  - Skin rash

- Very heterogeneous disease → many different subgroups

- Classification of DM subgroups evaluated by:
  - Clinical symptoms and their severity
  - Presence of different autoantibodies/immunological mediators


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Who does DM affect?

Incidence: 10 cases per 1 million persons per year*
Prevalence: 125 cases per 1 million persons*

Female > Males

Bimodal age distribution (2 peaks: 5-15 years old, 40-60 years old)

Association of DM with malignancy

*Estimates show that approximately 3,280 people are diagnosed with dermatomyositis every year, and there are upwards of about 41,000 people in America who are living with dermatomyositis.
Dermatomyositis (DM)

Typical Symptoms

- Common characteristics of DM include **symmetric proximal muscle weakness**, muscle inflammation and **skin rash**

- **Muscle involvement:**
  - **Symmetric proximal muscle weakness**: shoulder, hip girdle, limb muscle, muscles of the trunk
  - Patients often describe **difficulty** to rise from a low-seated chair, climbing stairs, or raising their arms to lift objects

- **Skin involvement:**
  1. Heliotrope rash: red discoloration over the upper eyelids
  2. V-sign: rash on front of neck and chest, and over the outside of the hip
  3. Gottron sign: erythematous eruptions on interphalangeal joints
  4. Poikiloderma: skin condition that consists of areas of hypo-, hyperpigmentation, telangiectasias (spider veins) and atrophy

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Myositis Specific Autoantibodies (MSAs)
Most important DM-specific Autoantibodies

- **Anti-Mi-2 Antibody:**
  - Most classical type of DM
  - Often no malignancy involved

- **Anti-MDA-5 Antibody:**
  - Present in different types of atypical DM
  - Associated with severe ILD

- **Anti-TIF1-Gamma**
  - Very high number of macrophages
  - High complement depositions (MAC)
  - Specific muscle biopsy features → high risk of cancer (up to 70%)

- **Anti-NXP-2**
  - High number of inflammatory infiltrates
  - Increased risk of cancer
  - Mostly seen in children

Benveniste, Stenzel and Allenbach, 2016, Current Opinion

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Clinical Study
ProDERM (GAM10-08) Trial Overview

- Prospective, double-blind, randomized, placebo-controlled, multicenter Phase III study to evaluate the efficacy and safety of Octagam 10% in patients with dermatomyositis

- 16-week double-blinded treatment phase followed by 24-week open label extension phase

- Conducted at 36 sites worldwide (17 sites in the United States)

- A total of 95 subjects who ranged in age from 22 to 79, mean 53.7 years of age were enrolled

- Subjects who were under treatment with corticosteroids and/or maximally 2 immune-suppressants and being on stable therapy for at least 4 weeks OR previous failure of response or intolerance to corticosteroids and at least 1 additional immunosuppressive drug were eligible

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ProDERM Study Endpoints

Primary and Secondary Objectives

Primary Objectives

• Proportion of responders* in the 2 g/kg Octagam 10% and placebo arms at week 16 compared to baseline based on Total Improvement Score (TIS)

Secondary Objectives

• Proportion of TIS responders by improvement category
• Mean change from baseline to end of First Period in the modified Cutaneous Dermatomyositis Disease Area and Severity Index (CDASI)
• Safety and tolerability of Octagam 10% in patients with DM

*A responder was defined as a subject with an improvement of ≥ 20 points on the Total Improvement Score (TIS) and who has not met “Confirmed Deterioration” criteria at 2 consecutive visits up to (including) Week 16

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The **Total Improvement Score (TIS)** is based on the assessment of six (6) Core Set Measures (CSMs)

1. Physician Global Disease Activity (GDA) as part of Myositis Disease Activity Assessment Tool (MDAAT) assessed by the Investigator on a Visual Analog Scale (VAS)
2. Patient GDA assessed by the Patient on a VAS
4. Health Assessment Questionnaire (HAQ) assessed by the Patient
5. Muscle Enzymes: Aldolase, Creatine Kinase, ALAT, ASAT, LDH
6. Extra Muscular Activity as part of MDAAT assessed by the Investigator on a VAS
ProDERM Population Parameters
Inclusion Criteria

- Patients aged ≥ 18 and <80 years with a diagnosis of definite or probable DM according to Bohan and Peter Criteria
- Active disease as per independent adjudication committee
- Patient currently on standard immunosuppression* or previously failed or intolerant standard immunosuppression.
- MMT-8 score <142/150, with at least 2 other abnormal CSMs
  - Patient global activity ≥2 cm
  - Physician global disease activity ≥2 cm
  - Extra-muscular disease activity ≥2 cm
  - At least one muscle enzyme >1.5 times ULN
  - HAQ-DI ≥0.25

*Standard immunosuppression:
  Currently: corticosteroids and/or max of 2 immunosuppressants (stable doses)
  Failed/intolerant: corticosteroid and/or at least 1 immunosuppressants (washed out)

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GAM10-08 (ProDERM) Study Design

Prospective, parallel group, double-blind, randomized, placebo-controlled, multicenter, phase III study

Randomization 1:1

Screening

IVIG 2.0g/kg q4wk

Placebo q4wk

Stratified by mild, moderate or severe disease**

Week 0

Double-Blind FIRST PERIOD (16 weeks)

Week 16

*CD

IVIG

Week 28

Open-label EXTENSION PERIOD (24 weeks)

Week 40

*CD: Confirmed Deterioration

For stable patients optional dose reduction 1.0g/kg q4wk

*CD: Confirmed Deterioration

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Patient Flow

Screened = 126

Screen Failures = 31

Randomized to IVIG = 47

Randomized to Placebo = 48

Treated with IVIG = 47

Treated with Placebo = 48

Completed First Period = 45 (95.7%)

Completed First Period = 46 (95.8%)

Completed Extension Period = 34 (72.3%)

Completed Extension Period = 35 (72.9%)

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## GAM10-08 ProDERM Study
### Patient Demographics

<table>
<thead>
<tr>
<th>Parameter</th>
<th>Octagam 10% N=47</th>
<th>Placebo N=48</th>
<th>Total N=95</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Age [Years]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean (SD)</td>
<td>54.04 (13.838)</td>
<td>51.35 (12.979)</td>
<td>52.68 (13.407)</td>
</tr>
<tr>
<td><strong>Gender [N (%)]</strong></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Female</td>
<td>36 (76.6%)</td>
<td>35 (72.9%)</td>
<td>71 (74.7%)</td>
</tr>
<tr>
<td>Male</td>
<td>11 (23.4%)</td>
<td>13 (27.1%)</td>
<td>24 (25.3%)</td>
</tr>
</tbody>
</table>

N= number of patients; SD= standard deviation

*Please see Boxed Warning on slide 4 and Highlights of Prescribing Information shown at the end of this presentation*
Primary Endpoint: TIS score Responders at Week 16

<table>
<thead>
<tr>
<th>Treatment</th>
<th>Proportion of Responders</th>
<th>N</th>
</tr>
</thead>
<tbody>
<tr>
<td>Octagam 10%</td>
<td>78.7% (n=37)</td>
<td>47</td>
</tr>
<tr>
<td>Placebo</td>
<td>43.8% (n=21)</td>
<td>48</td>
</tr>
</tbody>
</table>

*Δ = 34.97% p=0.0008

Δ = percent change
n = number of responders
N = total number of patients

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GAM10-08 (ProDERM) TIS – Proportion of Responders

Secondary Endpoint: Proportion of responders with at least moderate or major improvement at Week 16

Δ = 45.17% p<0.0001

Δ = 23.58% p=0.0062

Δ= percent change
n= number of responders

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GAM10-08 (ProDERM) TIS – Proportion of Responders

Secondary Endpoint: TIS Responders at Week 40

- Octagam 10%
  - 71.1% (n=32/45)
- Placebo-Octagam 10%
  - 69.6% (n=32/46)

n= number of responders out of total number of patients at week 40
Note 45 patients in the Octagam 10% group and 46 patients in the placebo group completed the first period and entered the 24-week extension period where both groups received Octagam 10%

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The mean TIS was significantly higher in IVIG [48.4] vs. placebo [21.6] at week 16.
Mean total activity score decreased from baseline in both treatment groups with a more marked decrease from baseline in the Octagam 10% group.
Safety and Tolerability
Treatment with Octagam 10% was generally well tolerated

- During the entire study, 62 patients (65.3%) experienced 282 TEAEs
- Drug-related adverse reactions experienced by >5% of subjects in the Overall Period:

<table>
<thead>
<tr>
<th>Reactions</th>
<th>Number of subjects (% of subjects [n=95])</th>
</tr>
</thead>
<tbody>
<tr>
<td>Headache</td>
<td>40 (42%)</td>
</tr>
<tr>
<td>Pyrexia</td>
<td>18 (19%)</td>
</tr>
<tr>
<td>Nausea</td>
<td>15 (16%)</td>
</tr>
<tr>
<td>Vomiting</td>
<td>8 (8%)</td>
</tr>
<tr>
<td>Chills</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Musculoskeletal pain</td>
<td>7 (7%)</td>
</tr>
<tr>
<td>Blood pressure increased</td>
<td>6 (6%)</td>
</tr>
</tbody>
</table>

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Serious Treatment Emergent Adverse Events (TEAEs)

- During the First Period the incidence of serious TEAEs was similar in the two treatment groups, with
  - 3 patients (5.8%) experiencing 5 serious TEAEs in the Octagam 10% ‘at risk’ group and
  - 2 patients (4.2%) experiencing 4 serious TEAEs in the placebo ‘at risk’ group

- Most common related serious TEAEs in the Overall Period:
  - 5 patients (5.2%) experiencing 5 serious TEAEs: deep vein thrombosis and pulmonary embolism in one subject, cerebrovascular accident in one subject, cerebral infarction in one subject, hypoesthesia in one subject and pulmonary embolism in one subject

- No hemolytic transfusion reactions (HTR) or deaths were reported in the study

PE = pulmonary embolism; CVA = cerebrovascular accident; DVT = deep vein thrombosis

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Thromboembolic Events in DM patients
Implications for ProDERM study

- Some retrospective reports show increased risk of TEE in patients with DM
- Gaitonde and Ballou, 2006 showed 20% risk of DVT in DM (compared to 11% in IIM in general and 1.22% in cohort of persons 45-65 years)
- NO known cause for increased risk, but acute inflammation seems to contribute to TEE risk via components of the innate immune system

ProDERM study:
- IDMC assessed all possible TEEs
- An infusion rate titration with adjustments for adverse reactions was included in protocol
- In 2018: Amendment: reduction of max infusion rate from 0.12 ml/kg/min to 0.04 ml/kg/min due to TEE overall rate of 1.54 per 100 patient months
- After reduction was implemented TEE overall rate decreased to 0.54 per 100 patient months

DVT: Deep Vein Thrombosis
PE: Pulmonary Embolism
IIM: Idiopathic inflammatory myopathy
IDMC: Independent Data Monitoring Committee

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The primary endpoint of the study was met with a significantly higher proportion of responders in the Octagam 10% group compared to the Placebo group (78.7% versus 43.7%; p=0.0008).

Safety was as expected for IVIG administration with common adverse events including headache, pyrexia, nausea/vomiting occurring in > 5% of subjects.

ProDERM is the first large placebo-controlled clinical study evaluating the efficacy and safety of IVIG in DM patients.

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**Octagam 10% Highlights of Prescribing Information**

**HIGHLIGHTS OF PRESCRIBING INFORMATION**

These highlights do not include all the information needed to use Octagam 10% safely and effectively. See full prescribing information for Octagam 10%.

Octagam 10% [Immune Globulin Intravenous (Human)]

**WARNING THROMBOSIS, RENAL DYSFUNCTION AND ACUTE RENAL FAILURE**

See full prescribing information for complete boxed warning

- Thrombosis may occur with immune globulin intravenous (IGIV) products, including Octagam 10%. Risk factors may include advanced age, prolonged immobilization, hypercoagulable conditions, history of venous or arterial thrombosis, use of estrogen, indwelling vascular catheters, hypertension, and cardiovascular risk factors.

- Renal dysfunction, acute renal failure, oesmotic nephropathy, 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. Octagam 10% does not contain sucrose.

- For patients at risk of thrombosis, renal dysfunction or renal failure, administer Octagam 10% at the minimum 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.

**RECENT MAJOR CHANGES**

Indications and Usage (1.2), Dosage and Administration (2.1)

**INDICATIONS AND USAGE**

- Octagam 10% is an immune globulin intravenous (human) liquid preparation indicated for the treatment of:
  - Chronic immune thrombocytopenic purpura (ITP) in adults
  - Dermatomyositis (DM) in adults

**DOSAGE AND ADMINISTRATION**

For intravenous use only:

<table>
<thead>
<tr>
<th>Condition</th>
<th>Initial Dose</th>
<th>Maintenance</th>
<th>Maintenance Infusion Rate (if tolerated)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Chronic ITP</td>
<td>2 g/kg divided in equal doses given over 2 consecutive days</td>
<td>1.0 mg/kg/day (0.01 mg/mL)</td>
<td>Up to 12.0 mg/kg/day (Up to 0.12 mg/mL)</td>
</tr>
<tr>
<td>Dermatomyositis</td>
<td>2 g/kg divided in equal doses given over 2-3 consecutive days</td>
<td>1.0 mg/kg/day (0.01 mg/mL)</td>
<td>Up to 4.0 mg/kg/day (Up to 0.04 mg/mL)</td>
</tr>
</tbody>
</table>

- Patients with dermatomyositis are at increased risk for thromboembolic events; monitor carefully and do not exceed an infusion rate of 0.04 mg/kg/min.

- Ensure that patients with pre-existing renal insufficiency are not volume depleted; discontinue Octagam 10% if renal function deteriorates.

- For patients at risk of renal dysfunction or thromboembolic events, administer Octagam 10% at the minimum infusion rate practicable.

**ADVERSE REACTIONS**

Chronic ITP: The most common adverse reactions reported in greater than 3% of subjects during a clinical trial were headaches, fever and increased heart rate.

Dermatomyositis: The most common adverse reactions reported in greater than 3% of subjects during a clinical trial were headaches, fever, nausea, vomiting, increased blood pressure, chills, musculoskeletal pain, increased heart rate, dyspnea, and infusion site reactions.

To report SUSPECTED ADVERSE REACTIONS, contact Octapharma at 1-866-766-4885 or FDA at 1-800-FDA-1088 or www.fda.gov/medwatch.

**DRUG INTERACTIONS**

The passive transfer of antibodies may:

- Confound the results of serological testing.
- Interfere with the immune response to live viral vaccines, such as measles, mumps, and rubella.

**USE IN SPECIFIC POPULATIONS**

- Pregnancy: no human or animal data. Use only if clearly needed.
- Geriatric Use: in patients over age 65 or in any patient at risk of developing renal insufficiency, do not exceed the recommended dose, and infuse Octagam 10% at the minimum infusion rate practicable.

See 17 for PATIENT COUNSELING INFORMATION.

*Octagam 10% Full Prescribing Information is available at request*
Thank You