Important Information Regarding
IVIG-Associated Hemolysis

Customer Letter #2009-02

2009-02-19

Dear Colleague:

This letter pertains to IVIG-associated hemolysis.

Attached please find information provided by the IVIG Hemolysis Pharmacovigilance Group. This information provides a brief description of IVIG-associated hemolysis, a rare but well described adverse event of IVIG therapy as well as an overview of the IVIG hemolysis issue, proposed standardized case definition and information to assist in the investigation and reopening of suspected cases of IVIG-associated hemolysis.

If you have additional questions or comments that have not been addressed or you would like to receive further information about this topic; contact information for your Canadian Blood Services regional Hospital Liaison Specialist or local Medical Director is available at www.Blood.ca listed under Hospitals then Customer Letters.

Sincerely,

Dana Devine, Ph.D.
Vice-President,
Medical Scientific and Research Affairs
Canadian Blood Services


**Topic:**

**Intravenous-Immunglobulin Associated Hemolysis:**

Hemolysis is a rare but well described adverse event of IVIG therapy. The hemolysis has been characterized and reported most often:

- in patients with blood group A or AB;
- with high total dose (≥ 2g/kg) and
- occurring within 10 days after IVIG infusion.

In order to monitor for this adverse event, you may consider:

- asking your patients to report any changes in urine colour;
- monitoring change in hemoglobin and
- additional testing to confirm the diagnosis of hemolysis if hemoglobin has dropped significantly.

Clinically significant hemolysis should be reported to the hemovigilance network and the IVIG manufacturer in your jurisdiction.

Further information about clinical grading, hemolysis investigation and reporting can be found in the attached document.

Prepared by IVIG Hemolysis Pharmacovigilance Group

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The purpose of this document is to propose a standardized case definition of intravenous immunoglobulin (IVIG)-associated hemolysis and to assist in the investigation and reporting of suspected cases. Hemolysis is a rare, well-described, but poorly understood adverse event of IVIG therapy. IVIG-associated hemolysis has been reported most often in patients with blood group A or AB receiving high total IVIG dose (≥ 2g/kg). The hemolysis usually occurs within 10 days after IVIG infusion. At-risk patients should be closely monitored for hemolysis.

To diagnose and report a case of IVIG-associated hemolysis there must be evidence of red cell destruction.

**Definition of IVIG-associated hemolysis**

For the purpose of case report standardization, the definition of IVIG-associated hemolysis is based on the International Society of Blood Transfusion (ISBT) 2006 definition of hemolytic transfusion reaction, with some modifications.

An IVIG-associated hemolytic reaction is one in which there is evidence of a new hemolytic process within 10 days of IVIG administration. The following laboratory signs must be present:

1. a fall of at least 10 g/L in hemoglobin (Hb)  
   **AND**
2. a positive direct antiglobulin test (DAT)  
   **AND**
3. at least two of the following:  
   - increased reticulocyte count  
   - increased lactate dehydrogenase  
   - low haptoglobin  
   - unconjugated hyperbilirubinemia  
   - hemoglobinemia  
   - hemoglobinuria  
   - presence of significant spherocytosis

Cases detected more than 10 days after treatment should also be reported when it is considered likely that the hemolytic process started within 10 days of treatment.
**Notes**

Positive DATs are common, occurring in approximately one-third of patients following IVIG infusion. A positive DAT by itself does not imply hemolysis and is usually clinically insignificant. The overwhelming majority of literature reported and Canadian hemovigilance-reported cases have been DAT-positive. In a case of suspected-IVIG associated hemolysis with negative DAT, repeat testing with alternate methodologies should be considered. True DAT-negative cases will be exceedingly rare. When reporting a case, be sure to include the patient’s ABO blood group.

**Exclusion criteria**

Patients who receive high doses of IVIG are often severely ill and may have anemia for a number of reasons, therefore it is important to exclude the underlying condition and concomitant medications as a cause of anemia. The exclusion criteria are:

- history or examination consistent with an alternative cause of anemia including blood loss, other drug-induced hemolysis, anemia associated with cancer chemotherapy, or hemolysis associated with an underlying disease
- negative DAT
- absence of other inclusion criteria, in particular absence of evidence of hemolysis
Severity Grade

Severity Grade was designed using a decrease in hemoglobin concentration as the main severity grading criteria because of its objective nature and clinical significance. Other parameters such as "need for transfusion" were deemed too subjective.

Severity Grade for IVIG associated hemolysis

<table>
<thead>
<tr>
<th>Grade</th>
<th>Description</th>
</tr>
</thead>
<tbody>
<tr>
<td>Grade 0</td>
<td>Hb fall &lt; 10 g/L</td>
</tr>
<tr>
<td>Grade 1</td>
<td>Hb fall of 10-20 g/L; if starting Hb &gt; 100 g/L</td>
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<tr>
<td>Grade 2</td>
<td>Hb fall of 10-20 g/L; if starting Hb ≤ 100 g/L &lt;br&gt;OR &lt;br&gt;Hb fall of 21-30 g/L if starting Hb &gt; 100 g/L</td>
</tr>
<tr>
<td>Grade 3</td>
<td>Hb fall of 21-30 g/L, if starting Hb ≤ 100 g/L &lt;br&gt;OR &lt;br&gt;Hb fall of 31-40 g/L if starting Hb &gt; 100 g/L</td>
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<tr>
<td>Grade 4</td>
<td>Hb fall of 31-40 g/L; if starting Hb ≤ 100 g/L &lt;br&gt;OR &lt;br&gt;Hb fall greater than 40 g/L if starting Hb &gt; 100 g/L</td>
</tr>
<tr>
<td>Grade 5</td>
<td>any Hb fall resulting in severe organ failure or death as a direct consequence of hemolysis and anemia.</td>
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</tbody>
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