Understanding Subcutaneous Immunoglobulin Therapies For Primary Immunodeficiency Diseases

Introduction

According to the World Health Organization (WHO), there are more than 150 primary immunodeficiency diseases (PIDs).1 PIDs are characterized by deficiencies involving B and T cells and phagocytes—antibodies necessary for normal immune responses. Many PIDs have been linked to single genetic deviations (eg, a mutation in the Btk gene that underlies X-linked hypogammaglobulinemia), whereas others emerge as manifestations of an underlying set of abnormalities.2 Impairments in antibody production, often due to inadequate or dysfunctional B cells, are observed in about 60% of patients with PID.3 Based on a study employing a large community sample, the estimated prevalence of diagnosed PID in the United States is 1 in 1,200 individuals or approximately 250,000 cases,4 but the likelihood of a substantial number of undiagnosed cases suggests that the actual number of individuals with PID is far greater.4

Immunoglobulin (IgG) replacement therapy, particularly intravenous (IVIG), has long been a standard for treatment of PID associated with defects in antibody production.5 The burden of lifelong treatment for PIDs makes it particularly important to consider the relative attributes of the full array of options, including the recent availability of subcutaneous alternatives—Vivaglobin® and Hizentra® (CSL Behring)—in an effort to match patients with the treatment that best preserves an optimal quality of life.

Primary Immunodeficiency Disease: Clinical Issues

The clinical impact of PID depends on the degree of severity: Severe PID is recognized at an early age and is associated with high rates of mortality in the absence of immediate efforts to restore immune response, whereas mild impairments in immune dysfunction may go undiagnosed into adulthood, complicating efforts to produce accurate prevalence estimates.4,6 Early detection is encouraged by identifying other warning signs, such as 2 or more pneumonias in a single year, and other clinical signs, such as failure to thrive in infants, that should prompt further evaluation.7,8 It is important to avoid overlooking the potential for PID as the underlying cause of recurrent, difficult-to-control infections in adults as well as children because the peak onset of some disorders, such as common variable immunodeficiency, is not reached until the second or third decade of life.9

The large number of potential abnormalities associated with PID has led several groups, including the Centers for Disease Control and Prevention and the American Academy of Allergy Asthma and Immunology, to advocate diagnostic algorithms that include tests of humoral...
immunity function, such as IgG levels, cellular immunity, and the presence of specific antibodies, early in a rational sequence of evaluations to identify the underlying cause.6,17 Genetic testing, which may be useful in confirming the cause of the PID, can provide the basis for family counseling, but treatment of antibody deficiency associated with PID can be considered urgent and is generally appropriate even in the absence of a diagnosis for the specific genetic disorder.6 “In patients with a known deficiency in IgG, the specific cause of the diagnosis has only a modest influence on treatment. Although some forms of PID are more closely associated with infections at one site, such as the lung, than another, the basis for preventing infection with immunoglobulin replacement does not vary,” said Jerry Siegel, PharmD, clinical associate professor of pharmacy at the Ohio State University College of Pharmacy.

**Treatment Considerations for PID**

In the United States, IVIG has been considered the standard treatment for B-cell PID since the 1980s.5,17 IVIG administration results in an immediate increase in IgG levels (ie, >1,000 mg/dL) that is followed by a rapid decrease over the next few days as the IgG concentration redistributes from the vascular and extracellular space.12 This is followed by a slower catabolic loss of IgG over 3 to 4 weeks.15 IVIG has several advantages over intramuscular formulations, including less discomfort when administering treatment and the potential for delivering higher amounts of IgG to more closely approximated physiologic levels.15 Subsequent advances in IVIG manufacturing, including additional viral removal and inactivation steps and novel stabilizers have improved the safety and tolerability of these agents.13

Because patients with PID require lifelong therapy, IVIG treatment can be challenging and inconvenient. Although there are a number of IVIG formulations that differ in concentration, volume, osmolality, sodium, and sugar content, they share a substantial risk for systemic adverse events (AEs).14 IVIG may cause allergic reactions, the most severe being anaphylaxis.15 This type of reaction requires pretreatment with corticosteroids and antihistamines. Other reactions may be related to the rate of IVIG infusion, such as fever, chills, nausea, vomiting, and back pain; this type of reaction may be obviated by slowing the rate of IVIG infusion. Headaches are especially troublesome and may occur during or after the IVIG infusions.16

**Subcutaneous Immunoglobulins**

Poor venous access can be problematic when administering IVIG. For patients who experience difficulty with the administration of IVIG, the availability of subcutaneous immunoglobulin (SCIG) has proven to be an effective, convenient, and tolerant option.17,18 Additionally, the side effects associated with IVIG are less frequent with SCIG administration.19 The administration of SCIG has been used broadly in Europe for more than 20 years for the treatment of PIDs in both adults and children.17 The recent introduction in the United States of a higher concentrated subcutaneous formulation of IgG provides an opportunity to reconsider the features and attributes of this route of administration relative to IV infusions.

SCIG is administered locally into the subcutaneous tissue and then slowly diffuses into the vascular and extracellular spaces.12 With SCIG, patients are able to use a pump to self-administer treatment, making it more convenient and improving overall quality of life.20 Studies have provided evidence that home administration of SCIG is safe and effective.21-23 In one of the earliest and most influential studies, 25 patients with hypogammaglobulinemia, of whom 15 had adverse reactions to IVIG or intramuscular IgG, were evaluated after self-administering 3,232 SCIG infusions.18 The majority of infusions were administered at home.19 Not only were IgG levels adequate, the number of adverse reactions was significantly lower on SCIG administration when compared with the previous experience with IVIG or intramuscular IgG (P<0.001 for both).21

Patients or caregivers can be instructed for administration, permitting home treatment and greatly improving the convenience of IgG therapy. The subcutaneous formulations in the United States and Europe also have proven to be substantially better tolerated than IVIG because they greatly reduce the risk for systemic side effects relative to IVIG, primarily as a result of the slower distribution even when compared with IVIG that is infused slowly after premedication with analesgics or anti-inflammatory drugs.24,25 Although local injection-site reactions do occur and can vary in range from 20% to 55% of patients treated with SCIGs, systemic AEs occur about half as frequent with subcutaneous administration than with IVIG.26-28

However, these local site reactions diminish as the drug is absorbed (24-48 hours) and over time with continued therapy.26 In the prospective trial cited in the approval of SCIG in the United States, there was a 1.6% incidence of infusion-related headache, but no other systemic AE occurred at a rate greater than 1%.26 “In some patients, the systemic side effects on IVIG are quite significant, including chills and vomiting. Although we often can reduce the severity of these events by slowing the infusion rate or by pretreating the patient, the SC administration is less likely to produce the systemic effects, and this can be a major advantage for some individuals,” explained Alan Knutsen, MD, professor of pediatrics at St. Louis University Health Sciences Center.

In addition to the greater convenience and the safety advantages of SCIG, this form of delivery also yields better pharmacokinetics (PK). Although the half-life of IgG is about 23 to 25 days in healthy patients and longer in some individuals with PID regardless of route of administration, the dosing and administration schedules of IgG differ markedly by route. Whereas IVIG is administered every 3 to 4 weeks in a customary dose of 200 to 800 mg/kg depending on patient differences in metabolism, SCIG delivery is typically administered once per week in doses derived from previous IgG treatment or serum trough levels.29,30 This dosing schedule results in a sustained and steady state of serum IgG similar to physiologic levels, which are a potential advantage for reducing the risk for infection at the end of the dosing interval as well as the risk for wear-off effects such as fatigue that have been associated with IVIG.19

<table>
<thead>
<tr>
<th>Dose</th>
<th>Hizentra</th>
</tr>
</thead>
<tbody>
<tr>
<td>Hizentra mg/kg</td>
<td>228</td>
</tr>
<tr>
<td>IgG peak levels</td>
<td>1,616 mg/dL</td>
</tr>
<tr>
<td>IgG trough levels</td>
<td>1,448 mg/dL</td>
</tr>
</tbody>
</table>

Based on reference 33.
IVIG, were administered Vivaglobin (34-352 mg/kg) for 1 year.29 To evaluate the efficacy of SCIG against IVIG, a therapeutic dose. The results showed that the IgG levels remained stable, while the IgG trough levels were 1.3 times higher than with IVIG treatment.33 After 12 weeks of treatment, results showed that the rate of infection had decreased to 4.4 per patient.29 AEs were not exceed 20 mL per hour per site.29 Multiple infusion sites can be used simultaneously to reduce the time for delivery of a therapeutic dose. To evaluate the efficacy of SCIG against IVIG, 65 adult and pediatric patients with PID, previously treated with IVIG, were administered Vivaglobin (34-352 mg/kg) for 1 year.29 The results showed that the IgG levels remained stable, while the rate of infection had decreased to 4.4 per patient.29 AEs were comparable to those seen with IVIG administration, with local reaction at the injection site being the most common.29

**Hizentra**

Although the minimum IgG plasma concentration recommended in published guidelines is greater than 500 mg/dL, guidelines from the Immune Deficiency Foundation reported that trough levels greater than 800 mg/dL may be needed for some conditions, such as those that are likely to increase risk for pulmonary infections.31,32 Although the 16% concentration was shown able to provide these levels of IgG in most children and many adults, a recently approved 20% concentration, Hizentra, may help even more patients maintain desired IgG levels above an IgA.33 The licensing trial for Hizentra included PK analyses as well as efficacy and safety endpoints. In the PK substudy, 18 patients were administered an adjusted weekly dose between 141 and 381 mg/kg.33 After 12 weeks of treatment, results showed that the IgG trough levels were 1.3 times higher than with IVIG treatment. IgG serum levels remained stable throughout treatment (Table 1).33 There were no annual serious bacterial infections (SBIs) reported with Hizentra during the trial, thus meeting the FDA required end point SBI rate for licensing of less than 1.0.34

Because the IgG from the subcutaneous tissue slowly diffuses into the vascular fluid, the 20% concentration of the SCIG does not appear to increase the risk for systemic AEs substantially based on the Hagan et al Phase IIIb study that consequently led to FDA approval.35 Common side effects occurring in 5% or more patients include local reactions such as swelling, redness, heat, pain, and itching at the injection site, as well as, headache vomiting, pain, and fatigue. With the 20% solution (Hizentra), as with the 16% solution (Vivaglobin), a maximum of 4 and 6 injection sites, respectively, can be employed simultaneously with infusion rates for Hizentra of up to 25 mL per hour per site as tolerated if the total infusion does not exceed 50 mL per hour for all combined sites.33 The rapid infusion time further increases the convenience of a home delivery method. Moreover, as this product is stabilized with l-proline, the 20% solution can be stored at room temperature.33 This offers patients the convenience of having a product readily available for self-administration without additional preparation or wait time. The 16% solution (Vivaglobin), which is stabilized with glycine, requires refrigeration (Table 2).29,36

“The advantage of the 20% solution is that it allows less volume to be used to reach the target IgG concentrations. It is basically the same preparation, but the greater IgG concentration may mean fewer needle sticks,” reported Dr. Knutsen. For good clinical practice he advises monitoring trough IgG levels periodically regardless of what delivery method of IgG administration is employed to ensure that patients are above their target, which is generally regarded as being greater than 800 mg/dL for most individuals with B-cell immunodeficiencies.32 He expects that although some patients could not be maintained above desired trough levels on the 16% concentration, many more will be adequately maintained with the 20% concentration, increasing the proportion of patients with PID who can be treated with home administration of IgGs.

Although the availability of the 20% solution of SCIG to expand current options for management of PID is substantial, the adaptation of SCIG products has been slower in the United States as compared with Europe and simply may be a question of awareness. Particularly now that a 20% concentration is available, all patients suitable for subcutaneous therapy can consider subcutaneous administration as a viable option; however, the challenge is making clinicians aware of the option and not reserving it only for children or others who may have poor IV access. “Periodically, I receive a call asking whether an alternative IVIG might reduce some of the side effects that a patient is receiving on their current agent. When I suggest substituting a subcutaneous therapy, I am often surprised to hear that this option had never been considered. This is something that should change, because this route of administration can be very well received by patients,” said Dr. Siegel.

**Patient Preference**

Quality-of-life studies have substantiated several advantages associated with SCIG. Health Related Quality of Life studies have demonstrated increased treatment satisfaction and overall good health. In addition to surveys documenting improved convenience, SCIG is associated with objective advantages over IVIG such as fewer absences from work and school. Patients who have switched from IVIG to SCIG also have reported the perception of fewer limitations on routine activities in general.37 In one study evaluating preferences after patients on IVIG were switched to SCIG, the majority preferred SCIG regardless of having received IVIG previously in the outpatient setting. The preference for home treatment was greater among patients receiving IVIG regardless of whether it was in the outpatient

---

**Table 2. Characteristics of Subcutaneous Immunoglobulin Products**

<table>
<thead>
<tr>
<th></th>
<th>Vivaglobin</th>
<th>Hizentra</th>
</tr>
</thead>
<tbody>
<tr>
<td>Concentration</td>
<td>16% liquid SCIG</td>
<td>20% liquid SCIG</td>
</tr>
<tr>
<td>Stabilizer</td>
<td>Glycine</td>
<td>Proline</td>
</tr>
<tr>
<td>Storage</td>
<td>36°F-46°F refrigeration</td>
<td>Room temperature up to 77°F</td>
</tr>
<tr>
<td>Infusion rate</td>
<td>Initial infusion at ≤5 mL/h per site as tolerated; increase gradually to 20 mL/h per site as tolerated</td>
<td>Initial infusion at ≤15 mL/h per site; increase to 25 mL/h per site as tolerated</td>
</tr>
<tr>
<td>IgA content</td>
<td>≤1,700 mcg/mL</td>
<td>≤50 mcg/mL</td>
</tr>
</tbody>
</table>

IgA, immunoglobulin A; SCIG, subcutaneous immunoglobulin

**Vivaglobin**

Vivaglobin was the first subcutaneous IgG formulation to receive FDA approval. Approved in 2006, Vivaglobin is a subcutaneous formulation with a concentration of 16%.29 It contains 96% IgG, 2.25% glycine, and 0.3% sodium for injection; it does not contain sucrose.29 Initial dosing of Vivaglobin is determined based on the previous dose of IVIG and may be adjusted to reach an optimal serum IgG level. The infusion rate should not exceed 20 mL per hour per site.29 Multiple infusion sites can be used simultaneously to reduce the time for delivery of a therapeutic dose. To evaluate the efficacy of SCIG against IVIG, 65 adult and pediatric patients with PID, previously treated with IVIG, were administered Vivaglobin (34-352 mg/kg) for 1 year.29 The results showed that the IgG levels remained stable, while the rate of infection had decreased to 4.4 per patient.29 AEs were comparable to those seen with IVIG administration, with local reaction at the injection site being the most common.29

---

**Hizentra**

Although the minimum IgG plasma concentration recommended in published guidelines is greater than 500 mg/dL, guidelines from the Immune Deficiency Foundation reported that trough levels greater than 800 mg/dL may be needed for some conditions, such as those that are likely to increase risk for pulmonary infections.31,32 Although the 16% concentration was shown able to provide these levels of IgG in most children and many adults, a recently approved 20% concentration, Hizentra, may help even more patients maintain desired IgG levels above an optimal trough level by delivering higher doses with less volume. Hizentra contains at least 98% IgG, trace amounts of sodium, and 250 mmol/L of l-proline, no sucrose, and 50 mcg/mL or less of IgA.32 The licensing trial for Hizentra included PK analyses as well as efficacy and safety endpoints. In the PK substudy, 18 patients were administered an adjusted weekly dose between 141 and 381 mg/kg.33 After 12 weeks of treatment, results showed that the IgG trough levels were 1.3 times higher than with IVIG treatment. IgG serum levels remained stable throughout treatment (Table 1).33 There were no annual serious bacterial infections (SBIs) reported with Hizentra during the trial, thus meeting the FDA required end point SBI rate for licensing of less than 1.0.34

Because the IgG from the subcutaneous tissue slowly diffuses into the vascular fluid, the 20% concentration of the SCIG does not appear to increase the risk for systemic AEs substantially based on the Hagan et al Phase IIIb study that consequently led to FDA approval.35 Common side effects occurring in 5% or more patients include local reactions such as swelling, redness, heat, pain, and itching at the injection site, as well as, headache vomiting, pain, and fatigue. With the 20% solution (Hizentra), as with the 16% solution (Vivaglobin), a maximum of 4 and 6 injection sites, respectively, can be employed simultaneously with infusion rates for Hizentra of up to 25 mL per hour per site as tolerated if the total infusion does not exceed 50 mL per hour for all combined sites.33 The rapid infusion time further increases the convenience of a home delivery method. Moreover, as this product is stabilized with l-proline, the 20% solution can be stored at room temperature.33 This offers patients the convenience of having a product readily available for self-administration without additional preparation or wait time. The 16% solution (Vivaglobin), which is stabilized with glycine, requires refrigeration (Table 2).29,36

“The advantage of the 20% solution is that it allows less volume to be used to reach the target IgG concentrations. It is basically the same preparation, but the greater IgG concentration may mean fewer needle sticks,” reported Dr. Knutsen. For good clinical practice he advises monitoring trough IgG levels periodically regardless of what delivery method of IgG administration is employed to ensure that patients are above their target, which is generally regarded as being greater than 800 mg/dL for most individuals with B-cell immunodeficiencies.32 He expects that although some patients could not be maintained above desired trough levels on the 16% concentration, many more will be adequately maintained with the 20% concentration, increasing the proportion of patients with PID who can be treated with home administration of IgGs.

Although the availability of the 20% solution of SCIG to expand current options for management of PID is substantial, the adaptation of SCIG products has been slower in the United States as compared with Europe and simply may be a question of awareness. Particularly now that a 20% concentration is available, all patients suitable for subcutaneous therapy can consider subcutaneous administration as a viable option; however, the challenge is making clinicians aware of the option and not reserving it only for children or others who may have poor IV access. “Periodically, I receive a call asking whether an alternative IVIG might reduce some of the side effects that a patient is receiving on their current agent. When I suggest substituting a subcutaneous therapy, I am often surprised to hear that this option had never been considered. This is something that should change, because this route of administration can be very well received by patients,” said Dr. Siegel.

**Patient Preference**

Quality-of-life studies have substantiated several advantages associated with SCIG. Health Related Quality of Life studies have demonstrated increased treatment satisfaction and overall good health. In addition to surveys documenting improved convenience, SCIG is associated with objective advantages over IVIG such as fewer absences from work and school. Patients who have switched from IVIG to SCIG also have reported the perception of fewer limitations on routine activities in general.37 In one study evaluating preferences after patients on IVIG were switched to SCIG, the majority preferred SCIG regardless of having received IVIG previously in the outpatient setting. The preference for home treatment was greater among patients receiving IVIG regardless of whether it was in the outpatient
setting (Figure).37 In an evaluation that associated SCIG therapy with increased vitality and better social function over IVIG, 73% of the adults and all of the children specifically expressed a preference for SCIG administration over IVIG.38 For many patients with primary immunodeficiency, subcutaneous delivery of immunoglobulins offers numerous advantages and may improve quality of life. Novel devices for subcutaneous administration that are in development may make this route even easier,” Dr. Knutsen said. “We still need IV formulations for some individuals, but there is a good rationale for more widespread use of the subcutaneous approach in appropriate patients,” he said.

Summary

In patients with PID, IVIG administration has been the dominant method of treatment in the United States for approximately 30 years. The 2006 introduction of a 16% concentration for SCIG delivery has led many clinicians to convert to this method of home treatment for patients who are experiencing problems with IVIG or for those who are suitable candidates for SCIG. It has been adapted widely with children, but has not as yet been offered on a routine basis as a viable option for immunoglobulin replacement. The recent introduction of a 20% solution, which can be stored at room temperature, may be the development that changes orientation of PID treatment from a once-monthly outpatient IV infusion to a once-weekly subcutaneous home administration method. For those patients for whom this route of administration is suitable, the advantages include greater convenience, a lower risk for systemic AEs, and more favorable PK for end-of-dose protection (eg, no wear-off effect) against infection.

References