

Subcutaneous Immunoglobulins (IGSC): Product Characteristics and Their Role in Primary Immunodeficiency Disease (PID)

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Abstract

RATIONALE: Study of the role of subcutaneous immunoglobulins (IGSC) in immune replacement/modulation and preferred concentrations for IGSC formulations is ongoing. We analyzed the pivotal studies for 2 new 10% products (Gammagard® [IGSC 10%] and Gamunex®-C [IGIV-C 10%]) as well as Vivaglobin® (IGSC 16%) and Hizentra® (IGSC 20%).

METHODS: Parameters examined included dose adjustment IV/SC, total volume administered per site, number of infusion sites, infusion time, adverse-event (AE) profiles, method used to collect AE data for each product, and improvements in tolerability over time.

RESULTS: Factors used to obtain equivalent area under the curve (AUC) levels IGIV to IGSC were 137% for 10% and 16% formulations, and 153% for IGSC 20%. Maximum volume infused was 30 mL/site for IGSC 10%, 20mL/site for IGIV-C 10%, ≤20 mL/site for 16%, and 25 mL/site for IGSC 20%. The maximum number of simultaneous infusion sites is unlimited for IGSC 10% and IGIV-C 10%, 6 for IGSC 16%, and 4 for IGSC 20% (Table 1). Percent of subjects who experienced 1 or more local AEs was 44.7%, 75%, 92%, and 100% for IGSC 10%, IGIV-C 10%, 16%, and 20%, respectively. The percent of infusions associated with a local adverse reaction were 2.7% for IGSC 10%, 59% for IGIV-C 10%, 49% for 16%, and 59.1% for IGSC 20%. A decrease in the incidence of local AEs over time was noted for IGSC 10%, IGIV-C 10%, and IGSC 16%, but not IGSC 20%.

Table 1. Characteristics of Subcutaneous Immunoglobulins

| | Gammagard® | Gamunex®-C | Vivaglobin® | Hizentra® |
|-------------------------------|------------------------------|-----------------------------------|---------------|--|
| Dose adjustment | 137% | 137% | 137% | 153% |
| Maximum infusion rate | 30 mL/site | 34 mL/site (mean volume in study) | 15 mL/hr/site | 25 mL/hr/site with a limit of 50 mL/hr |
| Maximum no. of infusion sites | 10 (not limited in protocol) | 8 | 6 | 4 |

CONCLUSION: IGSC formulations are characterized by different features and benefits. Use of IGSC 10% allows for more infusion sites, so infusion time can be similar to that of higher concentration products. IGSC 10% is associated with the lowest rate of infusion site reactions. Further studies are needed to evaluate the benefits of higher concentrations on the immunomodulation effect.

Background

- Primary immunodeficiency disease (PID) is a heterogeneous group of disorders that affect the immune system.¹
- It is estimated that about 60% of PID cases involve antibody production defects.¹
- Before the discovery of antibiotics, patients with antibody deficiencies died early in life due to serious bacterial infections such as pneumonia.¹
- Today, patients with PID are treated successfully with immunoglobulin (IgG) replacement therapy.
- IgG can be administered intramuscularly (IGIM), subcutaneously (IGSC), or intravenously (IGIV).
- With the recent approval of a number of IGSC products in the United States, usage of these preparations is increasing.

Characteristics of IGSC preparations

- Based on approvals of several IGSC preparations in the United States, these formulations are now viewed as a safe and convenient method for many patients with PID.
- IGSC and IGIV have different characteristics.

Table 1. Aspects of IGSC and IGIV

| IGSC | IGIV |
|--|--|
| • Decreased bioavailability vs. IV | • Delivers therapy directly to systemic circulation |
| • Fewer systemic reactions compared to IV | • Increased systemic infusion reactions |
| • Frequent local infusion site reactions | • Dosing is every 3-4 weeks |
| • Possibly reduced occurrence of adverse reactions in IgA-deficient patients who have anti-IgA antibodies ² | • Allows for the administration of large amounts of IgG |
| • Weekly multiseite infusions | • Routine need for trained personnel to deliver/monitor |
| • High level of patient/family motivation necessary | • Some patients have difficult IV access |
| • Reported improvement in quality of life (QOL) due to self-administration ³ | • Approved for immunodeficiency, neuromuscular, and autoimmune indications |
| • Approved only for PID | |
| • Ongoing studies in neuromuscular disorders in EU | |

Objective

In the absence of head-to-head trials, our objective was to review parameters of the following 4 IGSC products:

- IGSC 10% (Gammagard Liquid[®]; pending FDA approval)
- IGIV-C 10% (Gamunex®-C)
- IGSC 16% (Vivaglobin[®])
- IGSC 20% (Hizentra[®])

Parameters Included:

- Dose adjustment IV/SC
- Infusion parameters (volume/rate/number of infusion sites/time to infuse)
- Local AE profiles

Table 2. Infusion Parameters of Subcutaneous Immunoglobulins⁴⁻⁹

| | Gammagard® | Gamunex®-C | Vivaglobin® | Hizentra® |
|-------------------------------|------------------------------|-----------------------------------|--------------|--|
| Dose adjustment | 137% | 137% | 137% | 153% |
| Maximum infusion rate | 30 mL/site | 34 mL/site (mean volume in study) | 15 mL/site | 25 mL/hr/site with a limit of 50 mL/hr |
| Maximum amount IgG/site | 3 000 mg | 3 400 mg (based on mean volume) | 2 400 mg | 5 000 mg |
| Maximum no. of infusion sites | 10 (not limited in protocol) | 8 | 6 | 4 |
| Infusion time | 1.2 hrs (median) | 2.3 ± 1.1 hrs (mean) | Not reported | 1.6-2 hrs (median) |
| Mean weekly dose | 182.6 mg/kg | Not reported | 165 mg/kg | 179.6-224.3 mg/kg |

Table 3. Characteristics of IGSC Products³⁻¹⁰

| | IGSC 10% | IGIV-C 10% | IGSC 16% | IGSC 20% |
|-----------------------|------------------|-----------------------|-----------------|------------------|
| Purity (% IgG) | ≥98% | ≥98% | 96% | ≥98% |
| Monomer-dimer content | ≥95% | 100% | N/A | ≥80% |
| Stabilizer | Glycine (0.25 M) | Glycine (0.16-0.24 M) | Glycine (2.25%) | Proline (0.25 M) |
| Sodium content | None added | None added | 3 mg/mL | Trace |
| Sugar content | None added | None added | None added | None added |
| pH | 4.6-5.1 | 4.9-4.5 | 6.4-7.2 | 4.6-5.2 |
| IgA content | 37 µg/mL | 46 µg/mL | ≤1700 µg/mL | ≤50 µg/mL |
| Osmolality | 240-300 mOsm/kg | 258 mOsm/kg | 445 mOsm/kg | 380 mOsm/kg |

N/A=not available

Clinical Study Results

Table 4. Clinical Study: IGSC 10%

| Description | Endpoints | Results |
|---|--|--|
| Multicenter trial of IGSC 10% in 49 subjects with PID | • Efficacy (rate of all serious bacterial infections [SBIs]) • Tolerability (interrupted, reduced, or stopped infusions) • Biopredictability (total IgG AUC for subjects ≥12 years of age and IgG trough levels for subjects 2 to 12 years of age) | • Annual rate of SBIs: 0.867 infections/subject year • Annual rate of all infections was 4.1 infections/subject year • The rate of all local AEs was 2.8% per infusion • The rate of all local AEs at the start of SC treatment per infusion was 4.9% which reduced to 1.1% in the study extension period |

Table 5. Clinical Study: IGIV-C 10%

| Description | Endpoints | Results |
|---|--|--|
| Open-label pharmacokinetic (PK) trial in 22 subjects with PID | • Non-inferiority of SC vs. IV routes of 10% IGIV-C • Compared steady-state AUC of total plasma IgG | • No SBIs were reported • Annual rate of any infections: 4.1 infections/subject year • The rate of all local AEs was 0.59 per infusion • At the beginning of the SC phase, a rate of approximately 1 local AE per infusion was reported; this decreased to 0.3 local AEs per infusion at the end of the study |

Table 6. Clinical Study: IGSC 16%

| Description | Endpoints | Results |
|--|---|--|
| Open-label, prospective, multicenter clinical study in 65 adult and pediatric subjects with PID previously receiving monthly infusions of IGIV | • Evaluated the pharmacokinetics, efficacy, safety, and tolerability of IGSC 16% • Evaluated annual rate of SBIs • First report of first time, direct initiation of IGSC in previously untreated patients | • Annual rate of SBIs: 0.04 infections/subject year • Annual rate of any infections: 4.4 infections/subject year • The rate of all local AEs was 0.49 per infusion • 85% of patients reported infusion-site reactions after the first IGSC infusion; this declined to 41% after the 3rd infusion and remained stable thereafter |

Table 7. Clinical Study: IGSC 20%

| Description | Endpoints | Results |
|--|--|---|
| Prospective, open-label, multicenter, single-arm study in 38 adult and pediatric patients with PID | • Efficacy, tolerability, and safety of IGSC 20% • Study evaluated annual rate of SBIs • Evaluated the annual rate of any infections | • No SBIs were reported • Annual rate of any infections: 2.76 infections/subject year • The rate of all local AEs was 0.59 per infusion • Investigator assessed incidence of local AEs 45 minutes after infusion remained stable over time • Patient assessed incidence of local AEs 24 hours after infusion showed a slight tendency to decrease |

Safety and Tolerability

Because we compared different studies, we looked at the way AE information was collected in each study.

Table 8. Collection of AE Information in Studies of IGSC

| Product | Approach for AE Collection |
|------------|--|
| IGSC 10% | • All AEs occurring during the time of infusion were documented by the investigator at the study site or at home by a home care nurse • Subjects were followed up by telephone 72 hrs after completion of infusion • All post-infusion AEs were recorded by the subject in a diary and transcribed to the case report form at regular intervals at scheduled clinic visits |
| IGIV-C 10% | • No available information in the study manuscript or prescribing information |
| IGSC 16% | • Infusion-site reactions were monitored before infusion, during the procedure, and 30 min after completion of the infusions • Monitoring was performed during every fourth IGSC infusion |
| IGSC 20% | • Investigator assessments were performed at 15-45 min after infusion at study visits (every 4 weeks) • Patient assessments were made 24 ± 3 hours after every infusion until the completion visit |

Figure 1 compares the percent of subjects experiencing AEs for IGSC 10%, IGIV-C 10%, IGSC 16%, and IGSC 20%.^{7,8,11,12} Figure 2 depicts the rates of local AEs per infusion for the 4 products.

Figure 1. Percent of Subjects Experiencing Local AEs

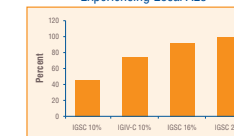


Figure 2. Rate of Local AEs per Infusion

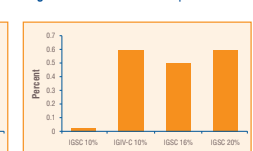
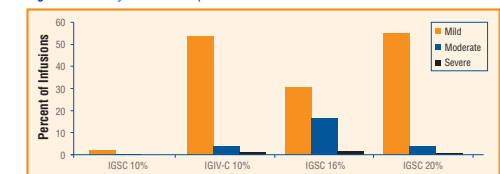


Figure 3 depicts the severity of local AEs per infusion.

Figure 3. Severity of Local AEs per Infusion



Over time, decreased local AE incidence was noted for IGSC 10%, IGIV-C 10%, and IGSC 16%, but not for IGSC 20%.

Conclusions

- Several IGSC products are currently being developed or marketed in the United States.
- While these products have similar efficacy profiles, their tolerability profiles differ.
- Reasons for these differences are unknown and warrant further research.

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