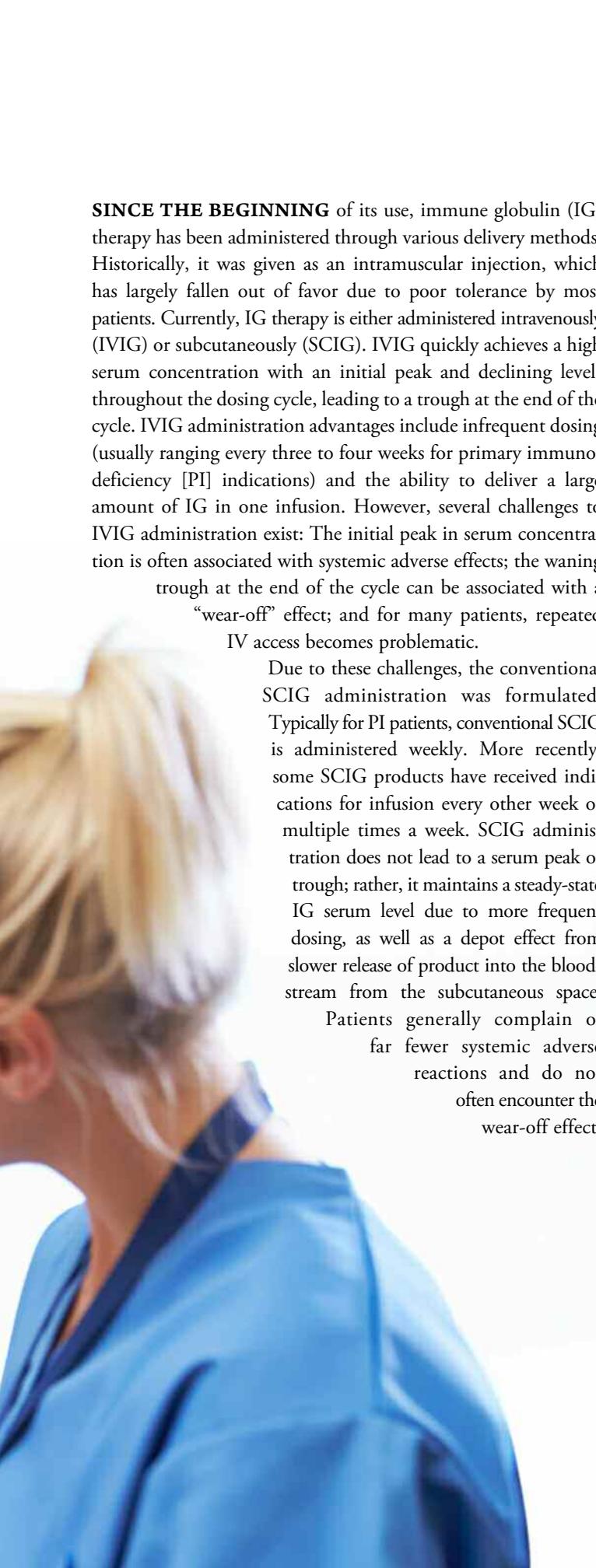


Hyaluronidase-Facilitated SCIG

While its novelty comes with challenges and concerns, the use of hyaluronidase to administer subcutaneous immune globulin has unique advantages.

By Bob Geng, MD





SINCE THE BEGINNING of its use, immune globulin (IG) therapy has been administered through various delivery methods. Historically, it was given as an intramuscular injection, which has largely fallen out of favor due to poor tolerance by most patients. Currently, IG therapy is either administered intravenously (IVIG) or subcutaneously (SCIG). IVIG quickly achieves a high serum concentration with an initial peak and declining levels throughout the dosing cycle, leading to a trough at the end of the cycle. IVIG administration advantages include infrequent dosing (usually ranging every three to four weeks for primary immunodeficiency [PI] indications) and the ability to deliver a large amount of IG in one infusion. However, several challenges to IVIG administration exist: The initial peak in serum concentration is often associated with systemic adverse effects; the waning trough at the end of the cycle can be associated with a “wear-off” effect; and for many patients, repeated IV access becomes problematic.

Due to these challenges, the conventional SCIG administration was formulated. Typically for PI patients, conventional SCIG is administered weekly. More recently, some SCIG products have received indications for infusion every other week or multiple times a week. SCIG administration does not lead to a serum peak or trough; rather, it maintains a steady-state IG serum level due to more frequent dosing, as well as a depot effect from slower release of product into the bloodstream from the subcutaneous space.

Patients generally complain of far fewer systemic adverse reactions and do not often encounter the wear-off effect.

Challenges of SCIG Administration

Although some challenges of IVIG administration have been overcome by conventional SCIG administration, the latter has presented its own set of challenges. First, due to limited capacity of delivery at any particular site, more frequent injections in multiple injection sites are needed. This leads to a greater number of needle sticks, as well as higher potential for local adverse reactions, even though the frequency of systemic adverse reactions is decreased compared with the IV route. Second, SCIG therapy is approved for self-administration or administration by family members or caretakers. Therefore, most insurance plans will approve only initial nursing visits to teach patients or caregivers to administer the medication; they will not approve home administration by a healthcare professional. While self-administration has led to a great deal of convenience and independence for many patients, some patients (particularly the elderly,

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disabled or those with cognitive impairment) have difficulty with it. Lastly, more frequent administration can become a hindrance to patients who travel frequently or have less-predictable schedules.

Given the benefits and challenges of the IV and conventional SC routes of administration, hyaluronidase-facilitated SC delivery was developed. Hyaluronidase-facilitated SCIG is designed to mitigate many of the challenges with the other routes, while preserving their advantages. It is the only SC delivery system that allows for once-a-month administration, bypassing the need for multiple injections in multiple sites with the conventional SC approach. It also bypasses the initial high serum peak of IVIG and the need to establish IV access. Furthermore, the hyaluronidase-facilitated product is approved for healthcare provider administration. Theoretically, then, hyaluronidase-facilitated SCIG achieves the best of both worlds.

What Is Hyaluronidase-Facilitated Delivery?

Hyaluronidase-facilitated delivery of SCIG therapy combines two components: 10% IG product and recombinant human hyaluronidase. Hyaluronidase is an enzyme that assists in breaking down hyaluronan, or hyaluronic acid, that exists as a gel-like substance underneath the skin. This enzyme exists naturally in the body to help turn over hyaluronan, which is naturally replenished on a daily basis. With conventional SCIG therapy, the amount of IG that can fit into the subcutaneous space underneath the skin is limited due to the presence of hyaluronan, which hinders the flow and volume of substance that can be delivered. Therefore, the purpose of hyaluronidase is to temporarily clear away the hyaluronan so a higher volume of IG can flow more easily into the subcutaneous space.

Unique Aspects of Hyaluronidase-Facilitated Subcutaneous Immune Globulin (fSCIG)

In clinical trials, hyaluronidase-facilitated SCIG (fSCIG) achieved similar efficacy in reducing the frequency of infections compared with IVIG. While the frequency of local reactions was higher (expected from all SCIG products), the frequency of systemic adverse reactions was lower compared with IVIG. And, the potential adverse reactions and warnings for all IG products apply to the hyaluronidase-facilitated product. However, there are some unique aspects of the product and the administration process that deserve discussion.

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First, unlike IVIG or conventional SCIG, fSCIG is packaged in two vials in a fixed ratio of 2.5 grams of IG with 200 units of hyaluronidase. It comes in five strength combinations: 2.5 g/200 U, 5 g/400 U, 10 g/800 U, 20 g/1,600 U and 30 g/2,400 U.

Second, a lingering concern regarding the development of

anti-hyaluronidase antibodies following repeated administration led to a delay in the commercialization of fSCIG. However, it has been demonstrated that while 18 percent of subjects in a Phase III study developed antibodies to hyaluronidase, the antibodies are nonneutralizing, meaning they do not block the effect of hyaluronidase. An additional concern was that since hyaluronidase is expressed on the adult male reproductive system, the development of antibodies against hyaluronidase might affect male fertility. To date, there has been no evidence that the use of hyaluronidase is associated with male infertility. However, long-term studies are lacking in this area, and additional longitudinal studies are needed for more definitive assessment.

Third, the administration process is more involved than conventional SCIG. Prior to infusion, the hyaluronidase needs to be injected at the rate of 1 mL to 2 mL per minute through manual push. Then, within 10 minutes of the hyaluronidase injection, the IG infusion needs to occur. Unlike IVIG or conventional SCIG, there is a ramp-up phase for fSCIG. This phase involves increasing the amount of IG given over the first seven weeks during which therapy is received in weeks one, two, four and seven, and therapy is not received during weeks three, five and six. The rate of infusion is also a changing variable during the first several infusions. The package insert for fSCIG recommends gradually increasing the infusion rate in five steps up to the maximum rate (300 mL per hour per site). The uniqueness of fSCIG is that it allows for up to 600 mL of product to be infused in one SC site for patients who weigh more than 40 kg and up to 300 mL of product per site for patients who weigh less than 40 kg. Therefore, given the maximum rate allowed, many patients could have the entire monthly IG dose administered in one site in one hour.

However, due to the fluctuating parameters and the need for high flow rates, traditional fixed flow rate pumps commonly used for conventional SCIG are not compatible. Instead, programmable pumps that allow for adjustable infusion rates are needed for successful fSCIG administration.

Lastly, from a pharmacologic standpoint, unlike conventional SCIG, fSCIG has a small peak and results in a trough at the end of the month. Compared with IVIG, the peak serum level is delayed (a few days following the initial infusion) rather than at the very beginning, and the peak serum level is a lot lower. And, similar to IVIG but distinct from conventional SCIG, the trough at the end of the month is at a similar level compared with IVIG, and lower than the steady-state level seen in conventional SCIG. Throughout the dosing cycle, the decline in serum level parallels that of IVIG administration.

Potential Concerns

Hyaluronidase-facilitated delivery presents significant advantages, yet its unique aspects also present certain challenges and concerns.

While the rate of systemic adverse reactions is lower compared with IVIG, very little evidence has been presented comparing the rate of systemic adverse reactions compared with conventional SCIG. The serum peak level is much lower than with IVIG, but it is still higher than the steady-state level with conventional SCIG.

The waning serum level throughout the cycle is an additional concern. One advantage of conventional SCIG is that it produces a steady-state consistent serum level rather than fluctuating levels. Some people have suggested that the trough at the end of the cycle with hyaluronidase-facilitated delivery is associated with the wear-off effect seen with IVIG. According to the pharmacokinetic studies of fSCIG, the trough level is at the same level as IVIG and significantly lower than the steady-state with SCIG. Some experts believe more frequent IG replacement therapy helps to mimic the natural production of IG compared with less-frequent administration.

The safety of hyaluronidase has been demonstrated in clinical trials and in postmarketing use during the past two years. However, the safety of hyaluronidase in the quantity and duration needed for PI patients (decades of persistent use) has not been established. Conventional SCIG and IVIG have had a much longer track record for safety. And, while hyaluronan is replenished on a daily basis by the body and there have not yet been any reported permanent structural changes in the skin at injection sites, the dermatologic effect of repeated breakdown of hyaluronan by exogenous hyaluronidase over the long run is still unknown.

Lastly, compared with conventional SCIG and IVIG, the administration of fSCIG is more involved, with the need to first administer the hyaluronidase, ramp-up and adjust the infusion rate. The more steps involved in a process, the more room there is for error. While steps can be taken to minimize error with proper education and training by nurse educators, as well as pre-programming infusion pumps to automate infusion rate escalations, the process itself is still more complicated, particularly if the patient or caregiver chooses to administer it themselves.

Possible Future Directions

Hyaluronidase-facilitated delivery of IG is an innovative approach that has significant potential beyond its current approved use. For children, it can be of tremendous value since IV access is often difficult and traumatic. Frequent needle sticks in conventional SCIG is often unpleasant for young children, and a once-a-month stick with a 24-gauge small needle

is likely to be far more tolerable than two sticks every week.

The ability to use hyaluronidase to deliver 300 mL to 600 mL per site opens up the opportunity to use it for high-dose replacement therapy for patients with significant pulmonary complications who need higher trough levels or PI patients with concomitant protein-losing processes that need higher replacement dosing.

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Lastly, the ability to deliver higher doses more efficiently also opens up the possibility of using it for immunomodulation. Neurology, rheumatology, dermatology and hematology patients who need immunomodulation doses between 1 gram/kg and 2 grams/kg may benefit tremendously from hyaluronidase-facilitated SCIG infusions, particularly if they could not tolerate IVIG in the past or have poor venous access.

A Novel Delivery Approach

The use of hyaluronidase to facilitate the administration of SCIG is an attempt to improve the efficiency, tolerability and delivery of IG replacement therapy in PI patients. The unique features provided by hyaluronidase combine some of the advantages seen in IVIG and conventional SCIG. However, the collective clinical experience of using hyaluronidase for IG replacement therapy is limited due to its novelty, and there are some potential concerns and drawbacks that need to be considered. Nonetheless, this novel delivery approach provides an additional helpful option in the therapeutic modalities that exist for IG replacement. The potential of this delivery approach far exceeds the bounds of PI, and, hopefully, will be considered for other conditions that require far higher doses to achieve immunomodulation. ■

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