

Enzyme-Facilitated Subcutaneous IgG: Changing the Paradigm of IgG Therapy

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KEYWORDS

- Hyaluronan • IGHy • Immunoglobulin G • Primary immunodeficiency disorders
- Subcutaneous IgG • rHuPH20

KEY POINTS

- IGSC has less systemic side effects than IVIG, but require frequent infusions at multiple sites with reduced bioavailability. The frequent infusions limits acceptance by many patients.
- IGHy facilitates rapid infusion of large volumes of IGSC with one needle stick. This can achieve therapy at 3 to 4 week intervals.
- IGHy improves bioavailability and improves patient acceptance of SCIG by making it's use more convenient. There are less systemic side effects than IVIG with the same dosing interval in most patients.

Immunoglobulin G (IgG) is the cornerstone of treatment for patients with primary immunodeficiency disorders that are associated with the inability to produce adequate antibodies. Preparations of IgG are available for administration either intravenously (IV) or subcutaneously (SC). One benefit of the IV route is that IgG can be given in large volumes so as to allow dosing only once every 3 or 4 weeks.¹ Alternatively, the SC route offers the advantage of avoiding the high serum IgG peaks associated with IV infusion.² High peaks increase the risk of side effects such as severe headaches and more serious consequences, including aseptic meningitis.^{1,3,4} In addition, low trough IgG levels are much less pronounced with SC versus IV administration, resulting in more even IgG concentrations over time.² However, therapies injected by the SC route must pass through the interstitial matrix of the subcutaneous space to reach their targets.⁵ This matrix controls the rate of drug flow and limits the quantity that can be given by SC infusion.⁵

The interstitial matrix is a complex 3-dimensional structure comprising macromolecules including collagens, elastin, and fibronectin.^{5,6} Proteoglycans and glycosaminoglycans (such as hyaluronan) fill the matrix between the collagen and elastin fibers, forming a barrier to bulk fluid flow through the interstitial space. Hyaluronan is a high molecular weight molecule that is particularly important in allowing the extracellular matrix to resist compressive forces.⁵ The rate and volume of SC administration of IgG, like other SC

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therapies, is thereby limited by the flow restrictions associated with the collagen/elastin/hyaluronan interstitial matrix.⁶ A new technique that incorporates the use of rHuPH20, a highly purified recombinant human hyaluronidase enzyme, breaks down hyaluronan and enhances the interstitial transport of SC therapeutics, including IgG.⁵

CHARACTERISTICS OF RHUPH20

As is the case with all hyaluronidases, rHuPH20 has the ability to fragment hyaluronan (formerly known as hyaluronic acid) so as to enhance the dispersion of locally injected drugs.⁵ Work in animal models has shown that local depolymerization of hyaluronan, as facilitated by rHuPH20, increases hydraulic conductivity in the interstitium and, consequently, permits increased rates of infusion of SC immunoglobulin (IGSC).⁵ This allows the administration of much larger doses than is normally possible.

Furthermore, greater dispersion of therapeutics decreases residence time in the interstitium, and more rapid uptake leads to significantly improved pharmacokinetics, resulting in greater bioavailability.⁵ Fig. 1 shows data obtained following IV, SC, and SC/rHuPH20-facilitated administration of IgG in an animal model.⁵ The IV infusion produced a high peak followed by a rapid decrease in IgG serum levels. The SC dose did not result in a pronounced peak and was associated with relatively steady IgG levels. The addition of rHuPH20 to IGSC resulted in an even more favorable pharmacokinetic profile, decreasing the time to maximum concentration from 48 to 18.7 h ($P < .002$), increasing the maximum concentration from 531,866 to 875,369 CPM/g ($P < .00002$), and increasing absolute bioavailability from 59% to 94% ($P < .00001$).⁵ Notably, within 24 hours of injection, the integrity of interstitial viscoelastic barriers were restored, with no indications of histologic alterations.⁵ The enhanced injection rates and penetration associated with the use of rHuPH20 did not provoke inflammation, vascular permeability, nor immunogenic or allergic reactions.⁵

CLINICAL STUDIES OF RHUPH20

In 2006, a phase I/II feasibility study was undertaken to assess rHuPH20-facilitated SC infusion of IgG in humans.⁷ Fig. 2 shows results from a typical study patient who received the same IgG product through both IV and rHuPH20 enhanced (IGHy) SC

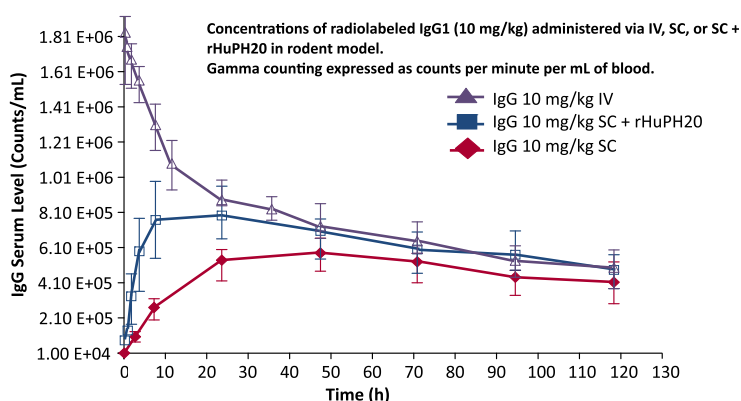


Fig. 1. Effect on IgG pharmacokinetics with addition of rHuPH20 to SC injection in an animal model. IgG, immunoglobulin G; IV, intravenous; SC, subcutaneous. (From Bookbinder LH, Hofer A, Haller MF, et al. A recombinant human enzyme for enhanced interstitial transport of therapeutics. *J Control Release* 2006;114:238; with permission.)

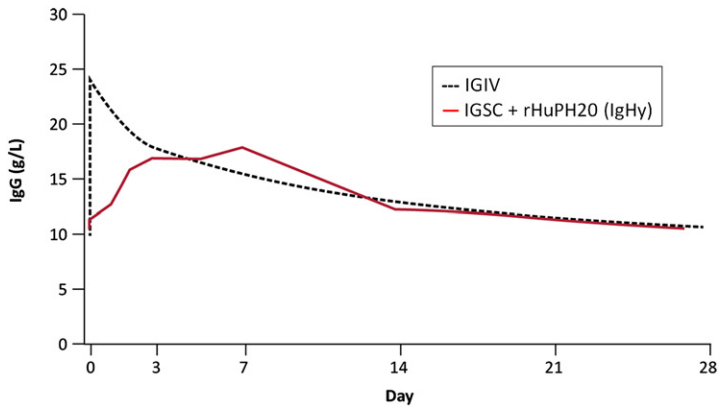


Fig. 2. Areas under the curve (AUC) for IgG after IV infusion versus SC administration with rHuPH20 in an individual study patient. IgG, immunoglobulin G; IV, intravenous; SC, subcutaneous. (From Misbah S, Sturzenegger MH, Borte M, et al. Subcutaneous immunoglobulin: opportunities and outlook. *Clin Exp Immunol* 2009;158(Suppl 1):56; with permission.)

administration. The area under the curve (AUC) with SC administration was 97.3% of that seen with the IV dose. Nearly equivalent AUCs were obtained when IGHy was given at approximately 108% of the IV dose.⁷ This result is superior to observations with standard IGSC therapy, which must be dosed at 137%–153% of the IGIV dose (depending on the product) to achieve equivalent AUCs.^{8,9}

A subsequent phase III study confirmed the pharmacokinetic profile of rHuPH20 facilitated administration of IGSC that was observed in the earlier work.¹⁰ Again, IGHy had to be dosed at approximately 108% of the IV dose to achieve the same AUC. The side effect profile of the enzyme facilitated treatment was similar to that seen with IGSC alone, without the increased incidence of systemic side effects that is typical of IGIV. Compared with regular SC injection, IGSC plus rHuPH20 (IGHy) was associated with similar degrees of infection control and a lack of the serious systemic side effects associated with IGIV.

Other analyses suggest that patients accept IGHy, with more than 70% of individuals indicating that they wanted to continue receiving this treatment at the conclusion of the study.¹⁰ Moreover, 100% of parents who had children in the study stated that they would want their child to continue on this product if it were available.

SUMMARY

Although SC administration of IgG offers several advantages over the IV route, it remains limited by the rate of flow and quantity of therapy that can be delivered. The addition of rHuPH20 to IGSC acts to break down the hyaluronan component in the interstitial matrix that restricts the rate and volume of SC therapies. Pilot clinical studies have confirmed enhanced bioavailability with IGHy, and a phase III clinical trial has shown that this technique preserves the greater safety of SC versus IV administration.

REFERENCES

1. Berger M. Subcutaneous immunoglobulin replacement in primary immunodeficiencies. *Clin Immunol* 2004;112:1–7.

2. Bonilla FA. Pharmacokinetics of immunoglobulin administered via intravenous or subcutaneous routes. *Immunol Allergy Clin North Am* 2008;28(4):803–19.
3. Hamrock DJ. Adverse events associated with intravenous immunoglobulin therapy. *Int Immunopharmacol* 2006;6(4):535–42.
4. Pierce LR, Jain N. Risks associated with the use of intravenous immunoglobulin. *Transfus Med Rev* 2003;17(4):241–51.
5. Bookbinder LH, Hofer A, Haller MF, et al. A recombinant human enzyme for enhanced interstitial transport of therapeutics. *J Control Release* 2006;114: 230–41.
6. Day TD. The permeability of interstitial connective tissue and the nature of the interfibrillary substance. *J Physiol* 1952;117:1–8.
7. Misbah S, Sturzenegger MH, Borte M, et al. Subcutaneous immunoglobulin: opportunities and outlook. *Clin Exp Immunol* 2009;158(Suppl 1):51–9.
8. Berger M, Rojavin M, Kiesseling P, et al. Pharmacokinetics of subcutaneous immunoglobulin and their use in dosing of replacement therapy in patients with primary immunodeficiencies. *Clin Immunol* 2011;139:133–41.
9. Wasserman RL, Irani AM, Tracy J, et al. Pharmacokinetics and safety of subcutaneous immune globulin (human), 10% caprylate/chromatography purified in patients with primary immunodeficiency disease. *Clin Exp Immunol* 2010; 161(3):518–26.
10. Wasserman RL, Melamed I, Stein MR, et al. Recombinant human hyaluronidase-facilitated subcutaneous infusion of human immunoglobulins for primary immunodeficiency. *J Allergy Clin Immunol*, in press.