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I D C A S E

Hyaluronidase-Facilitated High-Dose Subcutaneous IgG Effectively Controls Parvovirus B19 Infection in a Pediatric Cardiac Transplant Patient With Severe T-Cell Lymphopenia

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We treated three pediatric cardiac transplant patients with chronic parvovirus viremia with high-dose intravenous immunoglobulin (HD-IVIG). One patient with severe T-cell lymphopenia suffered recurrent viremia and aseptic meningitis, which resolved remarkably when he was switched to high-dose hyaluronidase-facilitated subcutaneous immunoglobulin (HD-SCIG-Hy). We discuss the advantages of HD-SCIG-Hy vs HD-IVIG treatment for similar cases.

Keywords. parvovirus B19; heart transplant; pediatric; immunodeficiency; subcutaneous immunoglobulin.

Solid organ transplantation requires immunosuppression, which renders organ recipients vulnerable to infections. Viral infections are common in pediatric heart transplants, especially parvovirus B19 (PVB19) infection, and independently increase risk of transplant failure [1]. PVB19 preferentially infects erythroid progenitor cells, and chronic infection may induce bone marrow failure, including pure red-cell aplasia (PRCA), and various inflammatory disorders [2–4]. PVB19 is largely contained by antibodies, but cytotoxic T cells also aid its control [5]. In immunocompetent children, PVB19 causes a transient mild illness with a skin rash known as fifth disease or erythema infectiosum, whereas in immunocompromised individuals, infection can persist, resulting in chronic anemia, especially PRCA. Risk factors for chronic anemia due to PVB19 infection involve disorders or treatments compromising humoral and/or cell-mediated immunity, including congenital and acquired immunodeficiency syndromes, acute and chronic leukemias, antibody deficiencies, solid organ and bone marrow transplantation, and cancer chemotherapy and other immunosuppressive therapies [3].

Parvovirus B19 was the most common viral genome detected in endomyocardial biopsies (83%) of pediatric heart transplant patients (n = 99), and chronic infection (>6 months) was associated with early development of advanced transplant coronary artery disease, which can lead to graft rejection [6]. PVB19 infection in transplant patients can cause significant morbidity, as 98% of such patients (n = 98) had anemia after solid organ and bone marrow transplantation [7]. These cases require treatment with high-dose intravenous immunoglobulin (HD-IVIG; up to 2 g/kg/dose), as no specific antiviral treatment or enriched Ig product exists for PVB19 infection [3]. In some cases, HD-IVIG is repeated for a prolonged period to suppress PVB19 viral load, and it is not uncommon for patients to develop complications such as aseptic meningitis. Few alternatives to HD-IVIG exist to treat these often recurring and debilitating complications in patients with heart transplant and parvovirus viremia.

Despite its numerous benefits for treating other illnesses, high-dose subcutaneous immunoglobulin (HD-SCIG) has not been approved for viral infections or other conditions requiring anti-inflammatory treatment, except for a rare autoimmune disorder, chronic inflammatory demyelinating polyneuropathy [8]. The benefits of HD-SCIG include no venipuncture, self-administration at home, fewer systemic side effects, and more constant serum IgG levels [9–11]. The latter effect might explain its improved efficacy relative to IVIG in some patients. For example, switching from HD-IVIG to HD-SCIG resolved aseptic meningitis associated with IVIG, improved the disease score, and decreased immunosuppressive therapy in a myasthenia gravis patient [12]. Switching to SCIG also reduces fluid overload and hyperosmolarity, which benefits patients with fluid balance disorders such as renal failure [11].

Recombinant human hyaluronidase (rHuPH20) degrades hyaluronan to expand the infusion capacity of subcutaneous tissue. Hyaluronidase administered with HD-SCIG enables higher dosing than HD-SCIG without hyaluronidase, thus decreasing the dosage interval [13]. Dosage frequency can be as low as once per month, whereas nonfacilitated HD-SCIG is typically given every 1–2 weeks. Although the standard of care for pediatric heart transplant patients with chronic PVB19 infection is infusing HD-IG intravenously, we propose that the subcutaneous route may be a better option to control PVB19 viremia and reduce systemic side effects.

Received 9 September 2019; editorial decision 24 February 2020; accepted 10 March 2020.

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DOI: 10.1093/ofid/ofaa076

CASE SERIES

We present a cohort of three patients who received cardiac transplantation, complete thymectomy, and antithymocyte globulin in infancy and later acquired PVB19 infection that was treated with repeated HD-IVIG infusions. One patient (patient A) was more immunocompromised than the other two and did not respond to conventional treatment. This study was approved by the Institutional Review Board of Johns Hopkins All Children's Hospital.

Patient A is a 21-year-old male who underwent a heart transplant as a newborn for hypoplastic left heart syndrome, which was complicated by coarctation of the aorta. He also suffers from extensive chronic warts on his limbs, which remain refractory to medical treatment and are likely related to worsening T-cell lymphopenia. He also has severe chronic kidney disease (stage 4) with proteinuria as he awaits a kidney transplant.

Patients B and C are 10- and 11-year-old males, respectively, who received cardiac transplants due to pulmonary atresia and hypoplastic left heart syndrome, respectively. Patient B did not have any major surgical complications, whereas patient C developed post-transplant lymphoproliferative disorder and late severe acute rejection.

Two of the three patients (patients B and C) responded to HD-IVIG with undetectable PVB19 viral load, but patient A failed firstline HD-IVIG treatment as his viral load rebounded repeatedly (Figure 1A). As this patient was refractory to treatment, our immunology team was consulted.

Immune evaluation (Figure 1B,C) revealed that all three patients presented with abnormally low CD4+ T-cell counts, and two patients also had low CD8+ T cells (patients A and B). However, patient A exhibited more severe T-cell lymphopenia, especially with naïve T cells (average was 5 CD4+ cells/μL and 20 CD8+ cells/μL). Patient A also had severe aplastic anemia more than once (lowest hemoglobin 6.5 g/dL), whereas patients B and C had mild anemia (lowest hemoglobin 10.3 and 10.4 g/dL, respectively).

Patient A suffered from persistent PVB19 infection for >7 years (Figure 1A). He began treatment with HD-IVIG (1 g/kg) at age 14, which continued nearly 5 years. HD-IVIG treatment temporarily decreased his viral load, but he had recurring bouts of debilitating aseptic meningitis that led to frequent hospitalizations, requiring sedative pain control and spacing of HD-IVIG treatments. These episodes severely diminished his quality of life, so we considered an alternate route for administering IG. Hence, we began infusing SCIG at age 18 initially with a low dose (LD) injected weekly for 2 months (0.5 g/kg per month), however, rescue IVIG therapy was required for viral flares. Thus, to increase the dose of SCIG, we transitioned to HD hyaluronidase-facilitated SCIG (HD-SCIG-Hy),

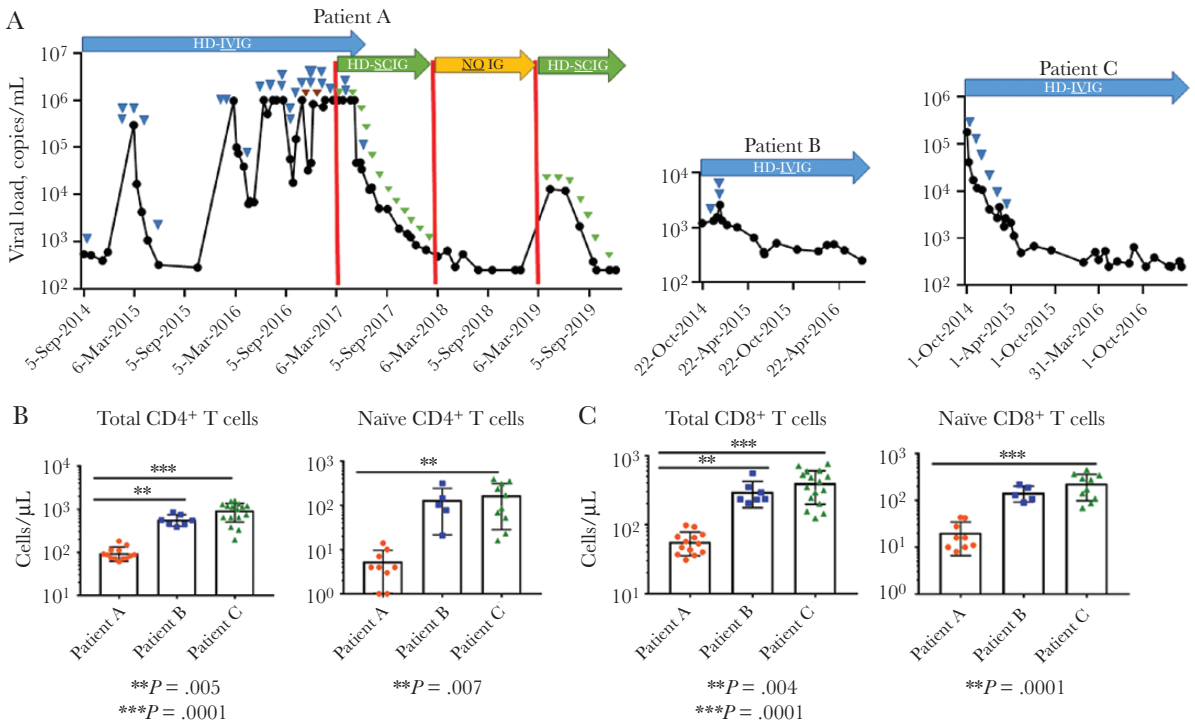

Figure 1. Viral load in response to immunoglobulin treatment and T-cell counts of patients. A, Viral load of patients and immunoglobulin infusions. Blue arrowheads signify monthly dosage of high dose intravenous immunoglobulin infusions (1 g/kg per month), whereas brown arrowheads signify low dose subcutaneous (0.5 mg/kg) and green arrowheads indicate high dose subcutaneous immunoglobulin infusions (1 g/kg) per month. Stacked blue arrowheads indicate 2x dosage, whereas partially superimposed blue arrowheads indicate 1.5x dosage. NO IG (yellow arrow) indicates no immunoglobulin infusions. The high and low viral titers were rounded to >1 000 000 and <250 copies/mL, respectively. B, Mean total and naïve $CD4^+$ T-cell counts of patients during treatment. C, Mean total and naïve $CD8^+$ T-cell counts during treatment.

which was given at home every 2 weeks (1 g/kg per month) 3 months after beginning LD-SCIG. On this regimen, the patient required less rescue HD-IVIG, which ended three months after initiating HD-SCIG-Hy. Upon receiving HD-SCIG-Hy as the only Ig treatment, the patient no longer had aseptic meningitis and his viral load consistently dropped and remained below 1000 copies/μL. Consequently, treatment was stopped for a year but was reinitiated due to a rising viral load (Figure 1A). During HD-IVIG treatment, his IgG trough levels varied between 542 and 2600 mg/dL; during HD-SCIG-Hy therapy, his IgG trough levels were 737–1590 mg/dL, and when treatment was withheld, they were 442–1060 mg/dL. Switching to HD-SCIG-Hy improved the patient's quality of life as it ceased hospitalizations for aseptic meningitis, reduced the variability of plasma IgG levels, decreased the quantity of IG given, and consequently lowered medical costs.

In contrast to patient A, patients B and C required short-term HD-IVIG, which consistently controlled their viral load (Figure 1A) without inducing systemic adverse effects. Only one IgG trough level was recorded for patient B (828 mg/dL); IgG trough levels for patent C ranged between 417 and 1060 mg/dL. Patients B and C had considerably more $CD4^+$ and $CD8^+$ T cells (Figure 1B,C) and required HD-IVIG infusions less frequently than patient A (Figure 1A).

All three patients had normal total immunoglobulin G, A and M levels, but IgG levels were low occasionally for patients A and C. PVB19-specific antibody levels were not measured. All patients were maintained on mild oral immunosuppressive medications. Pharmacological immunosuppression was greatest in patient A, who received tacrolimus (1.5 mg daily) when he developed PVB19 viremia but was switched to sirolimus (1 mg/d) and mycophenolate (720 mg/d) due to renal insufficiency. Patient B received tacrolimus (2 mg/d) monotherapy. Patient C received sirolimus (0.8 mg/d) and prednisone (5 mg/every other day); in addition, tacrolimus (0.3 mg/d) was added when he developed late severe rejection.

DISCUSSION

Pediatric heart transplant patients often are fully thymectomized, which further suppresses their immunity and augments their susceptibility to infections such as PVB19. Our case series associates severe naïve T-cell lymphopenia with greater PVB19 load and decreased response to HD-IVIG. It is not surprising that viremia in patient A was less controlled with HD-IVIG than in patients B and C, as the former had significantly fewer T cells and received more immunosuppressive therapy. Nor is it unprecedented that switching from HD-IVIG to HD-SCIG-Hy resolved aseptic meningitis in patient A, as this has been reported previously [8]. It is noteworthy, however, that switching from HD-IVIG to HD-SCIG-Hy markedly and continuously reduced the viral load in patient A. This may be due to the kinetics of maintaining more constant Ig levels through gradual diffusion in the hypodermis [13].

Numerous studies underscore the importance of preserving the thymus as much as possible during pediatric cardiac operations. Avoidance of a full thymectomy during pediatric cardiac surgery facilitates normal T-cell development and adaptive immunity. Complete or near-complete thymectomy (>90% removal) in pediatric patients (<6 months old; n = 11) undergoing cardiac surgery led to considerable lymphopenia of CD4+ and CD8+ T cells and other abnormalities of cell-mediated immunity [14]. Immunodeficiency due to early childhood thymectomy (<5 years) impaired health outcomes several years later [15].

Our case series is the first to report use of HD-SCIG-Hy to successfully treat chronic PVB19 in an immunosuppressed patient. A multicenter study is needed to determine if HD-SCIG is able to control PVB19 load more effectively and with fewer systemic side effects than HD-IVIG in other immunosuppressed patients. The mechanisms of viral control and kinetics of these two modalities should be further investigated *in vivo*. In conclusion, our report supports consideration of HD-SCIG-Hy early in the treatment of chronic PVB19 infection in pediatric cardiac transplant patients or other cases of persistent PVB19 infection with severe naïve T-cell lymphopenia.

Acknowledgments

We thank Drs. Sonia Joychan and David Lindsay for assisting with the medical care of the patients in our case series. We also thank Dr. Frank Ayestaran Cassani for providing patient consultation and information regarding nephrology.

Financial support. This study was funded by the Robert A. Good Endowment and Foundation at the University of South Florida.

Potential conflicts of interest. J.E.W. has been an advisory board member and speaker for Shire (Takeda). The authors have no other relevant affiliations or financial involvement with any organization or entity with financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

Author contributions. R.C. performed data analysis, drafted the initial manuscript, and helped revised it. J.D. analyzed the data, and extended and revised the manuscript. C.D., D.K., Z.L., and D.N. cared for the patients and provided patient information. M.E. also provided patient information and completed regulatory stipulations, including obtaining internal review board approval for the study. A.K. acted as a primary cardiology consultant, whereas P.S. and J.W. served as primary immunology consultants for the patients. J.W. also conceptualized and directed the study. All authors reviewed and provided feedback on the initial manuscript and revised manuscript, and agree to its contents.

References

1. Moulik M, Breinholt JP, Dreyer WJ, et al. Viral endomyocardial infection is an independent predictor and potentially treatable risk factor for graft loss and coronary vasculopathy in pediatric cardiac transplant recipients. J Am Coll Cardiol **2010**; 56:582–92.
2. Ganaie SS, Qiu J. Recent advances in replication and infection of human parvovirus B19. Front Cell Infect Microbiol **2018**; 8:1–12.
3. Landry ML. Parvovirus B19. Microbiol Spectr **2016**; 4:1–13.

4. Young NS. Parvovirus infection and its treatment. Clin Exp Immunol **1996**; 104 (Suppl 1):26–30.
5. Kumar A, Perdomo MF, Kantele A, et al. Granzyme B mediated function of parvovirus B19-specific CD4(+) T cells. Clin Transl Immunology **2015**; 4:e39.
6. Breinholt JP, Moulik M, Dreyer WJ, et al. Viral epidemiologic shift in inflammatory heart disease: the increasing involvement of parvovirus B19 in the myocardium of pediatric cardiac transplant patients. J Heart Lung Transplant **2010**; 29:739–46.
7. Eid AJ, Brown RA, Patel R, Razonable RR. Parvovirus B19 infection after transplantation: a review of 98 cases. Clin Infect Dis **2006**; 43:40–8.
8. Berger M, Harbo T, Cornblath DR, Mielke O. IgPro20, the polyneuropathy and treatment with Hizentra study (PATH), and the treatment of chronic inflammatory demyelinating polyradiculoneuropathy with subcutaneous IgG. Immunotherapy **2018**; 10:919–933.
9. Suez D, Stein M, Gupta S, et al. Efficacy, safety, and pharmacokinetics of a novel human immune globulin subcutaneous, 20% in patients with primary immunodeficiency diseases in North America. J Clin Immunol **2016**; 36:700–12.
10. Guo Y, Tian X, Wang X, Xiao Z. Adverse effects of immunoglobulin therapy. Front Immunol **2018**; 9:1–13.
11. Abolhassani H, Sadaghiani MS, Aghamohammadi A, et al. Home-based subcutaneous immunoglobulin versus hospital-based intravenous immunoglobulin in treatment of primary antibody deficiencies: systematic review and meta analysis. J Clin Immunol **2012**; 32:1180–92.
12. Rae W. Successful loading and maintenance subcutaneous immunoglobulin (SCIG) therapy in a patient with myasthenia gravis (MG). J Allergy Clin Immunol. **2015**; 135(Suppl):AB93.
13. Wasserman RL. Recombinant human hyaluronidase-facilitated subcutaneous immunoglobulin infusion in primary immunodeficiency diseases. Immunotherapy **2017**; 9:1035–50.
14. Gudmundsdottir J, Óskarsdóttir S, Skogberg G, et al. Early thymectomy leads to premature immunologic ageing: an 18-year follow-up. J Allergy Clin Immunol **2016**; 138:1439–43.e10.
15. Gudmundsdottir J, Söderling J, Berggren H, et al. Long-term clinical effects of early thymectomy: associations with autoimmune diseases, cancer, infections, and atopic diseases. J Allergy Clin Immunol **2018**; 141:2294–7.e8.