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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ABSTRACT: 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 switched to high-dose hyaluronidase-facilitated subcutaneous immunoglobulin (HD-SCIG-Hy). We discuss advantages of HD-SCIG-Hy versus HD-IVIG treatment for similar cases.

KEY WORDS: parvovirus B19, heart transplant, pediatric, immunodeficiency, subcutaneous immunoglobulin
INTRODUCTION: 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 nor 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 that patients 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, less systemic side effects and more constant serum IgG levels [9-11]. The latter effect might explain its improved efficacy relative to IVIG reported 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 dosage interval [13]. Treatment can be given once per month whereas non-facilitated 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.

CASE SERIES: We present a cohort of three patients who received cardiac transplantation, complete thymectomy and anti-thymocyte 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, 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 first line HD-IVIG treatment as his viral load rebounded repeatedly (Fig. 1A). Since this patient was refractory to treatment, our immunology team was consulted.

Immune evaluation (Fig. 1B,C) revealed 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/ul & 20 CD8+ cells/ul). 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 over seven years (Fig. 1A). He began treatment with HD-IVIG (1 mg/kg) at age 14, which continued nearly five 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 HD hyaluronidase-facilitated IG (HD-SCIG-Hy) subcutaneously at age 18 and the patient no longer had aseptic meningitis. He received HD-SCIG-Hy at home (0.5 mg/kg every 2-3 weeks) and his viral load consistently dropped and remained below 1,000 copies/ul. Consequently, treatment was stopped for a year, but was reinitiated due to a rising viral load (Fig. 1A). During HD-IVIG treatment, his IgG trough levels varied between 542-2600 mg/dL; during HD-SCIG-Hy therapy, it was 737-1590 mg/dL, and when treatment was withheld, it was 442-1060 mg/dL. Switching to HD-SCIG-Hy improved the patient’s quality of life as it ceased hospitalizations for aseptic meningitis, reduced 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 (Fig. 1A) without inducing systemic adverse effects. Only one IgG trough level was recorded for patient B (828 mg/dL); IgG trough levels for patient C ranged between 417-1060 mg/dL. Patients B and C had considerably more CD4+ and CD8+ T cells (Fig. 1B,C) and required HD-IVIG infusions less frequently than patient A (Fig. 1A).

All three patients had normal total immunoglobulin G, A and M levels except 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/day) and mycophenolate (720 mg/day) due to renal insufficiency. Patient B received tacrolimus (2 mg/day) mono therapy. Patience C received sirolimus (0.8 mg/day) and prednisone (5 mg/every other day); in addition, tacrolimus (0.3 mg/day) 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 since the former had significantly less 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, since 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, leads 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) impairs 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 less 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 treatment of chronic PVB19 infection in pediatric cardiac transplant patients or other cases of persistent PVB19 infection with severe naïve T cell lymphopenia.
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Author Contributions

RC performed data analysis, drafted the initial manuscript and helped revised it. JD analyzed the data as well as extended and revised the manuscript. CD, DK, ZL, and DN cared for the patients and provided patient information. ME also provided patient information and completed regulatory stipulations including obtaining internal review board approval for the study. AK acted as primary cardiology consultant while PS and JW served as primary immunology consultants for the patients. JW also conceptualized and directed the study. All authors reviewed and provided feedback on the initial and revised manuscript, and agree to its contents.

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Conflict of Interests

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.
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Legend for Figure 1

Figure 1. Viral load in response to immunoglobulin treatment and T cells counts of patients. A. Viral load of patients; blue arrows signify time points of IV-IG infusions (1 mg/kg) while green arrows signify SC-IG infusions (0.5 mg/kg). Stack blue arrowheads indicate doubled dosage while partially superimposed blue arrowhead indicates one and a half dosage. 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.
Figure 1

A. Viral Load (log10 copies/ml)

B. Total CD4+ T cells

C. Total CD8+ T cells

**p<0.001

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**p<0.01

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**p<0.05

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