



Letter

Congenital nephrotic syndrome and agammaglobulinemia: A therapeutic dilemma

The primary immunodeficiency practice parameters outline use of gamma globulin as treatment for diseases of hypo- and agammaglobulinemia. There is no consensus, however, on use of immunoglobulin replacement in secondary immunodeficiencies such as protein-losing disease states. Congenital nephrotic syndrome is an exceedingly rare disorder lacking data on comorbid conditions such as agammaglobulinemia, although infection risk is known to be high as serious bacterial infection was demonstrated in 85% of a 41-patient cohort.¹ Harris examined the use of intravenous immunoglobulin (IVIG) in a congenital nephrotic patient and showed that, within 30 hours, 55% could be found in the urine.² A review evaluating the use of IVIG in pediatric nephrotic syndrome illustrated a significant benefit on preventing infection; however, the quality and sample sizes of the reviewed studies were called into question.³ IVIG treatments have even been shown to resolve proteinuria and improve kidney function in 1 small cohort of patients with congenital nephrotic syndrome secondary to diffuse mesangial sclerosis.⁴ In adult-onset nephrotic syndrome, IVIG has been shown to mitigate infections.⁵

Intravenous immunoglobulin use has been evaluated in other protein-losing states. Studies have reported that IVIG can decrease infections, resolve edema, and result in better overall clinical status in patients with protein-losing enteropathy.^{6,7} Despite some of these successful case reports, most reviews do not support the use of IVIG in nephrotic syndrome given the expected quick urinary losses.^{8–10} No studies, however, evaluate the use of subcutaneous immunoglobulin infusions in this disease process. We report a case of congenital nephrotic syndrome with agammaglobulinemia and unsuccessful treatment with subcutaneous immunoglobulin infusions.

A 1-month-old African American boy presented with increased work of breathing and low oxygen saturations, as well as periorbital edema. Evaluation was notable for a right-sided pleural effusion, very low serum protein (<2.8 g/dL) and albumin (1.6 g/dL), and large proteinuria. The patient was diagnosed with congenital nephrotic syndrome, with positive genetic analysis for a mutation in NPHS1 (nephrin gene), which is also known as the Finnish-type congenital nephrotic syndrome. During the course of his admission, the patient's immunoglobulin levels were IgG < 70 mg/dL, IgA < 15 mg/dL, and IgM 24 mg/dL. Absolute lymphocyte count was in the low normal range for age at 3,869 cells/mm³. Flow cytometry showed a normal CD19+ cell count of 1,061 cell/μL and a low CD3+ cell count of 1,832 cells/μL. The patient was placed on antibiotic prophylaxis, but given his agammaglobulinemia it was thought that the patient should

receive immunoglobulin replacement to further decrease the risk of infections. Because of previous reports of quick urinary losses of IVIG,² subcutaneous immunoglobulin (SCIG) was initiated. A dose of 1 gram per week was calculated based on Hizentra dosing guidelines and patient's weight.

The patient had weekly subcutaneous infusions, with “trough” levels obtained before each infusion. After his fourth subcutaneous infusion, minimal improvement in serum immunoglobulin levels was noted, and the infusion frequency was increased from weekly to 3 times per week. Despite the increased frequency, trough levels remained low. A “peak” level was obtained 12 hours after one of his infusions that showed a detectable level of IgG (129 mg/dL). Before starting immunoglobulin infusions, the patient had no documented infections. Subsequently, 2 weeks after initiating SCIG, the patient developed tachycardia, tachypnea, and fever to 104.8°F (40.4°C) with positive blood cultures for extended-spectrum beta-lactamase producing *Klebsiella oxytoca* from both Broviac lines. After initiating antibiotics, the patient clinically improved and defervesced.

Given the lack of measurable improvement in immunoglobulin levels and no significant change in his clinical status, immunoglobulin replacement was discontinued. The patient's nephrotic syndrome continued to worsen. A few weeks after discontinuing SCIG, he received a right nephrectomy. While recovering, he developed respiratory syncytial virus bronchiolitis and was intubated for pulmonary edema and respiratory failure. He was managed with supportive care by the primary team and recovered over a few days. Despite medical management, his proteinuria and clinical status further deteriorated, resulting in left nephrectomy and initiation of dialysis. At the present time, the patient is maintained on dialysis awaiting a kidney transplant. He has not experienced any significant infections after the second nephrectomy. Additionally, his serum protein and albumin levels have normalized, and he showed measurable response on vaccine titers.

Congenital nephrotic syndrome is a rare disorder; therefore few studies or case reports describe the use of immunoglobulin replacement in these patients. Antibiotic prophylaxis should always be part of the patient's regimen, as it was in this case; however, the use of immunoglobulin replacement is not as certain. Although subcutaneous replacement when compared with intravenous may provide a better steady-state and slower diffusion into tissues through the lymphatic system, a dilemma remains as to how to measure immunoglobulin levels or titrate dosing other than through monitoring for clinical effect. Increased dosing of SCIG beyond manufacturing recommendations, such as daily dosing, has not yet been studied in the literature for infection prevention in this subset of patients; however, given the extreme expense and growing demand for pooled immunoglobulin therapy, the use of SCIG in these patients may be limited. No data are available on the pharmacokinetics and tissue distribution of immunoglobulins

Disclosures: Authors have nothing to disclose.

Disclaimer: The views expressed in this letter are those of the authors and do not reflect the official policy of the Department of Army, Navy, Department of Defense, or U.S. government.

when given subcutaneously to a patient with hypogammaglobulinemia or agammaglobulinemia secondary to a protein-losing disease. More studies are warranted to help protect this precious resource.

Kathryn M. Payne, MD
Michael R. Nelson, MD, PhD
Maureen M. Petersen, MD
Allergy-Immunology-Immunizations Service
Department of Medicine
Walter Reed National Military Medical Center
Bethesda, Maryland
Katie.payne@us.army.mil

References

- [1] Mahan JD, Mauer SM, Sibley RK, Vernier RL. Congenital nephrotic syndrome: evolution of medical management and results of renal transplantation. *J Pediatr*. 1984;105:549–557.
- [2] Harris HW, Umetsu D, Geha R, Harmon WE. Altered immunoglobulin status in congenital nephrotic syndrome. *Clin Nephrol*. 1986;25:308–313.
- [3] Wu HM, Tang JL, Cao L, Sha ZH, Li Y. Interventions for preventing infection in nephrotic syndrome. *Cochrane Database Syst Rev*. 2012;18:4.
- [4] Gentner JE, Wood EG, Vogler CA, Beck AM, Knutsen AP. Remission of congenital nephrotic syndrome from diffuse mesangial sclerosis with IVIG therapy. *J Allergy Clin Immunol*. 2008;121:S83.
- [5] Ogi M, Yokoyama H, Tomosugi N, et al. Risk factors for infection and immunoglobulin replacement therapy in adult nephrotic syndrome. *Am J Kidney Dis*. 1994;24:427–436.
- [6] De Giacomo C, Maggiore G, Scotta MS, Ugazio AG. Administration of intravenous immunoglobulin in two children with hypogammaglobulinaemia due to protein losing enteropathy. *Clin Exp Immunol*. 1985;60:447–448.
- [7] Zaupper LB, Nielsen BW, Herlin T. Protein-losing enteropathy after the total cavopulmonary connection: impact of intravenous immunoglobulin. *Congenit Heart Dis*. 2011;6:624–629.
- [8] Schwartz S. Intravenous immunoglobulin treatment of immunodeficiency disorders. *Pediatr Clin North Am*. 2000;47:1355–1369.
- [9] Liunbruno GM, Bennardello F, Lattanzio A, Piccoli P, Rossettias G. Recommendations for the use of albumin and immunoglobulins. *Blood Transfus*. 2009;7:216–234.
- [10] Leong H, Stachnik J, Bonk ME, Matuszewski KA. Unlabeled uses of intravenous immune globulin. *Am J Health Syst Pharm*. 2008;65:1815–1824.