Compassionate use experience with high-titer respiratory syncytial virus (RSV) immunoglobulin in RSV-infected immunocompromised persons

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Abstract

Background: Respiratory syncytial virus (RSV) may cause fatal lower respiratory tract infection (LRTI) in immunocompromised patients. Ribavirin with or without standard intravenous immunoglobulin (IVIG) is frequently given although efficacy is debated. Infusion of IVIG with high levels of neutralizing antibody against RSV may offer benefit in these patients.

Methods: RI-001 contains standardized levels of high-titer anti-RSV neutralizing antibody and was provided for compassionate use to 15 patients with RSV LRTI who either failed conventional therapy or had significant risk of progression. Patients were treated on day 1 with RI-001 1500 mg/kg, followed 2 days later with 750 mg/kg. Pre- and post-infusion sera were measured for RSV neutralizing antibody. Patient data were analyzed for safety related to infusion of RI-001, and clinical outcomes.

Results: Patients ranged in age from 2 months to 71 years and 80% had hematologic malignancy or were bone marrow or hematopoietic stem cell transplant recipients. Administration was well tolerated. Pre-infusion neutralizing titers ranged from 51 to 1765 geometric mean titer (mean 646±519) and all patients demonstrated at least a 4-fold rise (mean 6410±4470) 5-10 days post infusion. Eleven of 15 improved and were discharged from the hospital. Days from positive RSV test to RI-001 treatment was shorter in survivors compared to non-survivors (4.4±2.8 vs. 20.3±21.0 days, P=.02).

Conclusion: Administration of RI-001 was well tolerated and resulted in significant increases in serum neutralizing antibody titers to RSV. Our data suggest that early identification of RSV and treatment with RI-001 may offer benefit.

KEYWORDS
immunoglobulin, pneumonia, respiratory syncytial virus, RI-001, transplant

1 INTRODUCTION

Respiratory syncytial virus (RSV) is the most common cause of serious respiratory infection in infants and young children, leading to >100 000 hospitalizations and 300 deaths each year in the United States.1 Reinfection is common throughout life and generally results in mild disease in healthy young adults. However, severe RSV disease may occur in the elderly and in adults with chronic cardiopulmonary disease or compromised immune function.2-3 Recipients of lung transplant or hematopoietic stem cell transplant (HSCT) are at particularly high risk of severe RSV infection.4 Mortality rates in HSCT patients who develop RSV lower respiratory tract disease (LRTI) range from...
20% to 40% and may be as high as 100% in those with respiratory failure.5–9 Optimal therapy for immunocompromised patients with RSV infection has not been defined and data on treatment are limited. Inhaled ribavirin (Virazole®) is US Food and Drug Administration (FDA) approved only for use in RSV-infected hospitalized infants and young children. This drug has been used off-label in oral, intravenous, and inhaled formulations in immunocompromised patients with RSV, despite questionable efficacy.10,11 A second option for treatment of RSV infection is immunoglobulin, generally combined with ribavirin.8,12,13 Presently, two immunoglobulin products are available, including the monoclonal antibody palivizumab (Synagis®, MedImmune, Gaithersburg, MD, USA), approved for prophylaxis in high-risk infants, and pooled human intravenous immunoglobulin (IVIG). Because palivizumab is dosed based on weight and is costly, IVIG is generally used in adults when an immunoglobulin product is used.14 RespiGam® was an IVIG product containing high titers of neutralizing antibody to RSV with demonstrated efficacy for prevention of serious lower respiratory tract infection caused by RSV infection in high-risk infants. However, RespiGam® was voluntarily discontinued in 2003 by Medimmune with the introduction of palivizumab and is no longer an option for seriously ill immunocompromised adults with RSV infection.

RI-001 (ADMA Biologics, Inc, Ramsey, NJ, USA) is an IVIG prepared from plasma donors selected to have high-titer neutralizing anti-RSV antibody, similar to RespiGam®. We report its use under investigator-requested emergency investigational new drug applications on a compassionate use basis in patients with lower respiratory tract RSV disease who failed conventional therapy or were at high risk for progression of RSV infection. Data on the treatment and clinical course of these patients were collected and analyzed for safety related to the infusion of RI-001 and clinical outcomes.

2 | METHODS

2.1 | Patients

Data were collected from patients who received compassionate use RI-001 at 6 centers in the United States, 3 centers in Australia, and 1 center in New Zealand from December 2008 to February 2011. Hospitalized patients with documented RSV, who were either unresponsive to standard of care therapy including some combination of ribavirin, corticosteroids, palivizumab, or standard IVIG or who were at high risk for mortality because of their RSV infection, were eligible for compassionate use of RI-001. Patients were identified by their treating physicians after being diagnosed with RSV by reverse-transcription polymerase chain reaction (RT-PCR), direct fluorescent antibody test, indirect fluorescent antibody test, or viral culture from respiratory secretions.

The sponsor evaluated potential study participants after receiving unsolicited compassionate use requests for the use of RI-001. Treatment with the investigational drug, RI-001, was provided on an emergency use basis for compassionate use. ADMA policy required US sites to document that the FDA single patient Emergency Investigational New Drug (EIND) form (Form FDA 3926) was submitted to the agency and that an approval was granted.

Clinical information provided for each patient included the following: RSV diagnosis including date of sample collection and type of sample, test type used to diagnose RSV (e.g., rapid antigen, PCR, or other), and date of result, and patient's use of oxygen, ribavirin, palivizumab, IVIG, and steroids. Sites were instructed to provide a brief summary of each patient's medical history, respiratory signs and symptoms, other relevant symptoms or conditions that contributed to the need for RI-001, and a summary of the patient's response to the administration of RI-001. In addition to the clinical information, serum samples from the patient were requested prior to infusion and at 1, 3, 8, and 18 days post infusion for measurement of serum RSV neutralizing antibody titers.

2.2 | Study product

RI-001 is polyclonal human immunoglobulin G (IgG) made from pools of source plasma from up to 3000 screened healthy US adult donors with high neutralizing anti-RSV titers. The immunoglobulin pool contains standardized high levels of RSV neutralizing antibodies, consisting of various immunoglobulins specificities representative of the diversity of human antibodies made against the virus. All plasma used in the production of RI-001 was collected in International Quality Plasma Program-certified and FDA-licensed facilities, under Good Manufacturing Practices guidelines and in accordance with the Code of Federal Regulations. Trace amounts of immunoglobulin A and immunoglobulin M are contained in RI-001. The formulation is in 0.150 M sodium chloride, 0.30 M glycine, and 0.20% polysorbate 80, at pH 4.0–4.6. The product, which does not contain preservatives, was supplied in single-dose vials.

2.3 | Product infusion

Patients were treated on day 1 with RI-001 1500 mg/kg, followed 2 days later with 750 mg/kg on day 3. RI-001 drug concentration was 100 mg/mL. Infusion rate was gradually increased from 0.3 mL/kg/hour to 2.0 mL/kg/hour (maximum 150 mL/hour) at 15 minute intervals over a 2-hour period. If an infusion reaction occurred, sites were instructed to slow or stop the infusion until symptoms resolved and to re-start the infusion at a lower rate, slowly increasing the rate as tolerated by the patient. Pre-medication per institutional guidelines was permitted.

2.4 | Microneutralization antibody assay

Serum neutralizing antibody titers were performed by use of an established microneutralization method for RSV A strain.15 In brief, serum dilutions were incubated with 75 pfu of RSV A2 strain (group A virus) for 30 minutes at room temperature, followed by the addition of 1.5×10^4 HEP-2 cells in 96-well culture plates. After 3 days, the quantity of RSV antigen was determined by enzyme immunoassorbent assay
using monoclonal antibody to the RSV F protein. The neutralization titer was defined as the serum dilution that results in a 50% reduction in color development.

2.5 | Statistical analysis
Means between groups were compared by Student’s t-test; proportions were compared by Fisher’s exact test.

3 | RESULTS

3.1 | Population
A total of 15 patients ranging in age from 2 months to 71 years of age received compassionate use RI-001 (Table 1). Sixty percent were male and 53% were <18 years of age. Patients with a variety of underlying medical conditions received RI-001 including the following: recipients of bone marrow transplants or HSCT (9), hematologic malignancy (3), severe combined immunodeficiency (1), liver transplant (1), and interstitial lung disease (1). Four HSCT recipients were pre-engraftment and 3 had chronic graft-versus-host disease at the time their RSV infection was identified.

3.2 | RSV illness
Diagnosis of RSV was most often made by detecting RSV in upper airway secretions by antigen detection or PCR, but RSV was also detected in the sputum of 3 patients and in bronchoalveolar lavage fluid from one individual. All but one patient was thought to have pneumonia or LRTI caused by RSV. The single patient with a clear chest radiograph was a 16-month-old child with hemophagocytic lymphohistiocytosis diagnosed with persistent RSV infection relapsing over several months, and who was treated for a RSV relapse prior to HSCT. A variety of radiographic changes were reported with bilateral or diffuse involvement with ground-glass or interstitial infiltrates being most common. Co-infections during RSV infection were frequent (7/15), although only 2 subjects had concomitant infection with other respiratory viral pathogens (1 human metapneumovirus/rhinovirus and 1 influenza A).

3.3 | Treatment of RSV infection
All patients received ribavirin prior to or concomitant with RI-001 treatment. Seven were treated with inhaled, 4 with intravenous, 1 with oral, and 3 with a combination of oral and inhaled ribavirin. Eight patients received prior antibody treatments; 6 received standard IVIG and 4 children received palivizumab (2 with IVIG); 1 patient received IVIG after RI-001. Six patients received RI-001 as part of their initial treatment for RSV (within 4 days of diagnosis) and 9 were considered to be failing treatment because of persistent or worsening symptoms after ≥5 days of ribavirin±IVIG or palivizumab treatment. Other concomitant treatments included: bronchodilators (33%), corticosteroids (80%), and antibiotics or antifungals (93%).

3.4 | RI-001 treatment
All patients received a minimum 2 doses of RI-001 of whom 13 (87%) were dosed per the sponsor’s instructions, receiving 1500 mg/kg of RI-001 as an IV infusion, followed 2 days later by 750 mg/kg. Two patients did not receive product according to the sponsor’s instructions: One patient received the second dose of RI-001 on day 4 and one patient received 4 doses of RI-001 at 1500 mg/kg on days 1, 3, 5, and 7. Three patients were judged to have infusion-related adverse events. One subject had back pain and elevated blood pressure with the first dose, but tolerated the second dose without incident. Two patients had infusion-related symptoms that resolved after slowing the infusion, and the second doses were well tolerated with pre-medication.

No serious adverse events related to study product were noted.

3.5 | Antibody measurements
Fourteen patients had pre-treatment and at least one post-infusion serum sample available for measurement of serum neutralizing antibody against RSV (Table 2). The pre-infusion titers ranged from 51 to 1765 geometric mean titer (GMT), with a mean of 646±519. Notably, 2 of 5 patients who received standard IVIG had serum neutralizing titers of <330 before receiving RI-001. All patients demonstrated at least a 4-fold rise post infusion, with all but one patient having persistently higher RSV antibody than baseline 18-33 days after infusion. The increases between mean GMT titers from baseline compared to days 1, 3, and 5-10 post infusion were all significantly higher (5625±3109, 6176±4061, 6410±4470, respectively, all P<.0001).

3.6 | Illness outcomes
Of the 15 patients treated, 7 required intensive care treatment, 6 assisted ventilation (2 non-invasive and 4 mechanical ventilation) during their RSV infection (Table 3). All patients who required mechanical ventilation died, and 3 of the 4 had respiratory failure before receipt of RI-001. Eleven of 15 (73%) patients had improvement of their respiratory infection and survived the hospitalization. Of these, one had refractory leukemia and was discharged to home with comfort care. Four patients (2 children and 2 adults) died of progressive respiratory failure during the hospitalization. No apparent differences in survival were observed between patients with underlying malignant diseases (9 patients, 2 deaths) and those with non-malignant diseases (6 patients, 2 deaths). In addition, no differences in survival were observed in patients who had undergone bone marrow or HSCT vs those who had not. Survival was 0/4 (0%) for patients with respiratory failure compared to 11/11 (100%), P<.001 in those without respiratory failure.

Time from onset of respiratory symptoms and time from RSV diagnosis to initiation of RI-001 treatment were evaluated (Table 4). Patients who had significant underlying illness, such as congestive heart failure, that complicated interpretation of dyspnea, or had chronic relapsing RSV, were evaluated in two ways: time from onset of any respiratory symptom and time from new respiratory symptoms
| Summary data | Age <18 years | Male gender No. (%) | BMT or HSCT No. (%) | Abnormalities on CXR No (%) | Low SaO2 Mean (SD) | PCR+ No (%) | Clinical diagnosis of pneumonia No (%) | Other therapies No (%) | Co-Infection No (%) |
|--------------|--------------|---------------------|---------------------|-----------------------------|-------------------|------------|----------------------------------------|-----------------------|-------------------|
| 8 (53)       | 9 (60)       | 9 (60)              |                     |                             | 13/14 (93)        | 90 (6)     | 6 (40)                                 | 12 (80)               | 15 (100)          |

**Detailed subject characteristics**

| Subject number | Age (years) | Gender | Underlying diseases | CXR/CT Scan results | Low SaO2 | Method RSV Diagnosis | RSV clinical diagnosis | Other RSV therapy during Illness | Co-Infection |
|----------------|-------------|--------|---------------------|---------------------|----------|----------------------|------------------------|-------------------------------|-------------|
| 1              | 59          | M      | Hepatitis C, Liver transplant ×2, ESRD on dialysis, CHF       | Diffuse nodular ground-glass infiltrates, right mid lung consolidation | 92       | NPS Antigen          | Pneumonia               | Inhaled ribavirin              | None         |
| 2              | 66          | F      | Reinduction chemotherapy, Relapsed AML                      | Diffuse interstitial infiltrates | 93       | Sputum viral culture | Pneumonia               | Inhaled ribavirin IVIG             | None         |
| 3              | 44          | M      | CLL                  | Diffuse tree-in-bud | 93       | Sputum PCR           | Bronchiolitis/ Pneumonia | Inhaled ribavirin              | None         |
| 4              | 2           | F      | ALL, post BMT 10 months prior, GVHD                        | Bilateral atelectasis and consolidation | 88       | NPA IFA              | Pneumonia               | IV ribavirin IVIG             | Clostridium difficile |
| 5              | 8           | F      | AML HSCT pre engraftment                                    | Left-sided diffuse alveolar opacities | 85       | NPS RSV              | Pneumonia               | IV ribavirin                 | Clostridium difficile |
| 6              | 46          | M      | AML HSCT 2 years prior Chronic GVHD                         | Bronchiectasis Ground-glass infiltrates | 93       | NPA RSV              | LRTI                   | Oral ribavirin IVIG            | None         |
| 7              | 9           | M      | ALL cord blood HSCT pre engraftment                         | NA                                  | 94       | BAL and NPA RSV     | LRTI                   | IV ribavirin IVIG             | Blood culture |
| 8              | 47          | M      | ALL, HSCT 11 months prior, GVHD                             | Diffuse patchy opacities CT - ground glass | 92       | Sputum & NPS rapid antigen | Pneumonia               | Inhaled & oral ribavirin              | None         |
| 9              | 1.5         | M      | HLH Persistent RSV HSCT pre engraftment                     | Clear                                | 100      | NPA RSV              | Persistent RSV          | IV ribavirin Palivizumab         | None         |
| 10             | 0.75        | M      | Osteopetrosis RSV prior to HSCT                              | Bilateral opacities, Interstitial markings | 79       | NPS, wash PCR & culture | Pneumonia               | Inhaled & oral ribavirin Palivizumab | HMPV, HRV, CONS, lactobacillus |
| 11             | 0.17        | M      | SCID                                                            | RUL infiltrate                      | 89       | NPS PCR              | Pneumonia               | Inhaled ribavirin Palivizumab | CONS         |
| 12             | 20          | F      | APLM prior BMT HSCT pre engraftment                          | Diffuse ground-glass small nodules | pO2-55   | NPS PCR              | Pneumonia               | Inhaled ribavirin IVIG             | None         |
| 13             | 1           | F      | ALL, seizures, history of pulmonary Aspergillus            | Bilateral patchy infiltrate          | NA       | Nasal wash IFA & PCR | Pneumonia               | Inhaled ribavirin Palivizumab | None         |
| 14             | 71          | F      | Interstitial lung disease                                    | Diffuse interstitial alveolar infiltrate | 81       | NPS PCR              | Pneumonia               | Inhaled ribavirin              | Influenza A |
| 15             | 15          | M      | Aplastic anemia PNH HSCT                                     | Bilateral lower lobe infiltrates     | 93       | Nasal wash RSV      | Pneumonia               | Oral & inhaled ribavirin              | Clostridium difficile |

BMT, bone marrow transplant; HSCT, hematopoietic stem cell transplant; CXR, chest radiograph; SaO2, percutaneous oxygen saturation; SD, standard deviation; PCR, polymerase chain reaction; CT, computed tomography; RSV, respiratory syncytial virus; ESRD, end-stage renal disease; CHF, congestive heart failure; NPS, nasopharyngeal swab; AML, acute myelogenous leukemia; IV, intravenous; IVIG, intravenous immunoglobulin; CLL, chronic lymphocytic leukemia; ALL, acute lymphocytic leukemia; GVHD, graft-versus-host disease; NPA, nasopharyngeal aspirate; IFA, immunofluorescent assay; LRTI, lower respiratory tract infection; BAL, bronchoalveolar lavage; CONS, coagulase-negative staphylococcus; HMPV, human metapneumovirus; HRV, human rhinovirus; SCID, severe combined immunodeficiency; NA, not available/applicable; RUL, right upper lobe; HLH, hemophagocytic lymphohistiocytosis; APML, acute promyelocytic leukemia; PNH, paroxysmal nocturnal hemoglobinuria.
TABLE 2

| Subject | 1 | 2 | 3 | 4 | 5 | 6 | 7 | 8 | 9 | 10 | 11 | 12 | 13 | 14 | 15 |
|---------|---|---|---|---|---|---|---|---|---|----|----|----|----|----|----|
| Mean (SD) | IVIG Paliviz Pre-infusion immunoglobulin therapy | Day 1 pre-infusion RI-001 | 1158 | 882 | 662 | 1765 | 5025 (3109) | 362 | 1448 | 5194 | 322 | 5361 | 7723 | 5148 | 3861 | 7723 | 3861 |
|         | Paliviz | Day 1 post-infusion RI-001 | 926 | NA | NA | 290 | 297 | 290 | 7038 | 2647 | 6176 | 6176 | 6176 | 6176 | 6176 | 6176 | 6176 |
|         | Paliviz | Day 3 post-infusion RI-001 | 2896 | 5792 | 2574 | 11584 | 1241 | 1241 | 4945 | 3088 | 3088 | 3088 | 3088 | 3088 |
|         | Paliviz | Day 5-10 | NA | NA | NA | NA | NA | NA | NA | 12352 | 622 | 1765 | 646 (519) | 646 (519) | 646 (519) | 646 (519) |
|         | Paliviz | Day 18-20 | NA | NA | NA | NA | NA | NA | NA | 221 | 882 | 28233 | 6176 | 6176 | 6176 | 6176 |
|         | Paliviz | Day 21-28 | NA | NA | NA | NA | NA | NA | NA | 1287 | 2574 | 1655 | 1544 | 1544 |
|         | Paliviz | NA | NA | NA | 926 | 926 | 926 | 926 | 926 | 926 | 926 | 926 | 926 | 926 | 926 | 926 |
|         | Paliviz | NA | NA | NA | 12352 | 622 | 1765 | 646 (519) | 646 (519) | 646 (519) | 646 (519) | 646 (519) | 646 (519) | 646 (519) | 646 (519) | 646 (519) |

SD, standard deviation; IVIG, intravenous immunoglobulin; Paliviz, palivizumab; RI-001, investigational IVIG with high-titer neutralizing anti-respiratory syncytial virus antibody; NA, not available.

Lack of definitive randomized controlled trials. Small case series, the body was a risk factor for severe RSV infection.15,19 High serum antibody levels may lead to greater transudation of IgG from serum to the lower airways, thereby ameliorating disease or preventing progression to the lower airways. Although treatments of immunocompetent children with monoclonal antibodies (palivizumab and motavizumab) have not demonstrated clinical advantage, it is possible that immunodeficient patients might derive benefit.20 Supporting this concept, immunosuppressed cotton rats treated with RI-002 (the second derivative of RI-001) were protected from RSV infection in the lower airways and resultant pulmonary inflammation.21 In addition to an antiviral effect, immunoglobulins are known to have anti-inflammatory effects that may be beneficial when used in combination with antiviral agents.22

Despite the theoretical benefit, the use of immunoglobulin products to treat RSV infection in immunosuppressed patients remains controversial, in part because standard IVIG or palivizumab was used in combination with ribavirin at the discretion of the treating physician.9 In a review of 407 HSCT patients, treatment with aerosolized relating to RSV infection. Time from RSV diagnosis and from onset of new respiratory symptoms to treatment with RI-001 was significantly shorter among survivors compared to non-survivors.

4 | DISCUSSION

RSV remains a cause of significant morbidity and mortality in patients with immune deficiencies and, although mortality rates from RSV LRTI have dropped from 50%–100% in initial reports to 20%–40% in more recent reviews, better therapies are clearly still needed.24 Lower mortality rates likely reflect more sensitive diagnostics, better supportive care, and earlier more aggressive treatment. Yet the benefit of specific antiviral treatment remains difficult to define. Optimal treatment of RSV infection in this population is controversial primarily owing to the lack of definitive randomized controlled trials. Small case series, heterogeneous populations, and lack of standardized treatment regimens make interpretation of the literature challenging. However, several retrospective studies and a recent pooled analysis suggest that ribavirin in any form is associated with decreased progression of upper respiratory tract infection (URTI) to LRTI (45% down to 16%) and decreased mortality (70% down to 13%).8,9 Although observational data suggest benefit of early treatment with ribavirin, multiple issues remain, including high cost ($29,953/day) toxicity, and administration difficulties with the inhaled preparation and of IV ribavirin.21 New and more potent antiviral agents are currently in clinical development, but are not currently available.17,18

Immunotherapy is an option for adjunctive therapy with antiviral agents for the treatment of RSV infection in immunosuppressed persons. Although antibody is traditionally considered most important for prevention rather than treatment of established infection, immunotherapy, if given early in the course of illness, may offer benefit in this select population. All adults have measurable antibody to RSV and although a precise correlate of immunity does not yet exist, two earlier studies of older adults found that low serum-neutralizing antibody was a risk factor for severe RSV infection.15,19 High serum antibody levels may lead to greater transudation of IgG from serum to the lower airways, thereby ameliorating disease or preventing progression to the lower airways. Although treatments of immunocompetent children with monoclonal antibodies (palivizumab and motavizumab) have not demonstrated clinical advantage, it is possible that immunodeficient patients might derive benefit.20 Supporting this concept, immunosuppressed cotton rats treated with RI-002 (the second derivative of RI-001) were protected from RSV infection in the lower airways and resultant pulmonary inflammation.21 In addition to an antiviral effect, immunoglobulins are known to have anti-inflammatory effects that may be beneficial when used in combination with antiviral agents.22

Despite the theoretical benefit, the use of immunoglobulin products to treat RSV infection in immunosuppressed patients remains controversial, in part because standard IVIG or palivizumab was used in combination with ribavirin at the discretion of the treating physician.9 In a review of 407 HSCT patients, treatment with aerosolized
ribavirin plus either IVIG, palivizumab, or high-titer RSV immunoglobulin (RespiGam®), Shah⁹ and Chemaly⁸,¹⁰ noted a trend toward decreased progression from URTI to LRTI in those who received dual treatment compared to those treated with ribavirin alone (12% vs 25%, P=.13). Notably, the RSV-specific mortality rate in patients with LRTI was significantly lower in the combination therapy group (24% vs 50%, P<.001). Prior to RespiGam® being discontinued, two reports described its use in immunosuppressed patients.¹² Two adult patients and 11 children undergoing bone marrow transplant were treated with inhaled ribavirin and RespiGam® and all but one child survived. The mortality rate of 8% in this small case series was seen as favorable when compared to historical data citing mortality rates of 20%-24% with ribavirin alone.¹²

The importance of achieving a specific level of RSV antibody in transplant patients is unknown. In one study of HSCT patients, serum neutralizing antibody levels were not significantly different in those who progressed from URTI to LRTI compared to non-progressors.⁶ In contrast, in a study of 56 RSV-infected HSCT recipients, of whom 71%
developed LRTI and 35% of those with LRTI died, investigators found that hypogammaglobulinemia (<6 g/L of IgG) was an independent risk factor for prolonged viral shedding and death.23

Many factors likely contribute to the difficulty of demonstrating consistent benefit of immunotherapy including heterogeneous populations, time from onset of infection to treatment, underlying diseases, and treatment regimens. In addition, commercial IVIG contains variable concentrations of RSV antibody and lacks standardization from batch to batch.24 For patients treated with palivizumab, resistant escape mutants caused by selective pressure are of potential concern. Such mutants have been produced in vitro and have been found in 5%-9% of children with RSV breakthrough episodes while receiving palivizumab prophylaxis.25,26 Although not a significant clinical problem in immunocompetent children, resistant viruses might be more likely to develop because of prolonged shedding and higher levels of virus in immunosuppressed children. Polyclonal RSV antibody preparations such as RI-001, which has standardized concentrations of RSV antibody and meets the FDA guidance for treatment of patients with immune deficiency, could address both these issues.27

Our experience with 15 patients who received RI-001 as compassionate use indicates the product is safe and well tolerated with minimal side effects. RI-001 produced at least a 4-fold rise in RSV neutralizing titers in all patients, and in some had 24- to 76-fold increases. These results highlight the advantage of using RI-001 over standard IVIG in achieving high serum neutralizing titers in patients.

Caution is necessary in drawing conclusions regarding efficacy of RI-001 in the absence of a randomized study. While the mortality rate of 27% in our cohort is similar to the 22%-24% mortality rates in similar patients using ribavirin alone or with IVIG, it is important to note that 9 patients in our cohort were judged to be failing conventional therapy with ribavirin±IVIG or palivizumab when RI-001 was requested. Five of these patients subsequently improved and cleared their RSV infection. Although 4 patients died, 3 required mechanical ventilation prior to receiving the drug, which is known to be associated with death rates nearing 100%. The significant difference in time from diagnosis to treatment with RI-001 among survivors suggests that treatment should be administered early for the greatest benefit.

Despite the lack of randomized clinical trials and uncertainty regarding benefit, the European Conference on Infections in Leukemia (ECIL-4) recommends the treatment of RSV-infected H SCT patients with URTI who have risk factors for progression to be treated with ribavirin and IVIG.28 The British Committee for Standards in Hematology echoes this recommendation, as well as recommending treatment of RSV LRTI with both ribavirin and IVIG.29 Thus, a high RSV neutralizing antibody immunoglobulin preparation such as RI-001 or its subsequent derivatives may offer advantages over standard IVIG in the treatment of RSV-infected immunocompromised patients.

### TABLE 4 Timing of RI-001 treatment

| Time to treatment with RI-001 | Survived (N=11) | Died (N=4) | P-value |
|-----------------------------|----------------|-----------|---------|
| Days from initial respiratory symptoms | 19.5 (15.8) | 34.5 (20.5) | .15     |
| Days from new respiratory symptoms | 10.7 (5.4)  | 34.5 (20.5) | .003    |
| Days from diagnosis of RSV | 4.4 (2.8)    | 20.3 (21.0) | .02     |

RI-001, investigational IVIG with high-titer neutralizing anti-respiratory syncytial virus (RSV) antibody.

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