POLYCLONAL HUMAN INTRAVENOUS IMMUNE GLOBULIN (IGIV) WITH HIGH-LEVELS OF RSV NEUTRALIZING ANTIBODIES: A SUMMARY OF ANIMAL AND HUMAN STUDIES

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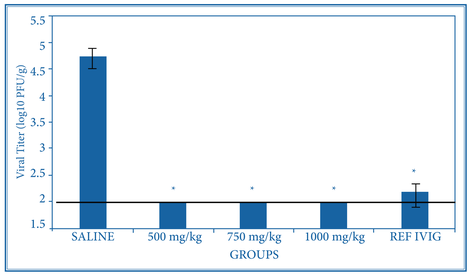
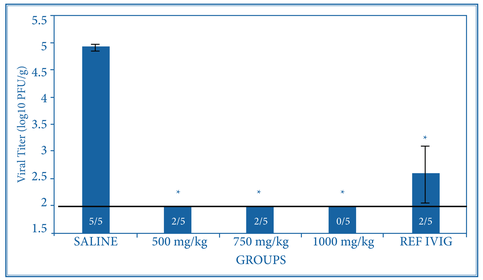
INTRODUCTION

Immunocompromised patients, particularly bone marrow transplanted patients are at the highest risk of having upper RSV respiratory tract infections progress to lower respiratory tract infection . Transplant recipients are particularly susceptible to fulminant RSV infection within two years after transplantation. The reported mortality rate in human stem cell transplant patients who develop lower respiratory tract infections approaches 70-100% for those not treated or treated late with standard of care therapy. A safe and effective treatment that will resolve and/or ameliorate RSV infection in the LRT is therefore urgently needed in these patients. RI-002 is a newly developed human immunoglobulin product supplied as a solution for intravenous infusion for the proposed use in the primary immune deficient population. It is made from plasma collected from individuals that have naturally circulating high titers of neutralizing antibody to RSV. We used the cotton rat RSV infection model as the surrogate for human RSV infection to test the efficacy of this product to prevent and to treat RSV mediated pulmonary and nasal infection. This high titer RSV IVIG was also used in a compassionate use study in attempt to rescue patients with lower tract RSV disease who failed conventional therapy. The current RSV high titer IVIG product RI-002 is now fully enrolled in a phase three trial to prevent serious infections in patients with primary immune deficiency.

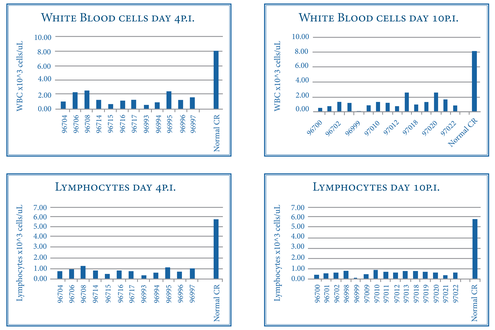
ADMA IVIG PREVENTS RSV INFECTION IN THE LUNG OF IMMUNE COMPETENT COTTON RATS



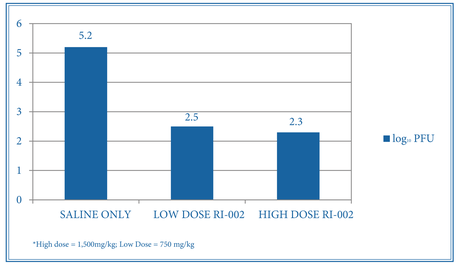
ADMA IVIG PREVENTS RSV INFECTION IN THE NOSE OF IMMUNE COMPETENT COTTON RATS



WHOLE BLOOD ANALYSIS DATA- IMMUNE SUPPRESSED COTTON RATS

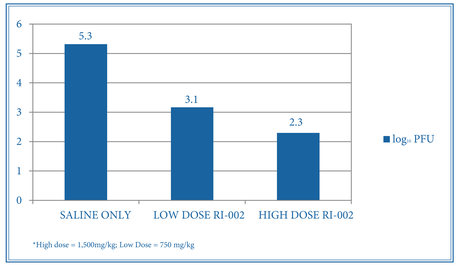


REDUCTION OF VIRAL LOAD IN THE LUNGS OF COTTON RATS TREATED WITH RI-002 (log_{10} PFU)*



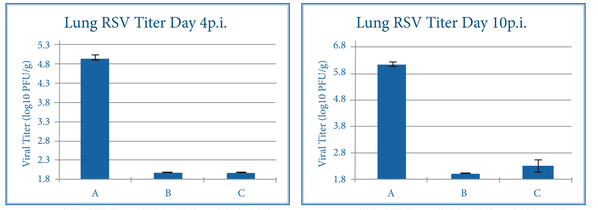
*High dose = 1,500mg/kg; Low Dose = 750 mg/kg

REDUCTION OF VIRAL LOAD IN THE NASAL TISSUE OF COTTON RATS TREATED WITH RI-002 (log_{10} PFU)*



*High dose = 1,500mg/kg; Low Dose = 750 mg/kg

ADMA IVIG PREVENTS RSV INFECTION IN THE LUNGS OF IMMUNE SUPPRESSED COTTON RATS



PHASE II MULTICENTER DOSE RANGING STUDY IN RSV INFECTED IMMUNOCOMPROMISED PATIENTS

- Randomized, double blind, placebo controlled
- US, Canada, Australia, New Zealand
- RSV by RT-PCR URI at time of enrollment
- BMT/HSCT or solid organ transplant within 2 years on concurrent immunosuppressive treatment
- Ages 2-65 (mean age 38 years)
- Three Arms 1:1:1
  - -1500mg/kg, followed by 750mg/kg day 2
  - -750mg/kg followed by 750mg/kg day 2
  - -Placebo

PHASE II PRIMARY OUTCOME

PRIMARY ENDPOINT

Define the dose which produced a > 4-fold rise in neutralizing titer at day 18 compared to baseline

RESULTS (N=21)

- Primary endpoint met
- Well tolerated, no SAEs related to infusion

DOSE	*#> 4-FOLD RISE*	*MEAN FOLD RISE*
High Dose (7)	6 (86%)	9.2
Low Dose (7)	3 (43%)	4.9
Placebo (7)	0	1.4

High Dose 1500mg/kg followed on day 3 with 750mg/kg
Low Dose 750 mg/kg followed by 750 mg/kg

COMPASSIONATE USE STUDY

- 15 unsolicited compassionate use requests
- Age 3 months to 71 years
- All patients were immunosuppressed and diagnosed with RSV lower respiratory tract infection
- All were unresponsive to conventional therapies
  - Some had received Ribavirin and/or Standard IVIG
  - 3 young children received palivizumab
- Patients were treated with RI-002 (1500mg/kg followed 2 days later with 750 mg/kg
- 11 of 15 patients improved rapidly on RI002
- Those that died were treated already had ARDS secondary to RSV pneumonitis

VIGNETTES FROM COMPASSIONATE USE TRIAL

PATIENT #1

- 59 year old male post liver transplant
- 2 weeks PTA increasing SOB
- CXR R mid lung consoloidation
- RSV+ (LRI)
- Failed conventional Therapy
- ADMA IVIG administered day 6 after RSV + diagnosis.

Patient clinically and symptomatically improved 2 days later.

PATIENT #2

- 45 year old male with CLL
- 12 days PTA URI, fever, increasing SOB
- CXR diffuse bronchiolitis
- RSV+ (LRI)
- Failed conventional therapy
- ADMA IVIG administered day 2 after RSV + diagnosis.

Patient clinically and symptomatically improved 3 days later.

PATIENT #3

- 2 year old female post BM transplant
- 3 days PTA cough, nasal congestion, increasing SOB
- CXR RUL consolidation
- RSV+ (LRI)
- Failed conventional therapy
- ADMA IVIG administered day 9 after RSV + diagnosis.

Patient clinically and symptomatically improved 2 days later.

SUMMARY FOR ADMA-IVIG (RI-002)

- Contains high neutralizing titers to RSV
- Prevents RSV pneumonia in normal and immune suppressed cotton rats
- Reduces viral load in the lungs and nasal tissue by 99.9% of infected animals
- When infused into human subjects there is a greater than 4 fold increase in RSV neutralizing titers in the serum.
- In compassionate use studies in 15 patients with RSV lower tract disease and progressive respiratory distress which was refractory to conventional treatment, administration of RI001 was associated with improved clinical outcomes in 11 patients.
- The above data suggests that this high titer ADMA RSV immune globulin product may be a useful adjunct for the treatment of RSV lower tract disease in the solid organ and bone marrow transplant population.

SUMMARY

RSV in the nasal tissue often progresses from mild upper respiratory tract disease to pneumonia which frequently is fatal. Highly effective antiviral agents are not available and current treatment options are limited. To determine whether high titer neutralizing antibody to RSV might be of benefit in this patient population we prepared a plasma derived, human polyclonal immune globulin using plasma obtained from donors tested for the presence of high levels of neutralizing titers to RSV. To ascertain whether this polyclonal RSV enriched pool of antibodies translated into in vivo efficacy we studied its ability to prevent and to treat infection in the cotton rat RSV model. For the protection model animals were injected with the investigational product, RI-002, 10% IVIG, ("ADMA IVIG"), and one day later, animals were infected intranasally with RSV/A/Long 105 PFU/ animal. Four days after infection with RSV, animals were euthanized and nose and lungs were harvested for viral titrations. Plaques were counted and viral titers were expressed as PFU per gram of tissue. The control group treated with saline had mean titers of ~4.7 Log10 PFU/g of tissue in the lungs and the experimental groups given 500, 750, and 1000 mg/kg had undetectable RSV viral titers in the lungs of all animals. The mean nasal titers were ~5 Log10 PFU/g of tissue on day 4 post-infection in the control animals whereas in animals given 1000 mg/kg titers were undetectable. Four of ten animals in the 500 and 750 mg/kg groups had titers near the limit of detection (mean 1.3 Log10 PFU/g tissue) and titers were undetectable in the remaining six animals. For the treatment model animals were infected with RSV and 24 hours later given RI-002. Treatment resulted in a greater than 99.9% reduction in viral load in the nasal tissue and the lung.This product was also used in a compassionate use study after receiving unsolicited requests for the use of ADMA IVIG in patients with progressive RSV disease unresponsive to conventional therapy . From April 2009 through February 2011,15 compassionate use patients aged 3 months to 71 years were treated with ADMA IVIG at a dose of 1,500 mg/kg followed by 750 mg/kg on day three. All patients were immunosuppressed and had evidence of lower respiratory tract infection. Many had been ill with RSV for days or weeks. Some patients had received ribavirin and/or palivizumab as well as standard IVIG. Pre and post infusion serum samples were obtained from 12 out of 15 compassionate use patients not administered palivizumab and all showed a > 4-fold rise in RSV neutralizing antibody between days 8-18 post infusion. The majority of these seriously ill patients had favorable outcomes and there were no reports of serious adverse events attributable to the study drug. Early administration of ADMA IVIG was associated with a significantly higher survival rate compared to those who received late treatment. These data support the further development of ADMA IVIG for the prevention and treatment of RSV disease in the immune suppressed and normal populations.

Annual Conference of the Canadian Blood and Marrow Transplant Group
June 11 to 14, 2014 • The Westin Nova Scotian • 1181 Hollis Street • Halifax, NS