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Polyclonal Human Intravenous Immune Globulin (IGIV) with High-Levels of RSV Neutralizing Antibodies: A Summary of Animal and Human Studies

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Respiratory syncytial virus (RSV) is a common cause of respiratory infections in children and adults. Despite infection control efforts, RSV not uncommonly infects immunocompromised individuals and can progress from upper respiratory tract disease to pneumonia which can be 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 infection in the cotton rat RSV 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 10^5 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 $\sim 4.7 \text{ Log}_{10}$ 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 $\sim 5 \text{ Log}_{10}$ 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 Log_{10} PFU/g tissue) and titers were undetectable in the remaining six animals. 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 population.