Evaluation of Trough Levels of Antibodies to 12 Serotypes of S. pneumoniae in a Phase III Clinical Trial in Patients with Primary Immunodeficiency (PID)

Troy R. Torgerson1, Jean-Laurent Casanova2, Ricardo Sorensen3, James Mond4, Charlotte Cunningham-Rundles5, Jordan Orange6

1 University of Washington and Seattle Children's Hospital, 2 The Rockefeller University Howard Hughes Medical Institute, 3 Louisiana State University, 4ADMA Biologics, 5 Mount Sinai School of Medicine, 6 Baylor College of Medicine

ABSTRACT

Background: Despite what appear to be protective levels of circulating IgG in the plasma of patients with PID, reconstituted with regular infusions of IgG, chronic upper airways infections remain a problem. We postulated that this could be due in part to insufficient circulating specific antibody concentrations to specific pathogens.

Methods: Fifty-four patients with PID were enrolled in a Phase III trial studying the efficacy of an IVIG that had high antibody titers to RSV and other respiratory viruses. Anti-Streptococcus pneumoniae antibody levels to 12 different pneumococcal serotypes were measured by ELISA at trough time points.

Results: The maximum fold increase compared to baseline observed in the antibody binding titers to the 12 different serotypes ranged from 1.73 to 6.97 fold and depended on the doses of IgG administered and the particular lot of IgG infused. There was variation in the trough levels of antibodies to S. pneumoniae while the trough levels of neutralizing antibodies to RSV remained stable. The data demonstrate that despite protective trough serum IgG concentrations of 1000mg/dL a significant portion of patients fall below the levels of anti-S. pneumoniae antibodies that are regarded as protective for invasive bacterial infections.

Summary: At some point during their infusions subjects had trough levels of circulating antibodies to at least 6 serotypes that fell below 1.3 µg/mL of specific anti-pneumococcal antibody. This might contribute to the chronic upper airway infections seen in the PID populations. Measuring specific anti-pathogen antibody concentrations in IgG to be used for the patients with PID is essential.

RESULTS

Observed anti-pneumococcal antibody titer (µg/mL) by serotype over time after infusion among all subjects. Mean (+/- S.E.)

Observed anti-pneumococcal antibody titer (µg/mL) by serotype over time after infusion among all subjects divided by dose regimen (> 500 mg/kg/dose vs. > 500 mg/kg/dose). Mean (+/- S.E.)

CONCLUSIONS

- 7 of 12 pneumococcal serotypes were observed to fall below "protective" levels at trough in a significant percentage of patients.
- The risk of titers falling below the "protective" level is directly correlated to the dose of IgG (>500 mg/kg/dose vs. <500 mg/kg/dose) and to the dosing frequency (q21 days vs. q28 days).
- Titer to pneumococcal serotype 4 do not reach protective levels at trough in most patients on therapy with RI-002. Pneumococcal serotype 4 has been characterized as a highly invasive serotype in a number of population-based studies of invasive pneumococcal disease.
- We hypothesize that the fall in pneumococcal titers below the "protective" level at trough may put some patients at risk of developing invasive pneumococcal disease. Some of this may be mitigated by dose and frequency of administration of IVIG.