Human Complement Serum Bactericidal Activity Following Vaccination in a Phase 2 Safety and Immunogenicity Study of a New Meningococcal Group A Conjugate Vaccine in Healthy African Toddlers Residing in the Meningitis Belt

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Background

Meningitis Vaccine Project

- The Meningitis Vaccine Project was created in June 2001 by a grant from the Bill & Melinda Gates Foundation as a 10-year partnership between WHO and PATH
- Goal of eliminating epidemic meningitis as a public health problem in sub-Saharan Africa through the development, testing, licensure, and widespread use of conjugate meningococcal vaccines

PsA-TT Study 002 - Phase II

- Randomized Blinded Controlled Comparison of:
  - Group A conjugate vaccine, PsA-TT
  - Licensed polysaccharide vaccine, ACWY PS (Menvecon)
  - N meningitidis influenza vaccine as control, Hib-TT
- Safety, Immunogenicity, Memory Induction and Antibody Persistence among African Toddlers
  - 12 to 23 months of age
- Recruitment completed at two sites (Sept.-Nov. 2006)
- 601 eligible toddlers received primary immunizations; 592 received booster immunizations (July-August 2007) after parental consent
- No significant safety issue, high compliance for blood sampling

Study PsA-TT 002

MVP Phase II – African Children 12 to 23 Months of Age

hSBA Evaluation of MVP Phase II PsA-TT 002

- Subsets of each vaccine group
  - 80 / 200 PsA-TT
  - 80 / 200 PS ACWY
  - 80 / 200 Hib-TT
- Subset selection
  - Representative across age
  - Blinding maintained throughout
- 4 week Post Immunization Sera
  - Evaluate proportion above thresholds 1:4 and 1:8
  - Reverse cumulative distribution curves
  - GMT

Results: Post immunization hSBA

PsA-TT induced higher titer bactericidal antibodies in a greater proportion of study participants than the control Hib-TT or the meningococcal polysaccharide vaccines

Methods - hSBA

- Microbroth end point assay
  - 25 ul diluted serum
  - Buffer: CMPS with Mg++, Glucose, Gelatin
  - 10 ul bacterial suspension (10 CFU/ul)
  - 10 ul pooled human complement (lots 11-13)
  - 0.01M Tris buffer, plates sealed, rocking, 37°C CO2
  - 30 ul TSA semi-solid agar + 25 ul second overlay
  - Overnight incubation at 37°C with 5% CO2
  - Titers = reciprocal of the highest dilution resulting in 90% or greater decrease in bacterial cell count compared to average in complement only wells

Complement Source

- CH100, IgA, IgM, anti-class 4 Ab
- rSBA
- Intrinsic killing of strain F8238
- Heat inactivated sample for ELISA and rSBA
- Aliquots (on ice) immediately frozen
- Heated at 37 oC for 15 min, centrifuged place on ice
- Race: 74 C; 21 B;  4 H;  1 NA
- Age: 18-77 Average = 41, Median = 42

Summary

- Human complement was obtained by pooling suitable sera from healthy adult blood donors screened for lack of functional antibodies to N. meningitidis strain F23B
- hSBA titers were successfully determined for a randomized subset of sera from study PsA-TT 002
- hSBA results indicate that PsA-TT induced functional serogroup A immune responses in a high proportion of African toddlers
- PsA-TT stimulated higher functional antibody responses by hSBA compared to PsACWY vaccine at 30 days post immunization
- These results are consistent with and support results obtained with rSBA and ELISA assays conducted on the total study coxsackie

Future Plans

- Continued evaluation of PsA-TT by hSBA:
  - Pre- and post immunization
  - Dose response
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  - Pre- and post immunization
  - Dose response
- Additional pooled human complement for hSBA:
  - Screening of blood donors
  - Additional screening of blood donors
  - Additional screening of blood donors
  - Additional screening of blood donors
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  - Additional screening of blood donors