B-501d

RSV F Protein Vaccine is Well-Tolerated and Immunogenic in Elders

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Abstract B-501d

Background: Viewed as a pathogen of children, respiratory syncytial virus (RSV) is now recognized as an important cause of morbidity in the elderly, especially those with underlying cardio-pulmonary disease. We evaluated 4 formulations of a recombinant RSV F protein vaccine in adults ≥ 60 years of age.

Methods: We enrolled 220 subjects randomized to one IM dose of 60 or 90µg of RSV F protein with or without $AlPO_4$ adjuvant; or placebo. All also received influenza vaccine (TIV), to mimic co-administration likely to occur in use. Safety was assessed using reactogenicity diaries, safety laboratory tests, and open-ended queries concerning changes in health. Immunogenicity parameters included anti-F protein IgG, neutralizing (MN) antibody titers against RSV/A and B viruses, and titers of antibodies to neutralizing antigenic site II measured by competition with labeled palivizumab and also direct binding to antigenic site II peptide.

Results: Mean ages in the treatment groups were 67.7 to 69.1 years; 15% were ≥ 75 y.o. The majority of subjects were Caucasian and men comprised 43% overall; 99% of subjects provided data through Day 56. Among placebo recipients 70% reported at least 1 adverse event (AE), compared with 58-75% of active vaccinees in various groups. Transient injection site pain was 15-20% more frequent in active vaccinees, but otherwise the vaccine safety profile differed little from placebo; the 1 serious AE occurred in the placebo group. Levels of serum anti-F IgG rose 3.1 to 5.6 fold, with best responses in recipients of 90µg with Al; and no change in placebo recipients. Serologic response rates in the Al-adjuvanted groups were 89-92%. Titers of IgG reactive with antigenic site II peptide rose 5.3 to 12.5-fold; and titers of antibodies competing with palivizumab rose 2.6 to 4.9-fold; response rates were 74-78% without Al and 97.4% with adjuvant. Increases in RSV/A and B MN titers were less dynamic, but best responses occurred in subjects with low baselines (rises of 1.7 to 2.4-fold). Changes in all measures of RSV antibody were positively correlated. HAI responses to TIV were unaffected by co-administration of RSV vaccine.

Conclusions: RSV F vaccine is compatible with TIV co-administration, well-tolerated by elders, and elicits increases in antibodies with potentially protective specificities. Further evaluation is planned.

Background

- RSV disease in the elderly lacks the well-defined clinical syndrome of influenza, but can be a substantial contributor to hospitalization rates in this population, in whom it often presents as an exacerbation of pre-existing cardio-pulmonary disease (1,2)
- Novavax is developing an RSV F protein-based nanoparticle vaccine; near-full length F protein is expressed in *Sf*9 insect cells using recombinant baculovirus.
- In young adults, the vaccine induces anti-F IgG, IgG antibodies binding to antigenic site II peptide, antibodies which compete efficiently with palivizumab for binding to F protein, and significant neutralizing responses (3).
- The vaccine has potential application in pediatrics, in maternal immunization programs, and the elderly.

Study Objectives

- To describe the safety in subjects ≥ 60 y.o. of the RSV F protein vaccine, at 60 or 90µg doses, with or without aluminum phosphate, and co-administered with standard dose, licensed trivalent inactivated influenza vaccine (TIV).
- To describe the immunogenicity of the RSV F vaccine, at 60 or 90µg doses, with or without $AlPO_4$, based on anti-F IgG units, palivizumab-competitive antibody titers, IgG titers specific for RSV F antigenic peptide II, & microneutralization titers.
- To determine whether the RSV vaccine interferes with the immunogenicity of co-administered TIV.

Study Methods

- The protocol and study documents were reviewed and approved by an appropriately constituted institutional review board; all subjects gave written informed consent.
- Design was randomized, age-stratified, and observer-blinded.
- ELISAs were performed by Novavax as described (3).
- RSV microneutralization (MN) assays were performed at the Baylor College of Medicine as previously described (4).
- Influenza hemagglutination-inhibition (HAI) assays were performed at Novavax essentially as per the WHO method.
- Operators for assays were blinded to subject treatments.

Demography and Treatments

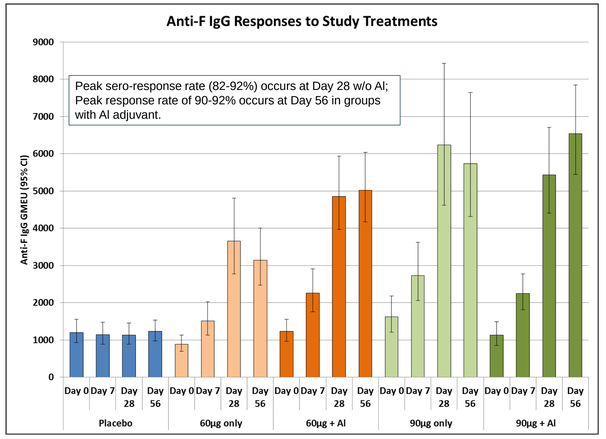
Group	E	A	B	C	D
RSV F	0 (placebo)	60	60	90	90
$AlPO_4$	No	Yes	No	Yes	No
N	60	40	40	40	40
Age (yrs)					
Mean	69.1	69.1	67.7	68.0	68.7
Median	68.0	68.0	67.0	68.0	68.0
% ≥75	15	15	15	15	15
Male/female	37/63%	45/55%	40/60%	53/47%	42/58%
Mean BMI	27.4	28.5	27.7	29.6	27.6

Key Safety Outcomes

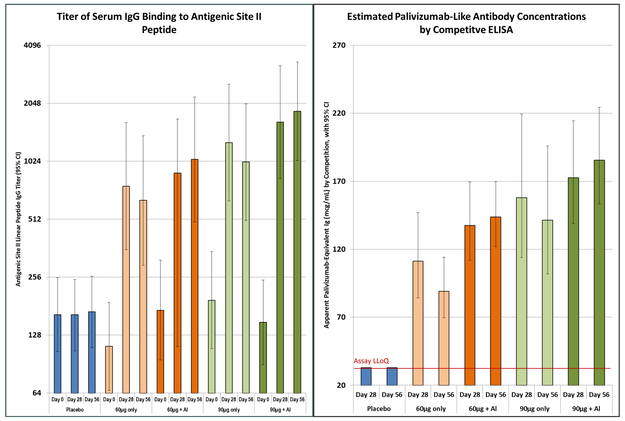
Group	E	A	B	C	D
RSV F	0 (placebo)	60	60	90	90
$AlPO_4$	No	Yes	No	Yes	No
N	60	40	40	40	40
Completed D56	59	40	39	40	40
Adverse Events*					
Any	42 (70%)	30 (75%)	25 (63%)	27 (68%)	23 (58%)
Solicited AEs	28 (47%)	22 (55%)	12 (30%)	21 (53%)	19 (48%)
Local Sol. AEs	14 (23%)	17 (43%)	9 (23%)	17 (43%)	15 (38%)
Systemic Sol. AEs	22 (37%)	12 (30%)	6 (15%)	16 (40%)	10 (25%)
Severe Sol. AEs	1 (2%)	1 (3%)	0	0	0
Unsolicited AEs	31 (52%)	18 (45%)	19 (48%)	16 (40%)	16 (40%)
Severe & related AEs	2 (3%)	0	0	0	0
Serious AEs	1 (2%)	0	0	0	0

* Tabulated values are counts of subjects with one or more events per category; parenthetic values are % of treatment group
Local solicited AEs are primarily transient injection site pain, systemic solicited AEs included primarily myalgia, arthralgia, headache and fatigue.

Immunogenicity Outcomes



Immunogenicity Outcomes



Additional immunologic endpoints:

- RSV microneutralizing GMTs rose modestly, 1.3-1.5 fold for RSV/B and 1.5-1.7-fold for RSV/A.
- The increases in RSV MN titers correlated with anti-F responses, and were greatest in those with low baselines
- TIV responses, as measured by post-immunization HAI seroconversions and GMTs, were *entirely unaffected by RSV F co-administration.*

Conclusions

- RSV F protein nanoparticle vaccine was well-tolerated in the elderly
- Co-administration of RSV F nanoparticle vaccine had no negative impact on responses to TIV.
- Anti-F IgG and immune responses to neutralizing antigenic site II were readily demonstrated
- Continued development of this vaccine in elders is warranted

1. Zhou H, et al. Clin Infect Dis 2012; 54:1427.
2. Falsey AR, et al. N Engl F Med 2005; 352:1749
3. Glenn GM, et al. Vaccine 2013; 31:524
4. Piedra PA, et al. Vaccine 2003; 21:3479