Assessment of 23-Valent Pneumococcal Vaccine Response in Critically-ill Burn Patients

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BACKGROUND & PURPOSE

• Administration of the pneumococcal polysaccharide 23-valent vaccine (PPSV-23) to qualified patients prior to hospital discharge is a standard of care and deemed a core measure by the Centers for Medicare and Medicaid Services.

• Many institutions immunize acutely ill patients including the critically ill.

• No evidence exists to support the effectiveness or safety of this practice.

• Both a high level of inflammation and/or the compensatory anti-inflammatory response in critically ill patients may result in a dysregulated immune phenotype.

• Both animal and human studies confirm an immune-depressed state following large total body surface area (TBSA) burn injuries evidenced by down regulation of immune signaling genes, decreased circulating dendritic cells, decreased monocyte human leukocyte antigen-DR, and derangements in cytokine production.

• The purpose of this study is to assess immunogenicity and safety of PPSV23 in critically-ill burn patients when given within the first 6 days of admission.

METHODS

Open-label prospective study

Admission to Burn ICU
• >10% TBSA burn
• Expected >14 day ICU stay

Risk factor requiring PPSV23 administration prior to discharge
• Exclusion: organ or bone marrow transplant, HIV, known immune deficiency.

Blood Draw Study Day 0
• Baseline C-reactive protein
• Baseline Cortisol
• Pre-vaccination serotype-specific IgG levels

PPSV23 administered after sample collection

Blood Draw Study Day 14-35
• Post-vaccination serotype-specific IgG levels
• Sample processed for opsonophagocytic kill assay

Primary Immunogenicity Endpoints

• Proportion of responders by ‘absolute’ IgG concentration >1.3 mcg/mL = 0.938 (95% CI: 0.71-0.99)

• Proportion of responders by ‘relative’ IgG increase >4 fold baseline = 0.688 (95% CI: 0.44-0.96)

• Each vs historic control (% positive response): p>0.1

SECONDARY IMMUNOGENTICITY ENDPOINTS

• Proportion of responders by ‘absolute’ IgG concentration >1.3 mcg/mL = 0.938 (95% CI: 0.71-0.99)

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CONCLUSIONS

• ‘Absolute’ response, defined as a serotype-specific IgG concentration of >1.3 mcg/mL in 10 of the 14 measured, and ‘relative’ response, defined as a 4 fold increase in serotype-specific IgG, was not statistically different than an expected 80% proportional response.

• Short term titer response was greater than expected. No correlations were noted by anpipli analysis. Post-hoc multivariate analysis revealed trends that require further assessment.

• Critically ill burn patients exhibit a response to PPSV23 despite belief they are immune-depressed. This may provide insight into patient ability to respond to a T-cell independent antigen challenge.

• Serotype-specific IgG functionality and durability remains unknown.

• Few adverse events were identified.

• PPSV-23 appears safe in this population.

• Further study in various critically ill populations is needed to define vaccine effectiveness and better describe response to antigen challenge.

LIMITATIONS

• Lack of a prospective control

• Analyzed relative to published historic data

• Small sample size

• Uncertainty in interpatient, safety

• Functionality and durability of measured IgG not assessed

• Variable for opsonophagocytic kill assay, durability unknown

• Greater than expected response rate

• Difficult to correlate responders by logit model, therefore post-hoc multiple linear regression utilized for future follow-up

• Biomarkers of immune function not assessed

• Further study is needed in critically ill populations

ACKNOWLEDGMENTS

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REFERENCES


Table 1: Enrollment characteristics (N=16)

<table>
<thead>
<tr>
<th>Age, y, median</th>
<th>40 ± 12</th>
</tr>
</thead>
<tbody>
<tr>
<td>Sex, male, n (%)</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Weight (kg), mean ± SD</td>
<td>77 ± 20.3</td>
</tr>
<tr>
<td>Current smoker, n (%)</td>
<td>9 (56)</td>
</tr>
<tr>
<td>Known alcohol dependence, n (%)</td>
<td>8 (50)</td>
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<tr>
<td>TBSA, %, median (IQR)</td>
<td>20 (15-25.6)</td>
</tr>
<tr>
<td>Cortisol (mg/dL), median (IQR)</td>
<td>15.85 (6.5-21)</td>
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<tr>
<td>CRP (mg/dL), median (IQR)</td>
<td>10.85 (5.0-21)</td>
</tr>
</tbody>
</table>

Table 2: Immunogenicity - Patient Response Meeting Criteria

| Pneumococcal Capsular Serotypes | 3, 4, 9N, and 12F had lowest median ‘absolute’ response; Pneumococcal Capsular Serotypes 5 and 12F had lowest median ‘relative’ response (Table 3) |

Table 3: Select: Pneumococcal serotype specific IgG Concentrations

<table>
<thead>
<tr>
<th>Pneumococcal serotype specific IgG Concentrations</th>
<th>Absolute</th>
<th>Median Post IgG Concentration (mcg/mL)</th>
<th>Fold Increase (Post/Pre)</th>
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<tbody>
<tr>
<td>PN type 3</td>
<td>2.37</td>
<td>21</td>
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<tr>
<td>PN type 4</td>
<td>2.68</td>
<td>10</td>
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</tr>
<tr>
<td>PN type 9N</td>
<td>2.40</td>
<td>10</td>
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<tr>
<td>PN type 12F</td>
<td>1.11</td>
<td>3.5</td>
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<tr>
<td>PN type 5</td>
<td>16.5</td>
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</tbody>
</table>

Figure 1: PPSV-23 Response by Serotype-specific IgG levels in 10 of 14 (‘absolute’ and ‘relative’)