Macrolide treatment for “chlamydial asthma”: Evidence for enrollment bias in an effectiveness trial

A WREN Study

DL Hahn, M Grasmick, S Hetzel
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What this talk covers

- Rationale for macrolide treatment for asthma
  - Atypical infections are common and causal
- Definition of effectiveness trials in asthma
  - Currently lacking for guideline therapies
- Results of current RCT: AZMATICS
  - Challenges to external validity
Rationale for macrolide treatment

- Atypical infection potentially causal
  - Inception
  - Severity
- *C. pneumoniae*
  - Attributable risk ~50%
    - Seroepidemiology
    - PCR from BAL
    - Treatment trial results
Rationale for macrolide treatment

Secondary Outcomes of a Pilot Randomized Trial of Azithromycin Treatment for Asthma

David L. Hahn¹, Mary Beth Plane², Olaimatu S. Mahdi³, Gerald I. Byrne³

Clinically significant improvement*: 53% v 13% (P=0.03)
*≥1 unit AQLQ increase and/or ≥50% rescue BD decrease
Effectiveness: Definition

- Externally valid
- Internally valid
- Patient-oriented outcomes
- Preferably long term
Effectiveness trials in asthma

Management of Chronic Asthma

Future Research

The following future research priorities are recommended:

- The overriding priority is to develop a national research agenda for long-term studies to improve the effectiveness of asthma management. Short-term drug efficacy studies are over-represented in the present literature. It is imperative to develop an evidence base that supports clinical decisionmaking on the intensity of treatment, optimization of medication regimens, and utility of disease management interventions for various asthma populations.

AZMATICS: Design

- Long term (1-yr) effectiveness trial
- Adjunctive azithromycin (weekly for 12 weeks)
- Patient-oriented outcomes (sx, QOL, control, med use etc)
- Final outcome assessment (48 weeks)
  - Long after active treatment was completed
  - “Anti-inflammatory” mechanism not plausible at 24-48 weeks
AZMATICS: Challenges

- “Approved but not funded”: NIH
- Internet enrolment & follow up
  - Low cost
  - PBRNs, voluntary, nationwide
  - Patient-reported outcomes
  - Motivated (+), uncompensated (+/-), unsupervised (-)
  - No biomarkers, no PFTs, limited staff (-)
AZMATICS: Challenges

- Eligibility limited
  - Internet-savvy subjects

- Unanticipated effects of Clinical Trial registration*
  - Self-referral via Internet
    - <clinicaltrials.gov>; <asthmastory.com>
    - Prior experience with azithromycin (see email)

- Open-Label (OL) arm implemented

*Hahn DL. An unanticipated effect of clinical trial registration. BMJ online at http://www.bmj.com/cgi/eletters/325/7376/1314#178926 2007.
Fig. 1: Accrual by Month
Drug Compliance

Percent of Compliance

Week

<table>
<thead>
<tr>
<th>Week</th>
<th>Percent of Compliance</th>
</tr>
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<tbody>
<tr>
<td>1</td>
<td>98.51</td>
</tr>
<tr>
<td>2</td>
<td>100</td>
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<td>3</td>
<td>100</td>
</tr>
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<tr>
<td>11</td>
<td>95.38</td>
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<tr>
<td>12</td>
<td>89.66</td>
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### Baseline characteristics

<table>
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<tr>
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<th>Randomized N=75</th>
<th>Open Label N=22</th>
<th>P-value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, median, Min-max</td>
<td>47 20-80</td>
<td>48 22-77</td>
<td>0.73</td>
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<tr>
<td>Gender, %M</td>
<td>68%</td>
<td>45%</td>
<td>0.08</td>
</tr>
<tr>
<td>Smoking, % Curr/Prev/No</td>
<td>15%/41%/44%</td>
<td>0%/27%/73%</td>
<td>0.03</td>
</tr>
<tr>
<td>Chronic Sinusitis, %</td>
<td>33%</td>
<td>77%</td>
<td>0.0004</td>
</tr>
<tr>
<td>ST, % 0/1-3/4+, %</td>
<td>53% 8%/19%/72%</td>
<td>86% 32%/42%/26%</td>
<td>0.006  0.004</td>
</tr>
</tbody>
</table>
## Baseline characteristics

### Asthma severity

<table>
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<th>Randomized</th>
<th>Open Label</th>
<th>P-value</th>
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</thead>
<tbody>
<tr>
<td></td>
<td>N=75</td>
<td>N=22</td>
<td></td>
</tr>
<tr>
<td>Hospitalized</td>
<td>3%</td>
<td>9%</td>
<td>0.02</td>
</tr>
<tr>
<td>Previous 2y</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td></td>
<td>64%/28%/8%</td>
<td>32%/36%/32%</td>
<td>0.01</td>
</tr>
<tr>
<td>Day Severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild/Mod/Sev</td>
<td>12%</td>
<td>50%/18%/32%</td>
<td>0.02</td>
</tr>
<tr>
<td>Night Severity</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mild/Mod/Sev</td>
<td>51%/37%/12%</td>
<td>50%/18%/32%</td>
<td></td>
</tr>
</tbody>
</table>
Asthma symptom frequency

Randomized subjects

Open-label subjects
Results
Improved v Not Improved

Subjects with no increase in controller medication use:
≥1 unit increase in AQLQ and/or ≥50% decrease in rescue bronchodilator medication use

* P=0.017
Summary

- Subjects with severe treatment-resistant asthma - who declined to be randomized - demonstrated clinically important improvement lasting at least 6 months after completing open-label azithromycin.

- Subjects with milder asthma - who agreed to randomization - did not demonstrate comparable benefit.
Strengths

- Effectiveness RCT design
- Remarkable completion rate given lack of resources
- Demonstrates feasibility of effectiveness RCTs in community practices/primary care
Limitations

- No objective markers
  - Biomarkers
  - Pulmonary function
- Completion <80%
- Underpowered for subgroup analyses
Conclusions

- The results of this trial are inconclusive.
  - “Open label” results were due to placebo effects OR
  - The RCT was biased towards a null effect because of systematic (self-) exclusion of subjects most likely to benefit.

- In AZMATICS, this “enrollment bias” was unanticipated and accounted for.

- In NIH clinical trials, “enrollment bias” is purposeful, unaccounted for, and results in degraded guideline treatment recommendations.
Guideline treatment trials: Lacking external validity

Typical exclusions:
- No comorbidity
- FEV1 50-85 %predicted
- \( \geq 12\% \) reversibility
- Current non-smoking
- Past hx <10 pack years

Additional exclusions:
- Being symptomatic
- Regular use of inhaled steroids

Herland et al. How representative are clinical study patients with asthma or COPD for a larger “real life” population of patients with obstructive lung disease?. Respiratory Med 2005; 99:11-19
Guideline treatment trials: Lacking external validity

The proportion of people with asthma eligible for the major RCTs (n=17) cited in the Global Initiative for Asthma (GINA) guidelines.

- **Current asthma**
  - Eligible: 96%
  - Ineligible: 4%

- **Current asthma on treatment**
  - Eligible: 94%
  - Ineligible: 6%

Travers et al. External validity of randomised controlled trials in asthma: to whom do the results of the trials apply?. Thorax 2007;62:219-223
Guideline treatment for asthma is inadequate

Asthma prevalence = 6.1% (France, Germany, Italy, Spain and UK, 2008)

Demoly et al. Update on asthma control in five European countries. Eur Respir Rev 2010
Guideline treatment for asthma is inadequate

Not Well Controlled asthma (vs Controlled asthma):

- More activity limitations (40.8% vs 1.5%)
- More breathlessness ≥3 times weekly (72.5% vs 5.4%)
- More sleep difficulties ≥1 times weekly (60.3% vs 4.6%)
- More rescue medication ≥2-3 times weekly (77.4% vs 15.9%)
- More healthcare utilization (17.4% vs 9.9%)
- More absenteeism (12.2% vs 5.5%)
- More work impairment (30.0% vs 15.4%)
- Decreased quality-of-life (P<.001)

Demoly et al. Update on asthma control in five European countries. Eur Respir Rev 2010
Guideline treatment is ineffective in smokers

No patient-oriented benefits of inhaled steroids in smokers

- Lazarus et al. Smoking affects response to inhaled corticosteroids or leukotriene receptor antagonists in asthma. *Am J Respir Crit Care Med* 2007;175:783-790.
Guideline treatment is also less effective in non-smokers with severe asthma*

Severe (versus Not Severe) Asthma associated with:

• Steroid resistance.
• More pneumonia.
• Fewer eosinophils and less skin test positivity.
• Longer disease duration.
• Lower lung function.

These are all characteristics of *Chlamydia*-associated “infectious asthma.”
