MACROLIDE TREATMENT FOR "CHLAMYDIAL ASTHMA": EVIDENCE FOR ENROLLMENT BIAS IN AN EFFECTIVENESS TRIAL

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Context: Increasingly robust *in vitro*, animal model, epidemiological and clinical evidence supports macrolide treatment for chlamydia-associated asthma, characterized by increased severity, steroid resistance, concomitant chronic bronchitis and/or COPD (i.e., the "overlap syndromes" that have been systematically excluded from US asthma treatment trials). Another challenge when performing effectiveness randomized clinical trials (RCTs) for "chlamydial asthma" is off-study treatment sought by severely affected patients. **Objectives:** To assess the impact of off-study macrolide treatment on the generalizability of RCT results. **Design:** RCT with an open-label (OL) arm for eligible subjects who declined randomization. **Setting:** Primary care practices throughout North America. **Patients:** 96 adults with persistent asthma and reversible airway obstruction, of whom 22 (23%) elected the OL arm. **Intervention:** Azithromycin (600 mg) or placebo, daily for 3 days, then once weekly for 11 weeks as an adjunct to usual care. Outcomes were assessed until 48 weeks post-randomization. **Main and Secondary Outcome Measures:** *Main:* asthma symptoms. *Secondary:* asthma quality of life (AQLQ) and asthma control (ACQ). **Results**: *Baseline:* compared to randomized subjects (n=74), OL subjects (n=22) reported greater asthma severity (P=0.03), higher frequency of asthma initiation after an acute lower respiratory tract illness (P=0.04) and more chronic sinusitis (P<0.001). Most OL subjects also reported temporary asthma remission after prior conventional azithromycin treatment for unrelated illnesses. *Outcomes:* there were few significant differences for any outcome between subjects randomized to azithromycin or placebo (RCT groups). Compared to the RCT groups at 6 months after treatment completion, OL subjects demonstrated persistent clinically and statistically significant improvements in symptoms (P=0.001), AQLQ (P=0.003) and ACQ (P=0.005). **Conclusions**: Compared to randomized subjects, the OL group had more severe disease and a greater likelihood of long-lasting treatment benefit. Future asthma macrolide effectiveness RCTs should focus on more severe asthma, and should include an open-label arm as an external validity control to mitigate the risk of "enrollment bias."