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Challenges in assessing the efficacy of systemic corticosteroids for severe wheezing episodes in preschool children

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Challenges in Assessing the Efficacy of Systemic Corticosteroids for Severe Wheezing Episodes in Preschool Children

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Summary

This letter addresses the controversial issue of the use of oral corticosteroids during wheezing exacerbations in preschool-aged children by demonstrating findings of a prematurely terminated multi-center clinical trial, discussing lessons learned, and suggesting future directions.

Keywords

Preschool Wheezing; oral corticosteroids; multi-center clinical trial; Preschool-aged Children; efficacy; Lower respiratory tract infections

To the Editor:

Children with episodes of severe wheezing are often treated with oral corticosteroids (OCS) based on their efficacy in the management of asthma in older children. However, the benefit of OCS use remains unclear[1, 2], and the adverse reactions have been well described[3]. Thus, identifying which children with recurrent wheezing most likely to benefit from OCS use during acute severe wheezing episodes is warranted.

OCELOT (**O**ral **C**orticosteroids for treating **E**pisodes of significant **LO**wer respiratory **T**ract symptoms) was a multi-site clinical trial conducted by AsthmaNet to assess the efficacy of OCS in preschool-aged children with recurrent severe wheezing. OCELOT and its companion trial, APRIL (**A**zithromycin for **P**reventing the development of upper **R**espiratory tract **I**llness into **L**ower respiratory tract symptoms in children)[4] were two separate but linked trials conducted in 607 children 12-71 months of age with a history of clinically significant wheezing in the prior year (Online supplement E-Figure 1). These studies began enrollment in April 2011. The APRIL trial examined the efficacy of the macrolide azithromycin versus placebo administered at the early signs of a respiratory tract illness (RTI)[4]. **OCELOT** was a randomized, double-blind, placebo-controlled trial (RDBPCT) in children enrolled in the APRIL trial, who were randomized to receive either OCS (prednisolone 1mg/kg twice daily for 5 days, maximum dose 60mg/day) or placebo when an RTI had progressed to a significant lower respiratory tract illness (LRTI).

Families were instructed to contact either the study staff during the day or a centralized phone triage center after hours when the child had specific LRTI symptoms, including respiratory symptoms that had not improved after 3 albuterol treatments in 1 hr, or if symptoms required 2 albuterol treatments within 4 hrs, or if 7 or more albuterol treatments were used in 24 hrs, or for concerning cough or wheeze for several days. Nurses at the phone triage center utilized an algorithm to determine the appropriateness of initiating OCELOT therapy, followed by research physician confirmation by telephone. Albuterol and blinded trial medications were available at home, and OCELOT therapy was started based upon this telephone assessment. The primary outcome measure of OCELOT was the Pediatric Respiratory Assessment Measure (PRAM) score (score range 0-12)[5] 15 minutes post-bronchodilator, measured in the AsthmaNet clinic by a physician 36-72 hrs after the initiation of OCELOT medication. Trial participation was terminated after one course of OCELOT therapy and then discharge care plan was prescribed by the research physician. Parents received asthma education and customized action plans.

149 out of 607 children enrolled in the APRIL trial received either OCELOT treatment or open-label OCS during the trial, and these occurred under one of four conditions (Figure 1). A total of 61 children received OCELOT treatment in a per-protocol fashion, while 88 received open-label OCS as part of clinical care outside of the trial (early terminators). Given the high rate of off-protocol use of open label OCS, combined with a small number of children managed per-protocol and the potential for selection bias of children with more severe episodes being managed with open-label OCS by providers outside the trial, the OCELOT Data Safety and Monitoring Board (DSMB) recommended premature termination of the trial due to lack of feasibility in April 2013. Thus, the primary outcome was not able

to be evaluated. However, several important observations from the conduct of this trial warrant discussion and future consideration.

Compared to children treated per-protocol, children that received open-label OCS were more likely to have at least one positive aeroallergen skin prick test, higher IgE, higher blood eosinophils, higher asthma-related hospitalization rate in year prior to enrollment, and/or self-report Black race at baseline (Table 1). However, both groups of children had similar rates of OCS courses and ICS use in the year prior to enrollment (Table 1). This suggests that children that received open-label OCS may have been predisposed to experience a LRTI that rapidly progressed in severity due to greater baseline markers of type 2 inflammation and prior severe episodes requiring hospitalization. These children also share several of the criteria that predict wheezing exacerbations in children with asthma[6, 7].

Of the 61 children treated per-protocol, 54 had PRAM scores recorded and 92.6% had mild symptoms (score < 4) at 36-72 hrs. During the visit, 27.8% had wheezing, 20.4% had poor air entry, 3.7% had suprasternal retractions, and the mean oxygen saturation in room air was 97.1%. Oral corticosteroids may be more effective in treating children with more severe respiratory symptoms during LRTIs; however, this could not be evaluated because severity of the index episode could not be objectively evaluated. Adverse events reported within 4 days of initiation of OCELOT therapy included otitis media (1 participant), acute bronchitis (1), asthma exacerbation (3), respiratory abnormality (1), fever (1), chest pain (1), vomiting (1), and pneumonia (1).

Although OCELOT was carefully designed by the AsthmaNet Steering Committee and reviewed by clinical trials experts, including the NHLBI Protocol Review Committee and DSMB, the FDA, and numerous IRBs, we encountered several problems that proved more challenging to deal with than we anticipated. The major barrier was frequent use of open-label OCS despite careful informed consent with parental education to encourage communication with research staff during illness, written action plans, letters about trial medications to the primary care physician and for the parents to bring to the emergency department, and real-time support from triage nurses and experienced research personnel. The fact that OCELOT was the first OCS efficacy trial that employed a sequential trial design may have exacerbated these challenges by generating parent- or provider-perceived ineffectiveness of the first trial medication (APRIL treatment). This may have led them to seek open-label OCS rather than to begin the OCELOT blinded treatment as OCS were considered the accepted treatment for preschool wheezing at the time this study was conducted. There also may be a rapid course due to the child's inability to report symptoms and the parents' inability to detect symptoms in these young children that leads to a more rapidly evolving course that does not allow time for an effective intervention at this stage of severity. Furthermore, the equipoise of this trial was compromised by the inertia of clinical practice relying on OCS treatment as the standard for rescue during such episodes rather than allowing for conduct of a placebo-controlled evaluation, despite the relatively low PRAM score these children exhibited at 36-72 hours of their LRTI.

There are several lessons and implications for future studies. Ultimately, there remains a significant need to conduct efficacy trials evaluating OCS treatment in preschool-aged

children with recurrent wheezing[8] targeting specific phenotypes. Large observational and pragmatic trials may provide valuable additional data on the comparative effectiveness and safety of OCS in this population. It may be useful to compare OCS in a RDBPCT to another active therapy such as high-dose ICS or azithromycin given at doses previously shown to be effective in preschool-aged children. Children would be stratified by clearly defined clinical phenotypes that predict future wheezing LRTI and response to these therapies[9]. Finally, it may be helpful to conduct this study in a clinical setting to confirm that protocol-defined criteria for OCS intervention are met.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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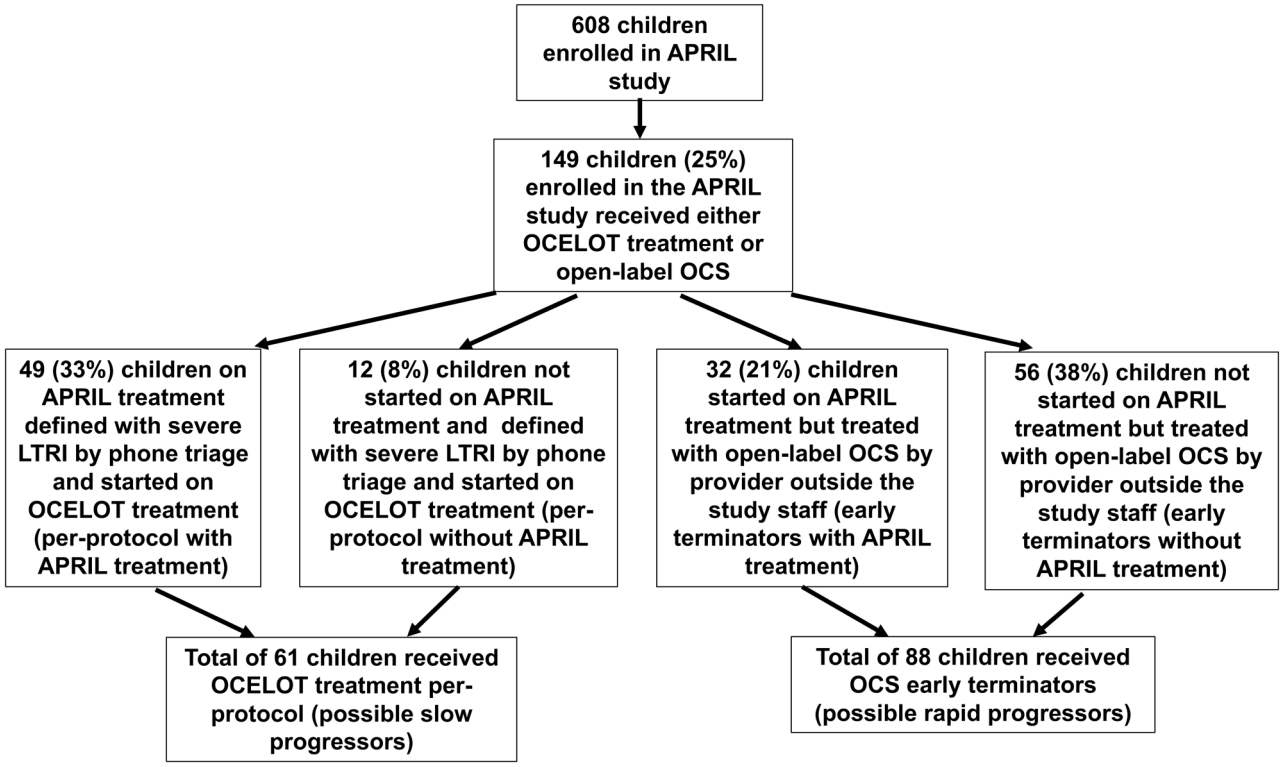

Figure 1.

Number of participants enrolled in OCELOT (Oral Corticosteroids for treating Episodes of significant LOwer respiratory Tract symptoms) trial that received OCELOT treatment (per-protocol) or open-label oral corticosteroids (OCS) outside of the trial (termed early terminators) with or without APRIL treatment.

Table 1.

Baseline Characteristics at Enrollment

Baseline Characteristic	Early Terminators n=88*	Per-Protocol n=61*
Age – mos-mean (+/− SD)	41.1 (+/− 16.2)	40.3 (+/− 16.8)
Gender – males n (%)	60 (68.2%)	41 (67.2%)
Family reported race– n (%)		
White	59 (67%)	44 (72.1%)
Black/African-American	19 (21.6%)	8 (13.1%)
Other	4 (4.6%)	1 (1.6%)
More than 1 race reported	6 (6.8%)	8 (13.1%)
Family reported ethnicity – n (%)		
Hispanic/Latino	27 (30.7%)	16 (26.2%)
Family Reported Highest Education Level		
No highschool diploma	4 (4.5%)	1 (1.7%)
GED or Highschool diploma	13 (14.8%)	5 (8.8%)
Post-highschool education	71 (80.7%)	51 (89.5%)
Family reported income – n (%)		
<$25,000	19 (21.6%)	16 (27.6%)
$25,000-$49,999	19 (21.6%)	14 (24.1%)
$50,000-$99,999	22 (25%)	17 (29.3%)
$100,000 or more	20 (22.7%)	11 (19.0%)
Number of asthma-related hospitalizations in the past year - mean (+/− SD)	0.25 (+/− 0.44)	0.16 (+/− 0.37)
Number of OCS courses in the past year - mean (+/− SD)	1.17 (+/− 0.96)	1.36 (+/− 1.11)
ICS use in the past year - n (%)	22 (25%)	26 (42.6%)
≥ 1 positive aeroallergen sensitivity - n (%)	46 (54.1%) n=85	22 (36.7%) n=60
Serum IgE – median kU/L (quartile range)	115.8 (19.7, 307.6) n=81	77.6 (14.5, 190.5) n=56
Blood eosinophils - median % (quartile range)	3.8 (2, 6.15) n=84	3 (1.4, 5) n=58

*Unless different sample sizes noted below