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Emerging Therapies in the Treatment of Early Childhood Wheeze

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Phenotypic variation in asthma, especially early childhood asthma, is increasingly recognized. Although inhaled corticosteroids are recommended as first-line therapy, it has less efficacy in controlling intermittent wheeze due to viral-induced symptoms in early childhood. This article reviews 2 emerging therapies in particular for early childhood wheeze: azithromycin and bacterial lysate therapy. Azithromycin's effects are both antibacterial and anti-inflammatory, and it has been shown in 2 studies in preschoolers to prevent progression to severe respiratory tract infection and decrease duration of wheeze. Bacterial lysates work at multiple stages in the innate and adaptive immune response and have been shown to decrease mean wheeze duration in particular in the preschool age. More research is required although both therapies offer a promising future approach, in particular in the nonatopic preschool wheezer, as we move toward a more personalized approach to childhood asthma.

Keywords: asthma, asthma medications, childhood, wheeze

Introduction

Asthma is the most common chronic disease of childhood.[1] Asthma also has 1 of the top 10 highest rankings for disability-adjusted life years in school-aged children.[2] Asthma begins in early childhood,[3] and complications of asthma, including airway remodeling, can begin in the early preschool years.[4]

Multiple international guidelines recommend the use of daily inhaled corticosteroids (ICS) in children of any age with symptoms of asthma.[5,6] However, response to ICS therapy varies, with atopic characteristics predicting a favorable response.[7,8] As a result, less is known about how to treat phenotypically nonatopic or ''neutrophilic'' asthma in children. In addition, ICS therapy, although effective at day-to-day symptom control, has shown less efficacy in controlling intermittent wheeze due to infection-induced symptoms in the preschool-aged group, colloquially termed ''viral wheeze.''[9–11]

Children have an average of 6–8 acute respiratory tract infections (ARTIs) per year,[12] which are a leading cause of intermittent wheeze/asthma exacerbations. Although viral infections remain the most common triggers of wheezing episodes in early childhood (hence the term ''viral wheeze''),[13] it is also recognized that bacterial infection is a common cause of intermittent wheeze and asthma exacerbations; nasal samples have shown bacteria such as *Streptococcus pneumoniae* and *Moraxella catarrhalis*, among others.[14,15] In fact, it has been noted that airway bacteria are equally likely as viral infection to be associated with asthma exacerbations or intermittent wheezing episodes especially in early childhood, and that bacterial and viral infection can occur together.[14]

In light of increasing recognition of phenotypic variation within asthma in childhood, as well as lack of evidence around the treatment of wheezing episodes that are largely related to ARTIs, there is a need for new therapies to address this knowledge gap in early asthma treatment. The goal of this review is to discuss 2 emerging therapies that may have a role in treatment and prevention of ARTI-associated wheezing, especially in early childhood.

Azithromycin

Azithromycin's effects are antimicrobial but also anti-inflammatory, and both these effects may play a role in the treatment of childhood wheeze. Azithromycin decreases neutrophilic airway inflammation, potentially through the mechanism of modulation of interleukin (IL)-8 production.[16]

There have been 2 studies that have looked at the use of azithromycin in the treatment of early childhood wheeze. The Early Administration of Azithromycin and Prevention of Severe Lower Respiratory Tract Illnesses in Preschool Children (APRIL) study randomized 607 children aged 12–71 months with recurrent severe wheeze with ARTIs to

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azithromycin (12 mg/kg per day for 5 days) or placebo at the start of symptoms usually associated with the development of ARTIs in the child.[17,18] Children were eligible for enrollment if they were on low-dose ICS monotherapy but stopped their controller medication upon study entry, consistent with recommendation for step-down therapy. Over a 12–18 month period, there was a significant reduction in the progression to a severe respiratory tract infection (defined as triggering prescription of oral corticosteroids) compared with placebo (hazard ratio 0.64; confidence interval [95% CI] 0.41–0.98; $P = 0.04$). There was no significant difference in treatment effect based on atopic status. Adverse events, including antibiotic resistant organisms, were rare.

Another study from the Copenhagen Prospective Studies on Asthma in Childhood (COPSAC) birth cohort randomized 72 children aged 1–3 years with recurrent asthma-like symptoms to azithromycin (10 mg/kg per day for 3 days) or placebo.[19] Supplemental therapy for these troublesome lung symptoms in the study included montelukast for children who had previously benefited from it, ICS therapy, and/or oral corticosteroids for severe episodes at the discretion of the attending physicians. For the 158 asthma-like episodes during the 4 years of study, there was a 63% (95% CI: 56.0–69; $P < 0.0001$) reduction in average number of symptom days with azithromycin compared with placebo. In addition, the effect size increased if treatment was initiated early. For example, there was an 83% reduction in average episode duration if treatment was initiated before day 6 of symptoms compared with a 36% average reduction if treatment was initiated after day 6. No difference in adverse events was noted between groups, but antibiotic resistance was not specifically examined. Concurrent treatment with either montelukast or ICS therapy did not significantly modify the treatment effect. There were too few oral corticosteroid courses or hospital admissions for these outcomes to be analyzed statistically.

At present, the role of macrolides in the management of early childhood wheeze is unclear.[5,20] Further studies are required to support their efficacy, as well as to further elucidate the potential risk of antibiotic resistance. However, this approach represents an interesting alternative to daily asthma therapies, especially in preschool-aged children with intermittent infection-triggered symptoms.

The Microbiome

There have been emerging studies on the role of bacterial lysates such as Broncho-Vaxom (OM-85 BV) or polyvalent mechanical bacterial lysates (PMBL) in the treatment of early childhood wheeze. Both of these therapies contain lysates of 8 bacterial pathogens that are primarily from the upper respiratory tract—*Haemophilus influenzae, S. pneumoniae, Streptococcus pyogenes, Streptococcus viridans, Klebsiella pneumoniae, Klebsiella ozaenae, Staphylococcus aureus,* and *Neisseria catarrhalis*. These lysates at multiple stages in the immune response including enhancing innate immune responses,[21] increasing IgA and IgG,[22] upregulating T-helper (Th)1 cytokines such as interferon-γ and downregulating Th2 cytokines involved in the allergic response such as IL-4.[23] It has been hypothesized that bacterial lysolates could ''preferentially restore Th1 response that is altered in children with asthma.''[24]

Until recently, studies on OM-85 BV had excluded children with recurrent wheeze and/or asthma but shown a reduction in the number of acute respiratory tract illnesses in children.[25,26] More recently, a few studies have supported the potential role of bacterial lysates in preschool and school-aged children with asthma.

A randomized double blind placebo controlled trial examined the use of OM-85 BV (1 capsule or 3.5 mg/day for 10 consecutive days for each of 3 months) in children aged 1–6 years of age with recurrent wheeze (3 or more episodes in the past month) compared with placebo.[27] It found that use of OM-85 BV compared with placebo over the course of the 12-month study resulted in 37.9% lower mean incidence of wheezing attacks ($P < 0.001$) and decreased mean wheezing duration (mean difference = −2.09; 95% CI: −3.06 to −1.10; $P = 0.001$). In multiple linear regression, the main difference between the OM-85 BV and placebo groups was reduction in number of acute respiratory tract illnesses ($P < 0.001$).

Bacterial lysates are also being studied in the school-aged asthmatic population. A randomized double blind placebo controlled parallel-group study of 152 school-aged children (6–16 years of age) with partially controlled or uncontrolled atopic asthma (with perennial aeroallergen sensitization) and at least 2 asthma exacerbations in the previous year found that PMBL (1 tablet sublingually per day on first 10 days of each month for 3 consecutive months) reduced mean number of asthma exacerbations compared with placebo at week 12 (0.3 ± 0.6 versus 0.8 ± 1.1; $P = 0.009$) and over the total study period of 9 months (1.1 ± 1.3 versus 1.9 ± 2.0; $P = 0.01$).[24] Exacerbations were defined as mild/moderate if requiring increase in ICS/beta-agonist therapy or an emergency room (ER) visit, or severe if requiring hospitalization, ER visit with prescription systemic corticosteroid therapy, or isolated systemic corticosteroid therapy for ≥3 days (but less than a week in duration). PMBL reduced the mean number of days with each exacerbation (13.3 ± 11.2 versus 19.8 ± 15.7; $P = 0.009$), and prolonged the time to second exacerbation by 55% (hazard ratio = 0.45; 95% CI: 0.27–0.77; $P = 0.002$) and to third exacerbation by 74% (hazard ratio = 0.26; 95% CI: 0.12–0.58; $P < 0.001$). However, no significant difference in asthma control test scores was noted between the groups [as measured by Childhood-Asthma Control Test (c-ACT)/ACT scores]. No serious adverse events were noted.

Trials are ongoing such as a 36-month randomized trial of the use of OM-85 BV (10 days/month for 2 years) in young children aged 6–18 months with increased risk of asthma and wheezing respiratory illnesses defined as one of the following criteria: parental history of asthma, physician-diagnosed atopic dermatitis in the participant, or physician-diagnosed asthma in a blood sibling aged 4 years or more. The primary outcome of this trial is time to occurrence of first lower respiratory tract infection with wheezing during a third observational year (NCT02148796).

Conclusion

Studies are emerging supporting alternative approaches in the treatment of infection-induced wheeze, in particular in the preschool-aged population. The studies on azithromycin and bacterial lysates used different patient populations with different doses and durations of therapy, and further studies are required to determine the optimal dose and duration of

therapy, as well as to elucidate any possible preferential phenotypic responders. In particular, as ICS therapy is less effective in nonatopic populations, a focus on this preschool population would be interesting. Studies incorporating other measures such as biomarkers may also be helpful in determining which preschoolers are most likely to benefit from these therapies. Although current guidelines recommend ICS therapy in preschoolers with recurrent wheeze, moving forward a more personalized approach may be possible.

Author Disclosure Statement

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