Short- and long-term efficacy of prednisolone for first acute rhinovirus-induced wheezing episode

Tuomas Jartti, MD,[a] Riitta Nieminen, BM,[a,b] Tytti Vuorinen, MD,[b] Pasi Lehtinen, MD,[a] Tero Vahlberg, MSc,[c] James Gern, MD,[d] Carlos A. Camargo, Jr, MD, DrPH,[e] and Olli Ruuskanen, MD[a] *Turku, Finland, Madison, Wis, and Boston, Mass*

Background: Rhinovirus-induced wheezing is an important risk factor for recurrent wheezing. There are no randomized controlled trials on the effect of systemic corticosteroids in patients with this disease.
Objective: We sought to study the short- and long-term effects of prednisolone treatment of the first acute, moderate-to-severe, rhinovirus-induced wheezing episode in young children.
Methods: After confirming rhinovirus from nasopharyngeal aspirate by using PCR, 79 children with a first wheezing episode at age 3 to 23 months were randomized to receive oral prednisolone (first dose of 2 mg/kg, followed by 2 mg/kg/d in 2 divided doses for 3 days) or placebo. The trial was double blind throughout the 12-month follow-up. The primary outcomes were long term: new physician-confirmed wheezing episode within 2 months, number of physician-confirmed wheezing episodes within 12 months, and initiation of regular controller medication for asthma symptoms within 12 months. The primary interaction analysis examined rhinovirus load.
Results: Seventy-four patients completed the study (mean age, 13 months; 28% atopic). Long-term outcomes did not differ between groups (all $P \geq .30$). For short-term outcomes, the prednisolone group had less cough, rhinitis, noisy breathing, severe breathing difficulties, and nocturnal respiratory symptoms at home within 2 weeks (all $P < .05$). The 25 children with greater than 7000 rhinovirus copies/mL (most sensitive cutoff) benefitted from prednisolone in terms of less risk of physician-confirmed recurrence within 2 and 12 months compared with placebo (both $P < .05$).
Conclusions: Prednisolone cannot be routinely recommended for all young children experiencing their first acute, moderate-to-severe, rhinovirus-induced wheezing episode. Prednisolone might be beneficial in a subgroup of children with high viral loads. (J Allergy Clin Immunol 2014;■■■:■■■-■■■.)

Key words: *Bronchiolitis, child, corticosteroid, glucocorticoid, treatment, prednisolone, rhinovirus, virus, wheeze, wheezing*

Rhinovirus has been detected in 20% to 40% of wheezing children during the first 2 years of life in both hospital and emergency care settings.[1-3] Rhinovirus-related cause of early wheezing is of particular interest because of its strong association (odds ratios of 3-10 during early life) with recurrent wheezing and doctor-diagnosed asthma up to 13 years of age.[4-9] The suggested explanations for this striking association are low interferon responses (ie, impaired viral defense), early airway inflammation (ie, a broken epithelial barrier), and genetic variation at the 17q21 locus in rhinovirus-affected children (ie, might markedly increase the risk of asthma).[10-13]

Overall, randomized controlled trials (RCTs) on the efficacy of systemic corticosteroids in the treatment of early wheezing have not reported clinical efficacy.[14-16] Virus-specific RCTs on respiratory syncytial virus (RSV)–induced lower airway illness have focused on bronchiolitis and have not found any efficacy of systemic corticosteroids.[17,18] Previously, in the Vinku study we reported a *post hoc* analysis of RCT data showing that oral prednisolone during the first wheezing episode with a rhinovirus-related cause and/or eczema reduced the risk of recurrent wheezing over the next 2 months, 12 months, and 7 years.[4,9,19] Although no prior study has identified a subgroup of young wheezing children who benefit from systemic corticosteroids, they have not focused on rhinovirus as a cause. The high asthma risk associated with rhinovirus-induced wheezing episodes and our earlier results led us to perform the current RCT on the effect of systemic corticosteroids on a patient's first rhinovirus-induced wheezing episode. We hypothesized that prednisolone decreases the risk of relapse in children with their first rhinovirus-induced wheezing episode.

METHODS

Subjects

Recruitment for the Vinku2 trial was carried out in Turku University Hospital from June 2007 to March 2010 (*vinku* means "wheeze" in Finnish). The inclusion criteria were age of 3 to 23 months, delivery at 36 gestational

From [a]the Department of Pediatrics, Turku University Hospital; the Departments of [b]Virology and [c]Biostatistics, University of Turku; [d]the Departments of Pediatrics and Medicine, University of Wisconsin School of Medicine and Public Health, Madison; and [e]the Department of Emergency Medicine and Division of Rheumatology, Allergy and Immunology, Department of Medicine, Massachusetts General Hospital, Harvard Medical School, Boston.

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Corresponding author: Tuomas Jartti, MD, the Department of Pediatrics, Turku University Hospital, PO Box 52, FIN-20520 Turku, Finland. E-mail: tuomas.jartti@utu.fi.

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Abbreviations used
HR: Hazard ratio
RCT: Randomized controlled trial
RSV: Respiratory syncytial virus

weeks or later, first wheezing episode (based on parental report and confirmed from medical records), rhinovirus detected in a nasopharyngeal aspirate sample by using PCR, ongoing signs of lower respiratory tract symptoms (cough, noisy breathing, or wheezing) at the time when PCR results were available, and written informed consent from a parent or guardian. Exclusion criteria were the presence of a chronic nonatopic illness, previous systemic or inhaled corticosteroid treatment, participation in another study (excluding long-term follow-up studies in childhood), varicella contact in a patient without a previous varicella illness, need for intensive care unit treatment, or poor understanding of Finnish (Fig 1). The study was commenced only after obtaining written informed consent from a parent. The study protocol was approved by the Ethics Committee of Turku University Hospital.

Study protocol

At study entry, the guardian filled out a standard questionnaire on host and environmental risk factors for asthma. Then the child was physically examined, a nasopharyngeal aspirate sample was obtained for viral diagnostics by using a standardized procedure,[2] and a baseline blood sample was drawn. The randomly assigned study drug (prednisolone vs placebo) was initiated as soon as possible for rhinovirus-positive children by a study physician if the child still fulfilled all the study criteria. During the 12-month follow-up period, the guardian was asked to fill out a symptom and medication diary and to bring the child to the study physician each time the child had breathing difficulties. Scheduled follow-up visits were arranged at 2 weeks, 2 months, and 12 months by the study physicians. The study protocol was registered at ClinicalTrials.gov in August 2008 (ClinicalTrials.gov number, NCT00731575). For more details of the protocol, see the Methods section and Figs E1-E5 in this article's Online Repository at www.jacionline.org.

Randomization

Subjects were randomized to receive either oral prednisolone (first dose of 2 mg/kg, followed by 2 mg/kg/d in 2 divided doses for 3 days; maximum, 60 mg/day; Prednisolon 5-mg tablets) or placebo; both were provided by Leiras Takeda (Helsinki, Finland). A double-blind RCT design was used. For more details, see the Methods section in this article's Online Repository.

Definitions

Wheezing refers to expiratory breathing difficulty with a high-pitch sound during expiration. We refer to the concomitant presence of rhinovirus, as detected by means of PCR, as a rhinovirus-induced wheezing episode because this positivity has been linked to the severity of respiratory symptoms, specific rhinovirus genotypes show in most cases relatively short shedding (generally up to 2 weeks), dual-rhinovirus genotype detections are rare, rhinovirus detection has been associated with immune responses *in vivo*, and rhinovirus is able to infect the lower airways.[12,20,21] Atopy was defined as a positive IgE antibody result (≥0.35 kU/L) to any of the following allergens: codfish, cow's milk, egg, peanut, soybean, wheat, cat, dog, horse, birch, mugwort, timothy grass, *Cladosporium herbarum*, and *Dermatophagoides pteronyssinus* (Phadiatop Combi; Phadia, Uppsala, Sweden). Aeroallergen sensitization was defined as positive IgE antibodies to any of the latter 8 allergens. Perennial aeroallergen sensitization was defined as positive IgE antibody results to dog, cat, or *D pteronyssinus.* Birch, mugwort, timothy grass, and *C herbarum* were considered seasonal aeroallergens. Atopic eczema was defined as a physician's diagnosis of eczema according to typical symptoms that included pruritus, typical morphology, and chronicity of disease. Eczema was defined as atopic eczema if a child was atopic. For more details, see the Methods section in this article's Online Repository.

Laboratory methods

Rhinovirus species A, B, and C; enteroviruses; and RSV A and B were detected by using "in-house" reverse transcriptase PCR at the Virus Diagnostic Laboratory, Department of Virology, University of Turku.[22,23] A nasal swab (nylon flocked dry swab, 520CS01; Copan, Brescia, Italy) was dipped into the nasopharyngeal aspirate and stored at −70°C. In analysis the swab was diluted in 1 mL of PBS, which was analyzed for viral load (ie, copy number). A multiplex PCR test (Seeplex RV12 ACE Detection; Seegene, Seoul, Korea) was used for detection of rhinovirus A and B, RSV A and B, parainfluenza virus types 1 to 3, human metapneumovirus, adenovirus, coronavirus (229E, NL63, OC43, and HKU1), and influenza A and B virus from frozen samples. Human bocavirus-1 was analyzed by using PCR and serology, as previously described.[24] Blood eosinophil counts and serum levels of allergen-specific IgE were analyzed by using the routine diagnostic procedures of the Central Laboratory of Turku University Hospital. Serum 25-hydroxyvitamin D measurements were done by means of liquid chromatography–tandem mass spectrometry at Massachusetts General Hospital (Boston, Mass). For more details, see the Methods section in this article's Online Repository.

Outcomes

The 3 primary outcomes were the occurrence of a new physician-confirmed wheezing episode during the 2-month follow-up, the number of physician-confirmed wheezing episodes during the 12-month follow-up, and the initiation of regular controller medication for asthma symptoms during the 12-month follow-up. Regular medication was initiated according to 2007 guidelines for initiating daily long-term control therapy for 0- to 4-year-old children.[25] Rhinovirus load was the primary interaction analysis to investigate whether the effects of prednisolone compared with placebo on the 3 primary outcomes were dependent on the rhinovirus copy number.

Secondary outcomes included the occurrence and severity of respiratory symptoms (cough, expiratory breathing difficulty, noisy breathing, rhinitis, and nocturnal wakening for breathing difficulties) on a 4-point scale, medications, and unscheduled doctor's appointments recorded by the parents on a 2-week daily symptom diary. Within 2 months after discharge, outpatient clinic visits, hospitalizations, oral corticosteroid courses, and initiations of inhaled corticosteroids for wheezing were also recorded. As an exploratory outcome, we decided to extend the time to a new physician-confirmed wheezing episode up to the 12-month follow-up with a double-blind design.

Statistics

According to our previous RCT,[19] a sample size of 62 children would be sufficient for 80% power (with a 5% type I error rate) to detect a 34% absolute difference in relapse rate between prednisolone (22%) and placebo (56%) within 2 months after a rhinovirus-induced first wheezing episode. Because the follow-up time was 12 months (ie, 10 months longer) in the current study, with increased risk of dropout, we recruited 79 children.

Baseline differences between groups were analyzed by using 2-sample *t* test for normally distributed and Wilcoxon rank sum tests for nonnormally distributed continuous variables. Categorical variables were analyzed by using χ^2 or Fisher exact tests. The difference between the prednisolone and placebo groups in primary outcomes, new physician-confirmed wheezing episodes within 2 months, and initiation of regular controller medication for asthma symptoms within 12 months was tested with Cox regression. Time to event was defined from baseline to the time of occurrence of the event. Survival times were censored if the event did not occur within 2 months (wheezing episode) or 12 months (asthma symptoms) of follow-up. Poisson regression analysis was used to investigate the difference between the prednisolone and placebo groups in the number of physician-confirmed wheezing episodes within 12 months. The modifying effect of rhinovirus load at study entry on