Online Supplement

Participant Selection for Original Cohort

Children between 10 and 17 years of age with asthma, receiving daily controller therapy, and fitting the age- and sex-adjusted body mass index (BMI) parameters for lean (20-65th percentile) and overweight/obese (BMI $\geq$ 85th percentile) were enrolled through the Nemours multispecialty pediatric asthma clinic in Jacksonville, FL. We used common BMI-percentile conventions for overweight/obesity[1, 2], and selected from a narrower BMI-percentile range among normal weight individuals to avoid misclassification. Asthma was defined by accepted convention: physician-diagnosis of asthma and either a ≥12% improvement in forced expiratory volume in 1 second (FEV1) following bronchodilator or FEV1 methacholine PC20 ≤ 16 mg/ml[3, 4]. Participants were excluded if they had any smoking history, been on controller daily oral steroids, had a change in controller therapy in the previous 8 weeks, had any interval illness in the past 4 weeks, or had another significant chronic disease.

Clinical Data

Two to three clinic visits within 3 weeks were conducted, with no two visits occurring on successive days. At visit 1, participants signed an IRB-approved parental permission form and minor assent. Participants completed staff-directed, structured interviews and questionnaires providing past asthma and medical history, family and environmental history, quality-of-life information and a comprehensive interview of asthma symptoms, controller treatment and past healthcare utilization. Each participant's controller step prescribed by his/her asthma physician was determined[5]. Participants underwent a physical examination, anthropometric measurements, and spirometry (before and after bronchodilator). Highest parental education level, median household incomes, and poverty index (percent below poverty level) was determined for each patient's household. Participants completed a methacholine challenge test and exhaled nitric oxide (FENO) at visits 2 and 3, respectively, adhering to recommended guidelines[6, 7].

Symptom and Quality-of-Life Analyses

Participants and parents answered structured interview questions regarding symptom patterns, common asthma triggers and the primary symptom experienced with loss of control. The structured interviews also documented asthma symptom frequency and severity, digestive symptoms, and sleep characteristics. Asthma symptom control was assessed at visit 1 using multiple questionnaires (Asthma Control Questionnaire (ACQ)[8], Asthma Control Test (ACT)[9, 10], and childhood ACT (c-ACT)[11]) to measure the broad array of symptoms that asthmatic children experience and report. Symptoms were measured using the Asthma Symptom Utility Index (ASUI)[12].

Asthma-related quality-of-life was measured using the Paediatric Asthma Quality of Life Questionnaire (PAQLQ)[13, 14] and the Paediatric Caregiver's Asthma Quality of Life Questionnaire (PACQLQ)[15]. Properties of the asthma control scores, symptom scores, and asthma quality of life scores can be found in the repository.

Digestive Symptoms assessed from the GSAQ

Digestive symptoms were measured using the Pediatric Gastroesophageal Reflux (GER) Disease Symptom Assessment Questionnaire (GSAQ) which is a 10-item tool[40] that has been validated in children in the assessment of gastroesophageal reflux disease and digestive symptoms such as chest/abdominal pain, pain/choking with eating, swallowing dysfunction, regurgitation and nausea. It assesses symptom severity from the previous 7-days on an 8-point scale with 0 and 7 indicating the least and greatest severity, respectively.

Lung Function Testing

Participants completed spirometry (Jaeger MasterScreen, San Diego, CA) adhering to recommended ATS standards[16, 17]. Participants also completed fractional exhaled nitric oxide (FENO) (Sievers 280 NOA analyzer, Boulder, CO) maneuvers according to recommended standards[18]. Participants

completed a methacholine challenge by experienced staff using the ten Provacholine® concentrations dosing scheme with a five-breath dosimeter protocol[6].

Participant Selection for Replicate Cohort

The replicate cohort was taken from a study conducted by the American Lung Association Asthma Clinical Research Centers (ALA-ACRC). The study design has been published[3]. All participants signed written informed consents for the Study of Acid-Reflux in Childhood Asthma (SARCA) study, which was approved by the Nemours Florida IRB (82404-29) and by all other ALA-ACRC IRBs, and registered at ClinicalTrials.gov (NCT00604851). We included baseline data from 306 participants age 6-17 years with inadequately controlled persistent asthma. For inclusion, participants required physician diagnosis of asthma, prescription of an asthma controller medication, and either ≥12% post-bronchodilator FEV1 improvement or methacholine PC20 < 16mg/ml. Inadequate control was defined by poor ACQ score (≥1.25), frequent bronchodilator use or exacerbations. Participants required a recent absence of GERD symptoms that would require treatment with a proton pump inhibitor (PPI) at the time of enrollment. Medications for treatment of gastrointestinal symptoms in the past month (including PPI, H2 blockers, bethanechol, and metoclopramide) were exclusionary. Participants with history of anti-reflux or peptic ulcer surgery were excluded. 2453 participants were screened in order to randomize 306 participants into the 24-week multicenter clinical trial assessing the efficacy of daily oral lansoprazole versus placebo for patients with inadequately controlled asthma.

Data Collected

We collected demographics, body mass index percentiles, spirometry (before and after bronchodilator), Asthma Control Questionnaire (ACQ) and GERD Symptom Assessment Questionnaire (GSAQ) at baseline. We grouped participants as underweight, normal weight, overweight or obese by CDC classification[20] based on age and sex-adjusted BMI-percentile. Since we were primarily interested in serving as a replicate to the original study, we included only participants with a BMI-percentile between the 20^{th} and 65^{th} percentile (leans) and ≥95^{th} percentile (obese). Asthma

symptoms were assessed using the ACQ[8] and modified ACQ6[21]. Spirometry with bronchodilator challenge testing was performed using ATS/ERS standard procedures.

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