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Effect of a Soy Isoflavone Supplement on Lung Function and Clinical Outcomes in Patients With Poorly Controlled Asthma:

A Randomized Clinical Trial

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Abstract

IMPORTANCE—Soy isoflavone supplements are used to treat several chronic diseases, although the data supporting their use are limited. Some data suggest that supplementation with soy isoflavone may be an effective treatment for patients with poor asthma control.

OBJECTIVE—To determine whether a soy isoflavone supplement improves asthma control in adolescent and adult patients with poorly controlled disease.

DESIGN, SETTING, AND PARTICIPANTS—Multicenter, randomized, double-blind, placebo-controlled trial conducted between May 2010 and August 2012 at 19 adult and pediatric pulmonary and allergy centers in the American Lung Association Asthma Clinical Research Centers network. Three hundred eighty-six adults and children aged 12 years or older with symptomatic asthma while taking a controller medicine and low dietary soy intake were randomized, and 345 (89%) completed spirometry at week 24.

INTERVENTIONS—Participants were randomly assigned to receive soy isoflavone supplement containing 100 mg of total isoflavones (n=193) or matching placebo (n=193) in 2 divided doses administered daily for 24 weeks.

MAIN OUTCOMES AND MEASURES—The primary outcome measure was change in forced expiratory volume in the first second (FEV_1) at 24 weeks. Secondary outcome measures were symptoms, episodes of poor asthma control, Asthma Control Test score (range, 5–25; higher scores indicate better control), and systemic and airway biomarkers of inflammation.

RESULTS—Mean changes in prebronchodilator FEV_1 over 24 weeks were 0.03 L (95% CI, −0.01 to 0.08 L) in the placebo group and 0.01 L (95% CI, −0.07 to 0.07 L) in the soy isoflavone group, which were not significantly different ($P = .36$). Mean changes in symptom scores on the Asthma Control Test (placebo, 1.98 [95% CI, 1.42–2.54] vs soy isoflavones, 2.20 [95% CI, 1.53–2.87]; positive values indicate a reduction in symptoms), number of episodes of poor asthma control (placebo, 3.3 [95% CI, 2.7–4.1] vs soy isoflavones, 3.0 [95% CI, 2.4–3.7]), and changes in exhaled nitric oxide (placebo, −3.48 ppb [95% CI, −5.99 to −0.97 ppb] vs soy isoflavones, 1.39 ppb [95% CI, −1.73 to 4.51 ppb]) did not significantly improve more with the soy isoflavone supplement than with placebo. Mean plasma genistein level increased from 4.87 ng/mL to 37.67 ng/mL ($P < .001$) in participants receiving the supplement.

CONCLUSIONS AND RELEVANCE—Among adults and children aged 12 years or older with poorly controlled asthma while taking a controller medication, use of a soy isoflavone supplement, compared with placebo, did not result in improved lung function or clinical outcomes. These findings suggest that this supplement should not be used for patients with poorly controlled asthma.

Asthma is a complex disease whose prevalence and severity are determined by genetic and environmental factors. Increases in asthma prevalence and severity over the last several decades[1] are likely due at least in part to environmental factors. Diet is one environmental factor that is associated with asthma prevalence and severity.[2] During an evaluation of the link between diet and asthma, we found an association between dietary intake of the soy isoflavone genistein and forced expiratory volume in the first second (FEV_1), a marker of asthma severity.[3] We subsequently confirmed the association in an independent asthma population[4] and explored the mechanistic basis for this finding. We found that genistein inhibits a key pathway that may contribute to asthma severity, eosinophil leukotriene C_4 synthesis. We also found that administration of a soy isoflavone supplement containing genistein reduces exhaled nitric oxide and ex vivo leukotriene C_4 synthesis in a small group of patients with inadequately controlled asthma.[5]

With the increasing cost of prescription drugs for asthma, it is important to identify effective, safe, and less expensive therapies than those currently available. Patients with asthma frequently seek alternative therapies in the belief that they are less toxic. Soy isoflavones clearly fit this role. However, previous reports of an association between dietary intake of individual nutrients and asthma prevalence and severity have not been confirmed in adequately powered intervention studies.[6–8] To determine whether this novel treatment is effective in patients with asthma, we conducted a 6-month randomized, double-blind, placebo-controlled, parallel-group clinical trial of soy isoflavones among individuals aged 12 years or older with symptomatic, poorly controlled asthma who were receiving at least 1 controller medication.

Methods

Study Design

The Study of Soy Isoflavones in Asthma was a multisite randomized clinical trial conducted at 19 clinical centers in the United States from May 2010 through August 2012. Most clinical centers were specialty care clinics associated with academic medical centers. All study centers received approval from their respective institutional review boards. All participants or their legal guardians provided written informed consent. Participants younger than 18 years signed assent forms according to local regulatory policies. The trial protocol is available in Supplement 1.

Participants were randomly assigned in a 1:1 allocation ratio to receive either a soy isoflavone supplement or a matching placebo twice daily for 6 months (Figure 1). Each isoflavone tablet contained 49 mg of soy isoflavones (genistein, daidzein, and glycitein), approximately 32 mg as the aglycone form (nearly evenly distributed between genistein and daidzein). The soy isoflavone and placebo tablets were reanalyzed twice during the study. On each occasion, the isoflavone content was between 48 and 49 mg, while the isoflavone content of the placebo tablets was consistently less than 0.05 mg. The treatment assignment schedule was created by the coordinating center using a documented, auditable SAS program and was stratified by center with randomly permuted blocks of varying size. Unique treatment assignment numbers were issued via an online randomization system for each participant after all eligibility criteria were evaluated. The assignment number was used

to distribute and track study treatment with soy isoflavone supplement or placebo. Personnel at the coordinating center involved in creating the randomization system or in treatment packaging and distribution had access to treatment identification information. No personnel at clinical centers had access to treatment assignments. Analysts looked at treatment identity after data collection was complete and were aware of the treatment assignment when performing the analyses of the completed data set.

After randomization, participants kept daily diaries to record morning peak expiratory flow, medication use, and asthma symptoms. They returned for assessment every 4 weeks for 24 weeks. Procedures performed at each visit included an interval medical history, spirometry (Koko Spirometer, Ferris Respiratory) performed according to American Thoracic Society standards,[9] exhaled nitric oxide measurement (NIOX MINO, Aerocrine) following American Thoracic Society/European Respiratory Society guidelines,[10] and asthma control and asthma quality-of-life questionnaires (described below). At randomization (visit 2) and select follow-up visits, urine and blood were collected (visits 4 and 9). The Block 2005 Food Frequency Questionnaire for adults, Block Kids 2004 Food Frequency Questionnaire for children aged 12 to 17 years,[11,12] and Block Soy Foods Screener (NutritionQuest) were administered at randomization and at visit 9. Adverse and toxic effects were assessed by questionnaire and open-ended questions at each visit. Race and ethnicity were self-reported by participants at baseline and at each spirometry test.

Participant Selection

Inclusion criteria were age 12 years or older; physician diagnosis of asthma; current or previous (within 2 years) evidence of at least a 12% increase in FEV_1 after inhaling 2 to 4 puffs of albuterol or a positive methacholine challenge (20% decrease in FEV_1 at <16 mg/mL); FEV_1 equal to or greater than 50% predicted prebronchodilator; currently prescribed daily controller asthma medication(s) (eg, inhaled corticosteroids and/or leukotriene modifier); nonsmoker for 6 months or longer and less than 10 pack-year smoking history; and evidence of poor asthma control. Poor asthma control was defined as having 1 or more of the following: a score of 19 or less on the ACT,[13] use of β-agonist for asthma symptoms 2 or more times per week, nocturnal awakening with asthma symptoms more than once per week, and 2 or more episodes of asthma symptoms in the past 12 months, with each requiring at least 1 of the following: emergency department visit, unscheduled physician visit, prednisone course, or hospitalization.

Patients were excluded if they had chronic illness that in the judgment of the physician would interfere with study participation; history of physician diagnosis of chronic bronchitis, emphysema, or chronic obstructive pulmonary disease; oral corticosteroid use within the past 6 weeks; current consumption of soy isoflavone supplements; intake of soy or soy-containing foods 1 or more times a week; use of an investigational treatment in the previous 30 days; known adverse reaction to genistein, other phytoestrogens, or soy products; pregnancy or lactation; asthma exacerbation within 6 weeks; upper respiratory tract infection within 2 weeks; body weight less than 77 lb (35 kg); or change in diet over the past month or expected change in diet (eg, initiation of weight loss diet) during the study.

Outcome Measures

The primary outcome measure was FEV_1. Secondary outcomes included the ACT (score range, 5–25; higher scores indicate better control),[13] the Asthma Symptoms Utility Index (score range, 0–1.0; higher scores indicate fewer symptoms),[14,15] and the Marks Asthma Quality of Life Questionnaire (score range, 0–80; higher scores indicate worse quality of life) for participants aged 17 years or older[16] or the Children's Health Survey for Asthma (score range, 0–100; higher scores indicate better quality of life) for participants aged 12 to 16 years.[17] Other outcomes included peak expiratory flow; symptom-free days (defined as days with no asthma episodes reported on diary card); and rates of episodes of poor asthma control defined from diary cards by 1 of the following: 30% or greater decrease in morning peak expiratory flow (from personal best) for 2 consecutive days (definite yellow zone event according to the National Heart, Lung, and Blood Institute's Asthma Action Plan[46]), addition of oral corticosteroid to treat asthma symptoms, unscheduled contact with a health care practitioner (emergency department, physician office, hospital) for asthma symptoms, and increased use of bronchodilator rescue medication since baseline by 4 or more puffs of metered dose inhaler or 2 or more nebulizer treatments on 1 day.[18]

Additional outcomes included exhaled nitric oxide, peripheral blood eosinophil count, serum interleukin 6 (Quantikine HS ELISA kit, R&D Systems), serum C-reactive protein (DSL ultrasensitive coated-well CRP ELISA kit, Diagnostic Systems Laboratories), and urinary leukotriene E_4 measured by high-performance liquid chromatography.[19]

Quantification of Total Blood Genistein

Blood for total genistein concentration (unconjugated genistein plus genistein conjugated to glucuronide and sulfate) was collected in 10-mL heparinized Vacutainer tubes (BD, Franklin Lakes), centrifuged, and the plasma collected and stored at −70°C. A 200-μL aliquot of plasma was incubated in a solution contain β-glucuronidase and sulfatase overnight to de-conjugate genistein and extracted with diethyl ether as previously described.[20] The mixture was evaporated to dryness and the dry residues were quantified by time-resolved fluoroimmunoassay (TR-FIA Genistein kits, Labmaster) as previously described.[21]

Sample Size

The planned sample size of 380 participants provided 80% power to detect a difference in the change in prebronchodilator FEV_1 of 0.134 L or greater based on a 2-sample *t* test assuming a standard deviation for the 24-week change in FEV_1 of 0.400 L, a cumulative 2-sided type I error rate of 2.5% (adjusting for 2 interim analyses based on O'Brien-Fleming boundaries), and 10% inflation to account for missing data and loss to follow-up. The 0.134-L difference approximated the 4% to 5% change in percentage predicted FEV_1 observed between those with the highest and lowest consumption of soy genistein in our 2 previous analyses[3,4] and is similar to the lower bound for clinically important changes (0.100–0.200 L).[22] The study also provided 80% power to detect clinically meaningful differences for changes in exhaled nitric oxide (8 ppb, which translates to a 20% change)[23] and the asthma control test (3 units)[24] assuming a 2-sided type I error rate of 0.0125 for each.

Data Analysis

The data were analyzed at the Data Coordinating Center at Johns Hopkins University. All analyses were performed according to treatment assignment, and all available data from all patients were included in the analyses, following the intention-to-treat principle. The primary analysis was performed using a linear mixed-effects model incorporating all available longitudinal patient data on FEV_1 unadjusted for additional covariates. The fixed effects included indicator variables for genistein treatment (placebo = 0; genistein = 1), visit time indicators (baseline and 4, 8,12,16, 20, and 24 weeks), and treatment × time interaction terms. The random effects included random intercepts for clinics as well as an adjustment for the correlation between repeated measures. An unstructured covariance structure was used. Prespecified subgroup analyses relied on the same approach by adding appropriate covariates and treatment group interaction terms into the models.

Analyses for continuous outcomes related to secondary hypotheses followed the same analytic approach proposed for the primary outcome. Laboratory values were censored at the lowest level of detection to allow for log-transformations to address skewness in the data. Random effects for batch replaced the clinic-level random effects for the analysis of plasma genistein levels. Rates of episodes of poor asthma control were evaluated using negative binomial models to allow for over-dispersion with random intercepts for clinics.[25] Kaplan-Meier estimates of the survival function were used to estimate the proportion of individuals who developed a particular symptom after being free of that symptom at randomization. Frailty models with a random effect for clinic were used to compare the risk of developing each symptom.

Data from daily diaries and pill counts were used to evaluate adherence to the treatment protocol. Each participant's overall diet and dietary soy intake at baseline and at the end of the study were analyzed using the Block Food Frequency Questionnaire and Block Soy Foods Screener to assess stability of diet and nutrient intake during the study.

Data were assumed to be missing at random. Mixed-effects models were fit using residual maximum likelihood to accommodate data missing at random in a manner equivalent to multiple imputation. Best- and worst-case scenarios were used to quantify the robustness of our findings to the missing-at-random assumption. Robust standard error estimates were used for all regression models. All tests were 2-sided. The type I error was split between the primary outcome (FEV_1; $\alpha = .025$) and the 2 most important secondary outcomes (exhaled nitric oxide and ACT score; $\alpha = .0125$ each). All other tests were performed at the $\alpha = .05$ level without adjustment for multiple comparisons. Analyses were performed using SAS version 9.1 (SAS Institute Inc), STATA release 13 (Stata Corp) and R version 2.11.1 (R Project for Statistical Computing; http://www.r-project.org/).

Results

Participant Characteristics

A total of 1214 individuals were assessed for eligibility (Figure 1); 828 were excluded either before enrollment or during the run-in period. Three hundred eighty-six adults and children aged 12 years or older with symptomatic asthma and low dietary soy intake were

randomized. The baseline characteristics of the participants are shown in Table 1. Of the 386 participants, 345 (89%) completed the study. A completer was defined as an individual who had an evaluable primary outcome measurement at 24 weeks. Participant characteristics were similar in the 2 groups. The median age was 36 years, a majority were women, 59% were from minority groups, and most were taking a combination inhaled corticosteroid/long-acting β-agonist. Participants had reduced FEV_1 (82% of predicted), substantial symptom burden (mean ACT score, 17), and frequent use of health care resources. Exhaled nitric oxide and peripheral blood eosinophil counts were mildly increased; serum interleukin 6 and C-reactive protein levels were normal. Baseline dietary genistein intake was low. Dietary intake of vitamins A, C, D, and E were in the low to normal range (eTable 1 in Supplement 2).

Adherence to Study Treatment and Stable Diet

Participants reported taking at least 1 dose of the study treatment on more than 90% of follow-up days. Analysis of dietary nutrient intake after study completion showed that there were no significant changes in overall diet or in dietary intake of genistein and vitamins A, C, D, and E in either group over the 24-week study period.

Primary Outcome

The mean changes in prebronchodilator FEV_1 over 24 weeks were 0.03 L (95% CI, −0.01 to 0.08 L) in the placebo group and −0.001 L (95% CI, −0.07 to 0.07 L) in the soy isoflavone group, which were not significantly different (Table 2 and Figure 2). The distribution of FEV_1 responses was the same in the 2 groups (eFigure in Supplement 2). These results are robust to all but the most extreme forms of informative missingness (eg, imputation of values on the order of 1.1 L and −1.32 L).

Secondary Outcomes

The only lung function measure that was significantly different between the 2 treatment groups was forced vital capacity, which had a slightly greater but not clinically meaningful improvement after 24 weeks in the placebo-treated group (Table 2). Mean changes also were not significantly different between the groups for ACT symptom scores (placebo, 1.98 [95% CI, 1.42–2.54] vs soy isoflavones, 2.20 [95% CI, 1.53–2.87]), Marks Asthma Quality of Life Questionnaire scores (placebo, −4.30 [95% CI, −6.07 to −2.54] vs soy isoflavones, −2.99 [95% CI, −4.73 to −1.24]), number of episodes of poor asthma control (placebo, 3.3 [95% CI, 2.7–4.1] vs soy isoflavones, 3.0 [95% CI, 2.4–3.7]), and measures of systemic inflammation (se-rum interleukin 6 and C-reactive protein, peripheral blood eosinophil counts, urinary leukotriene E_4) (Table 2 and Table 3). The biomarker that differed between the 2 treatment groups was exhaled nitric oxide, which had a small, statistically significant improvement after 24 weeks in the placebo-treated group. This was not seen in the soy isoflavone group.

Association Between Patient Characteristics and Response

We sought to determine whether specific characteristics influenced the response to the soy isoflavone supplement. In prespecified subgroup analyses, we looked at the effect on change

in prebronchodilator FEV_1 of the following measures: higher vs lower lung function (percentage predicted FEV_1 ≤80% vs >80%), symptom burden (ACT score >19 vs ≥19), race (non-African American vs African American), sex (male vs female), body mass index (<30 vs ≥30; calculated as weight in kilograms divided by height in meters squared), and exhaled nitric oxide (≤25 ppb vs >25 ppb). We found no significant difference in the effect of treatment over 6 months when stratifying by any patient or disease characteristics or inflammatory markers including peripheral blood eosinophil counts and urinary leukotriene E_4 (P=.31 to P>.99 by test for interaction).

Association Between Genistein Intake and Levels and Asthma Outcomes

Plasma genistein levels were analyzed at baseline and 24 weeks for a subset of 143 patients (37%; n=83 in the placebo group and n=60 in the soy isoflavone group). In the group that received the soy isoflavone supplement, the mean plasma genistein level increased during the study from 4.87 ng/mL to 37.67 ng/mL (P < .001) (eTable 2 in Supplement 2), although individual responses were highly variable. Mean plasma genistein increased slightly in the placebo group (from 5.10 ng/mL to 7.11 ng/mL; P = .22). Overall, the ratio of the estimate of mean week 24 plasma genistein divided by mean baseline plasma genistein for those receiving soy isoflavone compared with placebo was 5.5 (95% CI, 2.70–11.39; P < .001). In this subset, there was no association between the increase in plasma genistein achieved during treatment and the change in FEV_1.

Treatment-Related Adverse Events and Symptoms

There were few serious adverse events in either treatment group and no statistically significant differences between the groups (Table 4). Multiple symptoms were reported by both groups during the study (Table 5), but there were no statistically significant differences in any of them, including breast tenderness. In the subset of participants who were menstruating women (46%), the number reporting a change in menstrual symptoms or menstrual cycle was not statistically different between the 2 treatment groups.

Discussion

Providing a soy isoflavone supplement twice daily to patients with poorly controlled asthma who were already taking a controller medicine did not improve their FEV_1 The supplement also did not improve additional aspects of asthma control, including other measures of lung function, symptoms, quality of life, and airway and systemic inflammation. This finding is despite evidence that plasma genistein increased to levels that inhibit eosinophil cysteinyl leukotriene synthesis in vitro and ex vivo. Although the study results are disappointing in view of the preclinical, epidemiologic, and pilot clinical data, they illustrate the limitations of cross-sectional, population-based studies of dietary nutrient intake and the use of surrogate markers of disease to predict clinically relevant outcomes of well-designed, carefully performed, and adequately powered intervention studies in patients with asthma.

Of the several mechanisms proposed to explain the increased prevalence and severity of asthma over the last several decades,[1,2,26] change in diet is a likely candidate. In the general population, decreased consumption of fresh fruits, green vegetables, potatoes, and fresh fish,

important sources of antioxidants and essential nutrients, has been associated with decreased lung function,[27] a characteristic feature of asthma. Both epidemiologic and mechanistic studies support a role for diet as a risk factor for asthma.[28] Yet the exact contribution of specific nutrients and antioxidant vitamins remains controversial and at times confusing.[6–8,28–31] This could be due at least in part to the studies being underpowered, enrolling patients with asthma whose disease was well controlled and unlikely to show improvement, and choosing interventions for which there was limited preclinical support.

We tested a soy isoflavone mix consisting primarily of genistein and daidzein because of the strong epidemiologic and preclinical data supporting a role for genistein in health and disease[32–34] and asthma in particular. Genistein is a small-molecule (molecular weight, 270 g/mol), broad-spectrum inhibitor of tyrosine kinases[35] with biological effects that one might predict would have beneficial effects in patients with asthma. For example, genistein reduces antigen-induced guinea pig airway inflammation and airway hyperresponsive ness in vivo,[36] facilitates bronchial vascular smooth muscle relaxation,[37] and, in combination with daidzein, inhibits antigen-induced eosinophilia in guinea pigs.[38] At the cellular level, genistein exerts potent antioxidant effects that are equal to or greater than those of vitamin C.[35,39] These molecular, cellular, and physiological properties and others make genistein a seemingly attractive agent for treating asthma.

Previous studies in 2 broadly representative groups of patients with asthma demonstrated that those who consume soy isoflavones have better lung function than those who do not.[3,4] A report from Japan identified an association between high intake of soy isoflavones and a lower prevalence of allergic rhinitis,[40] a disease linked to asthma. To our knowledge, only 1 other study has explored the association between dietary intake of flavonoids and asthma in adults.[32] That study failed to find an association between flavonoid intake and asthma prevalence or severity, but it did not specifically examine the effect of soy isoflavones. Recent in vitro results from our group showed that genistein, at levels achievable in plasma, inhibits synthesis of human peripheral blood eosinophil cysteinyl leukotrienes, important mediators of asthma. This effect occurred via inhibition of 5-lipoxygenase.[5]

In view of these preclinical and clinical findings and the low baseline intake and plasma levels of genistein and inadequately controlled asthma in the current study population, why did this study not demonstrate a positive effect? There are several possible explanations. First, the dosage administered (49 mg/d of soy isoflavones) may have been too low. We chose a dosage that was deemed physiologically relevant[3,4] and supported by our in vitro eosinophil leukotriene C_4 experiments,[5] in which the IC_{50} was80nM(21 ng/mL). The dosage was approximately twice the genistein and daid-zein consumed by men and women in Japan (typically 25–50 mg/d),[40,41] where the prevalence of asthma symptoms among children and adolescents is lower than in Western nations,[42] and well above the median intake in our participants (eTable 1 in Supplement 2). The dosage was also chosen to avoid potential adverse effects.

A second possibility is that this particular soy isoflavone supplement was not adequately absorbed. In our pilot study, we observed ex vivo inhibition of blood eosinophil leukotriene C_4 synthesis after ingestion of the same dose. Trough plasma levels of genistein in the

majority of participants receiving the supplement in the current study exceeded the IC_{50} identified in the in vitro study. Nonetheless, we found substantial variability in plasma genistein levels after administration of the supplement, consistent with previous studies demonstrating variable uptake of genistein in the general population.[43]

Third, the beneficial effects of soy isoflavones may be related to intestinal production of the estrogenic metabolite equol,[44] and differences in equol production between racial/ethnic groups (about 80% of individuals in China and Japan are equol producers in contrast to 25% in the United States[45]) may explain the reported differences in benefits. Fourth, there may be confounding by intake of other nutrients; however, we found no differences in diet between the groups, nor did we observe changes in diet over time. Fifth, asthma is a heterogeneous disease, which may make it difficult to identify the effects of novel treatments if benefit is limited to a subgroup with specific phenotypic or genetypic characteristics.

This study has some limitations. One is the population chosen for the study. Although the participants had inadequately controlled asthma as defined by low ACT scores and reduced lung function, which increased the likelihood of seeing a beneficial effect, they had little evidence of airway or systemic inflammation at baseline. Although we did not have induced sputum samples to directly assess airway inflammation, it is possible that a group that may have benefited most, those with airway inflammation, was not adequately represented. Another limitation is that the 6-month treatment period was not long enough to see a beneficial effect on secondary outcomes such as episodes of poor asthma control. A third limitation is that, knowing the purpose of the study, participants may have altered their diet to include more soy isoflavones, including isoflavone supplements. We specifically addressed this possibility by having all individuals complete food frequency and soy intake questionnaires at the beginning and at the end of the treatment period, by measuring plasma genistein levels, and by counseling participants on maintaining their usual diet throughout the study.

Conclusions

Among adults and children aged 12 years or older with poorly controlled asthma while taking a controller medication, use of a soy isoflavone supplement, compared with placebo, did not result in improved lung function or clinical outcomes, including symptoms, episodes of poor asthma control, or systemic or airway inflammation. These findings suggest that this supplement should not be used for patients with poorly controlled asthma.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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Daniels Midland) otherwise had no role in the design and conduct of the study; collection, management, analysis, and interpretation of the data; preparation, review, or approval of the manuscript; or decision to submit the manuscript for publication. They did see a near-final version of the manuscript before its submission.

Group Information

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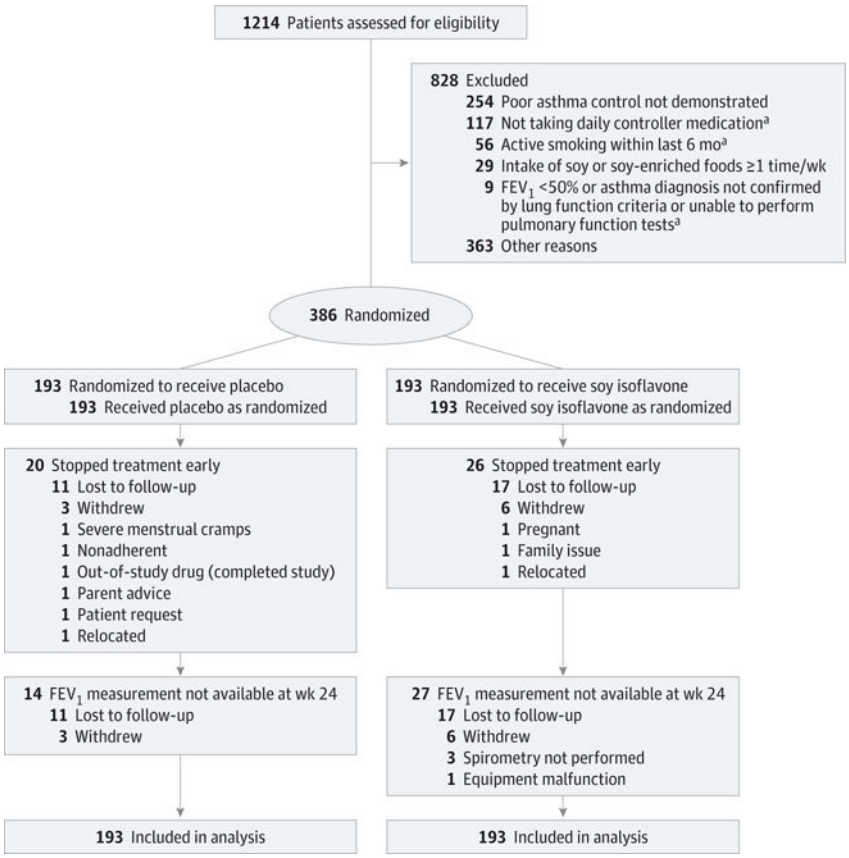

Figure 1. Flow of Participants in the Study of Soy Isoflavones in Asthma Randomized Clinical Trial

FEV_1 indicates forced expiratory volume in the first second.

[a]For 1 individual in this group, it was also reported that poor asthma control was not demonstrated.

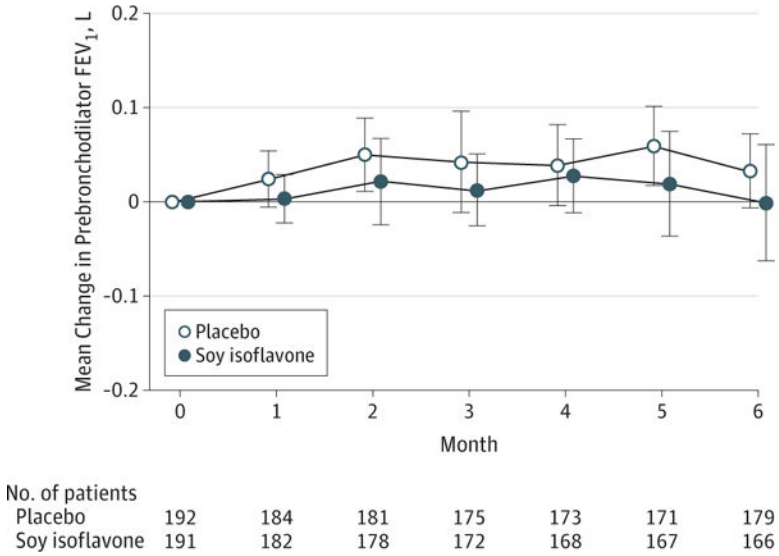

Figure 2. Change in Prebronchodilator FEV_1 During 24 Weeks of Treatment

Model-based mean change in prebronchodilator forced expiratory volume in the first second (FEV_1) at each study visit compared with baseline values. Error bars indicate with 95% confidence intervals. Evaluable FEV_1 results were not available at the randomization visit for 1 participant in the placebo group and 2 participants in the soy isoflavone group.

Table 1

Baseline Characteristics of Participants in the Study of Soy Isoflavones in Asthma

Characteristics	All (n=386)	Placebo (n=193)	Soy Isoflavone (n=193)
Age, median (IQR), y	36 (18–49)	38 (17–49)	34 (20–49)
Female, No. (%)	254 (66)	125 (65)	129 (67)
Race or ethnic group, No. (%)			
White	147 (38)	75 (39)	72 (38)
Black	179 (47)	90 (44)	89 (47)
Hispanic	47 (12)	23 (12)	24 (13)
Other	10(3)	4(2)	6 (3)
Body mass index, median (IQR)[a]	28 (24–35)	27 (23–34)	29 (24−35)
Age at asthma onset, median (IQR), y	8(2−22)	6 (1−20)	9 (2−23)
Emergency visit in past 12 mo, No. (%)	296 (77)	148 (77)	148 (77)
Steroid burst in past 12 mo, No. (%)	195 (51)	94 (49)	101 (53)
Controller medications, No. (%)			
Inhaled corticosteroids alone	89 (23)	49 (25)	40 (21)
Inhaled corticosteroids + long-acting β-agonists	283 (74)	135 (70)	148 (77)
Oral antileukotrienes	129 (34)	64 (33)	65 (34)
Other	10(3)	3 (2)	7 (4)
Asthma score, median (IQR)			
Asthma Control Test (range, 5–25)[b]	17 (14–19)	17 (14–20)	17 (14–19)
Asthma Symptoms Utility Index (range, 0–1)[b]	0.80 (0.67–0.89)	0.80 (0.67–0.89)	0.82 (0.69–0.89)
Quality-of-life scores, median (IQR)			
Marks Asthma Quality of Life Questionnaire (range, 0–80)[c,d]	15 (9–27)	16 (8–26)	15 (10–28)
Children's Health Survey for Asthma (range, 0–100)[b,e]			
Physical health	89 (75–95)	89 (75–95)	89 (76–94)
Activity, child	90 (75–100)	95 (75–100)	90 (75–100)
Activity, family	100 (91–100)	100 (91–100)	100 (91–100)
Emotion, child	85 (50–100)	90 (55–100)	82 (50–95)
Emotion, family	79 (64–89)	80 (63–92)	76 (64–86)
Lung function, median (IQR)			
FEV_1, L	2.43 (1.99–2.91)	2.44 (1.96–2.93)	2.40 (2.01–2.91)
FEV_1, % predicted	82.1 (69.8–92.6)	83.4 (71.9–92.1)	80.1 (68.3–93.3)
FEV_1 bronchodilator response, %[f]	8.77 (3.94–14.29)	7.90 (3.44–14.26)	9.04 (4.57–14.49)
Forced vital capacity, L	3.39 (2.77–4.09)	3.40 (2.77–3.99)	3.39 (2.78–4.16)
Forced vital capacity, % predicted	93.7 (83.8–103.8)	93.7 (83.5–103.7)	94.0 (84.0–104.0)
Peak flow, L/min	350 (300–420)	360 (300–423)	350 (300–420)
Peak flow, % predicted	83.8 (69.3–95.1)	85.8 (69.7–96.2)	82.4 (68.6–94.7)

Characteristics	All (n=386)	Placebo (n=193)	Soy Isoflavone (n=193)
Biomarkers, median (IQR)[g]			
Exhaled nitric oxide, ppb	25 (15–46)	25 (17–52)	25 (15–43)
Eosinophil count, /μL	235 (130–430)	230 (122–410)	240 (140–450)
Interleukin 6, serum, pg/mL	1.4 (0.9–2.6)	1.4 (0.9–2.3)	1.4 (0.9–2.7)
Serum C-reactive protein, mg/L	1.8 (0.6–4.9)	1.7 (0.6–4.3)	2.1 (0.6–5.4)
Urinary leukotriene E_4/creatinine, nmol/mol	12.1 (7.2–20.7)	12.3 (7.2–20.3)	11.9 (7.2–21.0)

Abbreviations: FEV,, forced expiratory volume in the first second; IQR, interquartile range.

[a] Body mass index is calculated as weight in kilograms divided by height in meters squared.

[b] Higher scores indicate less severe disease.

[c] Lower scores indicate less severe disease.

[d] The Marks Asthma Quality of Life Questionnaire was assessed in participants aged 17 years or older.

[e] The Children's Health Survey for Asthma was assessed in participants aged 12 to 16 years.

[f] FEV_1 bronchodilator response is calculated as 100 × (postbronchodilator FEV_1 - prebronchodilator FEV_1)/prebronchodilator FEV_1.

[g] Normal ranges for biomarkers are as follows: exhaled nitric oxide, 2–25 ppb; eosinophil count, 0–600/μL; interleukin 6, 0.31–5.0 pg/mL; C-reactive protein, 0–10 mg/L; urinary leukotriene E_4/creatinine, 0.7–28.9 nmol/mol.

Table 2

Model-Based Estimates of Mean Change From Baseline to 24 Weeks for Lung Function, Asthma Scores, and Laboratory Markers

Outcomes	Mean Difference, 24 Weeks - Baseline (95% CI)		*P* Value
	Placebo (n = 193)	Soy Isoflavone (n = 193)	
FEV_1, L	0.03 (−0.01 to 0.08)	−0.001 (−0.07 to 0.07)	.36
FEV_1 bronchodilator response, %[a]	−1.24 (−3.35 to 0.88)	−0.05 (−1.71 to 1.61)	.49
Forced vital capacity, L	0.03 (−0.01 to 0.08)	−0.03 (−0.08 to 0.02)	.04
Peak flow, L/min	15.8 (4.4 to 27.2)	9.6 (−0.4 to 19.6)	.34
Asthma Control Test score (range, 5–25)[b]	1.98 (1.42 to 2.54)	2.20 (1.53 to 2.87)	.53
Asthma Symptoms Utility Index score (range, 0–1)[b]	0.06 (0.03 to 0.09)	0.06 (0.04 to 0.09)	.79
Marks Asthma Quality of Life Questionnaire score (range, 0–80)[c,d]	−4.30 (−6.07 to −2.54)	−2.99 (−4.73 to −1.24)	.25
Children's Health Survey for Asthma score (range, 0–100)[b,e]			
Physical health[f]	4.77 (−0.29 to 9.82)	7.52 (1.92 to 13.13)	.49
Activity, child	4.65 (1.59 to 7.72)	5.53 (0.78 to 10.28)	.69
Activity, family	2.49 (0.62 to 4.36)	−0.37 (−1.54 to 0.79)	.03
Emotion, child	4.34 (−1.78 to 10.47)	7.13 (3.17 to 11.09)	.44
Emotion, family	3.50 (0.95 to 6.06)	1.23 (−1.68 to 4.14)	.29
Exhaled nitric oxide, ppb	−3.48 (−5.99 to −0.97)	1.39 (−1.73 to 4.51)	.007
Eosinophil count, /μL[g]	1.09 (0.71 to 1.66)	1.06 (0.72 to 1.56)	.91
Interleukin 6, pg/mL[g]	0.98 (0.90 to 1.09)	0.98 (0.90 to 1.06)	.98
Serum C-reactive protein, mg/L[g]	1.03 (0.91 to 1.15)	0.98 (0.86 to 1.12)	.61
Urinary leukotriene E_4/creatinine, nmol/mol[g]	1.01 (0.86 to 1.18)	1.04 (0.89 to 1.22)	.81

Abbreviation: FEV_1, forced expiratory volume in the first second.

[a] FEV_1 bronchodilator response is calculated as 100 × (postbronchodilator FEV_1 - prebronchodilator FEV_1)/prebronchodilator FEV_1.

[b] Higher scores indicate less severe disease.

[c] Lower scores indicate less severe disease.

[d] The Marks Asthma Quality of Life questionnaire was assessed in participants aged 17years or older.

[e] The Children's Health Survey for Asthma was assessed in participants aged 12 to 16 years.

[f] No random intercept for clinic was included in the model for Children's Health Survey for Asthma physical health score because of lack of convergence.

[g] Differences were calculated on a log scale and transformed to give the ratio of the estimates of the week 24 value divided by the baseline value.

Table 3

Secondary Outcomes Based on Participant Diary Cards

Outcomes	Treatment Group			
	Placebo (n=185)	Soy Isoflavone (n=182)	Relative Risk (95% CI)	*P* Value
No. of person-years of follow-up	80.3	78.6		
Episodes of poor asthma control[a]				
No. of events	269	235		
No. of individuals with >1 event	102	93		
No. of events/ person-year (95% CI)	3.3 (2.7–4.1)	3.0 (2.4–3.7)	0.89 (0.66–1.21)	.46
Exacerbation components				
Peak flow, 30% decrease				
No. of events	123	117		
No. of individuals with >1 event	45	43		
No. of events/ person-year (95% CI)	1.5 (1.0–2.2)	1.4 (0.9–2.2)	0.98 (0.57–1.68)	.94
Urgent care				
No. of events	29	27		
No. of individuals with >1 event	25	22		
No. of events/ person-year (95% CI)	0.3 (0.2–0.5)	0.3 (0.2–0.5)	0.95 (0.54–1.66)	.85
New use of oral steroids				
No. of events	35	30		
No. of individuals with >1 event	31	28		
No. of events/ person-year (95% CI)	0.4 (0.3–0.6)	0.4 (0.2–0.5)	0.87 (0.54–1.43)	.59
Rescue medications				
No. of events	147	124		
No. of individuals with >1 event	60	60		
No. of events/ person-year (95%CI)	1.8 (1.3–2.5)	1.6 (1.1–2.4)	0.92 (0.61–1.39)	.69
Symptom-free days, median (interquartile range), %	65 (17–84)	60 (2–86)		.41

[a]Episodes of poor asthma control are defined by one of the following: ≥30% decrease in morning peak expiratory flow (from personal best) for 2 consecutive days (definite yellow zone event according to the National Heart, Lung, and Blood Institute's Asthma Action Plan), addition of oral corticosteroid to treat asthma symptoms, unscheduled contact with a health care practitioner (emergency department, physician office, hospital) for asthma symptoms, increased use of bronchodilator rescue medication from baseline by 4 or more puffs of metered-dose inhaler or 2 or more nebulizer treatments on 1 day.

Table 4

Treatment-Related Serious Adverse Events by Treatment Group

	Placebo (n=193)	Soy Isoflavone (n=193)
Follow-up time, person-years	85.61	83.79
Events, No. (%)		
Pulmonary, including asthma exacerbations	8(4)	3(2)[a,b]
Cardiovascular, circulatory, and lymphatic	0	1 (0.5)[b]
Renal/urinary	1 (0.5)	0
Gastrointestinal	0	2(1)
Neuropsychiatric	0	4(2)
Musculoskeletal	1 (0.5)	3 (2)
Reproductive	1 (0.5)	1 (0.5)
Integumentary	1 (0.5)	0
Total	12	14

[a]One patient had both a pulmonary and a gastrointestinal serious adverse event.

[b]One patient had both a pulmonary and a cardiovascular serious adverse event.

Table 5

Treatment-Related Symptoms by Treatment Group

Symptoms	No. at Risk[a]	With Symptoms at 24 wk, %[b]		Hazard Ratio (95% CI)[c]	*P* Value[c]
		Placebo	Soy Isoflavone		
Rash	327	25	23	0.97 (0.62–1.51)	.91
Itching	286	32	32	1.00 (0.66–1.51)	>.99
Difficulty breathing	158	61	57	0.94 (0.61–1.43)	.77
Difficulty swallowing	350	21	18	0.85 (0.52–1.37)	.50
Hypotension	362	5	7	1.42 (0.63–3.20)	.40
Breast tenderness	355	13	12	0.91 (0.51–1.65)	.78
Change in menstrual symptoms/cycle[d]	133	55	59	1.23 (0.78–1.94)	.37

[a] Thirteen individuals were excluded because of lack of follow-up. The number at risk includes all individuals who did not have the particular symptom at baseline.

[b] Estimates of the percentage with a symptom are based on Kaplan-Meier estimates of the survival function.

[c] Hazard ratios were computed using a frailty model with a random effect for clinic and robust confidence limits.

[d] Analysis limited to women with a menstrual period within the last 12 months. Changes were defined as experiencing a heavier or lighter flow, spotting between periods, or more or less discomfort or cramping than usual.