Individualized therapy for persistent asthma in young children

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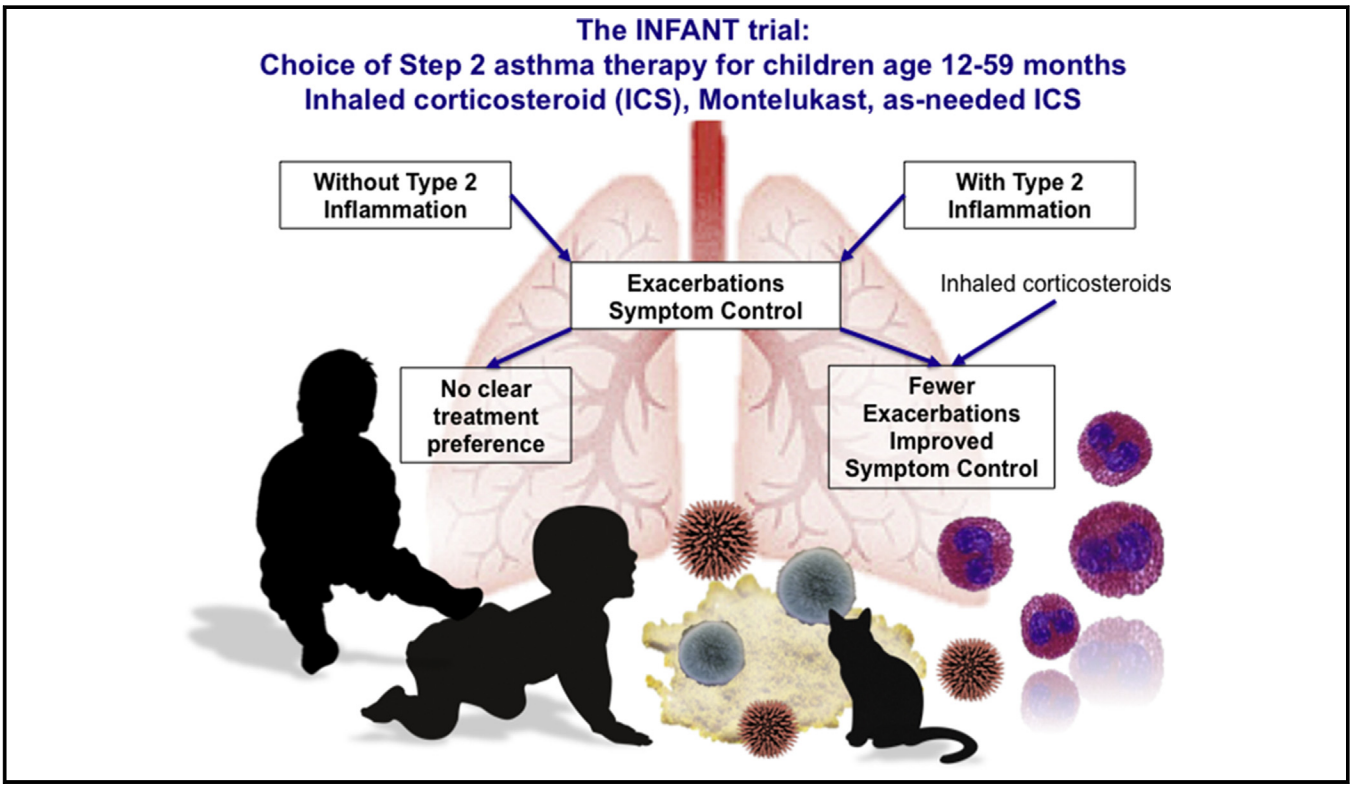
GRAPHICAL ABSTRACT



Background: Phenotypic presentations in young children with asthma are varied and might contribute to differential responses to asthma controller medications.

Methods: The Individualized Therapy for Asthma in Toddlers study was a multicenter, randomized, double-blind, double-dummy clinical trial in children aged 12 to 59 months (n = 300) with asthma necessitating treatment with daily controller (Step 2) therapy. Participants completed a 2- to 8-week run-in period followed by 3 crossover periods with daily inhaled corticosteroids (ICSs), daily leukotriene receptor antagonists, and as-needed ICS treatment coadministered with albuterol. The primary outcome was differential response to asthma medication based on a composite measure of asthma control. The primary analysis involved 2 stages: determination of differential response and assessment of whether 3 prespecified features (aeroallergen sensitization,

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previous exacerbations, and sex) predicted a differential response.
Results: Seventy-four percent (170/230) of children with analyzable data had a differential response to the 3 treatment strategies. Within differential responders, the probability of best response was highest for a daily ICS and was predicted by aeroallergen sensitization but not exacerbation history or sex. The probability of best response to daily ICS was further increased in children with both aeroallergen sensitization and blood eosinophil counts of 300/μL or greater. In these children daily ICS use was associated with more asthma control days and fewer exacerbations compared with the other treatments.
Conclusions: In young children with asthma necessitating Step 2 treatment, phenotyping with aeroallergen sensitization and blood eosinophil counts is useful for guiding treatment selection and identifies children with a high exacerbation probability for whom treatment with a daily ICS is beneficial despite possible risks of growth suppression. (J Allergy Clin Immunol 2016;138:1608-18.)

Key words: *Asthma, asthma treatment, asthma biomarkers, asthma phenotype, inhaled corticosteroid, leukotriene receptor antagonist, personalized medicine, treatment response*

Although asthma treatment guidelines[1,2] have proved useful in care standardization and reduction of adverse outcomes,[3] there is phenotypic heterogeneity within the disorder and growing appreciation for "personalized" medicine as opposed to a "one-size-fits-all" treatment approach.[4,5] Young children are particularly diverse, with numerous and variable phenotypic presentations in early life that correspond to different outcomes,[6-9] yet they are incompletely studied, and significant treatment gaps remain.[10,11] Even among young children who warrant treatment with daily inhaled corticosteroids (ICSs), the response to ICSs is inconsistent,[12] perhaps because of differences in symptom presentation, persistence,[13] or both or other underlying inflammatory features.[14] Indeed, many young children have asymptomatic periods between viral respiratory illnesses,[15] raising the question of whether daily therapy with ICSs is warranted in all children because ICS administration does not significantly alter the long-term disease course[16] and might contribute to dose-dependent and sustained reductions in linear growth in selected subpopulations.[17,18]

Given these challenges and the mandate for personalized and more efficient medicine,[19] the Individualized Therapy for Asthma in Toddlers (INFANT) trial characterized phenotypic heterogeneity in young children with asthma necessitating treatment with daily controller medications (ie, Step 2 therapy[2]) and examined the relationship of phenotypic features and biomarkers to asthma medication response profiles. For the first time, this study demonstrates differential responses to asthma medications in young children that can be predicted with clinical biomarkers. The results support personalization of asthma therapy and highlight a phenotype of children with aeroallergen sensitization and increased blood eosinophil counts at risk for exacerbation for whom daily ICS treatment is beneficial despite the possible risk of growth suppression.

Abbreviations used
ACD: Asthma control day
ECP: Eosinophil cationic protein
ICS: Inhaled corticosteroid
INFANT: Individualized Therapy for Asthma in Toddlers
LTE_4: Leukotriene E_4
LTRA: Leukotriene receptor antagonist
mAPI: Modified Asthma Predictive Index
PEAK: Prevention of Early Asthma in Kids

METHODS

Study design and oversight

The INFANT trail was a multicenter, randomized, double-blind, double-dummy clinical trial conducted from March 2013 through April 2015. A run-in period of 2 to 8 weeks was followed by a randomized crossover of three 16-week treatment periods with daily ICS (fluticasone propionate, 2 inhalations, 44 μg each, twice daily; GlaxoSmithKline, Evreux, France), daily leukotriene receptor antagonist (LTRA) (montelukast, 4 mg, once daily at bedtime; Merck and Co, Whitehouse Station, NJ), and as-needed ICSs coadministered with an open-label short-acting bronchodilator for symptom relief (fluticasone propionate, 2 inhalations, 44 μg each; albuterol sulfate, 2 inhalations, 90 μg each; GlaxoSmithKline, Research Triangle Park, NC; Fig 1, *A*). Antipyretic/analgesic therapy was blinded and controlled in a linked protocol (NCT01606319) through a factorial design. Details of that study were previously published.[20] Children were randomized in 2 processes: the first determined the crossover sequence of asthma therapy, and the second determined the blinded antipyretic/analgesic medication to be used as needed for fever or pain throughout the 48-week duration of the crossover study, with stratification by clinical center.

The National Heart, Lung, and Blood Institute's Asthma Network (AsthmaNet) funded the study, which was managed by a Data Coordinating Center (Hershey, Pa). The protocol was developed by the AsthmaNet Steering Committee (NCT01606306) and was approved by an external protocol review committee, a data safety monitoring board, and each site's institutional review board. Caregivers provided written informed consent.

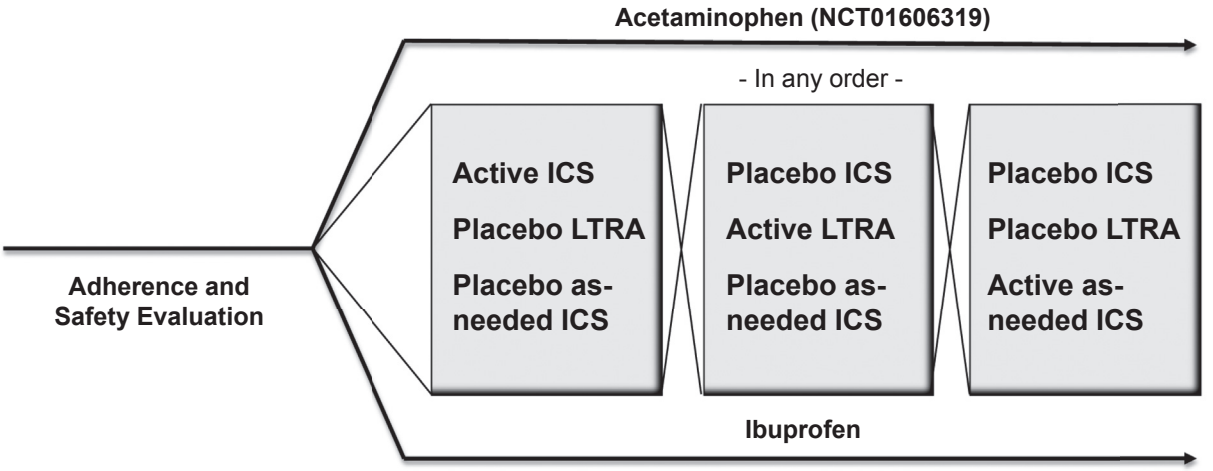
Sites and patients

The study was conducted in children 12 to 59 months of age at 18 sites in the United States. Children were recruited for the study through a variety of methods, including advertisements, primary care and specialty care clinic referrals, and screenings of urgent care facility visits and after-hours telephone logs. Children were eligible for study entry if they met guideline-based criteria for daily asthma controller medication (ie, Step 2 treatment).[2] To encourage recruitment and generalization of results, this protocol enrolled ICS- and LTRA-naive children treated only with intermittent bronchodilators who required step-up therapy, as well as children currently treated with low-dose ICSs or LTRAs for whom daily controller therapy was warranted. Children symptomatic on current ICSs or LTRAs were enrolled with the rationale that (1) they might require treatment with LTRAs and not ICSs or *vice versa*, (2) they might benefit from the ICS formulation (ie, directly inhaled vs nebulized), and (3) medication delivery might be improved with educational intervention and adherence monitoring.

Children were eligible for the study irrespective of current medication use if their caregivers reported daytime asthma symptoms more than 2 days per week (averaged over the preceding 4 weeks), nighttime awakening from asthma at least once over the previous 4 weeks, or 4 or more wheezing episodes, each lasting 24 or more hours, in the preceding 12 months. Children not receiving current ICS or LTRA treatment were also eligible if they reported 2 or more exacerbations requiring systemic corticosteroids in the preceding 6 months. Children receiving current ICS or LTRA treatment were also eligible if they reported ICS or LTRA receipt for more than 90 days during the preceding 6 months or 2 or more exacerbations requiring systemic corticosteroids in the preceding 12 months.

Run-in period

Eligible children received 1 oral medication and 1 inhaled medication for daily use: open-label albuterol sulfate and open-label prednisolone. The run-in



Run-in: 2-8 Weeks	Treatment Phase: 48 weeks						
	Period 1		Period 2		Period 3		
Week	0	4	16	20	32	36	48
Diary	+	+	+	+	+	+	+
Height	+	+	+	+	+	+	+
Blood	+						
Urine	+						

FIG 1. Study diagram and procedures. *Blood,* Blood collection; *Diary,* electronic diary distribution and data review; *Height,* height measurement; *Urine,* urine collection. +, Procedure was performed.

duration was variable and based on whether the child was currently receiving Step 2 therapy (ie, daily low-dose ICS or LTRA) and whether the child qualified based on exacerbation history. Children not receiving Step 2 therapy during the 6 months before enrollment (including children who received ICSs or LTRAs intermittently) received placebo oral and inhaled therapy during the run-in period. The run-in period was completed in 2 weeks if the participant had a previous exacerbation requiring systemic corticosteroids. If the participant did not have an exacerbation, the run-in period could be extended up to 8 weeks to elicit symptoms. Children who were currently receiving Step 2 therapy received active ICSs or active LTRAs during the run-in period. If the participant had a previous exacerbation requiring systemic corticosteroids, the run-in period was completed in 2 weeks. If not, the run-in period lasted 4 weeks in total. Caregivers recorded symptoms, health care use, and medication use in electronic diaries each day at bedtime (Spirotel; Medical International Research, Rome, Italy). Children were ineligible for randomization if the following were observed during the run-in period: (1) completion of less than 75% of daily electronic diaries, (2) an exacerbation requiring systemic corticosteroids, (3) daily asthma symptoms if not receiving active therapy, or (4) asthma symptoms for more than 2 days per week if receiving active therapy. Further details are provided in Fig 1 and in the Methods section in this article's Online Repository at www.jacionline.org.

Biomarker determination

Peripheral blood eosinophil counts were determined from one aliquot of whole blood by using an automated assay at each clinical site. Eosinophil cationic protein (ECP)[21] and total serum IgE and specific IgE concentrations were quantified by a commercial laboratory (Advanced Diagnostic Laboratories, National Jewish Health, Denver, Colo). Specific IgE measurement (ImmunoCAP) was performed for a nationally representative panel of inhalant aeroallergens (details provided in the Methods section in this article's Online Repository). Aeroallergen test results were considered positive if values were 0.35 kU/L or greater. Urinary leukotriene E_4 (LTE_4) concentrations were measured by using mass spectrometry, as previously described,[22,23] and were expressed per milligram of creatinine.

Outcome measures

The primary outcome was the differential response to 3 therapies based on fixed threshold criteria for the following asthma control measures, which encompassed domains of risk and impairment[1,2]: the time from the start of the treatment period to an asthma exacerbation treated with systemic corticosteroids and the annualized number of asthma control days (ACDs) from within that period. ACDs were defined as full calendar days without symptoms, rescue medication use, or unscheduled health care visits. Children were defined as differential responders if (1) the time to an asthma exacerbation was at least 4 weeks longer or (2) if the number of annualized ACDs was at least 31 days more for one treatment than another in that order. If neither threshold was met, the participant was considered a nondifferential responder. Four weeks between the onset of treatment and an asthma exacerbation was selected as a clinically meaningful outcome based on the results of a previous study in school-aged children that noted differences in asthma exacerbation prevalence in children treated with fluticasone (16%) versus montelukast (32%) over a 16-week period.[24] A difference of 31 days or more with regard to ACDs was also thought to be clinically meaningful based on the results of a prior study in school-aged children[24] and preschool children at high risk for asthma development.[16]

Differential response was determined in children completing at least 2 treatment periods and at least 50% of the daily diary entries for each period.

Because placebo washouts were not performed, data collected during the first 2 weeks of each period were not included in the analysis of ACDs. Days with missing diary data were also excluded from ACD determination. Secondary outcomes included exacerbations, ACDs, albuterol use, unscheduled health care for asthma, and protocol-defined treatment failures.

Criteria for treatment period failure and study failure

Treatment period failure was achieved if a child experienced 2 exacerbations separated by at least 1 week in a single 16-week treatment period. When 2 exacerbations occurred, the child was advanced to the next treatment period. The criteria for study failure were met if the participant (1) received 4 courses of prednisolone after randomization, (2) was hospitalized for greater than 24 hours for an acute asthma exacerbation, or (3) was moved forward to the next treatment period 2 times during the course of the study.

Statistical analysis

The primary analysis involved 2 stages: (1) testing the null hypothesis of all 3 treatments having equal probability to yield the best response, as defined by the criteria described above, and (2) to determine whether any of 3 prespecified phenotypic characteristics (sensitization to ≥1 aeroallergen, previous exacerbations requiring systemic corticosteroids, and sex) predict different patterns of treatment response. The overall type I error rate for the primary analysis was 0.05 using a significance level of 0.0125 for the first-stage test and for each of the 3 prespecified predictors. Rank-ordered logistic regression[25] was used to model the probability of yielding best response for each treatment, and bootstrapping was used to calculate CIs. Secondary analyses used the generalized linear model framework to compare treatments with respect to secondary outcomes by using the generalized estimating equations approach to incorporate the longitudinal aspect of the crossover design and including period and treatment-by-period interaction effects to examine potential carryover effects. Exploratory analyses used rank-ordered logistic regression to examine other phenotypic characteristics that might predict patterns of treatment response. Prespecified exploratory analyses focused on serum ECP levels[21] and urinary LTE_4 concentrations[26] as predictors of treatment response. Blood eosinophil measurements, specific aeroallergen test results, serum IgE measurements, and modified Asthma Predictive Index (mAPI)[27] status, as defined by a history of 4 or more wheezing episodes plus 1 major criterion (parental history of asthma, physician-diagnosed atopic dermatitis, or allergic sensitization to ≥1 aeroallergen) or 2 minor criteria (allergic sensitization to milk, egg, or peanut; wheezing unrelated to colds; or blood eosinophil counts ≥4%),[28] were examined *post hoc* as potential predictors. Secondary and exploratory analyses used a 0.05 significance level without adjustment for multiple testing. Exploratory models also included allergic sensitization, history of exacerbations, and sex as covariates.

A sample size of 294 participants was selected to test the primary null hypothesis of all 3 treatments having equal probability (one third) to yield the best response with a statistical power of at least 0.90 if any one of the 3 treatments actually has probability of at least one half to yield the best response. This study was also powered to detect differences in patterns of treatment response for the prespecified predictors. The sample size allowed for up to 25% of participants to drop out and up to 45% of participants to not demonstrate differential response.[29] These sample size assumptions were met. SAS statistical software (version 9.4; SAS, Cary, NC) was used for all analyses.

RESULTS

Study patients

Four hundred forty-three children were enrolled, and 300 were randomized (Fig 2). Of these, 42% were sensitized to at least 1 aeroallergen, and 60% had a positive mAPI result (Table I).[28] Specific aeroallergen test results are shown in Table E1 in this article's Online Repository at www.jacionline.org. Two hundred twenty-six children completed all 3 periods, whereas 230 children completed at least 2 periods with adequate diary completion, permitting assessment of a differential response.

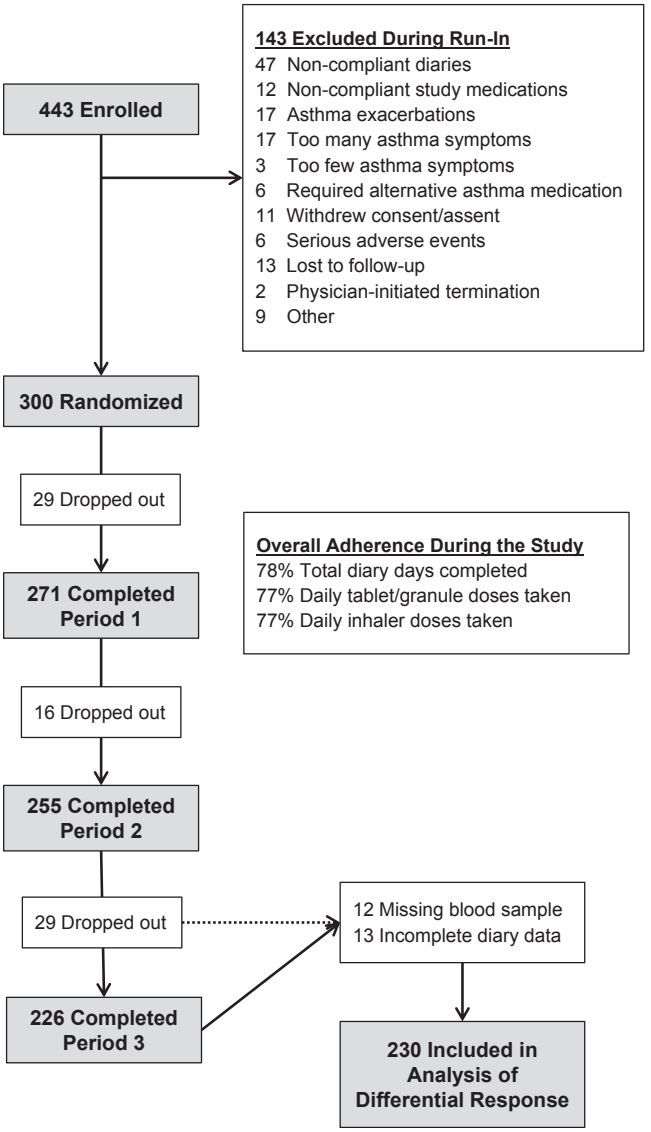


FIG 2. Flow chart depicting the number of participants who enrolled in the study, underwent randomization, completed the study, and provided analyzable data for analysis.

Differential response to the treatment strategies

A differential response to the 3 treatments occurred in 170 (74%) of the 230 children with evaluable data. Among the differential responders, the probability of best response was highest for daily ICS (Fig 3, *A*). Sixty (26%) children did not demonstrate a differential response and had indicators of less disease activity, including more ACDs and lower exacerbation probability (Fig 3, *B* and *C*). Seasonal adjustment did not affect results. No interactions with antipyretic/analgesic use (NCT01606319) were noted. Sensitivity analyses also indicated no interactions based on ICS treatment during the run-in period (see Fig E1, *A*, in this article's Online Repository at

TABLE I. Features of the study participants

	All participants (n = 300)	Not evaluable (n = 70)	Evaluable* (n = 230)	Nondifferential response (n = 60)	Differential response (n = 170)
Age at enrollment (mo)	39.9 ± 13.2	40.3 ± 14.1	39.7 ± 13.0	40.8 ± 12.3	39.4 ± 13.2
Male sex	179 (59.7%)	36 (51.4%)	143 (62.2%)	37 (61.7%)	106 (62.4%)
Race/ethnicity					
African American	97 (32.3%)	31 (44.3%)	66 (28.7%)	23 (38.3%)	43 (25.3%)
White	148 (49.3%)	28 (40.0%)	120 (52.2%)	23 (38.3%)	97 (57.1%)
Hispanic	72 (24.0%)	16 (22.9%)	56 (24.3%)	14 (23.3%)	42 (24.7%)
Parental asthma	178 (59.3%)	36 (51.4%)	142 (61.7%)	36 (60.0%)	106 (62.4%)
Positive mAPI result	181 (60.3%)	39 (55.7%)	142 (61.7%)	39 (65.0%)	103 (60.6%)
Exacerbation history					
Systemic corticosteroid use (previous 12 mo)	224 (74.7%)	51 (72.9%)	173 (75.2%)	39 (65.0%)	134 (78.8%)
Systemic corticosteroid courses (previous 6 mo)	1 (0-2)	1 (0-2)	1 (0-2)	1 (0-1)	1 (0-2)
Urgent/ED visits in past year	3 (1-4)	2 (1-4)	3 (1-4)	2.5 (1-4)	3 (2-5)
Wheezing episodes in past year	5 (3-7)	4.5 (3-7)	5 (3-7)	5 (3.5-7.5)	5 (3-7)
Hospitalized in past year	65 (21.7%)	18 (25.7%)	47 (20.4%)	9 (15%)	38 (22.4%)
Allergic/inflammatory features					
Positive aeroallergen test result	126 (42.0%)	26 (37.1%)	100 (43.5%)	21 (35.0%)	79 (46.5%)
Eczema	160 (53.3%)	34 (48.6%)	126 (54.8%)	35 (58.3%)	91 (53.5%)
Blood eosinophils >4%	123 (41.0%)	27 (38.6%)	96 (41.7%)	21 (35.0%)	75 (44.1%)
Blood eosinophils (per μL)	257.6 (158.4-492.0)	246.6 (175.6-463.5)	257.6 (153.4-495.0)	232.2 (133.2-487.0)	259.6 (162.0-495.6)
Serum IgE (kU/L)	70.0 (22.0-208.0)	64.0 (19.0-313.0)	70.0 (24.0-206.0)	64.0 (26.5-195.0)	77.5 (21.0-208.0)
Serum ECP (μg/L)	11.1 (5.8-21.4)	11.1 (5.8-18.0)	11.1 (5.9-22.2)	10.2 (4.7-22.4)	11.3 (6.3-21.5)
Urinary LTE_4 (pg/mg creatinine)	117.3 (72.0-182.1)	124.2 (74.8-193.7)	115.6 (70.3-178.5)	123.5 (79.1-189.3)	112.4 (64.6-176.3)
Environmental exposures					
Tobacco smoke exposure	110 (36.7%)	33 (47.1%)	77 (33.5%)	20 (33.3%)	57 (33.5%)
Pets in home	139 (46.3%)	27 (38.6%)	112 (48.7%)	25 (41.7%)	87 (51.2%)
Run-in characteristics					
Run-in ICS	189 (63.0%)	40 (57.1%)	149 (64.8%)	38 (63.3%)	111 (65.3%)
Run-in LTRA	18 (6.0%)	3 (4.3%)	15 (6.5%)	4 (6.7%)	11 (6.5%)
Run-in percentage ACDs	85.5% ± 17.6%	86.6% ± 17.4%	85.2% ± 17.7%	89.0% ± 14.4%	83.8% ± 18.6%

Data represent means ± SDs, medians (interquartile ranges), or numbers (percentages) of participants.
ED, Emergency department.
*Includes participants who completed at least 2 study periods with adequate diary completion.

www.jacionline.org) or based on the order in which the study treatments were received (see Fig E1, *B* and *C*).

Primary analysis of prespecified predictors of differential response

The second stage of the primary analysis focused on sensitization to at least 1 aeroallergen, previous exacerbations requiring systemic corticosteroids, and sex as predictors of differential response. Aeroallergen sensitization, but not exacerbation history or sex, was associated with a differential response favoring daily ICS (Fig 4, *A*-*C*).

Exploratory analyses of predictors of differential response

Blood eosinophil counts of 300/μL or greater were also associated with a higher probability of responding best to daily ICS (Fig 4, *D*), and predictive ability was significantly enhanced when both increased eosinophil counts and aeroallergen sensitization were included in the model (Fig 4, *E*). Further analyses demonstrated that serum ECP levels of 10 μg/L or greater and dog and/or cat sensitization also predicted better response to a daily ICS, whereas mAPI status, serum IgE levels, and urinary LTE_4 concentrations did not predict differential response pattern (see Fig E2 in this article's Online Repository at www.jacionline.org). Cut points for quantitative biomarker predictors were identified based on analyses in which they were treated as continuous predictors. No predictor identified a group in which LTRAs or as-needed ICSs were more likely than a daily ICS to yield the best response.

Secondary outcomes

Daily ICS treatment was associated with more ACDs, fewer rescue albuterol inhalations, and fewer exacerbations (see Table E2 in this article's Online Repository at www.jacionline.org). The average weekly ICS dose was approximately 1200 μg of fluticasone in the daily ICS group versus 270 μg of fluticasone in the as-needed ICS group. Descriptive analyses further indicated greater improvement in ACDs (see Fig E3 in this article's Online Repository at www.jacionline.org) and a prolonged time to exacerbation (Fig 5) with daily ICS treatment in children with aeroallergen sensitization, children with blood eosinophil counts of 300/μL or greater, and children with both aeroallergen sensitization and blood eosinophil counts of 300/μL or greater.

Adherence to the study therapies

Seventy-five percent of daily diaries were completed throughout the study. Self-reported adherence to daily medication

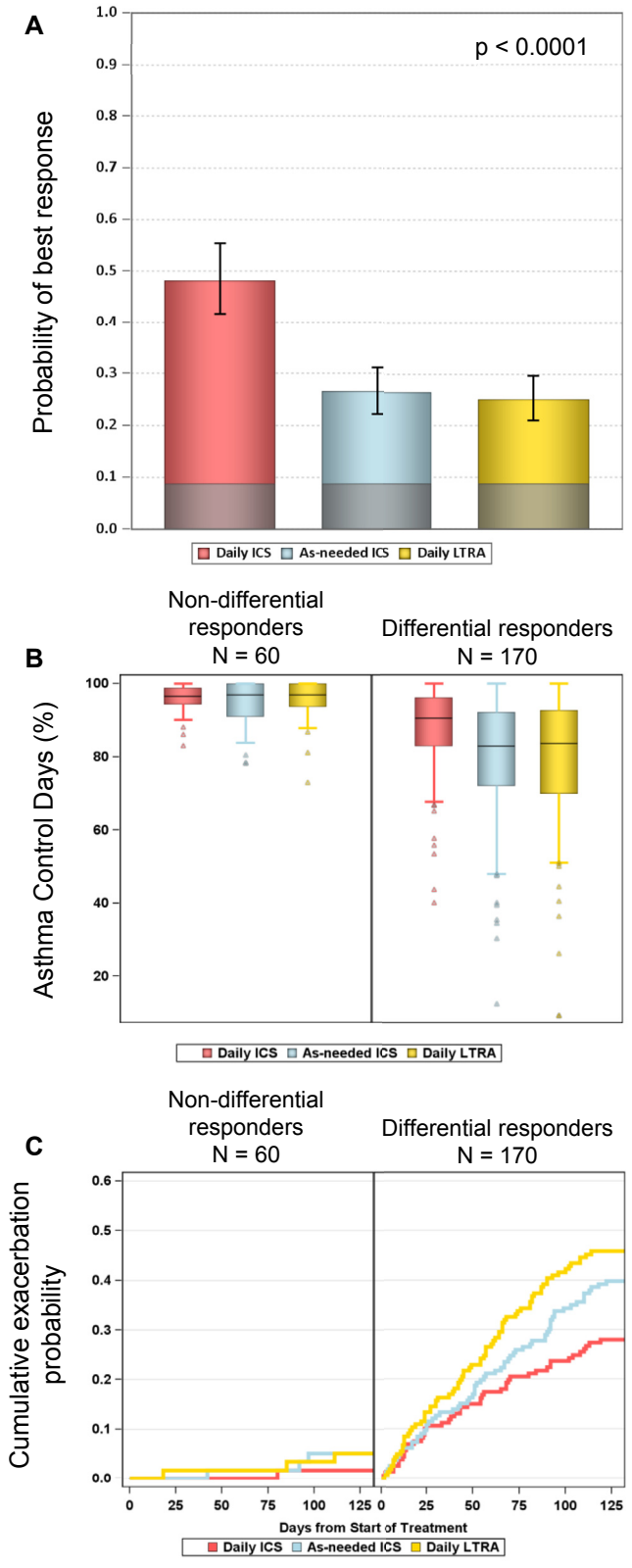


FIG 3. A, Probability of each asthma treatment being the best of the 3. *Gray shading* depicts participants who did not have a differential response. **B** and **C,** Percentage of ACDs (Fig *2*, B) and probability of an exacerbation (Fig 2, *C*). *Box plots* represent the median value, 25th to 75th percentiles *(shading)*, and 5th to 95th percentiles *(whiskers)*. Outliers are shown as *triangles*.

was 96% or greater for all treatments. As-needed ICSs were used concomitantly with albuterol on 99% of occasions per electronic diary report. Albuterol was administered on approximately 70% and 90% of days with mild and moderate-to-severe symptoms reported, respectively.

Adverse events

There were no marked differences in adverse events between treatments (see Table E3 in this article's Online Repository at www.jacionline.org). There was a nonsignificant trend toward decreased height velocity in children treated with a daily ICS (see Table E4 in this article's Online Repository at www.jacionline.org).

DISCUSSION

Young children with asthma are a heterogeneous group of patients with significant morbidity and health care use who are challenging to treat.[30,31] Initial medication selection and timing of delivery are controversial[32,33] given the limited number of studies and overall low quality of evidence in this age group.[34,35] Moreover, although differential responses to asthma medications have been observed in older children[36,37] and argue against a universal treatment approach, no study has assessed how treatment decisions should be made in young children using phenotypic characteristics and biomarkers to estimate the likelihood of improvement. Using a composite measure of asthma control, we found that 74% of young children demonstrated clinically relevant improvements in response to one treatment versus others, most often a daily ICS, and that clinically accessible biomarkers can be used to predict the medication strategy associated with the best response in these children. Furthermore, we noted a phenotype of children with type 2 inflammation evidenced by aeroallergen sensitization and increased blood eosinophil counts for whom daily ICS treatment conferred the most protection against symptoms and exacerbations. Given that young children have nearly 2 to 3 times the rate of emergency department visits and hospitalizations compared with older children,[30,38] these results are clinically important and demonstrate the potential effect of phenotype-directed asthma care in this age group.

Although we were adequately powered for our primary analysis of best response, the proportion of children with a nondifferential response (24%) was substantially greater than in a previous study that found a differential response to Step 3 asthma therapy in greater than 97% of older children.[36] Because pulmonary function testing is challenging in young children, our composite outcome of asthma control included only 2 components, exacerbations and ACDs, which might explain this finding. We were not specifically powered for subanalyses of nondifferential responders, and therefore it remains unclear whether those children have unique inflammatory profiles. However, the asthma control in those children throughout the study might also suggest that some children became candidates for stepdown therapy despite initial qualification for controller medication.

Overall, children with a differential response in this study were most likely to respond best to a daily ICS, which is consistent with other studies demonstrating the efficacy of a daily ICS in this age group overall[12] and regardless of other factors, such as mAPI status.[13,39] However, the overall probability of a best response

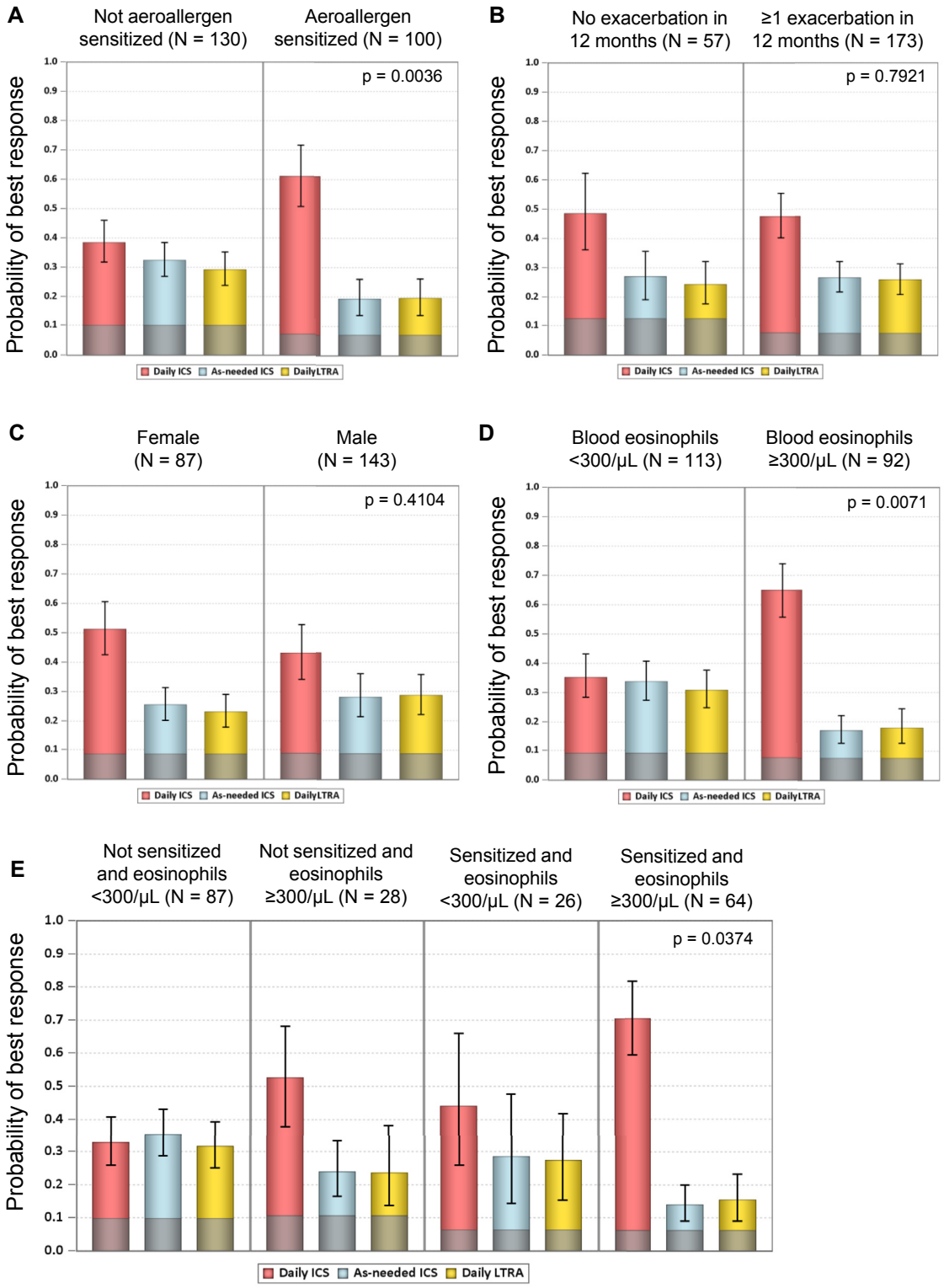


FIG 4. Probability of best response based on aeroallergen sensitization **(A)**, previous exacerbation **(B)**, sex **(C)**, eosinophil count of 300/μL or greater **(D)**, and combination of sensitization and eosinophil counts **(E)**. *P* values correspond to the test of interaction between the predictor and treatment and indicate whether the pattern of treatment response differs according to subgroup. Sample sizes correspond to participants with evaluable data (n = 230).

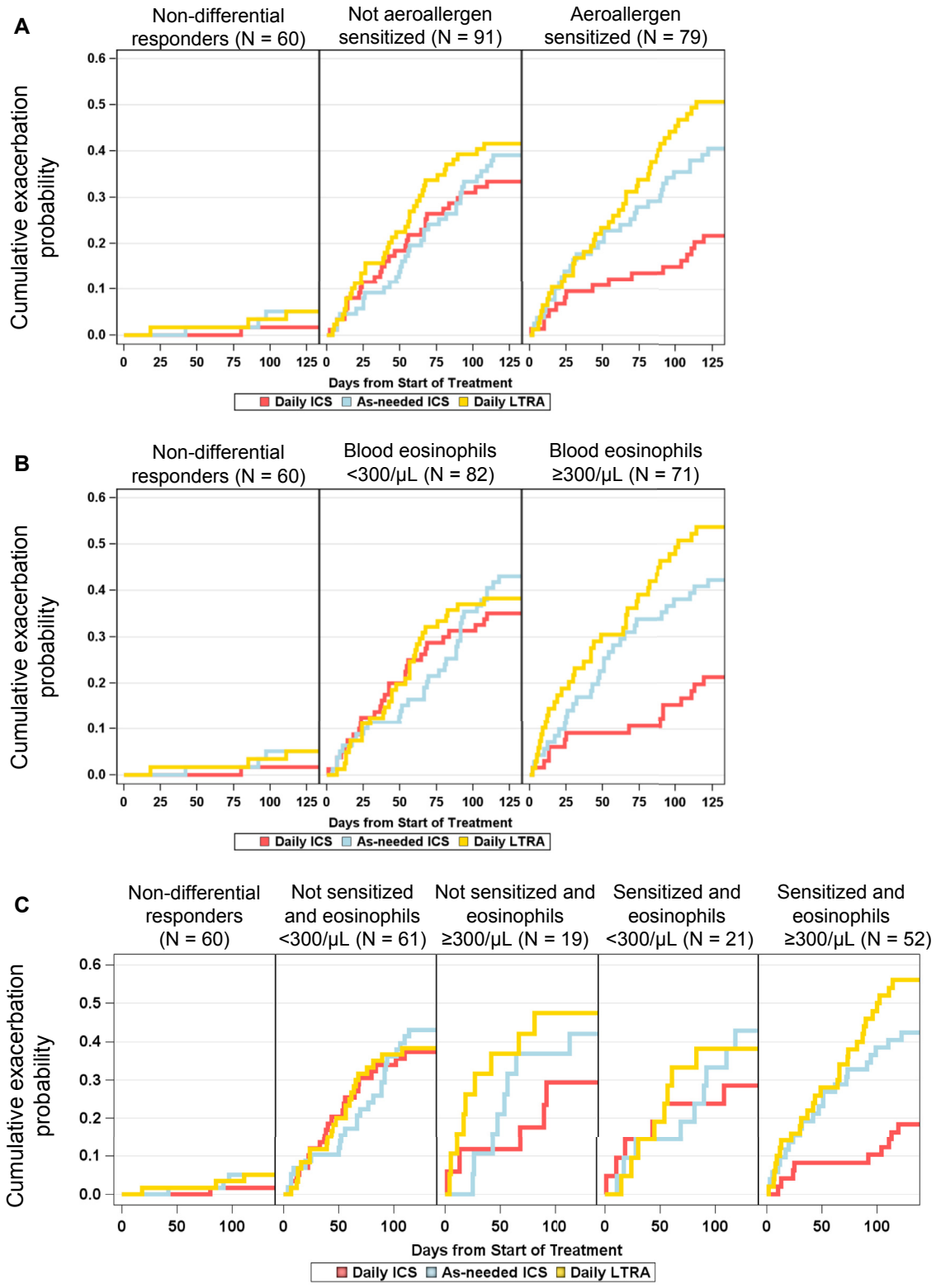


FIG 5. Cumulative probability of an exacerbation requiring systemic corticosteroids for all participants with evaluable data (n = 230) stratified by aeroallergen sensitization **(A)**, blood eosinophil counts of 300/μL or greater **(B)**, and combinations of aeroallergen sensitization and blood eosinophil counts **(C)**.

to ICS was only 0.40 when nondifferential responders are considered, highlighting the need for personalized medicine with the right therapies for the right patients.[19] Indeed, many participants had a best response to a daily LTRA or as-needed ICS.

Although we were unable to identify clear predictors of best response to these therapies, further study is warranted because these therapies are useful for many children. For example, a study of older children with mild persistent asthma noted similar efficacy between intermittent low-dose ICS and daily ICS treatment with regard to exacerbations.[40] Other studies in preschool children demonstrate that pre-emptive high-dose ICS treatment (ie, 1500-2000 μg of fluticasone equivalent) can reduce systemic corticosteroid requirements,[29,41] although a recent systematic review was unable to firmly conclude equivalence between daily low-dose and pre-emptive high-dose ICS therapy because of the limited number of head-to-head comparisons.[13] The double-dummy design of the present study prevented a similar treatment strategy and is acknowledged as a potential limitation. Other studies in young children have also demonstrated improved asthma outcomes with LTRA, with minimal adverse effects[42-44] and greater tolerability.[45]

The INFANT trial was not designed to study treatment group means for individual outcomes as a whole but rather to study responses at the individual patient level based on the composite outcome incorporating both the risk and impairment domains, with an emphasis on clinically accessible features and biomarkers that have not been well studied in this age group.[46] A secondary analysis of a previous study in children with positive mAPI results at high risk for asthma development[16,47] found that episode-free days were increased with daily ICS versus placebo among boys and participants who were white, who had an emergency department visit or hospitalization for asthma within the past year, and who were more symptomatic at baseline.[14] Systemic corticosteroid use and health care use were also significantly reduced in children with aeroallergen sensitization in that study.[14]

Our primary predictor analysis was based on these prior observations,[14] as well as findings from older children.[24,37,48,49] The fact that sex and previous exacerbations did not differentiate best response in the present study was surprising but might be due to differences in the baseline severity of the populations studied. However, a recent analysis of a birth cohort similarly found no association between sex and phenotype in young children at high risk for asthma.[50] Previous exacerbations might also have limited predictive potential given their self-reported nature and lack of standardization for systemic corticosteroid administration in general practice.[51] However, aeroallergen sensitization and blood eosinophil counts of 300/μL or greater were strong predictors of differential response and identified a phenotype of children at high risk for disease morbidity who benefit from treatment with a daily ICS, although these medications are not without some risk. A previous study in preschool children demonstrated dose-dependent reductions in linear growth with a daily ICS that might be worse in selected subpopulations, including children of lesser age and lesser weight.[17] In school-aged children with long-term ICS exposure, these height reductions can also persist into the adult years.[52] However, asthma exacerbations in children do carry a significant risk of hospitalization and, in rare cases, death.[53,54] Therefore phenotype-directed daily ICS therapy is beneficial in selected children but might not be the optimal choice for other children with non–type 2 patterns of inflammation. Other biomarker analyses are needed to guide treatment selection in those children.

This study does have limitations. Although overall adherence was quite good in children with evaluable data, adherence to study medications was self-reported on an electronic diary, and it is unclear whether medication dose counters would have yielded different adherence estimates.[55]

This study also did not include a placebo washout phase between the treatment periods because of ethical concerns, and therefore carryover effects might have been present. Although we excluded data collected during the first 14 days of each treatment period from the calculation of ACDs, it is possible that carryover effects from a daily ICS might be longer for children with less active disease.

There might also be an effect of seasonal exacerbations that influences the selection of the best treatment. Although we adjusted for this in the overall population, it might still be a factor for assessing individual preference.

We also measured biomarkers at the time of randomization, and these can change over time and in association with treatment response. This is particularly true for specific IgE measures because aeroallergen sensitization tends to develop with age and might not necessarily be present in young preschool children. Attrition and the number of participants with evaluable data, particularly among African Americans, is another consideration despite adequate power for the primary outcome analysis. Missing data from diary cards might also have resulted in underestimation or overestimation of ACDs and differential responses.

In conclusion, a daily low-dose ICS is the most effective therapy for the majority of young children with asthma symptoms and recurrent wheezing episodes for whom Step 2 treatment with daily controller medication is warranted.[2] However, phenotypic heterogeneity is abundant in this age group and is associated with differential responses to asthma medications. Readily available biomarkers of type 2 inflammation, namely aeroallergen sensitization and blood eosinophil counts, can also be used to identify a group of children for whom daily ICS treatment is beneficial. Other studies are needed to determine whether these findings would also apply to young children requiring higher treatment steps.

Clinical implications: Although young children requiring Step 2 asthma treatment are phenotypically diverse, children with aeroallergen sensitization and increased blood eosinophil counts respond best to a daily ICS, as opposed to an LTRA or an as-needed ICS.

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METHODS

Study overview

The INFANT trial was a multicenter, prospective, randomized, double-blind factorial study of children aged 12 to 59 months who met the criteria for treatment with long-term Step 2 asthma controller therapy.[E1] Children underwent a run-in period of 2 to 8 weeks according to their symptom presentation and prior medication exposure. After the run-in period was complete, children entered the treatment portion of the study, where they were randomized into 3 sequential 16-week treatment periods with one of the following agents: (1) fluticasone propionate –HFA (Flovent-HFA, 44 μg per actuation), 2 inhalations administered with a valved holding chamber and face mask twice daily; (2) 4-mg montelukast granules (or chewable tablet) once daily at night; and (3) fluticasone propionate–HFA (Flovent-HFA, 44 μg per actuation), 2 inhalations plus 2 inhalations of albuterol sulfate (90 μg per actuation) administered with a valved holding chamber and face mask as needed for symptom relief. There were no washouts between study treatments.

The primary outcome was a composite variable encompassing domains of risk and impairment similar to what was used in the Best Add-on Therapy Giving Effective Response (BADGER) study.[E2] ACDs were assessed as an indicator of impairment, whereas exacerbations (defined by a significant increase in asthma symptoms requiring treatment with systemic corticosteroids) were assessed as an indicator of risk, which is in keeping with asthma treatment guidelines.[E1] The primary analysis involved 2 stages: (1) testing the null hypothesis of all 3 treatments having equal probability to yield the best response as defined by the criteria described above and (2) determining whether any of 3 prespecified phenotypic characteristics (sensitization to ≥1 aeroallergen, previous exacerbations requiring systemic corticosteroids, and sex) predict different patterns of treatment response. The first 2 weeks of data will not be analyzed in the calculation of ACDs to ameliorate potential carryover effects between treatments.

Inclusion criteria

Inclusion criteria for study entry varied according to current asthma medication use. To encourage recruitment and generalization of results, this protocol enrolled ICS- and LTRA-naive children treated only with intermittent short-acting β-agonists who required step-up therapy, as well as children currently treated with daily low-dose ICSs, daily LTRAs, or intermittent ICSs or LTRAs. Children not receiving an ICS or LTRA at any time over the preceding 6 months were eligible for inclusion if they had at least 1 of the following features: (1) daytime asthma symptoms more than 2 days per week (averaged over the preceding 4 weeks), (2) at least 1 nighttime awakening from asthma over the preceding 4 weeks, (3) 2 or more asthma exacerbations requiring systemic corticosteroids in the preceding 6 months, or (4) 4 or more wheezing episodes, each lasting 24 hours or more, in the preceding 12 months. Children receiving an ICS or LTRA at any time (ie, daily or intermittently) over the preceding 6 months were eligible for inclusion if they had at least 1 of

the following features: (1) receiving an ICS or LTRA for more than 3 months (or >90 days) out of the preceding 6 months (or 180 days), (2) daytime asthma symptoms on more than 2 days per week (averaged over the preceding 4 weeks), (3) at least 1 nighttime awakening from asthma over the preceding 4 weeks), (4) 2 or more asthma exacerbations requiring systemic corticosteroids in the preceding 12 months, or (4) 4 or more wheezing episodes, each lasting 24 hours or more, in the preceding 12 months.

A child was considered ineligible for initial study entry if he or she had a history of an allergic reaction to the study medications or any component of the study drugs; other chronic medical disorders that could interfere with drug metabolism or drug-related safety; comorbid wheezing disorders associated with wheezing, such as premature birth before 35 weeks' gestation or airway anomalies; failure to thrive; or a history of a near-fatal asthma exacerbation requiring assisted ventilation. During the run-in period, children were considered ineligible for randomization if they (1) displayed inadequate adherence to the study protocol (ie, <75% of electronic diaries completed), (2) experienced an asthma exacerbation requiring systemic corticosteroids, (3) had daily asthma symptoms if not taking asthma controller therapy, or (4) had asthma symptoms more than 2 days per week if taking asthma controller therapy.

Run-in period

During the run-in period, each child received 1 oral medication and 1 inhaled medication for daily use. Each participant also had access to an open-label short-acting bronchodilator (albuterol sulfate, 90 μg each; GlaxoSmithKline, Research Triangle Park, NC) and open-label prednisolone. The run-in duration was based on whether the child was currently receiving Step 2 therapy (ie, daily low-dose ICS or LTRA) and whether the child qualified based on exacerbation history. Children not receiving Step 2 therapy during the 6 months before enrollment (including children who received an ICS or LTRA intermittently) received placebo oral and inhaled therapy during the run-in period. The run-in period was completed in 2 weeks if the participant had a previous exacerbation requiring systemic corticosteroids. If the participant did not have an exacerbation, the run-in period could be extended up to 8 weeks to elicit symptoms. Children who were receiving Step 2 therapy received active ICS or active LTRA during the run-in period. If the participant had a previous exacerbation requiring systemic corticosteroids, the run-in period was completed in 2 weeks. If not, the run-in period lasted 4 weeks in total.

Caregivers recorded symptoms, health care use, and medication use in electronic diaries each day at bedtime (Spirotel; Medical International Research, Rome, Italy). Children were ineligible for randomization if they (1) completed less than 75% of daily electronic diaries, (2) received systemic corticosteroids for an asthma exacerbation, (3) had daily asthma symptoms if not receiving active therapy, or (4) had asthma symptoms more than 2 days per week if receiving active therapy.

Study medications

Inhaled fluticasone propionate–HFA (Flovent, 44 μg each inhalation, delivered twice daily) and matching placebo were donated by GlaxoSmithKline (Evreux, France), and fluticasone propionate–HFA was used as the daily ICS of choice. Inhaled fluticasone or matching placebo was delivered through a pressurized metered-dose inhaler and a valved holding chamber with a face mask. Montelukast (Singulair, 4 mg, once daily at bedtime) and matching placebo were donated by Merck and Co and used for daily LTRA treatment. For the as-needed ICS arm, children received fluticasone (Flovent, 44 μg per inhalation, 2 inhalations) or matching placebo concurrently with open-label albuterol sulfate (90 μg per actuation, 2 inhalations, donated by GlaxoSmithKline). Study inhalers were color coded, and caregivers were provided with corresponding asthma action plans and electronic diary prompts to ensure proper medication delivery.

Children also had access to open-label prednisolone (2 mg/kg/d for 2 days followed by 1 mg/kg/d for 2 days), regardless of treatment assignment. The criteria for initiating oral prednisolone therapy were detailed on the asthma action plan and included the following: (1) no improvement in symptoms after 3 as-needed treatments with an ICS (or placebo) and albuterol administered every 20 minutes; (2) more than 6 rescue albuterol treatments (180 μg each) in a 24-hour period; (3) moderate-to-severe cough or wheeze for at least 5 of 7 days; (4) specified thresholds of as-needed ICSs were reached, as defined in the study protocol (ie, a 2-day average of >528 μg of fluticasone); and (5) unscheduled health care use for acute asthma requiring repeated doses of short-acting β-agonists. Physician discretion was also permitted, provided that a specific reason for prednisolone initiation was recorded.

Asthma action plans

A standardized asthma action plan was provided for each participant in the trial for daily reference by caregivers. For children in the "green zone" (ie, children doing well), caregivers were instructed to administer the daily morning medication (2 inhalations from the brown, blinded ICS or placebo inhaler) on awakening and to administer the daily evening medications (2 inhalations from the brown, blinded ICS or placebo inhaler plus the oral medication) before going to bed. They were also instructed to answer the electronic diary questions. For children in the "yellow zone" (ie, experiencing any asthma symptoms, such as cough, wheeze, shortness of breath, or chest tightness), caregivers were instructed to administer 2 inhalations of the red, open-label albuterol inhaler as well as 2 inhalations of the white, blinded as-needed ICS or placebo inhaler every 4 hours as needed for symptoms. These inhalers could also be used more often, up to every 20 minutes for 1 hour. Caregivers were instructed to contact the study team immediately if the child had the following: (1) symptoms requiring 2 albuterol treatments within a 4-hour period, (2) 7 or more albuterol treatments within a 24-hour period, (3) awakening at night with cough or wheeze for 2 consecutive days, or (4) a concerning cough or wheeze for several days. For children in the "red zone" with signs of severe respiratory difficulty, caregivers were instructed to seek emergency medical help.

Electronic diary

Caregivers received an electronic diary (Spirotel; Medical International Research) and were trained in its use at the beginning of the run-in period. Caregivers were instructed to complete the diary each day between 6 PM and noon the following day. Diaries were closed to reporting at noon the following day and did not permit entry of prior missing data.

With regard to diary use, caregivers were first prompted to answer whether their child had asthma symptoms in the past 24 hours (yes/no). If no, they were then asked to enter the number of puffs taken from the brown (blinded ICS or placebo) daily inhaler and whether the oral study medication was taken at bedtime. If the caregiver reported symptoms, he or she was asked the following questions in addition to daily study medication use: (1) nighttime awakening with difficulty breathing (yes/no), (2) cough severity (0 = absent, 1 = mild and did not affect normal activity or sleep, 2 = moderate and somewhat affected normal activity and sleep, and 3 = severe and so bad that normal activity and sleep were not possible), (3) wheezing severity (0-3), (4) difficulty breathing (0-3), (5) activity interference (0-3), and (6) number of inhalations from the red (open-label albuterol) and white (blinded as-needed ICS or placebo) inhalers. Caregivers were prompted to call the clinic as soon as possible if they indicated any of the following: (1) 8 or more inhalations from the red (open-label albuterol) and/or white (blinded as-needed ICS or placebo) study inhalers in 1 day, (2) any severe symptoms, (3) moderate or severe cough or wheeze at least 5 times in a 7-day period, or (4) receipt of 90 or more puffs from the red (open-label albuterol) or white (blinded as-needed ICS or placebo) inhaler over a 30-day period. Data collected in the electronic diary were uploaded at each study visit, and reports were reviewed with the caregiver.

Biomarker determination

Peripheral blood eosinophil counts were determined from 1 aliquot of whole blood by using an automated assay at each clinical site. Separate aliquots of whole blood were clotted at room temperature, and serum was frozen and shipped in batches for analysis. Total serum IgE and specific IgE levels to 12 aeroallergens were quantified by a commercial laboratory (Advanced Diagnostic Laboratories, National Jewish Health, Denver, Colo).

Specific IgE measurement (ImmunoCAP) was performed for a nationally representative panel of inhalant aeroallergens: (1) cat dander (ImmunoCAP test code E1), (2) dog dander (E5), (3) mouse urine proteins (E72), (4) mold mix (Mx1; *Penicillium chrysogenum*, *Cladosporidium herbarum*, *Aspergillus fumigatus*, and *Alternaria alternata*), (5) German cockroach (i6; *Blatella germanica*), (6) grass mix (gx2; Bermuda, rye, Timothy, Kentucky bluegrass, Johnson, and Bahia), (7) tree mix (Tx4; oak, elm, sycamore, cottonwood, and willow), (8) tree mix (Tx6; box elder, birch, beech, oak, and walnut), (9) weed mix (Wx1; common ragweed, mugwort, plantain, lamb's quarter, and Russian thistle), (10) weed (W3, giant ragweed), (11) mite (D2, *Dermatophagoides farinae*), and (12) mite (D1, *Dermatophagoides pteronyssinus*). Aeroallergen test results were considered positive if values were 0.35 kU/L or greater. ECP levels were also quantified by a commercial laboratory (Advanced Diagnostic Laboratories, National Jewish Health, Denver, Colo).[E3] Urine was collected by using clean-catch methods. Urinary LTE_4 concentrations were measured by using mass spectrometry, as previously described,[E4,E5] and were expressed per milligram of creatinine.

Growth assessment

Weight and height measurements were obtained at each study visit. Weight was recorded on a digital scale (model number BWB-800AS; 3R Resources, Kennewick, Wash) with shoes and heavy clothing removed. Standing height was measured without shoes and recorded in centimeters by using a stadiometer selected for AsthmaNet trials (Seritex/Holtain Harpenden stadiometer #602VR [wall mounted] or #603 [portable]; Seritex, East Rutherford, NJ). These stadiometers provide an accurate and direct reading to the nearest millimeter over a range of 600 to 2100 mmm. For infants unable to stand, length was measured instead of standing height by using the Seca Infantometer Baby Board II (model #416; Seca, Hanover, Md). Standing height or length values were averaged from 3 measurements.

Criteria for treatment-arm failure

Throughout the study, children had access to albuterol and prednisolone for asthma symptoms. Treatment-arm failure was achieved if a child experienced 2 exacerbations requiring systemic corticosteroids in a single 16-week treatment arm. For the purpose of this study, 2 courses of systemic corticosteroids had to be separated by at least 1 week to count as 2 exacerbations. When 2 exacerbations occurred, the child was advanced to the next treatment arm.

Criteria for study failure

Criteria for study failure were met if any of the following occurred during the course of the study: (1) the participant received 4 courses of prednisolone after randomization, (2) the participant was hospitalized for more than 24 hours for an acute asthma exacerbation, or (3) the participant moved forward to the next treatment arm because of recurrent exacerbations (protocol defined) 2 times during the course of the study.

Randomization

Given the 3 × 3 crossover design, the pattern of treatment assignment used the complete set of orthogonal Latin squares. Therefore children who satisfied the eligibility criteria were randomized to receive treatment according to one of 6 treatment sequences, with stratification according to clinical center. After a child at a particular clinical center was deemed eligible for the study, the clinic coordinator authenticated into the AsthmaNet server and indicated to the system that a participant required randomization. After entering the pertinent information with respect to clinical center and eligibility criteria, the clinic coordinator was asked to verify that all of the entered information was correct. The clinic coordinator was then given a packet number from which all medication for that child was dispensed. The data manager of the Data Coordinating Center automatically received a notice from the AsthmaNet Network server that a child had been randomized to maintain security of the randomization schedules. If no follow-up information was forthcoming on the child, the data manager contacted the clinic coordinator about the status of the child.

Calculation of annualized ACDs

The number of annualized ACDs during each treatment period was calculated by using only the last 14 weeks of the 16-week treatment period. First, the actual number of ACDs was determined by examining the electronic daily diary records. An ACD was defined as a full calendar day without (1) use of rescue medications for asthma symptoms, (2) any daytime asthma symptoms, (3) any nighttime asthma symptoms, and (4) unscheduled health care provider visits for asthma. The annualized number of ACDs was then calculated by dividing the actual number of ACDs by the number of days for which electronic diaries were completed, then multiplying by 365.25. In the event that no information was recorded on a specific day, that day was not included in the determination of ACDs. A day for which there was partial information was included in the determination of ACDs as follows. First, if there is any information recorded that identifies it as a non-ACD, then it was judged as such. Second, if there was partial information, none of which identifies it as a non-ACD, then it was judged as an ACD under specific conditions. For example, if there was no information recorded about the use of albuterol rescue but it was recorded that there were no daytime or nighttime asthma symptoms, then that day was judged an ACD. Finally, if less than 50% of diary days are usable during a treatment period, that period was considered missing.

Determination of differential treatment response

Differential treatment response was evaluated for each participant. This was accomplished by comparing each treatment head to head against the others with respect to asthma exacerbations and annualized ACDs. One treatment was deemed better than the other if the time from the start of the treatment period until an asthma exacerbation requiring systemic corticosteroid treatment was at least 4 weeks longer during one treatment than during either of the other 2 treatments. If there was no difference with respect to exacerbations, one treatment was deemed better than the other if the difference in annualized ACDs was at least 31 days more on one treatment than on either of the other 2 treatments. If there were no differences in exacerbations and annualized ACDs, then the treatments were deemed equivalent. After combining the results of the 3 head-to-head comparisons, the following 4 scenarios were possible:

1. one treatment is better than both of the others,
2. two equivalent treatments are both better than the third,
3. one treatment is better than one other and both are equivalent to the third intermediate treatment, or
4. all 3 treatments are equivalent.

If a subject completed only 2 treatment periods, he or she was identified as either a differential or nondifferential responder based on a comparison of the 2 completed treatments.

Rationale for choosing criteria for assessing the differential treatment response

The composite outcome selected for this trial was similar to that used in the BADGER study,[E2] which identified differential treatment responses to Step 3 therapy in school-aged children. The composite outcome consisted of 2 levels of assessment, specifically (1) the time from the start of the treatment period to an asthma exacerbation that required systemic corticosteroid therapy (protocol defined) and (2) the annualized number of ACDs within that treatment period. The rationale for the selection of asthma exacerbations and ACDs as the criteria for differential treatment response is provided below.

Asthma exacerbations. Asthma exacerbations requiring systemic corticosteroids are considered the primary indicator of asthma "risk" by

asthma treatment guidelines,[E1] given the high probability of future exacerbations in affected children.[E6] Therefore asthma exacerbations requiring treatment with systemic corticosteroids were selected as one of the primary criteria for differential treatment response. The AsthmaNet Steering Committee believed that a difference of at least 4 weeks between the onset of treatment and an asthma exacerbation requiring systemic corticosteroids would represent a clinically meaningful outcome in terms of child and caregiver well-being. We further anticipated finding differential treatment responses using exacerbations as one of the outcome measures. In the National Heart, Lung, and Blood Institute Childhood Asthma Research and Education (CARE) Network Pediatric Asthma Controller Trial (PACT)[E7] involving older school-aged children, asthma exacerbations requiring systemic corticosteroids differed according to fluticasone, fluticasone plus montelukast, and montelukast treatment assignment, such that the percentage of children requiring systemic corticosteroids within the first 16 weeks was 16%, 25%, and 32%, respectively ($P < .05$ for the difference between fluticasone and montelukast).

Although this study involved older children, we also had access to exacerbation data from the CARE Network Prevention of Early Asthma in Kids (PEAK)[E8] and Acute Intervention Management Strategies (AIMS)[E9] studies in preschool children to support the feasibility of this indicator. In the PEAK study children treated with daily inhaled fluticasone had a lower rate of exacerbations necessitating systemic corticosteroids than children treated with placebo (57.4 per 100 child-years vs 89.4 per 100 child-years, $P < .001$).[E8] Furthermore, in the AIMS study the average number of oral corticosteroids per participant was 1.0 (0.7-1.3) for the montelukast group and 0.7 (0.5-1.0) for the budesonide group (P = not significant for comparison), and the median time to the first oral corticosteroid course was 292 and 354 days for the montelukast versus budesonide groups, respectively (P = not significant for comparison).[E9]

ACDs. ACDs assessed based on the presence of symptoms were analyzed in this study as an indicator of "impairment" based on asthma treatment guidelines.[E1] For ACDs, the AsthmaNet Steering Committee believed that a difference of 31 days or more would represent a clinically meaningful outcome based on data from the PACT trial.[E7] Although the PACT trial enrolled older school-aged children with asthma, ACDs were also the primary outcome indicator of the PEAK study of high-risk preschool children.[E8] Because the PEAK study enrolled preschool children who were not yet given a formal diagnosis of asthma, "asthma control days" were instead termed "episode-free days" but were defined similarly by (1) no symptoms of cough or wheeze; (2) no unscheduled clinic, emergency department, urgent care, or hospital visits; and (3) no use of asthma medications, including short-acting bronchodilators, as pretreatment for exercise. In the PEAK trial the proportion of episode-free days successfully distinguished the treatment groups, such that during the 2-year treatment period, the proportion of episode-free days was significantly greater in children treated with daily fluticasone versus placebo (93.2% vs 88.4%, $P = .006$). This difference disappeared after the fluticasone was discontinued (86.8% vs 85.9% episode-free days for fluticasone vs placebo, P = not significant).[E8] Because the PEAK study included children who were not given a formal diagnosis of asthma, the overall symptom burden was less than what we expected to observe in this study. In the AIMS study, which enrolled a preschool population with significantly more symptom burden, the proportion of episode-free days was 73% for rescue montelukast and 76% for rescue budesonide, respectively (P = not significant for comparison).[E9]

Statistical analyses

The primary analysis used rank-ordered logistic regression,[E10] which is built on the concept that each treatment has an underlying utility that might differ from one subject to another. Mathematically, these utilities are represented by U_{it}, where i denotes the individual and t denotes the treatment (daily ICS *[D]*, LTRA *[L]*, or as-needed ICS *[A]*). Utility can be thought of as a latent variable quantifying treatment response in which higher values indicate better response. In this study utility is based on a composite measure incorporating exacerbations and ACDs. Although the utilities themselves are not directly observed, the model postulates that participant i will demonstrate better response to one treatment compared with another when the differences between the treatment utilities exceeds some threshold. For example, a daily ICS (D) will yield a better response than an LTRA (L) as follows:

$$U_{iD} - U_{iL} > \delta,$$

where $\delta > 0$ is the threshold that must be exceeded. The model is structured such that U_{it} depends on both the systematic component μ_{it} and the random component ε_{it} as follows:

$$U_{it} = \mu_{it} + \varepsilon_{it},$$

where the ε_{it} values follow an extreme value distribution and the μ_{it} values depend on participant-specific covariates (X_1, X_2, X_3, …) through a linear predictor:

$$\mu_{it} = \alpha_t + \beta_{1t} \times X_{1i} + \beta_{2t} \times X_{2i} + \beta_{3t} \times X_{3i} + \ldots.$$

The α values represent the average treatment response pattern (the main effect for treatment), whereas the β values represent the effect of each covariate on the treatment response pattern (the interaction between treatment and covariate). The linear predictor can be used to find the probability of best response for each treatment:

$$\pi_{it} = \exp(\mu_{it}) / [\exp(\mu_{iD}) + \exp(\mu_{iL}) + \exp(\mu_{iA})].$$

Nondifferential response occurs when $\pi_{iD} = \pi_{iL} = \pi_{iA} = 1/3$. Because the probabilities must sum to 1, constraints on the model parameters are necessary to ensure model identifiability.

The primary analysis tested whether the 3 treatments are equally likely to yield the best response and also whether there are phenotypic predictors of treatment response pattern. Three prespecified phenotypic characteristic covariates were examined: sex, allergic sensitization to at least 1 aeroallergen defined as a specific IgE level of greater than 0.35 kU/L, and a history of exacerbations requiring systemic corticosteroid treatment in the previous year. Model parameters were estimated by using maximum likelihood, and bootstrapping was used to calculate CIs. The statistical significance of the main effect and each of the 3 predictor interaction effects was assessed at the 0.0125 significance level, with an overall type I error rate for the primary analysis not exceeding 0.05. Participants who did not provide evaluable data for determining treatment response because of dropout or diary nonadherence were not included in the model. Bootstrap samples were based on all randomized participants, including those who dropped out or did not provide evaluable diary data, to account for the element of model uncertainty that was caused by missing data.

Secondary analyses compared treatments with respect to the individual outcomes that comprise the designation of differential response and other secondary outcomes, including albuterol use and unscheduled health care visits. Secondary analyses used a more traditional approach, examining each outcome individually. The generalized linear model framework was used to analyze binary and count outcomes by using generalized estimated equations to account for the longitudinal nature of the data. In addition to treatment effect, these models also included period and the treatment-by-period interaction effect. Covariate effects included sex, allergic sensitization, and history of exacerbations requiring systemic corticosteroid treatment in the previous year.

Because this study did not include a washout phase between treatment periods, carryover effects were likely present. However, we expected that carryover effects would not continue beyond 2 weeks. Therefore the data collected during the first 2 weeks of each period were not included in the analysis of ACDs and albuterol use.

Seasonal effects. Given the crossover design, it was recognized that seasonal effects could occur and that these seasonal effects could contaminate the differential response analysis. For example, an exacerbation during the month of September might not represent a worse risk domain outcome than the absence of an exacerbation during the month of July. Similar scenarios could be envisioned for other outcomes. In this context expression of the child's asthma does not remain stable over the seasons, even though the underlying disease might not change measurably. In that sense seasonal effects (hereafter called calendar effects for ease of mathematic expression) are analogous to period effects. Rather than test for period effects, we tested for seasonal effects as a precursor to the primary analysis.

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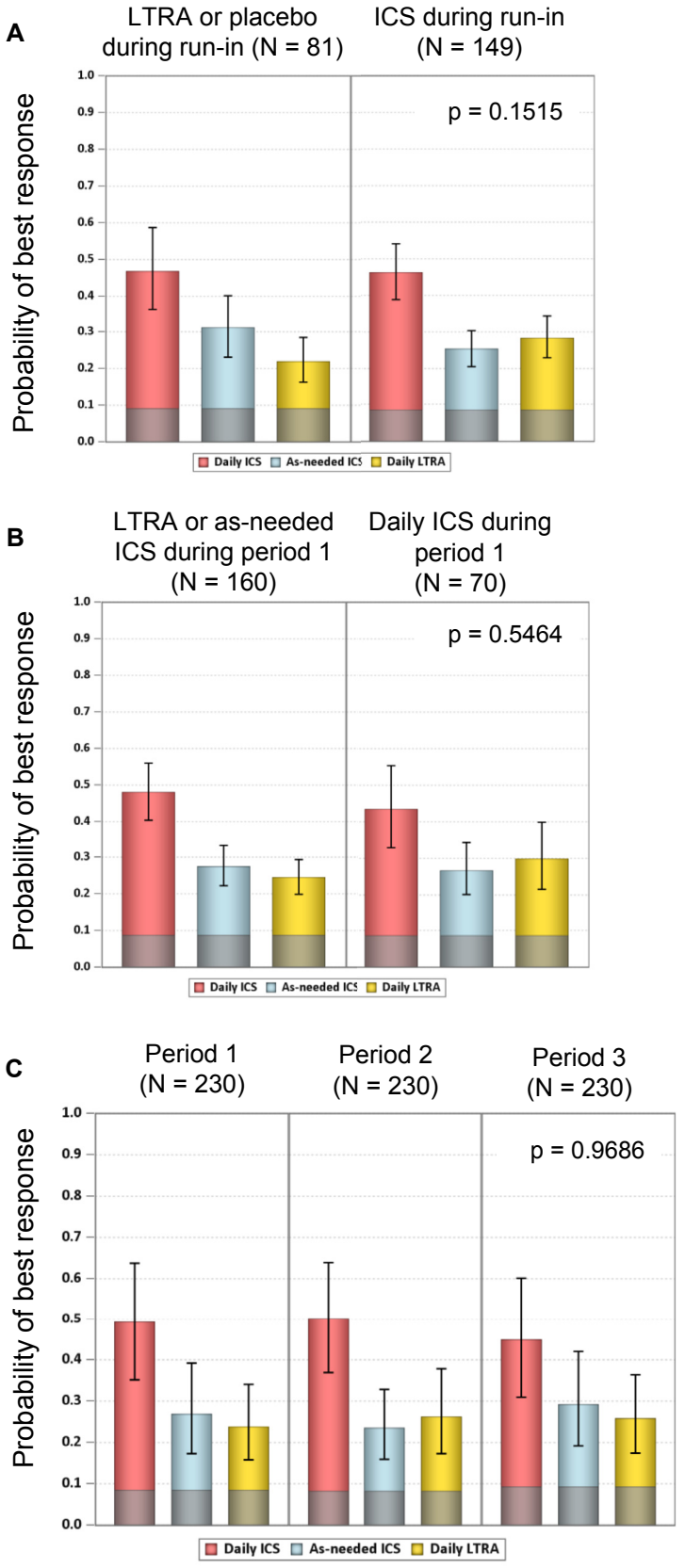

FIG E1. **A,** Patterns of treatment differences according to daily ICS versus LTRA or placebo during the run-in period. **B,** Patterns of treatment differences according to daily ICS versus LTRA or as-needed ICS receipt during the first treatment period. **C,** Patterns of treatment differences during each of the 3 treatment periods. Models included allergic sensitization, history of exacerbations, and sex as covariates. Best response probabilities and *P* values for each analysis were obtained from rank-ordered logistic regression with bootstrap CIs. *P* values correspond to the test of interaction between predictor and treatment in the logistic regression model and indicate whether the pattern of treatment response differs according to subgroup. *P* values are *post hoc* and not adjusted for multiple testing. Sample sizes correspond to all participants with evaluable data (n = 230).

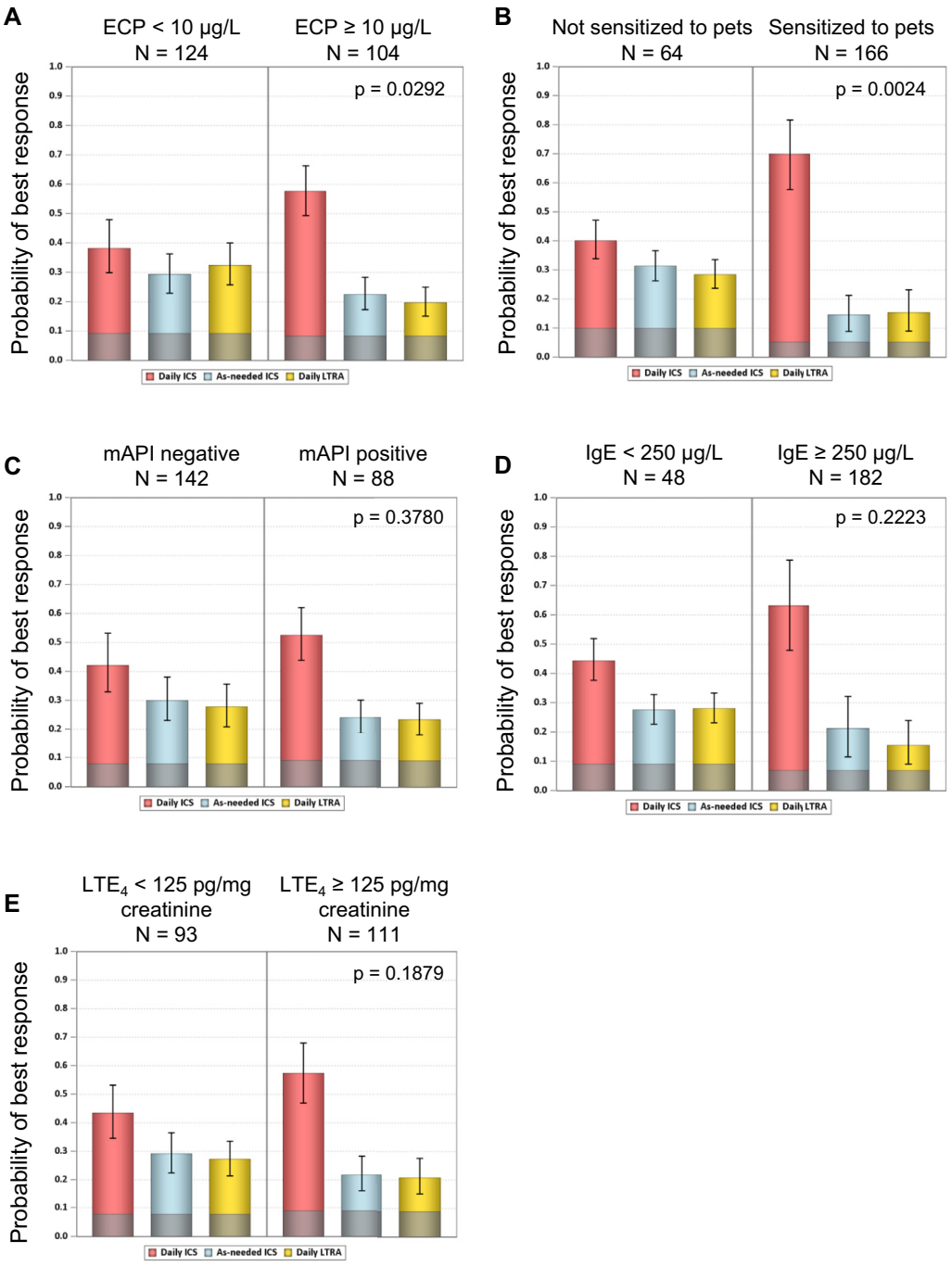

FIG E2. Patterns of treatment differences are shown according to serum ECP concentration **(A)**, sensitization to pet aeroallergens (dog, cat, or both; **B**), mAPI status **(C)**, serum IgE level **(D)**, and urinary LTE_4 concentration **(E)**. Greater superiority of daily ICS was associated with an ECP concentration of 10 µg/L or greater and sensitization to a pet aeroallergen. mAPI status, serum IgE level, and urinary LTE_4 concentration were not significant predictors. Probabilities and *P* values for each analysis were obtained from rank-ordered logistic regression with bootstrap CIs. *P* values correspond to the test of interaction between predictor and treatment in the logistic regression model and indicate whether the pattern of treatment response differs according to subgroup. Models included allergic sensitization, history of exacerbations, and sex as covariates, with the exception of the pet sensitization model, which was only adjusted for exacerbations and sex. *P* values for exploratory predictors are *post hoc* and not adjusted for multiple testing. Sample sizes correspond to all participants with evaluable data (n = 230, except where otherwise noted because of missing samples).

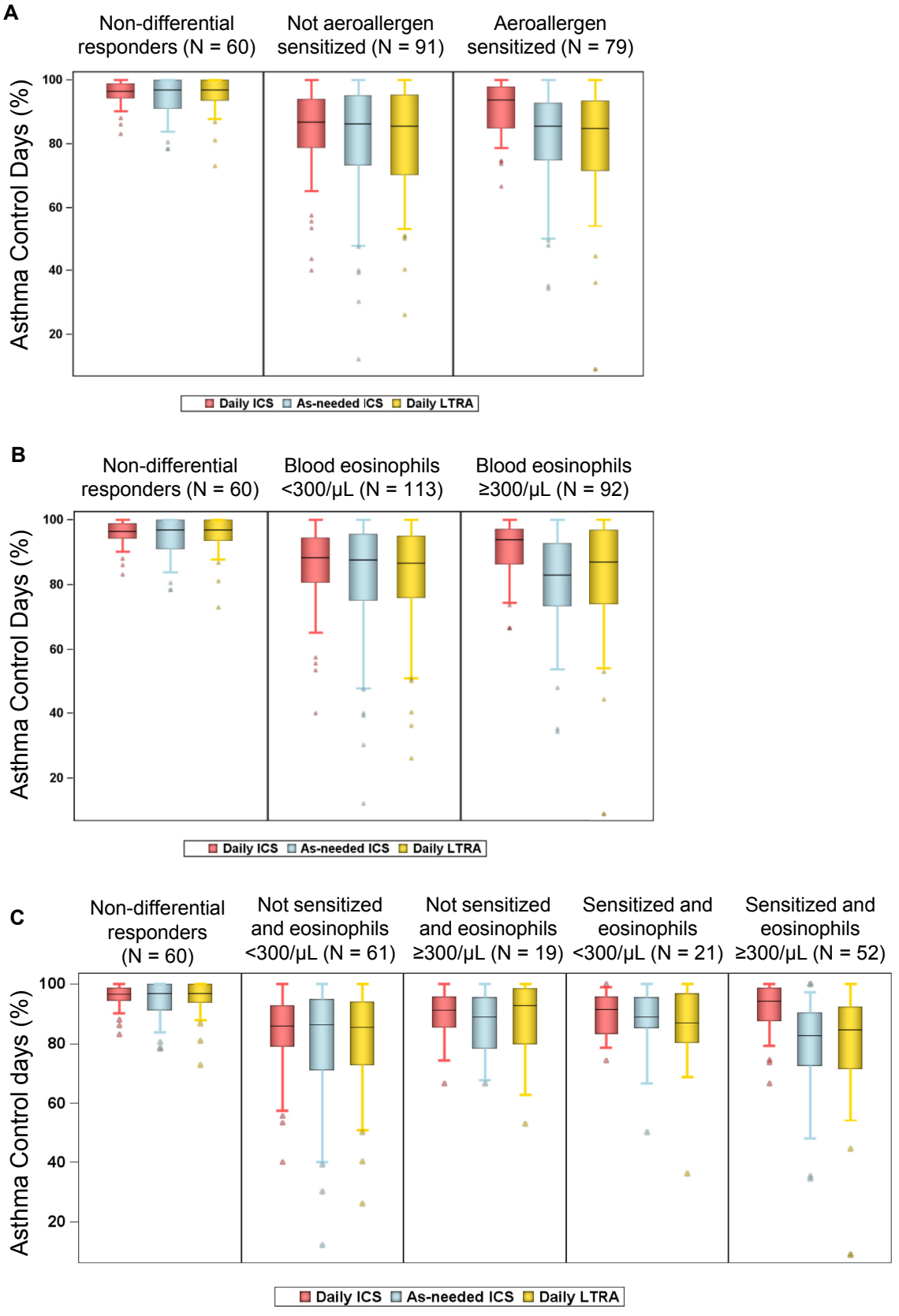

FIG E3. **A** and **B,** Percentage of ACDs during the course of the trial for all participants with evaluable data (n = 230), with nondifferential responders on the far left followed by differential responders on the right stratified by sensitization to at least 1 aeroallergen **(A)**, blood eosinophil counts of 300/mL or greater **(B)**, and combinations of sensitization and eosinophil counts **(C)**. *Box plot horizontal lines* represent the median value, *shaded boxes* represent the 25th to 75th percentile, and whiskers represent the 5th to 95th percentile. Outliers are shown as *triangles* and represent data values from individual participants.

TABLE E1. Aeroallergen test results

Positive test result	All participants (n = 300)	Not evaluable (n = 70)	Evaluable* (n = 230)	Nondifferential response (n = 60)	Differential response (n = 170)
Cat	59 (21)	10 (18)	49 (22)	7 (12)	42 (25)
Dog	71 (25)	12 (21)	59 (26)	9 (15)	50 (30)
Cockroach	34 (12)	7 (13)	27 (12)	4 (7)	23 (14)
Dermatophagoides pteronyssinus	47 (16)	14 (24)	33 (14)	8 (13)	25 (15)
Dermatophagoides farinae	48 (17)	14 (24)	34 (15)	8 (13)	26 (15)
Mouse urine proteins	25 (9)	9 (16)	16 (7)	1 (2)	15 (9)
Ragweed	38 (14)	9 (17)	29 (14)	4 (7)	25 (16)
Weed	43 (16)	9 (17)	34 (16)	5 (9)	29 (18)
Tree mix 6	29 (11)	6 (12)	23 (11)	2 (4)	21 (13)
Tree mix 4	46 (17)	10 (19)	36 (17)	6 (11)	30 (19)
Mold	47 (18)	12 (25)	35 (16)	5 (9)	30 (9)
Grass	35 (13)	9 (17)	26 (12)	3 (5)	23 (14)

Results were considered positive if serum values were greater than 0.35 kU/L. Values represent numbers (percentages) of participants.
*Includes participants who completed at least 2 study periods with adequate diary completion.

TABLE E2. Secondary outcomes

	Daily ICS (n = 249)	As-needed ICS (n = 250)	Daily LTR (n = 256)	*P* value, daily vs as-needed ICS	*P* value, daily ICS vs daily LTRA
ACDs (%)*	94.0 (84.7-97.7)	88.4 (76.6-96.5)	89.4 (78.0-96.2)	.001	.001
Albuterol inhalations per week*	1.7 (0.6-5.0)	3.1 (0.9-7.4)	2.9 (0.6-7.4)	.001	.001
Exacerbations requiring systemic corticosteroids					
0	202 (81%)	181 (72%)	169 (66%)	.027	.001
1	35 (14%)	52 (21%)	68 (27%)		
2†	12 (5%)	17 (7%)	19 (7%)		
Unscheduled health care visits					
0	228 (92%)	224 (90%)	230 (90%)	.26	.73
1	21 (8%)	24 (9.5%)	25 (9.5%)		
2	0	2 (0.5%)	1 (0.5%)		
Hospitalizations					
0	249 (100%)	249 (99.5%)	250 (98%)		
1	0	1 (0.5%)	6 (2%)		

Data represent medians (interquartile ranges) or numbers (percentages). *P* values are based on generalized linear models incorporating treatment, period, treatment-by-period interaction, and covariate effects.

*Only includes periods for which at least 50% of diary days were completed.

†Treatment failure criteria were met if a child experienced 2 exacerbations requiring systemic corticosteroids in a single 16-week treatment arm.

TABLE E3. Adverse events coded as possibly or probably related to study treatments

	Daily ICS	As-needed ICS	Daily LTRA
Diseases of the nervous system and sense organs			
Parasomnia	1	0	0
Diseases of the respiratory system			
Allergic rhinitis	0	0	1
Bacterial pneumonia	1	0	0
Unspecified asthma	0	0	1
Infectious and parasitic diseases			
Oral candidiasis	1	0	1
Symptoms, signs, and ill-defined conditions			
Cough	3	4	1
Wheezing	0	0	1
Rash and other nonspecific skin eruption	0	1	0

TABLE E4. Height velocity

Treatment 1	Treatment 2	Difference	SE	*P* value
As-needed ICS	Daily ICS	0.2011	0.2097	.3381
As-needed ICS	Daily LTRA	−0.1862	0.2102	.3760
Daily ICS	Daily LTRA	−0.3873	0.2112	.0673

Data represent 16-week treatment intervals.