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Biomarker Profiles in Asthma with High vs. Low Airway Reversibility and Poor Disease Control

William W. Busse¹, Stephen T. Holgate², Sally W. Wenzel³, Paul Klekotka⁴, Yun Chon⁴,
JingYuan Feng⁴, Edward Ingenito⁴, and Ajay Nirula⁴

1. University of Wisconsin, Madison, WI, USA.
2. Clinical and Experimental Sciences, Faculty of Medicine, Southampton, UK.
3. University of Pittsburgh Medical Center, Pittsburgh, PA, USA
4. Amgen Inc., Thousand Oaks, CA, USA.

Running head: biomarker utility for assessing disease control

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Corresponding author:

Edward P. Ingenito MD PhD
Clinical Research Medical Director
Clinical Development Team
Amgen Inc.
360 Binney Street
Cambridge, MA 20141

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Abstract

Background: High bronchodilator reversibility (HR) in adult asthma is associated with distinct clinical characteristics. This analysis compares lung function, biomarker profiles and disease control in HR and low reversibility (LR) asthma patients.

Methods: A retrospective analysis was performed with data from 2 completed clinical trials of similar design (NCT01018550 and NCT01199289). Patients were divided into HR and LR subgroups based on their response to bronchodilators (HR = Δ FEV1 post-bronchodilator $\geq$ +20%). Serum IgE, blood eosinophils, and exhaled nitric oxide (FeNO), biomarkers commonly used to stratify patients into Th2-high vs. Th2-low phenotypes, were measured in “not well controlled” ($1.5 \leq \text{ACQ} \leq 2.143$) and “very poorly controlled” ($\text{ACQ} > 2.143$) patients.

Results: The majority of patients in HR and LR subgroups displayed Th2-low biomarker profiles and very poor disease control. HR was more frequently associated with Th2-high biomarkers (40.1% vs. 29.4%; $p=0.006$), lower lung function (FEV1: $63.5 \pm 7.7\%$ vs. $67.9 \pm 8.4\%$ pred; $p<0.001$), and atopy (93.7% vs. 86.5%; $p=0.005$).

Conclusions: HR is a physiological indicator of reduced lung function, and is more often associated with elevations in Th2 biomarkers than LR in moderate-to-severe asthma. However, the majority of HR and LR patients in this analysis displayed a Th2-low biomarker profile. Moreover, a Th2-high biomarker profile was not associated with worse disease control.

Keywords: asthma phenotypes, biomarkers of severe asthma, asthma control

Introduction

Data from large patient registries have identified “clusters” of asthmatic patients with severe airflow limitation and disease that is difficult to control using conventional therapy [1-4]. Characteristics that differentiate these patients from the general asthma population include longer duration of disease, greater airway reversibility following bronchodilator administration (HR), sputum neutrophilia, increased oral corticosteroid use, and increased health care resource utilization [1,4]. Indeed, HR is a distinctive physiological characteristic of Cluster 4 and 5 patients in the Severe Asthma Research Program (SARP), the two cohorts displaying the worst disease control and highest frequency of clinic and emergency room visits and hospitalizations. Recently, serum and bronchoalveolar lavage fluid biomarkers have been analyzed to characterize the immune processes modulating disease severity [2, 5]. However, there is limited information regarding how serum biomarkers define endotypes across the asthma population, correlate with disease control, and relate to distinctive physiological features such as HR.

This study utilizes combined baseline datasets from 2 randomized controlled trials involving moderate to severe asthmatics to examine the relationship between immune pathway biomarkers and disease control in patients with HR and low reversibility (LR).

Methods

A retrospective exploratory analysis was performed using data from two Phase 2 trials involving patients with partly or poorly controlled moderate-to-severe asthma (GINA Step 3 and 4). The first study (NCT01018550) was initiated 21 December 2009 to assess the efficacy of a

dual-inhibitor of the prostaglandin D2 and chemo-attractant receptor homologous molecule expressed on Th2 cells [CRTH2]. Full baseline datasets were available for 358 of 396 enrolled patients. The second study (NCT01199289) was initiated 04 October 2010 to assess the efficacy of a monoclonal antibody against the IL-17 receptor A subunit (mAb IL-17 RA) in a similar cohort. Full baseline datasets were available for 272 of 302 enrolled patients. While both trials were interventional, treatment responses were not considered in this analysis. Data collected beyond the baseline time point was utilized solely to assess stability of phenotypic characteristics in patients who did not receive experimental therapy.

Inclusion-exclusion criteria for the 2 studies were identical: 1) age 18-65 years; 2) disease requiring inhaled corticosteroids with/without long-acting beta agonist; 3) baseline asthma control questionnaire (ACQ) score ≥ 1.5 units; 4) FEV1 percent predicted between 50% and 80%; 5) reversibility in FEV1 $\geq 12\%$ (and at least 200 mL) following administration of short acting beta agonist; 6) no evidence of active infection; and 7) no medical conditions associated with immune suppression. Patients were excluded from study participation if they had COPD or asthma-COPD overlap syndrome [6], were receiving maintenance oral corticosteroids or IgE antibody therapy, were current or recent smokers, had a history of intubation within 3 years of enrollment, or had obstructive sleep apnea.

Subjects were classified into two groups: 1) HR: those with high airway reversibility, defined as a $\geq 20\%$ increase in FEV1 following administration of a short acting bronchodilator during screening and baseline pulmonary function testing; and 2) LR: those with reversibility below this level [1, 4]. Subgroups were further divided into those with “not well controlled”

(ACQ score ≥ 1.5 and ≤ 2.143) or “very poorly controlled” disease (ACQ > 2.143). The ACQ cut-point defining “very poorly controlled” disease was derived from a linear extrapolation of ACQ scores of “Well Controlled” (5 total ACQ points, corresponding to an ACQ cut-point = 0.75) and “Not Well Controlled” (10 total ACQ points corresponding to an ACQ cut-point = 1.5) disease [7]. “Very Poorly Controlled” disease was defined as corresponding to an additional 5 point increment in total ACQ score beyond the “Not Well Controlled” cut-point (i.e. an ACQ > 2.143). Disease control was summarized in terms of both ACQ6 and ACQ7 values. Biomarkers reflecting Th2 immune activation were assessed in each patient, and included serum IgE, circulating eosinophil count (Eos), and exhaled nitric oxide concentration (FeNO). For each biomarker, cut-points used to define a “high” level were as follows: high IgE ≥ 100 IU/mL; high Eos $\geq 300/\mu\text{L}$; high FeNO ≥ 30 ppb [8, 9]. Patients were classified as having either a positive or negative Th2 Immune Profile Index (IPI) as follows: positive IPI = elevation in two or more Th2 biomarkers; negative IPI = elevation in one or no Th2 biomarkers.

Results are reported using descriptive statistics as mean $\pm$ standard deviation, median, and/or quartiles as appropriate. Comparisons of baseline data between study NCT01018550 and NCT01199289, and between HR and LR patients were performed either by Student’s t test or Wilcoxon rank sum test. Correlations between baseline and Week-12 biomarker assessments were performed via the Pearson product correlation method. Assessments of the significance of relationships between Th2 biomarker elevations and disease control were performed by Chi square testing (applying Yates correction as appropriate). A classification and regression tree (CART) analysis was included in the sensitivity analysis of cut-points

defining TH2 biomarker status. Statistically significant differences between groups were defined as having $P < 0.05$.

Results

Demographics, biometrics, medical history, pulmonary function values and medication use for all patients (N=698) in studies NCT01199289 and NCT 01018550 are summarized in **Table 1**. Patients in study NCT01018550 were more likely to be atopic (93% vs. 83%, $p < 0.001$) and had a higher % predicted FEV₁ ($66.9 \pm 8.24\%$ vs. $65.2 \pm 8.53\%$, $p = 0.0081$) than patients in study NCT 01199289. However, these differences were small and not considered to be clinically significant or substantial enough to impact interpretation of results when considered as a single combined cohort.

Two hundred and thirty seven (237; 38%) patients in the combined study cohort met the HR criterion. Relative to those with LR (N=385), HR asthma patients tended to be younger, were more often atopic, had significantly lower BMI, lower baseline pulmonary function, higher mean FeNO and IgE values, and higher ACQ7 scores than patients with LR (**Table 2**). One hundred and thirty six (136; 63.6%) HR patients met the criteria for very poorly controlled (VPC) disease defined as ACQ6 score > 2.143 . Compared to HR patients with not well controlled (NWC) asthma (ACQ between 1.5 and 2.143), the subgroup with VPC asthma tended to be older (44.1 ± 11.0 yrs vs. 42.0 ± 12.3 yrs; $p = 0.184$), had lower baseline FEV₁ values (2.06 ± 0.51 L vs. 2.19 ± 0.59 L, $p = 0.1038$) and lower percent predicted FEV₁ ($62.8 \pm 7.50\%$ vs. $64.9 \pm 8.04\%$, $p = 0.062$) values (**Table 3**). Patients with HR and NWC disease did not differ from those reporting VPC disease with respect to gender distribution, body mass index, medication

use, or degree of airway reversibility. A parallel analysis utilizing ACQ7 as the measure of disease control applying the same cut-point showed similar findings.

To assess the consistency of Th2 biomarkers values as indicators of inflammatory status in this cohort, we compared measurements of blood eosinophils, serum IgE, and FeNO at baseline to measurements at Week-12 in subjects assigned to placebo treatment. Results are summarized in **Figure 1a, 1b, and 1c**, and show significant correlations between baseline and Week-12 values for all three Th2 biomarkers. We also examined within-patient temporal consistency of bronchodilator reversibility measurements and ACQ assessments using a similar approach. Results summarized in **Figure 1d and 1e** confirm that these were also quite stable over the 12 week assessment interval.

We next examined whether within-patient changes from baseline to week-12 in individual biomarkers correlated among one another, or with changes in either bronchodilator reversibility (BDR) or ACQ over this same interval. Analysis revealed no correlations of significance between baseline-to-week-12 changes among Th2 biomarkers, or between biomarker changes and changes in BDR or ACQ.

Relationships between biomarkers and disease control among patients with HR and LR are summarized in **Figure 2**. Among HR patients, an elevated blood eosinophil count was somewhat predictive (62% positive predictive value; $p=0.368$ by Chi Squared analysis) of VPC disease. However, circulating eosinophil count was not a sensitive indicator (sensitivity = 0.279) of disease control status as 98 of the 136 patients with VPC disease and HR had low

eosinophil counts. FeNO level and serum IgE level were also not associated with disease control in HR patients. An elevated serum IgE had moderate positive predictive value (PPV=0.548) for identifying patients with VPC disease, but lacked specificity (specificity = 0.375). Likewise, an elevated FeNO had moderate positive predictive of VPC (PPV=0.586), but was neither sensitive (sensitivity = 0.481) nor specific (specificity = 0.435) as an indicator of level of disease control. The aggregate Th2 IPI also failed to reflect disease control status in the HR subgroup. A positive profile was indeed associated with poor disease control, but the majority of patients with VPC disease did not display a Th2-high profile.

Similar poor associations between biomarkers status (High vs. Low) and extent of disease control were observed in LR patients (**Figure 2b**). Th2 biomarkers alone, and in aggregate when expressed as Th2 IPI failed to accurately reflect the level of disease control. This finding indicates that Th2 biomarkers in both the HR and LR subgroups are not reliable indicators of disease control.

To assess whether application of different biomarker cut-points might have rendered different findings, we performed a classification and regression tree analysis (CART). CART looked to maximize differences between subgroups by exploring the continuous range of values for each Th2 biomarker with the goal of identifying “optimal” cut-point values to differentiate patients with NWC from VPC disease. CART results were unrevealing, however, as no cut-point strategy including > 25% of either the HR or LR population clearly separated NWC from VPC patients.

Discussion

To better understand endotype diversity in asthma patients and identify profiles to guide therapy, asthma patients have been grouped, or “clustered,” based on clinical data and biomarkers. Using this approach, investigators of the Severe Asthma Research Program (SARP) have identified subgroups that differ with respect to age of disease onset, gender distribution, biometrics, health care resource utilization, airway hyper-responsiveness, and bronchodilator reversibility [1, 2]. High airway bronchodilator reversibility has emerged as a reliable “physiological biomarker” associated with severe airflow obstruction, increased health care resource utilization, and poor disease control. By contrast, classical serum and blood biomarkers have not consistently correlated with disease activity [2, 5]. Indeed, several studies paradoxically suggest that higher levels of some cytokines may be associated with milder phenotypes [5].

The present study attempts to better characterize this HR phenotype by comparing biomarker profiles and disease control status in HR and LR patients. Our analysis is focused on three biomarkers: 1) blood eosinophil count; 2) serum IgE concentration; and 3) exhaled nitric oxide concentration, and utilizes ACQ to assess disease control status.

Results presented in **Figure 1** show that these 3 biomarkers were stable indicators of immune status. Patients not receiving active therapy in studies NCT01018550 and NCT01199289 had 12-week biomarker values that were highly correlated with baseline values. While some variability was observed, 49 to 93% of the Week-12 signal, assessed in terms of r^2 value, was accounted for by the baseline value, with FeNO showing the poorest correlation

over time. A similar analysis involving ACQ and BDR indicated that within-subject measures of disease control and airway reversibility also remained relatively stable over this time frame.

While baseline Th2 biomarker levels appear to be stable indicators of inflammation in a given patient, they were not useful indicators of HR vs. LR phenotypes, or VPC vs NWC phenotypes. As shown in **Figure 2a** and **b**, the fraction of patients with a Th2-high biomarker profile in the HR subgroup was higher than in the LR subgroup (40.1% vs. 29.3%, $p=0.006$). However, the majority of patients in both subgroups displayed a Th2-low biomarker profile. Serum IgE was elevated in a similar fraction of HR (66.2%) and LR (57.9%) patients, consistent with the high incidence of atopy in both populations (93.7% and 86.5% respectively). However, blood eosinophils and FeNO were elevated in a minority of patients in both subgroups. This could reflect the effects of corticosteroid use on biomarker expression as this class of medication is known to affect circulating eosinophil counts and FeNO levels, and may influence cytokine expression [10, 11]. Thus, while the HR cohort relative to the LR cohort is enriched for patients with a Th2-high biomarker profile, the majority of moderate to severe asthmatics in studies NCT01018550 and NCT01199289 had a Th2-low profile.

Our results further indicate that within HR and LR subgroups, Th2 biomarker status does not align with disease control. Across both HR and LR subgroups, the proportions of patients displaying Th2-high biomarkers with very poorly controlled and not well controlled asthma were similar (HR Th2-high: VPC=39.0% vs. NWC=41.6%, $p=0.685$; LR Th2-high: VPC=27.% vs. NWC=31.1%, $p=0.461$). To the extent that Th2 biomarkers levels accurately

reflect inflammatory status, these findings do not support the hypothesis that disease activity in adult patients with poor asthma control is primarily driven by Th2 inflammation.

Several factors implicit in our analysis are relevant to interpreting these findings in the broader context of asthma research. Studies NCT01018550 and NCT01199289 excluded patients on oral corticosteroids and IgE immunotherapy (i.e. GINA Step 5 patients), and study eligibility required that patients have a baseline FEV1 value of >50% predicted and fewer than 5 exacerbations in the 12 month period prior to enrollment. Therefore, our findings apply specifically to a subset of GINA step 3 and 4 patients. Extension of these findings to patients with different disease characteristics may not be valid. In addition, allocation of patients to Th2-high vs. Th2-low subgroups in this analysis is based on published IgE, eosinophil, and FeNO cut-points. While values used in this study are generally accepted and reasonable, results would vary if different cut-points had been utilized. The CART analysis reported here failed to identify Th2 biomarker cut-points that reliably separated VPC and NWC patients in either HR or LR subgroups, however. Finally, the ACQ-based cut-points defining NWC and VPC are based on extrapolations from the literature, and while theoretically reasonable, are specific to this analysis. A difference in cut-point definition would affect comparisons of NWC versus VPC subgroups due to patient assignment. However, it would not likely change the overall conclusion that HR asthmatics often display poor disease control along with Th2-low biomarker profiles.

In conclusion, our results indicate that conventional Th2-biomarker levels, including blood eosinophils, serum IgE levels, and FeNO, are reasonably stable indicators of the

inflammatory state of individual asthmatics receiving fixed medical therapy. Findings support prior results from SARP indicating that asthma patients with HR represent a distinct phenotype with worse pulmonary function and less well-controlled disease. Our data further suggest that the HR population, relative to the LR population, is enriched in patients displaying a Th2-high biomarker profile. However, the majority of patients in both HR and LR subgroups, while atopic, displayed Th2-low biomarker profiles. Finally, within HR and LR subgroups with ACQ6 values ≥ 1.5 , there was a poor relationship between disease control and Th2-biomarker levels, suggesting that factors other than Th2-inflammation drive disease activity in a majority of patients with moderate to severe asthma.

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Author contributions

WWB – study investigator, data analysis, manuscript authorship and review

STH - study investigator, manuscript authorship and review

SSW - study investigator, manuscript authorship and review

PK – sponsor medical director, data analysis, manuscript review

JF – statistical analysis, table and figure preparation

YC - statistical analysis, table and figure preparation, manuscript review

EPI - sponsor medical director, data analysis, table and figure preparation, manuscript authorship and review

AN – sponsor senior medical director, data analysis, manuscript review

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Author Guarantor: Edward P. Ingenito

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TABLES

Table 1. Comparison of Patients in Studies NCT01018550 and NCT01199289 Used to Define HR and LR Subgroups for this Analysis

	Study NCT01018550 (N = 396)	Study NCT01199289 (N = 302)	p-value[^]
Baseline ACQ 7 score	2.5 (0.60)	2.5 (0.65)	0.4552
Baseline ACQ6 score	2.3 (0.67)	2.3 (0.74)	0.8223
Age (years)	44.8 (11.37)	45.7 (11.40)	0.3088
BMI (kg/m ²)	31.2 (7.08)	30.2 (7.12)	0.0917
Baseline Eos (cells/uL), median (Q1, Q2)	199.5 (122, 292)	191.5 (130.5, 294.5)	0.8815
Baseline FeNO (ppb), median (Q1, Q2)	23.5 (15.0, 36.3)	23.5 (14.8, 35.8)	0.6111
baseline FEV1 (L)	2.22 (0.54)	2.16 (0.57)	0.1945
baseline FEV1 (% predicted)	66.9 (8.24)	65.2 (8.53)	0.0081
Baseline IgE (IU/mL), median (Q1, Q2)	176.2 (58.6, 423.3)	132.2 (51.7, 319.7)	0.0572
Airway Reversibility (%Δ)	17.9 (12.13)	19.4 (13.29)	0.1168
Gender (% female)	60	59	0.8777
(+) Atopy status (%)	93	83	<0.0001
% with Elevated Eos	24	24	0.9746
% on HD ICS	47	53	0.1312
% on HD ICS + LABA	40	41	0.6811

BMI, body mass index; Eos, eosinophils; FeNO, Fractional exhaled nitric oxide; FEV1, first second of a forced exhalation; HD ICS, high dose inhaled corticosteroid; LABA, long-acting beta agonist

Data represent mean (SD) unless otherwise indicated

[^]p-value from two sample t-test for means and from Wilcoxon rank sum test for medians

Table 2. Comparison of HR (N=237; Δ FEV1 $\geq$ 20%) vs. LR (N=385; Δ FEV1 < 20%) Subgroups from Studies NCT01018550 and NCT01199289

	HR (N = 237)	LR (N = 385)	p-value[^]
Baseline ACQ7 score	2.6 (0.62)	2.4 (0.63)	0.0247
Baseline ACQ6 score	2.3 (0.70)	2.2 (0.71)	0.2799
Age (years)	43.1 (11.63)	46.4 (11.14)	0.0004
BMI (kg/m ²)	29.9 (6.71)	31.3 (7.03)	0.0154
Baseline Eos (cells/uL), median (Q1, Q2)	214.0 (136.0, 303.0)	191.0 (126.0, 288.0)	0.173
Baseline FeNO (ppb), median (Q1, Q2)	25.7 (16.0, 40.0)	22.0 (14.3, 31.7)	0.004
Baseline FEV1 (L)	2.1 (0.54)	2.2 (0.56)	0.006
Baseline FEV1 (% predicted)	63.5 (7.72)	67.9 (8.35)	<0.0001
Baseline IgE (IU/mL), median (Q1, Q2)	192.9 (71.7, 400.3)	127.5 (50.3, 357.6)	0.0111
Airway Reversibility (%D)	31.2 (11.39)	11.2 (5.76)	<0.0001
Gender (% female)	149 (62.9%)	223 (57.9%)	0.2217
(+) Atopy status (%)	222 (93.7%)	333 (86.5%)	0.0050
BMI, body mass index; Eos, eosinophils; FeNO, Fractional exhaled nitric oxide; FEV1, first second of a forced exhalation; HD ICS, high dose inhaled corticosteroid; LABA, long-acting beta agonist Data represent mean (SD) unless otherwise indicated [^]p-value from two sample t-test for means and from Wilcoxon rank sum test for medians			

Table 3. Comparison of Patients with HR Based on Disease Control Assessed Via ACQ6

	Very Poorly Controlled (N = 136)	Not Well Controlled (N = 78)	P-value [^]
Baseline ACQ7 score	3.0 (0.45)	2.1 (0.18)	<.0001
Baseline ACQ6 score	2.8 (0.51)	1.8 (0.17)	<0.0001
Age (years)	44.1 (11.04)	42.0 (12.28)	0.1841
BMI (kg/m ²)	30.0 (6.44)	29.6 (6.73)	0.6767
Disease duration at study enrollment	25.3 (13.44)	23.4 (12.66)	0.3081
Baseline Eos (cells/uL), median (Q1, Q2)	219.5 (146.5, 311.0)	188.0 (129.0, 298.0)	0.2486
Baseline FeNO (ppb), median (Q1, Q2)	25.3 (15.5, 40.1)	26.0 (15.0, 42.0)	0.7655
baseline FEV1 (L)	2.06 (0.51)	2.19 (0.59)	0.1038
baseline FEV1 (% predicted)	62.8 (7.50)	64.9 (8.04)	0.0620
Baseline IgE (IU/mL), median (Q1, Q2)	197.7 (61.1, 396.2)	192.8 (91.6, 430.7)	0.4567
Age at disease onset	18.9 (16.79)	18.6 (16.35)	0.9000
Airway Reversibility (%D)	31.8 (12.39)	30.3 (10.06)	0.3663
Gender (% female)	67	60	0.2443
(+) Atopy status (%)	91	99	0.0262
Fraction on HD ICS	48	49	0.8271
Fraction on ICS +LABA	39	39	0.9989

ACQ, Asthma quality control; BMI, body mass index; Eos, eosinophils; FeNO, Fractional exhaled nitric oxide; FEV1, first second of a forced exhalation; HD ICS, high dose inhaled corticosteroid; LABA, long-acting beta agonist
Data represent mean (SD) unless otherwise indicated

[^]p-value from two sample t-test for means and from Wilcoxon rank sum test for medians

Table 4. Comparison of Patients with LR Based on Disease Control Assessed Via ACQ6

	Very Poorly Controlled (N = 202)	Not Well Controlled (N = 149)	P-value [^]
Baseline ACQ7 score	2.9 (0.52)	2.0 (0.19)	<.0001
Baseline ACQ6 score	2.8 (0.57)	1.8 (0.17)	<0.0001
Age (years)	47.3 (11.19)	45.8 (10.97)	0.2110
BMI (kg/m ²)	32.0 (7.48)	30.7 (6.46)	0.1092
Disease duration at study enrollment	26.6 (14.30)	27.9 (14.72)	0.4023
Baseline Eos (cells/uL), median (Q1, Q2)	188.0 (123.0, 288.0)	205.0 (140.0, 290.0)	0.2499
Baseline FeNO (ppb), median (Q1, Q2)	21.3 (14.0, 30.5)	24.5 (14.7, 34.3)	0.1074
baseline FEV1 (L)	2.17 (0.58)	2.33 (0.54)	0.0087
baseline FEV1 (% predicted)	67.4 (8.58)	69.0 (8.05)	0.0805
Baseline IgE (IU/mL), median (Q1, Q2)	112.9 (40.7, 311.0)	143.2 (64.7, 356.3)	0.0808
Age at disease onset	20.7 (16.25)	18.0 (15.01)	0.1021
Airway Reversibility (%D)	11.2 (5.66)	11.0 (6.09)	0.7280
Gender (% female)	62	54	0.1574
(+) Atopy status (%)	87	88	0.7217
Fraction on HD ICS	53	48	0.4141
Fraction on ICS +LABA	43	40	0.5720

ACQ, Asthma quality control; BMI, body mass index; Eos, eosinophils; FeNO, Fractional exhaled nitric oxide; FEV1, first second of a forced exhalation; HD ICS, high dose inhaled corticosteroid; LABA, long-acting beta agonist
Data represent mean (SD) unless otherwise indicated

[^]p-value from two sample t-test for means and from Wilcoxon rank sum test for medians

FIGURE LEGENDS

Figure 1 – Correlations between baseline and Week-12 measurements of blood eosinophils (1a), serum IgE levels (1b), exhaled nitric oxide (FeNO, 1c), disease control assessed in terms of ACQ 6 (1d), and bronchodilator reversibility (1e) are summarized for patients who did not receive active therapy in studies NCT01018550 and NCT01199289. The results confirm the stability of these measures out to 12 weeks.

Figure 2 - Patients with HR (2a) and LR (2b) are partitioned into those with poor and adequate disease control, and then further subdivided based on individual Th2 Biomarkers and the aggregate Th2 Immune Profile Index. The results of Chi squared analysis assessing the statistical significance of the association of each biomarker with disease control status, and positive (PPV) and negative (NPV) predictive values of each biomarker for predicting disease control status are shown.

FIGURES

Figure 1 Baseline vs. Week-12 Biomarker Data

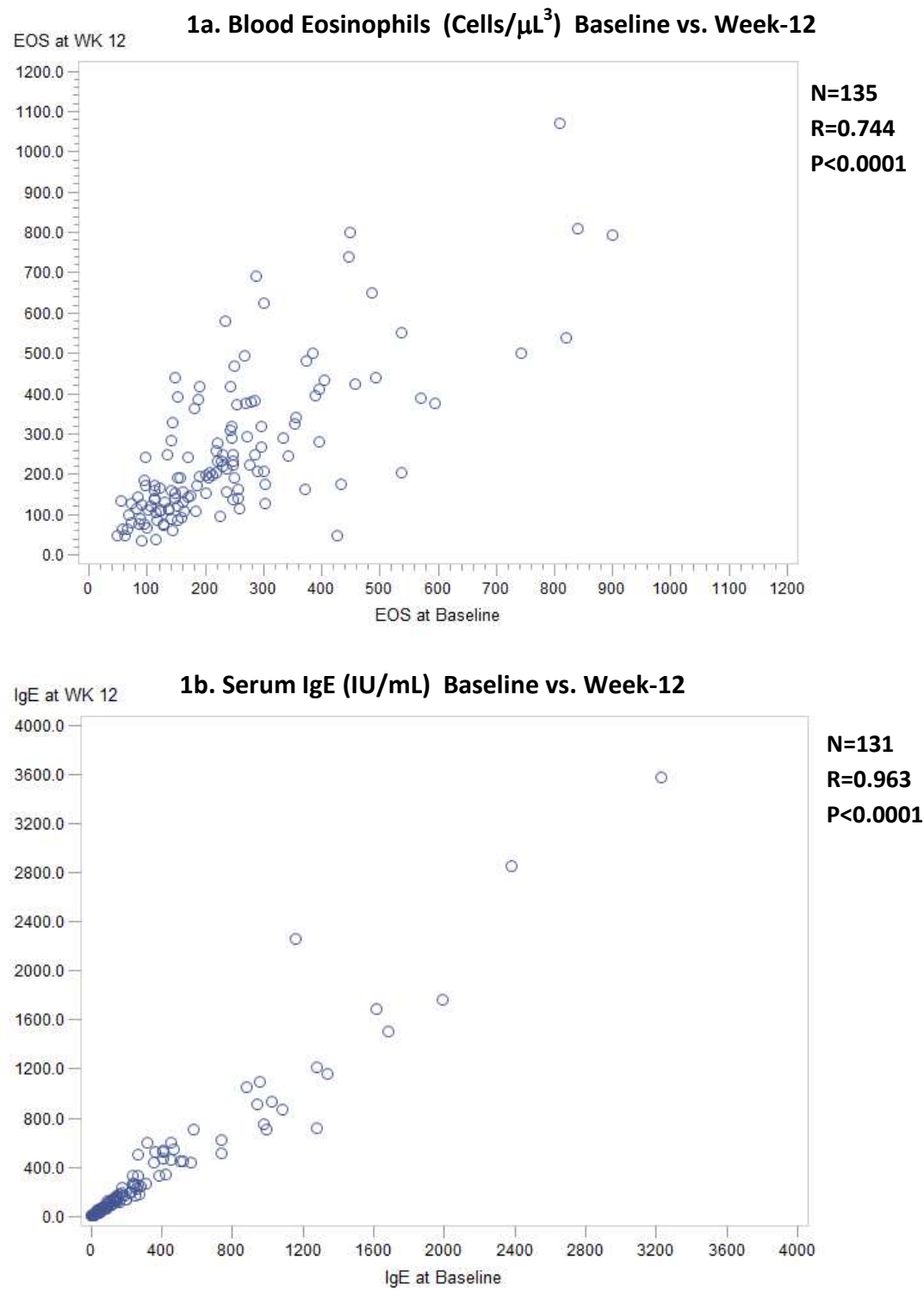
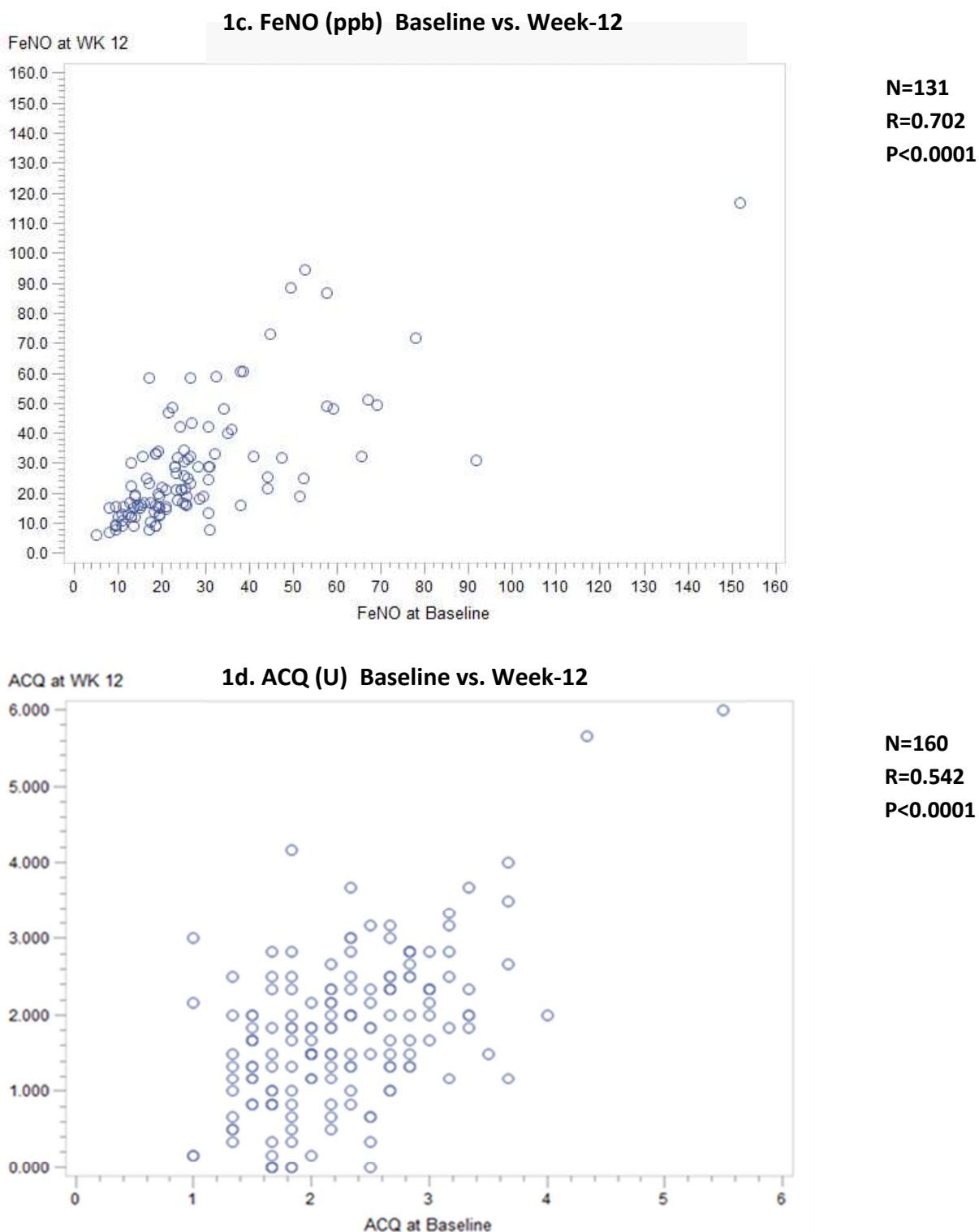


Figure 1 Baseline vs. Week-12 Biomarker Data

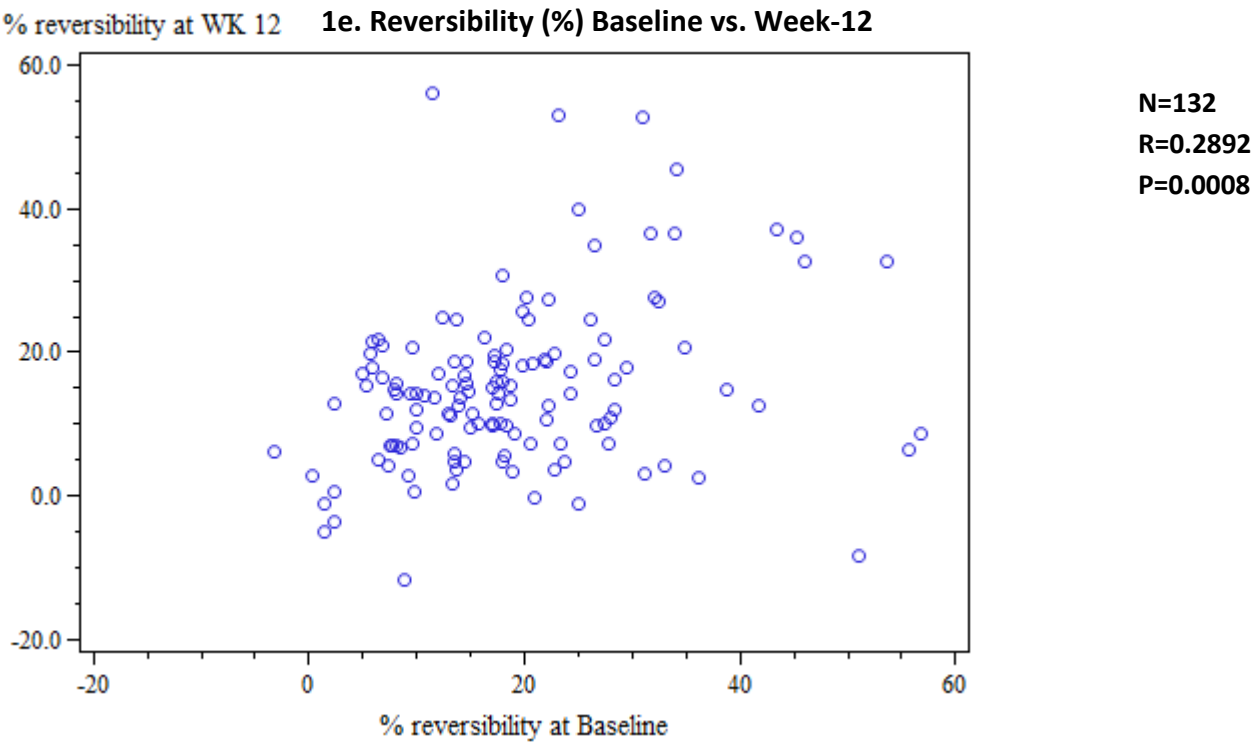


Figure 2a – Very Poorly Controlled and Not Well Controlled HR Patients Assessed Via ACQ6

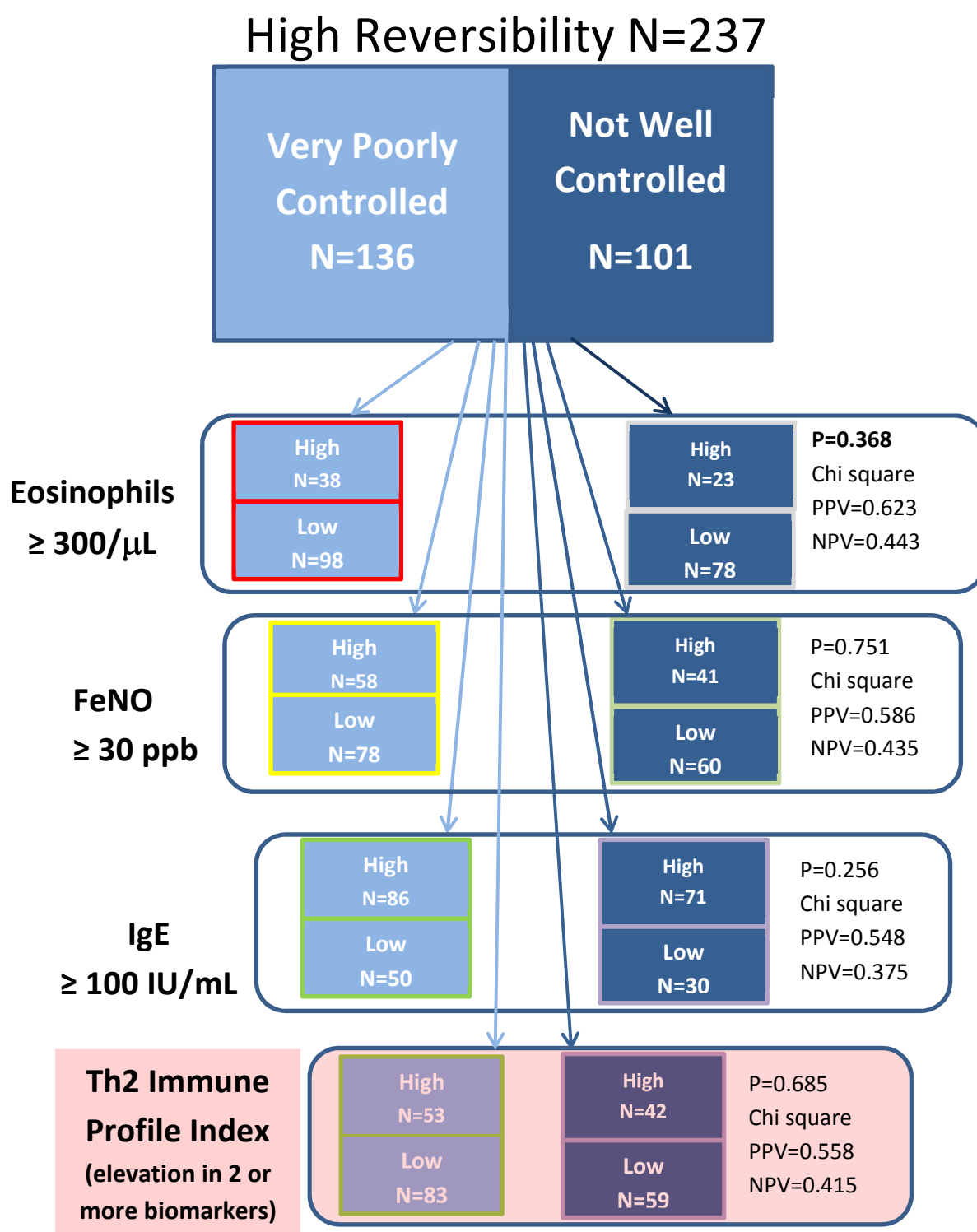


Figure 2b –Very Poorly Controlled and Not Well Controlled LR Patients Assessed Via ACQ6

