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Baseline sputum eosinophil+neutrophil subgroups' clinical characteristics and longitudinal trajectories for NHLBI Severe Asthma Research Program (SARP 3) Cohort

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Capsule Summary:

Combined elevated sputum eosinophils+neutrophils in asthma associated with lowest lung function, greater healthcare utilization, and longitudinally, further spirometric loss, implicating cell-cell interactions or overlapping inflammatory pathways while increased eosinophils or neutrophils alone show less effect.

Keywords

eosinophils; neutrophils; baseline sputum inflammation; longitudinal outcomes; healthcare utilization

To the Editor:

Cellular analysis of induced sputum allows noninvasive assessment of airway inflammation in comprehensively phenotyped subjects with different levels of asthma severity. Sputum analysis in a subset of subjects in the cross-sectional SARP1+2, revealed combined higher eosinophil and neutrophil percentages associated with more severe asthma phenotypes including lower lung function and greater healthcare utilization[3]. Cluster analysis incorporating sputum and blood inflammatory cells with clinical parameters showed that sputum neutrophils are an important variable associated with more severe asthma[5]. However, longitudinal observations are required to understand the impact of airway inflammation on progression of more severe asthma. Reports of longitudinal airway inflammation in asthma differ regarding whether inflammation is associated with accelerated decline in lung function or other important clinical characteristics; however, most study intervals are a year or less[1, 4, 7, 8, 9]. Therefore, utilizing Severe Asthma Research Program3 data with longitudinal assessment over 3 years for 526 adult subjects, we investigated whether baseline categorization of subjects by combined eosinophils (Eos) and neutrophils (Neu) identified a more severe asthma subgroup, and provided information on longitudinal changes in lung function and healthcare utilization.

Subjects and Assessments:

Adult subjects recruited at 7 clinical sites signed informed consent approved by site IRB and by NHLBI DSMB (ClinicalTrials.gov), underwent extensive clinical assessment at baseline,

including induced phenotype (single, intramuscular 40mg triamcinolone[6]), and annual visits for 3 years (details in online supplement).

Analyses and Statistics:

Subjects were stratified into 4 groups by baseline sputum cellularity (Low Eos+Low Neu: <2%Eos+<50%Neu; Low Eos+High Neu: <2%Eos+>50% Neu; High Eos+Low Neu: >2%Eos+<50%Neu; or High Eos+High Neu: >2%Eos+>50%Neu; similar to previous cross-sectional study[3,5]) and retained in these same groups for longitudinal analyses. Subjects without acceptable baseline sputum, or treated with biologic therapy during the study were excluded. Clinical characteristics for baseline, years 1, 2 and 3 data were analyzed by standard statistical tests.

Baseline Characteristics:

Baseline characteristics of the 4 sputum groups are in Table 1. Those groups with High Neu at baseline were older (p=0.0006) with greater length of time since diagnosis (p=0.0107), but did not differ for gender, or former smoker %. Those with High Eos at baseline had higher blood eosinophils (p<0.0001) and FeNO (p=0.0004). Total serum IgE was highest in High Eos groups (p=0.0246), but the number of positive specific IgEs, and frequency of >1 positive IgE did not differ. Controller medications did not differ between baseline groups (online supplement).

Pre- and post-bronchodilator (BD) FEV1%predicted were lower for combined High Eos +High Neu group than the other three groups, significant for High Eos+High Neu versus Low Eos+Low Neu groups for pre-BD and post-BD FEV1%predicted (both p=0.0200), and for High Eos+High Neu versus Low Eos+High Neu for pre-BD FEV1%predicted (p=0.0124). The change in absolute pre-BD FEV1%predicted following triamcinolone tended to be higher in the High Eos+High Neu group but not significant. Higher FEV1 response to albuterol was observed for the High Eos+Low Neu group (p=0.0001). Pre-bronchodilator FEV1/FVC was lowest in the group with combined High Eos+High Neu (p=0.0001)(Table 1).

Baseline healthcare utilization for the proportion of subjects reporting emergency department (ED) visits, unscheduled or ED visits, and number of exacerbations in the previous 12 months/year, were higher for combined High Eos+High Neu, but statistically significant for ED visits only (p=0.0213)(Supplement Table S3).

Longitudinal Characteristics:

Baseline sputum groups annually reassessed over 3 years (Years 1, 2 and 3, Table 1 and supplement Tables) showed reductions for %subjects classified as ‘severe’ in all groups over years 1, 2, and 3, but did not differ across 4 groups. Sputum eosinophil% in each baseline Eos+Neu group declined but remained significantly higher in High Eos groups (Table 1). High sputum eosinophil groups with or without High Neu had higher FeNO levels than Low Eos groups, (years 1 and 2, p=0.0002 and <0.0001, respectively).

Subjects in the High Eos+High Neu group continued to have the lowest pre-BD FEV1/FVC (years 1, 2, and 3: p=0.0001, 0.0008 and 0.0019, respectively). The High Eos+Low Neu group had the highest post-BD FEV1%predicted (Figure 1A), significantly differing from High Eos+High Neu at years 2 and 3 (p=0.0040, and p=0.0319, respectively). Absolute change in pre- and post-BD FEV1%predicted from baseline remained small and did not differ across groups, although post-BD FEV1% predicted was consistently negative in High Eos+High Neu throughout 3 years compared to little change or small improvements in the other groups (Figure 1B).

Healthcare utilization generally declined in all groups from baseline reported levels. ED visits decreased across groups, but the Low Eos+Low Neu group had higher %subjects reporting these visits (year 1: p=0.0337; year 2: p=0.0317, supplement). Exacerbations were lower for all groups after baseline, although the High Eos+High Neu group had a significantly higher rate for year 2 (p=0.0163) than other Eos+Neu groups (Figure 1C).

Summary:

Baseline sputum High Eos+High Neu was associated with lowest lung function and greater healthcare utilization, as we reported earlier for a different, smaller cohort[3]. Longitudinally over the three years from baseline, all subject groups showed declines in %'severe' asthma, in % healthcare requirements and exacerbations. Despite these changes, the High Eos+High Neu group had consistently reduced post-BD FEV1%predicted and greater exacerbations compared to the other Eos+Neu groups with little change or even small improvements.

Loss of subjects at baseline, or dropout during study reduced numbers for total and sputum subgroups. Nevertheless, 80% of subjects remained from baseline groups in the large SARP3 cohort by year 3, compared to 31% unobtainable or missing in another recent report[9]. Retaining subjects in baseline groups for longitudinal assessment provides observation of groups' clinical changes over time, but individuals may have changes in inflammation. However, High Eos groups had significantly elevated Eos throughout compared to low Eos groups. Low Neu groups had increasing %Neu over time, but remained lower than High Neu groups.

Older age for High Neu groups may contribute not only to higher Neu, but also to a lower lung function[2]. However, lung function for High Eos+High Neu was significantly lower than for Low Eos+High Neu, indicating High Neu were not the only factor influencing lung function. Exacerbations dropped from baseline to year 1, and leveled off afterwards for all Eos+Neu groups. Exacerbations at baseline depended on subject recall, but in years 1–3 were captured more frequently (6 month phone calls and annual visits). Improved adherence or other factors related to study participation may have contributed to the observed decrease in "severe" classification and healthcare utilization in all groups over the 3 years. The only intervention for all SARP3 subjects was short-term induced phenotype response to triamcinolone within 1st month after enrollment[6]. The largest pre-BD FEV1% predicted response to triamcinolone was observed in the High Eos+High Neu group, but with continued higher exacerbations longitudinally.

In conclusion, baseline subjects with combined increased sputum eosinophils and neutrophils had lowest lung function and greater healthcare requirements. Longitudinally, this High Eos+High Neu group showed further loss in lung function compared to other Eos +Neu groups, while healthcare requirements generally declined for all groups. These observations were not attributable to High Eos or High Neu alone, but suggest cell-cell interaction or overlapping inflammatory pathways.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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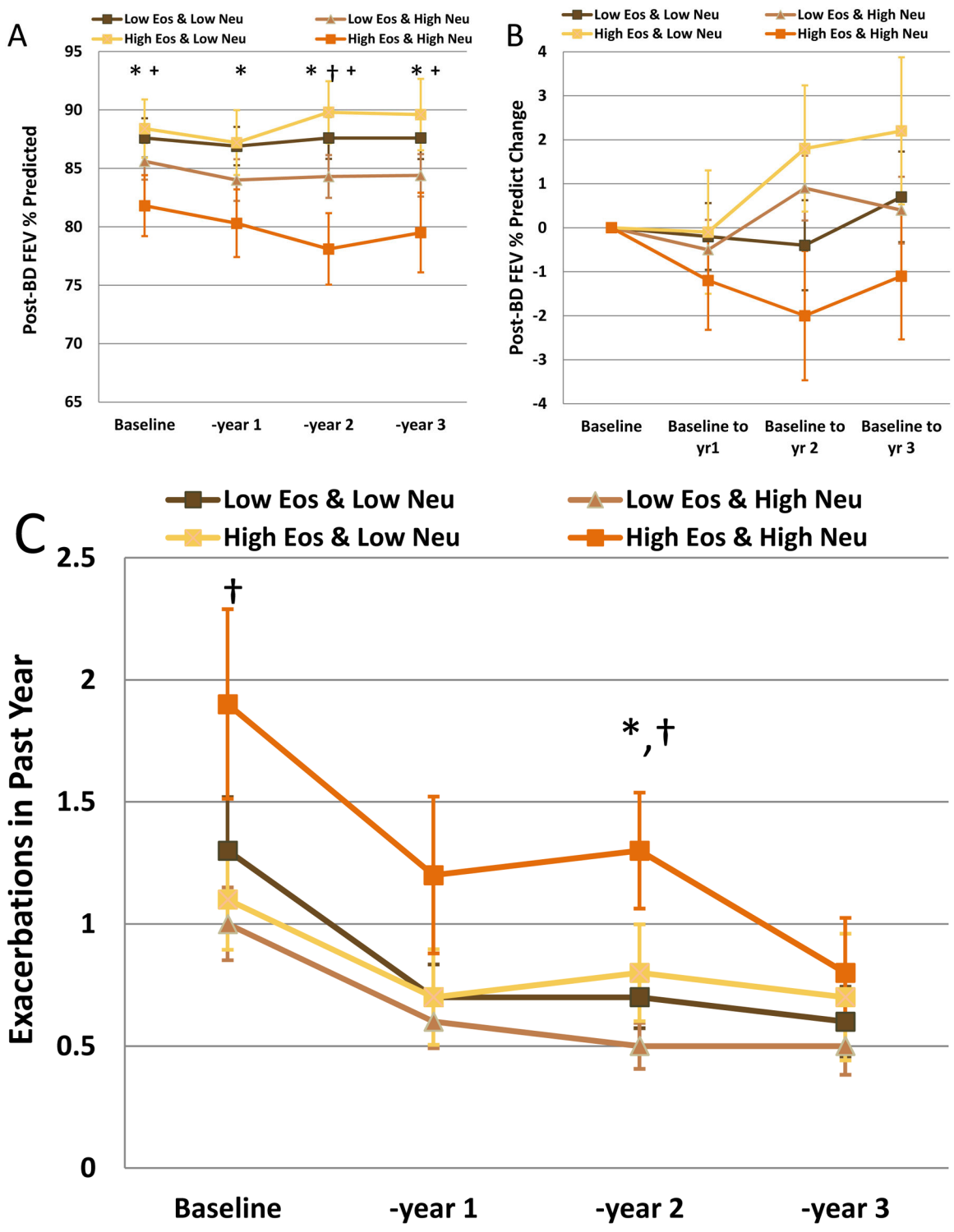

Figure 1. (A)

Post-bronchodilator FEV1%predicted (**B**) Absolute Change in Post-Bronchodilator FEV1%predicted and (**C**) Exacerbations at baseline and each annual visit for subjects stratified by sputum Eos + Neu differential categories determined at baseline. *High Eos

+High Neu vs Low Eos+Low Neu, p<0.05; †High Eos+High Neu vs Low Eos+High Neu, p<0.05; + High Eos+High Neu vs High Eos+Low Neu, p<0.05

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Table 1.

Demographic and clinical characteristics for subjects stratified by baseline sputum differential groups at enrollment (Baseline) and over the following 3 years.

Label	Low Eos+Low Neu	Low Eos+High Neu	High Eos+Low Neu	High Eos+High Neu	P value across 4 Eos+Neu groups
N Baseline	101	130	46	52	
N year 1	95	120	44	47	
N year 2	88	112	43	40	
N year 3	83	103	38	39	
Age at Baseline	42.3 ± 13.8	49.1 ± 14.3	45.6 ± 13.0	50.9 ± 13.4	**0.0006**[a,f]
Years since diagnosis of asthma	23.3 ± 14.0	29.7 ± 16.1	24.8 ± 13.0	30.0 ± 16.5	**0.0107**[a,f]
BMI - Baseline	34.1 ± 8.7	32.5 ± 9.6	31.4 ± 8.8	31.8 ± 8.9	0.0625[d,f]
-year 1	34.3 ± 8.9	32.3 ± 9.3	31.2 ± 8.3	30.4 ± 6.7	**0.0358**[a,d,f]
-year 2	33.7 ± 8.0	32.5 ± 9.5	30.5 ± 7.0	30.6 ± 7.2	0.0686[a,d,f]
-year 3	33.7 ± 8.0	32.6 ± 9.4	30.4 ± 7.5	30.6 ± 7.0	0.0767[a,d]
Male sex N (%)	35 (34.7%)	48 (36.9%)	12 (26.1%)	25 (48.1%)	0.1509
Race %White/%Black/%Other	63.4/25.7/10.9	70/23.1/6.9	63/21.7/15.2	53.8/25/21.2	0.2235/0.9433/**0.0451**[b]
Severe N (%)(by ATS criteria) Baseline	51 (50.5%)	60 (46.2%)	27 (58.7%)	31 (59.6%)	0.2794
-year 1	48 (50.5%)	45 (37.5%)	18 (40.9%)	26 (55.3%)	0.1024
-year 2	46 (52.3%)	38 (33.9%)	19 (44.2%)	20 (50%)	0.0550
-year 3	33 (39.8%)	36 (35%)	16 (42.1%)	16 (41%)	0.8222
Ever smoked N (%)	24 (23.8%)	32 (24.6%)	14 (30.4%)	20 (38.5%)	0.2052
PreBD FEV1 %Predicted - baseline	75.8 ± 18.5	76.1 ± 18.5	74.8 ± 17.7	68.9 ± 19.2	0.0721[a,b]
-year 1	77.3 ± 17.4	76.7 ± 19.9	73.7 ± 19.1	68.6 ± 21.8	**0.0394**[a,b]
-year 2	78.3 ± 18.8	76.2 ± 20.5	75.3 ± 21.2	66.9 ± 20.5	**0.0194**[a,b]
-year 3	77.8 ± 17.5	76.4 ± 19.2	75.2 ± 19.9	69.8 ± 21.5	0.1335[a]
PostBD FEV1 %Predicted - baseline	87.6 ± 16.8	85.6 ± 17.9	88.4 ± 16.9	81.1 ± 18.8	0.0807[a,c]

Label	Low Eos+Low Neu	Low Eos+High Neu	High Eos+Low Neu	High Eos+High Neu	P value across 4 Eos+Neu groups
-year 1	86.9 ± 16.0	84.0 ± 19.5	87.2 ± 18.4	80.3 ± 19.9	0.1741[a]
-year 2	87.6 ± 16.8	84.3 ± 19.4	89.8 ± 17.4	78.1 ± 19.4	**0.0123**[a,b,c]
-year 3	87.6 ± 16.4	84.4 ± 18.5	89.6 ± 18.8	79.5 ± 21.3	0.0593[a,c]
PreBD FEV1/FVC Baseline	0.71 ± 0.10	0.71 ± 0.10	0.68 ± 0.08	0.65 ± 0.10	**0.0001**[a,b,e]
-year 1	0.71 ± 0.09	0.71 ± 0.10	0.68 ± 0.08	0.64 ± 0.10	**0.0001**[a,b,c]
-year 2	0.71 ± 0.10	0.71 ± 0.11	0.68 ± 0.10	0.64 ± 0.10	**0.0008**[a,b,e]
-year 3	0.71 ± 0.09	0.71 ± 0.10	0.67 ± 0.09	0.65 ± 0.11	**0.0019**[a,b,d,e]
Triamcinolone response: Absolute change in Pre-BD FEV %predicted at baseline	2.1 ± 8.9	1.8 ± 6.3	3.7 ± 10.4	5.0 ± 8.9	0.0790[b]
FeNO - Baseline	20.0 (12.0, 34.0)	19.0 (13.0, 29.5)	35.0 (20.0, 53.0)	26.5 (16.0, 43.5)	**0.0004**[b,d,e]
-year 1	19.0 (14.0, 33.0)	19.0 (13.0, 29.0)	28.0 (19.0, 49.0)	38.0 (17.0, 55.0)	**0.0002**[a,b,d,e]
-year 2	21.0 (14.0, 32.0)	19.5 (12.0, 33.0)	45.5 (26.0, 73.0)	30.5 (17.0, 57.5)	**<0.0001**[a,b,d,e]
Sputum Eosinophils (percent) Baseline	0.3 (0.0, 0.7)	0.3 (0.0, 0.9)	5.6 (2.6, 16.7)	5.6 (3.6, 8.6)	**<0.0001**[a,b,d,e]
-year 1	0.5 (0.0, 1.1)	0.4 (0.0, 1.3)	2.6 (0.6, 17.6)	4.7 (2.0, 12.0)	**<0.0001**[a,b,d,e]
-year 2	0.4 (0.0, 1.4)	0.5 (0.0, 1.7)	5.1 (0.8, 16.7)	2.7 (1.2, 14.7)	**<0.0001**[a,b,d,e]
-year 3	0.2 (0.0, 0.9)	0.2 (0.0, 0.9)	2.7 (1.0, 11.6)	3.1 (0.2, 11.5)	**<0.0001**[a,b,d,e]
Sputum Neutrophils (percent) Baseline	28.6 (16.2, 39.3)	74.5 (61.9, 87.5)	35.2 (24.3, 42.6)	70.8 (60.0, 78.6)	**<0.0001**[a,c,d,e,f]
-year 1	38.3 (21.2, 62.6)	66.3 (46.5, 80.5)	49.3 (29.0, 58.3)	64.8 (49.3, 80.1)	**<0.0001**[a,c,e,f]
-year 2	49.2 (27.8, 59.5)	69.5 (50.0, 85.1)	44.8 (29.9, 54.9)	57.5 (48.9, 69.5)	**<0.0001**[a,c,e,f]
-year 3	53.4 (38.9, 70.3)	66.3 (55.6, 81.9)	51.8 (40.9, 69.5)	67.6 (53.8, 83.0)	0.0012[a,c,e,f]
Blood Eosinophils (count) Baseline	168 (105, 255)	168 (108, 281)	343 (222, 544)	344 (224, 489)	**<0.0001**[a,b,d,e]
Blood Neutrophils (count) Baseline	4,064 (3,045, 5,188)	3,949 (3,100, 4,988)	4,011 (3,180, 5,317)	3,996 (3,025, 5,857)	0.9394
Total IgE Baseline Geometric means	129.3 ± 3.7	87.2 ± 5.7	199.4 ± 3.8	166.8 ± 4.8	**0.0246**[b,e]
At Least One + Specific IgE	84 (84%)	103 (80.5%)	36 (78.3%)	38 (73.1%)	0.4472

Label	Low Eos+Low Neu	Low Eos+High Neu	High Eos+Low Neu	High Eos+High Neu	P value across 4 Eos+Neu groups
Number of + Specific IgE tests (of 15)	4.6 ± 3.7	4.1 ± 3.8	5.1 ± 4.6	4.0 ± 4.0	0.3855

[a]High Eos+High Neu vs Low Eos+Low Neu, p<0.05

[b]High Eos+High Neu vs Low Eos+High Neu, p<0.05

[c]High Eos+High Neu vs High Eos+Low Neu, p<0.05

[d]High Eos+Low Neu vs Low Eos+Low Neu, p<0.05

[e]High Eos+Low Neu vs Low Eos+High Neu, p<0.05

[f]Low Eos+High Neu vs Low Eos+Low Neu, p<0.05