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Ethnic variation in response to intramuscular triamcinolone in children with severe therapy resistant asthma

Sergio Koo, MPH, Royal Brompton& Harefield NHS Foundation Trust, London, United Kingdom

Atul Gupta, MD, Royal Brompton& Harefield NHS Foundation Trust; King's College Hospital NHS Foundation Trust, London, United Kingdom

Valentina Fainardi, MBBS, Royal Brompton& Harefield NHS Foundation Trust, London, United Kingdom

Cara Bossley, MD, Royal Brompton& Harefield NHS Foundation Trust; King's College Hospital NHS Foundation Trust, London, United Kingdom

Andrew Bush, MD, Royal Brompton& Harefield NHS Foundation Trust; Imperial College, London, United Kingdom

Sejal Saglani, MD, Royal Brompton& Harefield NHS Foundation Trust; Imperial College, London, United Kingdom

Louise Fleming MD, Royal Brompton& Harefield NHS Foundation Trust; Imperial College, London, United Kingdom

Correspondence:

Dr Louise Fleming

Senior Clinical Lecturer, National Heart and Lung Institute, Imperial College, London
Consultant Respiratory Paediatrician, Royal Brompton and Harefield NHS Foundation Trust

- **Address:** Department of Paediatric Respiratory Medicine, Royal Brompton Hospital, Sydney Street, London SW3 6NP, UK.
- **e mail:-** l.fleming@imperial.ac.uk

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Abstract

Background: Ethnicity may influence response to treatment of asthmatic patients, but this is controversial. This study's objective is to determine if ethnicity influences the response to intramuscular steroid (eliminating adherence as an issue).

Methods: Children with severe therapy resistant asthma who had previously undergone a detailed assessment when potentially modifiable factors had been identified and addressed were admitted for further evaluation including assessment of steroid response. Children were classified as Caucasian, black, Asian or mixed Caucasian / black. Steroid responsiveness was defined according to symptoms (Asthma Control Test), inflammation (sputum eosinophils and exhaled nitric oxide), and spirometry (FEV₁) which were measured before and 4 weeks after intramuscular triamcinolone. Data were collected regarding exacerbations. FeNO response was defined as a decrease to <24 ppb.

Results: 79 subjects were identified (Caucasian = 54 (68%), Black = 16 (20%), Asian = 5 (6%), Mixed Caucasian/Black = 4 (5%)). After triamcinolone, there was a significant drop in median FeNO in Caucasians (46.8 to 23.1 ppb, $p < 0.001$) but not in black children (52.2 to 34.5 ppb, $p = 0.58$). More Black children than Caucasian (86.7%) were FeNO non-responders (86.7 vs. 45.3%, $p < 0.05$). More Black children had exacerbations compared to Caucasian children (61 vs. 17%, $p < 0.05$).

Conclusions: Black asthmatic children were less likely to have a FeNO response and had more exacerbations 4 weeks after triamcinolone compared to Caucasians. Further research is needed to understand the mechanisms of these differences, but they cannot be due to differences in adherence or access to care.

Abbreviation list: ACT – Asthma Control Test, FeNO – Fractional exhaled nitric oxide, FEV₁ - first second forced expired volume, ICS – inhaled corticosteroid, IL – interleukin, LABA – long acting beta agonist, STRA – severe therapy resistant asthma, TH2 – type 2 T helper cells

Introduction

Problematic severe asthma is an umbrella term that encompasses those children with frequent symptoms and exacerbations despite treatment with high dose inhaled corticosteroid, long-acting beta agonist, and trials of other controller medications.¹ After addressing basic management, including adherence, the environment, and psychological issues, those with improved symptom control are termed “difficult asthma”; and those with on-going poorly controlled symptoms have genuine “severe therapy resistant asthma” (STRA). Those with difficult asthma have been shown to have a better medium term outcome with reduction in prescribed asthma medications.² The basic mechanisms underlying true STRA are unknown, although recent studies have proposed a non-type 2 T helper cells (non-TH2) driven airway eosinophilia as being important.³ Recent studies have attempted to delineate the ethnic differences in asthma severity. It has been shown that ethnic minorities have a higher mortality, hospitalizations and emergency department and urgent care visits related to asthma.⁴ Ethnic disparities in asthma are unlikely to be solely explained by socioeconomic status because there may also be differences in genetic composition and gene-environment interactions.⁵ Ethnicity may also influence the response to treatment of asthmatic patients, but this is controversial. African Americans were twice as likely as whites to experience treatment failure with long-acting beta-agonist but albuterol was equally efficacious between the two groups.⁵⁻⁷ Black people may have diminished response to glucocorticoids⁴ but evidence on ethnic variations in response to steroid is limited. We hypothesised that ethnicity influences the response to systemic steroids in children with STRA. We used an intramuscular depot corticosteroid to eliminate adherence and access to care as possible causes of any differential responses.

Methods

The study was conducted at the Royal Brompton Hospital, UK. Children with STRA who had previously undergone a detailed assessment including a nurse led hospital and home visit in which potentially modifiable factors had been identified and addressed⁸ were admitted for further evaluation including bronchoscopy and an assessment of steroid response. Only those children with ongoing poorly controlled

asthma despite attention to the basics of asthma management including adherence, and allergen avoidance and prescription of high dose inhaled corticosteroids (ICS) plus at least one other controller medication were included. Full details of the methods have been published elsewhere.⁹ This evaluation protocol was approved by the ethics committee of the Royal Brompton Hospital. Data were retrieved from the database for children with STRA from 2005-2011. Children were classified as Caucasian, Black (African or Afro-Caribbean), Asian (including Chinese) or mixed Caucasian / Black. Asthma Control Test (ACT), exhaled nitric oxide (FeNO), spirometry (first second forced expired volume, FEV₁) and sputum eosinophils were measured before and 4 weeks after administration of intramuscular triamcinolone. The dose of intramuscular triamcinolone was 40mg and 80mg for children with weight < 30kg and ≥30kg respectively.

Steroid responsiveness was measured according to three domains¹⁰:

- 1) symptom response: increase in ACT to ≥20 or by ≥5;
- 2) inflammatory response: decrease in sputum eosinophils to ≤2.5% (if paired samples were available) or if unavailable, decrease in FeNO to <24 parts per billion (ppb)
- 3) lung function response: increase in FEV₁ to ≥-1.96 Z-score or by ≥15%.

Data regarding exacerbations were collected over the 4 weeks following triamcinolone. An exacerbation was defined as a deterioration in symptoms requiring a course of oral steroids and / or emergency room attendance and / or hospital admission.¹¹

Statistical analyses

There are no published data to enable a power calculation, so sample size is opportunistic. Descriptive analyses were used to delineate the baseline characteristics. Fisher's exact test or Chi squared were used to assess the ethnic differences in the proportion of non-responders, partial responders and complete responders and the ethnic differences in proportion of responders in each domain (symptom, lung function, inflammatory (FeNO, sputum eosinophil)) and children having exacerbations.

For parametric and non-parametric data, t-test and Mann-Witney U test were used respectively to compare the baseline values in each domain between Caucasian and Black cohorts. Paired t-test and Wilcoxon test were used respectively for parametric and non-parametric data to compare the value for each domain at baseline and reassessment for both Caucasian and Black groups. p value < 0.05 was considered statistically significant. All analyses were carried out in GraphPad Prism version 6.

Results

Table 2 shows the baseline demographic data. There were 79 children (54 Caucasians (68%), 16 Blacks (20%), 5 Asians (6%) and 4 Mixed Caucasian/Blacks (5%)). Comparisons were made between Caucasians vs. Blacks, and Caucasian vs. non-Caucasians (combination of Blacks, Asians and mixed Caucasian/Blacks). There was no significant difference in height, weight, ICS dose or gender distribution between Caucasians, Blacks and non-Caucasian. All children were prescribed a long acting beta agonist (LABA) in addition to ICS.

At baseline Caucasians had a better baseline FEV₁ Z-score than Blacks (-2.00 vs. -3.1, $p=0.05$) and non-Caucasians (-2.00 vs. -3.0, $p<0.05$). and were more likely to have been admitted to intensive care because of asthma. There were no baseline differences in ACT score, FeNO or sputum eosinophils between the groups. Atopy and sensitisation to common aeroallergens was similar between the groups however Caucasian children were significantly more likely to own a pet and were more exposed to environmental tobacco smoke (ETS) than non-Caucasian children although this did not reach statistical significance ($p=0.067$)

Table 3 shows the pre- and post-triamcinolone values for each domain for Caucasian, Black and non-Caucasian children. Only those with paired values are included. After triamcinolone, there was a significant drop in median FE_{NO} in Caucasians (46.8 to 23.1 ppb, $p < 0.0001$) but not in black children (52.2 to 34.5 ppb, $p = 0.58$). (Fig. 1) After triamcinolone, Black children had a statistically higher FE_{NO} than Caucasian children ($p=0.003$) despite similar baseline values. (Fig. 1) Although the drop in median FE_{NO} was significant for all non-Caucasian children (57.7 to 32.7 ppb,

$p < 0.05$), non-Caucasians had a trend towards higher FeNO than Caucasians ($p = 0.07$) post triamcinolone. There was a drop in sputum eosinophils post-triamcinolone for Caucasian, Black and non-Caucasian children but only the drop in Caucasians was statistically significant. There was an improvement post-triamcinolone in FEV₁ Z-score and ACT score for all groups but only the increase in Caucasians and non-Caucasians was statistically significant. Post triamcinolone Caucasian children continued to have significantly better mean FEV z scores than Black children (-1.4 vs -2.43 $p < 0.05$) and all non-Caucasian children (-1.4 vs -2.40 $p < 0.05$)

Table 4 shows the response to intramuscular triamcinolone in Caucasian, Black and non-Caucasian children in each of the domains.

Significantly more Black children (86.7%) than Caucasian (45.3%) were FeNO non-responders ($p < 0.05$). Significantly more Black children ($n = 8$, 61%) had exacerbations despite triamcinolone compared to Caucasian children (17%, $n = 9$) ($p < 0.05$).

Discussion

The main finding of this study was that, despite no differences in baseline airway inflammation, there were differential responses to a standardised dose of depot triamcinolone between Caucasian and other ethnic groups with STRA in terms of exacerbations after triamcinolone, ACT, FEV₁, sputum eosinophilia and FeNO. There was no difference in the anthropometric parameters between the groups, including BMI, so differences in dosing could not account for these findings. Significantly more Black children than Caucasian were FeNO non-responders. Furthermore, black and non-Caucasian children had more asthma exacerbations after triamcinolone. We believe this is the first documentation of worse steroid response in black children with STRA.

The use of parenteral steroid eliminated any ethnic differences in adherence, a unique feature and strength of this study. Furthermore, these children had all undergone an extensive evaluation at which time potentially modifiable factors were addressed.

A limitation of this study is that there is no accepted definition of steroid response or steroid resistance in children. The definition of steroid resistance in adults (FEV₁ fails to improve from a baseline value of <75% by 15% or more despite demonstrating greater than 15% reversibility to an inhaled β_2 agonist)¹² is not appropriate for children who may have normal spirometry despite having severe asthma.¹³ Our previous study showed that the adult definition could not be applied to 50% of children with STRA.¹⁰ In this cohort, 69% and 67% of the Caucasian and Black children have normal spirometry at baseline so steroid responsiveness cannot be assessed in them using the adult criteria.¹² The criteria adopted in our centre¹⁰ incorporated symptom response and inflammatory response in addition to lung function in order to provide a more comprehensive assessment.

This study confirms previous reports that African children have lower FEV₁ when compared to Caucasian.^{14;15} A previous population-based study showed variable FE_{NO} among different ethnic groups¹⁶ but in our cohort of children with STRA, Caucasian and Black children had similar baseline FeNO.

It is acknowledged that the subjects in this study are from a highly selected cohort and the results may not be applicable to all populations. Another limitation is the small number of children with STRA, especially the small number of Black, Asian and mixed children. However, despite the fact that the number of subjects was small, the difference between the FeNO response in Black and Caucasian children was significant.

There are many potential mechanisms of steroid resistance, however, most studies have been conducted in adults, and the relevance in children is unclear.¹⁷ This study was not designed to elucidate underlying mechanisms for steroid resistance however, there are a number of plausible explanations for the differences seen between Caucasian and Black children. Previous studies have shown that Black children and adults have diminished T-lymphocyte response to glucocorticoid,⁴ and our present study may have demonstrated the clinical correlate of this finding. It was shown that in adults receiving inhaled corticosteroid, only those with TH2 high disease would

have improvement in terms of airway obstruction but not those with TH2 low disease,¹⁸ however we were not able to categorise children into these groups in our study.

Incomplete response to corticosteroid may also be due to ongoing exposure to environmental factors including ETS. Studies have shown that persistent allergen exposure in those sensitised can result in an interleukin (IL)-2 and IL-4 mediated corticosteroid resistance.¹⁹ We have also previously shown that exposure to ETS impairs histone deacetylase-2 function a known mechanism of cortico-steroid insensitivity.²⁰ However, in this cohort although sensitisation to aeroallergens was similar between the groups Caucasian children were significantly more likely to be pet owners and were more exposed to ETS, suggesting that these mechanisms were not responsible for the increased steroid resistance seen in the Black children. However, we accept that we do not have quantitative data on the degree of allergen exposure or on other environmental factors such as living in urban versus rural areas and it is possible these may have contributed to the increased steroid resistance seen in Black children.

We have previously reported the association between asthma severity and vitamin D levels.²¹ We started measuring vitamin D levels towards the end of this study and data are only available for a small number of participants. Vitamin D levels were not different between the three groups, however, larger numbers are needed for more meaningful analysis, particularly as black and Asian children are more susceptible to Vitamin D deficiency in countries such as the UK, which does not enjoy the sunniest of climates!

There are also ethnic differences in fraction of exhaled nitric oxide.^{16;22} This is likely due to genetics although environmental factors may play a role. There is also the possibility of genetic variation in nitric oxide synthase expression although its contribution has not been proven. The similar baseline FeNOs in the ethnic groups however suggests that genetic and environmental factors were similar and did not account for the differences seen.

Other studies have shown that African ancestry is associated with a higher rate of exacerbation.^{23;24} It has been suggested that this may be due to poor adherence to

inhaled corticosteroid (ICS) or the use of long-acting beta agonists (LABAs) used as a single agent. Psychosocial factors, particularly depression and anxiety are also associated with asthma morbidity.²⁵ In our cohort there were no significant differences between the groups in rates of referral to a psychologist. However, we do not have accurate data of the socio-economic status (SES) of this cohort. A number of studies have demonstrated a relationship between inflammation and low SES and more recently altered DNA methylation in candidate genes associated with SES-related inflammation, suggesting an epigenetic effect²⁶. This association warrants further investigation particularly looking at long term effects of both early and life course low SES.

The use of intramuscular steroid in this study eliminated adherence as a factor and all children were on combination ICS/LABA therapy, suggesting that the difference in exacerbations seen in this study is related to the intrinsic variation of the response to steroid. The poor FeNO response and higher exacerbation rate in Black children post-triamcinolone need to be explained and the other therapies found for Black STRA children in particular.

Prospective trials involving large number of well characterised STRA children with different ethnicity are necessary to further determine the mechanisms of, and interactions between, the differential response to asthma treatments and ethnicity. The difference in steroid responsiveness is one piece of the complex and multifactorial relationships between asthma and ethnicity.

In summary, Black children with STRA had worse baseline FEV₁, were less likely to normalise their FeNO and had more exacerbations following triamcinolone when compared to Caucasian children. There were significant responses in terms of ACT, FEV₁ and sputum responses in Caucasians but not in Black children. In this study these differences are not due to adherence or access to care and further research is needed to understand the underlying mechanisms.

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Author Contributions: Drs Koo and Fleming had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Dr Koo: contributed to patient enrolment, conception and design of the study, analysis and interpretation of the data, drafting of the manuscript, review of the report, and approval of the final version.

Dr Gupta: contributed to patient enrolment, conception of the study, review of the report and approval of the final version.

Dr. Fainardi: contributed to the analysis of the data, review of the report and approval of the final version.

Dr. Bossley: contributed to patient enrolment, conception and design of the study, review of the report and approval of the final version.

Prof. Bush: contributed to the conception and design of the study, patient enrolment, drafting of the manuscript, review of the report, and approval of the final version.

Dr. Saglani: contributed to the conception and design of the study, patient enrolment, review of the report, and approval of the final version.

Dr. Fleming: contributed to the conception and design of the study, analysis and interpretation of the data , patient enrolment, drafting of the manuscript, review of the report, and approval of the final version.

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Table 3. Values for each domain for Caucasian, Black, and non-Caucasian asthma children pre- and post-triamcinolone.

Table 4. Response to intramuscular triamcinolone in Caucasian, Black and non-Caucasian children.

Figure 1. FeNO value for Caucasian and Black children at baseline (pre-triamcinolone) and reassessment (post-triamcinolone).

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Table 1. Criteria for steroid responsiveness in children with severe asthma

Domain	Requirement
Symptom response	Asthma control test rises to a score of $\geq 20/25$ or by at least 5 points
Lung function response	FEV ₁ rises to normal (≥ -1.96 Z-score) or by $\geq 15\%$ No residual bronchodilator response
Inflammatory response (if paired induced sputum samples available)	Sputum eosinophil count normal ($\leq 2.5\%$)
Inflammatory response (if paired induced sputum samples not available)	Fractional exhaled nitric oxide* normal (< 24 parts per billion)

* Exhaled nitric oxide measured at flow 50mL/s.
FEV₁ = forced expired volume in one second.

Table 2. Baseline demographics for Caucasian, Black and non-Caucasian children before triamcinolone.

	Caucasian (n=54)	Black (n=16)	Non-Caucasian (n=25)	Caucasian vs Black p-value	Caucasian vs non-Caucasian p-value
Gender M:F	35:19	6:10	13:12	ns	ns
Height (cm)	144.3 (108.3 – 173)	153.0 (117.0 – 175.5)	151.6 (117.0 – 175.5)	ns	ns
Weight (kg)	41.0 (22.2 – 115.0)	54.20 (23.40 – 81.70)	51.7 (23.4 – 81.7)	ns	ns
BMI	18.56 (11.71 – 38.42)	19.6 (16.52 – 29.67)	19.62 (15.87 – 29.67)	ns	ns
ICS dose (mcg/day BUD equivalent)	1600 (400 -3200)	1600 (800 – 2400)	1600 (800 – 3200)	ns	ns
Psychology referral	16/33 (48%)	5/11 (45%)	11/18 (61%)	ns	ns
PICU admission ever	20 (37%)	10 (62%)	17 (68%)	ns	<0.05
FeNO, ppb	51.9 (42.1)	53.7 (20.2)	61.4 (39.7)	ns	ns
Sputum eosinophils	5.2 (0.0 – 92.0) N=32	9.4 (0.0 – 72.4) N=11	9.1 (0.0 (72.4) N=20	ns	ns
ACT score	12.96 (4.7) N=47	12.14 (5.4) N=14	12.41 (5.0) N=22	ns	ns
FEV1 z score	-2.0 (1.8)	-3.1 (1.7)	-3.0 (1.5)	0.05	<0.05
Atopic	46/52 (88%)	12/15 (80%)	19/24 (79%)	ns	ns
HDM sensitised	32/51 (63%)	11/15 (73%)	16/24 (67%)	ns	ns
Cat/dog sensitised	38/52 (73%)	9/15 (60%)	15/24 (63%)	ns	ns
Cat/dog owner	28/49 (57%)	1/15 (7%)	5/23 (22%)	<0.05	<0.05
Exposure to ETS	18/45 (40%)	2/15 (13%)	5/23 (22%)	ns	ns
Vitamin D level	29.5 (3.0 – 52.0) N=14	29.0 (15.0 -33.0) N=3	29.0 (8.0 – 37.0) N=5	ns	ns

Continuous data are shown as median (range) or mean (standard deviation). and analysed using the Mann Whitney U test or unpaired t test. Categorical data are shown as number (%) and analysed using Chi squared or Fischer’s exact test

Table 3. Values for each domain for Caucasian, Black, and non-Caucasian asthmatic children pre- and post-triamcinolone

		Pre-triamcinolone	Post-triamcinolone	Baseline vs Reassessment p-value
FeNO (ppb)	Caucasian (n=51)	51.9 (42.1)	28.2 (25.8)	<0.0001
	Black (n=15)	52.7 (20.5)	54.4 (40.6)	0.88
	Non-Caucasian (n=23)	62.7 (40.7)	41.6 (36.2)	0.056
% sputum eosinophil+	Caucasian (n=28)	3.9 (0.0 – 92.0)	1.5 (0.0 – 42.8)	<0.05
	Black (n=10)	15.2 (0.0 – 72.4)	9.5 (0.0 – 36.0)	0.43
	Non-Caucasian (n=18)	13.7(0 – 72.4)	2.5(0.0 – 36.0))	0.06
FEV ₁ Z-score	Caucasian (n=48)	-2.00(1.82)	-1.40(1.54)	<0.05
	Black (n=14)	-3.07(1.72)***	-2.43(1.06)***	0.07
	Non-Caucasian (n=23)	-2.77(1.49)***	-2.40(1.06)***	<0.05
ACT score	Caucasian (n=34)	12.8(4.6)	16.5(5.6)	<0.0001
	Black (n=13)	11.5(5.0)	13.6(5.6)	0.10
	Non-Caucasian (n=20)	12.0(5.0)	14.2(6.6)	<0.05

Values expressed as mean (SD) (FeNO, FEV₁ and ACT) or median and range (eos) and comparisons made using the paired t test or Wilcoxon signed ranks respectively

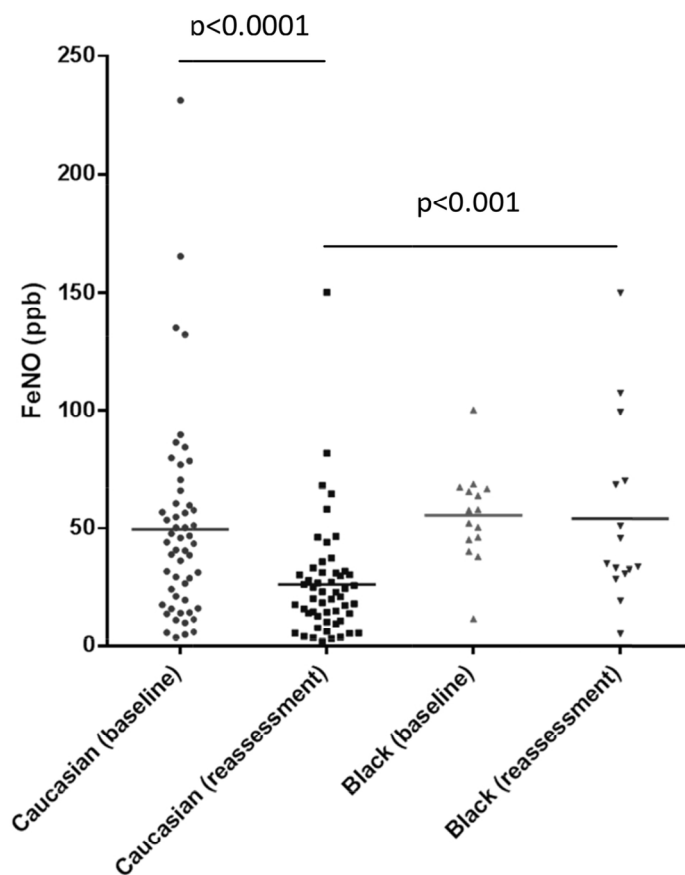
Abbreviations: ACT: Asthma Control Test, FeNO: Fractional exhaled nitric oxide, FEV₁: Forced Expired Volume in 1s, ppb: parts per billion

Table 4. Response to intramuscular triamcinolone in Caucasian, Black, and non-Caucasian Children

Response		Non-response n(%)	Response n(%)	Normal n(%)	Caucasian vs Black p-value	Caucasian vs non-Caucasian p-value
Inflammatory*	Caucasian(n=53)	22(41.5)	18(34.0)	13(24.5)	0.42	0.36
	Black(n=15)	9(60.0)	4(26.7)	2(13.3)		
	Non-Caucasian (n=24)	14(58.3)	5(20.8)	5(20.8)		
FeNO (FeNO < 24ppb)	Caucasian(n=53)	24(45.3)	20(37.7)	9(17.0)	<0.05	0.30
	Black(n=15)	13(86.7)	1(6.7)	1(6.7)		
	Non-Caucasian (n=24)	15(62.5)	5(20.8)	4(16.7)		
Sputum eosinophil (≤2.5%)	Caucasian(n=29)	11(37.9)	10(34.5)	8(27.6)	0.82	0.66
	Black(n=11)	5(45.5)	4(36.4)	2(18.1)		
	Non-Caucasian (n=18)	9(50)	5(27.8)	4(22.2)		
Lung function (FEV ₁ rise to normal (≥-1.96 Z-score) or by 15%)	Caucasian(n=48)	16(33.3)	9(18.8)	23(47.9)	0.16	0.16
	Black(n=14)	4(28.6)	6(42.9)	4(28.6)		
	Non-Caucasian (n=23)	9(39.1)	8(34.8)	6(26.1)		
Symptom (ACT to ≥20 or by at least 5)	Caucasian(n=34)	16(47.1)	15(44.1)	3(8.8)	0.15	0.26
	Black(n=13)	10(76.9)	3(23.1)	0(0)		
	Non-Caucasian (n=20)	14(70)	5(25)	1(5)		
		No Exacerbation	Exacerbation			
Exacerbation	Caucasian(n=51)	2(82.4)	9(17.6)		<0.01 ⁺	<0.01
	Black(n=13)	5(38.5)	8(61.5)			
	Non-Caucasian (n=21)	11(52.4)	10(47.6)			

Abbreviations: ACT: Asthma Control Test, FeNO: Fractional exhaled nitric oxide, FEV₁: Forced Expired Volume in one second

*(sputum eosinophils or FeNO if paired sputum samples not available)



FeNO value for Caucasian and Black children at baseline (pre-triamcinolone) and reassessment (post-triamcinolone)
 117x125mm (300 x 300 DPI)