

RESEARCH LETTER

Blood eosinophils: The forgotten man of inhaled steroid dose titration

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Blood eosinophil counts that were once regarded as normal, have become of increasing interest in the era of Interleukin-5 (IL-5) asthma treatment. Blood eosinophils as low as 150 cells/ μ L have been suggested as treatment cut-offs for eosinophil-depleting therapies such as mepolizumab,¹ whilst a value of 300 cells/ μ L has been deemed a more pragmatic cut-off by the National Institute for Health and Care Excellence (United Kingdom). In this era of eosinophil post-truths, inhaled corticosteroids (ICS), the eosinophil's oldest adversary, are very much the forgotten man.

Corticosteroids reduce the numbers of eosinophils in blood and sputum by inhibiting the expression of pro-eosinophilic cytokines such as IL-5 and increase the rate of apoptosis and associated phagocytosis. It is known that titrating ICS against sputum eosinophils results in improved asthma control.² Whilst it is also known that sputum eosinophils correlate well with blood eosinophils,³ the effects of increasing ICS dose on blood eosinophils are less well documented.⁴

We therefore wanted to know whether ICS dose titration suppresses blood eosinophil counts in patients with persistent asthma. In addition, we investigated whether leukotriene receptor antagonists (LTRA) have a similar effect when used as add-on therapy. Another surrogate marker of Th2-mediated inflammation is exhaled breath nitric oxide (FeNO), where it has already been demonstrated that there is a dose-response effect of ICS.⁵

We, therefore, performed a pooled analysis of our own studies performed by the Scottish Centre for Respiratory Research, where we measured blood eosinophils and FeNO from a baseline of none or low-dose ICS to medium-dose ICS with or without LTRA. Fourteen studies were included in this analysis and are listed in Table 1. All were approved by the East of Scotland Regional Ethics Committee and registered at clinicaltrials.gov.

A total of 217 non-smoking patients with mild-moderate persistent asthma were included in the ICS dose titration analysis, of these 144 also received additive LTRA. Patients had a mean age of 38 years and a mean FEV1 of 85% predicted. In all studies analysed,

patients must have been free from an asthma exacerbation requiring systemic corticosteroids in the 3 months prior to trial enrolment. In the nine of fourteen studies included, patients had at least one positive skin prick test to a common aeroallergen, with a mean number of positive tests of two.

Baseline median low-dose inhaled corticosteroid (ICS) dose was 200 μ g/day as beclometasone dipropionate (BDP) equivalent dose. Baseline mean eosinophils were 356 cells/ μ L, mean eosinophilic cationic protein (ECP) was 24.9 μ g/L and mean exhaled nitric oxide (FeNO) was 41.4 ppb. Participants were stepped up to medium-dose ICS as median 800 μ g/day BDP equivalent, with a median treatment duration of 2 weeks. Median treatment duration of additive LTRA was also 2 weeks.

Changes in blood eosinophils and FeNO are presented in Figure 1. We observed a significant mean fall in eosinophils of 71 cells/ μ L (95% CI 38-105) $P = .001$ comparing low- versus medium-dose ICS and a further non-significant fall with LTRA amounting to 20 cells/ μ L. FeNO also significantly fell by 14.5 ppb (95% CI 7.9-21.1), $P = .001$ comparing low- and medium-dose ICS but did not decrease further with addition of LTRA. Mean ECP levels for low- and medium-dose ICS were 24.9 and 18.8 μ g/L, respectively, representing a significant ($P = .005$) decrease of 6.1 μ g/L (95% CI 2.4-9.6), although there were insufficient data to assess effects of LTRA. FEV1% predicted did not significantly change between low-dose ICS and medium-dose ICS: 1.6% (95% CI -0.5 to 3.2).

We demonstrated that ICS even at a medium dose of 800 μ g BDP results in a significant fall in blood eosinophils over a period of 2 weeks. Our data showed a non-significant further fall in blood eosinophils amounting to 20 cells/ μ L when adding LTRA, whilst Laviolette et al⁶ found a significant additive effect of LTRA amounting to a mean change of 40 cells. In contrast, Greene et al⁷ found no significant additive fall with LTRA on top of ICS, albeit measuring sputum rather than blood eosinophils. Their study also found no significant additive effect on FeNO in keeping with our data. In terms of ICS dose response, Kips et al⁸ reported significantly lower sputum

TABLE 1 Source data

References	ICS dose (BDP µg equivalent)	Total Exposure (days)
1. Lipworth BJ et al. Am J Med 2000; 109:114-21.	600 µg ± LTRA	14
2. Aziz I et al. Chest 2000; 118:1049-58.	400-800 µg	28
3. Wilson AM et al. Chest 2001; 119:1021-6.	800 µg ± LTRA	14
4. Dempsey OJ et al. J Allergy Clin Immunol 2002; 109:68-74.	0-400 µg	28
5. Currie GP et al. Am J Respir Crit Care Med 2003; 167:1232-8.	500-1000 µg	21
6. Currie GP et al. Allergy 2003; 58:602-7.	0-400 µg	14
7. Sims EJ et al. Br J Clin Pharmacol 2003; 56:104-11.	500 µg ± LTRA	14
8. Anderson WJ et al. Clin Sci (Lond) 2014; 127:635-43.	200-800 µg	42
9. Anderson WJ et al. Chest 2012; 142:1553-61.	200-1000 µg	28
10. Lipworth BJ et al. Chest 2012; 141:607-15.	400-1200 µg	365
11. Menzies D et al. Allergy 2007; 62:661-7.	200-800 µg ± LTRA	35
12. Barnes ML et al. Allergy 2007; 62:73-80.	0-400 µg	70
13. Dempsey OJ et al. Chest 2002; 122:151-9.	100-400 µg ± LTRA	42
14. Wilson AM et al. Br J Clin Pharmacol 1999; 48:579-85.	1000-2000 µg	8

eosinophils comparing medium- and low-dose ICS, but no commensurate fall in sputum ECP, in contrast to our observation of a significant fall in both blood eosinophils and ECP.

In a retrospective observational cohort study, Price et al⁹ demonstrated that those with eosinophils ≥ 400 cells/ μ L experience more severe exacerbations and have worse asthma control. The fundamental question therefore is whether ICS dose should be titrated against blood eosinophils as a surrogate inflammatory marker, especially given that pulmonary function shows a plateau in response above 400 μ g/day BDP equivalent dose.¹⁰ In this regard, Green et al² showed that titrating ICS against sputum eosinophils resulted in significantly reduced exacerbations; whether the same outcome would be achieved by titrating against blood remains to be answered. We appreciate the limitations of our data, which were only short term, and we did not report any outcomes of asthma control. Furthermore, the observed effect might be due to possible systemic absorption from the lung, assessment of which would have required a surrogate marker of systemic cortisol suppression. Finally, our study lacks a placebo arm or a control arm with a fixed ICS dose, meaning we are unable to account for natural variation in blood eosinophils over time. In a more severe cohort of patients with asthma, it has been demonstrated for subjects who have an initial blood eosinophil count above 150 cells/ μ L, 85% of

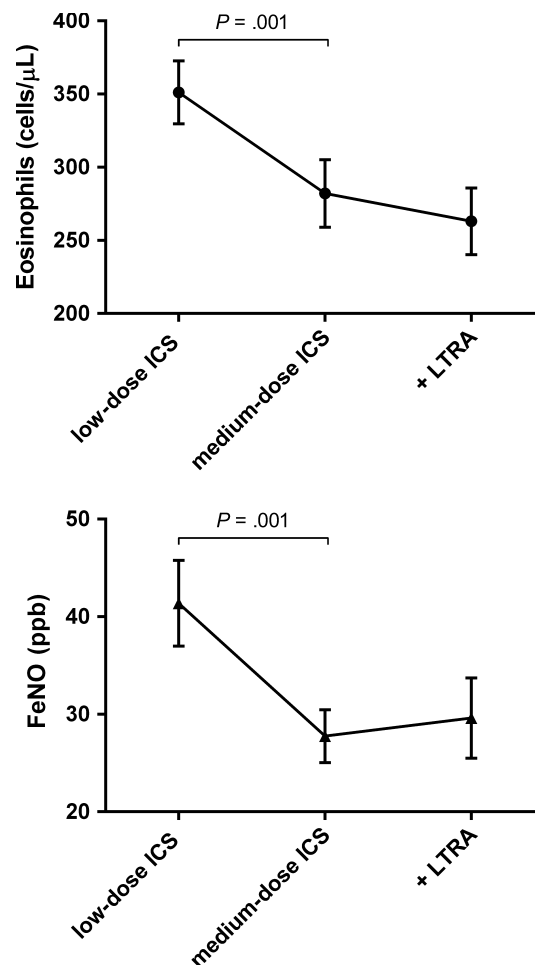


FIGURE 1 Comparison of low (200 μ g BDP equivalent)- and medium-dose (800 μ g BDP equivalent) inhaled corticosteroid (ICS) on blood eosinophils (top) and exhaled breath nitric oxide (bottom) in $n = 217$ patients with asthma, depicted as means and SEM. Effects of add-on therapy with leukotriene receptor antagonists (LTRA) are also shown in 144 patients

them remain above this value, even up to 56 weeks (based on four weekly blood eosinophil measurements).¹¹

As we consider ever more complex anti-inflammatory therapies as the future of asthma care, we must not overlook inhaled corticosteroids and their effects on blood eosinophils as the forgotten man of asthma therapy. Perhaps, a randomized control trial comparing ICS dose titration against conventional markers (pulmonary function, reliever use and symptoms) versus titration against blood eosinophils over 1 year might be worth pursuing.

CONFLICTS OF INTEREST

BJL has received payment for giving talks from Teva, Meda and Chiesi and Boehringer Ingelheim, for consulting activity from Chiesi, Cipla, Dr Reggys, Lupin and Sandoz, for attending meetings from Teva and Boehringer Ingelheim, for unrestricted research grants from Teva and Chiesi and Meda and multi-centre grants from Chiesi, Astrazeneca, Sanofi, Janssen and Teva. SJ has received reimbursement for

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