ORIGINAL ARTICLE

A randomised controlled trial of small particle inhaled steroids in refractory eosinophilic asthma (SPIRA)

David Hodgson,[1] John Anderson,[1] Catherine Reynolds,[1] Garry Meakin,[1] Helen Bailey,[1] Ian Pavord,[2] Dominick Shaw,[1] Tim Harrison[1]

[1]Nottingham Respiratory Research Unit, University of Nottingham, Nottingham, UK
[2]Nuffield Department of Medicine, University of Oxford, Oxford, UK

Correspondence to
Dr Tim Harrison, Nottingham Respiratory Research Unit, University of Nottingham, Clinical Sciences Building, Nottingham City Hospital, Hucknall Road, Nottingham NG5 1PB, UK; tim.harrison@nottingham.ac.uk

Received 28 October 2014
Revised 1 February 2015
Accepted 15 March 2015
Published Online First 9 April 2015

ABSTRACT

Background Some patients with refractory asthma have evidence of uncontrolled eosinophilic inflammation in the distal airways. While traditional formulations of inhaled steroids settle predominantly in the large airways, newer formulations with an extra-fine particle size have a more peripheral pattern of deposition. Specifically treating distal airway inflammation may improve asthma control.

Methods 30 patients with refractory asthma despite high dose inhaled corticosteroids were identified as having persistent airway eosinophilia. Following 2 weeks of prednisolone 30 mg, patients demonstrating an improvement in asthma control were randomised to receive either ciclesonide 320 μg twice daily or placebo in addition to usual maintenance therapy for 8 weeks. The primary outcome measure was sputum eosinophil count at week 8. Alveolar nitric oxide was measured as a marker of distal airway inflammation.

Results There was continued suppression of differential sputum eosinophil counts with ciclesonide (median 2.3%) but not placebo (median 4.5%) though the between-group difference was not significant. When patients who had changed their maintenance prednisolone dose during the trial were excluded the difference between groups was significant (1.4% vs 4.5%, p=0.028). Though alveolar nitric oxide decreased with ciclesonide the value did not reach statistical significance.

Conclusions These data demonstrate that patients with ongoing eosinophilic inflammation are not truly refractory, and that suppression of airway eosinophilia may be maintained with additional inhaled corticosteroid. Further work is needed with a focus on patient-orientated outcome measures such as exacerbation rate, with additional tests of small airway function.

Trial registration number NCT01171365. Protocol available at http://www.clinicaltrials.gov.

Key messages

What is the key question?

- Does treatment with an extra-fine particle size inhaled steroid reduce airway eosinophilia in patients with ongoing sputum eosinophilia despite high dose inhaled steroids?

What is the bottom line?

- Sputum eosinophils improved significantly in patients who did not change their baseline maintenance steroid dose, but markers of distal airway inflammation did not change significantly.

Why read on?

- Patients with persistent airway eosinophilia are not refractory to treatment, and targeting this group with higher doses of steroid is likely to be beneficial.

INTRODUCTION

P

fl - fi - - fl -
fl . M
fl ,
(ICS).[1] T ,
fl - . T ICS
,[2] . H
, ,

.[3–5] T
fl
, ,
fl ICS.[6]
N - -
,
O
(<2)
ICS. T
,
fi
,
fi fl
. I -

fi fl
,[7–13]
fi - - fl -
. .[14–16]
S
-
. T ICS
. H

To cite: Hodgson D, Anderson J, Reynolds C, *et al*. *Thorax* 2015;**70**: 559–565.

1.0–1.2 μ .[17] W (MDI) fl (CFC) , MDI fl (HFA) -fi .[18]

T -fi ICS fi 2- . T fl .

METHODS

S ATS - fl (≥3% ≥0.4 10^9/ L) fi N . L N 2010 A 2013.[19] E 10 - , - fi . A - . B - (NO), J A C Q (ACQ) , J A Q L Q (AQLQ) , .

A (=32) 2 30 - . C fi :

- N (<25) NO ≥40%,[20]
- A 1 (FEV_1)
- A J ACQ ≥0.5 .[22]

S (=30) , - 320 μ 8 - ; ICS . R 10 U N C T U . S - MDI, (=4) A C P (GSK, M , UK). T - 8. S ACQ , AQLQ , FEV_1, NO NO 8. S 8. S 4 8, 8. S fi - 12 . .

Exhaled NO

M NO . NIOX F (A AB, S , S). E NO fl (10 / , 30 / , 50 / , 100 / , 200 L/). E NO 50 L/ (F_{NO}) . A NO - (C) K *et al*.[23] T fl NO.

Lung function

S A T S / E R S ,[24] . V . G S (V , B , UK). S - . 4 . - - 12 . F . 4 100 μ MDI , 15 .

Asthma control and quality of life

A - ACQ - . A ≥1.5 fi , , fi . , . .[22] Q - AQLQ .[25]

Sputum differential cell count

I fl - . T ,[26] - . S ≥3%.[27]

Statistical analysis

S S SE V.11.2 (S , T , USA). D NO (F_{NO}) . C NO, - - . B ,[6] 16 . 40% 80% , 25%. W 20 . . W - . W - - . B . M -W U - . C - F_{NO} . , 95% CI. D . . U fi . , - . .

RESULTS

F - D 2010 A 2013. T

fl . T - fi , . T (=15) (=15) 29 (fi 1). R 40 . P (1). S (1600 µ BDP) . F . fi , , 2 (2, fi 2). T - 30 (80%) 8. T - 2.3% (IQR 0.5–13.5%), 2.3% (=0.263). I 8 4.5% (IQR 1.0–9.5%), 4.5% (=0.041). T <3% - fi (=0.317; 3, fi 3). T NO 8, fi . T fi , , NO (3).

T . fi (ACQ 0.7, =0.051). C , fi - (−62 /L, =0.327 +34 /L , =0.953). T . 8- (4 1) fi .

Effect of change in maintenance steroid

A - , fi (-) . 8 . I , - 8 (fi 3). A fl - 8 - - . A , fi 8 (4.5%, =0.014) (4) - - fi (=0.028). T fi .

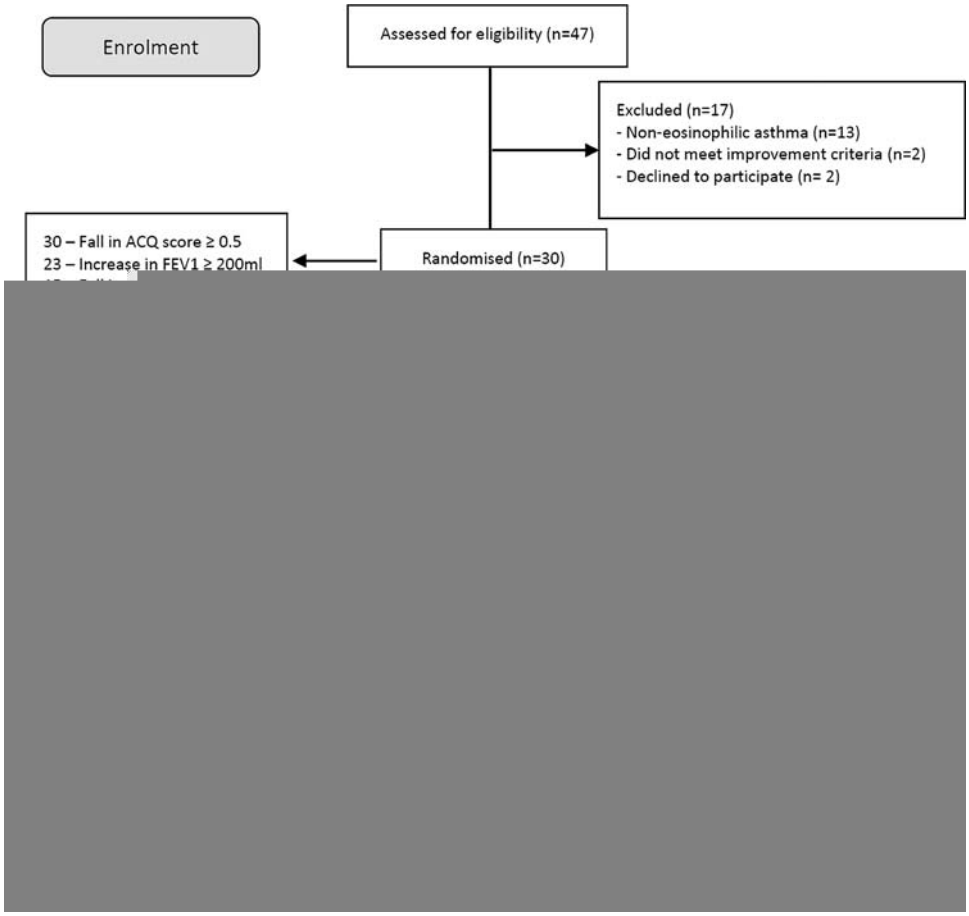

Figure 1 Consort flow diagram. Two patients in the run-in period did not reach our prespecified criteria for clinical improvement despite a reduction in sputum eosinophils. One patient in the placebo group dropped out in week 3 but was included in the final intention-to-treat analysis.

Table 1 Baseline characteristics

	Ciclesonide (n=15)	Placebo (n=15)
Age (years)*	48.5 (11.6)	53.3 (13.3)
Female (%)	7 (47%)	7 (47%)
BMI*	29.9 (4.6)	27.3 (4.6)
ICS dose (μg BDP)†	1600 (1200–2000)	1600 (1000–2000)
Regular prednisolone (%)	6 (40%)	4 (27%)
Prednisolone dose (mg)†	5 (5–10)	5 (5–10)
FEV_1 (L)*	2.0 (0.6)	1.8 (0.6)
FEV_1 (% predicted)*	61.8 (14.9)	60.1 (9.4)
ACQ score*	3.2 (1.0)	2.8 (0.8)
AQLQ score*	4.0 (1.1)	4.3 (1.1)
Fe_{NO} (ppb)‡	58.9 (0.3)	43.7 (0.3)
Corrected alveolar NO (ppb)†	3.3 (0.6–6.4)	2.6 (1.4–4.5)
Sputum eosinophils (%)†	23 (7.5–51.1)	9.6 (6.8–31.5)
Sputum neutrophils (%)†	43.5 (27.5–73.0)	50.5 (31.8–70.5)
Blood eosinophils ($\times 10^9$/L)†	0.5 (0.5–0.9)	0.4 (0.2–0.7)
Blood neutrophils ($\times 10^9$/L)†	4.5 (3.6–6.3)	5.0 (3.7–6.6)
Serum cortisol (nmol/L)†	266 (217–414)	254 (191–294)

*Mean (SD).
†Median (IQR).
‡Geometric mean (log SD).
ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; BDP, beclometasone dipropionate; BMI, body mass index; Fe_{NO}, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; ICS, inhaled corticosteroid; NO, nitric oxide.

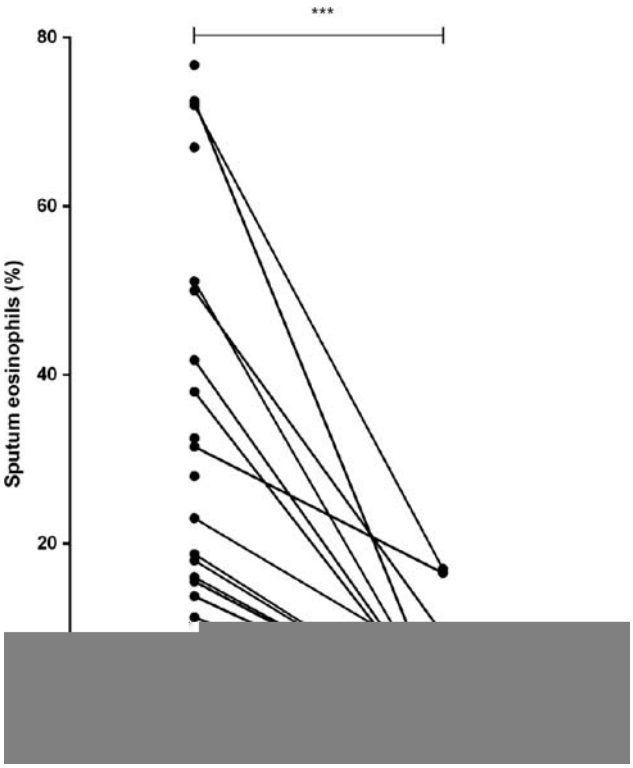

Figure 2 Sputum eosinophil count before and after 2 weeks of prednisolone.

DISCUSSION

T -
fl -
, 2 -
, . T
- ,
. T fi
-
8 -
. W

T
. S fi
, ,
,
fi
. T fi
fl
. T
1000 μ (BDP) ,[28 29]
4000 μ
. W , , fi
-
fi - , -
. W
NO -
-
fl . W
fi .
T
fi . . P -
fl ,
, -
.[13] T
, -

Table 2 Response to 2 weeks of prednisolone during the run-in period for all subjects (n=30)

	Baseline (preprednisolone)	Randomisation (postprednisolone)	p Value
Sputum eosinophils (%)*	16 (7.3–38.0) (n=29)	0 (0–2.3) (n=21)	<0.001
Sputum neutrophils (%)*	44.5 (31.8–70.5) (n=29)	78.3 (56.9–94.0) (n=21)	0.005
FEV_1 (litres)†	1.9 (0.6)	2.4 (0.7)	<0.001
ACQ score†	3.0 (0.9)	1.5 (0.9)	<0.001
AQLQ score†	4.1 (1.1)	5.6 (1.1)	<0.001
Fe_{NO} (ppb)‡	50.9 (0.3)	31.7 (0.3)	<0.001
Corrected alveolar NO (ppb)*	2.7 (1.3–6.4)	1.9 (0.9–2.9)	0.049

*Median (IQR).
†Mean (SD).
‡Geometric mean (log SD).
ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; Fe_{NO}, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; NO, nitric oxide.

Table 3 Primary and secondary outcome measures at randomisation and week 8

	Ciclesonide (n=15)			Placebo (n=15)			
	Randomisation	Week 8	p Value	Randomisation	Week 8	p Value	Between group p
Sputum eosinophils (%)*	0.0 (0.0–2.3) (n=10)	2.3 (0.5–13.5) (n=11)	0.263	0.0 (0.0–4.3) (n=11)	4.5 (1.0–9.5) (n=13)	0.041	0.317
Sputum neutrophils (%)*	77.5 (47.6–96.5) (n=10)	55.8 (38.8–88.5) (n=11)	0.017	79.5 (64.5–94.0) (n=11)	70.5 (56.8–89.3) (n=13)	0.799	0.155
FEV_1 (litres)†	2.6 (0.7)	2.5 (0.7)	0.252	2.1 (0.7)	2.0 (0.6)	0.115	0.699
ACQ score†	1.4 (1.1)	1.8 (1.4)	0.175	1.6 (0.8)	2.3 (1.3)	0.051	0.318
AQLQ score†	5.8 (1.0)	5.4 (1.5)	0.145	5.5 (1.2)	5.0 (1.4)	0.243	0.800
Fe_{NO} (ppb)‡	32.4 (0.4)	40.6 (0.4)	0.097	30.7 (0.3)	34.9 (0.3)	0.292	0.598
Corrected alveolar NO (ppb)*	1.7 (0.3–2.5)	1.4 (0.1–3.0)	0.925	2.0 (0.9–3.1)	2.4 (1.1–3.6)	0.730	0.528
Blood eosinophils ($\times 10^9$/L)*	0.1 (0.0–0.2)	0.3 (0.1–0.6)	0.013	0.2 (0.0–0.4)	0.3 (0.2–0.5)	0.065	0.128

*Median (IQR).
†Mean (SD).
‡Geometric mean (log SD).
ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; Fe_{NO}, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; NO, nitric oxide.

fl .[30] T - (FP), fl
fl ,
. W *et al*[9] HFA-BDP
. S - .[31] G *et al*[32] CT
, ,
- HFA-BDP CFC-BDP
, . I -
. R , V *et al*[33]
, , -
- HFA-BDP 30 .
CT , fl S
fi ,
.[12] -fi -
A -fi
. I . Y *et al*[34]
HFA-BDP CFC-fl ,

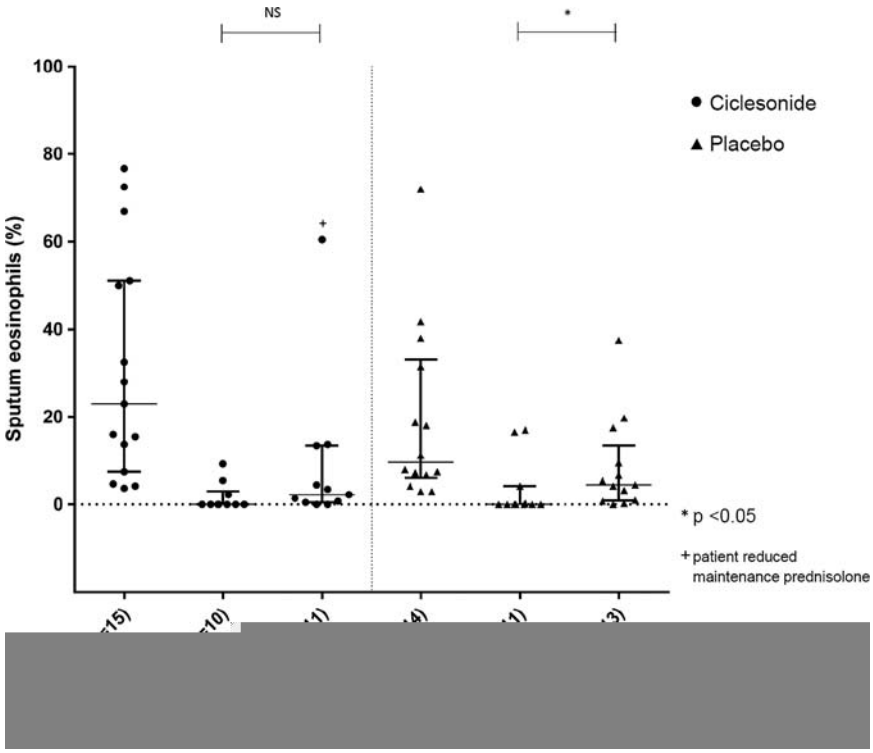

Figure 3 Median (IQR) sputum eosinophil count before and after 8 weeks of ciclesonide or placebo in addition to usual treatment.

Table 4 Primary and secondary outcome measures at randomisation and week 8 for subjects with no change in maintenance prednisolone dose

	Ciclesonide (n=12)			Placebo (n=12)			
	Randomisation	Week 8	p Value	Randomisation	Week 8	p Value	Between group p
Sputum eosinophils (%)*	0.0 (0.0–2.3) (n=8)	1.4 (0.5–3.5) (n=9)	0.499	0.0 (0.0–2.3) (n=8)	4.5 (1.0–17.5) (n=11)	0.014	0.028
Sputum neutrophils (%)*	85.5 (62.2–96.9) (n=8)	58.0 (51.2–88.5) (n=9)	0.028	84.0 (77.1–91.6) (n=8)	70.5 (56.5–90.0) (n=11)	0.400	0.297
FEV1 (litres)†	2.5 (0.7)	2.6 (0.8)	0.692	2.1 (0.7)	2.0 (0.7)	0.157	0.225
ACQ score†	1.5 (1.1)	1.5 (1.3)	0.779	1.5 (0.8)	1.9 (1.1)	0.186	0.281
AQLQ score†	5.8 (0.9)	5.5 (1.5)	0.295	5.5 (1.1)	5.5 (1.2)	0.826	0.658
Fe_{NO} (ppb)‡	27.8 (0.3)	32.9 (0.3)	0.241	26.4 (0.3)	29.7 (0.2)	0.359	0.787
Corrected alveolar NO (ppb)*	1.9 (1.0–2.5)	1.3 (0.1–3.0)	0.789	2.5 (0.9–3.1)	2.9 (1.1–3.6)	0.859	0.922
Blood eosinophils ($\times 10^9$/L)*	0.1 (0.0–0.2)	0.3 (0.2–0.4)	0.049	0.2 (0.1–0.4)	0.3 (0.2–0.5)	0.091	0.283

*Median (IQR).
†Mean (SD).
‡Geometric mean (log SD).
ACQ, Asthma Control Questionnaire; AQLQ, Asthma Quality of Life Questionnaire; Fe_{NO}, fractional exhaled nitric oxide; FEV_1, forced expiratory volume in 1 s; NO, nitric oxide.

HFA-BDP CFC-BDP I
12 . A ,
HFA-BDP
. O NO
. L ,
W *et al*[35] NO
ICS G *et al*[36]
NO
. W NO
fl
T -fi -
, -
CFC
BDP.[37] T -
-fi ,
,[37]
.[16]
T - -
. W -
fl , -
. A
-
fi fi
. T
, fl ,
. T fi
fi
fl . T -
, - , ,
. T
fl
(30% fi
- fl , fi 1)
. I
F NO -
,
T - ,
,
.
fi
.[27] F
-
fi - -fi
- ,
, . A
ICS
. I fi ,
-
IL-5 .

Twitter Follow David Hodgson at @dbhodgson

Acknowledgements This paper summarises independent research funded by the National Institute for Health Research (NIHR) under its Research for Patient Benefit Programme (Grant Reference Number PB-PG-0909-20101). The views expressed are those of the author(s) and not necessarily those of the NHS, the NIHR or the Department of Health. We are grateful to all trial participants who gave up their time to take part in the study, and thank Tekeda for supplying the active and placebo inhalers.

Contributors TH had full access to all of the data in the study, is the guarantor of the content of the manuscript, including the data and analysis, and takes responsibility for the integrity of the data and the accuracy of the data analysis, including any adverse effects. TH, DH, DS and IP were co-applicants on the NIHR research for patient benefit grant. DH, JA and CR contributed substantially to data collection. Sputum samples were processed by DH, GM and HB. TH, DH, JA, CR, GM, HB, IP and DS contributed substantially to the study design, data analysis and interpretation, and the writing of the manuscript.

Funding Department of Health-National Institute for Health Research (PB-PG-0909-20101).

Competing interests None declared.

Ethics approval The study was approved by the MHRA and Nottingham Research Ethics Committee 2.

Provenance and peer review Not commissioned; externally peer reviewed.

REFERENCES

1 Tattersfield AE, Knox AJ, Britton JR, *et al*. Asthma. *Lancet* 2002;360:1313–22.
2 Wenzel SE, Szefler SJ, Leung DY, *et al*. Bronchoscopic evaluation of severe asthma. Persistent inflammation associated with high dose glucocorticoids. *Am J Respir Crit Care Med* 1997;156(3 Pt 1):737–43.

3 Wenzel SE, Schwartz LB, Langmack EL, *et al*. Evidence that severe asthma can be divided pathologically into two inflammatory subtypes with distinct physiologic and clinical characteristics. *Am J Respir Crit Care Med* 1999;160:1001–8.
4 Miranda C, Busacker A, Balzar S, *et al*. Distinguishing severe asthma phenotypes: role of age at onset and eosinophilic inflammation. *J Allergy Clin Immunol* 2004;113:101–8.
5 ten Brinke A, Zwinderman AH, Sterk PJ, *et al*. Factors associated with persistent airflow limitation in severe asthma. *Am J Respir Crit Care Med* 2001;164:744–8.
6 ten Brinke A, Zwinderman AH, Sterk PJ, *et al*. "Refractory" eosinophilic airway inflammation in severe asthma: effect of parenteral corticosteroids. *Am J Respir Crit Care Med* 2004;170:601–5.
7 Martin RJ. Therapeutic significance of distal airway inflammation in asthma. *J Allergy Clin Immunol* 2002;109:S447–60.
8 Vignola AM, Chanez P, Campbell AM, *et al*. Airway inflammation in mild intermittent and in persistent asthma. *Am J Respir Crit Care Med* 1998;157:403–9.
9 Wagner EM, Liu MC, Weinmann GG, *et al*. Peripheral lung resistance in normal and asthmatic subjects. *Am Rev Respir Dis* 1990;141:584–8.
10 Wagner EM, Bleecker ER, Permutt S, *et al*. Direct assessment of small airways reactivity in human subjects. *Am J Respir Crit Care Med* 1998;157:447–52.
11 Grainge CL, Lau LCK, Ward JA, *et al*. Effect of bronchoconstriction on airway remodeling in asthma. *N Engl J Med* 2011;364:2006–15.
12 Gelb AF, Zamel N, Hogg JC, *et al*. Pseudophysiologic emphysema resulting from severe small-airways disease. *Am J Respir Crit Care Med* 1998;158:815–19.
13 Kraft M, Djukanovic R, Wilson S, *et al*. Alveolar tissue inflammation in asthma. *Am J Respir Crit Care Med* 1996;154:1505–10.
14 Richards J, Hirst P, Pitcairn G, *et al*. Deposition and pharmacokinetics of flunisolide delivered from pressurized inhalers containing non-CFC and CFC propellants. *J Aerosol Med* 2001;14:197–208.
15 Leach C, Davidson P, Boudreau R. Improved airway targeting with the CFC-free HFA-beclomethasone metered-dose inhaler compared with CFC-beclomethasone. *Eur Respir J* 1998;12:1346–53.
16 Newman S, Salmon A, Nave R, *et al*. High lung deposition of 99mTc-labeled ciclesonide administered via HFA-MDI to patients with asthma. *Respir Med* 2006;100:375–84.
17 Fink JB, Rau JL. New horizons in respiratory care: the pharmacology of inhaled aerosol drug therapy. *Respir Care* 2000;45:824–5.
18 Leach C, Colice GL, Luskin A. Particle size of inhaled corticosteroids: does it matter? *J Allergy Clin Immunol* 2009;124(Suppl 1):S88–93.
19 Wenzel SE. Proceedings of the ATS workshop on refractory asthma. Current understanding, recommendations, and unanswered questions. *Am J Respir Crit Care Med* 2000;162:2341–51.
20 Dweik RA, Boggs PB, Erzurum SC, *et al*. An official ATS clinical practice guideline: interpretation of exhaled nitric oxide levels (FENO) for clinical applications. *Am J Respir Crit Care Med* 2011;184:602–15.
21 GINA. http://www.ginasthma.com
22 Juniper EF, O'Byrne PM, Guyatt GH, *et al*. Development and validation of a questionnaire to measure asthma control. *Eur Respir J* 1999;14:902–7.
23 Kerckx Y, Michils A, Van Muylem A. Airway contribution to alveolar nitric oxide in healthy subjects and stable asthma patients. *J Appl Physiol* 2008;104:918–24.
24 Miller MR, Hankinson J, Brusasco V, *et al*. Standardisation of spirometry. *Eur Respir J* 2005;26:319–38.
25 Juniper EF, Guyatt GH, Epstein RS, *et al*. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax* 1992;47:76–83.
26 Pavord ID, Pizzichini MM, Pizzichini E, *et al*. The use of induced sputum to investigate airway inflammation. *Thorax* 1997;52:498–501.
27 Green RH, Brightling CE, McKenna S, *et al*. Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 2002;360:1715–21.
28 Adams NP, Jones PW. The dose–response characteristics of inhaled corticosteroids when used to treat asthma: an overview of Cochrane systematic reviews. *Respir Med* 2006;100:1297–306.
29 Holt S, Suder A, Weatherall M, *et al*. Dose-response relation of inhaled fluticasone propionate in adolescents and adults with asthma: meta-analysis. *BMJ* 2001;323:253–6.
30 Martin RJ, Cicutto LC, Smith HR, *et al*. Airways inflammation in nocturnal asthma. *Am Rev Respir Dis* 1991;143:351–7.
31 Thongngarm T, Silkoff PE, Kossack WS, *et al*. Hydrofluoroalkane-134A beclomethasone or chlorofluorocarbon fluticasone: effect on small airways in poorly controlled asthma. *J Asthma* 2005;42:257–63.
32 Goldin JG, Tashkin DP, Kleerup EC, *et al*. Comparative effects of hydrofluoroalkane and chlorofluorocarbon beclomethasone dipropionate inhalation on small airways: assessment with functional helical thin-section computed tomography. *J Allergy Clin Immunol* 1999;104:S258–67.
33 Verbanck S, Schuermans D, Paiva M, *et al*. The functional benefit of anti-inflammatory aerosols in the lung periphery. *J Allergy Clin Immunol* 2006;118:340–6.
34 Yamaguchi M, Niimi A, Ueda T, *et al*. Effect of inhaled corticosteroids on small airways in asthma: investigation using impulse oscillometry. *Pulm Pharmacol Ther* 2009;22:326–32.
35 Williamson PA, Short PM, Vaidyanathan S, *et al*. Inhaled and systemic corticosteroid response in severe asthma assessed by alveolar nitric oxide: a randomized crossover pilot study of add-on therapy. *Br J Clin Pharmacol* 2013;75:93–102.
36 Gelb AF, Taylor CF, Simmons M *et al*. Role of add-on zileuton on total exhaled, large airway, and small airway/alveolar nitric oxide in moderate-severe persistent adult asthmatics on fluticasone 250 microg/Salmeterol 50 microg. *Pulm Pharmacol Ther* 2009;22:516–21.
37 Thompson PJ, Davies RJ, Young WF, *et al*. Safety of hydrofluoroalkane-134a beclomethasone dipropionate extrafine aerosol. *Respir Med* 1998;92(Suppl A):33–9.