Online supplement

Method of airway hyperresponsiveness measurement

Bronchial provocation tests with methacholine were performed according to the dosimeter method with calibrated nebulizers (DeVilbiss 646, DeVilbiss Co, Somerset, USA) and dosimeters (KoKo, PSD instrumentation, Louisville, USA). ICS, bronchodilators, leukotriene receptor antagonists and antihistamines were stopped for at least 36 hours prior to the bronchial provocation test. Nebulized methacholine bromide was given in doubling concentrations (0.038 to 39.2 mg/ml) with mouth doses of 0.76 up to 786 ug. Doses causing a 20% fall in FEV1 from baseline (PD20) were calculated by means of linear interpolation of the logdose-response curve. For safety reasons PD20 methacholine was only measured in patients with FEV1/ FVC ratio > 0.7 or FEV1 >75% predicted. One center did not perform bronchial provocation tests because of different equipment (n=22).

Statistical analyses of PD20

For PD20 and FeNO a logtransformation was applied in all analyses and changes in PD20 were reported as doubling doses. For analysis of PD20 outcomes the program ‘cnreg’ from the STATA package was used to allow for patients who did not reach the FEV1 threshold of a 20% decrease (“censored” data).

Results on airway hyper responsiveness

At visit 1, bronchoprovocation tests could not be performed in 70 children (28%) due to FEV1 <75% predicted and/or FEV1/ FVC < 70% (n= 16), because they were too young

to perform reproducible spirometry (n=32), or for other reasons, including equipment failure (n=22). At visit 4, bronchoprovocation could not be performed in 88 children (too obstructive n=25, bad technique n=15, no bronchoprovocation test at visit 1 n=29, other n=19). In 12 children, no PD20 was reached after the maximal dose of methacholine at both visit 1 and 4. Because no conclusion could be drawn on changes in PD20 in these children, they were excluded from the analyses of changes in PD20. In the remaining 132 children, the mean change in PD20 was 0.8 doubling doses in the web group (p=0.4), 1.1 in the FeNO group (p=0.5), and 0.8 in the standard care group (p=0.8). The difference of these changes between the groups was not significant (p=0.5 and p=0.9, respectively).

Longitudinal data on symptom free days and ICS dose are presented in figure 1 and 2

Adherence

During the run-in period, 92% of the web-based diaries were completed. One hundred and forty-seven (54%) children completed all diaries twice daily, and 244 (90%) completed at least 21 days. After 1 year follow-up, adherence to filling in diary cards did not decrease (88%) and 141 (54 %) of the children completed all. Children randomized to the web group completed 88% (median) of the web-based ACTs. Forty-three % completed all and 85% completed >75% of diaries. Overall self-reported medication adherence during the study was 94.1% in the web group, 91.5% in the FeNO group, and 91.4% in the standard care group (p=0.3).

Deviation form study protocol

The study design allowed the physician to deviate from the recommended treatment step. This happened 32 times (mean 0.36 times per patient) in the web group, 52 times (0.57 times per patient) in the FeNO group, and 32 times (0.36 times per patient) in the standard care group. The distribution over the groups and over time was similar. The main reasons for deviations were suspected airways infections, or reaching the minimal or maximal treatment step.

Adverse Events

In total there were 13 adverse events; 4 children were admitted to the hospital because of an asthma exacerbation (1 during run-in, 1 web group, 1 FeNO group, 1 standard care group), 3 children had ENT surgery (FeNO and 2 standard care group), 4 children had abdominal complaints (2 web and 2 standard care group), and 2 children had hand/foot surgery (web and standard care group).

Table 1 Treatment dose steps.

Step	Treatment
1	Short acting beta-agonists (SABA) as needed
2	Budesonide 2 dd 100 ug or equivalent
3	Budesonide 2 dd 200 ug or equivalent
4	Budesonide 2 dd 200 ug or equivalent plus LABA
5	Budesonide 2 dd 400 ug or equivalent plus LABA
6	Budesonide 2 dd 400 ug or equivalent plus LABA plus LTRA
7	Budesonide 2 dd 800 ug or equivalent plus LABA plus LTRA

LABA: Long-acting β-agonist. LTRA: Leukotriene receptor antagonist. At all steps short acting beta-agonists as needed are prescribed.

Table 2 Changes from baseline of different outcome parameters in absolute numbers

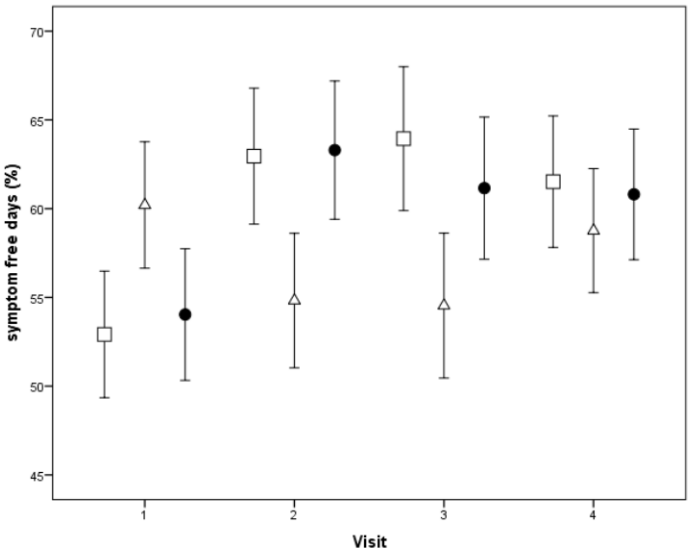
	Web (n=90)		FeNO (n=91)		Standard care (n=87)	
	Before	After	Before	After	Before	After
SFD, % (n=265)	60 (33)	58 (35)	53 (34)	62 (35)	54 (35)	61 (34)
ACT or C-ACT (n=269)	22.1 (3.5)	22.2 (3.9)	20.7 (4.3)	22.4 (3.5)	21.1 (3.3)	21.4 (3.9)
Daily symptom score (n=264)	1.1 (1.3)	1.2 (1.3)	1.4 (1.7)	1.0 (1.6)	1.3 (1.4)	1.2 (1.7)
Limitation of activities (n=258)	0.3 (0.3)	0.3 (0.4)	0.4 (0.4)	0.3 (0.4)	0.3 (0.3)	0.3 (0.4)
SABA use (puffs/day) (n=270)	0.4 (0.8)	0.3 (0.6)	0.6 (1.2)	0.4 (1.1)	0.4 (0.8)	0.3 (0.8)
ICS dose (ug) (n=270)	400 (400)	200 (400)	400 (400)	400 (600)	400 (400)	400 (550)
FEV_1 (n=229)	98.1 (12.6)	96.7 (12.3)	95.2 (12.6)	97.0 (12.6)	94.0 (14.0)	96.4 (12.5)
FVC (n=229)	103.3 (12.7)	102.4 (10.9)	100.3 (12.8)	102.1 (12.7)	101.0 (12.2)	103.0 (11.7)
FEF75 (n=221)	91.0 (35.7)	84.6 (34.4)	87.3 (33.1)	89.6 (35.6)	76.0 (29.3)	80.4 (25.7)
PD20,DD# (n=132)	178.5 (26.3-738.7)	153.6 (37.0-703.6)	118.1 (41.0-1084.4)	149.9 (40.5-1086.2)	158.2 (36.6-379.9)	164.3 (45.6-374.4)
FeNO (n=266)	17.1 (10.0-30.0)	25.2 (17.0-56.8)	15.4 (10.0-26.3)	27.0 (14.5-40.8)	21.4 (10.5-35.1)	23.0 (13.0-41.2)
PAQLQ child (n=89)	6.3 (5.9-6.6)	6.4 (6.1-6.8)	6.0 (5.6-6.6)	6.2 (5.8-6.9)	6.2 (5.9-6.6)	6.7 (6.2-6.9)

PACQLQ						
parent (n=176)	6.7 (6.2-7.0)	6.8 (6.2-7.0)	6.3 (5.7-6.8)	6.7 (6.1-6.9)	6.1 (5.8-6.8)	6.4 (5.9-6.9)

Data shown are mean values, except for ICS dose, PD20, FeNO, PAQLQ and PACQLQ scores (median (interquartile range)).

Figure 1

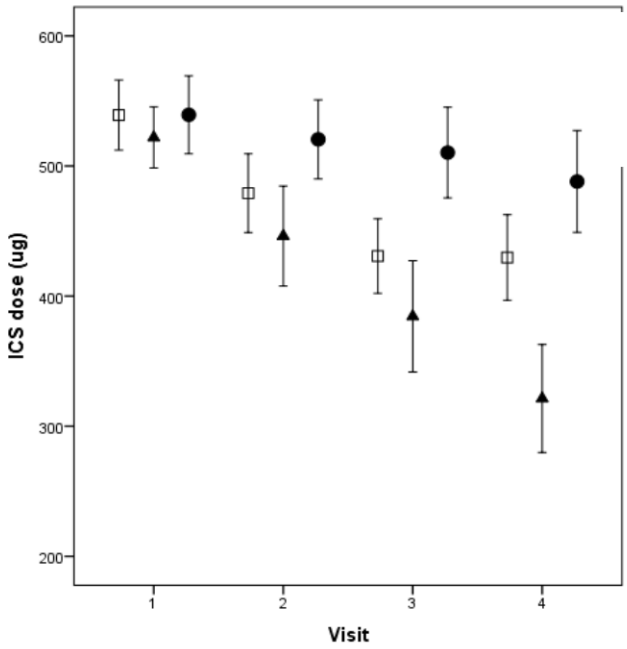
Longitudinal data on symptom free days in the 3 groups.



• standard care group
□ FENO group
∆ web group

Figure 2

Longitudinal data on ICS dose in the 3 groups.



• standard care group

□ FENO group

Δ web group