

Low-dose theophylline in childhood asthma: a placebo-controlled, double-blind study

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Regular anti-inflammatory treatment is essential in treating persistent asthma. Most commonly, inhaled corticosteroids (ICS) are used. However, especially in children, there is concern about the long-term safety of ICS such that doses should be kept to a minimum. The use of theophylline has decreased because of frequent side-effects in therapeutic doses. In adults, there have been reports about an immunomodulatory effect of low-dose theophylline. To study the clinical and immunomodulatory effect in children, 36 patients (mean age 12.5 SD 2.4 years) with moderate, persistent asthma on regular ICS were recruited into a placebo-controlled, double-blind study. After a 6-week run-in period, patients received either theophylline 10 mg/kg body-weight or placebo for 12 weeks. Diary cards, lung function, peripheral blood lymphocyte subpopulations and serum eosinophil cationic protein (sECP) were assessed. In the treatment group, mean serum theophylline was 7.1 mg/l. There was no change in symptoms or use of rescue medication. Mean (SD) peak expiratory flow (PEF) increased from 86% (24) to 95% (18) predicted. sECP decreased from 43.2 µg/l (32.5) to 26.5 µg/l (16.9) ($p = 0.02$). Lymphocyte subpopulations did not change. The study failed to show a beneficial clinical or an immunomodulatory effect of theophylline when used in low doses. These results do not support a more important role of theophylline in the long-term treatment of moderate childhood asthma.

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Asthma is the most common chronic respiratory disease in childhood. Persistent asthma requires long-term anti-inflammatory therapy. Most commonly, inhaled corticosteroids (ICS) are used. However, there is an ongoing debate whether long-term use of ICS is safe, especially in children. The dose–response curve is relatively flat, with a disproportional increase of side-effects if higher doses are used (1). Thus, current guidelines recommend a combination therapy using long-acting beta-2-agonists, leucotriene receptor antagonists or theophylline to avoid high doses of ICS (2).

Theophylline has been used for several decades in asthma therapy. In conventional doses of 15–20 mg/kg body weight (serum level 10–20 mg/l), the clinical effect is primarily due to bronchodilation. High-dose theophylline is frequently associated with unwarranted side-effects, e.g. headache, hyperactivity, nausea, failure to sleep

and cardiovascular symptoms. The frequency of these side-effects leads to reduced patient compliance if theophylline is prescribed for long-term treatment. In addition, the narrow therapeutic range requires regular measurement of serum levels (3, 4). In children, theophylline has been shown to have a negative effect on memory, concentration and behaviour (5). As a consequence, theophylline has largely been replaced by beta-2-agonists in the treatment of childhood asthma.

However, more recently, studies in adult asthmatics have shown an anti-inflammatory effect of theophylline at lower doses (serum level 5–10 mg/l) with a decrease in neutrophil and eosinophil activity in the airways (6–8). Kidney et al. found an increase of CD4⁺ and CD8⁺ lymphocytes after theophylline withdrawal mirrored by a decrease in peripheral blood lymphocyte subsets (9). Clinically, the

addition of low-dose theophylline was as effective as doubling the dose of ICS (10, 11).

The aim of the present study was to assess whether additional low-dose theophylline in asthmatic children on long-term inhaled steroids has a beneficial effect on symptoms and lung function, and whether an immunomodulatory effect can be detected.

Methods

Patients

Children and adolescents (age 6–18 years) with bronchial asthma were recruited from the paediatric pulmonology outpatient department at Hannover Medical School. Patients were eligible if they received ICS for at least 6 months prior to study entry and if the dose was unchanged for at least 3 months; needed beta-2-agonists as rescue medication >2/week; and had persistent airway obstruction with $MEF_{25} < 50\%$ predicted and/or $FRC_{pleth} > 130\%$ predicted.

Patients and parents gave their informed written consent before entering the study. The study protocol had been approved by the local ethics committee.

Study protocol

Study design was randomized, placebo-controlled and double-blind. Randomization was performed by Klinge Pharma GmbH (München, Germany) who provided study medication (slow-release theophylline 100 mg capsules, Bronchoretard junior[®]) and a matching placebo preparation.

After a run-in period of 6 weeks, patients were randomized to a 12-week treatment (theophylline 10 mg/kg/day, maximum daily dose 600 mg) period or placebo divided into two doses with clinic visits every 6 weeks (week –6, 0, 6 and 12). All other asthma medication (ICS and short-acting beta-2-agonists) continued.

Clinic visits included history and physical examination.

Lung function testing

Lung function testing (LFT) was performed at the beginning of the run-in period, and at the start and end of the study period. LFTs included whole body plethysmography and spirometry (Ganshorn Medizin Electronic GmbH, Niederauer, Germany) at all study visits, as well as a cold-air hyperventilation challenge [respiratory heat exchange system (RHES), Jäger, Würzburg, Germany] if baseline FEV_1 was >70% predicted,

or a bronchodilator challenge (baseline $FEV_1 < 70\%$ predicted) at the start and end of the study period. All measurements were performed according to American Thoracic Society (ATS) and European Community for Coal and Steel (ECCS) criteria. Results are expressed as percentage predicted according to Quanjer and Zapletal (12, 13). FVC , FEV_1 , MEF_{75-25} and PEF, as well as TGV (FRC_{pleth}), RV and Raw are reported. A cold-air hyperventilation challenge was considered positive if FEV_1 decreased by $\geq 10\%$ (14, 15). A bronchodilator challenge was considered positive if FEV_1 increased by more than 10% (14).

Patients were asked to record daily peak flow measurements (morning and evening) using a Wright Peak Flow Mini-Meter (Clement Clarke International Ltd, Cambridge, UK), symptoms (scale 0–3: 'no symptoms' to 'no time without symptoms' for day and night) and the use of rescue medication in a diary.

Peripheral blood measurements

Blood samples were taken at the start of the study period, i.e. week 0 (blood count and differential, sECP, lymphocyte subsets) and at the two subsequent visits, i.e. weeks 6 and 12 (including serum theophylline level).

sECP was measured using the Pharmacia CAP System ECP (Pharmacia, Freiburg, Germany). Results are expressed in $\mu\text{g/l}$.

The serum theophylline level was measured using the AXSYM (Abbott, Wiesbaden, Germany). The lower limit of detection was 0.8 mg/l.

The populations of leukocytes were identified by dual colour flow cytometry using directly conjugated monoclonal antibodies (Becton Dickinson and Company, San Jose, CA, USA; Immunotech, Marseille, France). Peripheral blood mononuclear cells were separated from EDTA-venous blood by Ficoll-Paque[®] (Pharmacia Biotech, Uppsala, Sweden) density gradient centrifugation, washed twice and adjusted to a concentration that 5×10^5 cells for one test could be used. These cells were incubated with 20 μl of fluorochrome-labelled monoclonal antibodies (MoAbs) for 15 min in the dark at 4°C. MoAbs were labelled either with fluorescein isothiocyanate (FITC) or phycoerythrin (PE).

The following MoAbs were used: CD3-FITC (T-lymphocytes), CD4-FITC (helper-T-cells), CD8-FITC (suppressor-T-cells), CD19-FITC (B-lymphocytes), CD14-FITC (monocytes) and as activation markers CD25-PE (interleukin-2 receptor) and HLA-DR-PE. In addition, the following double-labelled immunofluorescence

analyses were performed: CD3⁺/CD25⁺, CD3⁺/HLA-DR⁺, CD4⁺/CD25⁺, CD4⁺/HLA-DR⁺, CD8⁺/CD25⁺ and CD8⁺/HLA-DR⁺.

The cytofluorimetric measurements were performed on a FACScan flow cytometer (Becton Dickinson, Heidelberg, Germany) with scatter gates on the lymphocyte and monocyte fraction using laser excitation at 488 nm. The number of immunofluorescent positive cells was determined from 10,000 analysed cells and results expressed as percentage positive lymphocytes and the monocytes as a percentage of mononuclear cells without lymphocytes.

Statistics

Unless mentioned otherwise, results are from the intention-to-treat group and are presented as means and standard deviations.

Differences within patients groups between study visits were analysed using Student's paired *t*-tests. Differences between groups were analysed using unpaired *t*-tests.

It was estimated, that 18 patients were required in each group to find a difference in lung function with a power of 90% at an alpha level of 0.05. The sample size at the end of the study (excluding the three drop-out patients) was sufficient to detect a 15% difference in lung function with a power of 80% at a significance level of 5%. For statistical analysis, the package SPSS (Statistical Package for Social Sciences, Chicago, IL, USA) 6.1.3. for Windows was used.

Results

Thirty-six patients (29 male, 7 female) with a mean age of 12.5 years (2.4) were recruited. The mean daily dose of inhaled corticosteroids (budesonide or fluticasone) was 631.3 µg (263.7) (range 250–1200 µg).

At the start of the run-in period, there was no difference with regard to diagnosis, age, gender and dose of inhaled steroids (see Table 1). Also the lung function at the time of recruitment showed no significant differences in *FVC*, *FEV*₁, *MEF*₂₅, *MEF*₅₀, *MEF*₂₅, *TGV*, *RV*, *sRaw* and *sGaw*.

Table 1. Patient characteristics at the time of recruitment

	Placebo	Theophylline	p-value
Mean age (SD)	12.1 years (2.2)	12.8 years (2.5)	0.35
Gender	m = 15, f = 3	m = 14, f = 4	1.00
ICS products	budesonide (n = 7) fluticasone (n = 11)	budesonide (n = 11) fluticasone (n = 7)	0.32
Dose of ICS per day (SD)	554.2 µg (205.5)	708.3 µg (297.2)	0.08

Three patients withdrew from the study, two from the theophylline and one from the placebo group. One of the patients in the theophylline group reported nausea and vomiting as a reason for withdrawal. There were no other reported adverse effects.

Mean (SD) serum concentration of theophylline was 6.8 mg/l (1.2) and 7.1 mg/l (3.0) at weeks 6 and 12, respectively. Two patients had values < 5 mg/l at week 6, five patients at week 12.

Diary cards

There was no difference in symptoms or use of rescue medication either between groups or within groups over the study period (see Table 2). Home PEF increased in both groups with no significant differences between the groups.

Lung function

There was a significant increase in PEF in the theophylline group from weeks 0–12 (*p* = 0.02; 95% CI 16.94; 1.6 l/min). *FEV*₁ remained unchanged with 83.1% (20.5) and 85.8% (15.1) predicted (*p* = 0.5; 95% CI –12.16; 6.7) in the theophylline group and 88.5% (12.4) and 89.6% (11.6) predicted in the placebo group (*p* = 0.7; 95% CI –7.5; 5.4).

Specific resistance decreased in the theophylline group from 308.3% (128.3) predicted to 235.2% (88.0), (*p* = 0.06; 95% CI –2.3; 148.4) with no change in the placebo group.

There was a tendency for *RV* [from 134.9% (46.9) predicted to 115.4% (48.5), *p* = 0.14; 95% CI –7.5; 46.7] and *TGV* [from 122.3% (24.6) predicted to 113.7% (20.4), *p* = 0.16; 95% CI

Table 2. Diary card results [mean (SD) of symptom score and use of beta-2-agonists]

	Placebo	Theophylline
Daytime symptoms		
Weeks –6–0	0.5 (0.5) n = 14	0.5 (0.7) n = 12
Weeks 0–6	0.3 (0.3) n = 17	0.2 (0.3) n = 14
Weeks 6–12	0.3 (0.3) n = 17	0.3 (0.4) n = 15
Night-time symptoms		
Weeks –6–0	0.2 (0.3) n = 14	0.3 (0.4) n = 11
Weeks 0–6	0.3 (0.3) n = 17	0.2 (0.2) n = 14
Weeks 6–12	0.2 (0.3) n = 17	0.2 (0.4) n = 15
Beta-2-agonists/week		
Weeks –6–0	4.9 (5.6) n = 16	5.4 (7.5) n = 13
Weeks 0–6	5.3 (6.9) n = 17	5.0 (7.5) n = 16
Weeks 6–12	3.1 (4.1) n = 17	5.8 (9.7) n = 16

There are no significant differences between the study groups (data from unpaired *t*-tests).

−3.9; 21.0] to decrease in the theophylline group with no change in the placebo group.

The other lung function parameters did not change over the study period.

Bronchial hyperreactivity assessed using a cold-air hyperventilation challenge or bronchodilator responsiveness was not different between the groups and did not change over the study period, either.

Blood samples

The differential blood count showed mild eosinophilia in both groups [7.4% (5.0) and 5.9% (4.2)] with no change over time.

In the theophylline group, sECP decreased from 43.2 µg/l (32.5) to 26.5 µg/l (16.9) ($p = 0.02$; 95% CI 2.1; 26.5). In the placebo group, there was no significant change [23.8 µg/l (15.0) to 31.2 µg/l (16.9), $p = 0.09$ 95% CI −16.1; 1.2].

Lymphocyte subpopulations

Results are expressed as percentage of the total lymphocyte count.

At the start of the study, there were no differences between the two treatment groups. During the 12-week study period, activated T-cells ($CD3^+/CD25^+$) increased in the placebo group with a significant difference between the groups at the end of the study (see Fig. 1). Similarly, helper-T-cells ($CD4^+$) and $CD4^+/CD25^+$ cells increased in the placebo group, resulting in a significant difference between the

groups ($p = 0.03$, 95% CI 0.4; 7.7 and $p = 0.04$, 95% CI 0.1; 4.2, respectively).

Compared with age-matched reference data, activated T-cells ($CD3^+/CD25^+$) were reduced in both treatment groups (8.4% and 7.6%) (16, 17). Similarly, suppressor-T-cells ($CD8^+$) were reduced with a mean (SD) of 24.7% and 25.9% in the theophylline and placebo groups, respectively. $CD8^+/HLA-DR^+$ cells were only 2.9% (SD) and 3.1% (SD) in the theophylline and placebo groups, respectively. All other lymphocyte subsets, as well as monocytes, did not change.

Discussion

The present study shows, that low-dose theophylline in moderate childhood asthma is safe and well tolerated. However, we were unable to demonstrate a significant clinical or immunomodulatory effect in this group of children on regular inhaled corticosteroids.

Clinical effectiveness

Previous studies in adult asthmatics demonstrated an increase in asthma symptoms in patients on moderate to high doses of ICS when low-dose theophylline was withdrawn from therapy. This was accompanied by a deterioration in lung function. This effect was more marked in patients with a serum theophylline level > 5 mg/l (9, 18).

Introducing low-dose theophylline to asthma maintenance therapy improved lung function compared with placebo (7). Interpretation of this study is difficult, however, because initially, lung function in the theophylline group was worse than in the placebo group.

Adding theophylline to low-dose ICS had a similar effect on symptoms and use of rescue medication as doubling the steroid dose (10, 11). Moreover, lung function improved more with theophylline than with a doubled ICS dose (10). In a 6-month study, Lim et al. found an improvement in evening PEF, but not in symptoms or other parameters of lung function in a group of adult asthmatics on low-dose ICS plus low-dose theophylline compared with ICS alone in either a low or moderate dose (19).

The present study failed to show a beneficial effect of adding low-dose theophylline to ICS in children with moderate asthma. Symptoms, use of short-acting beta-2-agonists or lung function did not change significantly. There was only a minor effect on lung function with an increase in PEF in the theophylline group. However, a similar increase in PEF was observed in the

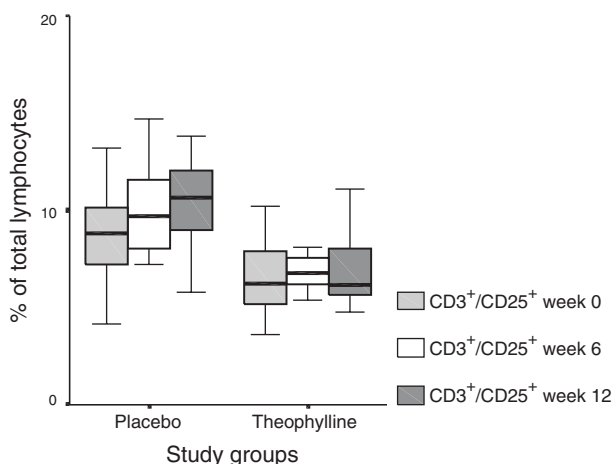


Fig. 1. Changes in $CD3^+/CD25^+$. Increasing activated T-cells ($CD3^+/CD25^+$) during the 12-week treatment period in the placebo group with a significant difference between the groups at the end of the study. The figure represents median and interquartile ranges.

placebo group during the run-in phase, thus making it unlikely that this change can be attributed to theophylline. Bronchial hyperreactivity did not change. This lack of effect in children with asthma compared with adult studies may have several reasons: first, adult and childhood asthma are not directly comparable with different phenotypes in different age groups. Second, the theophylline levels achieved in our treatment group were slightly lower than in the adult studies published. As the effect on lung function may depend on the theophylline level, this may at least partly explain the relatively small effect. In addition, we have to consider that the patients were already on moderate to high doses of inhaled steroids, yet had only mild to moderate changes in lung function at baseline which leaves little room for improvement.

Immunomodulatory effects

Potential immunomodulatory effects of theophylline are still matter of debate. Sullivan et al. found a decrease in eosinophils in peripheral blood and bronchial biopsies following a 6-week treatment with low-dose theophylline (7). Others failed to show such an effect on eosinophils, but found a decrease in sECP (20, 21). This is in accordance with our results. Eosinophils were mildly elevated in both groups at study entry, the mildly elevated sECP decreased in the theophylline group only. However, as the role of sECP for monitoring inflammatory changes in childhood asthma remains controversial, these findings should not be over-interpreted (22–25).

Adult studies have shown inhibition of neutrophilic and eosinophilic activity in asthmatic airways after low-dose theophylline (6–8). Ward et al. found attenuation of the allergen-induced increase in $CD4^+$ - and $CD8^+$ -peripheral blood lymphocytes after a 5-week treatment with low-dose theophylline (26). Another placebo-controlled study found a significant decrease in lymphocytes in bronchoalveolar lavages. This was most marked in $CD3^+$ lymphocytes including $CD4^+$ and $CD8^+$ subtypes with significant differences between the groups. In contrast, peripheral blood samples showed an increase in $CD4^+$ /HLA-DR and $CD4^+$ /VLA-1 T-cells (27). In a theophylline-withdrawal study, Kidney et al. found a significant decrease of monocytes ($CD14^+$), activated helper-T- ($CD4^+$ / $CD25^+$) and suppressor-T-cells ($CD8^+$ /HLA-DR $^+$) in peripheral blood samples. This was mirrored by a significant increase in $CD8^+$ lymphocytes in bronchial biopsies (9).

We were unable to reproduce these findings in peripheral blood lymphocytes in our group of children and adolescents with asthma. Any significant changes over the study period are due to changes in the placebo group. These changes may reflect spontaneous variability suggesting that measuring lymphocyte subsets is not ideal to assess the effect of theophylline in childhood asthma.

Oral theophylline has been shown to result in an increase in $CD8^+$ cells in peripheral blood samples (28–30). However, another paediatric study found a reduction in suppressor T-cells similar to that observed in our group of patients with no difference whether or not the children were treated with theophylline (31). This is in accordance with our results. Activated T-cells ($CD3^+$ / $CD25^+$), suppressor-T-cells ($CD8^+$) and $CD8^+$ /HLA-DR $^+$ cells did not change. We were unable to demonstrate any immunomodulatory and thus, anti-inflammatory effect of low-dose theophylline.

One of the limitations of the present study is that we had to rely on peripheral blood samples only. We did not consider it ethical to ask patients and their parents to undergo bronchoscopy with lavage and biopsy. With only 2% of the total lymphocyte pool in peripheral blood at any given time point and a complete turn-over of the migrating lymphocytes approximately 50 times per day, it remains speculative whether subpopulations measured in peripheral blood samples will truly reflect changes within the bronchial mucosa (32, 33).

In addition, the number of patients completing the study was lower than expected. Therefore, the sample size may have been insufficient to detect a difference between study groups. As stated before, the patients in our study were not homogeneous with regard to the type and dose of ICS used. However, with most of the patients requiring salbutamol inhalation as rescue medication at least 5 days per week our patients met the criteria for classification as moderate persistent (episodic) asthma. Although lung function was only mildly abnormal, there was room for improvement if there was a clinically relevant effect of low-dose theophylline in our study population.

There are other aspects when considering theophylline for maintenance asthma therapy. It is certainly less expensive than doubling the dose of inhaled steroids (34).

Especially in the paediatric age group, correct use of inhalers may be difficult to achieve. Oral therapy is easier and may increase compliance (35). However, adding low-dose theophylline in

patients with moderate asthma who are already on ICS complicates the therapeutic regimen potentially resulting in a reduction in compliance. In the present study, few patients had serum theophylline levels of < 5 mg/l which suggests that there may have been problems with treatment compliance.

While treatment should be as simple as possible, long-term safety requires that the dose of ICS used to control asthma will be kept to a minimum (36–38). Conventional doses of theophylline are known to produce significant side-effects. The narrow therapeutic range requires that serum levels are monitored regularly. In the present study, low-dose theophylline was well tolerated and serum levels were all below 10 mg/l, such that regular drug level monitoring may be omitted.

Nevertheless, with no significant clinical or anti-inflammatory effect observed, we were unable to provide objective evidence that low-dose theophylline in addition to low- to moderate-dose ICS should play a more important role in moderate childhood asthma.

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References

1. BARNES PJ. Efficacy of inhaled corticosteroids in asthma. *J Allergy Clin Immunol* 1998; 102: 531–8.
2. WARNER JO, NAPITZ CK. Third International Pediatric Consensus Statement on the Management of Childhood Asthma. *Pediatric Pulmonol* 1998; 25: 1–17.
3. TSIU S, SELF TH, BURNS R. Theophylline toxicity: update. *Ann Allergy* 1990; 64: 241–57.
4. BAKER MD. Theophylline toxicity in children. *J Pediatr* 1986; 109: 538–42.
5. FURUKAWA CT, DU HAMEL TR, WEIMER L, et al. Cognitive and behavioral findings in children taking theophylline. *J Allergy Clin Immunol* 1988; 81: 83–8.
6. KRAFT M, PAKT J, BORISH L, et al. Theophylline's effect on neutrophil function and the late asthmatic response. *J Allergy Clin Immunol* 1996; 98: 251–7.
7. SULLIVAN P, BEKIR S, JAFFAR Z, et al. Anti-inflammatory effects of low-dose oral theophylline in atopic asthma. *Lancet* 1994; 343: 1006–8.
8. VENGE P, DAHL R, KARLSTROM R, et al. Eosinophil and neutrophil activity in asthma in a one year double-blind trial with theophylline and two doses of inhaled budesonide. *J Allergy Clin Immunol* 1993; 89: 141.
9. KIDNEY J, DOMINGUEZ M, TAYLOR P, et al. Immunomodulation by theophylline in asthma: demonstration by withdrawal of therapy. *Am J Respir Crit Care Med* 1995; 151: 1907–14.
10. EVANS DJ, TAYLOR DA, ZETTERSTROM O, et al. A comparison of low-dose inhaled budesonide plus theophylline and high-dose inhaled budesonide for moderate asthma. *N Engl J Med* 1997; 337: 1412–8.
11. UKENA D, HARNEST U, SAKALAUSKAS R, et al. Comparison of addition of theophylline to inhaled steroid with doubling of the dose of inhaled steroid in asthma. *Eur Respir J* 1997; 10: 2754–60.
12. QUANER P, STOCKS J, POLGAR G, et al. Compilation of reference values for lung function measurements in children. *Eur Respir J* 1989; 2 (Suppl. 4): 184S–261S.
13. ZAPLETAL A, SAMANEK M, TUMA S, et al. Assessment of airway function in children. *Bull Physiopathol Respir* 1972; 8: 535–44.
14. NIGGEMANN B, FRIEDRICHS F, BROSI W, et al. Unspezifische Provokationsverfahren in der pneumologischen Diagnostik. *Monatsschrift Kinderheilkunde* 1999; 147: 601–9.
15. ZACH M, POLGAR G, KUMP H, et al. Cold air challenge of airway hyperreactivity in children: practical application and theoretical aspects. *Pediatric Res* 1984; 18: 469–78.
16. ERKELLER-YUKSEL FM, DENEYS V, YUKSEL B, et al. Age-related changes in human blood lymphocyte subpopulations. *J Pediatr* 1992; 120: 216–20.
17. HULSTAERT F, HANNEST I, DENEYS V, et al. Age-related changes in human blood lymphocyte subpopulations. *Clin Immunol Immunopathol* 1994; 70: 158.
18. MINOGUCHI K, KOHNO Y, ODA N, et al. Effect of theophylline withdrawal on airway inflammation in asthma. *Clin Exp Allergy* 1998; 28 (Suppl. 3): 57S–63S.
19. LIM S, JATAKANON A, GORDON D, et al. Comparison of high dose inhaled steroids, low dose inhaled steroids plus theophylline, and low dose inhaled steroids alone in chronic asthma in general practice. *Thorax* 2000; 55: 837–41.
20. HORIGUCHI T, TACHIKAWA S, KASAHARA J, et al. Suppression of airway inflammation by theophylline in adult bronchial asthma. *Respiration* 1999; 66: 124–7.
21. TOHDA Y, MURAKI M, IWANAGA T, et al. The effect of theophylline on blood and sputum eosinophils and ECP in patients with bronchial asthma. *Int J Immunopharmacol* 1998; 20: 173–81.
22. FERGUSON AC, VAUGHAN R, BROWN H, et al. Evaluation of serum eosinophilic cationic protein as a marker of disease activity in chronic asthma. *J Allergy Clin Immunol* 1995; 95: 23–8.
23. GRUBER W, EBER E, PFLEGER A, et al. Serum eosinophil cationic protein bronchial responsiveness pediatric adolescent asthma patients. *Chest* 1999; 116: 301–5.
24. KOLLER DY, HEROUY Y, GÖTZ M, et al. Clinical value of monitoring eosinophil activity in asthma. *Arch Dis Child* 1995; 73: 413–7.
25. ZIMMERMAN B, ENANDER I, ZIMMERMAN R, et al. Asthma in children less than 5 years of age: eosinophils and serum levels of proteins ECP and EPX in relation to atopy and symptoms. *Clin Exp Allergy* 1994; 24: 149–55.
26. WARD AJ, MCKENNIF M, EVANS JM, et al. Theophylline – an immunomodulatory role in asthma. *Am Rev Respir Dis* 1993; 147: 518–23.
27. JAFFAR Z, SULLIVAN P, PAGE C, et al. Low-dose theophylline modulates T-lymphocyte activation in

- allergen-challenged asthmatics. *Eur Respir J* 1996; 9: 456–62.
28. FINK G, MITTELMANN M, SHOHAT B, et al. Theophylline-induced alterations in cellular immunity in asthmatic patients. *Clin Allergy* 1987; 17: 313–6.
29. ILFELD D, KIVITY S, FEIERMAN E, et al. Effect of in vitro colchicine and oral theophylline on suppressor cell function of asthmatic patients. *Clin Exp Immunol* 1985; 61: 360–7.
30. SHOHAT B, VOLOVITZ B, VARSANO I. Induction of suppressor T cells in asthmatic children by theophylline treatment. *Clin Allergy* 1983; 13: 487–93.
31. HARPER TB, GRAUMER HR, WARING W, et al. A comparison of cell-mediated immunity and suppressor t cell function in asthmatic and normal children. *Clin Allergy* 1980; 10: 555.
32. PABST R, TSCHERNIG T. Lymphozyten in der bronchoalveolären Lavage (BAL). *Pneumologie* 1998; 52: 128–31.
33. WESTERMANN J, PABST R. Lymphocyte subsets in the blood: a diagnostic window on the lymphoid system? *Today* 1990; 11: 406–10.
34. BARNES P, JONSSON B, KLIM J. The cost of asthma. *Eur Respir J* 1996; 9: 636–42.
35. FABBRI LM, PIATTELLA M, CARAMORI G, et al. Oral vs inhaled asthma therapy: Pros, cons and combinations. *Drugs* 1996; 52 (Suppl. 6): 20S–8S.
36. PEDERSEN S. Do inhaled corticosteroids inhibit growth in children? *Am J Crit Care Med* 2001; 164: 521–35.
37. WOLTERS OD, PEDERSEN S. Growth of asthmatic children during treatment with budesonide: a double blind trial. *BMJ* 1991; 303: 163–5.
38. SKONER D. Balancing safety and efficacy in pediatric asthma management. *Pediatrics* 2002; 109: 381–92.