Safety, tolerability and acceptability of two dry powder inhalers in the administration of budesonide in steroid-treated asthmatic patients

H. Tukiainen* ON BEHALF OF THE FINNISH STUDY GROUP, P. Rytilä†, K. M. Hämäläinen‡, M. S. L. Silvasti† and J. Keski-Karhu‡

Abstract The purpose of this randomized, double-blind parallel group study was to compare the safety, tolerability and acceptability of Easyhaler® and Turbuhaler® dry powder inhalers for the delivery of budesonide 800 μg day⁻¹ in adult asthmatic patients who had already been treated with inhaled corticosteroids for at least 6 months prior to the study. Additionally, the efficacy of the products was evaluated. The main objective was to evaluate the systemic safety of budesonide inhaled from Easyhaler® (Giona® Easyhaler®, Orion Pharma, Finland) as determined by serum and urine cortisol measurements. The secondary objective was to compare the tolerability, acceptability and efficacy of the two devices in the administration of budesonide. After a 2-week run-in period (baseline), patients were randomized on a 2:1 basis to receive budesonide from Easyhaler® (n=103) or from Turbuhaler® (Pulmicort® Turbuhaler®, AstraZeneca, Sweden) (n=58), 200 μg dose⁻¹, two inhalations twice daily for 12 weeks. There was no statistically significant change in morning serum cortisol values from baseline to the end of treatment in either group. Urine free cortisol and urine cortisol/creatinine ratio increased from baseline in both groups. There were no significant differences between the groups in terms of morning serum cortisol, urine cortisol, adverse events or efficacy variables, but Easyhaler® was generally considered more acceptable to the patients. In conclusion, at 800 μg day⁻¹, Giona® Easyhaler® is as safe and efficacious as Pulmicort® Turbuhaler® in adult asthmatic patients previously treated with corticosteroids, but more acceptable to patients. © 2002 Elsevier Science Ltd doi:10.1053/rmed.2001.1261, available online at http://www.idealibrary.com on

Keywords budesonide; easyhaler®; turbuhaler®; steroid-treated; adult asthmatics.

INTRODUCTION

Airway inflammation is considered to be the cause of the symptoms and physiological abnormalities of asthma and it should be the primary target of asthma treatment (1). The inflammation is characterised by the presence of inflammatory cells such as eosinophils and neutrophils (2). Corticosteroids have been shown to suppress the airway inflammation and bronchial hyperresponsiveness associated with asthma, and are now recommended as first-line therapy for the treatment of asthmatic patients (1).

Clinically, the most important systemic adverse drug reactions (ADRs) of inhaled corticosteroids are hypothalamic–pituitary–adrenal (HPA) axis suppression (3–5), increased bone turnover (6) and impaired glucose and lipid metabolism (7). However, these effects are associated with high-dose therapy (>1000 μg day⁻¹) (8,9). At doses of up to 400 μg day⁻¹ in children, and up to 800 μg day⁻¹ in adults, inhaled corticosteroids have been shown to have minimal systemic effects, irrespective of preparation (10). The therapeutic goal should be to optimize asthma control with minimal systemic effects or ADRs by adjusting the dose of inhaled corticosteroid according to individual requirements.

It is generally acknowledged that the inhaler is a key element in determining the efficacy, adverse event profile, and safety of asthma therapy (11). Pressurized metered-dose inhalers (pMDIs) are currently the most common forms of delivery device for inhaled therapy in most European countries (12). However, these devices are associated with a number of problems,
notably difficulty in achieving the level of coordination necessary for correct dose delivery, leading to reduced effectiveness and poor compliance. Furthermore, most pMDIs contain ozone-depleting chlorofluorocarbons (CFCs) as propellants. Hence, these are being phased out to meet an imminent ban on the use of CFCs (12). Non-CFC pMDIs are now available. These pMDIs have chlorine-free hydrofluoroalkane (HFA) as a propellant (13).

In order to overcome these problems, breath-actuated powder inhalers were developed, and one of the first was Turbuhaler® (AstraZeneca, Sweden). Easyhaler® is a new generation breath-actuated multidose powder inhaler developed by Orion Pharma in Finland, and is currently available for the delivery of salbutamol and beclometasone dipropionate (BDP).

In the present study, primarily the safety, tolerability and acceptability of Easyhaler® and Turbuhaler® for the delivery of budesonide 800 μg day⁻¹ were compared in adult asthmatic patients who had already been treated with inhaled corticosteroids. Additionally, the efficacy of the products was evaluated. The main objective of the study was to evaluate the systemic safety of budesonide inhaled from Easyhaler®, as determined by serum and urine cortisol measurements. Secondary objectives were to compare the tolerability, acceptability and efficacy of the two devices. In addition, the bronchial inflammation and the effect of budesonide on it was studied in the patients of two study centres using induced sputum method.

METHODS

Patients

Non-smoking male and female asthma outpatients aged 18–70 years were recruited from 14 centres in Finland. All patients were required to have been diagnosed with bronchial asthma (ATS criteria) and to have used inhaled BDP or budesonide on a regular daily basis over at least the previous 6 months. For the 4 weeks prior to the study, they were also required to have inhaled BDP or budesonide at a dose level of 800–1000 μg day⁻¹. In order to be included in the study, patients had to have a forced expiratory volume in 1 sec (FEV₁) > 60% of the predicted value before taking a bronchodilator, measured within 4 weeks before the beginning of the run-in period or on the first visit (14).

Patients were excluded from the study if they had known hypersensitivity to either budesonide or lactose, or any exacerbation of asthma or respiratory infection during the previous 4 weeks. Ex-smokers could be included if they had stopped smoking at least 6 months prior to the study. Patients with a manifest heart condition (NYHA Class II–IV), severe hepatic or renal disease, inadequately controlled hyperthyroidism or diabetes mellitus (type I or II) were excluded from the study, as were women who were pregnant, breast-feeding or fertile and without reliable contraception. Patients were not allowed to have received oral corticosteroids or beta-blockers during the previous 4 weeks, nor could they have any regular treatment with anticholinergics, theophyllines, oral or inhaled cromoglycate, nedocromil, leukotriene antagonists, short- or long-acting antihistamines, or long-acting sympathomimetics during study entry. Patients who had previously participated in this study, or in any other clinical drug study within 8 weeks of this one, were also excluded.

Study design

This multicentre study was carried out according to a randomized, double-blind, double-dummy, parallel-group design. After a 2-week run-in period, patients were randomized on a 2:1 basis to receive either budesonide from Easyhaler® (Giona® Easyhaler®; Orion Pharma, Finland) or budesonide from Turbuhaler® (Pulmicort® Turbuhaler; AstraZeneca, Sweden) for 12 weeks (Fig. 1). Both devices delivered budesonide at a dose of 200 μg inhalation⁻¹ and patients were instructed to perform two inhalations twice daily at 6–8 a.m. and 7–9 p.m., giving a total budesonide dose of 800 μg day⁻¹. Concurrently, with inhalations of budesonide from Easyhaler®, the patient inhaled placebo from Turbuhaler® or vice versa. Patients were instructed to rinse their mouth with water and spit it out after each inhalation.

Patients were permitted to use salbutamol inhalation powder (Buventol Easyhaler® 100 μg dose⁻¹; Orion Pharma, Finland) as rescue medication. If necessary, they could also take a 1-week course of an oral corticosteroid (prednisolone 30–40 mg day⁻¹) or one course of an antibiotic, but could be withdrawn from the study if they exceeded these limits. Home peak expiratory flow (PEF) measurements were carried out using a standard Mini-Wright™ Peak Flow Meter (Clement Clarke International Ltd, England) before inhaling the drug and preferably, at least 6 h after any salbutamol inhalation.

After the run-in period and after the 6th, 10th and 14th study weeks, on the evening before the clinic visits, patients were asked to take the study drug (preferably at 8 p.m.) after they had emptied their bladder. They then started collecting all overnight urine for 10 h. No further corticosteroids were taken until completion of the follow-up visit the next morning. Use of salbutamol inhalation was to be avoided for 8 h before the follow-up visits.

Blood samples for measuring morning serum cortisol concentrations were taken after overnight fasting at the end of the run-in period and at the end of study weeks 6, 10 and 14, preferably at the same time at each visit (7–9 a.m.).

Sputum inductions for measuring eosinophils, neutrophils, macrophages, eosinophil cationic proteins (ECP)
and myeloperoxidase (MPO) were performed in the patients of two study centers after run-in period and at the end of the study.

Compliance was determined by patient diary records of corticosteroid use, and return of both used and unused study drugs to the study centre at the end of the treatment period.

All study documents were reviewed and approved by the Ethics Committees of the participating hospitals. All patients were required to give written informed consent and the study was conducted according to the principles of the current revision of the Declaration of Helsinki (15).

### Outcome variables

The primary safety variable was the systemic bioactivity of budesonide, which was determined by measuring single morning (7–9 a.m.) serum cortisol (normal reference range 190–700 nmol l⁻¹) and urine free cortisol alone and corrected by creatinine excretion [urine cortisol/creatinine (UCC) ratio].

All adverse events, whether considered to be drug-related or not, were recorded in the patients’ diaries, including type and severity (with a daily score of 0–3). Patients were specifically asked to record and score any occurrence of hoarseness and sore throat, sum scores for which were calculated for the run-in period and every 4 weeks during treatment. During all follow-up visits, the presence of oropharyngeal candidiasis was determined by visual examination and, if there was evidence of infection, by oropharyngeal swabs. The number of courses of antmycotic treatment prescribed was also recorded.

Patients evaluated the acceptability of the devices at the last follow-up visit by use of a questionnaire on handling and ease of use, and a visual analogue scale (VAS) score for overall opinion of the devices (ranging from extremely bad to extremely good).

The primary efficacy variables were mean morning and evening home PEF values, determined for the run-in period (weeks 1–2) and for weeks 3–4, 7–8 and 11–14. Secondary efficacy variables included spirometry at the study site [FEV₁ and forced vital capacity (FVC)]; diurnal variability in PEF, expressed as [(highest−lowest)/highest × 100% per day]; number of β₂-agonist inhalations during run-in and for each 4-week treatment period thereafter; and severity sum scores for day- and nighttime asthma symptoms (dyspnoea, wheezing and cough, where 0=no symptoms, 1=mild, 2=moderate and 3=severe), calculated for the run-in period and every 4 weeks thereafter.

In addition, at two of the study centres, the severity of bronchial inflammation was assessed by measuring eosinophils, neutrophils, ECP and MPO concentrations (µg l⁻¹ in each case) in induced sputum after the run-in period.
period and after the treatment period. The details of sputum induction and analysis have been reported earlier (16). Inflammatory cells in smears were examined on a scale from 0 to 4. ECP and MPO were measured from the supernatant. The reference ranges for total ECP and MPO were taken as <2500 µg l\(^{-1}\) and <1200 µg l\(^{-1}\), respectively.

**Statistical analysis**

The main aim of the study was to evaluate the safety of inhaled budesonide 800 µg day\(^{-1}\). The first hypothesis was that there would be no significant change in morning serum cortisol in the Easyhaler\(^{R}\) group from the end of the run-in period (baseline) to the end of the study. The second hypothesis was that there would be no significant difference between treatment groups in morning serum cortisol during the study period, as assessed from individual measurements on follow-up visits. The secondary aim of the study was to collect evidence about the acceptability, tolerability and efficacy of Giona\(^{R}\) Easyhaler\(^{R}\) compared to Pulmicort\(^{R}\) Turbuhaler\(^{R}\). A two-sided \(P\)-value of less than 5% was considered statistically significant.

For analyses concerning safety and tolerability, all available data were utilized. Conclusions concerning the safety and efficacy of the treatments were based primarily on ITT analyses.

Changes in morning serum cortisol, urine free cortisol and UCC ratio from baseline to the last visit were analysed using the Wilcoxon one-sample test. Between-treatment comparisons in these variables were performed using analysis of covariance with baseline measured as a covariate.

All adverse events were classified by severity and by causal relationship to study treatment. The difference in the number of oropharyngeal *Candida* infections was analysed only descriptively.

Improvement in morning and evening PEF was analysed separately for both treatment groups using an analysis of variance (ANOVA) model. Mean values for the 2-week run-in period and subsequent 4-week treatment periods for each treatment were calculated. These values were analysed using repeated measurement analysis of covariance. The main interest lay on the comparison at treatment weeks 9–12, but also the overall treatment difference, including the whole treatment period, was examined. Spirometric measurements were analysed accordingly, but instead of periodwise means actual values were used. Sum scores for asthma symptoms and symptom-prompted inhalations were analysed using the Mann–Whitney U-test.

Data of sputum induction are expressed as means. Some values for inflammatory markers lay beneath lowest standard values. Results of comparisons between the two groups were analysed using Mann–Whitney U-test or the chi-squared test, as appropriate. Two-tailed \(P\)-values below 0.05 were considered to indicate significance.

The estimated sample size was based on the planned treatment randomization ratio (2:1 for Easyhaler\(^{R}\):Turbuhaler\(^{R}\)), predefined clinically significant difference of 50 nmol l\(^{-1}\) and assumed sample standard deviation of 150 nmol l\(^{-1}\) in morning serum cortisol. The significance level in a two-sided test was set at 5% and the sample size was calculated to give a power of 0.9. This yielded a required sample size of 97 in the Easyhaler\(^{R}\) group (17). However, in order to allow for some premature discontinuations during the study period, target populations of 100 and 50 were established for the Easyhaler\(^{R}\) and Turbuhaler\(^{R}\) groups, respectively.

**RESULTS**

**Patients**

A total of 161 patients were enrolled in the study, of whom 103 were randomised to the Giona\(^{R}\) Easyhaler\(^{R}\) group and 58 to the Pulmicort\(^{R}\) Turbuhaler\(^{R}\) group (Table 1). The distribution of female subjects differed between the groups (58% in the Easyhaler\(^{R}\) group and 74% in the Turbuhaler\(^{R}\) group), which accounted for the observed differences in terms of cortisol, PEF and spirometry values. In addition to asthma, a baseline disease was reported by 60% of patients in Easyhaler\(^{R}\) group and 72% in Turbuhaler\(^{R}\) group, the most common one being rhinitis. The most common baseline symptoms were headache, dysphonia and coughing and they occurred equally in both groups.

One hundred and forty-six patients completed the study: 91 in the Easyhaler\(^{R}\) group and 55 in the Turbuhaler\(^{R}\) group. Reasons for premature discontinuation in each group are shown in Table 2.

**Compliance**

According to the daily diaries of all patients who completed the study, the mean (±) percentage of study drug usage was 98 (5)% in the Easyhaler\(^{R}\) group and 98 (3)% in the Turbuhaler\(^{R}\) group.

**Safety**

In the Easyhaler\(^{R}\) group, morning serum cortisol values remained almost unchanged from baseline (end of the run-in period) until the end of the 12-week treatment period [Fig. 2(a)]. In the Turbuhaler\(^{R}\) group, there was a slight decrease in morning serum cortisol values, but the difference was not statistically significant between the groups. Five patients (two in the Easyhaler\(^{R}\) group and three in the Turbuhaler\(^{R}\) group) had one morning serum cortisol reading <190 nmol l\(^{-1}\), which was considered to
be the lower limit of the normal reference value. In all except one patient (in the Turbuhaler® group) serum cortisol levels \(<190\ \text{nmol}\ \text{l}^{-1}\) were associated with a course of an oral corticosteroid during the study.

Urine free cortisol values increased from baseline to the end of the treatment period in both treatment groups, but only in the Easyhaler® group was the difference statistically significant (\(F^2=0.015\)). At the end of run-in period urine free cortisol value was 73.6 (74) nmol l\(^{-1}\) in the Easyhaler® group and 60.1 (53) nmol l\(^{-1}\) in the Turbuhaler® group. After 12 weeks of treatment urine free cortisol value was 91.3 (92) nmol l\(^{-1}\) and 67.5 (75) nmol l\(^{-1}\) in the Easyhaler® group and in the Turbuhaler® group, respectively. A similar trend was observed for UCC ratios [Fig. 2(b)].

During the first month of treatment there were more adverse events in both treatment groups than during the third month. Fifty-two adverse events (52%) were considered to be possibly, probably, or definitely related to study drug in the Easyhaler® group, and 31 (53%) were considered to be possibly, or probably drug-related in the Turbuhaler® group, and most were mild or moderate in nature (Table 3). In both treatment groups, mean scores (% of theoretical maximum) for hoarseness remained unchanged during the study and those for sore throat increased slightly. Only one patient (in the Easyhaler® group) discontinued the study due to an adverse event (coughing and worsening of asthma). Three serious adverse events (SAEs) occurred during the study: one hospitalization for haemorrhoid surgery in the Easyhaler® group; one hysterectomy for uterine myoma in the Turbuhaler® group; and one pregnancy ending in spontaneous abortion in the Turbuhaler® group. These were all considered to be unrelated to study drug by the investigators and by the sponsor, except for the spontaneous abortion, which was considered unlikely to be drug-related.

During treatment, the occurrence of oropharyngeal candidiasis (8/103 in the Easyhaler® group and 4/58 in the Turbuhaler® group), and the number of courses of antimycotics prescribed (7/103 and 4/58 in each group, respectively) were similar in both groups.

### Acceptability

In four out of 10 questions, a majority of the patients (>50%) rated Easyhaler® superior to Turbuhaler®, although more patients found Turbuhaler® ‘handier to carry’ (Fig. 3). In particular, with Easyhaler®, most patients found it easier to know when the drug had been received and how much drug was left. When asked
which device they would choose, 59% of patients said they would choose Easyhaler®, 29% Turbuhaler® and 12% expressed no preference. The mean (SD) VAS score for overall acceptability of the devices was significantly higher for Easyhaler® compared with Turbuhaler®: 74.9 (17) mm versus 64.3 (21) mm, respectively (P < 0.0001).

### Efficacy

There were no statistically significant differences in mean morning PEF values between the treatment groups, with no significant changes from baseline to the end of treatment (Table 4). The overall adjusted treatment difference was 1.5 l min⁻¹ (95% CI from −5.6 to 8.5). The results of mean evening PEF values were in accordance with the morning PEF results (Table 4).

Both FEV₁ and FVC values remained almost unchanged during the study in both treatment groups, with no significant differences between the groups (Table 4).

The use of additional inhaled salbutamol during the run-in and treatment periods was low and similar in both groups.

The incidence of daytime asthma symptoms (dyspnoea, wheezing and cough) was similar in each group and remained more or less unchanged throughout the study. Night-time asthma symptoms also remained similar in the Easyhaler® group but increased slightly from run-in to treatment weeks 9–12 for all three symptoms.

### Table 3. Number (%) of adverse events (considered to be at least possibly related to study drug) occurring during treatment

<table>
<thead>
<tr>
<th></th>
<th>Easyhaler® (n=103)</th>
<th>Turbuhaler® (n=58)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Dysphonia</td>
<td>20 (20)</td>
<td>12 (21)</td>
</tr>
<tr>
<td>Pharyngitis</td>
<td>14 (14)</td>
<td>10 (17)</td>
</tr>
<tr>
<td>Candidiasis</td>
<td>8 (8)</td>
<td>4 (7)</td>
</tr>
<tr>
<td>Taste perversion</td>
<td>4 (4)</td>
<td>—</td>
</tr>
<tr>
<td>Coughing</td>
<td>2 (2)</td>
<td>—</td>
</tr>
<tr>
<td>Glossitis</td>
<td>1 (1)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Stomatitis</td>
<td>1 (1)</td>
<td>—</td>
</tr>
<tr>
<td>Laryngitis</td>
<td>1 (1)</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Asthma</td>
<td>1 (1)</td>
<td>—</td>
</tr>
<tr>
<td>Dry mouth</td>
<td>—</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Tooth disorder</td>
<td>—</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Adrenal insufficiency</td>
<td>—</td>
<td>1 (2)</td>
</tr>
<tr>
<td>Total</td>
<td>52 (52)</td>
<td>31 (53)</td>
</tr>
</tbody>
</table>
However, there were no statistically significant differences between the treatment groups.

A total of 21 patients underwent sputum induction for analysis of inflammatory markers. Most patients (13/21) had low amount of sputum eosinophils (scale 0–1, less than 5%) at baseline. Sputum eosinophils in both groups decreased significantly during the budesonide treatment ($P=0.02$) (Fig. 4). There were no significant changes in ECP and MPO values during the study and no difference between treatments studied.

**DISCUSSION**

It has previously been reported that most of the benefits of inhaled corticosteroids are achieved within 3 months of starting therapy (18). The duration of treatment period in this study was selected not only because of the pharmacodynamics of budesonide, but also to obtain a reliable picture of the safety, tolerability and acceptability of the treatments studied. Pulmicort® Turbuhaler® was selected as the active control since its use and properties have been widely documented.

The uneven allocation of treatment (2:1 for Easyhaler®:Turbuhaler®) was considered justified since the main
aim of the study was to analyse systemic bioactivity of budesonide over the study period in the Easyhaler® group. The treatment groups were generally well matched in terms of demographic data and asthma history except for a predominance of females in the Turbuhaler® group. This had an inevitable effect on cortisol, and lung function values, both at baseline and during treatment, resulting in lower values in the Turbuhaler® group than in the Easyhaler® group. It has been shown that there is a correlation between lean body mass and urinary creatinine excretion (19) and that total plasma creatinine is an accurate measure of total striated muscle mass (20). Also oestrogens can have influence on corticosteroid binding globulin and cortisol concentration (21). Thus, difference in female/male distribution can have influence both on creatinine and cortisol concentration and also cortisol/creatinine ratio, which may explain the difference at baseline found in the present study.

Most multicentre studies have used single morning serum cortisol measurements as a practical means of assessing potential HPA axis suppression (22,23). However, this method is relatively insensitive, since there is marked diurnal variation in serum or plasma cortisol levels. Therefore, in this study overnight (10 h) urinary unbound cortisol was also determined, since it has been shown to be a more sensitive measure of HPA axis function (24,25). Overnight collection of urine for determination of urine free cortisol is also simple to carry out and has been reported to be as sensitive as 24-h collection, particularly when corrected for creatinine (24).

The results showed that mean morning serum cortisol values remained relatively unchanged in the Easyhaler® group and, although there was some decrease in the Turbuhaler® group, mean values were above 400 nmol l⁻¹ in both groups after the run-in period and after 12 weeks of treatment. In addition, urine free cortisol values and UCC ratio values increased in both groups during treatment and the changes from baseline were statistically significant in the Easyhaler® group. Other safety parameters did not differ significantly between the treatment groups. Most of the adverse events considered to have any possible relationship to study drug were mild or moderate in nature and there were no SAEs considered to be related to study drug.

There were no significant differences between the treatment groups in any of the efficacy variables, which remained largely unchanged during the study. This was expected because all patients had used inhaled corticosteroids (800–1000 μg day⁻¹ of BDP or budesonide) for at least 6 months prior to the study.

The analysis of induced sputum has become an accepted method for assessing the degree of inflammation and has been reported to be useful in the evaluation of asthma severity and the effect of inhaled corticosteroid treatment (26–28). Recent studies have demonstrated a correlation between the markers of inflammation used, ECP and MPO, and the clinical data (26–30). This method also has the advantage of being a non-invasive technique. Markers of inflammation in induced sputum varied between patients in both treatment groups. In most patients with asthma previously treated with inhaled steroids, sputum eosinophils are low (30). However, under controlled budesonide treatment eosinophils decreased significantly. Both inhalers studied had equal anti-inflammatory effects also on the basis of sputum results.

Response to the acceptability questionnaire showed that the majority of patients rated Easyhaler® superior to Turbuhaler®. The proportion of patients who preferred Easyhaler® (59%) is consistent with a meta-analysis from previous studies in which patients were asked which device they would choose; Easyhaler®, or Turbuhaler® (31). In addition, Easyhaler® scored significantly better than Turbuhaler® on VAS score for overall opinion of the device.

**CONCLUSIONS**

Budesonide 800 μg day⁻¹ inhaled from Easyhaler® or Turbuhaler® did not suppress the activity of the HPA axis, as determined by morning serum cortisol, urine free cortisol and UCC ratio values. Both Easyhaler® and Turbuhaler® were generally well tolerated for the delivery of budesonide and there were no significant differences between the treatment groups in terms of adverse events. There were also no significant between-treatment differences for any of the efficacy variables. However, the majority of patients considered Easyhaler® more acceptable than Turbuhaler®. In conclusion, Giona® Easyhaler® is as safe and efficacious as Pulmicort® Turbuhaler® for the treatment of asthmatic patients who have already been treated with corticosteroids, with better patient acceptability.

**Acknowledgements**

The study was sponsored by Orion Pharma, Kuopio, Finland. We are grateful to the following physicians who participated in the study: Dr Ari Lindqvist MD/Dr Laura Tapanainen MD, Dr Ulla Hodgson MD, Dr Annamari Rouhos MD, Dr Kari Alanko MD, Dr Jouhi Hedman MD, Dr Martti Torkko MD/Dr Päivi Torkko MD, Dr Pekka Saarelainen MD, Dr Lars-Henrik Plathin MD, Dr Matti Pietiläinen MD, Dr Timo Ylen MD, Dr Katriina Kilpiö MD, Dr Kari Liippo MD, Dr Eija-Riitta Salomaa MD, Dr Sirkka Koskinen MD/Dr Tari Hahtela MD/Dr Liisa Raatikainen MD, Dr Erkki Aalto MD, Dr Jukka Laitinen MD, Dr Eija Kallonen MD, Dr Matti Paananen MD and Dr Päivi Roiha.
REFERENCES