

TREATMENT

Montelukast as an Add-On Therapy to Inhaled Corticosteroids in the Treatment of Severe Asthma in Elderly Patients

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Background. Severe asthma remains a worldwide medical problem. However, this disease has not been adequately explored in the elderly. This study was performed to determine how the addition of montelukast to antiasthmatic therapy improves the control of severe asthma in elderly patients. **Methods.** Elderly patients (>60 years old) with diagnoses of severe asthma were observed over 24 months of therapy: the first 12 months using inhaled corticosteroids (ICS) and long-acting beta-agonists (LABA) and the second 12 months with oral montelukast added in two-thirds of the patients, with the remaining third representing the control group. The primary efficacy endpoint of the study was the percentage of days without asthma symptoms in the first 12 months of treatment compared with the percentage after adding montelukast therapy. **Results.** A total of 512 elderly, asthmatic patients were included in the study: seventy-one (13.9%) patients had well-controlled asthma, 211 (41.2%) had partly controlled asthma, and 230 (44.9%) had uncontrolled asthma. During the first year of treatment using ICS and LABA, an increase in the median percentage of days without asthma was observed from 50.1% to 62.1%, as well as a decrease in the percentage of days with short beta-receptor agonist use, from 52.2% to 46.8%. These differences were significantly greater after 12 months, when montelukast was added to the therapy (78.4% and 39.5%, respectively). This improvement was not observed in the control group. After 2 years of observation, the median number of asthma exacerbation incidents per patient decreased from 1.6 per year to 1.2 per year when montelukast was added. **Conclusion.** Severe asthma in elderly patients is very poorly treated, with this population exhibiting very low compliance with antiasthmatic therapy. Adding montelukast provides benefits and improved control; however, it does not resolve severe asthma control problems.

Keywords asthma, elderly patients, glucocorticosteroids, montelukast

BACKGROUND

Asthma is a common disorder in elderly patients. The prevalence of asthma in the elderly ranges from 6% to 17% (1), with the aging population and high prevalence of allergies making this a critical public health issue. Severe asthma accounts for 5–10% of all asthma cases, and these patients are particularly difficult to treat regardless of age group. Unfortunately, elderly asthmatic patients are often underdiagnosed and consequently mistaken as having chronic obstructive pulmonary disorder. Thus, the undertreatment of asthma is common in older people. Uncontrolled disease, poor quality of life, and a high mortality rate due to asthma in the elderly population may be related to insufficient antiasthmatic therapy (1–3).

The Global Initiative for Asthma (GINA) and other world guidelines focus on therapy for asthma in children and adults but not in patients aged >60 years (4). The needs of older people with asthma are similar in some ways to those of young asthmatics, but there are some differences as well. Worse adherence to therapy, an increased risk of antiasthmatic drug adverse events,

and fear of the use of corticosteroids have been observed with particular frequency in asthmatic patients aged >60 years with severe asthma (1). Uncontrolled chronic diseases can influence other concomitant diseases, including inducing decreases in cognitive function (1, 5).

Inhaled corticosteroids (ICS) still play a predominant role in asthma therapy. However, especially poor compliance with this type of therapy has been observed in elderly patients. This lack of compliance makes it necessary to add new drugs to the treatment regimen for these patients, including new inhalers. Of course, this addition results in further deterioration due to the use of additional drugs. This deterioration causes a lack of control over the patient's asthma and a poor quality of life. In elderly patients, a simpler but more effective therapy could improve the outcomes of asthma therapy. ICS are recommended in many clinical practice guidelines as first-line anti-inflammatory control agents for asthma (4). The second choice is leukotriene-modifying drugs, which act by blocking the effects of the cysteinyl leukotrienes and reducing markers of chronic inflammation in children and adults. However, their role in the treatment of severe asthma remains unclear. Several large clinical trials have compared the efficacy of leukotriene receptor agonists with ICS or other antiasthma treatments. Many reports have concluded that one of these drugs, montelukast, is highly effective in controlling asthma symptoms (6–9).

The study was performed in the Clinical Department of Internal Disease, Dermatology and Allergology, Zabrze, Poland and NZOZ ALERGOMED, Katowice, Poland.

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However, there have been no similar observations in homogenous groups of patients over 60 years of age, especially those patients with severe asthma.

The purpose of this study was to compare the efficacy of montelukast as an add-on therapy to ICS in patients with severe asthma to improve symptom control.

MATERIALS AND METHODS

Patients and Treatments

The recruitment of participants was based on a positive medical history and was confirmed by a positive reversibility bronchial test (increase of FEV1 $\geq 12\%$ and/or 200 ml after 30 min post-salbutamol $4 \times 100 \mu\text{g}$ inhalation, MES Lung Test 1000). Severe asthma was diagnosed based on the GINA criteria. Patients used a high or medium dose of ICS, and most (98%) also used long-acting beta-agonists (LABA), including theophylline (76%) and ipratropium (19%). All of the patients used short-acting beta-agonists (SABA). All participants had at least one episode of asthma exacerbation during the previous year (oral steroid intervention and/or an emergency caused by asthma). Finally, 512 participants with severe bronchial asthma aged 60 years or older (mean age 63.2 ± 5.01 years, range: 60–84) were included in the study, 320 of whom were women and 192 were men. Based on clinical criteria for controlled asthma according to GINA (4), the patients were classified into three subgroups based on whether they had well-controlled, partly controlled, or uncontrolled asthma (7). Patients' daytime symptoms of asthma, limitations in their activities, nocturnal symptoms/awakening, need for relief/rescue treatment, lung function (FEV1), and asthma exacerbation were evaluated. These clinical criteria were also analyzed for every year of treatment. A total of 355 patients (69%) had allergic asthma, and 428 subjects (84%) suffered from chronic rhinitis. Patients with allergic asthma were never treated by immunotherapy or omalizumab. Written informed consent was obtained from all patients, and the study was approved by the Ethical Committee of University School of Medicine in Katowice, Poland (no. 0602/08).

The study consisted of two periods of antiasthmatic treatment (2×12 months). During the first 12 months of the study, all patients received therapy appropriate for severe asthma. Daily doses of budesonide in turbuhaler powder ranging from 1400 to 2800 μg were administered, as well as salmeterol $2 \times 50 \mu\text{g}$, and 100 μg salbutamol was used as needed. Ipratropium and its derivatives were prohibited as well as theophylline. During this period, leukotriene modifiers and other antiasthmatic drugs were not allowed. After a year of therapy in the second period of the study, montelukast was added to the therapy in a randomly selected group consisting of two-thirds of the patients (active group) and continued for 12 months. The other patients remained on the existing ICS treatment, forming a control group. Finally, 341 patients (210 women and 131 men) received montelukast, and 171 patients (110 women and 61 men) continued with an unchanged

therapeutic regimen. Both groups were observed over the next 12 months. The gender distribution, age, and degree of asthma control were homogenous between the two groups. Oral steroids and antibiotics were only used as therapies during asthma exacerbations, and this use was noted. Every 2 months, all patients had clinical visits, during which the following procedures were performed:

- physical examination;
- spirometry;
- assessment of diaries, which were kept during the entire study;
- asthma control test (ACT);
- assessment of the use of drugs by assessing the used packaging and completion of a visual analog scale (VAS); and
- analysis of the documentation of asthma exacerbations (unscheduled visits).

Outside of the protocol, unscheduled visits were provided for any asthma problems, including exacerbations. The patients were always examined by a doctor during asthma exacerbations, and spirometry was performed.

On the VAS, the patients were asked to place an "x" at a point along a 100 mm line, showing their best guess regarding how much of their ICS and/or montelukast pills they had taken over each 3-month period during which they were using the drugs (range: 0–100%).

The patients' diaries included questions about drug use and asthma symptoms (daytime symptoms, nocturnal awakenings, need for relief, activity limitations, and exacerbation symptoms). The diary was filled out every morning and evening.

The ACT was developed as a screening tool for simple assessment in clinical practice. The ACT is a validated, patient-completed measure of asthma control. The ACT contains five questions concerning activity limitation, shortness of breath, nighttime symptoms, use of rescue medications, and an asthma control rating over the previous 4 weeks. The questions are scored from 1 to 5 (from the worst to the best). The maximum score is 25, and results over 20 points define well-controlled asthma over the previous 4 weeks.

Outcome Measurements

The primary efficacy endpoint of the study was the percentage of days without asthma symptoms in the patients during the first 12 months of treatment with the added montelukast therapy in two-thirds of the patients compared with the control group (without montelukast). The secondary endpoints were an estimation of compliance with asthma therapy, the average percentage of days with beta-receptor agonist use, the change from baseline in the prebronchodilator percentage of predicted FEV1, and exacerbations of asthma per year (defined as any period with worsening asthma that required an unscheduled visit to the doctor, emergency department, or hospital for treatment of asthma or treatment with systemic corticosteroids) in the montelukast group compared with the control group.

A statistical analysis was performed with the Statistica computer program, version 8.1 (SaftPol, Cracow, Poland). Significance testing was performed using chi-square tests for categorical variables and Student's *t*-test for continuous variables. A 95% confidence interval (95% CI) was calculated based on the least-squares means from analysis of variance tests, including the results of treatment effects (days without asthma symptoms, days with beta-agonist use) and compliance. $P < .05$ was considered significant.

RESULTS

At the beginning of the study, 71 patients (13.9%) had well-controlled asthma, 211 (41.2%) had partly controlled asthma, and 230 (44.9%) had uncontrolled asthma. During the first period of the study, the median percentage of days without asthma was 62.1% (95% CI: 52.3–69.9). The percentage of days with SABA use was 46.8% (95% CI: 37.5–52.1). Poor compliance was observed in most of the patients. According to the VAS, the mean compliance was 73.1% (95% CI: 46.1–88.4). The evaluation of the number of used drug packages revealed lower compliance, with a mean value of 65.7% (95% CI: 53.4–74.2). The percentage of patients with regular ICS use was 73.1% in the first year of the study. Sixteen patients (3%) had adverse reactions to or discontinued budesonide in powder form for other reasons, and their treatment was changed to budesonide metered dose inhaler (MDI) at the same dose. During the first year of the study, one or more asthma exacerbations were observed in 41.1% patients. The mean FEV1 values during exacerbations decreased by an average of approximately 39% compared with the best spirometry results obtained by the patients before the study. The median number of asthma exacerbations per patient was 1.7 (95% CI: 0.8–3.2) in the first year of the study. The average percentage of predicted FEV1 increased from 64.3% (95% CI: 55.2–79.3) at baseline to 72.5% (95% CI: 61.2–79.4) at 12 months ($p < .05$).

In the second year of the study, for the group that received montelukast in addition to the therapeutic regimen of ICS, the median percentage of days without asthma increased to 78.4% (95% CI: 71.4–86.7) compared with the baseline. This finding represents a statistically significant difference compared with the first year of treatment ($p < .05$), as shown in Table 1. In the control group, the

median percentage of days without asthma was 66.2 (95% CI: 60.2–77.5), which was not statistically significant compared with the first year of the study. The patients exhibited good compliance with montelukast: the mean percentage of compliance according to the VAS as 82.1% (95% CI: 73.2–91.2), and according to estimation of drug packages, it was 80.1% (95% CI: 73.9–84.1). In the second year of the study, an improvement in compliance with ICS therapy was observed from 69.4% (95% CI: 52.6–73.5) to 73.1% (95% CI: 66.7–87.9) (estimation from drug packages) and from 77.5% (95% CI: 44.1–89.2) to 84.9% (95% CI: 77.1–95.8) (VAS) in the active group compared with 75.1% (95% CI: 47.3–90.2) and 82.3% (95% CI: 75.2–87.3), respectively, in the control group. During the second year of the study, one or more asthma exacerbations were observed in 30.2% of patients treated with montelukast and the median number of asthma exacerbations per patient was 1.2 (95% CI: 0.9–3.1) compared with 38.4% and 1.4 (95% CI: 0.8–2.4), respectively, in the control group. This result was significantly less than in the first year of the study ($p < .05$) but only for the group treated with montelukast. The mean percentage of days with SABA use was 39.5% (95% CI: 31.1–54.3) in the active group, which was significantly less than that in the first year ($p < .05$). No significant differences were observed between the 2 years in the control group. The average percentage of predicted FEV1 increased from 72.5% (95% CI: 61.2–79.4) at the end of first year to 72.1% (95% CI: 58.6–87.6) in the active group and 71.5% (95% CI: 60.4–77.5) in the control group at 24 months; however, these changes were not statistically significant. At the end of the study, a significant improvement of asthma control was observed in all patients (Table 2).

DISCUSSION

Asthma in the elderly is often underdiagnosed and undertreated, regardless of its degree (1–3). The measurements before starting the study indicated that asthma in older patients was poorly controlled. The problem of the control of severe asthma, often described as being difficult to control, is still a challenge in all age groups (4, 10, 11). However, in patients older than 60 years of age, there are additional difficulties in controlling the disease such as aversion to therapy and poor compliance (1, 2). These

TABLE 1.—Changes in the parameters investigated during the 24-month observation.

	Baseline: 3 months of observation (95% CI)	ICS after 12 months (95% CI)	Montelukast + ICS after 24 months (95% CI) active group	ICS after 24 months (95% CI) control group
Days without asthma symptoms (%)	50.1 (46.1–61.2)	62.1 (52.1–69.9)	78.4*** (71.4–86.7)	66.2 (60.2–77.5)
Days with beta-agonist use (%)	52.2 (42.3–69.4)	46.8 (37.5–52.1)	39.5*** (31.1–54.3)	44.1 (32.6–53.6)
FEV1% of predicted	64.3 (55.2–79.3)	72.5 (61.2–79.4)	72.1 (58.6–87.6)	71.5 (60.4–77.5)
FEV1, L	—	+0.36 (0.17–0.54)	+0.41 (0.22–0.56)	+0.40 (0.28–0.54)
ACT mean score	12.24 (8.25–17.8)	16.45 (9.91–22.8)	18.98*** (10.22–24.1)	15.98 (8.98–21.11)

Note: * $p < .05$ for active group versus control group after 24 months of therapy; ** $p < .05$ for active group after 24 months versus baseline and versus ICS after 12 months.

TABLE 2.—Distribution of degrees of asthma control among the patients in this study.

Period of study	Well-controlled asthma	Partly controlled asthma	Uncontrolled asthma
On enrollment, <i>n</i> = 512	71 (13.9%)	211 (41.2%)	230 (44.9%)
After 12 months, <i>n</i> = 508	189 (37.2%)	177 (34.8%)	142 (28%)
After 24 months, active <i>n</i> = 287	128 (44.6%)	114 (39.7%)	45 (15.7%)
After 24 months, control <i>n</i> = 168	72 (42.9%)	59 (35.1%)	37 (22%)
<i>p</i>	<.05	<.05	<.05

Notes: *n* = number of patients; *p* represents the comparison between the active group after 24 months versus on enrollment and between the control group after 24 months versus on enrollment, with no significant changes observed between the active and control groups after 24 months.

facts corresponded with the low compliance in this study, according to the VAS at the baseline. Low compliance is observed for older patients, not only for asthma therapy but also in other chronic diseases. The improvement of compliance during the first 12 months of therapy with ICS may indicate that controlling adherence to therapy is very important and beneficial to older patients. Other studies have noted similar findings (1, 12). In particular, assessment of the amount of used drug packaging is valuable, as confirmed in a previous study (12). In this study, further increases in compliance after 24 months resulted from good adherence to montelukast therapy. One pill by mouth seems to be easier for patients than using other asthmatic therapies, including aerosolotherapy. However, during the second 12 months of this study, an improvement in the adherence to ICS was also observed in the control group. We observed that approximately one-third of the patients in this study remembered to use ICS with montelukast in the evening, but morning doses of ICS were frequently skipped. This finding could indicate that using ICS once daily with other drugs would be more effective. Thorough, frequent education of elderly asthmatic patients and their guardians is key to success. Many patients in this study with severe, uncontrolled asthma transferred to the group with controlled or partially controlled disease. Additionally, 21% of the patients were able to change their disease status from severe to moderate.

At the baseline of the study, all analyzed variables were at unsatisfactory levels indicative of uncontrolled asthma, such as the low mean value of FEV₁, the predominant asthmatic symptoms, the number of days using SABA, and especially the fact that only 50.1% of the patient days in the pre-intervention period were without asthma symptoms. We observed that LABA and SABA were subject to frequent overdoses. This practice is particularly dangerous in the elderly. We observed a significant increase in the number of days without asthma symptoms and a reduction in days where SABA was needed after the first 12 months of the study and a further improvement when montelukast was added compared with continuation therapy without montelukast. However, the reduction in SABA use may also be caused by increased compliance with the ICS treatment rather than because of montelukast itself. The improvement in asthma symptoms was similar to that in young asthmatic patients in other studies but not as evident (6, 7, 9). The efficacy of montelukast in severe asthma has been discussed in a few studies, but there is no clear

evidence for its efficacy in this patient group thus far (13–15). Both montelukast and budesonide were generally well tolerated. In contrast, some trials that compared therapy with ICS alone and ICS with montelukast as an add-on therapy (8, 9) concluded that combination therapy was more effective in reducing the number of days with asthma symptoms, days using beta-agonists, asthma exacerbations per year, and improvement of effort limitation, but this effect was greater in mild and moderate asthma than in severe asthma. Additionally, these studies were often conducted in younger age groups. In our study, we observed significant benefits using ICS and montelukast, apart from differences in effort limitation (there were no significant decreases). This finding probably resulted from the influence of overall efficiency. However, the significant increase in the number of days without asthma symptoms, the reduction in the number of days of beta-agonist use, and the decrease in asthma exacerbation events confirmed the efficacy of montelukast in elderly patients compared with the control group of patients who continued therapy without montelukast. Additionally, the improvement of the overall compliance with antiasthmatic treatment probably influenced these results. It was the first such observation in this type of study in homogenous patients aged >60 years.

Naturally, ICS are the most effective asthma control medications due to their wide spectrum of anti-inflammatory actions in severe asthma (4). However, incorrect techniques of ICS inhalation are common in elderly patients due to manual problems, weak vision, impaired cognitive function, and a lack of familiarity with MDI use, potentially resulting in a lack of efficacy of antiasthmatic therapy (1, 3), as was observed in this study. This lack of proper ICS technique probably influenced the results observed for the group treated with montelukast.

There were positive safety and efficacy results, although we did not analyze patients with a wide range of ages.

In conclusion, the effectiveness of montelukast as an add-on therapy to ICS for elderly patients was less than the benefits observed for young asthmatic patients; however, its use is promising in older subjects with severe asthma. It seems that the overall improvement in adherence to antiasthmatic therapy is crucial in elderly patients, as determined by the reduction of asthma exacerbation events and the increase in the number of days without asthma symptoms.

DECLARATION OF INTEREST

All authors confirm that there were no conflicts of interest in this study and that they received no personal or financial support.

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