INTERNATIONAL JOURNAL OF IMMUNOPATHOLOGY AND PHARMACOLOGY Vol. 15, no. 2, 149-155 (2002)

EFFECTIVENESS OF MONTELUKAST VERSUS BUDESONIDE ON QUALITY OF LIFE AND BRONCHIAL REACTIVITY IN SUBJECTS WITH MILD-PERSISTENT ASTHMA

G. RICCIONI[1], E. BALLONE[2], N. D'ORAZIO[3], S. SENSI[1], M. DI NICOLA[2], R. DI MASCIO[2], F. SANTILLI[1], MT GUAGNANO[1] and R. DELLA VECCHIA[1].

[1]Respiratory Pathophysiology Center - Department of Internal Medicine and Aging University of Chieti – [2] Biostatistics Laboratory [3]Section of Human Nutrition, University of Chieti, Chieti, Italy

Received February 10, 2002 - Accepted April 17, 2002

Insufficient data exist to evaluate the comparative effects of inhaled corticosteroids (ICS) versus leukotriene receptor antagonist (LTRA) on airway inflammation and quality of life (QoL). The aim of the study was to compare the effectiveness of montelukast compared to budesonide at different doses on QoL and bronchial reactivity in mild-asthmatic adult patients.

45 subjects with bronchial asthma were randomly assigned to a different treatment and divided in 3 treatment groups: A: 400 μg of budesonide twice a day; B: 10 mg of montelukast daily; C: 10 mg of montelukast daily plus 400 μg of budesonide twice a day. At the beginning of the study and at the end of the treatment period (16 weeks) all patients underwent complete clinical evaluation, pulmonary function testing and methacholine challenge test (MCHt).

In group A the increase from baseline was 153.4%, in group C was 133.2%, and in group B 247.7%, the latter increase being statistically significant compared to that in the other 2 groups ($p< 0.005$ Wilcoxon test). In all domains the improvement in quality of life in the group treated with montelukast (group B) was significantly greater than that in the group treated with both medications (group C): in particular, the improvement was consistent in the symptoms ($p< 0.01$) and emotions ($p< 0.01$) domains, and weaker in the physical activity ($p< 0.05$). A similar difference was observed between group B and A, but only in the symptoms ($p<0.01$), emotions ($p<0.01$), and environmental stimuli domains ($p<0.05$).

The personal perception of their own disease is important for a correct therapeutic management of asthma. In order to optimize the treatment, a complete adherence of the patient to the treatment itself is required, to be achieved through simplification of therapeutic schedule and easy administration of medications. Montelukast may be considered a valid alternative in the treatment of mild-persistent asthma, both for the clinical and functional benefits and for the great advantage of the once-daily dosage, which consistently improves the compliance with the chronic treatment of the disease.

Asthma is a chronic inflammatory disease characterized by reversible airway obstruction and increase bronchial hyperresponsiveness (BHR) (1).

Current guidelines recommended inhaled corticosteroids (ICS) as first-line control therapy in asthma, and emphasize the combination of symptom-controlling drugs such as long acting β2-agonists (LABA) with higher doses of ICS in patients with more severe asthma (2).

In clinical trials, treatment with ICS has consistently shown improvement in pulmonary function parameters, such as peak expiratory flow (PEF), and forced expiratory volume in 1 second (FEV1). ICS are also known to improve symptoms, decrease short acting β2-agonist (SABA) use and are the only drugs known to modestly impact airway hyperreactivity (3-4).

Leukotriene receptor antagonists (LTRA) have also been shown to improve FEV1, asthma symp-

Key words: Asthma therapy, bronchial hyperresponsiveness, budesonide, montelukast, quality of life.

Mailing address: Graziano Riccioni
Clinica Medica – Dept. of Internal Medicine and Aging
Ospedale Clinicizzato Colle dell'Ara
66013 Chieti - Italy
Phone ++39+3336366661
e-mail: griccioni@hotmail.com

0394-6320 (2002)

toms and reduce β2 agonists use in clinical trials, including studies in children (5-6).

Quality of life (QOL) measurements specifically focus on patient's physical and emotional well being. These specific questionnaires emphasize areas that are relevant to patient's relationship with a particular disease, such as their feelings about the disease, its impact on daily activities and its treatment.

QOL measurements are more responsive to clinically significant changes that are not evaluated by conventional clinical measures. The asthma quality of life questionnaire (AQLQ), which was developed by Juniper et al. (7) and previously validated (8), was used in this trial.

Insufficient data exist to evaluate the comparative effects of ICS versus LTRA on airway inflammation and QoL. The aim of the study was to compare the effectiveness of montelukast compared to budesonide at different doses on QoL and bronchial reactivity in mild-asthmatic adult patients.

MATERIALS AND METHODS

Subjects

From January to October 2000 at our Respiratory Pathophysiology Center we enrolled 45 atopic non smoking subjects (22 males, 23 females) with at least 1 year of mild-persistent bronchial asthma.

The entry criteria for this study were (1) a diagnosis of asthma established by the American Thoracic Society criteria (9), (2) confirmation of the presence of BHR on the initial visit, (3) regular attendance of the outpatient clinic for over four months from the initial visit, (4), PEF ≥ 80% predicted value with variability ≤ 20%, according to NIH criteria (1).

Exclusion criteria from the study were: emergency treatment for an asthma exacerbation within 1 month; upper airway infections in the last 4 weeks; hospitalisation for asthma in the 6 months previous to the enrolment; treatment with antihistamines, anticholinergics, teophyllinic and cromones, LABA, inhaled and oral corticosteroids, bronchiectasies, gastroesofageal reflux disease and poor knowledge of Italian language.

Study design

The randomized clinical study with parallel group consisting in a 4 weeks run-in period (Period 1) and 16 weeks of treatment period (Period 2).

A total of 45 patients were randomly assigned to a different treatment and divided in 3 treatment groups (A, B, C) as follows: group A: 400 μg of budesonide twice a day; group B: 10 mg of montelukast daily; group C: 10 mg of montelukast daily plus 400 μg of budesonide twice a day.

At the beginning of the study and at the end of the treatment period all patients underwent complete clinical evaluation, pulmonary function testing and methacholine challenge test (MCHt) according to the American Thoracic Society (ATS) standard protocol (10). Every patient could take SABA in case of asthmatic crisis. At the first visit, patient's inhaler technique was assessed. The tolerability profile was determined by adverse events reported and by physical examination at the end of 16 weeks. Patient's compliance was evaluated by the return of budesonide inhalatory device and blister packs.

Informed consent was obtained from each patient and the study was approved by the Chieti University Ethic's Committee.

Lung function and methacholine challenge tests

Patients had to complete at least 3 forced vital capacity (FVC) manoeuvres to reach the ATS standards (11). For every group we assessed FEV1 and FVC.

MCHt was performed, following the ATS protocol (10), using a dosimeter (Mefar MB3, Brescia, Italy) and starting by inhaling 0.0625 mg/mL of methacholine (lyophilised methacholine 6.4% Lofarma, Milan, Italy) up to a cumulative dose of 32 mg/mL. After a basal spirometry (the best among at least 3 significant tests) and inhalation of a buffered saline vehicle solution, patients inhaled increasing doses of methacholine up to a cumulative dose of 32 mg/mL; at the end of each inhalation of methacholine, after 120 seconds, a new FEV1 measurement was performed. The MCHt was considered positive when the amount of methacholine, which caused a 20 % fall in FEV1, was ≤ 16 mg/mL. Basal FEV 1 was obtained from the best among at least 3 significant tests (differences among the responses < 5 %).

Evaluation of Quality of Life

Patients were administered a trained interview at screening, before receiving randomised treatment, and at the end of the 16-week treatment period. The AQLQ contains 32 questions in 4 domains assessing the effects of drug treatment on activity limitations, symp-

toms, emotional function and exposure to environmental stimuli. For the activity limitations domain, each patients was instructed to select 5 activities from a list of 26 that were expected to remain important to them throughout the trial. The other 3 domains have standard response items. All items are rated on a scale ranging from 1 (maximal impairment) to 7 (no impairment).

Statistical analysis

The baseline characteristics of patients was expressed by mean ± standard deviation (SD) and percentage for age and sex respectively; mean (range) for spirometric values.

The results of treatment was expressed by mean of percentage increase compared to baseline.

The responses to the AQLQ questionnaire were analyzed directly from scores recorded. The scores for each subject for the items different groups of domain were summed and divided by the number of questions in the set of domains. This calculation provided an average score for each patient relative four domain and three treatment.

A one-way, non parametric analysis (Kruskal-Wallis test) was used to provide an overall comparison among treatment groups and the Wilcoxon rank sum test was used for pairwise comparisons the spirometric end PC20 values in three therapeutic regimes after treatment to baseline. The same test was used to provide an comparison among groups of AQLQ scores between randomization (baseline) and the end of treatment in the different therapy. The Mann-Whitney test was applicated to value the different efficacy between tree treatment. All statistical analysis was performed using SPSS® Advanced Statistics™ 7.5 software (1997, Chicago, IL, USA).

RESULTS

Baseline characteristics and personal details of 45 patients divided in the three treatment groups of the study population are shown in table 1.

We studied 45 subjects (22 males, 23 females) divided in three groups of 15 subjects each: group A with mean age 26.9 ± 12.3 years, group B with mean age 26.7 ± 8.6 years and group C with mean age 28.2 ± 10.1.

The basic parameters of respiratory function examined (FEV 1 and FVC) resulted > 80% predicted (Table 1).

Lung function

After a 16-week treatment, FEV1 and FVC were statistically significant increased from baseline only in group B (treated with Montelukast) ($p< 0.05$ Wilcoxon test) (Table 2), whereas the increase in such spirometric parameters after the entire period of treatment A or C did not reach statistical significance.

Airway responsiveness

After 16 weeks of treatment all the three treatments provided efficacy on bronchial responsiveness (expressed as mean of percentage increase of PC_{20}) compared to baseline. In group A the increase from baseline was 153.4%, in group C was 133.2%, and in group B 247.7% (Table 2), the latter increase being statistically significant compared to that in the other 2 groups ($p< 0.005$ Wilcoxon test).

Variable	Budesonide 800 µg (n=15)	Montelukast 10 mg (n=15)	Budesonide – 800 µg + Montelukast 10 mg (n=15)
Age (mean ± SD)	26.9 ± 12.3	26.7 ± 8.6	28.2 ± 10.1
Sex - no (%)			
Male (n=22)	8 (53.3)	9 (60.0)	5 (33.7)
Female (n=23)	7 (46.7)	6 (40.0)	10 (66.7)
Spirometric values (mean and range)			
MCHt (PC20) mg/mL	465 (50-800)	442 (6.25-800)	456 (50-1600)
FEV1 % predicted	97 (76-123)	97 (85-123)	99 (84-131)
FVC (% predicted)	98 (74-128)	96 (82-115)	100 (82-133)

Tab. I. *Characteristics of 45 patients divided in the three treatment groups.*

Variable	Budesonide 800 µg (n=15)	Montelukast 10 mg (n=15)	Budesonide – 800 µg + Montelukast – 10 mg (n=15)	Kruskal-Wallis Test
PC20	153.4%	247.7%	133.2%	ns
FEV1	2.1%	4.2%	4.1%	ns
FVC	3.1%	5.2%	4.0%	ns

Tab. II. *Mean of percentage increase compared to baseline of PC20, FEV1 and FVC for the three therapeutic regimens.*

DOMAINS	Group A		Group B		Group C	
	pre	post	pre	post	pre	post
Physical activities	4.6	5.2§	5.0	5.9§	5.1	5.3
Symptoms	4.9	5.3	5.3	6.3#	5.1	4.9
Emotions	5.1	5.0	5.5	6.4#	4.4	4.8
Environmental stimuli	4.6	4.9	5.0	6.4§	4.4	4.7

Tab. III. *Mean values of the 4 groups of items relative to quamity of life in the 3 treatment groups.*
§ p<0.01; # p<0.05

AQLQ

The table 3 illustrates, in the 3 treatment groups, the mean values of the 4 groups of items relative to quality of life, in particular: physical activity (11 items), symptoms (12 items), emotions (5 items), and environmental stimuli (4 items).

The physical activity domain shows a statistically significant improvement in the score over the 16-week treatment compared to the mean baseline values in group A (4.6 vs 5.2, p< 0.005) and B (5.0 vs 5.9, p<0.01), but not in group C (5.1 vs 5.3) (Fig 1.1).

In the symptoms domain a statistically significant difference was observed only in group B (5.3 vs 6.3, p<0.05), whereas in group A (4.9 vs 5.3) and C (5.1 vs 4.9) the differences did not result statistically significant.

Also in the emotions domain a statistically significant improvement was observed only in group B (5.5 vs 6.4, p< 0.05), while in groups A (5.1 vs 5.0) and C (4.4 vs 4.8) the differences from baseline were negative and non significant (Fig 1-3).

In the environmental stimuli domain an improvement was observed in the scores regarding quality of life, reaching a statistical significance only in group B (5.0 vs 6.4, p<0.01); in group A the improvement did not result fully significant, whereas in group C an impairment was observed (4.8 vs 4.4), (Fig 1-4).

In all domains the improvement in quality of life in the group treated with Montelukast (group B) was significantly greater than that in the group treated with both medications (group C): in particular the improvement was consistent in the symptoms (p< 0.01) and emotions (p< 0.01) domains, weaker in the physical activity one (p< 0.05). A similar difference was observed between group B and A,

but only in the symptoms ($p<0.01$), emotions ($p<0.01$), and environmental stimuli domains ($p<0.05$).

DISCUSSION

Our data confirm the different anti-inflammatory effects of budesonide and montelukast in the treatment of mild-persistent asthma, showing a greater efficacy of montelukast in modifying significantly the respiratory function parameters studied (FEV1 and FVC) by selectively blocking the binding to the receptors of leukotrienes, among the most powerful bronchoconstrictor agents (12,13). Furthermore, a consistent improvement in QoL has been observed in all domains, with particular reference to the physical activity and environmental exposure ones, but also, even though with less statistical significance, in symptoms and emotions domain. This is in agreement with some of the goals of the recent guidelines for the treatment of asthma, such as absence of symptoms, lack of limitations in the different physical activities, and a favorable pharmacological tolerability profile (1). Improvement of QoL is one of the most important aspects of asthmatic disease, since many trials have demonstrated a scarce correlation between functional parameters and patient's QoL (14,15). The use of montelukast in our study, besides significantly improving the functional parameters (FEV1 and FVC), determined a concomitant improvement in QoL as well, whereas budesonide was able to improve QoL only in the physical activity domain, without any significant increase in the functional parameters assessed.

Both the medications used in our study reduce bronchial inflammation and thus bronchial hyperresponsiveness; this observation confirms the variety of mechanisms intervening in bronchial inflammation, which are different from each other, complementary and not always agonist (14). Our study shows the equal efficacy of the two medications, even if montelukast proves more powerful in reducing bronchial hyper-responsiveness, as measured by the reduction of PC20.

Our data point out the importance of intervening in asthmatic disease, above all in the earlier phases of its clinical manifestation, when a variety of mechanisms play a role in the development of bronchial inflammation (16-25), involving many cells and cytokines, and when remodeling phenomena are not so advanced to determine persistent obstruction. In this early phase intervention with long-term anti-inflammatory medications, such as anti-leukotrienes, the consequences of remodeling on the bronchial wall, and thus persistent bronchial obstruction, bronchial hyper-responsiveness, decline of lung function may be avoided (26).

Therefore the use of montelukast may be considered a valid strategy to overcome the problem of potential adverse effects of long-term corticosteroid treatment, such as failure to thrive in children, and glaucoma and cataract in adults (27-28). Montelukast may be considered a valid alternative in the treatment of mild-persistent asthma, both for the clinical and functional benefits and for the great advantage of the once-daily dosage, which consistently improves the compliance with the chronic treatment of the disease.

Given the evidence from the literature of a different perception of symptoms between physicians and patients, the use of a questionnaire evaluating QoL may have great importance in addressing the appropriate treatment of asthma in each individual, focusing on the diverse deficits found in patients, even with normal spirometric values (29). The personal perception of their own disease is important for a correct therapeutic management of asthma. In order to optimize the treatment, a complete adherence of the patient to the treatment itself is required, to be achieved through simplification of therapeutic schedule and easy administration of medications.

REFERENCES

1. **US Department of Health and Human Services. National Asthma Education and Prevention Program**. 1997. Guidelines for the Diagnosis and Management of Asthma. Expert Panel Report II. Bethesda, MD: National Hearth, Lung and Blood Institute; National Institutes of Health (Publication no 97-4051), p. 1.
2. **US Department of Health and Human Services**. In *Global initiative for asthma: global strategy for asthma management and prevention*. National Hearth, Lung and Blood Institute/World Health Organisation Workshop Report Bethesda, MD: National Hearth, Lung and Blood Institute, National Institutes of Health (Publication no

95-3659), p. 1.

3. **Suissa S., R. Dennis, P. Ernst and O. Sheehy**. 1997. Effectiveness of the leukotriene receptors antagonist zafirlukast for mild-to-moderate asthma a randomized double-blind placebo controlled trial. *Ann. Intern. Med. 126:177.*
4. **Bell E. H., M.C. Timmers, J. Hermans, L.H. Dijkman and P.J. Sterk**. 1990. The long term effects of nedocromile sodium and beclometasone dipropionate on bronchial responsiveness to methacholine in non-atopic asthmatic subjects. *Am. Rev. Respir. Dis. 141:21.*
5. **Juniper E. H., P. A. Kline, M. A. Vanzieleghem, E. H. Ramsdale, P. M. O'Byrne and P. K. Hargreave.** 1990. Effect of long treatment with an inhaled corticosteroid (Budesonide) on airway hyperresponsiveness and clinical asthma in nonsteroid-dependent asthma. *Am. Rev. Respir. Dis. 142:832.*
6. **Reiss T. F., P. Chervinsky, R. J. Dockhorn, S. Shingo, B. Seidenberg and T.B. Edwards.** 1998. Montelukast, a once-daily leukotriene receptor antagonist, in the treatment of chronic asthma. *Arch. Intern. Med. 158:1213.*
7. **Juniper E. F., G. H. Guyatt, R. S. Epstein, P. J. Ferrie, R. Jaeschke and T. K. Hiller.** 1992. Evaluation of impairment of health-related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax. 47:76.*
8. **Juniper E. F., A. S. Buist, F. M. Cox, P. J. Ferrie and D. R. King.** 1999. Validation of a Standardized Version of the Asthma Quality of Life Questionnaire. *Chest. 115:1265.*
9. **American Thoracic Society**. 1987. Standards for the Diagnosis and Care of patients with Chronic Obstructive Pulmonary Disease (COPD) and Asthma. *Am. Rev. Respir. Dis. 136:225.*
10. **American Thoracic Society.** 2000. Guidelines for methacholine and exercise challenge testing. *Am. J. Respir. Crit. Care. Med. 161:309.*
11. **American Thoracic Society**. 1995. Standardization of spirometry. *Am. J. Respir. Crit. Care. Med. 152:1107.*
12. **Altman L. C., Z. Munk, J. Seltzer, S. Noonan, S. Shingo, J. Zhang and T. F. Reiss.** 1998. The Montelukast Asthma Study Group. A placebo-controlled, dose ranging study of montelukast, a cysteinyl leukotriene-receptor antagonist. *J. Allergy. Clin. Immunol. 102:50.*
13. **Jones T.R., M. Labelle, M. Belley, E. Champion, L. Charete, J. Evans, A. W. Ford-Hutchinson, J. Y. Gauthier, A. Lord, P. A. Masson et al.** 1995. Pharmacology of montelukast sodium (Singulair), a potent and selective leukotriene D4 receptor antagonist. *Can. J. Physiol. Pharmacol. 73:191.*
14. **Juniper E.F.** 1997. Rhinitis and quality of life. *Eur. Resp. Rev.* 7:300.
15. **Muldoon N.F., S. D. Barger, J. D. Flory and S. B.** Manuck. 1998. What are quality of life measurement measuring? *BMJ. 316:542.*
16. **Theoharides T.C., M. Alexandrakis, D. Kempuraj and M. Lytinas.** 2001. Anti-inflammatory actions of flavonoids and structural requirements for new design. *Int. J. Immunopathol. Pharmacol. 14:119.*
17. **Phipps P.A., A. R. Moore, G. Gowland and D.A. Willoughby.** 1998. Specific antibodies to OM-89 can account for its clinical anti-inflammatory properties. *Int. J. Immunopathol. Pharmacol. 11:139.*
18. **Marogna M., A. Tiri and G. Riva.** 2001. Clinical practice improvement program for immunotherapy of respiratory allergic diseases. *Int. J. Immunopathol. Pharmacol. 14:93.*
19. **Nowak D., J. Lewandowicz, B. Dabkowska, and J. Marczak.** 1999. Combination of methotrexate and prednisone decreases circulating concentrations of inteleukin10 and interleukin 6 in patients with rheumatoid arthritis. Poor correlation of cytokine suppression with clinical improvement. *Int. J. Immunopathol. Pharmacol. 12:13.*
20. **Lobefalo L., E. D'Antonio, L. Colangelo, G. Della Loggia, M. Di Gioacchino, D. Angelucci, A. Di Iorio and P.E. Gallenga.** 1999. Dry eye in allergic conjunctivitis: role of inflammatory infiltrate. Int. *J. Immunopathol. Pharmacol. 12:133.*
21. **Di Gioacchino M., N. Verna, E. Cavallucci, F. Paolini, R. Caruso, M. Grana, C. Schiavone, A. Di Iorio, S. Ramondo, M. Reale, R. Paganelli and T. C. Theoharides.** 2002. Steroid and antihistamines modulate RANTES release in cultured peripheral blood mononuclear cells of atopic patients. *Int. J. Immunopathol. Pharmacol. 15:27*
22. **Riccioni G., R. Della Vecchia, M. Castronuovo, V. Di Pietro, R. Spoltore, M. De Benedictis, A. Di Iorio, M. Di Gioacchino and M.T. Guagnano.** 2002. Bronchial hyperresponsiveness in adults with seasonal and perennial rhinitis: a link for asthma and rhinitis? *Int. J. Immunopathol. Pharmacol. 15:69*
23. **Scala E., M. Giani, L. Pirrotta, E.C. Guerra, O. De Pitta and P. Puddu.** 2001. Occupational asthma due to metoclopramide hydrochloride (MCPH). *Int. J. Immunopathol. Pharmacol. 14:145.*
24. **Verna N., E. Cavallucci, F. Di Stefano, S. Ramondo, F. Paolini, R. Caruso, M. Grana, M. Mariano, C. Schiavone, R. Paganelli and M. Di Gioacchino.** 2002. Cyclosporin-A in allergic diseases. *Int. J. Imunopathol. Pharmacol. 15 (S):29.*

25. **Riccioni G., M. Castronuovo, M. De Benedictis, V. Pace-Palitti, M. Di Gioacchino, R. Della Vecchia, C. Schiavone, S. Sensi and M.T.Guagnano.** 2001. Zafirlukast versus budesonide on bronchial reactivity in subjects with mild-persistent asthma. *Int. J. Immunopathol. Pharmacol. 14:87.*

26. **Vignola A.M., J. Kips and J. Bousquet.** 2000. Tissue remodelling as a feature of persistent asthma. *J. Allergy. Clin. Immunol. 105;1041.*

27. **Henderson W.R. Jr.** 1994. Role of leukotriene in asthma. *Ann. Allergy. 72:272.*

28. **Hofstra W.B., P. J. Sterk, H. I. Neijens, A. M. Van Der Weij, J. C. G. M. Van Zoest and E. J. Duiverman.** 1997. Short term treatment with zafirlukast, sodium cromoglycate or placebo in reducing exercise-induced bronchoconstrinction in adolescent asthmatics. *Eur. Resp. J. 10:220.*

29. **Rabe K.F., P. A. Vermeire, J. B. Soriano and W.C. Majer.** 2000. Clinical management of asthma in 1999: The asthma insights and reality in Europe (AIRE) study. *Eur. Respir. J. 16:802.*