Original Article

ISSN: 1735-0344 *Tanaffos 2015; 14(1): 1-9*

TANAFFOS

Efficacy of Low-Dose Ciclesonide and Fluticasone Propionate for Mild to Moderate Persistent Asthma

Hamidreza Jamaati [1], Majid Malekmohammad [2], Fanak Fahimi [3], Arvin Najafi [3], Seyed Mohammadreza Hashemian [3]

[1] Tobacco Prevention and Control Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences,Tehran, Iran, [2] Tracheal Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran, [3] Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran.

Received: 7 November 2014
Accepted: 14 January 2015

Correspondence to: Hashemian SM
Address: Chronic Respiratory Diseases Research Center, National Research Institute of Tuberculosis and Lung Diseases (NRITLD), Shahid Beheshti University of Medical Sciences, Tehran, Iran.
Email address: smrhashemian@sbmu.ac.ir

Background: The aim of this study was to compare the efficacy of ciclesonide (80 mg/day) and fluticasone propionate (200 mg/day) for mild to moderate persistent asthma.

Materials and Methods: Female and male patients older than 12 years with a history of persistent bronchial asthma for at least 6 months were enrolled. Patients were eligible to enter into a 2-week run-in period before randomization (baseline) if they had received inhaled corticosteroids (fluticasone propionate 250 µg/day or equivalent) at a constant dose during the last 4 weeks before the run-in period. In order to enter into the double blind 18-week treatment period, patients had to have a forced expiratory volume in 1s (FEV_1) of 61-90% of predicted and a decrease in FEV_1 throughout the run-in period of more than 10%. Patients (n =230) were assigned to ciclesonide 80 mg once daily or fluticasone propionate 100 mg twice daily group. The primary outcome variable was change in FEV_1 compared to its baseline value. Secondary outcome variables were asthma-specific quality of life and asthma control.

Results: Both drugs significantly increased FEV_1 and other lung function parameters compared to baseline (P< 0.0001, both groups, all variables). Progress in the percentage of days with no asthma symptoms and no use of rescue medication and asthma-specific quality of life were similar in the two treatment groups.

Conclusion: Ciclesonide at a dose of 80 µg once daily can provide efficient maintenance therapy for mild to moderate persistent asthma.

Key words: Asthma, Ciclesonide, Efficacy, Fluticasone Propionate

INTRODUCTION

Bronchial asthma is one of the most prevalent chronic diseases worldwide and is responsible for 1% of the entire annual global burden of disease (1). Although, there is no cure for asthma, pharmacotherapy can relief acute symptoms of the disease or reduce the underlying inflammatory processes in order to achieve effective asthma control. At present inhaled corticosteroids are the most commonly used anti-inflammatory drugs in asthma control and according to national and international guidelines, they are recommended as the first-line agents for persistent asthma, either alone or combined with long-acting beta-agonists (2,3). Ciclesonide is a glucocorticosteroid-ester pro-drug, presently approved for persistent asthma control in many countries worldwide. It is produced in the form of a solution for inhalation by means of a pressurized metered-dose inhaler (MDI) with hydrofluoroalkane (HFA) 134a as a propellant. Efficacy of ciclesonide has been shown in some placebo-controlled

comparative trials in children and adults (4, 5). In Europe, the preferred starting dose of ciclesonide in adults is 160 µg once daily. A lower dose of ciclesonide, 80 µg once daily, considerably improved lung function markers in comparison with placebo in patients with mild to moderate persistent asthma in two 12-week trials (6, 7). In addition, ciclesonide 80 µg once daily attenuated the early and late asthmatic reactions after allergen challenge and notably reduced exercise-induced bronchoconstriction after one week of therapy (8, 9). A comparative 12-week study in patients with persistent asthma (older than 12 years) demonstrated similar asthma control efficacy of two doses of ciclesonide, 80 µg and 160 µg once daily, and fluticasone propionate 100 µg twice daily (10).

The aim of the present study was to confirm the long-term efficacy of ciclesonide 80 µg once daily during 18 weeks in patients with mild persistent asthma. For this reason, ciclesonide was compared with fluticasone propionate 100 µg twice daily.

MATERIALS AND METHODS

Patients

Female and male patients older than 12 years with a history of persistent bronchial asthma (11) for at least 6 months were enrolled. Patients were eligible to enter into a 2-week run-in period before randomization (baseline) if they had received inhaled corticosteroids (fluticasone propionate 250 µg/day or equivalent) at a constant dose during the last 4 weeks before the run-in period and if they showed FEV_1 between 80% and 105% of predicted. The exclusion criteria were: other relevant lung disorders like chronic obstructive pulmonary disease, a severe concomitant pathology, a situation that prohibited the use of inhaled corticosteroids, or clinically related abnormal laboratory markers. Pregnant or breastfeeding female patients were excluded from the survey. Current smokers and ex-smokers with more than 10 packs/year, patients under immunotherapy, and patients with known history of allergy to inhaled corticosteroids were also excluded. The patients should not use systemic glucocorticosteroids during the past 4 weeks or more than twice during the past 6 months before the run-in period. For enrolling into the treatment period at baseline, patients had to have FEV_1 between 61% and 90% of predicted, and a decrease in FEV_1 of more than 10% compared to the onset of the run-in period.

Study design

This was a national, double center, randomized, double blind study with a 2-4 week run-in period and an 18-week double-blind treatment phase. During the run-in phase, patients were prescribed only the rescue drug (inhaled salbutamol, 100 µg/puff) if needed. Patients who met the criteria for entering into the treatment phase were randomly divided in a 1:1 ratio to receive ciclesonide 80 µg once daily in the evening or fluticasone propionate 100 µg twice daily in the morning and evening (200 µg/day). No other anti-asthma agents, except for the rescue medication, were allowed during the treatment period. Randomization was performed by means of a computer-generated list (Program RANDOM). The patient information, study protocol, and consent form were approved by the Ethics Committee of the Iranian Ministry of Health and Medical Education and the study was registered in the Iranian registry of clinical trials: http://www.irct.ir. All patients gave written informed consent before inclusion in the study.

Efficacy assessments

FEV_1 and forced vital capacity (FVC) were measured at the time of randomization (baseline) and after 2, 4, 8, and 18 weeks of therapy. Spirometry was carried out in accordance with the standards set by the American Thoracic Society. At each centre, the same spirometry equipment was used during the whole trial period and the same person measured the variables. Spirometry was performed after 15-30 minutes, about 12 hours after the last use of study drugs and at least 4 hours after the last use of the rescue medication. For daily assessment of asthma control, patients had to record their asthma symptoms (daytime and nighttime) and the need for rescue medication (salbutamol). Asthma-specific quality of life was evaluated by means of self administered, standardized version of the Asthma Quality of Life Questionnaire (AQLQ[S]), (11, 12) which includes 32 questions in 4 domains: symptoms, activity limitations, exposure to

environmental stimuli, and emotional function. Patients completed the questionnaire at baseline and at 8 and 18 weeks (or termination of the study) and answered to each question using a 7-point scale from 1 (maximal destruction) to 7 (no destruction). The net benefit in quality of life was measured as the proportion of patients with an increase of at least 0.5 in the total AQLQ(S) score (improvement) minus the proportion of patients with a decrease of at least 0.5 in total AQLQ(S) score (deterioration).

Tolerability and safety assessments

Adverse events (AEs) were recorded at every trial visit. The researcher defined the severity of AE as mild, moderate, or severe and evaluated the causal association between the AE and use of study drug. The patients' oropharynx was examined at each visit and a swab test was carried out if oral candidiasis was suspected. Vital sign items (blood pressure, heart rate) and physical examinations were conducted at the start of the run-in period and after 18 weeks of treatment (or at the time of premature discontinuation).

Statistical analysis

Efficacy variables were analyzed according to an intention-to treat (ITT) and a per-protocol (PP) basis. Patients who had shown a baseline value of efficacy and who had received at least one dose of ciclesonide or fluticasone propionate were enrolled in the ITT analysis. The PP analysis was based on patients in the ITT population without major protocol violations. The safety analysis included all randomized patients who had received at least one dose of study medication (ITT population). The primary efficacy variable was the alteration in FEV_1 [L] from baseline to the end of the treatment phase (18 weeks or the last [applicable] recorded measurement). Secondary efficacy variables consisted of changes in FVC from baseline to all scheduled visits, the percentage of patients with asthma exacerbations, the difference in the average percentage of days with asthma control in the last 14 days prior to baseline and the last 28 days of treatment, and the change from baseline to the end of the treatment period in the AQLQ(S) overall score. Variables assessed for tolerability and safety consisted of the number of patients with AEs, vital signs, physical examination, and the laboratory tests. The primary hypothesis of this survey was the non-inferiority of ciclesonide 80 µg once daily to fluticasone propionate 100 µg twice daily with reference to the primary variable. Non inferiority was also examined for the secondary variables FVC, and AQLQ(S) scores. The non-inferiority acceptance limits were set to -0.20 L for FEV_1 and FVC, and -0.5 for the AQLQ (S) scores. The PP analysis was the primary analysis for verifying non-inferiority testing. The ITT analysis was performed to confirm the robustness of the results. A sample size of 230 patients (i.e., 115 patients in each treatment group) in the PP analysis was sufficient to ensure a power of 90% for correctly concluding non-inferiority regarding the primary variable under the following assumptions: one-sided level of significance of 2.5%, a mean difference in FEV_1 for ciclesonide versus fluticasone propionate of -0.05 L with a standard deviation of 0.45 L, and a non-inferiority acceptance limit of -0.20 L. Primary and secondary lung function markers and AQLQ (S) scores were assessed by analysis of covariance, including baseline value and age as covariates and treatment, sex, and centre pool as factors. Non-inferiority was fulfilled if the entire 95% confidence interval (CI) of the difference between ciclesonide and fluticasone propionate (least square [LS] means) was above the predefined non-inferiority acceptance limit. Asthma symptom score sum and percentage of days with asthma control were tested non-parametrically (level of significance: 5%). The Wilcoxon signed-rank test modified according to Pratt was applied for within-treatment comparisons, and the Mann Whitney U-test was used for between treatment comparisons. Adverse events and other tolerability and safety variables were tested descriptively.

RESULTS

Study population

Of the 300 patients who enrolled in the run-in phase, 230 were assigned to one of the two treatment groups (ITT: ciclesonide 80 µg once daily, n =115; fluticasone propionate 100 µg twice daily, n =115). In total, 215 patients completed the study, 110 patients in the ciclesonide group and 105

patients in the fluticasone propionate groups (Figure 1). The main reason for premature trial discontinuation was patient's request or unwillingness to continue. All randomized patients received as a minimum one dose of study drug and were enrolled in the ITT and safety measurements. Except for smoking status (relatively more never-smokers were found in the ciclesonide group than in the fluticasone propionate group), the baseline characteristics were similar in both treatment groups (Table 1). Most patients had mild or moderate persistent asthma (ITT: ciclesonide, 92%; fluticasone propionate, 89%) based on the Global Initiative for Asthma (GINA) 2006 classification. According to the diary entries, the median acquiescence to study drug was 99% (range 99-100%) in the two treatment groups.

Lung function

Both agents, fluticasone propionate 100 µg twice daily and ciclesonide 80 µg once daily, improved FEV_1 [L] similarly during the 18-week treatment period. Progressions were statistically significant in comparison with baseline measurements (P< 0.0001, groups at all time points, PP and ITT analyses). After a quick FEV_1 improvement during the first 2 weeks of treatment, a plateau phase was detected about 8 weeks after treatment, which remained approximately steady until the end of the treatment phase at 18 weeks. At the end of treatment period, the LS mean change from baseline in FEV_1 was 0.45 L in the ciclesonide group and 0.51 L in the fluticasone propionate group (PP analysis); similar results were found in the ITT analysis (Table 2). Non-inferiority of ciclesonide 80 µg once daily to fluticasone propionate 100 µg twice daily was displayed for change in FEV_1 from baseline to the end of the treatment phase (PP and ITT analyses; Table 2). FVC as the secondary lung function variable significantly improved from baseline in the fluticasone propionate group and in the ciclesonide group (P < 0.0001, both groups, all post-baseline visits, PP and ITT analyses; Table 2). Non-inferiority of ciclesonide 80 µg once daily to fluticasone propionate 100 µg twice daily was confirmed for the changes in FVC from baseline to the end of the treatment period in both the PP and ITT analyses (Table 2).

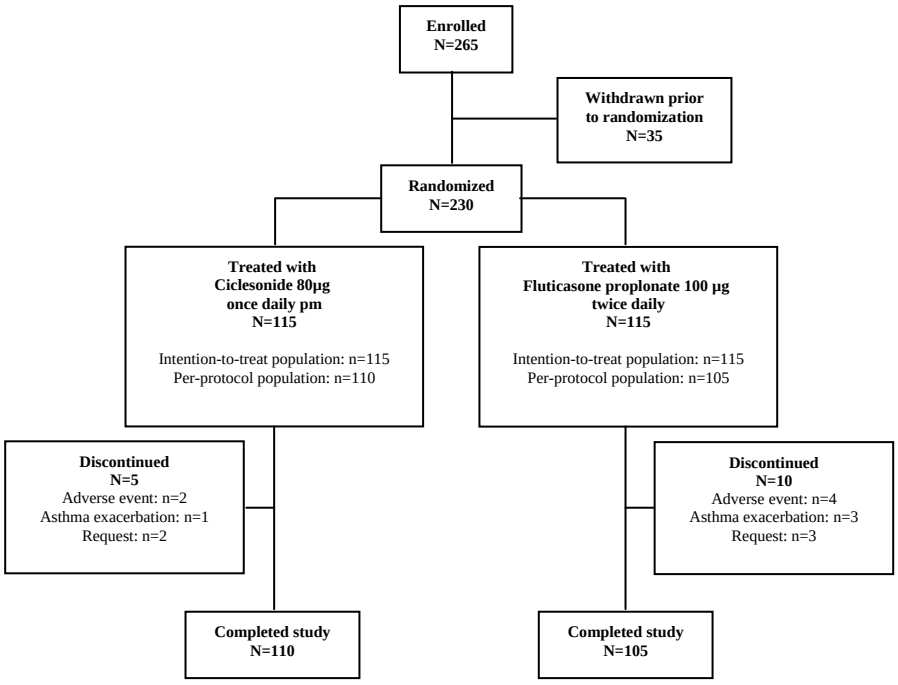

Figure 1. Demonstrates patients follow up follow up flowchart

Table 1. Demographic data and baseline characteristics

Variables	ITT (n=230)		PP (n=215)	
	CIC80 (n=115)	FP200 (n=115)	CIC80 (n=110)	FP200 (n=105)
Age (year), Median (range)	38 (15-65)	41(15-65)	37(15-65)	40(15-65)
Weight (Kg), mean± SD	73±16.2	72±15.0	74±17.5	73±17.1
Height (cm). Mean± SD	167±7.2	167±9.5	166±8.3	167±9.1
Sex, n (%)				
Male	60 (52)	59(51)	54(42)	44(36)
Female	55(48)	56(49)	75(58)	78(64)
Smoking status, n(%)				
Never-smoker	89(78)	79(69)	84(77)	73(70)
Ex-/current smoker [1]	26(22)	36(31)	26(23)	32(30)
Asthma duration (months), median (range)	121(7-577)	124(7-700)	117(7-577)	12(7-700)
FEV_1 (L), Mean± SD	2.34±0.7	2.36±0.5	2.36±0.6	2.37±0.6
FEV_1 (% predicted), Mean± SD	73.5±6.6	75.0±6.1	75.2±6.7	75.7±6.2
Reversibility, FEV_1 (% increase)	16.3±7.1	16.7±7.2	16.5±7.2	16.6±7.3

CIC80= ciclesonide 80µg once daily; FEV_1= Forced expiratory volume in 1s; FP200= Fluticasone propionate 100µg twice daily; ICS= Inhaled corticosteroid; ITT= Intention-to-treat; PP=Per-protocol; SD= Standard deviation.

[1] Ex-smoker: Smoking cessation at least one year ago

Table 2. Lung function measures and AQLQ score after 18 weeks of treatment with ciclesonide or fluticasone propionate

Variables	ITT (n=230)		PP (n=215)	
	CIC80 (n=115)	FP200 (n=115)	CIC80 (n=110)	FP200 (n=105)
Change from baseline [1] FEV_1 (L), Spirometry				
Baseline, LS mean	2.38	2.38	2.36	2.36
Change, LS mean± SD	0.45±0.03	0.51±0.03	0.45±0.03	0.51±0.03
P-value (2-sided)	<0.0001	<0.0001	<0.0001	<0.0001
FVC (L), Spirometry				
Baseline, LS mean	3.24	3.24	3.21	3.21
Change, LS mean± SD	0.5±0.03	0.56±0.03	0.56±0.04	0.59±0.04
P-value (2-sided)	<0.0001	<0.0001	<0.0001	<0.0001
Morning PEF (L/min), diary				
Baseline, LS mean	362.9	362.9	363.5	363.5
Change, LS mean± SD	23.0±3.4	34.5±3.5	22.9±3.8	32.9±3.8
P-value (2-sided)	<0.0001	<0.0001	<0.0001	<0.0001
Change from baseline in AQLQ (S) scores	0.40±0.05	0.45±0.05	0.40±0.06	0.42±0.06
P-value (2-sided)	<0.0001	<0.0001	<0.0001	<0.0001

CIC80= Ciclesonide 80µg once daily; FEV_1= Forced expiratory volume in 1s; FP200= Fluticasone propionate 100µg twice daily; FVC=Forced vital capacity; ITT= Intention-to-treat; LS= Least square; PEF= Peak expiratory flow; PP=per-Protocol; SE= Standard error

[1] Change from baseline to 18 weeks

Quality of life

Asthma-specific quality of life improved considerably from baseline in two treatment groups with regard to AQLQ (S) overall score (Table 2). Non-inferiority of ciclesonide 80 µg once daily to fluticasone propionate 100 µg twice daily was demonstrated for the change from baseline to the end of the treatment phase in the AQLQ(S) overall score and all individual domain scores ($P < 0.0001$, one-sided, all scores, PP and ITT analyses).

Tolerability and safety

The incidence of treatment-emergent adverse events was similar in both groups: 14% (n=30) of patients treated with ciclesonide 80 µg once daily and 18% (n = 38) of patients treated with fluticasone propionate 100 µg twice daily had at least one adverse event. Nasopharyngitis and upper respiratory tract infection were the most common adverse events in the two treatment groups. No deaths occurred over the trial period. At the end of the treatment phase, no clinically significant changes in physical examination and laboratory markers were seen in any of the groups. The mean blood pressure and the mean heart rate were stable during the study period in the two treatment groups.

DISCUSSION

The current survey evaluated the efficacy of low-dose ciclesonide (80 µg/day, prescribed once daily in the evening) in comparison with fluticasone propionate (200 µg/day, 100 µg prescribed twice daily) in patients with mild to moderate persistent asthma. Our findings showed that both agents improved lung function and led to asthma control during a prolonged treatment period of 18 weeks. These results are similar to the findings of a previous double-blind trial in patients with persistent asthma, which demonstrated similar efficacy of ciclesonide 80 µg once daily and fluticasone propionate 100 µg twice daily over a shorter treatment period of 12 weeks (10). The clinical efficiency of both fluticasone propionate 100 µg twice daily and ciclesonide 80 µg once daily has been shown in placebo-controlled trials (6, 7, 13). A randomized, double-blind survey in patients older than 12 years with mild to moderate persistent asthma showed that ciclesonide 160 µg once daily and fluticasone propionate 100 µg twice daily were similar in both improving lung function and reducing asthma symptoms and rescue drug use (14). HFA based, fine particle formulations like ciclesonide are largely deposited in the peripheral regions of the lung (15, 16). They seem to be more effective in controlling eosinophilic inflammation in the small airways than more conventional formulations with larger particle sizes (17-19). Optimal delivery to all parts of the lung may have special importance when using reduced corticosteroid doses. To prevent the incidence of unwilling side effects in association with long-term corticosteroid treatment, modern guidelines recommend prescribing the inhaled corticosteroids with the lowest effective dose (2, 20-23). It is necessary to sufficiently investigate and document the efficacy of low-dose inhaled corticosteroids, particularly in long-term treatments. A recent survey on mild asthma demonstrated beneficial effects of prolonged regular treatment with a minimal dose of fluticasone propionate 100 µg/day to preserve the progressions achieved via higher dose of 250 µg/day (24). Ciclesonide resulted in good asthma control in most asthma patients at a dose of 160 µg once daily (7, 10, 14, 25-27). However, efficacy information for low-dose ciclesonide was provided by trials with treatment periods not more than 12 weeks (6, 7, 28). The current survey confirmed that low-dose ciclesonide was an effective anti-inflammatory controller medication and showed its efficacy in mild to moderate asthma during a long-term treatment period of 18 weeks. Recent international asthma therapy guidelines suggest low-dose inhaled corticosteroids as initial controller treatment in persistent asthma. In a stepwise management approach, long-acting beta-agonists can be added to the inhaled corticosteroids for patients in whom adequate asthma control cannot be achieved with inhaled corticosteroids alone (2, 3). On the other hand, adding a long-acting beta-agonist to inhaled corticosteroids can

provide no additional improvement in these patients and may result in unnecessary costs (29, 30). Monotherapy with an inhaled corticosteroid often leads to sufficient control in the majority of patients with persistent asthma (2). In this 18-week survey, both inhaled corticosteroid monotherapy treatments demonstrated good asthma control in patients with mild to moderate persistent asthma. To confirm the need for inhaled corticosteroid therapy, patients had to display worsening in lung function following the baseline phase after discontinuation of their inhaled corticosteroid. As the patients demonstrated satisfactory response to the low-dose ciclesonide, there is a possibility that some of the patients known as having moderate asthma actually had mild asthma. In the general population, patients with mild persistent asthma account for a large proportion of all asthmatic patients (up to 70%) (31). Both ciclesonide 80 µg once daily and fluticasone propionate 100 µg twice daily significantly improved asthma-specific quality of life as examined by the standardized AQLQ. Non-inferiority of ciclesonide to fluticasone propionate with regard to the improvements in the AQLQ(S) overall score after 18 weeks of treatment was shown. The baseline AQLQ(S) scores were comparatively high in both groups. However, both treatments caused statistically significant improvements in the AQLQ(S) overall score. The incidence of adverse events during the 18-week trial period was low and similar in both groups. Relatively higher number of associated adverse events, which were mainly local reactions such as oral candidiasis, was detected in fluticasone propionate group than in the ciclesonide group. This is not unexpected, because the daily dose of fluticasone propionate was twice as high as that of ciclesonide. Nevertheless, the incidence of local oropharyngeal adverse events reported in previous trials evaluating comparable doses of the two inhaled corticosteroids also designated better local tolerability of ciclesonide (32, 33). Inhaled corticosteroids commonly result in minimal side effects at low to moderate doses. On the other hand, non-compliance is a trouble in long-term asthma management and patients who experience adverse effects are more likely to discontinue their drugs than patients who do not (34).

CONCLUSION

This 18-week study confirmed similar efficacy of fluticasone propionate 100 µg twice daily and ciclesonide 80 µg once daily in patients with mild to moderate persistent asthma and showed that low-dose ciclesonide was efficient for long-term treatments. According to these findings, it can be concluded that ciclesonide at a dose of 80 µg once daily can provide efficient maintenance therapy for mild to moderate persistent asthma.

REFERENCES

1. Masoli M, Fabian D, Holt S, Beasley R; Global Initiative for Asthma (GINA) Program. The global burden of asthma: executive summary of the GINA Dissemination Committee report. *Allergy* 2004; 59 (5): 469- 78.
2. Global Initiative for Asthma. Global strategy for asthma management and prevention, http://www.ginasthma.com; December 2009.
3. National Heart Lung and Blood Institute. Expert panel report 3 (EPR3): guidelines for the diagnosis and management of asthma, http://www.nhlbi.nih.gov; 2007.
4. Dahl R. Ciclesonide for the treatment of asthma. *Ther Clin Risk Manag* 2006; 2 (1): 25- 38.
5. Deeks ED, Perry CM. Ciclesonide: a review of its use in the management of asthma. *Drugs* 2008; 68 (12): 1741- 70.
6. Langdon CG, Adler M, Mehra S, Alexander M, Drollmann A. Once-daily ciclesonide 80 or 320 microg for 12 weeks is safe and effective in patients with persistent asthma. *Respir Med* 2005; 99 (10): 1275- 85.
7. Pearlman DS, Berger WE, Kerwin E, Laforce C, Kundu S, Banerji D. Once-daily ciclesonide improves lung function and is well tolerated by patients with mild-to-moderate persistent asthma. *J Allergy Clin Immunol* 2005; 116 (6): 1206- 12.
8. Gauvreau GM, Boulet LP, Postma DS, Kawayama T, Watson RM, Duong M, et al. Effect of low-dose ciclesonide on

allergen-induced responses in subjects with mild allergic asthma. *J Allergy Clin Immunol* 2005; 116 (2): 285- 91.

9. Subbarao P, Duong M, Adelroth E, Otis J, Obminski G, Inman M, et al. Effect of ciclesonide dose and duration of therapy on exercise-induced bronchoconstriction in patients with asthma. *J Allergy Clin Immunol* 2006; 117 (5): 1008- 13.
10. Magnussen H, Hofman J, Staneta P, Lawo JP, Hellwig M, Engelstätter R. Similar efficacy of ciclesonide once daily versus fluticasone propionate twice daily in patients with persistent asthma. *J Asthma* 2007; 44 (7): 555- 63.
11. Juniper EF, Guyatt GH, Epstein RS, Ferrie PJ, Jaeschke R, Hiller TK. Evaluation of impairment of health related quality of life in asthma: development of a questionnaire for use in clinical trials. *Thorax* 1992; 47 (2): 76- 83.
12. Juniper EF, Buist AS, Cox FM, Ferrie PJ, King DR. Validation of a standardized version of the Asthma Quality of Life Questionnaire. *Chest* 1999; 115 (5): 1265- 70.
13. Wolfe J, Rooklin A, Grady J, Munk ZM, Stevens A, Prillaman B, et al. Comparison of once- and twice-daily dosing of fluticasone propionate 200 micrograms per day administered by diskus device in patients with asthma treated with or without inhaled corticosteroids. *J Allergy Clin Immunol* 2000; 105 (6 Pt 1): 1153- 61.
14. Buhl R, Vinkler I, Magyar P, Györi Z, Rybacki C, Middle MV, et al. Comparable efficacy of ciclesonide once daily versus fluticasone propionate twice daily in asthma. *Pulm Pharmacol Ther* 2006; 19 (6): 404- 12.
15. Rohatagi S, Derendorf H, Zech K, Nave R, Banerji D. PK/PD of inhaled corticosteroids: the risk/benefit of inhaled ciclesonide. Allergy Clin Immunol 2003;111(2 Suppl) [abstract] S218:598.
16. Newman S, Salmon A, Nave R, Drollmann A. High lung deposition of 99mTc-labeled ciclesonide administered via HFA-MDI to patients with asthma. *Respir Med* 2006; 100 (3): 375- 84.
17. Hoshino M. Comparison of effectiveness in ciclesonide and fluticasone propionate on small airway function in mild asthma. *Allergol Int* 2010; 59 (1): 59- 66.
18. Ohbayashi H, Adachi M. Hydrofluoroalkane-beclomethasone dipropionate effectively improves airway eosinophilic inflammation including the distal airways of patients with mild to moderate persistent asthma as compared with fluticasone propionate in a randomized open double-cross study. *Allergol Int* 2008; 57 (3): 231- 9.
19. Leach CL, Davidson PJ, Hasselquist BE, Boudreau RJ. Lung deposition of hydrofluoroalkane-134a beclomethasone is greater than that of chlorofluorocarbon fluticasone and chlorofluorocarbon beclomethasone : a cross-over study in healthy volunteers. *Chest* 2002; 122 (2): 510- 6.
20. Haahtela T, Järvinen M, Kava T, Kiviranta K, Koskinen S, Lehtonen K, et al. Effects of reducing or discontinuing inhaled budesonide in patients with mild asthma. *N Engl J Med* 1994; 331 (11): 700- 5.
21. van Grunsven PM, Dompeling E, van Schayck CP, Molema J, Folgering H, van Weel C. Treatment of mild asthma with inhaled corticosteroids: is discontinuation of therapy possible? *Fam Med* 1996; 28 (1): 46- 51.
22. British Thoracic Society. British guideline on the management of asthma, http://www.brit-thoracic.org.uk; June 2009.
23. Buhl R, Berdel D, Criée CP, Gillissen A, Kardos P, Kroegel C, et al. Guidelines for diagnosis and treatment of asthma patients. *Pneumologie* 2006; 60 (3): 139- 77.
24. Boulet LP, Turcotte H, Prince P, Lemière C, Olivenstein R, Laprise C, et al. Benefits of low-dose inhaled fluticasone on airway response and inflammation in mild asthma. *Respir Med* 2009; 103 (10): 1554- 63.
25. Chapman KR, Patel P, D'Urzo AD, Alexander M, Mehra S, Oedekoven C, et al. Maintenance of asthma control by once-daily inhaled ciclesonide in adults with persistent asthma. *Allergy* 2005; 60 (3): 330- 7.
26. von Berg A, Engelstätter R, Minic P, Sréckovic M, Garcia Garcia ML, Latoś T, et al. Comparison of the efficacy and safety of ciclesonide 160 microg once daily vs. budesonide 400 microg once daily in children with asthma. *Pediatr Allergy Immunol* 2007; 18 (5): 391- 400.
27. Niphadkar P, Jagannath K, Joshi JM, Awad N, Boss H, Hellbardt S, et al. Comparison of the efficacy of ciclesonide 160 microg QD and budesonide 200 microg BID in adults with persistent asthma: a phase III, randomized, double-dummy, open-label study. *Clin Ther* 2005; 27 (11): 1752- 63.

28. Hansel TT, Benezet O, Kafé H, Ponitz HH, Cheung D, Engelstätter R, et al. A multinational, 12-week, randomized study comparing the efficacy and tolerability of ciclesonide and budesonide in patients with asthma. *Clin Ther* 2006; 28 (6): 906- 20.
29. O'Byrne PM, Barnes PJ, Rodriguez-Roisin R, Runnerstrom E, Sandstrom T, Svensson K, et al. Low dose inhaled budesonide and formoterol in mild persistent asthma: the OPTIMA randomized trial. *Am J Respir Crit Care Med* 2001; 164 (8 Pt 1): 1392- 7.
30. Ni CM, Greenstone IR, Ducharme FM. Addition of inhaled long-acting beta2-agonists to inhaled steroids as first line therapy for persistent asthma in steroid-naive adults. *Cochrane Database Syst Rev* 2005; (2): CD005307.
31. O'Byrne PM, Parameswaran K. Pharmacological management of mild or moderate persistent asthma. *Lancet* 2006; 368 (9537): 794- 803.
32. Boulet LP, Bateman ED, Voves R, Müller T, Wolf S, Engelstätter R. A randomized study comparing ciclesonide and fluticasone propionate in patients with moderate persistent asthma. *Respir Med* 2007; 101 (8): 1677- 86.
33. Bateman ED, Linnhof AE, Homik L, Freudensprung U, Smau L, Engelstätter R. Comparison of twice-daily inhaled ciclesonide and fluticasone propionate in patients with moderate-to-severe persistent asthma. *Pulm Pharmacol Ther* 2008; 21 (2): 264- 75.
34. Canonica GW, Baena-Cagnani CE, Blaiss MS, Dahl R, Kaliner MA, Valovirta EJ; GAPP Survey Working Group. Unmet needs in asthma: Global Asthma Physician and Patient (GAPP) Survey: global adult findings. *Allergy* 2007; 62 (6): 668- 74.