Assessment of Montelukast, Doxofylline, and Tiotropium With Budesonide for the Treatment of Asthma: Which Is the Best Among the Second-Line Treatment? A Randomized Trial

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ABSTRACT

Purpose: Data comparing various second-line treatments for asthma with subjective and objective assessment are lacking. This study aimed to compare the efficacy and safety of montelukast, doxofylline, and tiotropium with a low-dose budesonide in patients with mild to moderate persistent asthma.

Methods: Patients, all of whom were concurrently using inhaled budesonide (400 μg), were treated for 6 months with formoterol (12 μg), montelukast (10 mg), doxofylline (400 mg), or tiotropium (18 μg). Outcomes included forced expiratory volume in 1 second (FEV_1), Saint George Respiratory Questionnaire (SGRQ) scores, asthma symptom scores (daytime and nighttime), and assessment of tolerability and rescue medication use.

Findings: A total of 297 patients completed the study. In all 4 groups, significant improvements were observed in all the outcome measures, with formoterol treatment having greater and earlier improvements than the other 3 second-line controller medications with budesonide. Among the second-line treatments, monteradlukast improved the FEV_1 from day 45 ($P < 0.01$), SGRQ scores from day 30 ($P < 0.0001$), daytime scores from day 30 ($P < 0.05$), nighttime scores from day 30 ($P < 0.0001$), and rescue medication use from day 15 ($P < .0001$) at a faster rate than doxofylline or tiotropium with budesonide. No patients discontinued the treatment because of adverse reactions.

Implications: Among the tested second-line treatment regimens, the budesonide/montelukast combination was found to be superior to either the budesonide/doxofylline or budesonide/tiotropium combination in all the outcome measures without adversely affecting the tolerability of the patients. Further clinical studies with blinding techniques are likely to be useful. (*Clin Ther*. 2015;▮:▮▮▮–▮▮▮) © 2015 Elsevier HS Journals, Inc. All rights reserved.

Key words: budesonide, doxofylline, formoterol, montelukast, tiotropium.

INTRODUCTION

The brief background of this study was mentioned in the pilot study report.[1] No clinical data are available on comparing montelukast (leukotriene modifier [LT-M]), doxofylline (sustained-release tablet [SR-T]), or tiotropium (long-acting muscarinic antagonist [LAMA]) with budesonide (inhaled corticosteroid [ICS]); therefore, the benefits of these drugs within an asthma management program are not yet very clear. For this reason, we designed a study to compare the efficacy and safety of 3 different controller medications and to find the best second-line controller medication of 3 different treatment protocols in patients with mild to moderate persistent asthma.

PATIENTS AND METHODS

Study design, study criteria, treatment, pulmonary function, and rescue medication use procedures were same as those of the pilot study.[1] In addition to that,

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health-related quality of life (HRQoL) and asthma symptom scores were recorded. The HRQoL was assessed by the Saint George Respiratory Questionnaire (SGRQ). The SGRQ is a disease-specific instrument designed to measure effect on overall health, daily life, and perceived well-being. The SGRQ was scored according to the developer's guidelines.[2]

Patients regularly recorded their daytime and nighttime asthma symptom scores and rescue medication use on diary cards daily.[3] During the study period, patients were assessed for adverse events (nature, severity, and casual relationship), which were further classified according to their type, severity, and possible associations with the treatments. Patients' adherence with the study medication was assessed with the help of medication adherence records. Patients not obeying the study protocol were withdrawn from the study. All the clinical assessments and adverse event monitoring were performed at baseline (day 0) and on days 15, 30, 45, 60, 90, 120, 150, and 180 (end visit).

To calculate the sample size, we conducted a pilot study.[1] From the pilot study report, a sample size of 242 was calculated using the standard formula to detect a significant difference in forced expiratory volume in 1 second (FEV_1) measurements with 5% type I error (α) and 80% power of the study (β), and the dropouts considered were 20%. All the data are expressed as mean (SD). Descriptive analysis was performed on the baseline characteristics. One-way ANOVA was used for between-group comparisons across various periods. The Pearson correlation coefficient test was performed to find out the correlation between the FEV_1 and SGRQ scores. Multiple linear regression (MLR) analysis was used to standardize the study model by keeping the efficacy variable of FEV_1 baseline scores as the dependent variable and age, sex, duration of asthma, smoking history, and literacy levels as the independent variables. All hypothesis tests were 2-sided. $P < .05$ was considered statistically significant. All the analyses were performed with GraphPad Software, version 6.0 (GraphPad Software Inc, La Jolla, California) except for the MLR analysis, which was applied when testing determinants for the FEV_1 scores. The MLR analysis using backward method was performed with SPSS statistical software, version 16.0 (SPSS Inc, Chicago, Illinois). Per protocol analysis was performed.

RESULTS

The study was conducted between December 2011 and May 2014. Each patient in the study was followed up for a period of 6 months at regular predetermined intervals in the duration of 2½ years.

Patient Characteristics

A total of 559 patients attended the screening phase, and 362 patients met the study criteria. Finally, 297 patients completed the study, and 65 patients (21.8%) were lost to follow-up because of various reasons detailed in Figure 1. The demographic and baseline disease characteristics are similar between the groups (Table I).

Pulmonary Function

In each of the 4 treatment groups, the FEV_1 values were almost at the same level in the initial state, and no statistically significant difference was found among the groups ($P > 0.05$). In the formoterol/budesonide (FB), montelukast/budesonide (MB), doxofylline/budesonide (DB), and tiotropium/budesonide (TB) groups, statistically significant increases from baseline values were noted on days 30, 45, 60, and 90 ($P < 0.01$, $P < 0.05$, $P < .01$, and $P < .05$, respectively), and the increase in FEV_1 values continued during subsequent days until the end visit. Statistically significant difference was observed when comparing second-line treatments (MB, DB, and TB) with the first-line treatment (FB), which revealed that none of the second-line treatments can replace the first-line treatment in improving FEV_1 values. When data were analyzed for second-line treatments, no statistical difference was observed between the MB and DB groups (Figure 2).

Health-Related Quality of Life

After 6 months, the mean differences in the SGRQ symptom, activity, and impact and total scores statistically and significantly exceeded the threshold for a clinically relevant change in all the groups. The mean difference in the total SGRQ score was significantly higher in the MB- group followed by the DB and TB groups among the second-line treatments (Figure 3A, 3B, 3C, and 3D). No significant correlation was observed for FEV_1 values and SGRQ scores (Table II).