Formoterol, a long-acting \(\beta_2\)-agonist (LABA), and budesonide, an inhaled corticosteroid (ICS), in combination demonstrate an additive effect in alleviating asthma symptoms. Their fixed-dose combination in one inhaler simplifies the administration regimen, improves adherence, and ensures that a LABA will not be used as monotherapy. This combination product suppresses chronic inflammation seen in asthma and reduces airway hyperresponsiveness, which is important for the control of asthma. A post-marketing, multicenter, open-label, non-randomized non-interventional study was conducted by 220 unselected allergologists and pulmonologists with the participation of 2200 combination-naive adult outpatients with a diagnosis of asthma on the basis of the reversible (spontaneously or with treatment) clinical symptoms of airflow obstruction who had recently started combination therapy. The inclusion criterion was recently started combination therapy with budesonide/formoterol fumarate continued before enrolment for at least 14 days by an adult patient (age 18 years or older) with asthma. The exclusion criteria (in line with the summary product characteristics) were hypersensitivity to budesonide, formoterol, or lactose; pregnancy; breastfeeding; unstable asthma (defined as the use of oral steroid cycles three times during the last year or hospitalization due to asthma in the last 6 months), and participation in another study. The evaluation of therapy effectiveness and monitoring of adverse drug reactions was an element of routine patient management by the allergologists and pulmonologists. The study method included the collection of effectiveness and safety data during all three visits: on enrollment and during two control visits (the routine clinical check-ups during therapy) with 8–12-week intervals. The data were recorded in a study questionnaire completed at three subsequent visits between May and November 2016. Adherence was assessed during each visit on the basis of the Asthma Control Test (ACT). The Medication Adherence Questionnaire (MAQ) was used for the assessment of adherence. Patient satisfaction was analyzed on the basis of closed questions scored on a five-point scale (very easy/quite easy/not so easy/not easy/hard). In addition, overall self-assessment of the inhaler and the complexity of the instructions for use of the inhaler was done by the patient during the three visits. Adverse drug reactions were recorded during all three visits. The primary end point was the percentage of patients with well-controlled asthma or total control of asthma (ACT score 20–25 points) and the percentage of patients with poor control of asthma (ACT score less than 15 points). The percentage of patients with well-controlled asthma or total control of asthma (ACT score 20–25 points) increased from 46.6% at the first visit to 90.8% at the third visit (\(P<0.001\)). In addition, the percentage of patients with poor control of asthma (ACT score less than 15 points) decreased from 14.9% to 1.2% (\(P<0.001\)). The adherence rate increased from 88% at the first visit to 95.3% at the third visit. Patient satisfaction with the use of this inhaler increased with the duration of its use. Only one adverse drug reaction was reported. So, the results obtained confirm the effectiveness of single-inhaler combination therapy with budesonide/formoterol fumarate in the treatment of asthma in outpatient adults in daily clinical practice.
Smoking Duration, More Strongly Associated with COPD Disease Components than Pack-Years

Cigarette smoking is the strongest risk factor for COPD. Smoking burden is frequently measured in pack-years, but the relative contribution of cigarettes smoked per day versus duration towards the development of structural lung disease, airflow obstruction and functional outcomes is not known. The cross-sectional data from a large multicenter cohort (COPD Gene) of current and former smokers were analyzed. Airflow obstruction (FEV1/FVC) was evaluated as the primary endpoint. Additional measures of disease such as FEV1, computed tomography (CT) emphysema, CT gas trapping, functional capacity (6 min walk distance, 6MWD) and respiratory morbidity (St George’s Respiratory Questionnaire, SGRQ) were also assessed. Generalized linear models were estimated to compare the relative contribution of each smoking variable with the outcomes, after adjustment for age, race, sex, body mass index, CT scanner, age of smoking onset and current smoking status. The adjusted means of each outcome by categories of pack-years was estimated. The linear trends of adjusted means for each outcome by categorized cigarettes/day, smoking duration and pack-years was also evaluated. Ten thousand, one hundred and eighty seven subjects were included. For FEV1/FVC, standardized beta coefficient for smoking duration was greater than for cigarettes/day and pack-years ($P<0.001$). After categorization, there was a linear increase in adjusted means FEV1/FVC with increase in pack-years (regression coefficient $\beta=-0.033\pm0.003; P=0.003$) and duration over all ranges of smoking cigarettes/day ($\beta=-0.033\pm0.004; P<0.001$) but a relatively flat slope for cigarettes/day across all ranges of smoking duration ($\beta=0.009\pm0.009; P=0.34$). Strength of association of duration was similarly greater than pack-years for emphysema, gas trapping, FEV1, 6MWD and SGRQ. However it is shown that in a large cohort of smokers with and without COPD, smoking duration provides stronger risk estimates of COPD components than cigarettes smoked per day and the composite index of pack-years.

Long Acting Muscarinic Antagonist and Long Acting $\beta2$ Agonist Therapy to Optimize Chronic Obstructive Pulmonary Disease Prior to Lung Cancer Surgery

Chronic obstructive pulmonary disease (COPD) is the fourth leading cause of death and results in >2.5 million deaths per year worldwide. Lung cancer is frequently seen in patients with COPD and has been found to be the most frequent cause of death in patients with mild COPD. In COPD cohort studies, the incidence ratios for lung cancer ranged from 4.2 to 16.7 per 1,000 person years. It is crucial to improve the management of both COPD and lung cancer. Bronchodilators are essential for the perioperative management of patients with chronic obstructive pulmonary disease (COPD) undergoing surgery for lung cancer. A retrospective study was conducted to examine whether the usage of a long acting $\beta2$ agonist (LABA) with a long acting muscarinic antagonist (LAMA) could optimize preoperative lung function and reduce the risk for postoperative pulmonary complications. Thirty two consecutive patients with moderate to severe COPD who underwent a lobectomy for lung cancer and received preoperative LAMA (n=19) or LAMA/LABA (n=13) therapy were enrolled in this retrospective study. All patients in this study were confirmed to have ceased smoking more than 2 weeks before surgery. In the LAMA group, the patients received inhaled tiotropium bromide (n=19) from >2 weeks before surgery to at least 1 month after surgery without interruption. In the LAMA/LABA group, the patients received inhaled tiotropium bromide and LABA [formoterol (n=8), indacaterol (n=4)] or combined LABA/LAMA [indacaterol/glycopyrrylate (n=1)] from >2 weeks before surgery to at least 1 month after surgery without interruption. Postoperative pulmonary complications were defined as: i) pneumonia, defined by the presence of at least three of the following criteria: persistent lung infiltrate on chest X ray, fever $>38.3^\circ{C}$, white blood cell count $>10,000$ mm$^3$ or $<3,000$ mm$^3$; ii) acute respiratory failure, defined as postoperative ventilator dependence $>12$ h or reintubation for mechanical ventilation; iii) chronic respiratory failure, defined as the need for continuous oxygen therapy for more than 1 month after discharge. Postoperative cardiovascular complications were defined as arrhythmias (atrial fibrillation, paroxysmal supraventricular tachycardia, ventricular tachycardia), angina pectoris, myocardial infarction, congestive heart failure and thromboembolic events. Finally, surgical mortality was defined as death within 30 days following surgery. LAMA therapies resulted in the improvement of FEV1 (post therapy FEV1 1.41±0.09 l) and %FEV1 (post therapy %FEV1 63.7±2.95%). LAMA/LABA therapies resulted in the improvement of FEV1 (post therapy FEV1 1.72±0.12 l) and %FEV1 (post therapy %FEV1 78.3±3.74%). The increases in FEV1 and %FEV1 were significantly higher for LAMA/LABA therapy than LAMA (post therapy pre therapy FEV1 0.26±0.05 vs. 0.07±0.05 l, $P=0.0145$; post therapy pre therapy %FEV1 12.2±2.53 vs. 4.21±2.16%, $P=0.0251$, respectively). More patients in the LAMA/LABA group had a marked improvement of $>10$% in %FEV1 after bronchodilators than patients in the LAMA group (85 vs. 32%, $P=0.0046$). The incidence of postoperative pneumonia was significantly lower in the LAMA/LABA group than in the LAMA group (0 vs. 26%, $P=0.044$). In conclusions, the study showed that preoperative LAMA/LABA therapy was associated with greater improvements in preoperative pulmonary function than LAMA. These improvements in preoperative function tended to reduce the incidence of pneumonia in the postoperative period. These results may lead to not only larger improvements in FEV1 but also less post-operative pneumonia by encouraging the addition of inhaled LABA to LAMA in this patient population.
Women with asthma who only use short-acting asthma relievers take longer to become pregnant than other women, according to international research led by the University of Adelaide. However, the study of more than 5600 women in Australia, New Zealand, the United Kingdom and Ireland also shows that women with asthma who use long-acting asthma preventers conceive as quickly as other women. The study was led by Dr. Luke Grzeskowiak from the University of Adelaide's Robinson Research Institute and published in the European Respiratory Journal. Dr Grzeskowiak says the results provide reassurance for asthmatic women that using inhaled corticosteroids to prevent symptoms does not appear to reduce fertility. "Five to ten per cent of all women around the world have asthma and it is one of the most common chronic medical conditions in women of reproductive age. Several studies have identified a link between asthma and female infertility, but the impact of asthma treatments on fertility has been unclear. Studying the effect of asthma treatments in women who are pregnant or trying to get pregnant is important as women often express concerns about exposing their unborn babies to potentially harmful effects of medications," Dr Grzeskowiak says. The researchers examined data from the international Screening for Pregnancy Endpoints (SCOPE) study, which recruited more than 5600 women expecting their first babies in the early stages of pregnancy. Ten per cent of women in the study said they had asthma and, overall, these women took longer to get pregnant. When researchers separated this group according to the types of asthma treatments they were using, they found no difference in fertility between women using long-acting asthma treatments and women without asthma. Women using short-acting reliever medication (known as β-agonists) took 20% longer to conceive on average. They were also 30% more likely to have taken more than a year to conceive. Dr Grzeskowiak says: "This study shows that women using short-acting asthma relievers take longer to get pregnant. On the other hand, continued use of long-acting asthma preventers to control asthma seems to protect fertility and reduce the time it takes women with asthma to become pregnant. This could lead to a reduction in the need for fertility treatments, what we don't yet know is exactly how asthma or asthma treatments lead to fertility problems. As well as affecting the lungs, asthma could cause inflammation elsewhere in the body, including the uterus. It could also affect the health of eggs in the ovaries. The researcher says, "Inhaled corticosteroids suppress the immune system, whereas short-acting asthma treatments do not alter immune function. In women who are only using relievers it's possible that, while their asthma symptoms may improve, inflammation may still be present in the lungs and other organs in the body".

Tiotropium Reduces Asthma Exacerbation Risk in Children Aged 1-5 Years with Persistent Asthma

A new study found tiotropium, a long-acting anticholinergic drug, to be safe, well-tolerated and effective in children aged 1–5 years with persistent asthmatic symptoms. Tiotropium as an add-on to inhaled corticosteroids (ICS) apparently did not have any impact on the mean daytime asthma symptom scores in these children. However, the risk of asthma exacerbation reduced in children receiving tiotropium as compared to placebo. The data on safety and efficacy of various therapeutic options in asthma management in pediatrics is limited. The 12-week randomized trial evaluated the safety and efficacy of tiotropium in children aged 1–5 years with persistent asthmatic symptoms at 32 hospitals across 11 countries in Asia, Europe, and North America. The children between the ages of 1 and 5 years with at least a 6-month history of persistent asthmatic symptoms and a need for ICS were enrolled. One hundred and two children were randomized into 3 groups – 36 received once-daily tiotropium 2.5 µg, 32 received tiotropium 5 µg, and 34 received placebo as an add-on to inhaled corticosteroids with or without additional controller medication. The incidence of adverse events was used to assess safety. The change in weekly mean combined daytime asthma symptom score from baseline to week 12 was the primary efficacy endpoint. The study was completed by 101 children. There were no significant differences in the changes in adjusted weekly mean combined daytime asthma symptom scores at baseline and week 12 between the groups. The adjusted mean difference between the tiotropium 2.5 µg group and placebo group was −0.080 and the difference between tiotropium 5 µg and placebo group was −0.048. The incidence of adverse events was 56%, 58% and 74% in the tiotropium 2.5 µg, 5 µg, and placebo respectively. There was a significant reduction in the asthma exacerbations in the tiotropium 2.5 µg and 5 µg groups as compared to placebo (14%, 6% and 29% respectively. Although no adverse events led to discontinuation or death, serious adverse events were reported by 3 patients from the placebo group.
Early Control Treatment with Montelukast in Preschool Children with Asthma: A Randomized Controlled Trial

While Japanese guideline recommends initial control treatment for preschool children with asthma symptoms more than once a month, Western guidelines do not. To determine whether control treatment with montelukast was more effective than as-needed b2-agonists in the population, a randomized controlled trial was conducted. This multicenter, open-label, randomized controlled trial was conducted between September 2009 and October 2013 at 14 institutions in Japan. Eligible patients were children aged 1-5 years who had mild persistent asthma according to the classification by Japanese guideline for childhood asthma (JGCA). For children with 2-5 years of age, those who had episodes of asthma symptoms more than once a month but less than once a week were eligible for the study. Patients were excluded from the study if they had received either of the following treatment within 6 months before the study: oral anti-allergic medicine including leukotriene antagonists, inhaled or oral corticosteroids, sustained-release theophylline, or long-acting b2-agonists. Patients were randomly assigned in a 1:1 ratio to receive montelukast or as-needed b2-agonists using a minimization method with the stratification factors of age (1 year vs. 2-5 years), sex, with or without atopic dermatitis, and with or without parental history of asthma.

During the treatment period of 48 weeks, patients in the montelukast group received one packet of 4 mg oral granules once a day. In the no-controller group, patients inhaled b2-agonist as an as-needed reliever medication according to the GINA report. In both groups, concomitant use of oral anti-allergic drug, sustained-release theophylline, long-acting b2-agonist, or oral corticosteroid was prohibited. The primary endpoint was the number of acute asthma exacerbations before starting step-up treatment with ICS. From September 2009 to November 2012, 93 patients (47 in the montelukast group and 46 in the no-controller group) were enrolled into the study. All patients were included in the analysis. During the study, 13 patients (28%) in the montelukast group and 23 patients (50%) in the no-controller group had acute exacerbations with the mean numbers of 0.9 and 1.9/year, respectively (hazard ratio 0.45, 95% confidence interval 0.21 to 0.92; P=0.027). In addition, 10 (21%) and 19 (41%) patients received step-up treatment, respectively. Cumulative incidence of step-up treatment was significantly lower in the montelukast group (hazard ratio 0.45, 95% confidence interval 0.21 to 0.92; P= 0.033). In conclusion, it is found that montelukast is an effective control treatment for preschool children who have asthma symptoms more than once a month but less than once a week.

Clinical Effect of Treating Secondary Asthma Attacks of Children Caused by Mycoplasma pneumoniae with Combined Therapy of Montelukast and Azithromycin

Mycoplasma pneumoniae is one of the most common pathogens for respiratory tract infection. It can occur at any age, but children before the school age are more vulnerable. One of the reasons for this may be related to the fact that immunologic function in children is not fully developed. The clinical manifestation of Mycoplasma pneumoniae infection is not typical and may be easily misdiagnosed. During the early stages of the infection, sick children may show symptoms such as coughing and fever. As the condition deteriorates, children may develop cough-type-asthma. Delayed treatment will lead to persistent adult asthma. Usually, the outcome of treatment by single antibiotic is not ideal, and the wide application of antibiotics can lead to an increase in antibiotic resistance. Mycoplasma pneumoniae strains are drug-resistant. A study was conducted to discuss the clinical effects of treating secondary asthma attacks of children caused by Mycoplasma pneumoniae with combined therapy of montelukast and azithromycin, and in the study promising results were achieved. Ninety-six children diagnosed with secondary asthma attacks caused by Mycoplasma pneumoniae were enrolled in this study. Patients were divided into two groups: the control group (n=49) and the observation group (n=47). There were 23 males and 26 females in the control group, aged between 3 to 14 years. The course of disease was 5 to 28 days. In the observation group, there were 26 males and 21 females; aged 2 to 14 years. The course of disease was 4 to 25 days. Patients in both groups received regular anti-infection therapy, while antibiogram tests were conducted on the sputum and blood cultures. Patients in the control group were treated with azithromycin and bronchodilators or glucocorticoid and patients in the observation group were treated with combined therapy using montelukast and azithromycin, bronchodilators or glucocorticoid. The lung function indexes were measured before treatment and three weeks after treatment in both groups. These indexes included tidal volume (V-T), ratio of time to reach peak tidal expiratory flow to total expiratory time (t-PTEF/t-E%) and maximum inspiratory and expiratory flow (MIF/MEF). Also T lymphocyte subpopulation, cytokines levels, asthma control rate and recurrence rate were compared between groups before and after treatment. The levels of V-T, t-PTEF/t-E and MIF/MEF were in both groups increased after treatment, but a more significant improvement in the observation group was seen. The CD4+ and CD4+CD8+ levels in both groups also increased after the intervention, while the level of CD8+ decreased. The IL-10, IL-17 and TGF-β levels decreased more intensely in the observation group. Thus it is found that using combined therapy of montelukast and azithromycin for treating the secondary asthma attacks of children by Mycoplasma pneumoniae can relieve immunological and inflammatory reactions and improve the lung function.