Allergology International xxx (2017) 1–4

Contents lists available at ScienceDirect

Allergology International

journal homepage: http://www.elsevier.com/locate/alit

Invited review article

Therapeutic approaches of asthma and COPD overlap

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ARTICLE INFO

Article history:
Received 17 July 2017
Received in revised form
3 August 2017
Accepted 3 August 2017
Available online xxx

Keywords:
Inhaled corticosteroids
Long-acting bronchodilators
Long-term management of ACO
Severity of ACO
Treatment of ACO exacerbation

ABSTRACT

Asthma and COPD overlap (ACO) is an important clinical phenotype, due to the low-health-related quality of life (QOL), rapid decline in lung function, frequent exacerbation, and high economic burden. However, no large-scaled therapeutic trials of ACO have been conducted. At present, ACO is treated according to asthma/COPD guidelines. The goals of ACO treatment are to relieve symptoms and improve QOL and lung functions. Treatment must also prevent disease progression, airway remodeling, exacerbation, complications, and comorbidities. To achieve these goals, ACO needs first to be assessed based on pathophysiological findings. Comprehensive long-term management includes medication, reduction of risk factors, environmental improvement, patient education, rehabilitation, and vaccination. Drug treatment for ACO employs a combination of inhaled corticosteroids (ICSs) and long-acting bronchodilators; long-acting muscarinic antagonists and/or long-acting β_2-agonists. The dose of ICS is determined according to ACO severity. Leukotriene receptor antagonists and theophylline are used as add-on drugs. Macrolides and expectorants are recommended for reduction of mucus hypersecretion. Anti-IgE and anti–IL-5 antibodies, oral corticosteroids, and oxygen therapy are additional treatments for the most severe ACO. The therapeutic effects are evaluated using lung function tests, eosinophil counts in sputum and blood, FeNO, and symptom questionnaires. ACO exacerbation is treated by inhalation of short-acting β_2-agonist and systemic corticosteroids. The doses of corticosteroids are determined based on the asthma/COPD component of the exacerbation. Administration of antibiotics is recommended if sputum is purulent. Referral to specialists is necessary in cases of inability to control symptoms by medication, uncertain diagnosis with atypical features, or severe complications and comorbidities.

Introduction

Asthma and COPD overlap (ACO) is an important clinical phenotype, because relative to asthma and COPD alone, ACO is associated with a low-health-related quality of life,[1] a rapid decline in lung function,[2] more frequent exacerbation,[3–5] and a high economic burden.[6] There is currently no adequate evidence-based consensus on ACO treatment. Possible reasons for this are that in clinical trials for asthma, the patients with smoking history and the elderly patients are excluded, whereas in clinical trials for COPD, patients complicated with asthma have been excluded. No large-scaled clinical trial of ACO has been conducted so far. In this article, we propose therapeutic approaches for ACO based on guidelines of asthma and COPD.

Goals for treatment and management of ACO

The current recommended treatment for ACO refers to asthma and COPD guidelines. Since ACO has characteristics of both asthma and COPD, treatment goals and recommended management are determined as shown in Table 1. To achieve these goals, the following points are considered:

Assessment of ACO patients based on pathophysiological findings

The assessment of phenotype and severity from aspects of both asthma and COPD is done by referring to various biomarkers, lung function tests, image findings, and QOL questionnaires. Disease progression and response to treatment are then carefully evaluated.

Identification and reduction of exposure to risk factors

Identification and reduction of exposure to risk factors are important in the management of ACO. Risk factors that should be avoided include exposure to allergens and air pollutants, smoking, airway infections, drugs, stress, and overwork.

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Peer review under responsibility of Japanese Society of Allergology.

http://dx.doi.org/10.1016/j.alit.2017.09.002

Please cite this article in press as: Kondo M, Tamaoki J, Therapeutic approaches of asthma and COPD overlap, Allergology International (2017), http://dx.doi.org/10.1016/j.alit.2017.09.002

Table 1
Goals of ACO treatment.

1	Relieve symptoms and improve QOL
2	Improve pulmonary functions and bronchial hyperreactivity
3	Improve and maintain exercise tolerance and physical activities
4	Prevent disease progression and airway remodeling
5	Prevent exacerbation
6	Prevent and treat complications and comorbidities
7	Reduce mortality
8	Prevent adverse effects by therapeutic agents

Long-term management of stable ACO

Both asthma and COPD need appropriate long-term management. Similar to asthma and COPD alone, in addition to medication according to disease severity, ACO requires comprehensive management including improvement of the patient's environment, patient education, respiratory rehabilitation, vaccinations against influenza and pneumococcus, nutritional therapy, oxygen therapy, and ventilatory support.

Principle of ACO treatment

The principle of ACO treatment is to address both asthma and COPD. In practice, ACO should be treated more intensively because it tends to be more severe relative to asthma and COPD alone.

Inhaled corticosteroid (ICS) and bronchodilators

The criteria for diagnosis of ACO are not well defined. If ACO is suspected symptomatically, treatment is immediately required. ICS treatment will be initiated if it has not been previously administered (Table 2). Simultaneously, long-acting β_2 agonist (LABA) and long-acting muscarinic antagonist (LAMA) are added as bronchodilators (Table 3). An important principle of ACO management is to avoid treatment with LABA alone (LABA monotherapy) without ICS[7] in patients with asthma symptoms. There is no definite consensus about whether ICS/LABA or ICS/LAMA is beneficial for ACO treatment. It is reported that in COPD, LAMA is a better preventative of exacerbations compared to LABA.[8] A comparative study is also needed in ACO.

The recommended dose of ICS for ACO treatment has yet to be established. Most of ACO patients are smokers, and are generally less responsive to ICS than non-smokers.[9] As a result, the benefit of ICS for treatment of ACO relative to asthma alone needs to be studied. At present, a combination of ICS and a long-acting bronchodilator is required from the beginning of treatment, and it is reasonable to determine the dose of ICS according to severity.

Table 2
Recommended doses of inhaled corticosteroids (Treatment of asthma).

Drugs	Low dose	Medium dose	High dose
BDP-HFA (Qvar® Aerosol)	100–200 μg/day	400 μg/day	800 μg/day
FP-HFA (Flutide® Aerosol)	100–200 μg/day	400 μg/day	800 μg/day
CIC-HFA (Alvesco® Inhaler)	100–200 μg/day	400 μg/day	800 μg/day
FP-DPI (Flutide® Diskus, Flutide® Rotadisk)	100–200 μg/day	400 μg/day	800 μg/day
MF-DPI (Asmanex® Twisthaler)	100–200 μg/day	400 μg/day	800 μg/day
BDP-DPI (Pulmicort® Turbuhaler)	200–400 μg/day	800 μg/day	1600 μg/day
BIS (Pulmicort® Ampul)	0.5 mg/day	1.0 mg/day	2.0 mg/day

BDP-HFA, beclometasone dipropionate hydrofluoroalkane; FP-HFA, fluticasone hydrofluoroalkane; CIC-HFA, ciclesonide hydrofluoroalkane; FP-DPI, fluticasone propionate dry power inhaler; MF-DPI, monetasone furoate dry powder inhaler; BUD-DPI, budesonide dry powder inhaler; BIS, budesonide inhalation suspension.

Other therapeutic agents

Macrolides have a possibility to reduce exacerbations of ACO. Macrolides reduce the risk of acute exacerbations in patients with COPD due to their antiviral action and due to their ability to suppress activation of neutrophils. Macrolides also improve airway clearance by suppressing mucus hypersecretion.[10] Moreover, analysis of patients with non-eosinophilic severe asthma (blood eosinophils $\leq 200/\mu l$) revealed that macrolides were able to reduce the frequency of exacerbations.[11] Therefore, macrolides may be effective for treatment of patients with neutrophilic inflammation.

Anti-IgE and anti−IL-5 antibodies inhibit eosinophilic inflammation, and therefore may be useful for treatment of the asthmatic component in ACO pathophysiology. There is no evidence for the benefit of treating COPD with asthma therapeutic agents, such as leukotriene receptor antagonists (LTRA). As a result, it is unknown whether treatment with LTRA is effective on ACO. Mucolytic agents such as carbocysteine may improve airway clearance.

Practical application of ACO treatment

Based on the diagnosis, there are three approaches for treatment of ACO patients. The first approach is for untreated patients diagnosed with ACO for the first time. The second approach is for asthma patients diagnosed with ACO. The third approach is for COPD patients diagnosed with ACO. The treatment in each case is described below.

Patients diagnosed with ACO for the first time

First, ACO severity is determined. Asthma severity in the Japanese guidelines for asthma prevention/management[12] is classified as mild intermittent, mild persistent, moderate persistent, severe persistent, or most severe persistent. COPD severity in the Japanese guidelines for diagnosis/treatment[13] is classified as stages I to IV. Based on both guidelines, we propose to classify ACO severity as grades 1 to 4 (Table 4). If the severity of asthma does not correlate with COPD stage, a grade with a higher severity (or more advanced disease) is adopted. For example, if a patient was diagnosed with a moderate persistent asthma and COPD of Stage I, the severity of ACO is determined as Grade 2. Both ICS and bronchodilators are used to treat all ACO grades regardless of severity (Table 5).

Asthma patients diagnosed with ACO

ACO may be suspected in patients diagnosed with asthma alone, based on smoking history, insufficient airway reversibility in pulmonary function tests, emphysematous change, and chronic and progressive shortness of breath. In these cases, it is recommended to add LAMA for treatment of asthma (ICS or ICS/LABA ± LTRA) in order to improve symptoms. Importantly, ICS treatment is continued even if the airflow obstruction is fixed. LTRA may be also effective in cases of atopic predisposition.[14] Pharmacological agents are selected based on severity with reference to Table 5.

COPD patients diagnosed with ACO

ACO may be suspected in patients treated for COPD, based on symptoms of paroxysmal dyspnea, wheezing, airway reversibility,

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