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Targeted therapy of bronchitis in obstructive airway diseases ☆

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ABSTRACT

Guidelines for the management of obstructive airway diseases do not emphasize the measurement of bronchitis to indicate appropriate treatments or monitor response to treatment. Bronchitis is the central component of airway diseases and contributes to symptoms, physiological and structural abnormalities. It can be measured directly and reliably by quantitative assay of spontaneous or induced sputum. The measurement is reproducible, valid, and responsive to treatment and to changes in disease status. Bronchitis may be eosinophilic, neutrophilic, mixed, or paucigranulocytic (eosinophils and neutrophils not elevated). Eosinophilic bronchitis is usually a Th2 driven process and therefore a sputum eosinophilia of greater than 3% usually indicates a response to treatment with corticosteroids or novel therapies directed against Th2 cytokines such as IL-4, IL-5 and IL-13. Neutrophilic bronchitis which is a non-Th2 driven disease is generally a predictor of response to antibiotics and may be a predictor to therapies targeted at pathways that lead to neutrophil recruitment such as IL-8 (eg anti-CXCR2), IL-17 (eg anti-IL17) etc. Paucigranulocytic disease may not warrant anti-inflammatory therapy. Several novel monoclonals and small molecule antagonists have been evaluated in clinical trials with variable results and several more are likely to be discovered in the near future. The success of these agents will depend on appropriate patient selection by accurate phenotyping or characterization of bronchitis.

Contents

1. Introduction

Bronchitis or airway inflammation is the hallmark of obstructive airway diseases such as asthma and Chronic Obstructive Pulmonary Disease (COPD). Although "bronchitis" has been traditionally used to refer to symptom constellations such as in "acute bronchitis" or chronic bronchitis", the term has been used in this review to refer to the presence of "airway inflammation". In other words, "bronchitis" may be defined as the "presence of cellular inflammation in the bronchi". Other diseases affecting the airways such as bronchiectasis and cystic fibrosis are also associated with bronchitis; however these diseases will not be the focus of the review presented here.

Obstructive airway diseases are usually treated with bronchodilators, corticosteroids and other specific medications such as leukotriene antagonists and monoclonal antibodies directed against IgE based on the clinical judgment or physiological measures and guided

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by international guidelines which do not necessarily include measuring bronchitis (GINA guidelines for asthma, 2006; GOLD guidelines for COPD, 2011). The major focus of research in airway disease management is currently on development of drugs directed at various mediators involved in the pathogenesis of bronchitis (Catley et al., 2011). Airway disease is heterogeneous; therefore the success of these new drugs depends on accurate phenotyping of the disease. This is best done on the basis of the nature of underlying airway inflammation or bronchitis as this is also indicative of the mediators involved (Hargreave & Nair, 2009). It is therefore important to be able to measure bronchitis in a safe, reliable and cost-effective manner. Current evidence suggests that using methods such as sputum quantitative assays to examine bronchitis and guide treatment can lead to better outcomes (Green et al., 2002a, 2002b; Chlumsky et al., 2006; Jayaram et al., 2006; Siva et al., 2007) and is also therefore cost effective (D'silva et al., 2008).

This review will discuss the various components of airway diseases, measurement of bronchitis, phenotyping based on the nature of bronchitis and the treatment of obstructive airway diseases by targeting its bronchitic component as guided by sputum quantitative assays. Some investigational new drugs will also be reviewed subsequently.

2. Bronchitis as a component of airway diseases

Bronchitis or airway inflammation is one of the three fundamental components of all airway diseases in general (Hargreave & Parameswaran, 2006; Kraft, 2006). The other two are airflow obstruction and airway hyperresponsiveness. Obstructive airway diseases, therefore, have airflow obstruction in addition to one or both of the other two components. The bronchitic component has been thought to be the most important and the central component of airway diseases (Hargreave & Parameswaran, 2006). It is responsible for symptoms, variable airflow limitation through release of bronchoconstrictor mediators, and chronic airflow limitation through remodeling and structural changes. Bronchitis is also the primary cause for exacerbations and increased airway responsiveness (Hargreave & Parameswaran, 2006; Nair & Hargreave, 2010).

The relationship between these fundamental components is complex and each of these can be presently dissociated from each other. Therefore airflow obstruction may occur alone or together with airway hyperresponsiveness and/or airway inflammation. In fact, airflow obstruction may even be absent in asthma in stable disease. Such a situation might be encountered after adequate treatment of bronchitis. In COPD however, some amount of airflow obstruction is almost always present. The underlying pathophysiology of such dissociation is still not completely understood and may represent different phenotypes of airway diseases. However its occurrence has great implications in treatment. For example, treating a patient with isolated uncontrolled bronchitis with additional doses of bronchodilators for symptom control is inappropriate. Therefore, it is of prime importance to be able to tease out the three components (airway inflammation, airway hyperresponsiveness and airflow obstruction) of airway diseases and recognize the particular component that is responsible for increased symptoms in a certain patient prior to prescribing any form of therapy.

3. Measuring bronchitis

Bronchitis cannot be measured by measuring airflow by spirometry. In fact, only a weak association between airway inflammation and spirometry has been observed (Haley & Drazen, 1998; Van den berge et al., 2001). The clinical assessment of the presence of bronchitis is also often inaccurate, as uncontrolled bronchitis may be present even in the absence of clinical symptoms (Parameswaran et al., 2000). The relationship between airway hyperresponsiveness and bronchitis is variable too. This was affirmed when the anti-eosinophil drug, mepolizumab, did not reduce airway hyperresponsiveness despite significantly reducing sputum eosinophil counts in a severe asthma clinical trial (Haldar et al., 2009). These observations suggest that bronchitis needs to be measured directly and objectively and one way to achieve this is to utilize sputum quantitative assays. It is a specific, sensitive, repeatable and valid (Pizzichini et al., 1996; Nair & Hargreave, 2007) method of measuring sputum cell counts noninvasively and the normal values have also been well established (Belda et al., 2000). The sensitivity and specificity of sputum eosinophils were found to be 63% and 100% respectively when the cut-off for the differential count of sputum eosinophils was 2%. Sputum eosinophils are also more accurate than blood eosinophils for measuring airway inflammation as estimated by comparing area under Receiver Operating Characteristic ROC curves between asthmatics and normal controls (Pizzichini et al., 1997a, 1997b). The test also has a high within subject, within sample and inter-observer repeatability (Iredale et al., 1994; in 't Veen et al., 1996; Pizzichini et al., 1996). The measurement properties and validation of sputum cell counts are extensively summarized elsewhere (Parameswaran & Hargreave, 2000).

When patients cannot produce sputum spontaneously it can be safely induced with increasing concentrations of hypertonic saline (3%, 4% and 5%) or with isotonic saline even in patients with severe airflow limitation (Pizzichini et al., 1998a, 1998b; Vlachos-Mayer et al., 2000; Wilson et al., 2006). Patients are usually given pretreatment with inhaled salbutamol prior to administering hypertonic saline to inhibit possible bronchoconstriction during sputum induction. Also, after each inhalation period an FEV 1 is measured for safety; the procedure being abandoned if there occurs a 20% fall in FEV1 at any stage of sputum induction. Additional precaution is taken in patients with FEV1 of less than 1 l. Induction is commenced with inhalation of isotonic saline and a concentration of greater than 3% is not generally employed. The process of sputum induction may thus be considered a very safe procedure and can be implemented in routine clinical practice (D'silva et al., 2011). The sputum quantitative assay entails selection of a small quantity of sputum from either a spontaneous or induced sample, treatment with a sputolysin (dithiothreitol) and subsequent filtering to obtain a homogenous suspension of cells. The total cell count and viability are determined in a hemocytometer, while differential counts are obtained from Wright stained cytospins (Efthimiadis et al., 1997; Kelly et al., 2001).

However, sputum quantitative assays are not widely available, require special training, equipment and the facilities of a wet laboratory. Additionally, patients may not always be able to produce sputum in sufficient quantities even with saline induction. This has led to a search for surrogate measures reflective of the presence of airway inflammation that are easily available and need lesser expertise. Several such measures have been evaluated so far such as peripheral blood eosinophils or its activation marker eosinophil cationic protein (ECP) (Pizzichini et al., 1997a, 1997b, 1999a, 1999b), fraction of NO in exhaled breath (Pijnenburg et al., 2005; Smith et al., 2005; Taylor et al., 2006; Shaw et al., 2007; Pendharkar & Mehta, 2008; Nair et al., 2010), measuring hydrogen peroxide in exhaled breath condensate (Ko et al., 2007), sputum fluid phase measurements (ECP, eosinophil derived neurotoxin and eosinophil peroxidase) and urine metabolomics (Wojnarowski et al., 1999; Rabinovitch, 2007; Saude et al., 2011). The disadvantage of all these measures is that none of these can measure bronchitis directly (Table 1). Biopsies obtained at bronchoscopy (bronchial and/or transbronchial) or bronchalveolar lavage sample can be considered as "the gold standard" as it gives direct measures of airway inflammation. However its use is generally reserved for research purposes mainly due to its invasive nature.

4. Phenotypes of bronchitis

Bronchitis is the result of cells infitratinginto the airways in response to a variety of stimuli. Intuitively, the best method of phenotyping bronchitis is by the type of cellular infiltrate. As described earlier induced sputum is by far the best noninvasive method for estimating this