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Use of biologics to treat acute exacerbations and manage disease in asthma, COPD and IPF

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ABSTRACT

A common feature of chronic respiratory disease is the progressive decline in lung function. The decline can be indolent, or it can be accelerated by acute exacerbations, whereby the patient experiences a pronounced worsening of disease symptoms. Moreover, acute exacerbations may also be a marker of insufficient disease management. The underlying cause of an acute exacerbation can be due to insults such as pathogens or environmental pollutants, or the cause can be unknown. For each acute exacerbation, the patient may require medical intervention such as rescue medication, or in more severe cases, hospitalization and ventilation and have an increased risk of death.

Biologics, such as monoclonal antibodies, are being developed for chronic respiratory diseases including asthma, COPD and IPF. This therapeutic approach is particularly well suited for chronic use based on the route and frequency of delivery and importantly, the potential for disease modification. In recent clinical trials, the frequency of acute exacerbation has often been included as an endpoint, to help determine whether the investigational agent is impacting disease. Therefore the significance of acute exacerbations in driving disease, and their potential as a marker of disease activity and progression, has recently received much attention. There is also now a need to standardize the definition of an acute exacerbation in specific disease settings, particularly as this endpoint is increasingly used in clinical trials to also assess therapeutic efficacy. Moreover, specifically targeting exacerbations may offer a new therapeutic approach for several chronic respiratory diseases.

Contents

1. Introduction

The chronic respiratory diseases asthma, chronic obstructive pulmonary disease (COPD) and idiopathic pulmonary fibrosis (IPF), are generally characterised as stable or as causing a slowly progressive decline in lung function. All three are heterogenous in both progression

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and underlying pathology. For asthma, specific disease endotypes are being recognised and profiled. COPD patients have distinct and overlapping features ranging from chronic bronchitis and consolidated inflammation, to pronounced lung destruction and emphysema. Finally, in IPF, newly diagnosed patients can have drastically altered rates of disease progression that are unrelated to lung function. However one common feature of all is that acute exacerbations can have a dramatic effect on the health and well-being of patients, often leading to frequent and prolonged hospital stays, rapid disease worsening and even premature death. Indeed, exacerbations tend to cluster, meaning the strongest predictor of future exacerbations is a (recent) history of exacerbations. An acute exacerbation also worsens airway inflammation and oxidative stress, leading to tissue oedema, mucous hypersecretion and ultimately damage to lung structure (e.g. alveolar/airway wall thickening), all of which exacerbates the underlying chronic inflammation present in stable disease (Holland, 2014). The estimated costs of exacerbations vary widely across diseases and study design: For example, Blasi and colleagues calculated an average cost of €6785 per exacerbation of COPD (Blasi et al., 2014), for IPF very recent data puts an average cost of €11,666 per exacerbation (Morell et al., 2016). The largest component of the total costs was hospitalization and, not surprisingly, costs were correlated with exacerbation severity. Data for acute exacerbations with asthma are more difficult to find, although a recent Spanish study put the average cost at €1550 per exacerbation ranging up to €3543 for a severe exacerbation (Borderias Clau et al., 2005). Thus, attenuating acute exacerbations is becoming a well-recognized quantitative measure in the clinical development of novel therapeutics for these diseases. Preventing and managing exacerbations of respiratory disease, and how the development of new medications, and in particular, biological agents may provide a significant therapeutic benefit in these often devastating disease episodes will be the focus of this review. The biological agents discussed are summarised in Table 1.

Table 1
Summary of protein-based therapeutics discussed in this review that have been assessed clinically, the target/pathway they modulate and the relevant references associated with either the development of the therapeutic or the clinical study/studies that have been published on each molecule.

Name	Pathway	Relevant references
Altrakincept	Sol. Recomb IL4R	Borish et al. (2001)
Benralizumab	Anti-IL5R	Brightling et al. (2014); Castro et al. (2014); Ghazi, Trikha, and Calhoun (2012); Nowak et al. (2015))
Brodalumab	Anti-IL17RA	Busse et al. (2013)
Carlumab	Anti-CCL2	Raghu et al. (2015)
Daclizumab	Anti-CD25	Busse et al. (2008)
Dupilimab	Anti-IL4Ra	Wenzel et al. (2013)
Etanercept	TNFR2-Fc	Aaron et al. (2013); Holgate et al. (2011)
Golimumab	Anti-TNFa	Wenzel et al. (2009)
Infliximab	Anti-TNFa	Rennard et al. (2007)
Keliximab	Anti-CD4	Kon et al. (1998)
Lebrikizumab	Anti-IL13	Corren et al. (2011)
Ligelizumab	Anti-IgE	Gauvreau et al. (2016)
Mepolizumab	Anti-IL5	Abonia and Putnam (2011); Bel et al. (2014); Flood-Page et al. (2007); Leckie et al. (2000); Nair et al. (2009); Ortega et al. (2014)
Omalizumab	Anti-IgE	Busse et al. (2001, 2011); Corne et al. (1997); Garcia et al. (2013); Holgate et al. (2004); Hanania et al. (2013); Normansell, Walker, Milan, Walters, and Nair (2014); Shields et al. (1995)
Reslizumab	Anti-IL5	Castro et al. (2015)
Rituximab	Anti-CD20	Boross and Leusen (2012); Donahoe et al. (2015); Keir et al. (2014)
Simtuzumab	Anti-LOXL2	Barry-Hamilton et al. (2010)
Tralokinumab	Anti-IL13	Brightling et al. (2015); Murray et al. (2014); Piper et al. (2013)

2. Definitions of acute exacerbation in each disease setting

Our appreciation of the clinical significance of acute exacerbations of chronic lung disease (AE-CLD) has increased in the last few years. Formal definitions of acute exacerbation are based upon clinical findings and vary somewhat; in all cases the definitions include a subjective change in symptoms. Disease-specific definitions are outlined below:

The Global Initiative for Asthma (GINA) defines an exacerbation is an episode of progressive increase in shortness of breath, cough, wheezing or chest tightness (or some combination), accompanied by decreases in respiratory flow quantified by measurement of lung function. The American Thoracic Society and European Respiratory Society (Chung et al., 2014) have sought to also better define asthma exacerbations and their definition in clinical practice is that, "exacerbations are identified as events characterized by a change from the patient's previous status", further differentiating them into severe and moderate asthma exacerbations. Severe exacerbations are defined as events that require urgent action on the part of the patient and physician to prevent a serious outcome, such as hospitalization or death.

Definitions of acute exacerbations of COPD are varied. One commonly used definition from the Global Alliance of Obstructive Lung Disease (GOLD) defines a COPD exacerbation as 'an acute event characterized by a worsening of the patient's respiratory symptoms that is beyond normal day-to-day variations and leads to a change in medication' (Agusti et al., 2013).

In interstitial lung disease (ILD), a usually steady decline in lung function and symptoms may be interrupted by an acute deterioration in exercise capacity and lung function which often results in hospitalisation and death (Johannson & Collard, 2013; Ryerson, Cottin, Brown, & Collard, 2015). Definitions of acute exacerbations of pulmonary fibrosis (AE-PF), have been described as "an acute worsening of dyspnea and lung function with an unidentifiable cause" (Richeldi et al., 2011). For clinical trials, AE-PF have been defined as an unexplained worsening in dyspnea over the previous month. In conjunction with this there is a requirement for radiological evidence of new airspace opacities on high resolution computed tomography (HRCT) scanning and exclusion of underlying infection by bronchoalveolar lavage or endotracheal aspirate. These criteria are extremely difficult to satisfy, even in a research setting, where very unwell patients are often not able to tolerate bronchoscopy. It has recently been proposed that the exclusion of underlying causes may be irrelevant, as both underlying lung pathology and clinical outcome appear similar in patients with acute worsening of their disease, no matter whether the underlying precipitating factor is known or unknown (Collard et al., 2013; Johannson & Collard, 2013; Ryerson et al., 2015). Recently, a working group of the ERS and ATS defined an AE-PF as a clinically significant respiratory deterioration characterized by evidence of new, widespread alveolar abnormality (Collard et al., 2016). This last point distinguishes AE-PF from exacerbations of both asthma and COPD and also provides an explanation for the very high 30 day and 1 year mortality observed following a AE-PF.

3. Triggers of acute exacerbation

From the descriptions above, what is clear is that while there are likely to be both common and unique triggers, diverse terminology complicates comparisons and undermines perspectives on the aetiology of risk factors and other associations for acute exacerbation, which are in turn critical for both prevention strategies and disease management Table 2).

3.1. Asthma triggers

Asthma in particular exhibits substantial variability in its pathophysiological presentation, which has led to the concept of disease endotypes (Anderson, 2008; Corren, 2013; Hekking & Bel, 2014). In this context, AE-asthma are likely precipitated by different factors – thus it is possible and even probable that exacerbation endotypes also exist. The frequency and causes of AE-asthma are therefore complex