Unusual asthma syndromes and their management

Jaymin B. Morjaria and Jack A. Kastelik

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Abstract: Asthma usually presents with symptoms of wheeze, dyspnoea and cough. However, clinicians should be aware of atypical presentation of this disorder when cough is the main or only symptom in conditions such as cough-variant asthma, nonasthmatic eosinophilic bronchitis and atopic cough. Early diagnosis and treatment of these conditions with inhaled corticosteroids improves symptoms in the majority of patients. Up to 10% of patients with asthma remain poorly controlled in spite of optimal standard therapy. These patients have been encompassed under the term ‘treatment-refractory asthma’ (TRA), have the greatest morbidity and are responsible for more than 50% of healthcare costs. In this review we discuss investigations, management and pathophysiology of the various phenotypes of atypical presentations of asthma as well as novel biological agents licensed and those that have been reported in clinical trials in terms of their efficacy and safety in TRA.

Keywords: atopic cough, biologics, cough, eosinophilic bronchitis, monoclonal antibodies, severe asthma

Introduction

Asthma affects 5.4 million people in the UK [Asthma UK, 2010] and around 300 million people in the world [Braman, 2006]. Its prevalence is 15–20% in children and 5–10% in adults, and it is believed that it will continue to rise. Over 12 million working days in the UK are lost as a result of asthma-related problems [Asthma UK, 2010]. Moreover, in the financial year 2006–2007 around 80,000 emergency asthma admissions have been reported, with 41% of these being children under the age of 14 years. In the majority of patients, international guidelines-based management of the condition ensures that asthma is well controlled with inhaled corticosteroid (ICS) therapy either alone or in combination with long-acting β_2 agonists (LABAs) [BTS/SIGN, 2008]. Other agents such as antileukotriene agents and theophyllines have also been used with good effect. However, up to 10% of patients with asthma remain poorly controlled in spite of optimal standard therapy. Although this represents a small proportion of asthma sufferers, they have the greatest morbidity, are at risk of dying and are responsible for more than 50% of the healthcare costs related to asthma; hence, there is an unmet need in this group of poorly controlled asthmatics

[Chanez *et al.* 2007; Antoncelli *et al.* 2004; European Network for Understanding Mechanisms of Severe Asthma, 2003]

Asthma is a heterogeneous condition that at one end of the spectrum is difficult to diagnose because of the atypical presenting symptoms, for example cough, and at the other end in patients with established disease where the management is limited by the lack of current therapeutic options available to us. The latter is often termed severe asthma. However, it needs to be clarified that severe asthma can be divided further into ‘difficult-to-treat’ and ‘treatment-refractory asthma’ (TRA). Hence, it is pivotal that the two entities are managed appropriately.

Difficult-to-treat asthma may arise due to a number of reasons [Morjaria and Polosa, 2010; Holgate and Polosa, 2006]. The three main reasons are, excluding conditions that mimic severe asthma, comorbidities, asthma triggers and, most importantly, lack of compliance with asthma medications. Conversely, TRA includes patients who are inadequately controlled with their medication as per international guidelines [BTS/SIGN, 2008], i.e. on steps IV and V of the Global Initiative for Asthma (GINA) and

Correspondence to:

Jaymin B. Morjaria MD, MRCP

IIR Division, School of Medicine, University of Southampton, Southampton General Hospital, Southampton SO16 6YD, UK
jbm@soton.ac.uk

Jack A. Kastelik, MD, FRCP

Division of Respiratory Medicine, Hull and East Yorkshire NHS Trust, University of Hull, Hull York Medical School, Castle Hill Hospital, Castle Road, Cottingham HU16 5JQ, UK

Table 1. Atypical asthma syndromes.

Syndrome	PEF variability	Airway obstruction	Airway hyper-responsiveness	Sputum eosinophilia	Atopy	Steroid response	Biopsy findings
Classic asthma	Yes	Yes	Yes	Yes	±	Yes	-
Cough-variant asthma	—	No	Yes	Yes	No	Yes	↓ thickness subepithelial layer compared with classic asthma
Eosinophilic bronchitis	No	No	No	Yes	No	Yes	↓ mast cells in airways smooth muscles compared with classic asthma
Atopic cough	No	No	No	Yes	Yes	Yes	Eosinophils in submucosa of trachea and bronchi

PEF, peak expiratory flow; ±, may be present; ↓, reduction.

British Thoracic Society/Scottish Intercollegiate Guidelines Network where despite being on high-dose ICS, LABAs and other add-on medications, and managing to establish control over the components of difficult-to-treat asthma, patients remain symptomatic. In contrast, the majority of patients with atypical asthma such as cough-variant asthma, nonasthmatic eosinophilic bronchitis or atopic cough respond to a standard therapy with ICS and antihistamines. The awareness of existence of these conditions and the associated aptitude to diagnose them are the main issues associated with atypical asthma. If atypical asthma is not treated, a proportion of patients may progress to develop classic asthma. For example, over a third of patients with cough-variant asthma may progress to developing classic asthma [Johnson and Osborn, 1991; Braman and Corrao, 1985]. In contrast, only a very small proportion of patients with atopic cough progress to develop classic asthma [Fujimura *et al.* 2003].

In this review we discuss the challenges faced by the clinician in making the diagnosis of atypical asthma. Thus, we describe the investigations and management of cough-variant asthma, atopic cough and nonasthmatic eosinophilic bronchitis. In addition, we discuss the confirmation and phenotyping of TRA as well as providing an overview novel biological agents that are licensed and those that have been reported in clinical trials in terms of their efficacy and safety in TRA. We do not discuss difficult-to-treat asthma, assuming that this has been considered along with compliance before the diagnosis of TRA.

Atypical asthma

The current guidelines acknowledge that the diagnosis of asthma is a clinical one [BTS/SIGN, 2008]. Central to all definitions of asthma is the presence of symptoms such as wheeze, chest tightness, breathlessness or cough and variable airflow obstruction with more recent descriptions of asthma also included presence of airways hyperresponsiveness (AHR) and airways inflammation [BTS/SIGN, 2008]. In a large proportion of patients, the diagnosis of classic asthma is unlikely to cause any difficulties. The patients with classic asthma present with wheeze, dyspnoea or cough. There is day-to-day and diurnal variability in peak expiratory flow (PEF) measurements (Table 1). The bronchoprovocation tests to histamine or methacholine are positive. The spirometry if abnormal usually reveals airways obstruction. However, there are conditions such as cough-variant asthma, nonasthmatic eosinophilic bronchitis and atopic cough that differ from classic asthma in their phenotypic characteristics. Therefore, their diagnosis may be more difficult. Although these conditions may differ phenotypically, eosinophilic airway inflammation forms their common denominator. Whether these conditions embody the 'asthma syndrome' or whether they represent independent entities *per se* remains a matter of discussion [Mcgarvey *et al.* 2003]. In fact, there is a body of evidence to suggest that some patients with those conditions if not diagnosed or treated appropriately may in fact progress to develop full characteristics of classic asthma [Irwin *et al.* 2006; Fujimura *et al.* 2005a, 2005b, 2005c, 2003; Brightling *et al.* 2003, 2000a, 2000b, 1999a,

1999b]. Therefore, the awareness and the ability to early diagnose and treat these conditions have important clinical implications.

Cough-variant asthma

Cough-variant asthma remains a common cause of chronic cough [Chung and Pavord, 2008; Kastelik *et al.* 2005; Brightling *et al.* 1999a, 1999b; Palombini *et al.* 1999; Mcgarvey *et al.* 1998; Mello *et al.* 1996; Smyrnios *et al.* 1995; Hoffstein, 1994; Irwin *et al.* 1990, 1981; Poe *et al.* 1989]. In asthma, cough may be present with other symptoms such as wheeze or dyspnoea [Irwin *et al.* 1990, 1981]. However, in a proportion of patients, up to 57% of cases in some series, cough can be the sole manifestation of this condition [Chung *et al.* 2008; Kastelik *et al.* 2005; Brightling *et al.* 1999a, 1999b; Palombini *et al.* 1999; Mcgarvey *et al.* 1998; Mello *et al.* 1996; Smyrnios *et al.* 1995; Hoffstein, 1994; Irwin *et al.* 1997, 1990, 1981; Poe *et al.* 1989; Corrao *et al.* 1979]. In 1979, Corrao and colleagues defined 'cough-variant asthma' as AHR with chronic cough but with absence of wheeze or airway obstruction [Corrao *et al.* 1979]. Since this original description it became apparent that although cough is the predominant respiratory symptom in a proportion of patients with cough-variant asthma, wheeze may also be present [Kastelik *et al.* 2005; Palombini *et al.* 1999; Brightling *et al.* 1999a, 1999b; Mcgarvey *et al.* 1998; Mello *et al.* 1996; Smyrnios *et al.* 1995; Hoffstein, 1994; Irwin *et al.* 1990, 1981, Poe *et al.* 1989;]. In fact, one third of patients originally studied by Corrao and colleagues subsequently developed wheeze [Braman and Corrao, 1985; Corrao *et al.* 1979]. In cough-variant asthma, the peak expiratory flow (PEF) assessment does not show any day-to-day or diurnal variability and the spirometric measurements do not reveal airway obstruction. In addition, atopy is not usually reported. Moreover, AHR to histamine or methacholine are present as well as the sputum eosinophilia [Kastelik, 2008; Morice *et al.* 2007, 2006; Morice and Kastelik, 2003].

Nonasthmatic eosinophilic bronchitis

Nonasthmatic eosinophilic bronchitis was originally described by Gibson and colleagues and is characterized by sputum eosinophilia [Brightling, 2006; Brightling *et al.* 1999a, 1999b; Carney *et al.* 1997; Gibson *et al.* 1989]. In nonasthmatic eosinophilic bronchitis there is no airway obstruction as spirometry measurements are normal. There is also absence of PEF variability

and AHR. However, induced sputum analysis reveals eosinophilia defined as more than 3% of nonsquamous cell eosinophil count [Gibson *et al.* 2002]. Moreover, cough reflex sensitivity is increased.

Atopic cough

Fujimura and colleagues described patients with chronic bronchodilator-resistant nonproductive cough and atopy, and proposed a term of eosinophilic tracheobronchitis with airway hypersensitivity or 'atopic cough' [Fujimura *et al.* 1992]. 'Atopic cough' is characterized by atopy defined as one or more of the following: blood or sputum eosinophilia; elevated total or specific immunoglobulin (Ig) E levels; or positive skin prick test [Fujimura *et al.* 2000, 1997, 1992]. In addition, in atopic cough there is chronic bronchodilator-resistant nonproductive cough, absence of variable airflow obstruction and normal bronchial provocation challenge [Dicpinigaitis, 2006; Fujimura *et al.* 2000, 1997, 1992]. This condition is characterized by an increased cough response to inhaled capsaicin, presence of eosinophils in the sputum and the submucosal biopsies of trachea and bronchi but not in the bronchoalveolar lavage (BAL) [Fujimura *et al.* 2005, 2003, 2000, 1997, 1992]. However, there remains discussion amongst the experts whether atopic cough is a separate condition that causes chronic cough [Fujimura and Ogawa, 2003; Mcgarvey and Morice, 2003]. Some, in fact, suggested that patients with atopic cough are most likely atopic individuals with cough-variant asthma [Mcgarvey and Morice, 2003]. However, Fujimura and colleagues have defined atopic cough with its specific pathophysiology and lack of progress to classic asthma [Fujimura and Ogawa, 2003]. It is therefore important for clinicians that other common causes of chronic cough such as cough-variant asthma, gastro-oesophageal reflux and rhinitis are investigated and excluded prior to making a diagnosis of atopic cough.

Pathophysiology of atypical asthma

In the recent years there has been an increase in our understanding of the pathophysiology of cough-variant asthma, nonasthmatic eosinophilic bronchitis and atopic cough [Brightling *et al.* 2003, 2002, 2000a, 2000b; Brightling and Pavord, 2000; Niimi *et al.* 2000, 1998]. These three conditions have similar immunopathological characteristics with classic asthma in the form of an eosinophilic-driven inflammatory process.

Whilst eosinophilic inflammation forms a common pathophysiological characteristic of classic asthma, cough-variant asthma, nonasthmatic eosinophilic bronchitis and atopic cough are distinct due to the differences in the location of the inflammatory cells and the thickness of the subepithelial layer reported in these conditions, hence the likely reasons for the phenotypical disparity observed [Brightling *et al.* 2002; Niimi *et al.* 1998].

Cough-variant asthma

The eosinophils play a major part in the pathophysiology of cough-variant asthma [Niimi *et al.* 1998]. Thus, there is evidence for raised eosinophil counts in BAL and tissue from patients with cough-variant asthma [Niimi *et al.* 2000]. However, De Diego and colleagues showed that there was no significant difference between cough-variant asthma and classic asthma in the sputum levels of eosinophilic cationic protein (ECP), interleukin (IL)-8, tumour necrosis factor alpha (TNF- α) and the levels of exhaled nitric oxide (eNO) [De Diego *et al.* 2005]. Similarly, Kanazawa and colleagues were not able to find any difference in the levels of eNO and ECP between patients with cough-variant asthma and those with classic asthma [Kanazawa *et al.* 2005]. However, the levels of vascular endothelial growth factor (VEGF), which may have a role in vascular permeability due to inflammation, were significantly higher in classic asthma. Niimi and colleagues reported that thickening of subepithelial layer in cough-variant asthma was not as pronounced as in classic asthma [Niimi *et al.* 1998]. Matsumoto and colleagues observed that in patients with cough-variant asthma there was thickening of the wall of the central airways [Matsumoto *et al.* 2007]. Although the levels of eNO were raised in cough-variant asthma, they did not differ from the levels of eNO observed in classic asthma [Fujimura *et al.* 2008]. Fujimura and colleagues followed 41 patients with cough-variant asthma of whom seven developed classic asthma [Fujimura *et al.* 2005a, 2005b, 2005c]. AHR and the absence of use of ICSs were the most important predictors of developing classic asthma. As in classic asthma, ICSs in cough-variant asthma reduced AHR [Fujimura *et al.* 2005a, 2005b, 2005c]. However there was no change in cough threshold to inhaled capsaicin irrespective of the use of ICSs suggesting that cough reflex sensitivity is not involved in the mechanisms of cough-variant asthma.

Nonasthmatic eosinophilic bronchitis

The eosinophils have an important role in the pathophysiology of nonasthmatic eosinophilic bronchitis [Brightling *et al.* 2003, 2002, 2000a, 2000b, Brightling and Pavord, 2000; Gibson *et al.* 1998]. In nonasthmatic eosinophilic bronchitis there is eosinophilia in the sputum, BAL and bronchial biopsies. In addition, there are raised sputum levels of ECP and cysteinyl-leukotrienes [Brightling *et al.* 2008, 2000a, 2000b]. Moreover, the levels of BAL eosinophilia, granulocyte-colony stimulating factor and IL-5 gene expression were of similar magnitude in both nonasthmatic eosinophilic bronchitis and classic asthma [Gibson *et al.* 1998]. Brightling and colleagues showed that there was the same degree of submucosal eosinophilia and thickening of the basement membrane and lamina reticularis in both nonasthmatic eosinophilic bronchitis and in classic asthma [Brightling *et al.* 2003, 2002]. However, the number of tryptase positive mast cells in the bundles of airways smooth muscles was lower in nonasthmatic eosinophilic bronchitis compared with classic asthma. In addition, in nonasthmatic eosinophilic bronchitis, the levels of eNO are raised which is similar to the situation observed in classic asthma [Brightling *et al.* 2003, 2002].

Atopic cough

Atopic cough is characterized by eosinophilic tracheobronchitis without eosinophils in BAL fluid and by cough receptor hypersensitivity without AHR. In atopic cough the levels of eNO are lower compared with those observed in cough-variant asthma and classic asthma [Fujimura *et al.* 2008]. In contrast to cough-variant asthma and nonasthmatic eosinophilic bronchitis there is no data regarding the changes within the basement membrane or the distribution of inflammatory cells or process in patients with atopic cough. However, when Kita and colleagues studied the effects of the leukotriene receptor antagonist, montelukast, in atopic cough and cough-variant asthma, the authors observed that cough was suppressed only in patients with cough-variant asthma [Kita *et al.* 2010]. In contrast, montelukast had no effect on cough in patients with atopic cough suggesting different pathophysiological mechanisms of these two conditions. Another suggestion of different underlying mechanisms of these two conditions was suggested by the lower levels of eNO observed in atopic cough compared with those

measured in cough-variant of asthma [Fujimura *et al.* 2008].

Evaluation patients with atypical asthma

The diagnosis of patients with atypical asthma may prove to be a challenge for the clinicians. Therefore, evaluation of those patients and clinical suspicion of atypical asthma syndromes remain important issues. Clinical history may guide towards the diagnosis of atypical asthma. However, clinicians will be required to exclude other common causes of chronic cough including gastro-oesophageal reflux, rhinitis or medications such as angiotensin-converting enzyme (ACE) inhibitors. The spirometry may be of help although in atypical asthma syndromes it will be normal as will the chest radiograph. Bronchoprovocation tests may be positive in classical asthma and cough-variant asthma; however, they will be normal in nonasthmatic eosinophilic bronchitis and atopic cough. Sputum induction will show sputum eosinophilia in all of the atypical asthma conditions. In contrast, eNO levels may distinguish between nonasthmatic eosinophilic bronchitis, cough-variant asthma and atopic cough. Fujimura and colleagues showed that eNO in patients with atopic cough were significantly lower than those in cough-variant asthma and classic asthma [Fujimura *et al.* 2008]. Testing for atopy may be of help in patients with atopic cough. In cough-variant asthma and in nonasthmatic eosinophilic bronchitis atopy is less likely to be present. The evaluation of patients for atypical asthma syndromes should therefore include clinical history and examination, spirometry, chest radiography, bronchoprovocation testing, sputum induction and eNO measurements. However, the diagnosis of atypical asthma syndromes can only be confirmed if response to specific therapy is observed.

Treatment of atypical asthma

The presence of nonproductive cough and positive response to ICSs are characteristic of cough-variant asthma, nonasthmatic eosinophilic bronchitis and atopic cough [Irwin *et al.* 2006; Kastelik *et al.* 2005; Fujimura *et al.* 2005a, 2005b, 2003; Brightling *et al.* 2003, 2000a, 2000b, 1999a, 1999b]. There is some evidence that if cough-variant asthma is not treated early, it may progress to classic asthma and patients may develop symptoms of dyspnoea and wheeze [Kastelik, 2008; Fujimura *et al.* 2003]. In contrast, atopic cough was thought to progress to classic asthma less frequently, especially with

early introduction of treatment with ICSs [Fujimura *et al.* 2003]. Similarly, Matsumoto and colleagues revealed that treatment with ICSs prevent progression from cough-variant asthma to classic asthma [Matsumoto *et al.* 2006]. Fujimura and colleagues examined the effects of ICSs on changes in AHR and cough reflex sensitivity in patients with cough-variant asthma [Fujimura *et al.* 2005a, 2005b]. As with classic asthma, AHR was reduced with ICSs. However, there was no change in cough threshold in patients with cough-variant asthma irrespective whether they were on ICS or not. In some patients with cough-variant asthma, cough improves with leukotriene receptor antagonists, especially if the symptoms are refractory to inhaled bronchodilators or ICSs [Dicpinigaitis *et al.* 2002]. For example, Dicpinigaitis and colleagues observed that in response to the leukotriene receptor antagonist, zafirlukast, both the subjective cough score and cough-reflex sensitivity to inhaled capsaicin were improved in patients with cough-variant asthma that was refractory to inhaled beta agonists and ICSs [Kita *et al.* 2010; Dicpinigaitis *et al.* 2002]. In very severe cases of cough-variant asthma also termed 'malignant cough equivalent asthma' oral corticosteroids may be required [Millar *et al.* 1998]. In cases of nonasthmatic eosinophilic bronchitis, symptoms usually improve with ICSs [Brightling *et al.* 1999a, 1999b; Carney *et al.* 1997; Gibson *et al.* 1989]. More specifically, there is evidence that ICSs in patients with nonasthmatic eosinophilic bronchitis improve the sputum eosinophilia, cough severity and sensitivity [Brightling *et al.* 2000a, 2000b]. Atopic cough is successfully treated with histamine (H_1) antagonists and/or glucocorticoids and occasionally with antifungal agents [Fujimura *et al.* 2005a, 2005b, 2005c, 2003, 2000, 1992; Ogawa *et al.* 2004]. However, leukotriene receptor antagonists have been shown to have no effect on cough in patients with atopic cough [Kita *et al.* 2010].

Treatment-refractory asthma

TRA remains a frustrating problem not only for the medical staff looking after the patients, but also the patients themselves. A number of clinical definitions of severe asthma have been proposed over the last decade by various groups incorporating lung function, exacerbations and corticosteroids usage [Wenzel *et al.* 2009, 2000]. Hence, asthma and in particular TRA is increasingly recognized as a diverse condition.

Table 2. Investigations helping to delineate severe asthma from other conditions.

Full blood count (including an eosinophil count)
Total IgE levels (including RAST studies)
Autoimmune screen (and occasionally ABGs)
Oxygen saturations
Chest X-ray
Lung function testing
• FEV ₁
• FVC
• FEF ₂₅₋₇₅
• PEF
Reversibility assessment with salbutamol (and/or corticosteroid responsiveness)
Bronchial provocation tests (e.g. methacholine, mannitol or adenosine challenges)
FeNO
Skin prick tests
Sputum induction
High-resolution computed tomography of chest
Computed tomography of the sinuses
Bronchoscopy
Echocardiography
pH manometry

RAST, radioallergosorbent test; IgE, immunoglobulin E; ABGs, arterial blood gases; FEV₁, forced expiratory volume in 1 second; FVC, forced vital capacity; FEF₂₅₋₇₅, forced expiratory flow; PEF, peak expiratory flow; FeNO, forced exhaled nitric oxide levels.

Confirmation of TRA

In order to establish that the patient has TRA it is necessary to confirm in the clinical history that poor compliance (including inhaler technique and use of spacer device), comorbidities, other conditions and triggers have been excluded [Morjaria and Polosa, 2010]. This can be done reviewing old notes, blood tests, radiology and treatments in the past. For example, to exclude vocal cord dysfunction, a bronchoscopy can be performed, and for interstitial lung disease, blood tests as well as a high-resolution computed tomography scans should be used. Should the investigations not have been conducted previously then it would be prudent to do them to exclude another cause for the patient's symptoms. Also, a thorough history of their asthma and its control currently and previously is helpful, followed by a physical examination. Investigations that can be performed have been listed in Table 2.

Phenotyping of TRA

The clinical, physiological and immunopathological domains of TRA often co-exist, but are not related, hence, signifying that TRA is far from homogeneous and may be further divided into different phenotypes. A number of methods of phenotyping these TRA patients have been suggested, but the true significance of phenotyping

TRA can firmly be established once detailed characterization of a number of patients is conducted. These issues are currently being studied through an established network, U-BIOPRED (Unbiased Biomarkers for the Prediction of Respiratory Disease Outcomes) [U-BIOPRED, 2008].

Until recently, the phenotyping has been based on clinical or pathological features. Clinically, patients with severe asthma may be divided into three main categories of: frequent exacerbators interspersed by periods of no asthma symptoms; fixed airflow obstruction; and corticosteroid-dependent asthmatics [Polosa and Benfatto, 2009]. Pathologically, from the aspect of bronchial airways (sputum BAL and biopsies), two main categories are known: persistent eosinophilic and noneosinophilic subtypes [Wenzel *et al.* 1999]. However, there is also more recently the appreciation of the existence of neutrophilia as a separate subtype with or without eosinophilia [Hamilton *et al.* 2003; Jatakanon *et al.* 1999]. Furthermore, novel statistical approaches have been applied to clinical information from patients with asthma, and using data reduction techniques some asthma phenotypes have been identified [Haldar *et al.* 2008]. This is using a method called cluster analysis. In addition, using this method the multidimensionality of asthma

phenotypes have been constructed exhibiting clinically relevant differences in outcome, with management strategies that use a measure of eosinophilic inflammation for titrating corticosteroid therapy [Haldar *et al.* 2008].

In addition, infections (such as *Chlamydia pneumoniae*) and sensitization to *Aspergillus fumigatus* have been implicated in asthma. *C. pneumoniae* is an obligate intracellular parasite that can cause acute and chronic diseases of the respiratory tract especially asthma, but subclinical infection is common [Stephens, 2003; Cunningham *et al.* 1998; Grayston, 1992]. A number of groups have reported that there is a significant correlation in humans between asthma severity and *C. pneumoniae* infection and increases in IgG and IgA antibodies to *C. pneumoniae* (IgG and IgA) but not usually to other respiratory pathogens [Stephens, 2003; Wark *et al.* 2002; Ten Brinke *et al.* 2001; Martin *et al.* 2001; Black *et al.* 2000; Hammerschlag, 2000; Cook *et al.* 1998]. However, it is unclear whether these associations predominantly result from (1) infection fixing Th2 responses and facilitating the subsequent development of inflammation and asthma, or (2) immune responses that lead to inflammation and asthma also predisposing to atypical bacterial infection. Hence, it has been proposed that the timing of the infection relative to the exposure, the age of first infection, and/or the underlying immune phenotype of the individual that predispose to *C. pneumoniae*-induced allergy and asthma rather than the nature of the infection *per se* [Von Hertzen, 2002]. Similarly, it has recently been reported that patients with severe asthma sensitised to *A. fumigatus*, that do not conform to the conventional diagnostic criteria of allergic bronchopulmonary aspergillosis not only have radiological abnormalities on high-resolution computed tomography such as bronchiectasis, bronchial wall thickening and bronchial dilatation, but also air flow limitation due to air trapping [Menzies *et al.* 2011]. These observations propose pathophysiological phenotypes of TRA.

It is noteworthy that identified phenotypes are not necessarily fixed, and can vary over time and with treatment administered [Haldar *et al.* 2008]. Using this phenotypic information (and probably better definitions of the various subtypes in the future), there is the need to identify the mechanisms that are pivotal in the interaction between the various asthma phenotypes and to

untangle the underlying pathobiology in order to not only develop biomarkers of disease, but also to develop new therapies tailored to the needs of our patients.

Management of TRA

For most patients, asthma is not controlled as defined by guidelines. This was demonstrated by the Gaining Optimal Asthma Control (GOAL) Study, in that despite optimization, the combination inhaler of salmeterol/fluticasone only resulted in 62% of patients achieving total control of their asthma symptoms [Bateman *et al.* 2004]. Moreover, after a course of OCS this improved to 69%. The rest of the patients still had uncontrolled asthma symptoms.

Optimal treatment should be aimed at accomplishing the best asthma-related quality of life (QoL) and control with the lowest dose of medications, especially corticosteroids. The selection and formulation of the therapeutic agents used should not only take into account the disease severity and phenotype, patient's comorbidities and preferences, therapeutic responses, but also the adverse event reports. Hence, in addition to standard therapies of ICSs and LABAs, other agents such as antileukotriene agents (for aspirin-sensitive asthma [Tonelli *et al.* 2003] and exercise-induced asthma [Leff *et al.* 1998]), theophyllines [Vatrella *et al.* 2005; Roberts *et al.* 2003], anticholinergics [Peters *et al.* 2011] and intravenous (IV) magnesium [Beasley and Aldington, 2007; Silverman *et al.* 2002] should be trialled.

Oral corticosteroids (OCSs) have been used in unremitting disease, but there have been studies using immunomodulators to restrict the need for prolonged OCS use and thereby the adverse effect of corticosteroids. A number of such immunomodulatory drugs have been looked at with some efficacy and safety, including methotrexate, cyclosporine A, macrolide antibiotics, azathioprine, gold and IV immunoglobulins [Polosa and Morjaria, 2008]. It is noteworthy that methotrexate, cyclosporine A and macrolide antibiotics have been commonly assessed as corticosteroid-sparing agents.

More recently, biological agents have been examined for use as corticosteroid-sparing agents. The only licensed biological agent is omalizumab. Other agents have been studied with limited efficacy and safety, or are still in the preliminary

Table 3. Summary of studies discussed.

Agent	Evidence for efficacy	Parameter improvements
Anti-IgE: omalizumab (SC/IV)	Milgrom <i>et al.</i> [1999] (DBPC)	Improvements in morning PEF, asthma QoL; reduction in asthma exacerbations and reliever use
	Busse <i>et al.</i> [2001] (DBPC)	Improvements in symptom scores, FEV ₁ , morning PEF; reduction in asthma exacerbations and reliever use
	Soler <i>et al.</i> [2001] (DBPC)	Improvements in symptom scores, FEV ₁ , morning PEF; reduction in asthma exacerbations and reliever use
	Milgrom <i>et al.</i> [2001] (DBPC)	Reduction in asthma exacerbations and reliever use
	Holgate <i>et al.</i> [2004] (DBPC)	Reduction in reliever use; improvements in symptom score and asthma QoL
	Humbert <i>et al.</i> [2005] (DBPC)	Reduction in asthma exacerbations and attendances to ER; improvement in asthma QoL, morning PEF, asthma symptom scores
Anti-TNF- α : etanercept (SC) golimumab (SC)	Howarth <i>et al.</i> [2005] (open-labelled study)	Improvement in FEV ₁ , FVC, PEF, AHR and asthma control scores; voluntary cessation of nebulised reliever use
	Berry <i>et al.</i> [2006] (CS)	Improvement in FEV ₁ , FVC, PEF, AHR and asthma QoL
	Morjaria <i>et al.</i> [2008] (DBPC)	Improvement in asthma control; voluntary cessation of nebulised reliever use
	Wenzel <i>et al.</i> [2009] (DBPC)	No improvements in any parameters assessed (study terminated early due to SAEs)
Anti-IL-5: mepolizumab (IV)	Haldar <i>et al.</i> [2009] (DBPC)	Reduction in asthma exacerbations; improvement in asthma QoL
	Nair <i>et al.</i> [2009] (DBPC)	Reduction in asthma exacerbations and OCS dose reduction without exacerbations; improvement in FEV ₁ and asthma control
Anti-IL-4 receptor (IL-4R α): AMG 317	Corren <i>et al.</i> [2010] (DBPC)	No improvements in any parameters assessed
Anti-CD25: daclizumab (IV)	Busse <i>et al.</i> [2008] (DBPC)	Improvements in FEV ₁ , daytime asthma symptoms and reduction reliever usage; increased in time of exacerbations
Anti-SCF/c-kit and PDGF receptor: masitinib (PO)	Humbert <i>et al.</i> [2009] (DBPC)	Improvement in asthma control

IgE, immunoglobulin E; SC, subcutaneous; IV, intravenous; DBPC, double-blind placebo-controlled study; PEF, peak expiratory flow; QoL, quality of life; FEV₁, forced expiratory volume in 1 second; ER, emergency room; CS, crossover study; FVC, forced vital capacity; AHR, airway hyperresponsiveness; SAE, serious adverse event; OCS, oral corticosteroid; PO, *per os* (oral); IL, interleukin; TNF, tumour necrosis factor; PDGF, platelet-derived growth factor; SCF, stem cell factor.

stages of being assessed. We discuss these agents next (and they are summarized in Table 3).

Omalizumab. IgE plays a pivotal role in the development of allergic conditions [Corry and Kheradmand, 1999]. Allergen-specific IgE bind onto effector cells via the high-affinity (Fc ϵ RI) and low-affinity (Fc ϵ RII) receptors to produce their effects, such as induction of degranulation of mast cells and basophils causing resultant early- and late-phase reactions [Gould and Sutton, 2008; Morjaria *et al.* 2007]. Omalizumab is recombinant humanized

IgE-specific monoclonal antibody that interrupts the interaction between IgE and the Fc ϵ RI on effector cells [Presta *et al.* 1994]. Early pharmacodynamic omalizumab studies have demonstrated that it reduces inflammation, AHR, and allergen-induced airway and skin tests [Boulet *et al.* 1997; Fahy *et al.* 1997].

There have been six large phase III double-blind placebo-controlled (DBPC) studies using subcutaneous omalizumab, at dose of 0.016 mg/kg/IgE (IU/ml) either every 2 or 4 weeks, assessing its safety and efficacy in severe atopic asthma with

symptoms despite optimum therapy [Humbert *et al.* 2005; Holgate *et al.* 2004; Busse *et al.* 2001; Milgrom *et al.* 2001, 1999; Soler *et al.* 2001]. The studies ranged from 25 to 52 weeks in subjects with an IgE level of between 30 and 700 IU/ml). Together the analyses of the various studies as well as collective assessments have reported that the addition of omalizumab resulted in improvements in subjective parameters of asthma control and QoL, and objective improvements of lung function, and reductions in reliever use, corticosteroid use, emergency department attendances and number of asthma exacerbations [Bousquet *et al.* 2005, 2004; Chipps *et al.* 2005; Humbert *et al.* 2005; Holgate *et al.* 2004; Finn *et al.* 2003; Busse *et al.* 2001; Milgrom *et al.* 2001, 1999; Soler *et al.* 2001]. In the study periods omalizumab was safe with no significant adverse events compared with placebo. However, postmarketing reports have reported a marginally increased number of anaphylactic and anaphylactoid reactions, malignancies and helminth infections [Cruz *et al.* 2007; NICE, 2007; Vignola *et al.* 2004].

It is noteworthy that patients on omalizumab have a 16-week assessment of efficacy and safety assessments to ensure they are benefitting from anti-IgE therapy. This is partly because of the cost of the drug. Although omalizumab is safe and effective drug, it is important to remember that there are only a minor proportion of severe asthmatics who are atopic and even in those only two thirds would benefit from it; the majority of the TRAs are nonatopic and would not be eligible for anti-IgE therapy.

Tumour necrosis factor alpha antagonism. TNF- α is a multifunctional pro-inflammatory TH1 cytokine which has been suggested to play a critical role in the initiation, maintenance and progression of airway inflammation in asthma [Morjaria *et al.* 2006]. TNF- α levels in the airways has been reported to be elevated in severe disease. The failure of corticosteroids to reduce TNF- α and TH1-derived cytokines in asthmatics airways may explain why corticosteroids have limited efficacy in TRA. Hence, it was postulated that antagonizing TNF- α and, hence, interfering with TH1-derived cytokines may represent an advance in the management of TRA.

Based on this premise two small studies (one proof-of-concept [Howarth *et al.* 2005] and the

other a placebo-controlled crossover study [Berry *et al.* 2006]) of TNF- α antagonism using the soluble receptor, etanercept, were conducted. These reported significant improvements in asthma-related QoL (AQLQ) and asthma control, as well as spirometry, PEF and AHR. However, in a larger DBPC study using the same soluble receptor did not report such dramatic effects, with only minor improvements in the asthma control [Morjaria *et al.* 2008]. Akin to this study, an even larger DBPC study using a monoclonal antibody to TNF- α , golimumab, demonstrated no improvements in any parameters measured, but in fact the study was terminated early due to safety concerns [Wenzel *et al.* 2009]. There were not only increased numbers of solid malignancies but also serious infections such as pneumonia, sepsis and reactivation of tuberculosis. However, it should be noted that in the larger two studies [Wenzel *et al.* 2009; Morjaria *et al.* 2008] mentioned the patients enrolled had milder disease compared with those in the smaller studies [Berry *et al.* 2006; Howarth *et al.* 2005]. Therefore, even if subgroups can be identified in which anti-TNF- α may be efficacious, this will need to take these treatment-related severe adverse events into account. Presently, there are no studies using anti-TNF- α strategies that we are aware of.

Anti-IL-5: mepolizumab. Eosinophilia in the airways, and their degranulation, is a feature of asthma and has been associated with TH2 cytokines, namely IL-4, IL-5, IL-9, IL-13 and granulocyte-macrophage colony-stimulating factor [Rothenberg and Hogan, 2006; Simon *et al.* 2004; Menzies-Gow and Robinson, 2002; Sanderson, 1992]; all of which are expressed in elevated amounts in severe asthma [Desai and Brightling, 2009]. IL-5 is an important cytokine that is specific to eosinophils. Based on this principle, antagonizing IL-5 using a monoclonal antibody, mepolizumab, was conducted in patients with mild-to-moderate disease with no clinical improvements of note [Flood-Page *et al.* 2007, 2003a, 2003b; Buttner *et al.* 2003; Menzies-Gow *et al.* 2003; Leckie *et al.* 2000].

More recently, two DBPC studies have been conducted in patients who had persistent eosinophilia despite corticosteroid therapy using mepolizumab with good efficacy and safety [Haldar *et al.* 2009; Nair *et al.* 2009]. They reported significant reductions in asthma exacerbations [Haldar *et al.* 2009; Nair *et al.* 2009] and

OCSs dose reduction without exacerbations [Nair *et al.* 2009], as well as significant improvements in forced expiratory volume in one second (FEV₁) [Nair *et al.* 2009], asthma control [Nair *et al.* 2009], AQLQ [Haldar *et al.* 2009], and dramatic reductions in sputum and blood eosinophilia [Haldar *et al.* 2009; Nair *et al.* 2009]. In both studies there were no major adverse events of note. Larger studies are underway to confirm the findings of these two studies in this small subgroup of TRA.

IL-4 receptor alpha (IL-4R α) antagonism. As mentioned above (in the section on anti-IL-5), IL-4 and IL-13 are also TH2 cytokines that play a role in the pathogenesis of asthma, and hence targeting these cytokines may be efficacious in severe disease [Webb *et al.* 2000; Grunig *et al.* 1998; Wills-Karp *et al.* 1998]. Of note, the IL-4R α is used by both of these cytokines to manifest their activity [Rolling *et al.* 1996]. With this in mind, a large DBPC study in moderate-to-severe asthmatics was performed to assess the safety and efficacy of fully humanized monoclonal antibody to IL-4R α , AMG 317 [Corren *et al.* 2010]. It was noted that there was no improvement in any of the parameters assessed in the study. However, a *post hoc* analysis has shown that AMG 317 may have role in patients with the most symptoms. There were no major issues with adverse events with the use of AMG 317.

Anti-CD25: daclizumab. T cells have a role in airway inflammation in asthma, with elevated levels of CD25 T cells and the cytokine IL-2 noted in more severe disease [Kon and Kay, 1999; Park *et al.* 1994; Robinson *et al.* 1993; Azzawi *et al.* 1992]. Using this principle, Busse and colleagues conducted a study to assess safety and efficacy of a humanised monoclonal antibody to the alpha subunit (CD25) of the high-affinity IL-2 receptor, hence hampering the binding of IL-2 [Busse *et al.* 2008]. In this DBPC study in moderate-to-severe asthmatics it was reported that there were minimal significant improvements in FEV₁, daytime asthma symptoms, increase in time to asthma exacerbation and reduction in reliever usage in favour of daclizumab. Although there were more adverse events in the daclizumab group, these were not significant. The place of daclizumab in TRA needs to be further assessed with larger trials.

Stem cell factor receptor (c-kit)/platelet-derived growth factor receptor tyrosine kinase inhibitor: masitinib. Mast cells and dendritic cells are cells involved in TRA [Krishnamoorthy *et al.* 2008; Chanez *et al.* 2007; Holgate and Polosa, 2006; Reber *et al.* 2006]. They may be activated via stem cell factor (SCF) receptor c-kit resulting in mast cell accumulation, AHR and increased histamine levels, eosinophilic infiltration as well as IL-4 production. Moreover, platelet-derived growth factor (PDGF), a growth factor, has been implicated in airway remodelling [Chung *et al.* 2006; Ingram and Bonner, 2006]. Hence, antagonizing the SCF/c-kit and PDGF receptors may be a potential therapeutic target. With this in mind masitinib, a tyrosine kinase inhibitor which antagonises c-kit and PDGF receptors specifically, was used to assess its efficacy and safety in subjects with severe persistent asthma despite high-dose ICSs as well as OCSs [Humbert *et al.* 2009]. In this DBPC study, Humbert and colleagues randomized 44 subjects to receive oral masitinib at three doses of 3 ($n=12$), 4.5 ($n=11$) or 6 ($n=10$) mg/kg/day or placebo ($n=11$), i.e. 3:1, for 16 weeks. Neither the primary endpoint of OCS weaning, nor any airway function parameters showed any significant difference between the various doses of masitinib and/or placebo. There were 14 drop-outs in both groups, which were similar in both groups, due to either adverse events or lack of therapeutic efficacy. Of note, the only parameter of significant improvement was the ACQ score in the masitinib group compared with the placebo group. An observation reported by the researchers was that patients on high doses of OCSs who received masitinib ($n=6$) were able to be weaned off their OCS dose compared with none in the placebo group. It was also reported that patients on masitinib had more minor as well as serious adverse events compared with those on placebo. This phase IIa study shows that masitinib may play a minor role in TRA, if any, as there were only subjective improvements noted.

Conclusion

Asthma remains a very important condition with respect to health economics burden, morbidity, effects on patients' QoL, and therapeutic options. The management of patients with TRA is an enormous challenge for clinicians. The rise of potential novel immunomodulatory agents may provide new therapeutic options for TRA in the future. In contrast, the treatment options for mild and moderate asthma are well established.

However, in this population of asthmatics there is a subgroup of patients that may present in an atypical way. Thus, the awareness amongst clinicians of possible different phenotypical subgroups of asthma is very important. If those atypical asthma syndromes are diagnosed early, their treatment is relatively simple and the control of symptoms can be achieved in the great proportion of patients.

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Conflict of interest statement

The authors declare no conflicts of interest in preparing this manuscript.

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