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Remission of asthma: The next therapeutic frontier?

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ABSTRACT

Asthma treatment goals focus on disease control rather than remission as a therapeutic aim. This is in contrast to diseases where remission is frequently discussed and has well-defined criteria. In this review, we consider the similarities and differences between remission in asthma and another chronic inflammatory disease, rheumatoid arthritis, where new therapies have made remission a realistic treatment goal. Clinical remission of asthma is often defined as prolonged absence of asthma symptoms without requirement for medication while others insist on the demonstration of normal lung function and airway responsiveness. Even in those who develop a symptomatic remission of asthma, persistent physiological abnormalities and airway inflammation are common. There is a clear need to develop a precise, internationally accepted, definition of asthma remission that can be used as a therapeutic endpoint in studies of new asthma treatments. Spontaneous remission of asthma symptoms is relatively common, especially during adolescence. It is more likely in males, those with mild symptoms and normal lung function and in those who quit smoking, and may be linked to normalisation of immune function. Remission is less likely in severe asthma, atopy, eosinophilia, airflow obstruction, continued smoking and weight gain. Studies of spontaneous remissions may provide insight into how remission might be induced with therapy. Remission is not identical to cure, there remains a risk of subsequent symptomatic relapse of asthma and there is little evidence that current asthma treatments can induce remission. Long-term remission should be regarded as the next therapeutic frontier in asthma management.

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1. Introduction

Asthma is a chronic disease characterised by variable airflow obstruction, airway hyper-responsiveness (AHR) and airway inflammation, and risk of long-term airway remodeling and fixed airflow obstruction. Advances in asthma treatments, especially the introduction of inhaled corticosteroids and long-acting β-agonists, have improved the symptoms of asthma and reduced the frequency of severe life-threatening exacerbations of the disease. Asthma is now a treatable condition but is not curable. While it is logical to think that

Abbreviations: AHR, airway hyper-responsiveness; DMARDs, disease-modifying anti-rheumatic drugs; FEV_1, forced expiratory volume in first second; FVC, forced vital capacity; IgE, immunoglobulin E; ISAAC, International Study on Allergies and Asthma in Childhood; LRI, lower respiratory illness; RA, rheumatoid arthritis; TNF, tumour necrosis factor.

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optimal management might minimize disease progression and increase the chances of inducing remission, there is little evidence that this is true.

Most discussion of asthma treatment goals revolves around disease control (Bateman et al., 2008; Taylor et al., 2008), and little attention is paid to remission as an achievable therapeutic goal. This is in contrast to other inflammatory diseases such as rheumatoid arthritis where remission is frequently discussed and has well-defined criteria. In this review, we consider rheumatoid arthritis (RA), a chronic inflammatory disease, in which new therapies have made remission a realistic treatment goal, and contrast this with remission in asthma. We discuss the issue of what constitutes an appropriate definition of an asthma remission, and review current evidence concerning spontaneous remission of asthma: its prevalence and the clinical, physiological and inflammatory features that are associated with remission. Finally, the influences of interventions on asthma remission are also considered.

2. Remission in another chronic inflammatory disease: lessons from rheumatoid arthritis

In considering remission in asthma, it is instructive to consider RA, another chronic disease in which the introduction of new therapies has made remission a realistic treatment goal. There are some parallels between asthma and RA: both are chronic inflammatory diseases with no known cure, and in both instances inadequate control of tissue inflammation is associated with chronic organ dysfunction.

In the past, both spontaneous remission and treatment-induced remission in RA were uncommon, but over the last twenty years there have been considerable improvements in treatment with the introduction of combination disease-modifying anti-rheumatic drugs (DMARDs), and therapies that block the activity of tumour necrosis factor (TNF) (van Tuyl et al., 2010). The focus of management in RA has now moved to aggressive treatment of early disease, and remission is now regarded as the main goal of treatment (Goekoop-Ruiterman & Huizinga, 2010). In a recent report, remission of RA occurred in 43% of subjects after four years, with 13% of patients being able to cease drug therapy for a prolonged period (van der Kooij et al., 2009). More commonly, reported remission rates have ranged between 9% and 20% of patients (van Tuyl et al., 2009, 2010), though remission rates in community practice outside of clinical trials may be lower (Wolfe et al., 2007).

As remission has become an important outcome measure in the assessment of new therapies, the definition of remission in RA has become a matter for considerable debate in the rheumatology literature. Not surprisingly, clinical trials that employ more loose definitions of remission report much higher rates of remission than those trials that employ more strict definitions (van Tuyl et al., 2010). The American College of Rheumatology first published a definition of remission of RA in 1981 that included the relative absence of clinical features of arthritis and a normal or near normal erythrocyte sedimentation rate (Pinals et al., 1981). Recently, expert committees have attempted to develop a uniform, internationally accepted, definition of remission in RA that takes into account findings from clinical trials together with the views of patients and consumer groups (van Tuyl et al., 2009; Wolfe et al., 2009). Although a consensus definition is still debated, remission of RA is usually defined using disease activity scores that assess the number of tender and swollen joints; in some instances the duration of morning stiffness is also considered (Wells et al., 2005). Achieving remission in RA does not necessarily require that the patient be off treatment, in contrast to the situation in asthma (see below).

A short duration of symptoms, and the early introduction of DMARDs and anti-TNF therapy are the two most powerful predictors of remission of RA (van der Woude et al., 2009; Katchamart et al., 2010). Other factors associated with the achievement of remission include not smoking, male sex, minimal radiographic evidence of joint damage, absence of auto-antibodies and a variety of other immunological parameters, as discussed elsewhere (Katchamart et al., 2010).

Remission of RA has been shown to be associated with a favourable long-term prognosis. Patients who achieved a state of remission show less functional deterioration and less radiographic evidence of progressive joint damage in the long-term (van Tuyl et al., 2009, 2010). Remission cannot be equated with cure, as relapse will occur in a proportion of patients in clinical remission. A 15-year follow-up study reported that 29% of RA patients were able to cease therapy with DMARDs because remission was achieved, though subsequently therapy had to be restarted in almost half the patients because the disease relapsed (Tiippana-Kinnunen et al., 2010). In addition, detailed magnetic resonance imaging and ultrasound indicate that a proportion of patients with apparent clinical remission have subclinical joint inflammation (Brown et al., 2008). These patients are more likely to undergo a relapse and to show progressive joint damage over the subsequent twelve months (Brown et al., 2008). This subclinical joint damage may have some interesting parallels with the process of airway remodeling in asthma.

3. Definitions of remission of asthma

Unlike RA, clinicians and researchers in asthma refer to the absence of symptoms and absence of pathology (shown by normal lung function and normal airway responsiveness) in response to therapy as 'good control' or 'total control' (Bateman et al., 2008; Taylor et al., 2008), rather than remission. Control in asthma has been well defined by consensus, but in contrast to RA, there is no clear consensus on what constitutes a remission of asthma. In RA, the term remission seems analogous to 'control' in asthma and the more stringent type of remission in RA (no symptoms and no treatment) seems analogous to what many refer to as remission in asthma. Clinical remission of asthma is commonly defined as the current absence of asthma symptoms for a prolonged period of time, as outlined in Table 1 (Bronnimann & Burrows, 1986; Boulet et al., 1994; Ronmark et al., 1999; De Marco et al., 2002; Horak et al., 2003; Sears et al., 2003; Vonk et al., 2004; Holm et al., 2007). Various investigators require that symptoms be absent for between one and five years, though such definitions are arbitrary. If absence of symptoms is to be central to the definition of remission, how long should symptoms be absent? One year without symptoms would seem the minimum, given the frequent seasonal variability of asthma, but is five years without symptoms any better than one year without symptoms at predicting long-term outcomes? Another problem with a symptom-based definition is that it relies on patient report, and is subject to recall bias or under-estimation of current symptoms, especially in retrospective studies. Absence of symptoms is likely to be more reliable when documented by repeated prospective monitoring of well-characterised cohorts of individuals. In contrast to the usual definition of remission in RA, researchers who study asthma usually

Table 1
Various criteria employed in the literature for defining clinical asthma remission.

Study	Criteria for asthma remission	Time frame
Bronnimann & Burrows, 1986	No asthma attacks, symptoms or medications	1 year
Boulet et al., 1994	No symptoms or medication requirement	2 years
Ronmark et al., 1999	No wheeze, dyspnoea or medications	1 year
Horak et al., 2003	No wheeze	3 years
Sears et al., 2003	No wheeze	1 year
Vonk et al., 2004	No active symptoms, no inhaled steroids	3 years
de Marco et al., 2006	No asthma attack	2 years
	No asthma medications	1 year
Holm et al., 2007	No asthma symptoms, no medications	2 years