The Breathe *feature where we give you an expert and a topic, and you gave the chance to ask them any questions you wish via breathe@ersj.org.uk*

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Ask the expert: New directions in asthma therapy

Q1. Based on the new GINA guidelines for children, which include the use of montelukast in the two steps of persistent asthma (mild and moderate), what is your opinion about the use of this drug as an additional therapy to the usual regimen of higher-dose inhaled corticosteroids (ICS) in severe asthma?
S. La Grutta (Palermo, Italy)

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Cysteinyl leukotrienes act as potent bronchoconstrictors and are part of the inflammatory cascade initiated during an asthma attack. They are produced – along with other inflammatory agents – by inflammatory cells, including mast cells and eosinophils. Leukotriene modifiers act by either inhibiting leukotriene formation (zileuton) or as leukotriene receptor antagonists (LTRAs; montelukast and zafirlukast), and downgrade that component of the inflammatory response. However, they have no effect on other pathways in the inflammatory cascade. For this reason, their use is recommended in mild persistent asthma when the asthma is not controlled with ICS monotherapy, or as an alternative to a long-acting β_2-agonist (LABA) as add-on therapy for moderate or severe persistent disease. One rationale for the use of add-on LTRAs in severe asthma is the finding that high doses of oral or inhaled corticosteroids fail to suppress the increased production of cysteinyl leukotrienes in asthma, as measured by urinary leukotriene (LT) E4 concentrations. It is well known that urinary LTE4 levels are inversely associated with asthma control in children with persistent signs of moderate-to-severe asthma despite the use of ICS and LABA therapy [1]. In a UK montelukast survey [2], which evaluated the effects of LTRAs across a range of asthma severities, 37.5% of patients (out of 1,351) were aged <16 years. Montelukast was observed to be an effective and well-tolerated treatment in everyday life in as many as 66% of individuals, including symptomatic individuals already receiving ICS plus LABAs. It seems from this survey that prescribers are initiating montelukast in line with the published randomised controlled trial data on efficacy, as add-on therapy for poorly controlled asthma, for activity-induced asthma, and in an effort to treat other comorbid conditions that may be mediated by leukotrienes, including in children. In the same study, logistic regression analysis was performed in an attempt to identify baseline characteristics that may predict a response to LTRAs. The single most important factor was activity-induced asthma at initiation. This was associated with age (a child was more likely to be a responder), sex and sleep disturbance. However, the everyday activity indicates that the utility of these findings is disappointing in the clinical setting. Correctly, the authors of the survey have highlighted that we still lack clinical or biological predictors of likely responsiveness to LTRAs [2]; therefore, a therapeutic trial remains the only realistic strategy for assessing clinical responsiveness, including in severe asthma.

Q2. I would like to ask whether we should still use the terminology "intermittent, mild, moderate and severe persistent" asthma to help guide initial treatment of asthma followed by using the terms "controlled, partly controlled and uncontrolled" to increase or decrease therapy at subsequent follow-up.
D.K. Ng (Hong Kong)

Classifying asthma into different patient groups with different needs for management has been a key component of guideline development. In particular, GINA guidelines [3] highlight that classification of asthma by severity is useful when decisions are being made about management at the initial assessment of a patient, but it is important to recognise that asthma severity involves both the severity of the underlying disease and its responsiveness to treatment. Considering that the classification of asthma by severity is usually unable to predict what treatment will be required and what a patient's response to that treatment might be, a periodic assessment of asthma control seems to be more relevant and useful. Nonetheless, since a global definition of asthma control does not currently exist, it is unknown how strongly control assessment affects clinician treatment decisions, nor whether control is sufficient. Moreover, many patients overestimate their degree of control and have a perceived lack of need for medication.
Lately, DIETTE *et al*. [4] have documented that, although asthma control greatly influences physician decisions about asthma treatments, recent acute care, bother and direction of illness also influence decisions, particularly those that involve increasing the amount of medication prescribed. It is clear that from a clinical perspective, the separation between disease severity and symptom control needs to be maintained. The challenge is to develop a tool for asthma classification that is easy to use and applicable in a variety of clinical settings, and that effectively guides therapy that improves daily functioning and outcomes for patients with asthma. Since asthma is a multidimensional disease, we must develop classification of different aspects of the disease that in turn may require different management approaches [5]. Obviously, we cannot omit to also consider that the use of noninvasive markers of airway inflammation has suggested the presence of four distinct phenotypes: eosinophilic, neutrophilic, mixed inflammatory, and paucigranulocytic asthma [6]. Recent studies suggest that these subgroups may differ in their aetiology, immunopathology and response to treatment. It is likely that a reclassification of asthma severity also based on subphenotypes is needed.


C. Clark/NOAA

Q3. We live in Uzbekistan, in a hot climate, but see plenty of patients with asthma. Is there any evidence that asthma prevalence varies according to climatic features? Should this affect treatment regimes and might it lead to new options for therapy?
L. Nazirova (Uzbekistan)

One of the most predictable effects of global warming is that atmospheric CO_2 levels are going to increase; but in addition, seasonality is going to change. Springs are coming earlier, lengthening growing seasons. Both of these trends affect plant biomass, making them larger at maturity and, logically, able to produce more pollen [7]. The trend toward earlier spring onset is particularly evident in the early spring flowering of wind-pollinated tree species, whose reproductive development and bud burst in spring are highly temperature sensitive. However, early spring onset may also affect temperature-dependent processes occurring over the entire growing season, not just those in early spring. For example, an early spring could also influence developmental and reproductive processes in later-flowering plants. It is also important to highlight that the number of doctor visits for asthma peaks during thunderstorms in the grass-pollen season [8]. It is thought that during wet weather – another potential side-effect of global warming – water is absorbed by the grass pollen grains, which then shoot out starch granules that carry allergenic proteins. The air becomes filled with these tiny particles, which are smaller than pollen and therefore more deeply inhaled, precipitating attacks in those who are sensitive. It is clear, therefore, that global warming is a public health concern because it has the potential to alter the timing and abundance of aeroallergens, which could result in increased symptoms in those with allergic rhinitis or asthma [9]. Obviously, we cannot forget that climate change and air pollution are closely linked, although in applied scientific research and even more in political negotiations they have been largely separated. Air pollution may exacerbate asthma because several air pollutants may augment or modify immune responses to inhaled antigens in a manner that favours sensitisation or enhances the severity of respiratory tract reactions after a sensitised individual inhales the inducing

allergen. For example, diesel particles from truck and vehicle exhaust have been shown to act synergistically with pollen allergens to exacerbate disease and are now thought to be an important factor in the recent rise in allergic disease [10].
Everyday practice and an examination of the literature show that treatment of inflammatory airway disease induced or influenced by air pollutants is generally that usually prescribed for controlling inflammation in asthma. In any case, there are some pharmacological requirements related to the single pollutant that should be kept in mind when a patient with a particular risk of exposure to that pollutant must be treated. Unfortunately, information about the real impact of the different classes of anti-inflammatory drugs on air pollutant-induced airway disease is still inadequate [11]. In any case, all specialists believe that air-quality control programs and early public warning systems on pollution and atmospheric factors are needed to enable predisposed individuals and their physicians to preempt attacks through primary and secondary preventative measures. Pollen forecasting and pollen-avoidance strategies for sensitised individuals will be particularly important.

Q4. I have two questions: a) What do you think is the future of allergen immunotherapy in asthma management? and b) Is there a role for newer anti-inflammatory drugs such as choline?
S.N. Gaur (Delhi, India)


National Sunflower Association

The scientific basis and the proof of clinical effectiveness of allergen immunotherapy administered by subcutaneous injection (SCIT) are well established [12]. It is effective treatment for sensitivity to Hymenoptera venom, and for allergic rhinitis and allergic asthma. SCIT administered in the proper setting reduces the development of new sensitivities and progression from rhinitis to asthma. Immunotherapy is particularly indicated in subjects with a limited spectrum of allergies and in those who have failed to respond to the usual anti-allergic drugs. It is likely that adding treatment for asthma's allergic component with immunotherapy may be the solution to achieving the unmet goals of asthma therapy. Unfortunately, local, systemic and even fatal reactions are a recognised complication of SCIT [13]. Consequently, there are many attempts under way to improve on the safety and convenience – while retaining the benefits – of SCIT [14]. These include approaches using current allergen extracts, especially by administering them sublingually. Alternatively, through recombinant technology, extracts are being modified to reduce their allergenicity without reducing their immunogenicity. They are being linked to immunostimulatory DNA sequences that will modify their *in vivo* processing resulting in an enhanced nonallergic response, or they are being incorporated into fusion proteins with inhibitory properties for mast cells and basophils. Whether any of these approaches will replace current immunotherapy practices depends on the demonstration of increased safety and convenience, cost effectiveness, and retention of the efficacy of current injection immunotherapy [14].
About choline, your paper [15] that is in press in the *European Respiratory Journal* documented that choline treatment in sensitised mice before ovalbumin challenge *via* the oral/intranasal routes significantly inhibited eosinophilic airway inflammation and eosinophil peroxidase activity. It also reduced immunoglobulin (Ig)E and IgG1 production, inhibited the release of T-helper 2 cytokines and leukotrienes and influenced airway hyperresponsiveness. There is no question that these are intriguing findings. However, we need more information before we will be able to hypothesise a role for this drug in asthma treatment. We cannot forget that many potential therapies for asthma that were really exciting when explored in experimental setting have been without value when tested in humans.

Q5. While new pharmacological avenues seem to be leading mostly to blind alleys, do you think that there is hope that other approaches, such as sublingual immunotherapy and thermal bronchoplasty, may be useful in clinical practice? Or are these looking equally gloomy?
R. Jones (Plymouth, UK)

The sublingual route has emerged as an effective alternative to SCIT. The indications are broadly similar, and where both treatments are available, patient preference becomes an important determinant of choice. Selection of patients for sublingual immunotherapy (SLIT) remains the remit of physicians trained and experienced in allergy and immunotherapy, whereas a more favourable safety profile makes this treatment suitable for home use and therefore more accessible to a broader range of patients [16]. However, NELSON [14] has reviewed the scanty evidence directly comparing the subcutaneous and sublingual approaches and has concluded tentatively that improved safety of the

sublingual route may be associated with reduced efficacy. A single pre-seasonal course of SLIT with a dose 45–225 times higher than that given by SCIT will be about half as effective as SCIT. There are also conflicting results for studies of SLIT in children, mainly those suffering from allergic rhinitis, and PAJNO [17] rightly identified the need for more data on the mechanism of SLIT and more convincing evidence for the possible long-term effects of this immunotherapy. In particular, the difficulty for manufacturers in achieving the homogeneity of standardised vaccines, the magnitude of their clinical efficacy, and the pivotal question of an early intervention with SLIT in young children with IgE-mediated disorders are to be faced [17].

The elimination of airway smooth muscle *in vivo* by thermal bronchoplasty is a really unconventional but exciting approach. A rather small randomised, controlled study [18] has recently documented that bronchial thermoplasty in subjects with moderate or severe asthma results in an improvement in asthma control, with a reduction in the number of exacerbations. Interestingly, the improvements in objective and patient-centred outcomes did not diminish over the course of the study, and the outcomes assessed at 1 year showed the same degree of improvement as at 3 months. In a preliminary, non-randomised study, the benefits of bronchial thermoplasty persisted at 2 years [19]. SOLWAY and IRVIN [20], in an editorial that accompanied the study of COX *et al*. [18], correctly highlighted that thermoplasty represents a novel approach to targeting airway smooth muscle, but it ablates airway myocytes only in bronchi ≥3 mm in diameter, which can be treated directly. For this reason, and because of the considerable effort involved (three separate bronchoscopic procedures, each with a small but significant risk of complications), notable adverse effects (in the short term, at least), and likely expense, bronchial thermoplasty will probably need further refinement if it is to emerge as a widely applicable, practical treatment for moderate or severe asthma. In any case, I think that the benefit of any reduction in the number of exacerbations must not be outweighed by the side-effects of treatment and duration of hospital stay required for the procedures.

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