# POOR ASTHMA CONTROL, DEVICE HANDLING AND PHENOTYPE

## Summary of Presentations Given at the Teva Symposium, ERS Annual Congress 2013, Barcelona, Spain

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## INTRODUCTION

The aim of this symposium is to discuss the impact of poor treatment and poor inhaler technique on asthma outcomes. In addition, the symposium will explore the aetiology of asthma and the mechanistic role of IL-5 in severe asthma.

## Developing the 'Ideal Inhaler'

**J. Christian Virchow**

Generally in asthma management the hypothesis is that poor device techniques in asthma patients affect outcome; it is assumed that if the patient does not or cannot inhale correctly there will be no change in outcome (the outcome would not be worse, but there would be no effect because no inhalation has taken place). Secondly, it is predicted that the poorer the inhaler technique the poorer the outcome for the patient will be. Thirdly, it is likely that improvements in technique or device will improve compliance and possibly outcome.

The reasons for poor asthma control are: underestimation of disease severity by both the patient and the physician; delay in diagnosis or possibly the wrong diagnosis; under treatment including a delay in inhaled corticosteroid (ICS) therapy; poor compliance; incorrect inhaler choice; incorrect inhaler technique and insufficient instructions to the patient. In addition, guidelines are not always implemented correctly,[1] all of these reasons contribute to poor asthma control.

It is often thought that patients referred for uncontrolled asthma should receive more therapy however, this is not always accurate. Bush et al.[2] stated in a recent editorial that *'...at least half of those referred to specialists with so-called therapy resistant asthma, in fact need to get the basics right rather than indulge in expensive biologicals'*.

It is difficult to adequately define what constitutes errors that occur with inhalation devices. Therefore, it is important to establish a hierarchy of errors: important errors and less important errors. Important errors are probably those where no drug is delivered at all and less important errors are when a partial amount of the drug released is actually inhaled.

Many studies that have looked at the efficacy of inhalation technique contain a patient population

that are 'inhalation experts' due to patients who were unable to inhale being excluded. Consequently, the efficacy of inhalation therapy shown in controlled clinical studies has always been evaluated in patients who can inhale. However, in clinical practice many patients fail to inhale correctly.

The requirements of a device for optimal inhalation are that it tolerates errors and does not allow any crucial errors to occur that result in failure of the drug being delivered and consequently treatment failure. The choice of inhalation device is complex and the guidelines do not advise on the choice of device. It is considered that the correct choice of inhalation device is the cornerstone in the effective management of asthma and chronic obstructive pulmonary disease (COPD). The reality is that inhalation devices are often chosen on an empirical basis, e.g. some like red more than pink, others like powder more than pressurised metered-dose inhalers (pMDI). Device selection is rarely based on evidence based awareness, and a considerable number of physicians caring for asthmatics have poor knowledge on the appropriate selection and use of inhaler devices.[3,4]

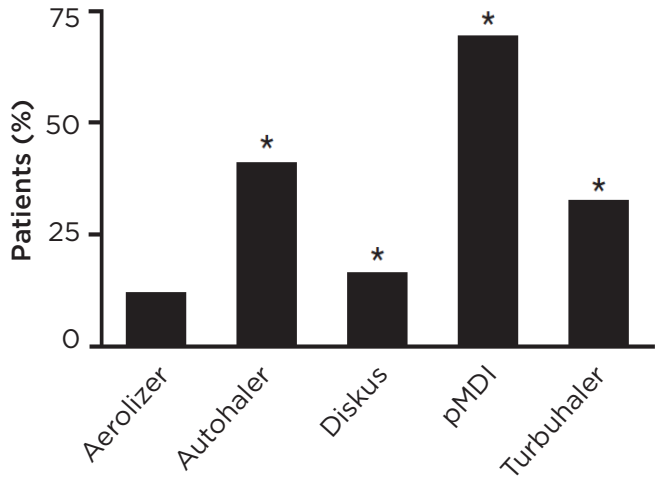



**Figure 1. Percentage of 3,811 patients with at least one device-dependent error.**
*p<0.05 versus best results adjusted by age and gender.
*Blaiss MS.*[6]

Poor inhaler technique is highly prevalent as shown in a study by Giraud et al.[5] The study of 3,955 patients classified patients into good users (29%) and misusers with at least one error or omission (71%). In addition, patients were sub classified into misusers with poor coordination who were unable to coordinate inhalation and actuation of the device (39%) and misusers with good coordination but made an error with the inhalation (32%). In a study of 3,811 patients a significant number of patients with poor inhaler technique had at least one device-dependent error ($p<0.05$ versus best results adjusted by age and gender).[6] The results showed a considerable difference between the types of device being used (Figure 1). pMDI were shown to be the most problematic inhalation device concerning device dependent errors.

Understanding and teaching inhaler technique is very important. A study from the United States[7] evaluated 56 medical interns (who were at the height of their theoretical medical knowledge) and assessed the process of correct pMDI administration this was:

1. Remove cap
2. Shake inhaler
3. Hold inhaler upright
4. Tilt head back or keep at level
5. Exhale to functional residual capacity or residual volume
6. Insert or keep mouthpiece 2–4 cm away from mouth
7. Begin breathing then actuate canister once
8. Continue slow, deep inspiration
9. Hold breath for 5–10 seconds
10. Exhale, wait 20–30 seconds before second dose
11. Shake again before a second actuation

56% of the group had not received any training with the devices; on the first attempt 5% of the group got the process of administration correct. After a large group lecture only 13% achieved the correct process of administration. It required one-on-one training to achieve the correct process of administration in 73% of the group. This is an important consideration when educating patients in the correct use of inhalers. When each specific step in the process was analysed, only 82% of the group removed the cap,

after one-on-one instruction this increased to 100%. In the most important part of the inhalation process in terms of lung deposition (begin breathing then actuate canister once), less than 40% of the group were correct, after group training there was a negligible increase in using the correct technique. It was only after one-on-one instruction that the number that used the correct technique increased to 79%. This study shows that correct pMDI administration was a challenge to healthy medical interns and should be considered in light of patients who have severe breathing difficulties.

Problems with the correct administration of pMDIs are extremely prevalent and teaching inhaler techniques has variable results, for example, in a study of 1,200 patients 86% used incorrect inhaler technique.[8] Following instruction and using a device that monitors correct inhalation 76% of patients used incorrect inhaler technique however, on the third attempt this reduced to 61% of the patients using the incorrect inhaler technique.

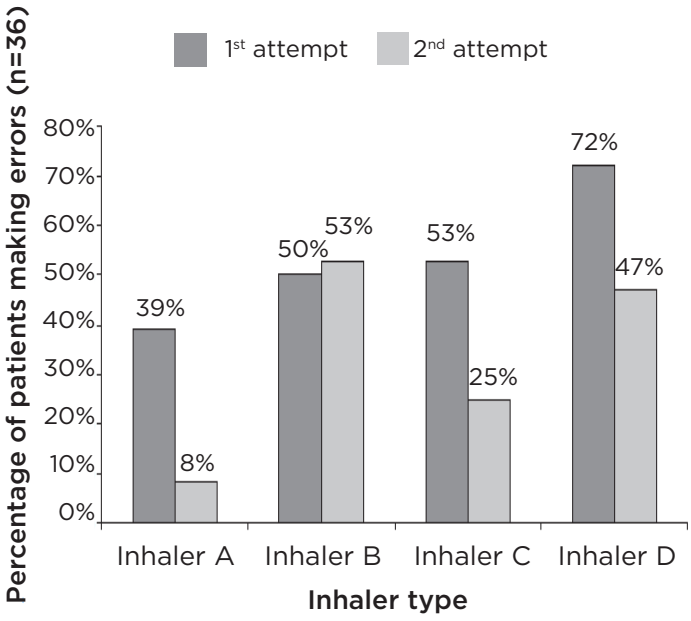



**Figure 2. Critical errors with four DPIs, after reading the instructions and after personal instruction.**
*Schulte M, et al.*[9]

Dry powder inhalers (DPIs) show different results; Schulte et al.[9] evaluated the use of DPIs after reading the instructions and after a personal instruction (Figure 2). The results showed that 72% of patients using inhaler 'D' made critical errors after reading the instructions, following personal instruction this reduced to 47%. Using inhaler 'B' 50% of patients made critical errors after reading the instructions and this number increased to 53% after personal instruction, indicating that personal instruction was detrimental to correct inhaler technique in this instance.

A study in the United States evaluated five visits (at 0, 1, 2, 3 and 6 months) to the pharmacist.[10] 97 patients received an average of 2.5 minutes of individual coaching on inhaler technique per visit. At entry 7% used the Turbuhaler correctly and 13% used the Diskus correctly. After 3 months this significantly improved to 85% and 96% respectively, however at the 6 month evaluation correct inhaler use reduced to 50% in the Turbuhaler group and 79% in the Diskus group, indicating that between the 3 and 6 month visits a large proportion had forgotten what they had been taught by the pharmacist. Even though there was a reduction in correct inhaler use at six months, the results showed that there was improvement in peak expiratory flow (PEF) and asthma quality of life (AQoL) at both 3 and 6 months.

It has been shown that switching inhalers is problematic and having more than one inhaler type can be confusing for the patient. There is an increased level of misuse if patients have different types of inhaler or their inhalers are switched.[11] In addition, patients can get confused over the appropriate inhaler technique for different devices.[12] Van der Palen et al.[13] compared the use of Diskhaler, Rotahaler and Turbuhaler and found that when used in combination with each other the percentage of patients who use the correct technique is low. For example, when using the Diskhaler and Turbuhaler only 35% of patients used the correct technique and attained 100% scores when using the two devices. The number of patients using the correct technique was even less with a DPI and pMDI (<35%). In practice many patients are on DPI fixed dose combinations because there is a lack of availability of short-acting beta2-agonists in the same device.

The consequence of switching inhalers was illustrated in a retrospective matched cohort study.[11] The study used the UK General Practice Research Database to identify patients who changed inhaler without consultation with their General Practitioner. The results showed

successful treatment in 19.7% of patients in the switched cohort compared with 34.3% in patients maintaining treatment with the same inhaler. Unsuccessful treatment was 50.7% and 37.9% respectively, indicating that if consultation had been sought it would possibly have reduced the number of patients who experienced unsuccessful treatment.

Improving inhalation technique can improve asthma control. In a study that evaluated patients with their own pMDI and inhalation technique compared with the use of a breath-actuated pressured inhaler,[14] the measurement of bronchodilation showed that if the patients used a breath-actuated pressured inhaler or were instructed on the use of their own pMDI, the effect was much better compared with the patient's own pMDI inhalation technique. This indicates that improved inhaler technique leads to improved pulmonary deposition and therefore improved asthma control. In addition, improved inhalation technique affects patient outcome, this was shown in a study of outpatient management by a paediatrician or asthma nurse in children with severe asthma.[15] The results showed an improvement of correct inhalation technique from 65% to 95% and this resulted in a lower corticosteroid dose and improved asthma control. Improving inhaler technique was the main factor in showing that it was possible to have improved asthma control with less corticosteroid.

Inhaler misuse is associated with decreased asthma stability. Giraud et al.[5] assessed whether the improper use of pMDIs was associated with decreased asthma control. The study of 3,709 patients were given an asthma instability score (AIS), a score of 0 indicated stable asthma and a score of 9 indicated totally unstable asthma. The results showed that asthma was less stable in pMDI misusers than in good users (AIS: 3.93 versus 2.86), and among misusers asthma was less stable in poor coordinators (AIS: 4.38 versus 3.56 in good coordinators). These results indicate that misuse of pMDIs, which is more frequent in poor coordinators, is associated with poor asthma control.

Medical visits for an exacerbated asthma condition or emergency visits have been shown to be more frequent in misusers with poor coordination, than in misusers with good coordination or in good users ($p<0.00001$).[5] Even if the device is used incorrectly but with good coordination, asthma stability is better than when the device

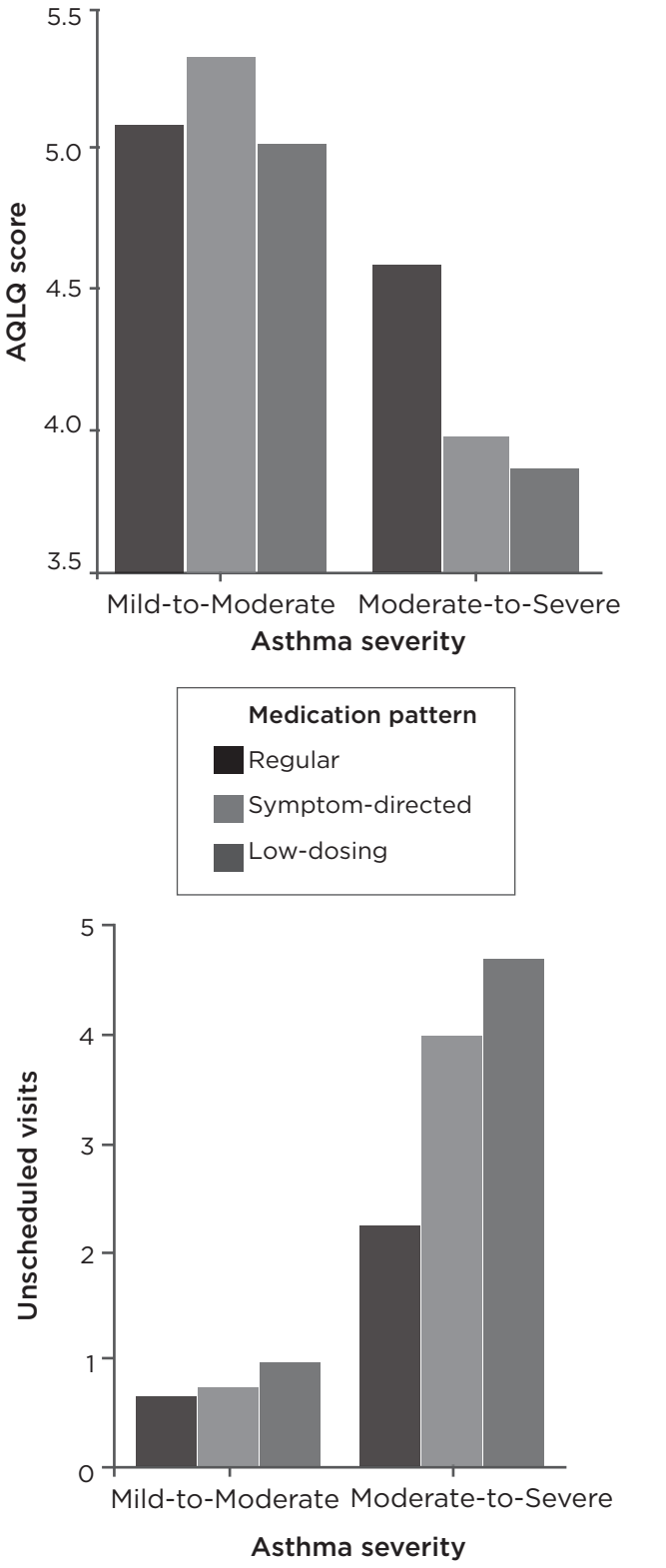



**Figure 3. Non-adherence can be effective in milder asthma.**
*Greaves CJ, et al.*[16]

is used correctly with bad coordination. This indicates rational non-compliance, which means that the device is more relevant for treatment success than the delivered drug, i.e. a patient may decide that the amount prescribed for them

may be more than they need for their personal feeling of control. This is shown in another study that assessed AQoL and unscheduled visits in mild-to-moderate asthmatics compared with moderate-to-severe asthmatics.[16] The results showed that mild-to-moderate asthmatics that take their medication regularly have a good AQoL and few unscheduled visits. In addition, in this group of patients, symptom directed medication use showed an increased AQoL and only a small increase in unscheduled visits. Patients receiving a low-dose experienced more unscheduled visits compared with patients that had a regular medication pattern or symptom directed medication (Figure 3). In moderate-to-severe asthmatics, an improvement in AQoL and a reduction of unscheduled visits was seen only if medication was taken regularly. In the mild-to-moderate asthma group, regular versus symptom directed inhaler use showed equally good asthma control.

Whether the compliance and the effect of treatment and inhaler competence are negatively correlated is an unresolved hypothesis. Patients need to take an increased number of inhalations per day if they have poor inhaler competence in order to compensate for the insufficient inhalation. If patients are competent at inhaling and are receiving the optimum dose from each inhalation, they may reduce their compliance because they feel they are getting enough relief and do not require anymore. Inhaler competence is the prerequisite for rational non-compliance but asthma management should not be controlled by patients who cannot inhale. There are economic advantages of correct inhaler use. Correct inhaler use results in improved asthma control, no stepping up, reduced medication needs, reduced medication costs, reduced need for additional prescriptions such as fixed dose combinations and programs to improve inhaler competence, compliance and adherence, all of which are likely to be cost saving.[12]

The recommendations for prescribing aerosol therapy are that all medications should come from the same device and only chlorofluorocarbon-free aerosol devices should be used. The decision for prescribing an inhaler should be based on the patient's ability to perform an inspiratory vital capacity manoeuvre. Inability to perform an inspiratory vital capacity manoeuvre requires inhalation from tidal volume e.g. a nebulizer or a hydrofluoroalkane (HFA) pMDI with a spacer and a valve. If the patient can perform an inspiratory vital capacity manoeuvre, the patient requires a single breath inhalation with a dry powder inhaler or HFA-pMDI (plus or minus a spacer).[1]

Poor device technique evidently affects outcome. This appears to be due to the fact that there is a large spectrum of handling errors that increase with the number of inhalers that individual patients have. Secondly, healthcare professionals' knowledge about inhaler technique is inadequate. These factors can be addressed by teaching patients to take their medication correctly; it has been shown that improved inhaler technique improves outcome. In addition, there are device-specific differences; DPIs appear to be more effective than pMDIs in terms of patient handling, therefore, checking a patient's inhaler technique prior to new prescriptions is essential; therapy should be individualised according to patient preferences and ability. The device should be simple and self-explanatory with no crucial errors and personal instructions should be repeated at every visit.[1,17]

The question is which is more important: the inhaler or the drug?

*'...an old but well-known drug in a new, more reliable inhaler is probably more useful than a new drug in an old (flawed) inhaler'.*[1]

## How Important is Inhaler Adherence to Asthma Outcomes?

**Cynthia Rand**

The discussion surrounding poor asthma control continues. In the United States there is a significant problem with poor asthma control among African-Americans and higher rates of morbidity are seen in this group of patients. The asthma hospital discharge rate by race in the United States, 1980 to 2006,[18] illustrates a fundamental issue in asthma treatment. 30 years ago the armamentarium for managing asthma was very limited because there were only a few drugs available. Over a period of 25 years this has increased enormously. Now there are an increasing number of therapies that have been shown to be effective in controlled clinical trials and yet there does not appear to have been dramatic changes in asthma control, this is reflected by the continued

number of asthma hospitalisations and emergency room visits. There are many potential reasons for this and there is no definitive solution or perfect drug for treatment.

Efficacious drugs require patient adherence in order to achieve effective treatment outcomes. Patient adherence is how patients use their asthma medications and the relationship between that behaviour (the fundamental link) and asthma control. The European Community Respiratory Health Surveys (ECRHS)[19] that were conducted across multiple continents in asthma patients asked 'if you have been prescribed medicine for your breathing do you normally take all the medicine?' Consistently across all patient populations, patients reported that they did not take all the medication prescribed, clinicians are aware that this is common practice in asthma patients.

In the United States a four-state survey that looked at paediatric asthma asked parents how they gave preventive medication to their child with persistent asthma.[20] The participants were subdivided into white children (n=822), black children (n=294) and Latino children (n=369), the overall results suggested that the overall rate of adherence was less than 50%. Self-reported use of any preventative medicine in the last 3 months was 44% in the white subgroup, 30% in the black subgroup and 30% in the Latino subgroup (p <0.001). Looking at utilization, the suggestion was that the highest rate of morbidity, as reflected by emergency department use (≥1 emergency department visit in the last 12 months), was seen in those children who reported the lowest use of preventer medication; 39% in the black subgroup and 24% in the Latino subgroup, compared with 18% in the white subgroup (p<0.001). These results are surprising because one would think that parental concern in controlling their children's health would play a significant role in how parents used the medication prescribed for their children.

The Childhood Asthma Management Program (CAMP) is the largest study ever conducted in the United States. In an ancillary study[21] conducted in three of the eight CAMP Clinical Centres, adherence was assessed by using self-reported

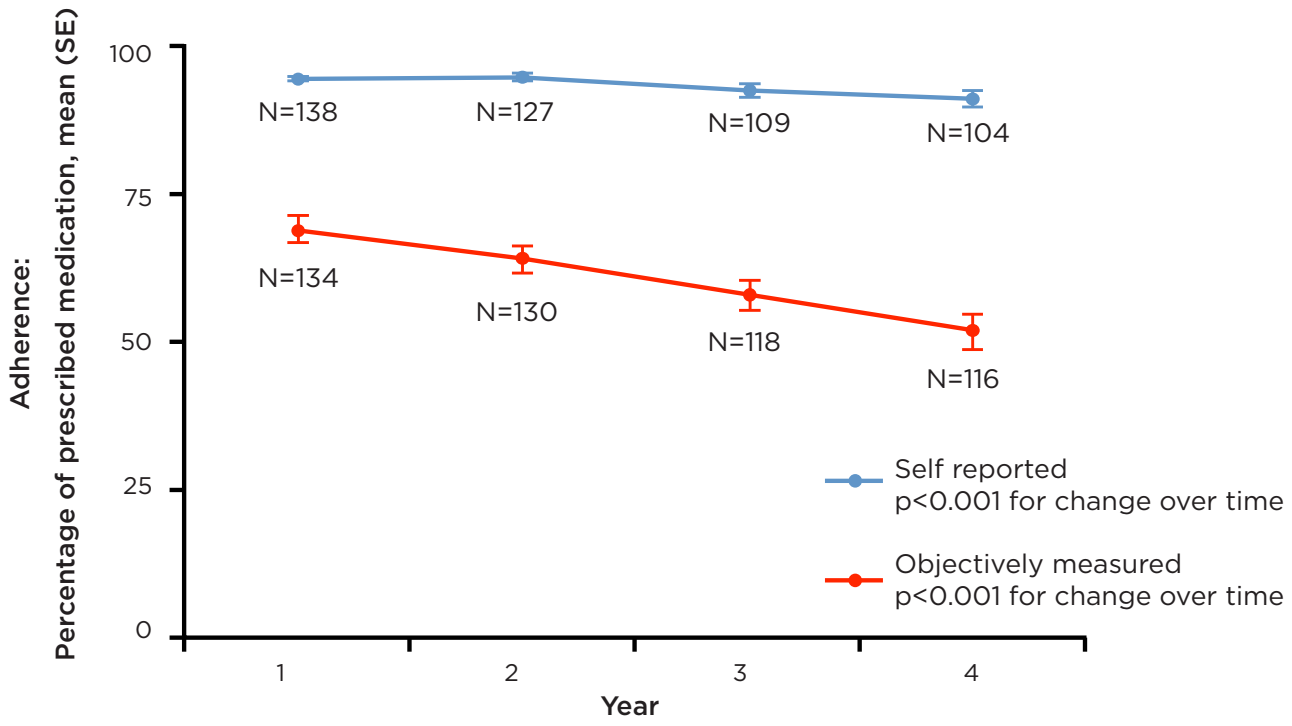



**Figure 4. 4-year asthma diary and counter measures of adherence in the CAMP study.**
CAMP: Childhood Asthma Management Program; SE: standard error.
*Krishnan JA, et al.*[21]

and objective data in 5-to 12-year-old children with mild or moderate asthma, who were randomly assigned to 200 mg of inhaled budesonide twice a day (n=84) or placebo (n=56) for 4 years. The Kappa statistic was used to evaluate agreement between self-reported adherence (daily diary cards), and objectively measured adherence (number of doses left in study inhalers) (Figure 4). It has been shown that, when asked to complete asthma diaries, patients consistently report a high use of therapy when asked to present the information in this form.

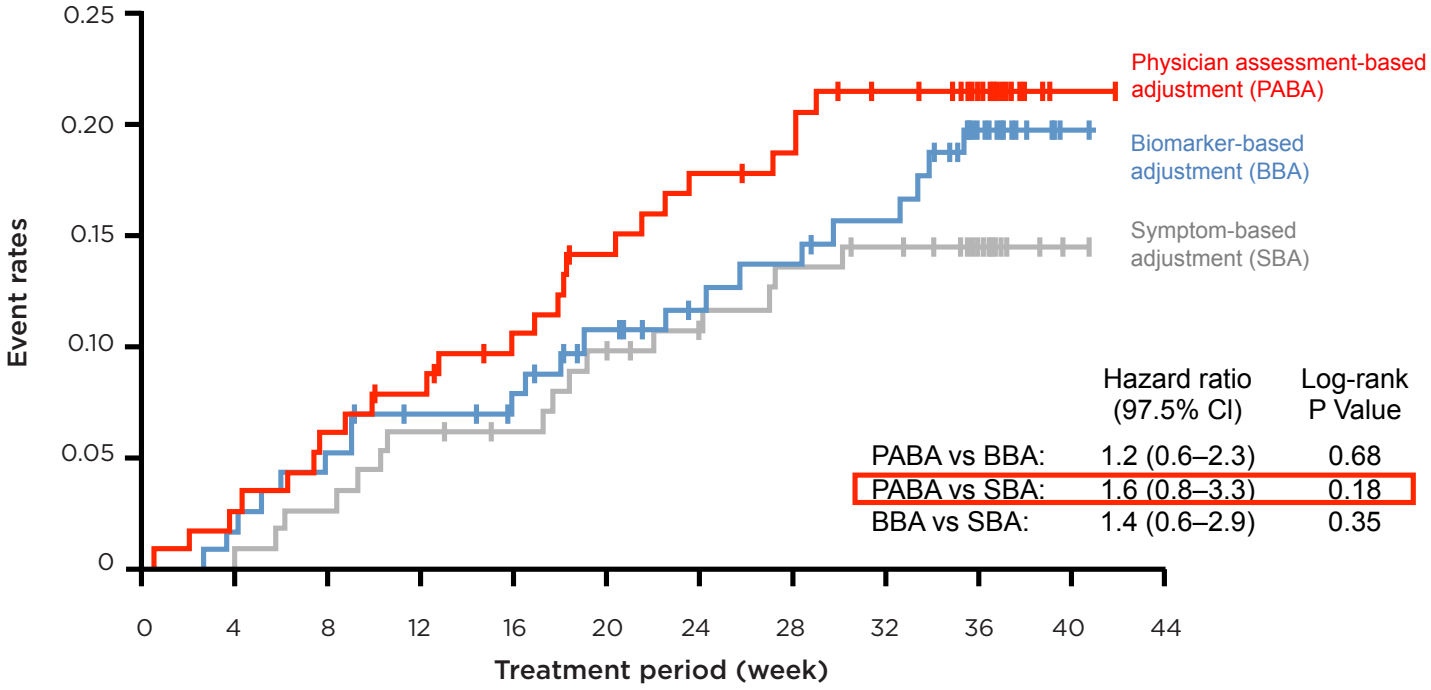
In this study self-reported asthma diary data suggested there was 85%-90% adherence. However, the data that were collected using objective measures showed that adherence was less than 75% at the beginning of the study, dropping to 50% by the end of Year four. The results revealed that overall adherence was low even among children who were in a carefully controlled trial with careful monitoring, nurse instruction at every visit and pre-selection of who was enrolled in the study; this shows that even under optimal conditions adherence was low.

The prevalence of no-adherence in severe brittle asthma (which is difficult to control) was examined in a retrospective, cross-sectional study of 182 patients attending the Northern Ireland Regional Difficult Asthma Service.[22] All 182 patients reported that they were taking their medication as prescribed. They all had 'difficult' asthma, which was defined as persistent symptoms despite treatment, and according to the Global Initiative for Asthma (GINA) guidelines,[23] were step 4 (reliever medication plus two or more controllers) or step 5 (reliever medication plus additional controller options). All of the patients were in specialist care consultation. The study evaluated the medication refill rates in the pharmacy records and found that 53% of the patients in this difficult to control asthma clinic had less than 75% adherence. Another study that evaluated the rate of adherence in patients receiving five different therapy types in a difficult to control asthma clinic, found that the majority of patients (74.8%) were non-adherent with their asthma medication.[24] This shows that, in the subgroup of patients with severe asthma, non-adherence is the missing link between effective therapies and effective control. In addition, Krishnan et al.[25] assessed medication adherence in patients who were hospitalised for asthma, 20% of whom had been intubated for asthma. Each patient's medication was electronically monitored following discharge from hospital. A monitoring device was used on the patient's inhaler and one on their medication bottle. This allowed data to be collected for inhaled steroids and oral corticosteroid adherence. The results showed that during the first 2 weeks following discharge from hospital, adherence dropped to less than 50%. This indicates that behaviour plays a fundamental role in adherence, even in life-threatening asthma.

Evidence suggests that inhaler adherence is associated with improved asthma outcomes. This was shown in a prospective study that evaluated patterns of steroid use among a range of patients with severe and mild-to-moderate asthma.[26] Adherence was assessed 6 months before a period in which exacerbation was monitored. A significant association with adherence of inhaled steroids and future events in this population was observed. Approximately 24% of asthma exacerbations were attributable to ICS non-adherence, and in this patient population, the benefit was only evident if the patients took 75% of their medication.

How much asthma morbidity could be averted by increased medication adherence? This question has been considered hypothetically using an algorithm, which was a very sophisticated modeling strategy. The algorithm looked at what is known about adherence and what is known about the association between adherence and outcomes.[27] The results suggested that in the United States alone, if patients were 100% adherent per year it would reduce unscheduled asthma visits by 3,700,000 visits (30%), reduce emergency department visits by 1,000,000 (20%), and would reduce hospitalisations by 300,000 (20%). Therefore, the potential benefit if adherence were improved is substantial.

It has been shown that the impact of adherence on AQoL and unscheduled visits in patients with mild-to-moderate asthma that are using asthma therapy on a symptom-directed-as-needed-basis, or lower dosing, does not appear to make a difference in terms of QoL or exacerbation. However, in patients with more severe asthma, the association between inhaler use and improved AQoL is clearly important.[16] This indicates that for patients with mild to moderate asthma, under-adherence may be acceptable. Similarly, in the BASALT trial[28] the outcomes of patients using symptom driven therapy versus physician




| No. at risk | | | | | | | | | | | |
|---|---|---|---|---|---|---|---|---|---|---|---|
| PABA | 114 | 111 | 107 | 104 | 99 | 94 | 90 | 88 | 82 | 60 | 1 |
| BBA | 115 | 112 | 108 | 104 | 101 | 94 | 89 | 87 | 83 | 58 | 1 |
| SBA | 113 | 113 | 110 | 106 | 104 | 100 | 95 | 90 | 87 | 68 | 1 |

**Figure 5. Asthma treatment failure with symptom-based use of ICS versus physician or biomarker-based use of ICS: The BASALT trial.**
BASALT: Best Adjustment Strategy for Asthma in the Long Term.
*Calhoun WJ, et al.*[28]

driven therapy showed that patients with mild-to-moderate asthma had improved outcomes compared with those using biomarker-based or physician-led therapy (Figure 5). The authors concluded that patients with mild-to-moderate asthma that under-adhere do quite well, this is consistent with physicians' observations in clinical practice. Whereas, the results show that the consequences of non-adherence to therapy are clearly more critical in patients with severe asthma.

The impact of adherence to therapy was evaluated by baseline forced expiratory volume in one second ($FEV_1$) in patients with mild-to-moderate asthma receiving prescribed fluticasone or montelukast asthma treatment.[29] Therapy was electronically monitored with the objective of identifying a dose response relationship between the amount of therapy patients took and the number of symptom free days. The only group that showed a dose response relationship was the group containing those patients who had slightly more severe disease (Figure 6), with baseline $FEV_1$ ≤86% of predicted. This supports the notion that adherence is fundamentally important in patients with greater underlying disease and less critical in patients with milder disease.

There are hidden barriers to adherence and asthma self-management; these include doctor-patient communication, depression and negative medication beliefs (patients do not like taking medications, are asymptomatic or fear side effects). Effective communication with patients is essential; in a study that used audio tapes of the physicians communicating with their patients about taking new drugs, it was found that 55% of the physicians only gave explicit instructions on the number of doses to take.[30] In addition, only 34% of the physicians discussed how long to take the medication for, and overall full medication directions were conveyed to less than 60% of

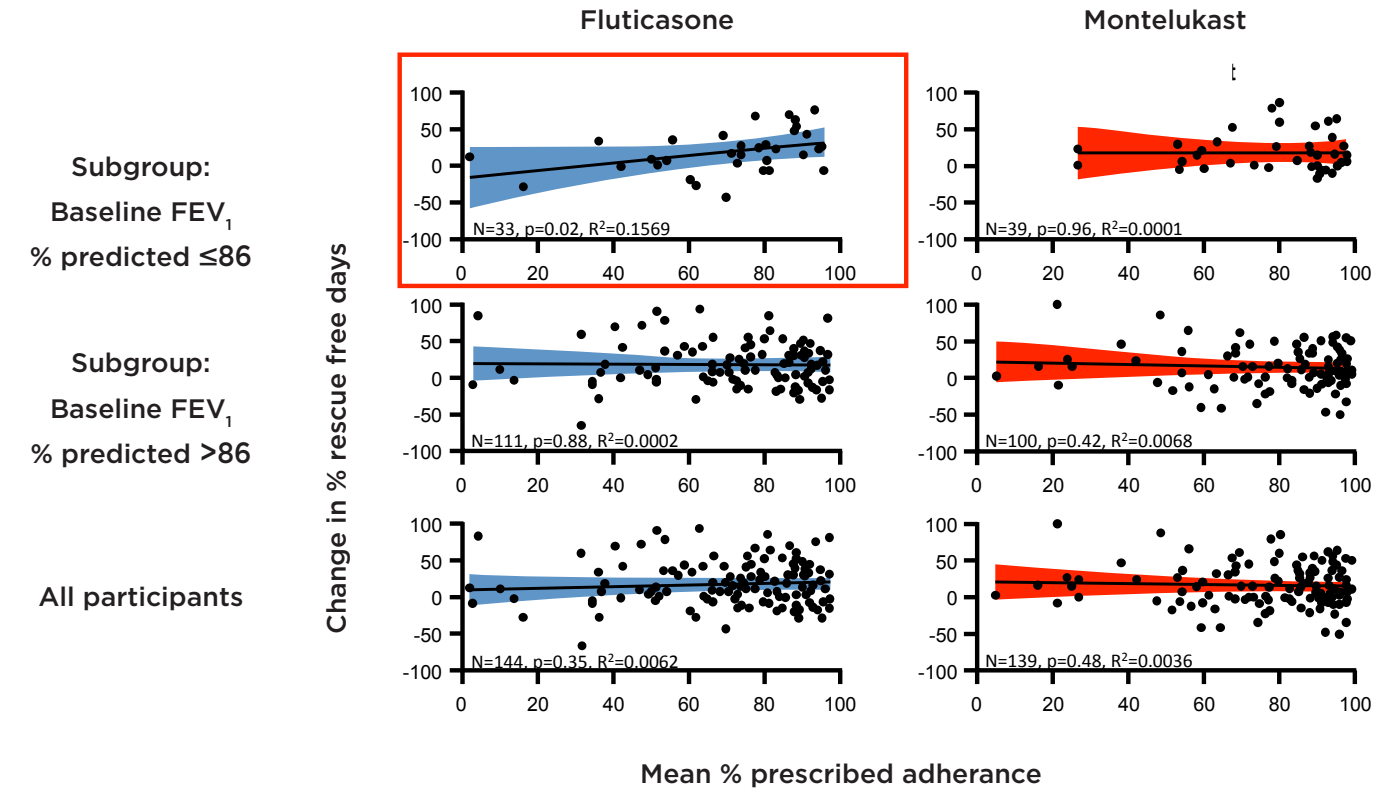



**Figure 6. The impact of adherence with therapy on symptoms by baseline $FEV_1$. Change in percentage of rescue-free days by mean percent prescribed adherence.**
*Rand C, et al.*[29]

patients. This highlights the fact that physicians should be explicit on how to use medication.

Beliefs about asthma medications are related to adherence with therapy. This was shown in a study in which parents of asthmatic children were asked their beliefs about asthma medication.[31] The study evaluated the association between what parents thought about therapy and whether the medication was actually taken. The results showed that when parents endorsed the statement 'my child does not need to take asthma medication every day', the child did not take the medication every day. When the parents endorsed the statement 'my child doesn't need as much medication as the doctor prescribed', the parents did not give full medication to their child. Overall, the study showed that when patients have high concerns about taking medication every day they are far more likely to be non-adherent. Therefore, ascertaining the medication beliefs of patients allows physicians to identify who is at risk from non-adherence.

Depression has been identified across every chronic illness as a substantial risk factor for non-adherence. Compared with non-depressed patients, depressed patients are three times more likely to be non-adherent with medical treatment recommendations.[32] In all racial and ethnic populations, patients with low economic status are at increased risk for both depression and poor adherence.[33] This was shown in a study in the United States that evaluated elderly asthma patients with depression.[34] The results showed that elderly patients with depression were substantially more likely to have poor medication adherence with their controller therapy and were substantially more likely to be hospitalised for asthma. This supports the fact that establishing whether depression is present may indicate whether patients are taking their medication as prescribed.

Adherence should be a component of personalised therapy, which can be accomplished by: 1) creating a paradigm shift and reframing adherence from good patient/bad patient to critical information or valuable clinical data that allow improved patient management; 2) routinely collecting refill data and self-reported adherence data, including behaviour, beliefs and concerns;

3) using patient adherence levels and patterns to identify patient-specific responses to treatment and personal risks of non-adherence; 4) personalising and tailoring asthma therapy not only for the drug, the dosing and the device, but for the adherence expectations in order to best fit each patient's risk, needs and preferences.

Non-adherence with inhaler therapy is common even in severe disease. Across all populations there is clear evidence that adherence is associated with better outcomes. In addition, there is evidence that patients with mild-to-moderate persistent asthma may tolerate lower levels of adherence with minimal impact. Clinicians should work together with their patients to personalise therapy by determining the optimal level of dosing and adherence necessary to effectively control asthma.

## The Various Types of Uncontrolled Asthma

**Richard Dekhuijzen**

The primary goal of asthma management is to achieve overall asthma control. Asthma management is aimed at the level of current control and the level of future risk. Current control is defined by symptoms, activity, reliever use, and lung function. Future risk is defined by instability or worsening of the disease, exacerbations and the severity of exacerbations, loss of lung function, and the adverse effects of long-term medication.[23]

The algorithm for assessing the level of asthma control is to check daytime symptoms, limitations of activities, nocturnal symptoms/awakening, need for rescue/reliever treatment, and lung function (PEF, $FEV_1$). Levels of control are defined as uncontrolled, partially controlled or controlled. The prevalence of uncontrolled asthma was evaluated in a large telephone survey of asthma patients;[35] the survey found that 95% of patients were uncontrolled. A later study evaluated patients who had a physician's diagnosis of asthma and a prescription for inhaled steroids.[36] The results showed that 51% of these patients were uncontrolled and 21% were partially controlled. Uncontrolled asthma is a huge problem; O'Byrne et al.[37] identified that the areas where problems occur are: learning abilities in younger children, focused attention, exercise limitation and reduced cardiovascular fitness, increased risk of severe exacerbations, accelerated lung function decline, increases in medical consumption, mortality, and costs.

There are three main categories of uncontrolled asthma. The first category is untreated asthma due to poor availability of diagnostic procedures and/or medication; this is an immense problem in low income countries. The second category is uncontrolled asthma due to inappropriate recognition and/or handling of modifiable factors and comorbidities. The third category is severe asthma with poor asthma control and/or frequent exacerbations, despite high dose ICS and a second controller such as oral corticosteroids (OCS).[38] It is important to know the specific cause or causes of uncontrolled asthma in an individual patient as this will initiate individualised non-pharmacological interventions, prevent over-prescription and/or overuse of medication, and initiate specific pharmacotherapy.

Several approaches have been suggested to find the cause of uncontrolled asthma, for example Bel et al.39 suggested an algorithm for uncontrolled/severe asthma (Figure 7). If a patient with asthma is uncontrolled despite 500 mcg ICS a day, with or without a long acting beta2-agonist (LABA) it is a concern, and a practical approach to treatment is required. The ABCDE(F) scheme[40] algorithm in uncontrolled asthma can help in the treatment of such patients:

**A** Is it really (and only) **A**sthma?

**B** Are all **B**ronchial triggers known?

**C** Is **C**ompliance optimal?

**D** Can the patient handle the **D**evice

**E** Is **E**very small airway reached?

**F** Is a specific **Ph**enotype present?

**A** Is it really (and only) **A**sthma?

There are a lot of diseases that will mimic or overlap asthma, e.g. a viral wheeze in children, emphysema, bronchiectasis, COPD, and chronic cough.[41] In addition, there are many suspected alternative or additional diagnoses in adults which are sometimes difficult to distinguish from asthma, e.g. vocal cord dysfunction, recurrent pulmonary embolism, bronchiolitis, Churg-Strauss

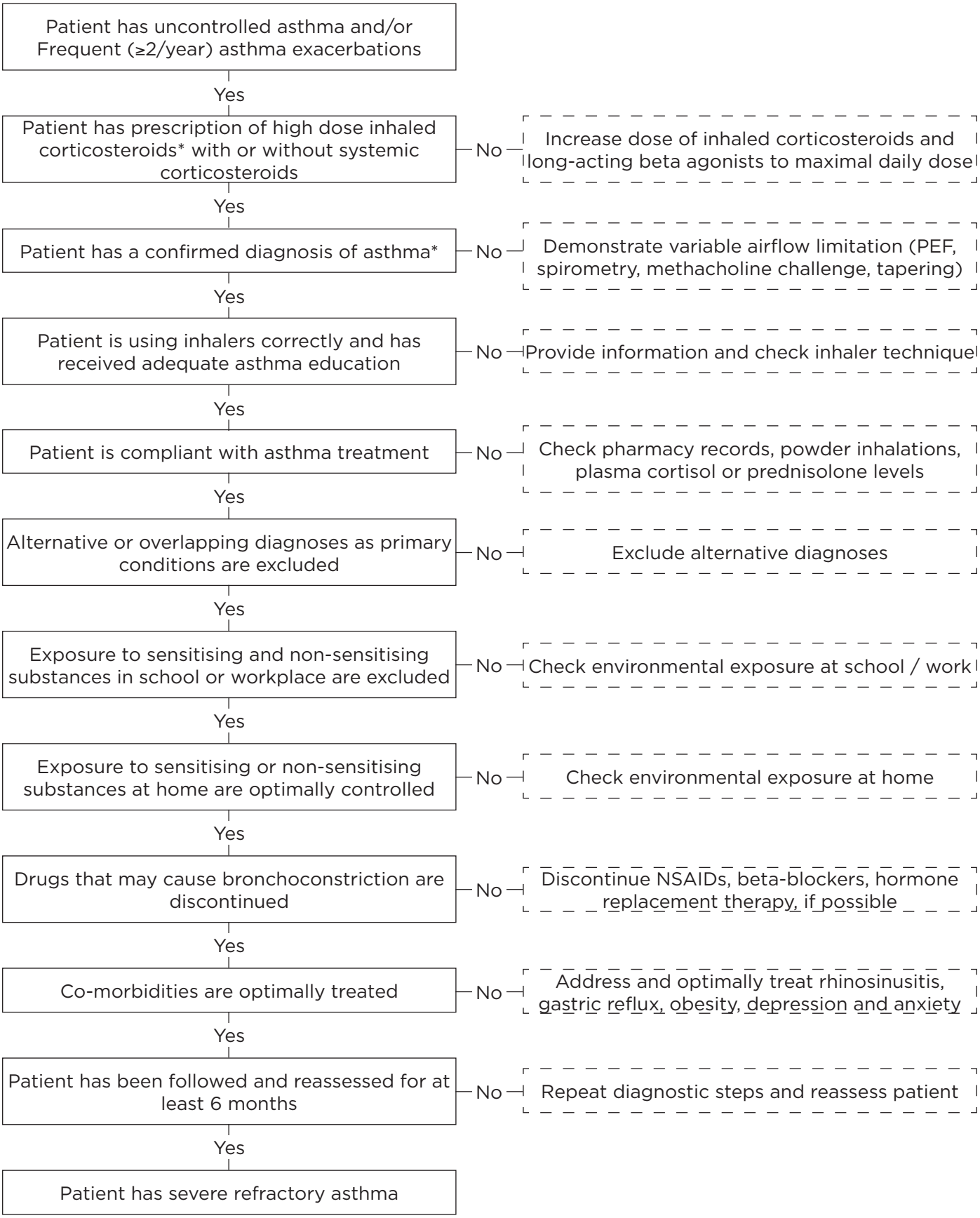



**Figure 7. An example of an algorithm in case of uncontrolled/severe asthma.**
NSAID: non-steroidal anti-inflammatory drug.
*Bel EH, et al.*[39]

syndrome etc.[39] Another consideration is that the asthma patient may have multiple comorbidities. In a study of risk factors of frequent exacerbations in difficult-to-treat asthma patients the frequency distribution of comorbid factors was significantly associated with frequent severe exacerbations.[42] In all patients with frequent exacerbations (n=39), more than one factor (severe sinus disease, gastric reflux, recurrent respiratory infections, psychopathology, or obstructive sleep apnoea) could be detected. In addition to asthma, 12% of the patient population had one comorbid factor, 36% had two comorbid factors and 40% had three comorbid factors. Comorbidities have an impact on outcome and the study showed that patients with >3 exacerbations per year had significantly more prevalent psychosocial dysfunction, severe sinus disease, gastric reflux, or recurrent respiratory infections compared with patients with only one severe exacerbation ($p<0.05$). This highlights the importance of establishing whether the patient really (and only) has asthma.

**B** Are all **B**ronchial triggers known?

There are many trigger factors which include: outdoor and indoor allergens, environmental pollutants, toxic fumes, occupational agents, and medication.[39] 10-15% of adults with asthma have work-related complaints; rhinitis is often the presenting symptom. Over 200 compounds have been associated with work-related asthma; a thorough history is required to enable the possibility of identifying the causative agent.[43] Some triggers are very well known for example smoking; patients with asthma who are current smokers have less asthma control compared with those who have never smoked or those who are ex-smokers.[44]

**C** Is **C**ompliance optimal?

In chronic asthma patients, inhaled medication is in the cluster of the lowest adherence; only 20% to 30% still use their asthma medication as prescribed after 2 years.[45] The consequence of low adherence is less asthma control.[44]

**D** Can the patient handle the **D**evice?

There are three important issues that need to be considered in order to make an optimal match between the patient and the device: 1) is the patient able to inhale consciously? The elderly, cognitively impaired, and children should be considered; 2) is the patient able to generate a sufficient inspiratory flow rate? 3) Is the patient able to coordinate well?[46] A patient who demonstrates that conscious inhalation is possible, and has sufficient inspiratory flow and good coordination, can be prescribed almost any device (Figure 8).

**E** Is **e**very small airway reached?

More attention is being paid to pathology in the small airways in patients with asthma. In the bronchioles, the patency of the small airways is significantly reduced in patients with asthma.[47] Closing volume (CV) and closing capacity (CC) are parameters for airway closure and air trapping, and thus measure small airway patency. Severe asthmatic patients with recurrent exacerbations (unstable asthma) have increased CV and CC compared with equally severe but stable asthmatic control patients, even in well-controlled episodes. Patients with recurrent exacerbations are prone to earlier airway closure and are at risk for excessive airway narrowing.[48] This suggests that airway closure at relatively high lung volumes but clinically stable conditions might be a risk for severe exacerbations in asthmatic patients.

Patients with less severe asthma (step 2, 3 and 4) have abnormal values of peripheral airway resistance. A study that assessed small-airways disease using alveolar nitric oxide (NO) and impulse oscillometry in asthma and COPD showed that 64-70% of step 2, 3 and 4 asthmatic patients were shown to have abnormal patency of the small airways.[49] This indicates that even in relatively mild disease, there is small airway involvement and this should be considered in terms of its contribution to the severity and lack of control in these patients. In patients with mild asthma, bronchial NO is not correlated with asthma control. However, asthma control and alveolar NO demonstrate a statistically significant relationship.[50] This suggests that inflammation in the periphery of the lung may contribute to less control of asthma. The involvement of the small airways is difficult to assess in clinical practice. If an assessment of the history of the patient's asthma is made, bronchial triggers excluded, compliance confirmed, and the device is satisfactory but there is still uncontrolled asthma, it may indicate small airway involvement. A suggested treatment would be to give an ICS

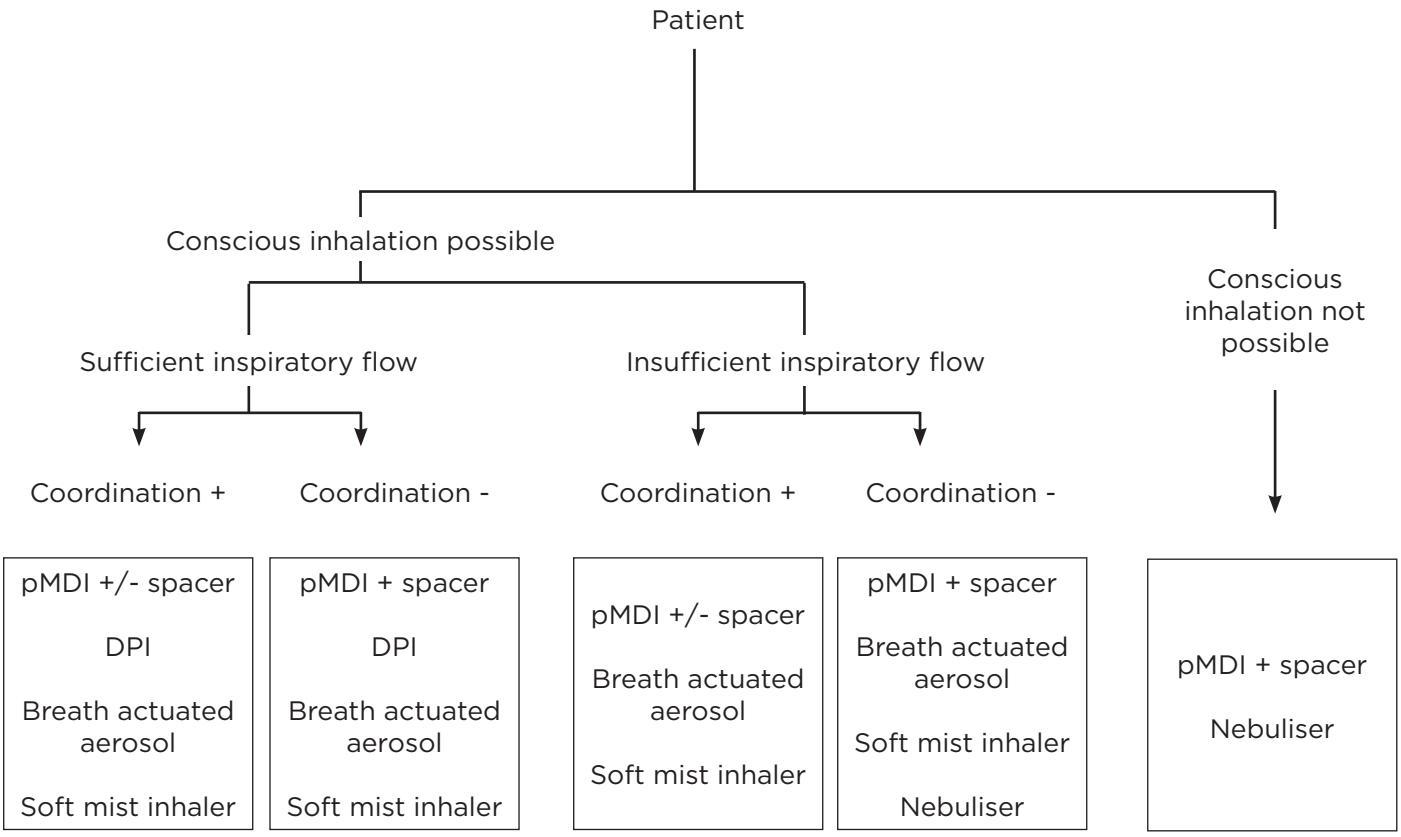



**Figure 8. Inhaler therapy for adults with asthma: can the patient handle the device?**
pMDI: pressurised metered-dose inhaler; DPI: dry powder inhaler.
*Dekhuijzen, PN.*[46]

with asmall particle size for 3 to 6 months, if the treatment is successful, the patient will indicate an improvement signified by fewer complaints, more exercise capacity and fewer exacerbations.

**F** Is a specific **Ph**enotype present?

Asthma is driven by T helper 2 ($T_H2$) (in children this includes allergic asthma, exercise-induced asthma and aspirin-exacerbated respiratory disease) and non-$T_H2$ phenotypes (in adults this includes very late-onset asthma in women, obesity-associated asthma, smoking-associated neutrophilic asthma, smooth muscle mediated paucigranulocytic asthma).[51] The phenotype may have therapeutic consequences. There is a difference between phenotypes and their response to therapy, for example the phenotype 'early-onset allergic' is corticosteroid responsive which is $T_H2$ targeted and is relatively easy to treat. Conversely, the treatment of adult onset obesity-related asthma is more difficult because there is a lack of $T_H2$ and the target for therapy is less clear. This type of asthma is responsive to weight loss, antioxidants and possibly hormonal therapy.

In summary, uncontrolled asthma occurs frequently and is a huge problem for the patients. There is a wide spectrum of causes of uncontrolled asthma and it is of great importance that the cause of uncontrolled asthma is found in individual patients. Several of the causes of uncontrolled asthma can be handled by non-pharmacological interventions. There are specific phenotypes where specific pharmacological interventions are indicated.

## Severe Asthma: The Role of IL-5

### Michael Wechsler

There is a huge proportion of the asthma population that remains poorly controlled. This is mainly due to poor inhaler technique and poor adherence. New options are required and many different therapies are being developed which will become available within the next decade. The main goal in the treatment of asthma patients is to optimise their asthma management. It is clear that adherence and inhaler technique need to

be addressed, but additional new therapies need to be developed to help in the management of these patients.

The national Asthma Education and Prevention Program (NAEPP) 2007 guidelines[52] for the management of asthma recommend escalation of therapy in patients who are poorly controlled. This means that as patients become increasingly inadequately controlled, doses of corticosteroids are increased and long acting beta-agonists, leukotriene modifiers and anti-immunoglobulin E (IgE) are added to the treatment regimen. However, despite these recommended measures and the use of the current therapies for asthma (short-acting beta-agonists, LABA, ICS, leukotriene modifiers, anti-IgE, systemic steroids, immunotherapy, anticholinergics [short-acting], and ipratropium), asthma control remains poor. The question is 'what to do next?'

The underlying pathophysiology of asthma denotes the specific cellular elements that need to be targeted; these are the mast cell, basophil, eosinophil, neutrophil, macrophage, dendritic cell, lymphocyte, and fibroblast, all of which are involved in asthma pathogenesis. One of the key cells involved in asthma pathogenesis is the eosinophil. Eosinophilic cytokines contribute to the chronic inflammatory process, in addition they have an interrelationship with other cells (epithelial, basophil, smooth muscle, mast, endothelial and neutrophil). Eosinophilic cytokines contribute to the activity, dysregulation and protonation of all the other cells that contribute to asthma pathogenesis. A number of cytokines released by eosinophils have autocrine growth-factor activities. These cytokines, Regulated on Activation, Normal T cell Expressed and Secreted (RANTES), IL-3, IL-5, and granulocyte-macrophage colony stimulating factor (GM-CSF), create a feedback loop for eosinophil expansion and activation. IL-5 is especially important in asthma and facilitates the maturation, activation and degranulation of eosinophils. In addition, IL-5 enhances the longevity of eosinophils by inhibiting apoptosis.[53] Other cytokines produced by human eosinophils that may have activities in acute and chronic inflammatory responses include IL-1, IL-6, IL-8, Tumour necrosis factor alpha (TNF-$\alpha$), and both transforming growth factors (TGF), TGF-$\alpha$ and TGF-$\beta$.[54]

The effector functions of eosinophil-derived cytokines are tissue repair and remodelling, innate immune cell interactions with mast cells, modulation of adaptive immunity, autocrine regulation, effects on nerve cells, and angiogenesis.[55] Eosinophils and their cytokines play a large number of roles in many of these different features of asthma.

There is a substantial amount of evidence linking eosinophils to asthma. It has been shown that there are increased numbers of eosinophils in symptomatic allergic asthma patients,[56] whether it is in the blood, the sputum or the tissue. Patients with airway hyper-responsiveness and airway limitation are associated with increased numbers of eosinophils. Understanding the role of eosinophils in the management of asthma is essential because treatments that decrease eosinophil numbers, whether it is systemic steroids, inhaled steroids, leukotriene modifiers, or IL-5 targeted therapy, result in improvement in asthma control.

Castro et al.[57] studied bronchial biopsies taken before and after treatment in 25 subjects with moderate persistent asthma. The subjects were treated for 30 days with inhaled fluticasone propionate (1760 $\mu$g/day) followed by a withdrawal period that lasted until peak expiratory airflow decreased by 25% and $FEV_1$ by 15%, or 6 weeks elapsed. The results showed that the number of eosinophils in the bronchial biopsies was increased by glucocorticoid withdrawal in both groups. This suggests that eosinophils play an important role in the inflammatory pathway. Similarly, allergen challenges result in increased eosinophils, this was demonstrated in a study of patients who underwent an allergen challenge.[58] The results showed that patients were shown to have a significant increase in sputum eosinophils after the allergen challenge compared with before the allergen challenge.

It has been suggested that asthma can be classified phenotypically as eosinophilic or non-eosinophilic.[59] It is estimated that 40-60% of asthma is in the eosinophilic subset,[60] and this number would probably increase significantly if corticosteroids were withdrawn. It has been shown that the severity of symptoms is increased in patients with eosinophilic asthma[61] and in those that have persistent eosinophilia despite the use of corticosteroids. Exacerbations are associated with sputum eosinophilia; Jatakanon et al.[62] studied the effect of changes in airway eosinophils in 15 patients with stable asthma. Mild exacerbations were induced in

the patients with stable asthma controlled with medium to high-dose ICS. The only significant difference between these two groups at baseline was a higher baseline sputum eosinophil count in subjects with subsequent exacerbations ($p<0.05$). Eosinophilia correlated with decreased lung function (PEF and $FEV_1$) and an increase in NO in these patients.

Further studies have shown the role of eosinophilia in poorly controlled asthma patients, Green et al.[63] studied 74 patients with moderate to severe asthma allocated randomly to management either by standard British Thoracic Society asthma guidelines (BTS management group) or by normalisation of the induced sputum eosinophil count and reduction of symptoms (sputum management group). The sputum eosinophil count was 63% (95% CI 24–100) lower over 12 months in the sputum management group than in the BTS management group (p=0.002). Patients in the sputum management group had significantly fewer severe asthma exacerbations than patients in the BTS management group (35 vs 109; p=0.01) and significantly fewer patients were admitted to hospital with asthma (1 vs 6, p=0.047). There were no differences between the groups in the average daily dose of inhaled or OCS. A treatment strategy directed at normalisation of the induced sputum eosinophil count as an inflammatory surrogate count reduces asthma exacerbations and admissions without the need for additional anti-inflammatory treatment. A similar study analysed data obtained from 164 subjects with mild to moderate asthma compared the effects of continued ICS use with the effects of a switch to salmeterol or placebo.[64] The study demonstrated that sputum eosinophils guided treatment strategy resulted in a 48% reduction in ICS therapy.

There are several potential eosinophil selective targets: chemoattractant receptor-homologous molecule expressed on $T_H2$ cells (CRTH2), mucin-like hormone receptor 1 (EMR-1), Siglec-8, chemokine receptor type 3 (CCR3), and IL-5 (Figure 9).[65] There is also the group of corticoid receptors, all of which are potential targets that could reduce the number of eosinophils in the airway.

IL-5 binds to a heterodimeric cell surface receptor comprising an alpha chain specific for IL-5 (IL-5Rα), and a beta chain that is shared with the IL-3 and GM-CSF receptors (βc). IL-5Rα is expressed on eosinophils and their precursors, basophils,

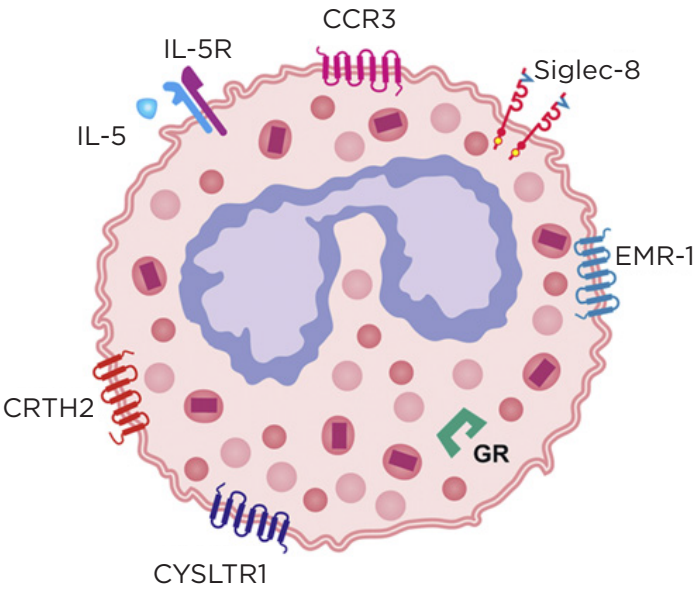



**Figure 9. Potential eosinophil selective targets.** CCR3: C-C chemokine receptor type 3; EMR-1: mucin-like hormone receptor 1; CRT: chemoattractant homologous receptor; GR: glucocorticoid receptor. *Wechsler ME, et al.*[65]

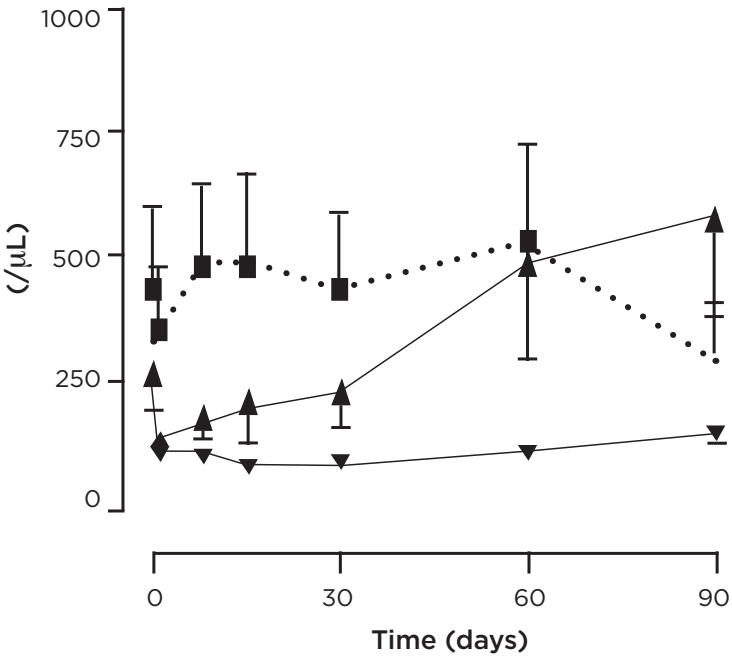
bronchial smooth muscle cells and murine B1 lymphocytes.[66] IL-5 promotes the intramedullary eosinophilopoietic development of eosinophil precursors to mature eosinophils and releases stored mature eosinophils from within the marrow.

IL-5/eosinophils may have a major role in asthma-associated remodelling. IL-5 is a major regulator of eosinophil proliferation and maturation. Cho et al.[67] sensitised wild-type (WT) and IL-5–deficient (IL-5 knock out [KO]) mice to ovalbumin (OVA), and challenged by repetitive administration of OVA for 3 months. WT mice had a significant increase in the number of peribronchial cells staining positive for major basic protein and TGF-β. In contrast, IL-5–deficient mice had a significant reduction in thenumber of peribronchial cells staining positive for major basic protein, which was paralleled by a similar reduction in the number of cells staining positive for TGF-β, suggesting that eosinophils are a significant source of TGF-β in the remodeled airway. OVA challenge induced significantly higher levels of airway epithelial Vβ6 integrin expression, as well as significantly higher levels of bioactive lung TGF-β in WT compared with IL-5–deficient mice. Increased airway epithelial expression of Vβ6

integrin may contribute to the increased activation of latent TGF-β. The IL-5 KO mice had significantly less peribronchial fibrosis (total lung collagen content, peribronchial collagens III and V) and significantly less peribronchial smooth muscle (thickness of peribronchial smooth muscle layer, smooth muscle actin immunostaining) compared with WT mice challenged with OVA. This indicates that IL-5, eosinophils and TGF-β appear to have an important role in airway remodeling.

Blocking IL-5 may significantly contribute to the management of asthma. There are at least three anti–IL-5 drugs in development: mepolizumab, reslizumab[68] and benralizumab.[65] These therapies target IL-5 (benralizumab targets the IL-5 receptor specifically); their mode of action is that they neutralise IL-5 and or have cytotoxic effects in the cells. The effects of the therapies are mainly a decrease in eosinophil counts and a decrease in eosinophil activation in the tissue, their aim is to improve asthma control.

In pre-clinical studies, reslizumab was administered to allergic mice resulting in pulmonary eosinophilia inhibition, and an anti-inflammatory effect was observed.[69] The anti-inflammatory activity is additive with oral prednisolone. In ovalbumin-sensitised guinea pigs reslizumab was administered before OVA challenge and resulted in the decrease of pulmonary eosinophilia and hyper-reactivity.[69] In addition, it significantly inhibited bronchoconstriction.[70]




Blood eosinophil counts after IV administration of placebo (N=8) (squares) or reslizumab at 0.3 mg/kg (N=6) (triangles) or 1.0 mg/kg (N=12) (inverted triangles)

**Figure 10. The effects of reslizumab on blood eosinophil counts.**
*Kips JC, et al.*[73]

In humans, Leckie et al.[71] showed that anti–IL-5 therapy resulted in a reduction of blood eosinophil count. 2-5 mg/kg and 10 mg/kg doses of anti–IL-5 caused a reduction in eosinophils that was sustained for up to 16 weeks, whereas placebo did not result in the reduction of eosinophils. It was also demonstrated that anti–IL-5 therapy resulted in a reduction of sputum eosinophil counts; significant reductions were seen in the 10 mg/kg anti–IL-5 group compared with placebo at 9 days and 30 days. The problem was that anti–IL-5 did not improve lung function in this study.[72] These were broad studies that looked at all asthmatics and did not stratify them according to baseline eosinophilia. Although there was a reduction in blood and sputum eosinophils there was no change in airway late phase reactivity to allergens, no change in lung function and no change in asthma symptoms.

It is becoming increasingly recognised that a wide group of asthmatics is not the most ideal study population. This is because asthmatics are heterogeneous, which indicates that different endotypes of asthma should be studied. This suggests that IL-5 therapy needs to be targeted at identified potential responders, and these should be stratified accordingly.

Kips et al.[73] studied anti–IL-5 in severe persistent asthma. Four different doses (0.03 mg/kg; 0.3 mg/kg; 0.1mg/kg; 1.0 mg/kg) of reslizumab versus placebo were given to 32 patients. The results showed there was a short-lived decrease in blood eosinophil count after the 0.3 mg/kg dose (52.5% reduction at 48 hours). There was a more pronounced response to reslizumab 1.0 mg/kg, remaining significant to 30 days post-treatment (p=0.05 versus placebo) (Figure 10). There was a substantial variability in sputum eosinophil counts, but no consistent changes over time were observed in any of the treatment groups. A trend towards increased $FEV_1$ was observed, with significant improvement at 24 hours with the 0.3 mg/kg dose (p=0.019 versus placebo). No significant changes in

$FEV_1$/FVC (forced vital capacity) ratio, peak flow, symptom score, or physician-evaluated overall condition were seen. Although there were no changes in peak flow or symptom score, it was thought that if stratified grouping was improved in larger patient populations, and as dosing regimens advance, it is possible that improvements in peak flow and symptom score would be seen.

In a further study, reslizumab was evaluated in poorly controlled eosinophilic asthma patients.[74] This Phase II, placebo-controlled, double-blind study randomised 106 patients with eosinophilic asthma who had ≥3% eosinophils at screening. Reslizumab at a 3 mg/kg dose was compared with placebo (IV dosing at weeks 0, 4, 8, and 12). The mean change in the asthma control questionnaire (ACQ) showed an improvement in the reslizumab group of -0.7 versus -0.3 in the placebo group (p=0.0541) (Figure 11). In addition, there was an improvement of ≥0.5 in ACQ scores in 59% of patients receiving reslizumab, versus 40% in the placebo group (odds ratio 2.06; p=0.0973), and a greater change from baseline in patients with nasal polyps of -1.0 in the reslizumab group compared with –0.1 in the placebo group (p=0.012). The mean change in $FEV_1$ was -0.08 in the placebo group compared with +0.18 in the reslizumab group (p=0.0023). The sputum eosinophil count was reduced by 95.4% in the reslizumab group compared with 38.7% in the placebo group (p=0.0068), and the reduction from baseline in blood eosinophil count was significantly greater in the reslizumab group (p<0.0001). Asthma exacerbations were reported in 8% of patients receiving reslizumab compared with 19% of those receiving placebo (p=0.0833), showing over a 50% reduction in asthma exacerbations in the reslizumab group.

A randomised trial of mepolizumab versus placebo in 20 patients with sputum eosinophilia and asthma symptoms despite prednisone, resulted in a significant reduction in exacerbations in the mepolizumab group compared with placebo (p=0.002).[75] In addition, there was a significant reduction in steroid dose (84% reduction in the mepolizumab group compared with 48% in the placebo group), there was a sustained benefit for 8 weeks of reduced eosinophils, and there were no serious adverse events. Another study evaluated mepolizumab and exacerbations of refractory eosinophilic

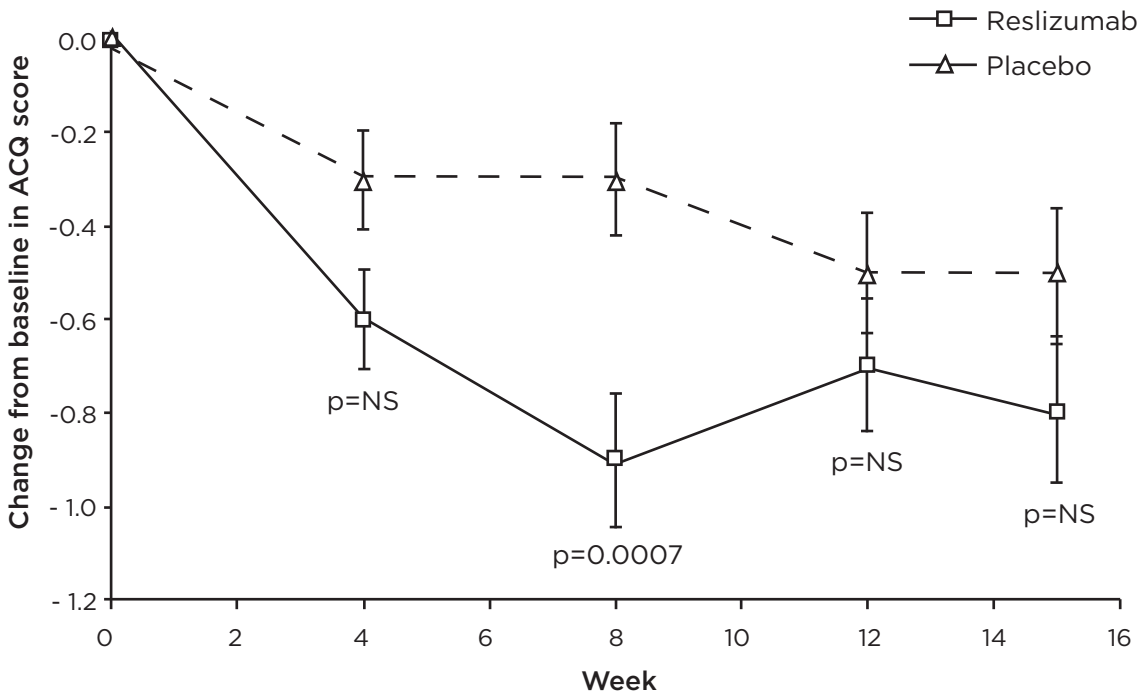



**Figure 11. The efficacy of reslizumab on ACQ score.**
*Castro M, et al.*[74]

asthma in 61 patients.[76] The patients were treated with mepolizumab or placebo for 12 months. The results showed that there was a significant reduction in exacerbations in the mepolizumab group compared with placebo; the cumulative number of exacerbations at month 12 was 57 versus 109, respectively. No effect on lung function, symptom scores or NO was seen. The results of this study are supported by another study, which found the total number of exacerbations over time was reduced with mepolizumab compared with placebo.[77] Patients with sputum eosinophils >3%, or fractional exhaled NO >50, or blood eosinophils >300, received 75,250 or 750 mg of mepolizumab or placebo. The results showed a significant reduction in asthma exacerbations in all three of the doses given (Figure 12). There were no effects on $FEV_1$, ACQ or in the AQoL. However, the reduction of the number of exacerbations equated to 50% per patient per year and this demonstrates a clinically important outcome.

Based on the studies that have been published to date, it has been shown that anti-IL-5 therapy is more likely to benefit patients with eosinophilic asthma. This group of patients not only shows a decrease in sputum eosinophilia but also an improvement in $FEV_1$ as well as an improvement in asthma control, and more importantly a decrease in exacerbations. Anti-IL-5 has been shown to be well tolerated with a similar percentage of patients with adverse events as placebo; the most commonly reported adverse events are headache, fatigue and nasopharyngitis.[74]

In the majority of the studies that have been done, eosinophilic asthma has been defined as persistent sputum eosinophils ≥2.5–3%.[78] Sputum cell count has been relied on because it is a valid, repeatable and responsive metric that is specific and comprehensive. Sputum cell counts have been independently evaluated in 18 different research laboratories across four continents. The

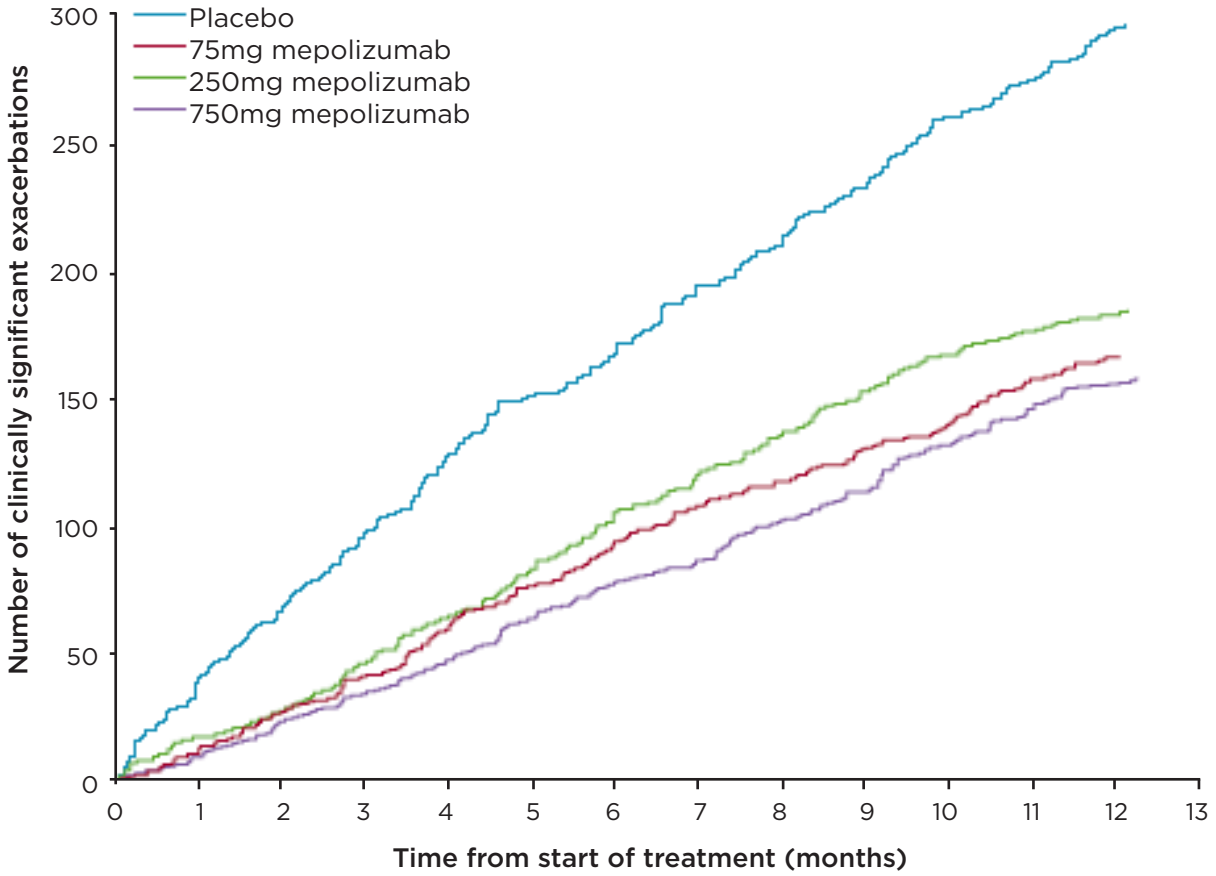



**Figure 12. Total exacerbations over time are reduced with mepolizumab versus placebo.**
*Pavord I, et al.*[77]

process for measuring sputum cell counts requires some training but produces excellent results.

In the persistent eosinophil phenotype, key metrics have shown that if patients are selected based on screening of eosinophils, good results are achieved. This has been illustrated in two studies that did not screen eosinophils in patients; in one study only 5% of the patient population had >3% eosinophils[73] and in the other, only 30% of the patient population had >3% eosinophils;[73] consequently, these studies did not demonstrate success with anti-IL-5 therapy. However, in studies with patients who have >3% eosinophils,[74-76] success has been demonstrated with this therapy.

The current gold standard in the diagnosis of eosinophilic asthma is sputum eosinophilia. The utilisation of blood eosinophilia is being considered as a marker and a metric because it is widely available and is a Food and Drug Administration standard. In the future it is hoped that other sputum biomarkers can be used to help identify responders and non-responders to anti-IL-5 therapy.

Anti-IL-5 is effective in reducing eosinophilia in blood and sputum. This has been established by improvements in lung function being apparent in patients with eosinophilic asthma. In addition, trends towards improved asthma control have been observed, with more pronounced effects being seen in patients with eosinophilic asthma and nasal polyps. Anti-IL-5 is well tolerated with a similar adverse event profile to placebo. Despite the fact that there are many other therapies available, newer therapies are required. Problems with adherence and inhaler technique require solving, and other ways to manage patients need to be identified. Accordingly, new therapies are required, and anti-IL-5 is a new therapy that appears to be effective, it targets a variety of different cells and makes biological sense. The future development of anti-IL-5 therapy provides an exciting option for the management of asthma patients.

## Panel discussion

**Question:** Why were sputum tests used when there are much easier and cheaper alternatives?

**Michael Wechsler:** The reason that sputum eosinophils were selected is because 1) eosinophils in sputum are in the compartments of interest. 2) There hasn't been a correlation between blood eosinophils and a response to therapy. It has been investigated, and, while in some patients' blood eosinophils there is a good response, not everyone with high blood eosinophils is necessarily a responder. Patients with low blood eosinophils do have higher sputum eosinophils because sputum is in the compartment of interest. I do think it is important to try and develop a simple assay; sputum is more difficult than the blood test. However, the more we do these kinds of studies the easier they will get, and certainly some people would argue that sputum is, in some ways, less invasive; you just spit into your pallet, and this maybe another reason for this approach. But we require a measure that predicts responsiveness whether it be in blood, sputum or urine.

**Question:** Which are better: leukotriene modifiers or an anti-IL-5?

**Michael Wechsler:** Leukotriene modifiers are effective therapies in patients with mild-to-moderate asthma and they do have some mild anti-eosinophilic properties. But in general you cannot use eosinophilia as a predictor of response to leukotriene modifiers, and the degree of benefit that has been seen with leukotriene modifiers compared with that seen with anti-IL-5 in patients, who are already on ICS and a LABA, is not to the same degree. So while leukotriene modifiers have beneficial properties and do have some anti-eosinophil effects they are not to the same degree as anti-IL-5.

**Question:** What do the other speakers think about anti-IL-5 therapy?

**Cynthia Rand:** So why would somebody who looks at adherence comment on this? Well I will make two comments and listen for a response. The first is that this is directly observed therapy, treatment where you confirm having received the treatment has been shown in other therapies to have a dramatic effect on outcome. So a study has not yet been done that actually teases out the difference between directly-observed therapy in this population, where you have matched and observed doses of inhaled steroids versus one of the biologics. So it raises a question for me as to what extent that is a contributor to outcome. And the second is the limitation we know we have in people who are non-adherent, the eosinophil count also goes up, so the question is to what extent in the studies that have been done have they sufficiently, that is really sufficiently, screened out non-adherence as a contributing cause for the increased eosinophils? So I think it is a really intriguing and promising area and clearly I absolutely agree it has had some impact on some populations, but what is a little less clear to me is whether or not it has actually provided a different way of delivering therapy to a population that was under-adherent in the first place.

**J. Christian Virchow:** From a clinical perspective, if you see patients who have eosinophilia, these are the ones that are easy to treat, and I would imagine that the number of patients with asthma who are difficult to treat usually lie in the high eosinophil range. These patients are not huge in numbers, but I do see a very clear need for these therapies in more complicated cases, such as allergic bronchopulmonary aspergillosis, where these patients have loads of eosinophils and need high doses of systemic corticosteroids. Secondly, there is a big need in patients who have asthma and eosinophilia; their problem is not so much the lower airways which can be treated, but the upper airways severe polyposis, and we know from these studies that if you give reslizumab to patients with nasal polyposis there is a reduction in the spores, whereas high doses, even toxic doses, of corticosteroids are required to get the disease in check. I certainly see a big need in these patients for anti-IL-5 therapy. I do see some patients with high steroid dosing-requiring asthma where you would go to a balance therapy with anti-IL-5 but also a dose of corticosteroids. I think that we need to keep in mind that our patients are well controlled on high doses of corticosteroids but only controlled according to GINA; they come to you and say I still feel miserable even though I take most of my inhalers but I hate taking this red stuff because it is not normal.

**Michael Wechsler:** Very recently, Sally Wenzel published a paper in *The New England Journal of Medicine* that examined patients with eosinophilia, who were poorly controlled on ICS and beta agonists; all patients were screened and there were still over 20% of patients who had persistent eosinophilia. So it is important to recognise that yes we can work on inhalers, we can work on compliance, but there are still a large proportion of patients that, no matter what you do, the patients take their medications, they take them properly and they are still symptomatic, and this is what this kind of therapy targets. We do need to work on those issues and other conditions need to be excluded.

**Question:** Can disease management programmes improve adherence?

**J. Christian Virchow:** Well I guess they could but the evidence for that is not from very well-controlled studies. Recently I saw a comprehensive care programme for asthma, very similar to a disease management programme in COPD, and saw higher mortality in the programme compared with those not in the programme. I think from what we have heard, anything that educates patients has at least the potential to increase compliance. Based on what we know I would say yes.

**Cynthia Rand:** There are lots of different flavours of disease management programmes and it depends on what they consist of. I think what the evidence suggests is that those which address more complicated issues have better outcomes. Clearly I think the theme that runs through all of our talks is that there is tremendous variability in asthma patients and, the extent to which you understand their

unique barriers and the phenotype underlying the severity, the better you can match the right treatment to help control their illness. Two comments that were raised by the audience, which I think are very important to raise: one that I failed to mention (as did others) is the cost of medication and the extent to which that can put up a barrier for a patient. I think it was highlighted before that many of our patients, and I speak from the US perspective where we do have some substantial cost issues, patients are not just treating one illness; they are having to cover costs for multiple different chronic illnesses, and indeed that has been shown to be a significant barrier, and that reducing that cost would improve adherence. And the second point that was made was that instead of searching for biomarkers for specialised therapies, perhaps we need behavioural studies in patients to increase adherence – well what am I going to say, I am going to say yes of course – but I truly do think we need to partner on these issues. There is no one solution for our patients, and behavioural strategies are not at the route of problems with asthma, but to manage any other chronic illness and how we can help patients better follow therapies.

**Question:** Coming back to the area of anti-IL-5 is there any experience in childhood asthma?

**Michael Wechsler:** There are some studies that are on-going in paediatric patients but nothing has been published to date.

**Question:** Another important question, which is particularly relevant to countries like many in Europe where we have consultation for free and access to medicine. How are you going to persuade the health authorities to fund this treatment how expensive will it be?

**Michael Wechsler:** The specific pricing for these therapies has not been developed as of yet; we have some experience based on anti-IgE therapy. The rationale for prescribing these expensive therapies is to prevent asthma exacerbations, and I showed you at least three different studies that demonstrate that anti-IL-5 reduced exacerbations. Exacerbations are very costly; they include hospitalisations, emergency room visits, and it is estimated in the United States that we spend at least 15 to 20 billion dollars a year treating patients with asthma, and at least two thirds to three quarters of that expenditure is in the management of asthma exacerbations and in hospitalisations, and so if we can reduce asthma exacerbations by 50%, as was shown in these studies, then this can result in significant savings, so that is the rationale we argue.

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