Looking back to go forward: adherence to inhaled therapy before biologic therapy in severe asthma

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Inhaler adherence may inform response to asthma biologic therapy and should continue to be assessed in patients receiving these treatments https://bit.ly/2RjMBED

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For decades inhaled corticosteroids have been central to the management of asthma and are proven to be effective in maintaining symptom control, reducing exacerbations and preserving quality of life through mediation of airway inflammation. However, a small minority of patients have disease which is refractory to high dose inhaled corticosteroid (ICS) therapy and require additional oral corticosteroids to achieve acceptable control of symptoms and exacerbations. Severe asthma represents less than 10% of the total asthma population [1] but is the most serious, life-affecting and costly form of the condition [2]. Whilst oral corticosteroids are usually very effective in achieving disease control, even short courses have very significant side-effects and negative long-term effects [3]. Visionary immunological researchers have defined the molecular mechanisms underlying asthma [4–6]. These insights in turn have led, in an amazingly short time span, to the development of a variety of safe, effective biological agents that target the specific immune pathways that drive airway inflammation and the subsequent clinical features of asthma [5–10].

However, under the umbrella term "severe asthma", there are many different reasons why some patients remain symptomatic despite high dose inhaled treatment. These people may not need the advanced biological treatments, as their condition remains uncontrolled due to one of a variety of real and practical reasons. For example, the diagnosis of asthma is correct but the presence of co-existing conditions [11] with similar symptoms such as obesity, deconditioning and dysfunctional breathing means that interpreting and ascribing symptoms to asthma is difficult. For others, the inhalers recommended for treatment are expensive and those who cannot afford them often ration its use, while others cannot master the use of the inhaler device [12, 13]. When recognised and addressed patients with apparently severe asthma can be managed with the usual treatments [14–16].

Suboptimal adherence to prescribed treatment has been widely reported in patients with chronic disease [17]. Ensuring adherence to inhaled therapy poses a particular challenge, due to the necessity to not only take the inhaler regularly and on time, but to master the correct inhaler technique [13]. Severe asthma is no exception; low adherence to inhaled therapy has been reported in this population and is associated with poor clinical outcomes [16, 18]. Adherence to inhaled therapy can be difficult to assess and self-report is not reliable [19, 20]. In order to address these issues, many hospital centres now take a multidisciplinary

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team (MDT) approach to the management of severe asthma [21]. The work of the MDT is of particular value where patients with severe asthma are being considered for biological treatment.

Large randomised controlled trials have shown that biologic therapies not only improve clinical outcomes in severe asthma [7–10] but facilitate significant reductions in maintenance oral corticosteroid dosage [22, 23]. However, the impact, if any, of these therapies on adherence to inhaled therapy or indeed whether they negate the need for continuing high dose ICS therapy remains unknown.

In this issue of the *European Respiratory Journal*, D'Ancona *et al.* [24] addressed these clinical questions by examining what happens to ICS adherence when patients are commenced on biologic therapy and the relationship between ICS adherence and the clinical response to therapy. Real-world data from 91 consecutive patients attending their expert severe asthma service in the UK and who completed 1 year of mepolizumab therapy was examined. All patients had confirmed severe eosinophilic asthma and were taking maintenance prednisolone at a dose of at least 5 mg daily. Prior to initiating biologic therapy, specific education in inhaler technique and adherence to high dose ICS was delivered to all patients by the specialist team. Pharmacy records were used to assess adherence to ICS in the 12 months prior to starting mepolizumab and for the first 12 months on treatment.

In the year prior to commencing mepolizumab one in five patients had poor adherence, *i.e.* they collected less than half of the prescriptions for inhaled corticosteroids from their pharmacy. There was no overall change in ICS adherence whilst on mepolizumab.

Reassuringly, 68% of patients had good adherence to ICS (collected more than 75% of ICS prescriptions) on treatment. However, in one-quarter of patients, ICS adherence worsened on mepolizumab and one-fifth of patients had poor ICS adherence on therapy. Factors predictive of poor adherence to ICS therapy were a history of smoking and poor adherence prior to mepolizumab treatment. More than 60% of patients with poor ICS adherence during mepolizumab treatment had poor adherence pre-treatment, despite receiving thorough inhaler adherence education.

Interestingly, their data shows that patients who had good ICS adherence during mepolizumab therapy achieved greater percentage decreases in daily OCS dose and demonstrated greater reductions in annual exacerbation rate. Less than 10% of those with good ICS adherence experienced treatment failure, defined as "inability to reduce either daily OCS dose or annual exacerbation rate by $\geqslant$50% after 12 months of mepolizumab therapy", compared to 37.5% of those with poor ICS adherence whilst on treatment.

Limitations of the study includes the relatively small sample size, although the clarity of the results more than make up for this. The medication possession ratio was used to assess adherence. While this is a recognised and widely used objective measure of adherence, it does have limitations; it assumes that refilling of a prescription equals medication-taking [19] and does not take into account timing of use or inhaler technique, both of which are important considerations when assessing inhaler adherence [13, 25–27]. A more detailed assessment of adherence, such as a digital system that also assessed inhaler technique, might have found deeper insights into adherence behaviour, to explain more clearly the relationships of adherence and outcomes [25, 28]. It would have been interesting to understand the drivers of adherence behaviour among the patients

The practical finding of this study is that biologic therapy appeared to be more effective in those who maintained good adherence to ICS therapy. This has important clinical implications and emphasises the importance of ensuring the basic principles of good asthma management are continued in patients receiving biologic therapy. Assessment of failure to respond to a particular biologic treatment should incorporate inhaler adherence review and an exploration of factors which may be contributing to non-adherence.

The finding of poorer treatment response associated with non-adherence to ICS should inspire further research in this area, looking to see why this is the case; for example, did the patients have a T2 low asthma and were non-adherent because they perceived no benefit from the treatment? As with all good research, one question is answered and this truth opens a box of new interesting questions.

This innovative study gives important insights into how an additional measure, objectively obtaining long term data on inhaler adherence, should be a routine part of MDT work prior to starting a biological agent. It is a sad reality that for some people their chaotic lives hamper their ability to follow through on the apparently simple task of getting and using an inhaler regularly. Detecting poor adherence should not be an automatic block to the use of a biological therapy for an individual but it can be the start of a diagnostic quest to understand our patients at a social as well as biological level.

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