

EXPERT  
REVIEWSEfficacy and safety of  
high-dose ciclesonide for the  
treatment of severe asthma*Expert Rev. Respir. Med.* 7(4), 339–348 (2013)**Eric D Bateman***Division of Pulmonology, Department  
of Medicine, University of Cape Town,  
George Street, Mowbray 7700, Cape  
Town, South Africa  
eric.bateman@uct.ac.za*

Asthma severity is classified according to the level of treatment required to control symptoms. Inhaled corticosteroids are the recommended first-line therapy for the treatment of persistent asthma, and when asthma remains uncontrolled, one option is to increase the inhaled corticosteroids dose. However, there is a concomitant risk of increasing local and systemic adverse events, which may impact patient adherence and physician prescribing practices. Ciclesonide is delivered as a prodrug, has high peripheral lung deposition and high protein-binding capabilities, and is rapidly eliminated from the systemic circulation. This article reviews the use of high-dose ciclesonide in patients with severe asthma and considers whether the pharmacology of ciclesonide translates into it being an efficacious and well-tolerated option for patients requiring a step-up in their asthma treatment.

**KEYWORDS:** adverse event • asthma • ciclesonide • exacerbation • HPA axis • inhaled corticosteroid

Inhaled corticosteroids (ICS) are the most effective anti-inflammatory medication for the treatment of persistent asthma and are recommended as first-line therapy by treatment guidelines [1,101]. Medium or high doses of ICS are an option for Step 3 of the Global Initiative for Asthma (GINA) strategy and are recommended in combination with a second controller for Step 4 and beyond (GINA Evidence A) [101]. However, increasing the dose of ICS does not always result in increased efficacy [2,3], and the addition of a long-acting  $\beta_2$ -agonist (LABA) is initially preferred [101]. Furthermore, the risk of adverse events (AEs) associated with high-dose ICS may make some physicians reluctant to increase ICS dosage [4] and patients reluctant to adhere to the treatment [5].

Nevertheless, a high dose of ICS may be necessary in some patients [101]. However, nonadherence to asthma treatments is common and is the most important reason for apparent treatment refractoriness. If not considered by physicians, nonadherence may lead to unnecessary ICS dose escalation and increased risk of associated AEs.

The reason for ICS refractoriness remains unclear in some patients. Proposed mechanisms range from inherent refractoriness of airway inflammatory cells to acquired and environmental factors such as current or previous tobacco smoking [6]. Approximately one-quarter of all

asthma patients are smokers [7], and even more are ex-smokers [8]; in such patients responsiveness to ICS is affected [9]. This effect can be partially overcome by the use of higher doses of ICS, at least in terms of lung function [9]. However, increasing the dose of ICS exposes patients to a greater potential for AEs. Furthermore, even at high doses of ICS the proportion of patients who achieve asthma control is lower in smokers and ex-smokers than in non-smokers [10].

The decision to increase the dose of ICS is made on the basis of the anticipated benefit of a higher dose versus what may be achieved by the addition of a second or third controller treatment. Asthma control comprises two domains: current asthma control and future risk. The latter includes risk of exacerbations, instability, decline in lung function and AEs [1,11,101]. For some end points, the risk is inversely proportional to the levels of current asthma control achieved [11]. For example, the risk of severe asthma exacerbations and hospitalizations remains highest in patients with uncontrolled asthma. If current control cannot be achieved with the preferred first-line options, approaches that target reduction of exacerbation risk become important. First among these is the use of higher maintenance doses of ICS, since ICS are the most effective treatment for this purpose [12]. Although doubling the dose has proven to be ineffective in clinical studies [13,14], increasing an

ICS dose by fourfold may be effective at preventing exacerbations [15]. Further to this strategy, additional controllers, in combination with an LABA, may be considered, including leukotriene receptor antagonists, theophylline, oral corticosteroids (OCS), omalizumab and bronchial thermoplasty [101]. Since medium and high doses of ICS remain the most important treatment of uncontrolled asthma and may be required in the long term, it is important to ensure that the dose is optimized, and that an ICS with a favorable therapeutic index is selected. Furthermore, the ICS should have a simple dosing schedule as this has been shown to improve patient adherence [16]. This review considers the pharmacology of ciclesonide and the clinical evidence for its efficacy and safety when used in high doses in the treatment of severe asthma.

### Ciclesonide pharmacology

Ciclesonide is an inactive prodrug. The inactive ciclesonide molecule is converted to its active metabolite, desisobutyryl-ciclesonide (des-cic) by esterases that are present in profusion in bronchial epithelia, but to a lesser extent in the mouth [17]. This helps restrict steroidal activity to the desired site of action and minimize local AEs [18,19], which have been reported infrequently compared with fluticasone propionate [20]. Mouth-rinsing studies have demonstrated a several-fold lower amount of des-cic in the oropharynx compared with budesonide or fluticasone propionate [19,21]. This reduces the need for mouth rinsing after ciclesonide use and may improve patient adherence.

Ciclesonide is administered via a pressurized metered-dose inhaler (pMDI) using a hydrofluoroalkane (HFA) propellant available in two different strengths: 80 and 160 µg per inhalation. The GINA strategy document considers a low daily dose of ciclesonide to be 80–160 µg, a medium daily dose to be > 160–320 µg and a high daily dose to be >320 µg. The ciclesonide HFA pMDI inhaler allows for the production of small, highly respirable particles (mass median aerodynamic diameter <2 µm) [22–24]. The resulting plume is soft (slow), reducing the force of impact of the spray on the posterior oropharynx (the ‘cold Freon’ effect) and ensuring that a high proportion of respirable particles are deposited in the lower respiratory tract. Imaging studies have confirmed lung deposition of >50% of the delivered dose of ciclesonide, with a high percentage reaching the peripheral lung [25]. Two small studies have shown that ciclesonide exerts anti-inflammatory effects on the small airways of patients with asthma [26,27]. Rapid clearance by the liver and high plasma protein-binding help limit the systemic adverse events of ciclesonide [28,29]. An additional minor advantage of the HFA formulation of ciclesonide is that the drug is in solution, so the inhaler does not have to be shaken before use, as is required for an ICS suspension in an HFA pMDI.

### Dosing frequency & time of dosing of high-dose ciclesonide

The pharmacokinetics and pharmacodynamics of ciclesonide allow once-daily (q.d.) use. High lipophilicity allows ciclesonide to pass through cell membranes in lung tissue more rapidly than some other ICS, and conjugation of des-cic with fatty acids creates an intracellular pool of drug that is released slowly over 24 h, thereby

prolonging the anti-inflammatory activity of ciclesonide [30]. For these reasons, studies of ciclesonide in patients with asthma have focused on q.d. administration, some of which compared ciclesonide with other ICS administered twice daily (b.i.d.). For example, Boulet *et al.* found similar improvements in lung function in patients with moderate asthma treated with ciclesonide 320 µg q.d. or fluticasone propionate 200 µg b.i.d. [31]; Dahl *et al.* reported a similar benefit in terms of lung function and other measures of asthma control with ciclesonide 80 µg q.d. compared with fluticasone propionate 100 µg b.i.d. in patients with mild-to-moderate asthma [32]; and Buhl *et al.* reported similar efficacy with ciclesonide 160 µg q.d. compared with fluticasone propionate 88 µg b.i.d. in a population where the majority of patients had mild-to-moderate asthma [33].

Asthma is frequently worse at night. Owing to chronobiologic considerations – the nocturnal cortisol nadir in the face of suppression of cortisol secretion by ICS – evening dosing may ensure better corticosteroid cover. A greater clinical benefit from evening versus morning dosing has been reported in some [34,35] but not all studies of q.d. ICS dosing [36], and evening dosing has also been shown to result in equivalent or reduced cortisol suppression [37]. Ciclesonide has been shown to be equally effective when administered in the morning or evening [38]. However, in a study comparing the effect of various doses of ciclesonide and fluticasone propionate with placebo, Derom *et al.* reported no significant changes in urinary or plasma cortisol levels following evening administration of 320 µg q.d., 640 µg q.d. and 640 µg b.i.d. ciclesonide, while both fluticasone 440 µg b.i.d. and 880 µg b.i.d. were associated with a significant reduction in plasma cortisol levels compared with placebo [39]. It is recommended that ciclesonide q.d. be administered in the evening.

Fluticasone propionate is associated with significantly greater efficacy when administered b.i.d. compared with q.d. [40] and is consequently approved for b.i.d. dosing in patients with asthma. Budesonide is approved for q.d. dosing in patients with mild or moderate asthma (budesonide q.d. is as efficacious as budesonide b.i.d. at the same total daily dose in patients with mild-to-moderate asthma [41], but b.i.d. dosing is recommended for patients with more severe asthma). Mometasone furoate is also approved for q.d. dosing in patients with mild or moderate asthma. Ciclesonide is approved for q.d. dosing in patients with asthma. However, q.d. dosing with most ICS is not recommended in severe asthma. Indeed, even four-times daily dosing for patients with severe asthma has been proposed [42,43]. Clinical trials of the efficacy of ciclesonide in patients with severe asthma have utilized b.i.d. dosing when the total dose is >320 µg/day (TABLE 1) [20,44–49]. These studies have reported improved outcomes with high- versus low-dose ciclesonide, although none of the studies compared high-dose ciclesonide administered as an q.d. versus a b.i.d. dose. As q.d. dosing is preferred by patients and may improve adherence [16], the dosing frequency of high-dose ciclesonide may be individualized.

### Efficacy of high-dose ciclesonide

Doses of ciclesonide ranging from 80 to 1280 µg/day have been studied in clinical trials, with the higher doses being administered

**Table 1. Efficacy of ciclesonide in severe asthma.**

| Author             | Ciclesonide dosing                              | Comparator                     | Treatment phase                    | Patients                                                                         | Main outcomes                                                                                                                                                                                    | Ref. |
|--------------------|-------------------------------------------------|--------------------------------|------------------------------------|----------------------------------------------------------------------------------|--------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------|------|
| Bateman 2006       | 640 µg/day (b.i.d.)<br><br>1280 µg/day (b.i.d.) | Placebo (b.i.d.)               | 12 weeks                           | Severe persistent asthma<br><br>n = 141<br>≥12 years of age                      | Oral steroid dose was significantly reduced with both ciclesonide doses, and increased with placebo                                                                                              | [44] |
| Adachi 2007        | 320 µg/day (q.d.)<br>640 µg/day (b.i.d.)        | BDP 800 µg/day (b.i.d.)        | 8 weeks                            | Moderate-to-severe persistent asthma<br><br>n = 319<br>16–75 years of age        | Morning PEF improved more with high-dose ciclesonide than with the lower dose or equivalent dose of BDP                                                                                          | [45] |
| Vermeulen 2007     | 320 µg/day (q.d.)                               | BUD 800 µg/day (q.d.)          | 12 weeks                           | Severe asthma<br><br>n = 403<br>12–17 years of age                               | Ciclesonide was as effective as BUD at improving FEV <sub>1</sub> , days without asthma symptoms, and rescue medication use                                                                      | [46] |
| Bateman 2008a      | 640 µg/day (b.i.d.)                             | FP 660 µg/day (b.i.d.)         | 24 weeks                           | Moderate-to-severe persistent asthma<br><br>n = 528<br>18–75 years of age        | Ciclesonide and FP had similar efficacy in improving FEV <sub>1</sub> , PEF, asthma symptom scores, and rescue medication use                                                                    | [20] |
| Bateman 2008b      | 160 µg/day (q.d.)<br>640 µg/day (b.i.d.)        | None                           | 24 weeks                           | Severe persistent asthma<br><br>n = 680<br>18–75 years of age                    | High-dose ciclesonide prolonged the time to first exacerbation and improved symptom scores and rescue medication compared with the low dose. FEV <sub>1</sub> improved similarly with both doses | [47] |
| van den Berge 2009 | 640 µg/day (b.i.d.)                             | Oral prednisolone 20 mg (q.d.) | 2 weeks                            | Worsening asthma (following ICS withdrawal)<br><br>n = 130<br>18–75 years of age | Morning PEF, asthma symptom scores, and FEV <sub>1</sub> improved similarly with high-dose ciclesonide and oral prednisolone                                                                     | [48] |
| O'Connor 2010      | 640 µg/day (b.i.d.)<br><br>1280 µg/day (b.i.d.) | None                           | 12 weeks + 40-week extension phase | Severe asthma<br><br>n = 365<br>18–75 years of age                               | Morning PEF and asthma symptom scores improved at both doses, and were maintained during the extension phase                                                                                     | [49] |

BDP: Beclomethasone dipropionate; b.i.d.: Twice daily; BUD: Budesonide; FEV<sub>1</sub>: Forced expiratory volume in 1 second; FP: Fluticasone propionate; ICS: Inhaled corticosteroids; q.d.: Once daily; PEF: Peak expiratory flow.

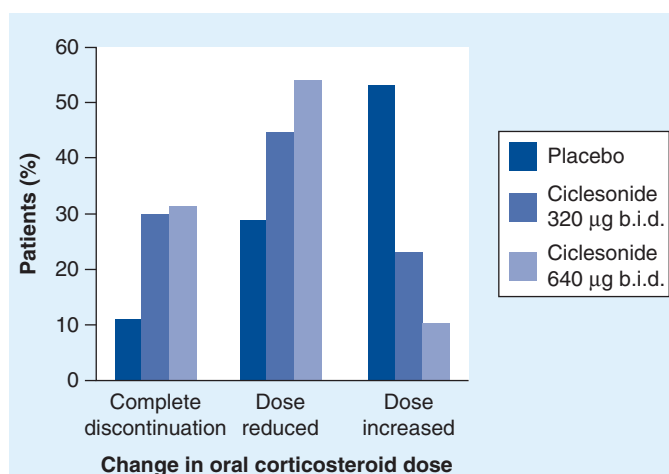


**Figure 1. Oral corticosteroid-sparing effects of high-dose ciclesonide in patients with severe asthma.**

b.i.d.: Twice daily.

Reproduced with permission from [44].

to patients with more severe asthma (TABLE 1). Ciclesonide >320–1280 µg/day is considered high-dose [101]. A consideration when prescribing higher doses of ciclesonide, which is available in aerosols containing either 60 or 120 doses, is the possibility that more than one canister might be required each month. The impact of this on adherence and reluctance to use the prescribed or required dose has not been studied.

A 12-week randomized, double-blind study in 680 patients with severe asthma found ciclesonide 320 µg b.i.d. superior in terms of time to first exacerbation compared with ciclesonide 160 µg q.d. ( $p = 0.005$ ) [47]. The higher dose also resulted in significantly greater improvements from baseline in lung function (% predicted forced expiratory volume in 1 s [FEV<sub>1</sub>] and peak expiratory flow [PEF];  $p < 0.05$ ), asthma symptom score sum ( $p = 0.01$ ) and rescue medication use ( $p = 0.0005$ ) compared with the lower dose. The results, confirming that a fourfold higher dose of ICS is superior in reducing the risk of exacerbations, are consistent with the studies reviewed by Kelly *et al.* [50].

Evidence from a separate 12-week randomized, double-blind study suggests that ciclesonide 640 µg/day is close to the top of the dose–response curve, at least in terms of lung function and asthma symptom score [49]. Morning PEF increased significantly from baseline with both 320 µg b.i.d. and 640 µg b.i.d. (16 l/min and 14 l/min, respectively; both  $p \leq 0.001$  vs baseline over 12 weeks), but there was no significant between-group difference. This improvement in lung function was maintained over a 40-week extension phase with both doses.

#### Oral corticosteroid-sparing efficacy of high-dose ciclesonide

Although in most circumstances a ciclesonide dose of 640 µg/day is the recommended maximum, the use of a higher dose may be effective in reducing reliance on maintenance treatment with OCS. Bateman *et al.* examined the OCS-sparing effects of ciclesonide compared with placebo in patients with severe asthma in a 12-week,

multicenter, randomized, double-blind study [44]. Patients received continuous ICS therapy during the 6 months before inclusion, and prior to randomization to ciclesonide (either 320 µg b.i.d. or 640 µg b.i.d.) or placebo, each patient's OCS dose was adjusted to ensure that they were on the lowest dose effective for maintaining control. At randomization, their currently prescribed ICS was stopped, and the OCS dose was reduced at weekly intervals if no evidence of asthma worsening was observed. By the end of the study, OCS dose was stopped in approximately 30% of patients receiving ciclesonide versus 11% of those receiving placebo (FIGURE 1) and the mean OCS dose reductions were 47.4% and 62.5% in the 320 µg b.i.d. and 640 µg b.i.d. ciclesonide groups (no statistical difference), respectively. An increase in prednisone dose of 4.2% occurred in the placebo group. In the placebo group, 53.3% of patients increased OCS use compared with 23.4 and 10.4% of patients in the ciclesonide 320 µg b.i.d. and 640 µg b.i.d. groups, respectively (FIGURE 1). The mean FEV<sub>1</sub> improved in both ciclesonide groups but worsened in the placebo group.

In a further study examining the potency of high-dose ciclesonide as an alternative to OCS, van den Berge *et al.* compared these treatments in 130 patients with worsening asthma resulting from a systematic reduction of ICS [48]. In this 2-week, randomized, double-blind study, ciclesonide 640 µg b.i.d. was comparable with prednisolone 40 mg q.d. in improving FEV<sub>1</sub>, morning PEF, patient-recorded asthma symptoms, PC<sub>20</sub> methacholine and markers of airway inflammation, and resulted in significantly less reduction in morning cortisol levels ( $p < 0.0001$ ).

#### High-dose ciclesonide compared with other inhaled corticosteroids

Studies comparing ciclesonide with other ICS provide insights into its relative efficacy and safety and serve as a guide to dose selection when prescribing ciclesonide. Although the GINA strategy provides tables of recommended dose ranges for different ICS preparations and suggests equipotent doses in the low-, medium-, and high-dose ranges, few of these doses are based on direct comparisons of different ICS doses in randomized clinical trials. For ciclesonide, although doses above 320 µg are not approved in some countries, the high-dose range is considered to be >320–1280 µg/day; the equivalent high-dose range for fluticasone propionate is >500–1000 µg/day; for budesonide is >800–1600 µg/day and for beclomethasone dipropionate is >500–1000 µg/day [101]. The difficulties in evaluating the relative potencies of ICS are well known and relate to the limited number of dose comparisons that can be made in one study. Moreover, the relatively flat dose–response curve of ICS makes it difficult to compare even different doses of the same ICS in the medium- to high-dose range.

Several comparator studies have been performed with high-dose ciclesonide. For example, in a 6-month, randomized, parallel-group, open-label study of ciclesonide 320 µg b.i.d. versus fluticasone propionate 330 µg b.i.d. in patients with moderate-to-severe asthma, no significant differences in efficacy were detected between the treatment groups [20].

In an 8-week, multicenter, randomized, open-label study of ciclesonide 320 µg q.d., ciclesonide 320 µg b.i.d., and beclomethasone dipropionate 800 µg/day in patients with moderate-to-severe asthma, ciclesonide 320 µg b.i.d. was superior to beclomethasone dipropionate 800 µg/day in change in morning PEF values from baseline (24.0/min vs 5.9/min, respectively;  $p = 0.001$ ; 95% CI: 6.9–29.2 l/min) [45]. In addition, the use of rescue medication decreased significantly with ciclesonide 320 µg b.i.d. compared with beclomethasone dipropionate 800 µg/day ( $p = 0.007$ ). Improvements in asthma scores were greater with ciclesonide 320 µg b.i.d. compared with beclomethasone dipropionate 800 µg/day, and the differences at both week 6 and week 8 were significant ( $p = 0.03$  and  $p = 0.008$ , respectively).

In adolescents (12–17 years of age) with severe asthma, a 12-week, randomized, parallel-group study showed comparable and significant increases in FEV<sub>1</sub> from baseline to study end in patients treated with either ciclesonide 320 µg q.d. or budesonide 800 µg q.d. ( $p < 0.0001$  for both) [46]. Median percentage of days without asthma symptoms and without rescue medication use was 84% with ciclesonide and 85% with budesonide.

### Safety and tolerability of high-dose ciclesonide

Inhaled corticosteroids differ in their safety and tolerability profiles. This is understandable given that local AEs relate not only to the potency of the ICS but also to the characteristics of the aerosol (dry powder vs pMDI, particle size, plume velocity and use or not of a spacer device). The physicochemical interaction of the drug with mucus membranes is also important and is determined by ICS solubility, lipophilicity and affinity for, and dwell-time on, glucocorticosteroid receptors. Systemic exposure is determined by the pattern of drug deposition (being greater with particles of smaller size and peripheral lung deposition), the proportion of ICS that is swallowed (which is higher with less efficient delivery devices and when spacers are not used) and the pharmacokinetic and pharmacodynamic properties of the ICS.

### Local adverse events

Several studies have reported the local AE profile of high-dose ciclesonide. One 12-week study comparing ciclesonide 320 µg b.i.d. and 640 µg b.i.d. in patients with severe asthma recorded no cases of patient-reported oral candidiasis [49]. A separate 24-week study comparing ciclesonide 320 µg b.i.d. and fluticasone propionate 330 µg b.i.d. reported a significantly higher incidence of oropharyngeal AEs (confirmed candidiasis and dysphonia) in the fluticasone propionate group compared with the ciclesonide group (12.8% and 5.1%, respectively;  $p = 0.002$ ) [20].

The Inhaled Corticosteroid Questionnaire (ICQ) is a validated measure for the presence and severity of patient-perceived AEs. Three separate randomized studies of patients with moderate or moderate-to-severe asthma treated with ciclesonide 320 µg q.d., ciclesonide 320 µg b.i.d. or fluticasone propionate (200 µg, 375 µg or 500 µg) b.i.d. reported that ciclesonide was associated with improved ICQ scores, and generally reported less intense AEs compared with patients treated with fluticasone propionate (FIGURE 2) [51].

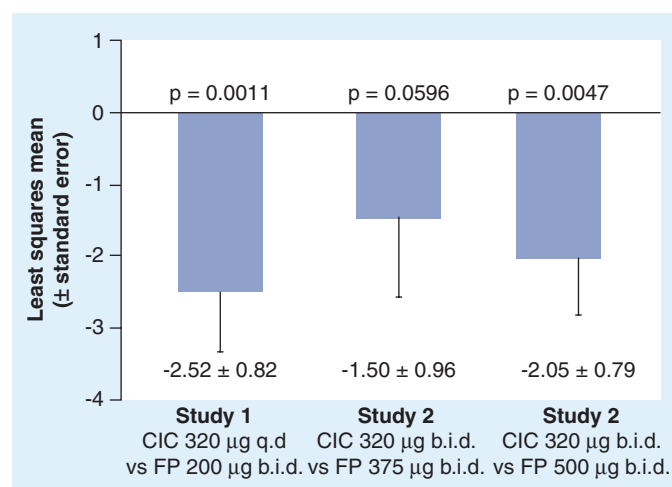


**Figure 2. Between-treatment differences (ciclesonide–fluticasone propionate) in Inhaled Corticosteroid Questionnaire total score in three separate studies of patients with moderate or moderate-to-severe asthma.**

A negative between-treatment difference corresponds to a decrease in patient-perceived adverse events. Differences were significant if  $p < 0.025$  (one-sided).

b.i.d.: Twice daily; CIC: Ciclesonide; FP: Fluticasone propionate; q.d.: Once daily.

Reprinted with permission from [51].

### Systemic adverse events

Reduced hypothalamic–pituitary–adrenal (HPA)-axis function is a sensitive measure of the systemic bioavailability of an ICS. Long-term systemic exposure to ICS treatment may lead to AEs such as reduced bone mineral density, which may be permanent, and slowing of growth velocity in children, which, while largely reversible (associated with ‘catch-up’ if the ICS is stopped or the dose reduced) [52], may interfere with both emotional and social development, and poor self-image [53].

Studies of ciclesonide doses of up to 1280 µg/day report no clinically relevant suppression of HPA-axis function and minimal associated AEs (FIGURE 3) [39,44,46,48,49,54–58]. For example, a 12-week study of ciclesonide 320 µg b.i.d. and 640 µg b.i.d. in patients with severe asthma found that serum and 24-h urine cortisol levels were not suppressed by either ciclesonide dose [49]. Furthermore, serum and 24-h urine cortisol levels remained unchanged during the 40-week extension phase of this study.

In a 52-week, randomized study (Steroid Titration Against Mannitol in Persistent Asthma: STAMINA), the dose of ciclesonide was selected and adjusted according to airway hyper-responsiveness to mannitol or according to standard clinical criteria [55,56]. The higher doses of ciclesonide used in the mannitol group did not significantly suppress overnight urinary cortisol/creatinine levels or suppress bone metabolism as measured by markers of bone turnover.

The systemic profile of high-dose ciclesonide has also been assessed in adolescents and children. In adolescents aged 12–17 years with severe asthma treated for 12 weeks with either budesonide 800 µg q.d. or ciclesonide 320 µg q.d., urine cortisol measurements significantly decreased from baseline with

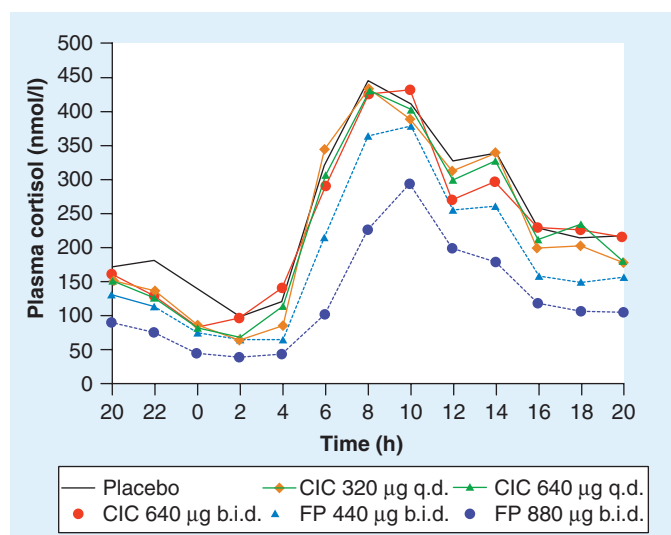


**Figure 3. Plasma cortisol levels following treatment with placebo, high-dose ciclesonide or high-dose fluticasone propionate in patients with mild or moderate persistent asthma.**

b.i.d.: Twice daily; CIC: Ciclesonide; FP: Fluticasone propionate. OD: Once daily.

Reprinted with permission from [39].

budesonide ( $p = 0.009$ ) but not with ciclesonide ( $p = 0.1$ ) [46]. In a separate study, ciclesonide 160 µg b.i.d. had no significant effect on lower-leg growth rate in children aged 6–12 years, whereas fluticasone propionate 330 µg/day significantly reduced lower-leg growth rates when compared with placebo ( $p = 0.0002$ ) and ciclesonide ( $p = 0.04$ ) [57]. In addition, cortisol levels in 12-h overnight urine were significantly lower with fluticasone propionate compared with ciclesonide ( $p < 0.05$ ). There is evidence that HPA-axis suppression associated with fluticasone propionate treatment of pediatric asthma can be reversed by switching to ciclesonide, although this is based on data from only four patients [59].

Finally, a 1-year study of the effects of ciclesonide (640 µg/day) and beclomethasone dipropionate (640 µg/day) on the eyes of adult patients with moderate-to-severe asthma confirmed no impact of ciclesonide or beclomethasone dipropionate on the development or progression of cataracts [58].

## Conclusion

For patients with uncontrolled asthma, the GINA strategy recommends that therapy is stepped up until control is achieved. High-dose ciclesonide is as effective as other ICS at equipotent doses and reduces the risk of exacerbation compared with low-dose ciclesonide. Moreover, the incidence of local adverse events associated with ciclesonide is low, and doses of up to 1280 µg/day do not significantly suppress HPA-axis function.

## Expert commentary

Asthma severity is classified according to the level of treatment required to control symptoms. Asthma control comprises both current control of symptoms and future risk of AEs such as exacerbations – patients with uncontrolled asthma have a high future

risk of severe exacerbations and consequent hospitalizations [11]. Exacerbations are triggered by airborne allergens, pollution and tobacco smoke; they are difficult to predict, are frightening for the patient and have a high economic burden. However, the majority of patients can achieve control of their asthma with the correct treatment.

ICS are the most effective treatment for reducing exacerbation risk. However, treatment must be individualized to the patient. For example, neutrophilic asthma is more corticosteroid-refractory than eosinophilic asthma [60], and smokers have reduced responsiveness to corticosteroids [61]. Therefore, the decision to increase ICS dose in uncontrolled patients must be made on the basis of the anticipated increased efficacy versus the increased risk of AEs. As AEs may negatively impact patient adherence, which in turn may lead to loss of control, ICS that have favorable safety and tolerability profiles at high doses should be preferred.

Guidelines recommend stepping up treatment when asthma remains uncontrolled. However, once stepped up, physicians may fail to review the level of treatment after asthma control has been maintained for >3 months, which can result in overtreatment. Measurements of inflammatory markers such as sputum eosinophils and exhaled nitric oxide have been shown to be effective in guiding the selection of ICS dose and distinguishing patients who require higher dose ICS from those in whom a dose reduction may be appropriate [62,63]. However, sputum analysis is not feasible in most clinical settings, and questions remain over whether the use of nitric oxide levels is effective [64]. Therefore, ICS dose selection remains a clinical decision, and safety concerns associated with high-dose ICS use continue to be relevant.

Concerns regarding corticosteroid use relate to both short- and long-term AEs. HPA-axis suppression occurs relatively rapidly, whereas long-term corticosteroid use is associated with skin thinning, cataracts, diabetes, osteoporosis and slow growth in children. Corticosteroid-associated AEs may contribute to an under-utilization of high-dose ICS by physicians.

Clinical trials have demonstrated the OCS-sparing efficacy of beclomethasone dipropionate, budesonide, fluticasone propionate and ciclesonide, and that high-dose ciclesonide is as effective as other ICS at equipotent doses, with minimal local and systemic AEs. Therefore, ciclesonide may be considered when higher doses of ICS are warranted; either as initial therapy or as a switch option.

## Five-year view

The increased risk of lower respiratory tract infections and pneumonia in patients with asthma treated with ICS requires further study. Although confirmed in patients with chronic obstructive pulmonary disease (COPD), an initial retrospective analysis of budesonide in patients with asthma failed to show evidence of an increased risk of pneumonia when compared with non-ICS treatment, even in patients receiving a high dose of budesonide [65]. However, recent prospective studies suggest an increased risk of infections associated with ICS use in patients with asthma [66–68]. In addition, the risk might be different for different ICS. For example, in an observational study of COPD patients, the incidence of pneumonia with fixed-combination

budesonide/formoterol was lower compared with fixed-combination fluticasone propionate/salmeterol [69]. However, it is likely that for all ICS, the risk will be small in patients with asthma, and this, like other risks, needs to be balanced against the benefits of ICS use. These benefits are greater than those with ICS use in the treatment of COPD where LABAs and roflumilast have similar efficacy in reducing COPD exacerbations. Indeed, the role of ICS in asthma is pivotal, and alternatives are not as effective, especially for preventing exacerbations. In addition, the significance of the infections observed in COPD is unclear, as a retrospective cohort study has suggested that these infections are not associated with a higher risk of mortality [70].

Fixed-combination ICS/LABAs simplify administration, which may improve adherence. Ciclesonide is an attractive option for development in combination with an LABA. An initial trial, the EXCITED study, has reported that the fixed combination of ciclesonide/formoterol is non-inferior to fluticasone propionate/salmeterol in patients with moderate asthma ( $p < 0.0001$ ) [71]. Further clinical trials of fixed-combination ciclesonide/LABA in patients with severe asthma and COPD are awaited.

A likely future development is a fixed-combination ICS/ultra-LABA suitable for q.d. dosing.

With the advent of 'personalized medicine,' novel classes of therapeutic agents for specific phenotypes of asthma are being developed [72]. For example, the anti-IL5 antibody mepolizumab significantly reduced exacerbations requiring treatment with OCS, hospitalization or an emergency room visit compared with placebo in patients with eosinophilic airway inflammation ( $p \leq 0.0005$ ) [73]. Clinical trials of antibodies targeting IL-4 and IL-13 are underway.

Other anti-inflammatory drugs such as phosphodiesterase-4 inhibitors are at varying stages of development for the treatment of COPD and asthma, with roflumilast having been approved for

maintenance treatment of severe COPD patients with a history of frequent exacerbations. It is feasible that delivery direct to the lungs may enhance the therapeutic ratio of phosphodiesterase-4 inhibitors, although to date their efficacy via this route in COPD patients has been disappointing [74].

Finally, long-acting anti-muscarinic drugs have been shown to improve lung function and reduce exacerbations in severe asthma [75]. However, these and other approaches such as bronchial thermoplasty are unlikely to replace high-dose ICS in the foreseeable future, particularly in severe asthma. Thus, efforts to further improve ICS and emphasize the use of ICS with the most favorable therapeutic ratios remain important objectives.

### Acknowledgments

*Editorial assistance was provided by Synergy Vision, London, UK, on behalf of Takeda Pharmaceuticals International GmbH. Takeda was given the opportunity to review the final version of the manuscript and provided comments. However, consideration of these comments remained at the full discretion of the author.*

### Financial & competing interests disclosure

*ED Bateman has served as a consultant to Actelion, Almirall, AstraZeneca, Boehringer Ingelheim; has been on advisory boards for Almirall, AstraZeneca, Boehringer Ingelheim, Forest, GlaxoSmithKline, Merck, Napp, Novartis and Takeda; has received lecture fees from AstraZeneca, Boehringer Ingelheim, Chiesi, GlaxoSmithKline, Novartis, Pfizer and Takeda; and his institution has received remuneration for participation in clinical trials sponsored by Actelion, Aeras, Almirall, AstraZeneca, Boehringer Ingelheim, Forest, GlaxoSmithKline, Hoffman La Roche, Merck, Novartis and Takeda. The author has no other relevant affiliations or financial involvement with any organization or entity with a financial interest in or financial conflict with the subject matter or materials discussed in the manuscript apart from those disclosed.*

*No writing assistance was utilized in the production of this manuscript.*

### Key issues

- Asthma control comprises both current control of symptoms and future risk of adverse events, such as exacerbations.
- If asthma control cannot be achieved with first-line options, approaches that target reduction of exacerbation risk become important.
- High-dose ciclesonide reduces the risk of exacerbations compared with low-dose ciclesonide.
- The oral corticosteroid-sparing efficacy of high-dose ciclesonide has been demonstrated in clinical trials.
- Ciclesonide may be administered once daily. When high doses of ciclesonide are indicated, twice-daily dosing is recommended.
- High-dose ciclesonide is associated with fewer of the typical local and systemic adverse events that are associated with other inhaled corticosteroids.

### References

Papers of special note have been highlighted as:

• of interest

•• of considerable interest

- 1 National Heart, Lung, and Blood Institute Expert Panel Report 3. Guidelines for the Diagnosis and Management of Asthma. (2007).
- 2 Powell H, Gibson PG. Inhaled corticosteroid doses in asthma: an evidence-based approach. *Med. J. Aust.* 178(5), 223–225 (2003).
- 3 Bateman ED, Boushey HA, Bousquet J *et al.* Can guideline-defined asthma control be achieved? The Gaining Optimal Asthma Control study. *Am. J. Respir. Crit. Care Med.* 170(8), 836–844 (2004).
- 4 Wisnivesky JP, Lorenzo J, Lyn-Cook R *et al.* Barriers to adherence to asthma management guidelines among inner-city primary care providers. *Ann. Allergy Asthma Immunol.* 101(3), 264–270 (2008).
- 5 Foster JM, Smith L, Bosnic-Anticevich SZ *et al.* Identifying patient-specific beliefs and behaviours for conversations about adherence in asthma. *Intern. Med. J.* 42(6), e136–e144 (2012).
- 6 Holgate ST, Polosa R. The mechanisms, diagnosis, and management of severe

- asthma in adults. *Lancet* 368(9537), 780–793 (2006).
- 7 To T, Stanojevic S, Moores G, *et al.* Global asthma prevalence in adults: findings from the cross-sectional world health survey. *BMC Public Health* 12, 204 (2012).
  - 8 Siroux V, Pin I, Oryszczyn MP, Le MN, Kauffmann F. Relationships of active smoking to asthma and asthma severity in the EGEA study. Epidemiological study on the Genetics and Environment of Asthma. *Eur. Respir. J.* 15(3), 470–477 (2000).
  - 9 Tomlinson JE, McMahon AD, Chaudhuri *et al.* Efficacy of low and high dose inhaled corticosteroid in smokers versus non-smokers with mild asthma. *Thorax* 60(4), 282–287 (2005).
  - 10 Pedersen SE, Bateman ED, Bousquet J, *et al.* Determinants of response to fluticasone propionate and salmeterol/fluticasone propionate combination in the Gaining Optimal Asthma control study. *J. Allergy Clin. Immunol.* 120(5), 1036–1042 (2007).
  - 11 Bateman ED, Reddel HK, Eriksson G, *et al.* Overall asthma control: the relationship between current control and future risk. *J. Allergy Clin. Immunol.* 125(3), 600–608, 608.e1 (2010).
  - **Defines the two domains of asthma control.**
  - 12 O'Byrne PM. Therapeutic strategies to reduce asthma exacerbations. *J. Allergy Clin. Immunol.* 128(2), 257–263 (2011).
  - 13 Harrison TW, Osborne J, Newton S, *et al.* Doubling the dose of inhaled corticosteroid to prevent asthma exacerbations: randomized controlled trial. *Lancet* 363(9405), 271–275 (2004).
  - 14 Fitzgerald JM, Becker A, Sears MR, *et al.* Doubling the dose of budesonide versus maintenance treatment in asthma exacerbations. *Thorax* 59(7), 550–556 (2004).
  - 15 Osborne J, Mortimer K, Hubbard RB, *et al.* Quadrupling the dose of inhaled corticosteroid to prevent asthma exacerbations: a randomized, double-blind, placebo-controlled, parallel-group clinical trial. *Am. J. Respir. Crit. Care Med.* 180(7), 598–602 (2009).
  - 16 Guest JF, Davie AM, Ruiz FJ, *et al.* Switching asthma patients to a once-daily inhaled steroid improves compliance and reduces healthcare costs. *Prim. Care Respir. J.* 14(2), 88–98 (2005).
  - 17 Mutch E, Nave R, McCracken N, *et al.* The role of esterases in the metabolism of ciclesonide to desisobutryl-ciclesonide in human tissue. *Biochem. Pharmacol.* 73(10), 1657–1664 (2007).
  - 18 Dahl R. Systemic side effects of inhaled corticosteroids in patients with asthma. *Respir. Med.* 100(8), 1307–1317 (2006).
  - 19 Richter K, Kannies F, Biberger C, *et al.* Comparison of the oropharyngeal deposition of inhaled ciclesonide and fluticasone propionate in patients with asthma. *J. Clin. Pharmacol.* 45(2), 146–152 (2005).
  - 20 Bateman ED, Linnhof AE, Homik L, *et al.* Comparison of twice-daily inhaled ciclesonide and fluticasone propionate in patients with moderate-to-severe persistent asthma. *Pulm. Pharmacol. Ther.* 21(2), 264–275 (2008).
  - 21 Nave R, Zech K, Bethke TD. Lower oropharyngeal deposition of inhaled ciclesonide via hydrofluoroalkane metered-dose inhaler compared with budesonide via chlorofluorocarbon metered-dose inhaler in healthy subjects. *Eur. J. Clin. Pharmacol.* 61(3), 203–208 (2005).
  - 22 Derendorf H, Nave R, Drollmann A, *et al.* Relevance of pharmacokinetics and pharmacodynamics of inhaled corticosteroids to asthma. *Eur. Respir. J.* 28(5), 1042–1050 (2006).
  - 23 Martin RJ. Therapeutic significance of distal airway inflammation in asthma. *J. Allergy Clin. Immunol.* 109(Suppl. 2), S447–S460 (2002).
  - 24 Leach CL, Bethke TD, Boudreau RJ, *et al.* Two-dimensional and three-dimensional imaging show ciclesonide has high lung deposition and peripheral distribution: a nonrandomized study in healthy volunteers. *J. Aerosol Med.* 19(2), 117–126 (2006).
  - 25 Newman S, Salmon A, Nave R, *et al.* High lung deposition of 99mTc-labeled ciclesonide administered via HFA-MDI to patients with asthma. *Respir. Med.* 100(3), 375–384 (2006).
  - 26 Cohen J, Douma WR, ten Hacken NH, *et al.* Ciclesonide improves measures of small airway involvement in asthma. *Eur. Respir. J.* 31(6), 1213–1220 (2008).
  - 27 Hoshino M. Comparison of effectiveness in ciclesonide and fluticasone propionate on small airway function in mild asthma. *Allergol. Int.* 59(1), 59–66 (2010).
  - 28 Nave R, Bethke TD, van Marle SP, *et al.* Pharmacokinetics of [<sup>14</sup>C]ciclesonide after oral and intravenous administration to healthy subjects. *Clin. Pharmacokinet.* 43(7), 479–486 (2004).
  - 29 Rohatagi S, Luo Y, Shen L *et al.* Protein binding and its potential for eliciting minimal systemic side effects with a novel inhaled corticosteroid, ciclesonide. *Am. J. Ther.* 12(3), 201–209 (2005).
  - 30 Nonaka T, Nave R, McCracken N, *et al.* Ciclesonide uptake and metabolism in human alveolar type II epithelial cells (A549). *BMC Pharmacol.* 7, 12 (2007).
  - 31 Boulet LP, Bateman ED, Voves R, *et al.* A randomized study comparing ciclesonide and fluticasone propionate in patients with moderate persistent asthma. *Respir. Med.* 101(8), 1677–1686 (2007).
  - 32 Dahl R, Engelstatter R, Trebas-Pietras E, *et al.* A 24-week comparison of low-dose ciclesonide and fluticasone propionate in mild to moderate asthma. *Respir. Med.* 104(8), 1121–1130 (2010).
  - 33 Buhl R, Vinkler I, Magyar P *et al.* Comparable efficacy of ciclesonide once daily versus fluticasone propionate twice daily in asthma. *Pulm. Pharmacol. Ther.* 19(6), 404–412 (2006).
  - 34 Pincus DJ, Szeffler SJ, Ackerson LM, *et al.* Chronotherapy of asthma with inhaled steroids: the effect of dosage timing on drug efficacy. *J. Allergy Clin. Immunol.* 95(6), 1172–1178 (1995).
  - 35 Pincus DJ, Humeston TR, Martin RJ. Further studies on the chronotherapy of asthma with inhaled steroids: the effect of dosage timing on drug efficacy. *J. Allergy Clin. Immunol.* 100(6 Pt 1), 771–774 (1997).
  - 36 Zetterstrom O, Dahl R, Lindqvist A, *et al.* Comparable morning versus evening administration of once-daily mometasone furoate dry powder inhaler. *Respir. Med.* 102(10), 1406–1411 (2008).
  - 37 Meibohm B, Hochhaus G, Rohatagi S, *et al.* Dependency of cortisol suppression on the administration time of inhaled corticosteroids. *J. Clin. Pharmacol.* 37(8), 704–710 (1997).
  - 38 Postma DS, Sevette C, Martinat Y, *et al.* Treatment of asthma by the inhaled corticosteroid ciclesonide given either in the morning or evening. *Eur. Respir. J.* 17(6), 1083–1088 (2001).
  - 39 Derom E, Van DV, V, Marissens S, *et al.* Effects of inhaled ciclesonide and fluticasone propionate on cortisol secretion and airway responsiveness to adenosine 5'-monophosphate in asthmatic patients. *Pulm. Pharmacol. Ther.* 18(5), 328–336 (2005).
  - 40 Masoli M, Weatherall M, Beasley R. Fluticasone given once versus twice a day:

- meta-analysis. *Respirology* 10(2), 183–188 (2005).
- 41 Selroos O, Edsbacker S, Hultquist C. Once-daily inhaled budesonide for the treatment of asthma: clinical evidence and pharmacokinetic explanation. *J. Asthma* 41(8), 771–790 (2004).
  - 42 Toogood JH, Baskerville JC, Jennings B, *et al.* Influence of dosing frequency and schedule on the response of chronic asthmatics to the aerosol steroid, budesonide. *J. Allergy Clin. Immunol.* 70(4), 288–298 (1982).
  - 43 Malo JL, Cartier A, Merland N, *et al.* Four-times-a-day dosing frequency is better than a twice-a-day regimen in subjects requiring a high-dose inhaled steroid, budesonide, to control moderate to severe asthma. *Am. Rev. Respir. Dis.* 140(3), 624–628 (1989).
  - 44 Bateman E, Karpel J, Casale T, *et al.* Ciclesonide reduces the need for oral steroid use in adult patients with severe, persistent asthma. *Chest* 129(5), 1176–1187 (2006).
  - **Oral corticosteroid-sparing efficacy of ciclesonide.**
  - 45 Adachi M, Ishihara K, Inoue H, *et al.* Efficacy and safety of inhaled ciclesonide compared with chlorofluorocarbon beclomethasone dipropionate in adults with moderate to severe persistent asthma. *Respirology* 12(4), 573–580 (2007).
  - 46 Vermeulen JH, Gyurkovits K, Rauer H, *et al.* Randomized comparison of the efficacy and safety of ciclesonide and budesonide in adolescents with severe asthma. *Respir. Med.* 101(10), 2182–2191 (2007).
  - 47 Bateman ED, Cheung D, Lapa e Silva J, *et al.* Randomized comparison of ciclesonide 160 and 640 microg/day in severe asthma. *Pulm. Pharmacol. Ther.* 21(3), 489–498 (2008).
  - **High-dose ciclesonide reduces the risk of exacerbations in patients with severe asthma compared with low-dose ciclesonide.**
  - 48 van den Berge M, Arshad SH, Ind PW, *et al.* Similar efficacy of ciclesonide versus prednisolone to treat asthma worsening after steroid tapering. *Respir. Med.* 103(8), 1216–1223 (2009).
  - 49 O'Connor BJ, Kilfeather S, Cheung D, *et al.* Efficacy and safety of ciclesonide in patients with severe asthma: a 12-week, double-blind, randomized, parallel-group study with long-term (1-year) follow-up. *Expert Opin. Pharmacother.* 11(17), 2791–2803 (2010).
  - 50 Kelly HW. Inhaled corticosteroid dosing: double for nothing? *J. Allergy Clin. Immunol.* 128(2), 278.e2–281.e2 (2011).
  - 51 van der Molen T, Foster JM, Caesar M, *et al.* Difference between patient-reported side effects of ciclesonide versus fluticasone propionate. *Respir. Med.* 104(12), 1825–1833 (2010).
  - **Patient-reported adverse events lower with ciclesonide compared with fluticasone propionate.**
  - 52 Kelly HW, Sternberg AL, Lescher R *et al.*; CAMP Research Group. Effect of inhaled glucocorticoids in childhood on adult height. *N. Engl. J. Med.* 367(10), 904–912 (2012).
  - 53 Peters SP. Safety of inhaled corticosteroids in the treatment of persistent asthma. *J. Natl. Med. Assoc.* 98(6), 851–861 (2006).
  - 54 Szefer S, Rohatagi S, Williams J, *et al.* Ciclesonide, a novel inhaled steroid, does not affect hypothalamic-pituitary-adrenal axis function in patients with moderate-to-severe persistent asthma. *Chest* 128(3), 1104–1114 (2005).
  - 55 Lipworth BJ, Short PM, Williamson PA, *et al.* A randomized primary care trial of steroid titration against mannitol in persistent asthma: STAMINA trial. *Chest* 141(3), 607–615 (2012).
  - 56 Anderson WJ, McFarlane LC, Lipworth BJ. Prospective follow-up of novel markers of bone turnover in persistent asthmatics exposed to low and high doses of inhaled ciclesonide over 12 months. *J. Clin. Endocrinol. Metab.* 97(6), 1929–1936 (2012).
  - 57 Agertoft L, Pedersen S. Lower-leg growth rates in children with asthma during treatment with ciclesonide and fluticasone propionate. *Pediatr. Allergy Immunol.* 21(1 Pt 2), e199–e205 (2010).
  - 58 Chylack LT Jr, Gross GN, Pedinoff A; Ciclesonide Lenticular Safety Study Group. A randomized, controlled trial to investigate the effect of ciclesonide and beclomethasone dipropionate on eye lens opacity. *J. Asthma* 45(10), 893–902 (2008).
  - 59 Heller MK, Laks J, Kovesi TA, *et al.* Reversal of adrenal suppression with ciclesonide. *J. Asthma* 47(3), 337–339 (2010).
  - 60 Fahy JV. Eosinophilic and neutrophilic inflammation in asthma: insights from clinical studies. *Proc. Am. Thorac. Soc.* 6(3), 256–259 (2009).
  - 61 Spears M, Cameron E, Chaudhuri R, *et al.* Challenges of treating asthma in people who smoke. *Expert Rev. Clin. Immunol.* 6(2), 257–268 (2010).
  - 62 Shaw DE, Green RH, Bradding P. Asthma exacerbations: prevention is better than cure. *Ther. Clin. Risk Manag.* 1(4), 273–277 (2005).
  - 63 Green RH, Brightling CE, McKenna S, *et al.* Asthma exacerbations and sputum eosinophil counts: a randomised controlled trial. *Lancet* 360(9347), 1715–1721 (2002).
  - 64 Petsky HL, Cates CJ, Lasserson TJ *et al.* A systematic review and meta-analysis: tailoring asthma treatment on eosinophilic markers (exhaled nitric oxide or sputum eosinophils). *Thorax* 67(3), 199–208 (2012).
  - 65 O'Byrne PM, Pedersen S, Carlsson LG *et al.* Risks of pneumonia in patients with asthma taking inhaled corticosteroids. *Am. J. Respir. Crit. Care Med.* 183(5), 589–595 (2011).
  - 66 Hojo M, Iikura M, Hirano S, *et al.* Increased risk of nontuberculous mycobacterial infection in asthmatic patients using long-term inhaled corticosteroid therapy. *Respirology* 17(1), 185–190 (2012).
  - 67 Andrejak C, Nielsen R, Thomsen VO, *et al.* Chronic respiratory disease, inhaled corticosteroids and risk of non-tuberculous mycobacteriosis. *Thorax* 68(3), 256–262 (2013).
  - 68 Zhang L, Prietsch SO, Mendes AP *et al.* Inhaled corticosteroids increase the risk of oropharyngeal colonization by *Streptococcus pneumoniae* in children with asthma. *Respirology* 18(2), 272–277 (2013).
  - 69 Janson C, Larsson K, Lisspers K, and Stalberg B. Pneumonia in COPD patients treated with fixed ICS/LABA combinations. *ERS Vienna Abstract* 2897 (2012).
  - 70 Chen D, Restrepo MI, Fine MJ *et al.* Observational study of inhaled corticosteroids on outcomes for COPD patients with pneumonia. *Am. J. Respir. Crit. Care Med.* 184(3), 312–316 (2011).
  - 71 Korn S, Buhl R. Efficacy of a fixed combination of ciclesonide and formoterol: the EXCITED-study. *Respir. Med.* 106(1), 57–67 (2012).
  - 72 Thomson NC, Chaudhuri R, Spears M. Emerging therapies for severe asthma. *BMC Med.* 9, 102 (2011).
  - **A review of the many novel therapies in development for the treatment of severe asthma.**

- 73 Pavord ID, Korn S, Howarth P *et al.* Mepolizumab for severe eosinophilic asthma (DREAM): a multicentre, double-blind, placebo-controlled trial. *Lancet* 380(9842), 651–659 (2012).
- 74 Vestbo J, Tan L, Atkinson G, Ward J. A controlled trial of 6-weeks' treatment

with a novel inhaled phosphodiesterase type-4 inhibitor in COPD. *Eur. Respir. J.* 33(5), 1039–1044 (2009).

- 75 Kerstjens HA, Engel M, Dahl R *et al.* Tiotropium in asthma poorly controlled with standard combination therapy. *N. Engl. J. Med.* 367(13), 1198–1207 (2012).

### Website

- 101 GINA. Global Strategy for Asthma Management and Prevention, Global Initiative for Asthma (GINA). 2011. [www.ginasthma.org](http://www.ginasthma.org)

- Evidence-based strategy for the treatment and management of asthma.

Reproduced with permission of the copyright owner. Further reproduction prohibited without permission.