

# Restriction of LABA use to combination ICS/LABA inhaler therapy in asthma

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In 2011 the British asthma guidelines recommended for the first time that long-acting beta agonists (LABAs) should be prescribed in fixed dose combination inhaled corticosteroid (ICS)/LABA inhalers in the treatment of asthma.<sup>1</sup> This represented a revision to the 2009 BTS guidelines in which LABAs were recommended if used with ICS, either as separate inhalers or as a combination ICS/LABA inhaler.<sup>2</sup> The revision was based on the evidence that LABAs have the potential to increase the risk of asthma mortality when used by patients with unstable asthma without concomitant ICS therapy or scheduled medical review,<sup>3</sup> that there is no evidence of an increased risk of asthma mortality with combination ICS/LABA inhaler therapy in asthma,<sup>4</sup> and that it is only with combination ICS/LABA products that it could be guaranteed that LABA monotherapy can be avoided.<sup>5</sup> It recognised that the use of separate inhalers inevitably results in periods of LABA monotherapy in a proportion of patients, because patients who are poorly adherent to prescribed ICS therapy may continue using their LABA inhaler for symptomatic relief.<sup>5–7</sup>

The extent to which this may occur is now described in an audit of prescribing from a Scottish GP database, reported in this edition of the journal by Morales *et al.*<sup>8</sup> Of the 29% of patients with asthma who were prescribed a LABA during the 2006 calendar year, about one in four were prescribed a LABA in the form of a separate inhaler (aptly described as the population at risk). Of these 18% had a period of episodic or sustained LABA monotherapy. Sustained LABA monotherapy, defined as at least one LABA prescription without any ICS prescription in the calendar year, occurred in 6%; episodic monotherapy, defined as one or more periods in 2006 without an ICS prescription within 12 weeks before and 8 weeks after a LABA prescription, occurred

in another 12%. The authors infer that sustained monotherapy may relate to poor prescribing, whereas episodic monotherapy may be a result of non-adherence to ICS. This is consistent with their finding that an asthma review was associated with lower odds of sustained monotherapy, but no difference in the rate of episodic monotherapy. The findings complement an earlier USA study in which LABA monotherapy, defined as having at least one dispensing event for a LABA medication in the absence of any other maintenance therapy, was documented in about 11% of LABA users.<sup>9</sup>

Thus there is a small but important population of 'at risk' asthma patients prescribed LABAs as a separate inhaler without regular ICS use. Ensuring that such high risk patients are prescribed combination ICS/LABA therapy would reduce their risk of life-threatening attacks and of death, through both the avoidance of LABA monotherapy and the concomitant use of ICS therapy. Combination ICS/LABA therapy also has the potential advantage over separate ICS and LABA inhalers of improving adherence with ICS therapy.<sup>10–11</sup> This can be expected to lead to improved clinical outcomes including a reduced risk of asthma mortality in the real world setting, in which there is a dose-dependent reduction in mortality with ICS use and in which an intermittent discontinuation of therapy markedly increases the risk.<sup>12</sup> Less well recognised is the potential for combination therapy to increase overall use of ICS therapy through a change in prescribing patterns, resulting from the preference of doctors and patients for combination inhaler therapy.<sup>13</sup> Thus combination therapy may improve clinical outcomes and reduce the risk of asthma mortality by increasing the overall prescription of ICS and improving ICS adherence, in addition to preventing sustained or episodic LABA monotherapy.

The British asthma guidelines recommend that the use of combination ICS/LABA therapy is the only appropriate way to prescribe LABA therapy.<sup>1</sup> However, there is inevitably a gap between guidelines and translation into clinical practice, and regulatory restriction may represent the simplest and most effective method to ensure that this guidelines recommendation is implemented. The main practical difficulty with

implementing such a regulatory measure is the need to give prescribers the continued capability to prescribe LABAs as a separate inhaler for patients with chronic obstructive pulmonary disease (COPD). However, as suggested in the TORCH study,<sup>14</sup> the recent finding that LABA/ICS combination inhaler therapy is associated with the lowest risk of death amongst all treatments for COPD<sup>15</sup> suggests that a move to combination therapy may in fact have benefits for COPD patients as well. Further studies are required to confirm the generalisability of this finding, but even if separate LABA inhalers remain available for use in COPD, this would not prevent withdrawal of its approval for use in asthma.

A related uncertainty is the approach in patients with the 'overlap syndrome',<sup>16–17</sup> an important phenotypic group of current or ex-smokers with features of atopic asthma, chronic bronchitis and emphysema. There is a limited evidence base for the treatment of these patients, as they do not meet the inclusion criteria of the major randomised controlled trials of COPD,<sup>18</sup> or asthma.<sup>19</sup> We propose that it would be reasonable to restrict the use of LABAs to combination ICS/LABA inhaler therapy in this overlap group, due to the dominant asthma component with severe and markedly variable airflow obstruction.<sup>16–17</sup> This approach is supported by the evidence that ICS have greater efficacy in asthma patients with marked bronchodilator reversibility,<sup>20</sup> although counter-balanced by the reduced efficacy of ICS in smokers with asthma.<sup>21</sup>

To date there have been varied regulatory responses to this clinical dilemma. In 2010 the US Food and Drug Administration appropriately recommended that the use of LABAs without the concomitant use of ICS is contraindicated.<sup>22</sup> However, the use of combination ICS/LABA inhaler therapy was recommended only in paediatric and adolescent patients on the basis that it would ensure adherence, despite data demonstrating that poor adherence also applies to adults with asthma.<sup>23–24</sup> In 2011 the New Zealand Pharmaceutical Management Agency rescinded the previous requirement that patients had to be exposed to a 3 month trial of single LABA inhaler therapy before being eligible for the combination product.<sup>25</sup> In the UK in 2010, the Medicines and Healthcare Products Regulatory Agency confirmed its earlier recommendations that LABA therapy should always be used with concomitant ICS, in line with British Thoracic Society guidelines, and that combination ICS/LABA inhalers should be considered as an aid to compliance.<sup>26–27</sup>

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While these regulatory responses acknowledge the risks of LABA monotherapy, they do not adequately respond to the fact that the prescription of ICS and LABAs as separate inhalers will inevitably result in LABA monotherapy in some patients, as shown in the Scottish study.<sup>8</sup> It is evident that the only way in which LABA monotherapy can be avoided in asthma is through the mandatory prescription of combination ICS/LABA products. Thus the jury is in—it is time for LABAs to be restricted to combination ICS/LABA therapy in the management of asthma.<sup>5</sup> The withdrawal of LABAs as single inhaler therapy in asthma would then bring regulations in line with the most recent consensus asthma guidelines.

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