Making simple things complicated using anti-inflammatory reliever therapy

To the Editor:

We appreciated reading the eloquent editorial from Beasley *et al.* [1], who make a cogent evidence-based case for using budesonide/formoterol (BUD/FM) on demand (*p.r.n.*) as the preferred asthma reliever, in keeping with the latest GINA guidelines. They proffer what appears at first sight to be a pragmatic stepwise treatment algorithm and associated action plan for using BUD/FM *p.r.n.* as anti-inflammatory reliever (AIR)±maintenance therapy across Global Initiative for Asthma steps 1 to 3.

It is worth noting that a large proportion of the evidence base was using BUD/FM as maintenance and reliever therapy. Despite the overwhelming evidence in favour of AIR described by Beasley *et al.* [1], the only study comparing BUD/FM AIR *versus* BUD/FM maintenance showed a 10.3% difference in treatment failure in favour of the latter [2].

However, we believe their proposal over complicates what should be an intuitive patient-centred regimen that always ensures perfect concordance between inhaled corticosteroid (ICS) and reliever therapy. In particular, we feel their suggested asthma action plan might be difficult to penetrate and be confusing for patients taking AIR in terms of artificially distinguishing between maintenance and reliever therapy, especially when referring to various treatment steps. Surely the whole point of using AIR is to make things simpler for the patient. In this respect, our proposed mantra for using AIR would be to simply advise patients to "use more puffs of BUD/FM when they need it and less when they don't" [3] (figure 1). This way the patient will effectively self-titrate their ICS dose requirement according to prevailing type 2 inflammation, so that there is a seamless process of escalation and de-escalation, rather than considering distinct treatment steps *per se*. The current licensed indication states that a total daily dose of up to 12 puffs per day may be used for a limited period with the usual regimen being up to 8 puffs per day. This is presumably based on the adverse effects of the FM moiety, such as tremor, tachycardia and hypokalaemia. Nonetheless, it has been shown that with regular exposure to FM in conjunction with ICS there is blunting of systemic responses due to beta-2 receptor downregulation and uncoupling [4]. It is also worth noting that an application has been submitted for BUD/FM metered dose inhaler to mirror the same indications as BUD/FM dry powder inhaler, including AIR. There are no data to support the AIR indication in children.

The flexible dosing regimen with BUD/FM *p.r.n.* empowers the patient to be in control of their own asthma and avoids patients being continually exposed to unnecessarily higher fixed doses of ICS. Indeed,

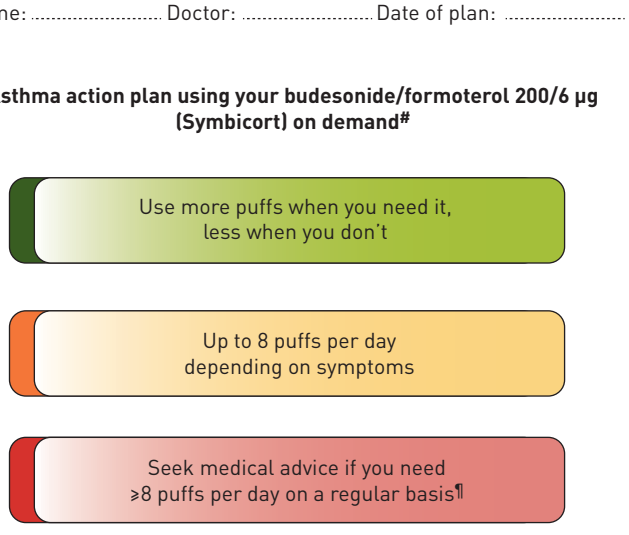

FIGURE 1 Proposed asthma action plan using budesonide/formoterol 200/6 µg on demand as long-term treatment for patients with mild to moderate asthma. #: budesonide/formoterol 200/6 µg does not presently have a licensed indication in the UK for treatment on demand unless used with concomitant maintenance therapy, albeit now recommended by the Global Initiative for Asthma as the preferred reliever; ¶: a total daily dose of up to 12 puffs may be used for a limited period.

this reflects the nature of the disease in that asthma severity can vary over time depending on prevailing trigger factors. The challenge for prescribers will be to persuade patients that they no longer need a separate short-acting β-agonist reliever inhaler, especially for those who have become over dependent on salbutamol. Thus, we would also advocate checking the glycine-16-arginine β_2 receptor genotype for those patients who end up requiring persistently higher doses of BUD/FM [5]. Furthermore, using fractional exhaled nitric oxide at routine follow up will allow the clinician to assess whether AIR is adequately suppressing underlying type 2 inflammation [6].

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Use more budesonide/formoterol when you need it, and less when you don't http://bit.ly/2PKsCOH

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References

1 Beasley R, Braithwaite I, Semprini A, *et al.* ICS-formoterol reliever therapy stepwise treatment algorithm for adult asthma. *Eur Respir J* 2020; 55: 1901407.
2 Papi A, Marku B, Scichilone N, *et al.* Regular *versus* as-needed budesonide and formoterol combination treatment for moderate asthma: a non-inferiority, randomised, double-blind clinical trial. *Lancet Respir Med* 2015; 3: 109–119.
3 Lipworth B, Chan R, Kuo CR. Anti-inflammatory reliever therapy for asthma. *Ann Allergy Asthma Immunol* 2020; 124: 13–15.
4 Newnham DM, Grove A, McDevitt DG, *et al.* Subsensitivity of bronchodilator and systemic beta 2 adrenoceptor responses after regular twice daily treatment with eformoterol dry powder in asthmatic patients. *Thorax* 1995; 50: 497–504.
5 Lee DKC, Currie GP, Hall IP, *et al.* The arginine-16 β2-adrenoceptor polymorphism predisposes to bronchoprotective subsensitivity in patients treated with formoterol and salmeterol. *Br J Clin Pharmacol* 2004; 57: 68–75.
6 Kuo CR, Spears M, Haughney J, *et al.* Scottish consensus statement on the role of FeNO in adult asthma. *Respir Med* 2019; 155: 54–57.

Achieving the balance between evidence and simplicity

From the authors:

We thank B. Lipworth and colleagues for their insightful comments and for raising the important issue of distinguishing between maintenance and reliever budesonide–formoterol use within the anti-inflammatory reliever (AIR) therapy regimen. We agree that such a distinction may be artificial and not be possible in clinical practice. We consider that this is an important conceptual issue but one that may have limited clinical relevance, when prescribing budesonide–formoterol according to a maintenance and reliever therapy regimen in asthma. Indeed it has been shown, from electronic monitoring of inhaler use, that there is such marked variation in medication use when budesonide–formoterol is used as a maintenance and reliever therapy, both long term and prior to severe exacerbations, that such differentiation is both unrealistic and not required in clinical practice [1, 2]. Despite the potential for confusion as to how to differentiate between

maintenance and reliever medication use, there is substantive evidence that when inhaled corticosteroid (ICS)–formoterol is prescribed according to the regular maintenance ICS–formoterol and reliever regimen, greater efficacy is obtained compared with regular maintenance ICS or ICS–long-acting β-agonist together with short-acting β-agonist (SABA) reliever therapy [3, 4]. The conceptual schematic video is provided to illustrate the importance of both the maintenance and reliever components of this regimen [5].

The other proposal put forward by B. Lipworth and colleagues is that to implement the budesonide–formoterol AIR regimen, it is preferred to simply advise patients to "use more puffs of BUD/FM when they need it and less when they don't", *i.e.* as a reliever therapy alone without regular scheduled maintenance use. While this may well be how many patients end up using ICS–formoterol when prescribed as maintenance and reliever therapy, current evidence would suggest this is not the preferred approach. The only clinical trial that has examined budesonide–formoterol reliever *versus* regular maintenance budesonide–formoterol (plus as-needed terbutaline) has reported that the budesonide–formoterol reliever regimen had less efficacy (composite primary outcome variable), although there was no difference in severe exacerbation risk [6]. By comparison, budesonide–formoterol maintenance and reliever therapy markedly reduces severe exacerbation risk compared with maintenance budesonide–formoterol plus as-needed terbutaline [3, 4]. This strongly suggests that budesonide–formoterol maintenance and reliever therapy would likewise reduce severe exacerbation risk compared with budesonide–formoterol reliever alone.

Another issue raised is the balance between simplicity and evidence with the implementation of treatment regimens. To date the budesonide–formoterol "on demand" regimen has been assessed in mild and moderate asthma only, and not in severe disease, whereas it has been assessed together with maintenance use in this population, which has the greatest morbidity and risk [3, 4, 6]. The simple asthma action plan proposed for "on demand" use is novel, whereas the proposed AIR asthma action plan is a modified version of those in current use in New Zealand and Australia, which are based on prototypes shown to improve outcomes in adult asthma [7]. However, we acknowledge that despite the evidence on which the AIR algorithm and associated plan are based [4], it will still be necessary to undertake research to determine how the plan is used in clinical practice, and what modifications may be required. The importance of research of the integration of treatments across asthma severity, as well as the treatments at each step, is evident from the review of the historical Global Initiative for Asthma (GINA) algorithms, in which it was proposed that the stepwise approach to asthma management may have led to excessive doses of ICS therapy in clinical practice [8]. Similarly, the new 2019 GINA algorithm will need to be formally assessed, to determine whether it has the right balance between simplicity and evidence [9].

B. Lipworth and colleagues conclude by suggesting that the challenge for prescribers will be to persuade patients that they no longer need a separate SABA reliever inhaler, especially those who have become over dependent on salbutamol. We suggest a caveat to their conclusion, that an even greater and more important challenge may be to persuade prescribers to accept this evidence-based paradigm change in asthma management [9]. We hope our proposed AIR algorithm and action plan may provide the practical guidance needed for such a change.

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The proposed anti-inflammatory reliever (AIR) therapy algorithm and action plan provides practical guidance for the use of this regimen in clinical practice https://bit.ly/3c0W7EC

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References

1 Patel M, Pilcher J, Pritchard A, *et al.* Efficacy and safety of maintenance and reliever combination budesonide–formoterol inhaler in patients with asthma at risk of severe exacerbations: a randomised controlled trial. *Lancet Respir Med* 2013; 1: 32–42.

2 Patel M, Pilcher J, Hancox RJ, *et al.* The use of β_2-agonist therapy before hospital attendance for severe asthma exacerbations: a *post-hoc* analysis. *NPJ Prim Care Respir Med* 2015; 25: 14099.

3 Sobieraj DM, Weeda ER, Nguyen E, *et al.* Association of inhaled corticosteroids and long-acting β-agonists as controller and quick relief therapy with exacerbations and symptom control in persistent asthma a systematic review and meta-analysis. *JAMA* 2018; 319: 1485–1496.

4 Beasley R, Braithwaite I, Semprini A, *et al.* ICS-formoterol reliever therapy stepwise treatment algorithm for adult asthma. *Eur Respir J* 2020; 55: 1901407.

5 Kearns C, Beasley R, Harrison TW, *et al.* Anti-inflammatory Reliever (AIR) based therapy for asthma. https://youtu.be/x5mo4kTfIKk. Date last updated: 6 March, 2020. Date last accessed: 6 March, 2020.

6 Papi A, Marku B, Scichilone N, *et al.* Regular *versus* as-needed budesonide and formoterol combination treatment for moderate asthma: a non-inferiority, randomised, double-blind clinical trial. *Lancet Respir Med* 2015; 3: 109–119.

7 Reddel HK, Bateman ED, Becker A, *et al.* A summary of the new GINA strategy: a roadmap to asthma control. *Eur Respir J* 2015; 46: 622–639.

8 Beasley R, Braithwaite I, Semprini A, *et al.* Optimal asthma control: time for a new target. *Am J Respir Crit Care Med* 2020; in press [https://doi.org/10.1164/rccm.201910-1934CI].

9 Reddel HK, FitzGerald JM, Bateman ED, *et al.* GINA 2019: a fundamental change in asthma management: Treatment of asthma with short-acting bronchodilators alone is no longer recommended for adults and adolescents. *Eur Respir J* 2019; 53: 1901046.