

# Anti-inflammatory reliever therapy for asthma

Lipworth, Brian; Chan, Rory; RuiWen Kuo, Chris

*Published in:*
Annals of Allergy, Asthma & Immunology

*DOI:*
10.1016/j.anai.2019.10.002

*Publication date:*
2020

*Document Version*
Peer reviewed version

Annals of Allergy, Asthma & Immunology

# Anti-inflammatory reliever therapy for asthma

--Manuscript Draft--

| | |
|---|---|
| **Manuscript Number:** | 19-07-0364R2 |
| **Article Type:** | Perspective |
| **Keywords:** | asthma; anti-inflammatory reliever therapy |
| **Corresponding Author:** | Brian Lipworth, MD<br>University of Dundee<br>Dundee, Scotland United Kingdom |
| **First Author:** | Brian Lipworth, MD |
| **Order of Authors:** | Brian Lipworth, MD |
| | Rory Chan, MBChB |
| | Chris RuiWen Kuo, MBChB |

Title Page

# Anti-inflammatory reliever therapy for asthma

Authors: Dr Brian Lipworth, MD
Dr Rory Chan, MBChB
Dr Chris RuiWen Kuo, MBChB

Affiliation: Scottish Centre for Respiratory Research
Ninewells Hospital and Medical School
University of Dundee
Scotland UK
DD1 9SY

Correspondence: Dr Brian Lipworth
Scottish Centre for Respiratory Disease
Ninewells Hospital and Medical School
University of Dundee
Scotland UK
DD1 9SY
Tel: +44 (0) 1382 383188
b.j.lipworth@dundee.ac.uk

Figure: 1
Table: 1

Funding statement: none

Conflicts of interest
Dr. Lipworth reports grants, personal fees and non-financial support from Astra Zeneca, grants, personal fees and non-financial support from Chiesi, other from GSK, during the conduct of the study; grants, personal fees and non-financial support from Boehringer Ingelheim, personal fees from Sanofi, personal fees from Teva, personal fees from Novartis, personal fees from Cipla, personal fees from Circassia, personal fees from Vectura, personal fees from Glenmark, personal fees from Dr Reddys, personal fees from Lupin, personal fees from Genentech, personal fees from Circassia, outside the submitted work.
Dr. Chan has nothing to disclose.
Dr. Kuo reports personal fees from Circassia, personal fees from AstraZeneca, outside the submitted work.

Word count 1132

The potential concern with using fixed dose inhaled corticosteroid (ICS) or ICS with long acting beta-agonist (ICS/LABA) is the possibility that patients will stop using their controller and become over-reliant on their short acting beta-agonist (SABA) reliever. It has been suggested that underuse of preventers and overuse of relievers may be a possible contributor to asthma deaths (NRAD),[1] which at least in the UK appears to be on the increase. In addition, such a regimen often entails having to use two different inhalers which may be confusing for patients. Notably, there is a temporal relationship between the ratio of SABA to ICS use and increased monthly admission rates for asthma in the UK.[2]

One way of obviating the discordance between controller and reliever is to have them both in the same single inhaler in a symptom driven regimen using so-called anti-inflammatory reliever therapy (AIR) with budesonide/formoterol (BUD/FM). Indeed this is now acknowledged in current global asthma guidelines which advocate the use of needed BUD/FM across all treatment steps either on its own or in conjunction with maintenance therapy – otherwise known as maintenance and reliever therapy (i.e. MART).[3] Another potential advantage of such a regimen is that it avoids patients being left on unnecessarily high doses of ICS or ICS/LABA in the long term.

The evidence to support using AIR alone in mild persistent asthma is compelling comprising four key randomised controlled trials (table). The pragmatic Novel START trial in adults showed that BUD/FM Turbuhaler dry powder inhaler (DPI) combination used on demand (PRN) was superior to PRN salbutamol (SALB) pressurised metered dose inhaler (pMDI) and was non inferior to maintenance BUD DPI on the primary outcome of asthma exacerbations, as well as reducing overall

inhaled corticosteroid (ICS) exposure.[4] The other pragmatic trial in adults was PRACTICAL which found using BUD/FM Turbuhaler to be non-inferior versus BUD DPI on the primary end point of exacerbations, again using a lower overall ICS dose.[5] Unsurprisingly, FeNO levels were 13% higher with AIR versus maintenance BUD in NOVEL START and PRACTICAL, reflecting the higher ICS dose exposure with the latter. This was supported by two other trials (SYGMA 1/2) in patients aged 12 and older using the same AIR regimen where exacerbations were the primary end point in SYGMA 1 and secondary in SYGMA 2.[6, 7] In SYGMA 1[6] the primary outcome of well controlled asthma weeks was 14% more likely with AIR versus terbutaline PRN but 36% less likely versus maintenance budesonide, while AIR exhibited 64% and 17% fewer exacerbations respectively. It is worth noting that in SYGMA 1 weeks with well controlled asthma were driven by on demand inhaler use such that BUD/FM AIR was always biased against maintenance BUD. Pointedly in all four studies despite abnormally high rates of adherence with maintenance BUD, using AIR was shown to be non-inferior to BUD on exacerbations. Real world ICS adherence rates are in the region of 29-46%. The observed differences in ACQ were all of small magnitude and less than the minimal clinically important difference of 0.5.

Using BUD/FM as AIR plus maintenance (i.e. MART) is superior to using salbutamol or formoterol as reliever in conjunction with maintenance BUD/FM in terms of exacerbation reduction.[8] Moreover using BUD/FM as AIR plus maintenance is superior to fixed dose ICS/LABA with SABA in regards to exacerbation reduction along with lower ICS exposure.[9] Thus patients can simply escalate or de-escalate BUD/FM as AIR +/- maintenance as a continuum of inhaled therapy for mild to moderate asthma in keeping with current guidelines [3] (Figure). This makes sense as patients

often flip between mild to moderate persistent asthma over time depending on prevailing extrinsic trigger factors – in other words use more AIR when you need it and less when you don't. The AIR regimen involves treating type 2 inflammation as the underlying tenet of asthma control, which in turn empowers patients to be in command of their own disease. Clearly this requires a degree of educational input to explain to the patient the role of treating inflammation and smooth muscle constriction with the one inhaler. Our own experience is that most patients prefer to use a single inhaler and be empowered to have control of their own disease.

It appears that we have inadvertently missed an intermediate step in asthma guidelines, namely using ICS/SALB combination instead of SALB as PRN reliever therapy – indeed a BUD/SALB Aerosphere pMDI formulation (PT027, AstraZeneca) is currently in development for this purpose. This would also ensure perfect concordance between preventer and reliever when used as AIR like BUD/FM. BUD/SALB could also be used instead of SALB as AIR on top of any preventer such as fixed dose maintenance ICS or ICS/LABA. However, this would still entail using two separate and possibly different inhaler devices which is not as simple or intuitive as using the same BUD/FM Turbuhaler device as AIR +/- maintenance.

One potential concern with using BUD/FM as AIR is that patients may be unable to use the DPI device in the setting of acute asthma in terms of being able to generate a sufficient inspiratory flow. In reality few patients can use their salbutamol pMDI properly or would ever carry around a spacer to use in an emergency.[10] There are reassuring data in patients presenting to hospital with acute severe asthma where 98% of cases were able to generate sufficient peak inspiratory flow (i.e. > 30 l/min) through the Turbuhaler DPI device,[11] while inhaling terbutaline via Turbuhaler

produced an improved bronchodilator response compared to using pMDI plus large volume spacer.[12]

At least in Europe BUD/FM is delivered via DPIs of which there are currently three available devices, namely Turbuhaler (AstraZeneca), Spiromax (Teva) and Easyhaler (Orion). However, all of the data for AIR alone were derived for Turbuhaler, hence other devices do not have the same indication. Beclomethasone/formoterol pMDI and Nexthaler DPI (Chiesi) like BUD/FM have data and an indication supporting AIR plus maintenance (MART) but not AIR alone, while fluticasone/formoterol pMDI and breath actuated k-haler (Mundipharma) do not have any data on AIR or MART and are only licensed for maintenance. Hence, at present the simplest regimen for patients is to use BUD/FM Turbuhaler as AIR +/- maintenance as a single inhaler.

We duly acknowledge that the FDA do not presently mandate the use of BUD/FM as AIR +/- maintenance therapy because of unfounded concerns regarding potential overuse of LABA's in terms of down-regulation and tachyphlyaxis. Higher doses of LABA like SABA may also produce systemic effects such as tachycardia and hypokalaemia. Pointedly concomitant BUD reverses beta-2 receptor down-regulation and associated sub-sensitivity of response with FM.[13] Nonetheless the evidence suggests that using BUD/FM as AIR +/- maintenance is a way of simplifying asthma treatment to attain optimal long term control along with less ICS exposure. At present AIR does not have a paediatric indication.

References

**1.** Levy ML, Winter R. Asthma deaths: what now?. *Thorax.* 2015;70:209-210.

**2.** Gonem S, Cumella A, Richardson M. Asthma admission rates and patterns of salbutamol and inhaled corticosteroid prescribing in England from 2013 to 2017. *Thorax.* 2019;74:705-706.

**3.** Global Initiative for Asthma. Global Strategy for Asthma Management and Prevention 2019. www.ginasthma.org. Accessed September 16, 2019.

**4.** Beasley R, Holliday M, Reddel HK, et al. Controlled Trial of Budesonide-Formoterol as Needed for Mild Asthma. *N Engl J Med.* 2019;380:2020-2030.

**5.** Hardy J, Baggott C, Fingleton J, et al. Budesonide-formoterol reliever therapy versus maintenance budesonide plus terbutaline reliever therapy in adults with mild to moderate asthma (PRACTICAL): a 52-week, open-label, multicentre, superiority, randomised controlled trial. *Lancet (London, England).* 2019.

**6.** O'Byrne PM, FitzGerald JM, Bateman ED, et al. Inhaled Combined Budesonide-Formoterol as Needed in Mild Asthma. *N Engl J Med.* 2018;378:1865-1876.

**7.** Bateman ED, Reddel HK, O'Byrne PM, et al. As-Needed Budesonide-Formoterol versus Maintenance Budesonide in Mild Asthma. *N Engl J Med.* 2018;378:1877-1887.

**8.** Rabe KF, Atienza T, Magyar P, Larsson P, Jorup C, Lalloo UG. Effect of budesonide in combination with formoterol for reliever therapy in asthma

exacerbations: a randomised controlled, double-blind study. *Lancet (London, England).* 2006;368:744-753.

**9.** Kuna P, Peters MJ, Manjra AI, et al. Effect of budesonide/formoterol maintenance and reliever therapy on asthma exacerbations. *Int J Clin Pract.* 2007;61:725-736.

**10.** Thompson J, Irvine T, Grathwohl K, Roth B. Misuse of metered-dose inhalers in hospitalized patients. *Chest.* 1994;105:715-717.

**11.** Brown PH, Ning AC, Greening AP, McLean A, Crompton GK. Peak inspiratory flow through Turbuhaler in acute asthma. *European Respiratory Journal.* 1995;8:1940-1941.

**12.** Tonnesen F, Laursen LC, Evald T, Stahl E, Ibsen TB. Bronchodilating effect of terbutaline powder in acute severe bronchial obstruction. *Chest.* 1994;105:697-700.

**13.** Aziz I, Lipworth BJ. A bolus of inhaled budesonide rapidly reverses airway subsensitivity and beta2-adrenoceptor down-regulation after regular inhaled formoterol. *Chest.* 1999;115:623-628.

Table 1 - Pivotal randomised controlled trials with budesonide/formoterol on demand in mild asthma

| **Study** | **Exacerbations*** BUD/FM PRN vs: | **ICS dose** BUD/FM PRN vs BUD bid | **Adherence** (to BUD bid) | **ACQ⁺** BUD/FM PRN vs: |
|---|---|---|---|---|
| **NOVEL START[4]** | • ALB PRN = 51% lower ($p < 0.001$)<br>• BUD bid = 12% greater ($p = 0.65$) | 52% lower | 56% | • ALB PRN = - 0.15<br>• BUD bid = 0.14 |
| **PRACTICAL[5]** | • BUD bid = 31% lower ($p < 0.05$) | 40% lower | 76% | • BUD bid = 0.06 |
| **SYGMA 1[6]** | • TERB PRN = 64% lower ($p < 0.001$)<br>• BUD bid = 17% lower ($p = 0.28$) | 83% lower | 79% | • TERB PRN = - 0.15<br>• BUD bid = 0.15 |
| **SYGMA 2[7]** | • BUD bid = 3% lower ($p = 0.75$) | 75% lower | 63% | • BUD bid = 0.15 |

**Legend**

ALB PRN – Albuterol on demand

BUD bid – Budesonide 200ug twice daily

BUD/FM PRN – Budesonide/Formoterol 200/6ug on demand

TERB PRN – Terbutaline on demand

*Exacerbations were the secondary end point in SYGMA 1

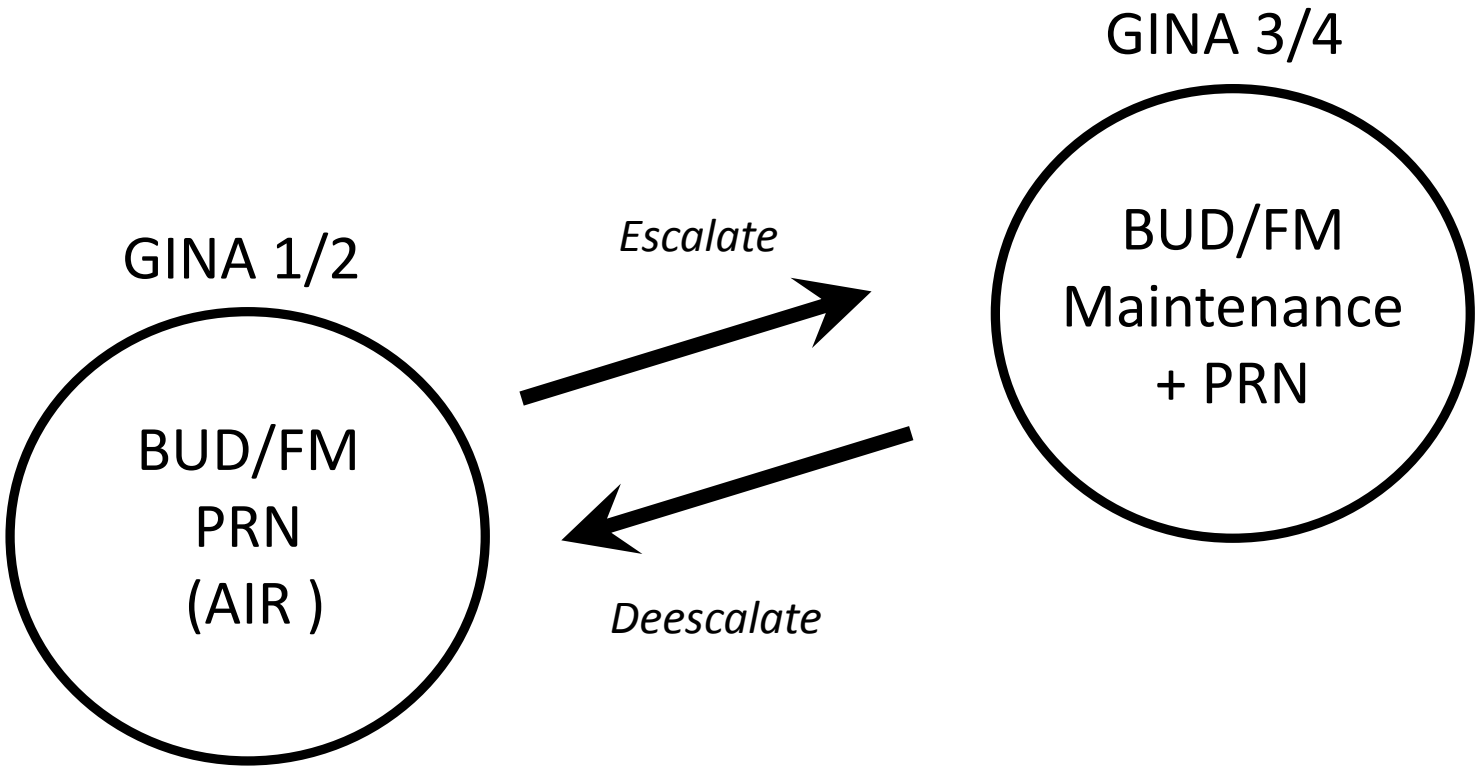
⁺Minimal clinically important difference in ACQ is 0.5

Figure Legend

Escalation and de-escalation of budesonide/formoterol (BUD/FM) combination as AIR +/- maintenance therapy for the treatment of mild to moderate persistent asthma, to achieve optimal long term control while reducing ICS exposure.

Figure

Budesonide/formoterol used as anti-inflammatory reliever




- Patient centered flexible dosing
- Ensures perfect concordance between reliever and controller