

Journal Pre-proof

Pragmatic reappraisal of long acting muscarinic antagonists at steps 4/5 for persistent adult asthma

Dr Brian Lipworth MD , Ms Kirsten Stewart MBChB ,
Dr Rory Chan MBChB

PII: S1081-1206(22)00449-5
DOI: <https://doi.org/10.1016/j.anai.2022.05.017>
Reference: ANAI 3964



To appear in: *Annals of Allergy, Asthma Immunology*

Received date: 6 May 2022
Revised date: 13 May 2022
Accepted date: 16 May 2022

Please cite this article as: Dr Brian Lipworth MD , Ms Kirsten Stewart MBChB ,
Dr Rory Chan MBChB , Pragmatic reappraisal of long acting muscarinic antagonists at
steps 4/5 for persistent adult asthma, *Annals of Allergy, Asthma Immunology* (2022), doi:
<https://doi.org/10.1016/j.anai.2022.05.017>

This is a PDF file of an article that has undergone enhancements after acceptance, such as the addition of a cover page and metadata, and formatting for readability, but it is not yet the definitive version of record. This version will undergo additional copyediting, typesetting and review before it is published in its final form, but we are providing this version to give early visibility of the article. Please note that, during the production process, errors may be discovered which could affect the content, and all legal disclaimers that apply to the journal pertain.

© 2022 American College of Allergy, Asthma & Immunology. Published by Elsevier Inc.
This is an open access article under the CC BY license (<http://creativecommons.org/licenses/by/4.0/>)

Invited Perspective article for Annals of Allergy, Asthma and Immunology

Pragmatic reappraisal of long acting muscarinic antagonists at steps 4/5 for persistent adult asthma

Dr Brian Lipworth MD,
Ms Kirsten Stewart MBChB,
Dr Rory Chan MBChB

Scottish Centre for Respiratory Research
Ninewells Hospital and Medical School
University of Dundee, Scotland, UK

Correspondence: b.j.lipworth@dundee.ac.uk

Other author emails:
kstewart004@dundee.ac.uk
r.chan@dundee.ac.uk

Word count: 931

References: 5

Funding source: None

NCT: not applicable

Conflicts of interest:

Ms Stewart reports holding shares in GlaxoSmithKline.

Dr Chan reports personal fees from AstraZeneca for giving talks.

Dr Lipworth reports support from AstraZeneca for grants (external supported research grant and multicentre trial), meeting attendance (ERS) and personal fees (consulting, talks); and support from Chiesi for grants (external supported research grant), meeting attendance (BTS) and personal fees (talks); support from Sanofi for grants (external supported research grant); and personal fees from Glenmark (consulting, talks); and support from Cipla (consulting); and the son of BJL is presently an employee of AstraZeneca.

Key words: long acting muscarinic antagonist; long acting beta-agonist; inhaled corticosteroid; triple inhaler; asthma exacerbations; asthma control

Abbreviations:

AER: annualised exacerbation rate
COPD: chronic obstructive pulmonary disease
FeNO: fractional exhaled breath nitric oxide
FEV1: forced expiratory volume in 1s
GINA: global initiative for asthma

ICS: inhaled corticosteroid
 LABA: long acting beta-agonist
 LAMA: long acting muscarinic antagonist
 Ppb: parts per billion
 TTT: time to treat to prevent an exacerbation

Current GINA asthma guidelines advocate the use of long acting muscarinic antagonists (LAMA) as add on therapy to inhaled corticosteroid/long acting beta-agonist (ICS/LABA) at steps 4 and 5 to improve control and reduce exacerbations in persistent adult asthma. Such triple therapy (ICS/LABA/LAMA) can either be open as two separate ICS/LABA and LAMA inhalers or closed as a single triple inhaler. Musier et al recently provided an excellent overview on LAMA's in asthma as either open or closed therapies.¹ Here we will briefly critique the current evidence appertaining to pivotal phase 3 trials involving closed single inhaler triple therapy particularly focussing on exacerbations. Such trials allow for a valid head to head comparison of single triple vs dual therapy via the same inhaler platform. There are three currently available single triple and corresponding dual inhalers approved for asthma (Table). In choosing a particular triple; consideration should be given to the dosing regimens, patient preference for a particular device, inhaler technique, lung deposition, cost, formulary availability and insurance cover.

The pivotal phase 3 trials are summarised for effects on moderate to severe annualised exacerbation rates (AER), with medium and high doses of each formulation, comparing triple versus dual inhalers (Table). The TRIGGER/TRIMARAN trials² differed from either the CAPTAIN³ and IRIDIUM⁴ trials in that the absolute AER's on treatment were approximately two fold higher, where AER was the primary outcome.

In TRIGGER/TRIMARAN² and in IRIDIUM trials⁴ comparing triple versus dual inhalers the rate ratios as relative % difference in AER were broadly similar. However in IRIDIUM the time to treat (TTT) to prevent an exacerbation was approximately three fold longer than in TRIGGER/TRIMARAN trials when comparing triple vs dual inhalers at either dose, in turn suggesting there is little benefit using the once daily Enerzair triple. This might perhaps reflect that glycopyrronium is more suited to twice than once daily dosing, along with a lower absolute AER on treatment in IRIDIUM⁴.

The CAPTAIN trial³ showed a ten fold longer TTT comparing the relative impact of high and medium doses of Trelegy vs Breo, inferring futility for the higher dose. However such a comparison does not take into account type 2 inflammatory status which is predictive of ICS efficacy in terms of AER reduction. Post hoc pooled analysis (ie Trelegy and Breo combined) in patients with blood eosinophils ≥ 300 cells/ul and FeNO > 50 ppb shows a clear dose response effect for the FF moiety resulting in a 65% relative difference in exacerbations. This teaches the importance of first optimising the dose of ICS to attain the greatest impact of exacerbations before ever considering adding in a LAMA in patients with type 2 high asthma.

All of the trials showed the addition of LAMA conferred no clinically meaningful impact on the asthma control questionnaire, while changes in FEV1 were also modest and less than the minimal clinical important difference of 230 ml. For example, in the CAPTAIN trial³ comparing medium and high doses of Trelegy vs Breo amounted to mean differences in trough FEV1 of 100 ml and 92ml.

This therefore begs the pertinent question as to where triple inhaler therapy should be best employed. Perhaps patients with increased cholinergic drive such as asthmatic smokers might benefit from triple therapy akin to COPD, where effects of LAMA on cough and mucus hypersecretion may also play a part. This question remains unanswered given that smokers were excluded from the phase 3 trials. One randomised crossover trial in asthmatic smokers

looked at open triple combinations showing superiority over ICS/LABA at trough after chronic dosing for peripheral airway resistance and compliance measured by oscillometry⁵. A possible role for triple might be in those patients with the arginine-16 beta-2 receptor polymorphism who are susceptible to LABA induced beta-2 receptor down regulation and uncoupling associated with subsensitivity of response.

Another relevant question is whether medium dose triple might be used as an ICS sparing strategy instead of high dose dual inhaler. In the CAPTAIN trial³ high dose Breo vs medium dose Trelegy showed a relative TTT of 9.1 years and a 16% difference in AER in favour of the former, while comparing high vs medium doses of Breo revealed a TTT of 3.3 years and a 35% difference in AER. Hence the use of medium dose triple might be a cogent strategy in type 2 low asthma patients including those who smoke or are obese where there is relative resistance to the ICS moiety. The risk benefit of using higher dose ICS as either triple or dual inhalers would need to take into account the increased propensity for local and systemic corticosteroid related adverse effects.

Is there any role moving forwards for open triple therapy given the potential inherent issues with regards to issues of inhaler technique and worse adherence associated with two different inhalers? One possible reason for choosing open triple therapy might be for those patients who prefer the inherent flexibility of a patient centred variable dosing regimen using maintenance and reliever therapy with ICS/Formoterol formulations in conjunction with a separate LAMA such as tiotropium. This would allow the patient to adjust the dose of ICS/formoterol according to prevailing trigger factors or during an exacerbation instead of using a separate albuterol reliever and a closed triple inhaler.

In conclusion the available data from phase 3 trials does not appear to endorse a convincing argument for the wide scale use of single triple inhaler therapy at step 4/5 of asthma guidelines. Prescribers should focus first on optimising the dose of ICS/LABA, especially for asthma patients with evidence type 2 inflammation, in order to achieve better control and fewer exacerbations.

References

1. Muiser S, Gosens R, van den Berge M, Kerstjens HAM. Understanding the role of long-acting muscarinic antagonists in asthma treatment. *Ann Allergy Asthma Immunol.* 2022;128:352-360.
2. Virchow JC, Kuna P, Paggiaro P, Papi A, Singh D, Corre S, et al. Single inhaler extrafine triple therapy in uncontrolled asthma (TRIMARAN and TRIGGER): two double-blind, parallel-group, randomised, controlled phase 3 trials. *Lancet.* 2019;394:1737-1749.
3. Lee LA, Bailes Z, Barnes N, Boulet LP, Edwards D, Fowler A, et al. Efficacy and safety of once-daily single-inhaler triple therapy (FF/UMEC/VI) versus FF/VI in patients with inadequately controlled asthma (CAPTAIN): a double-blind, randomised, phase 3A trial. *Lancet Respir Med.* 2021;9:69-84.
4. Kerstjens HAM, Maspero J, Chapman KR, van Zyl-Smit RN, Hosoe M, Tanase AM, et al. Once-daily, single-inhaler mometasone-indacaterol-glycopyrronium versus mometasone-indacaterol or twice-daily fluticasone-salmeterol in patients with inadequately controlled asthma (IRIDIUM): a randomised, double-blind, controlled phase 3 study. *Lancet Respir Med.* 2020;8:1000-1012.
5. Jabbal S, Kuo CR, Lipworth B. Randomized controlled trial of triple versus dual inhaler therapy on small airways in smoking asthmatics. *Clinical & Experimental Allergy.* 2020;50:1140-1147.

Table 1. Pivotal phase 3 trials comparing medium or high doses of ICS/LABA/LAMA vs ICS/LABA for effects on annualized exacerbation rate (AER) as moderate to severe exacerbations. Comparisons between triple and dual therapy at either dose are expressed as values for the relative time to treat to prevent an average patient experiencing an asthma exacerbation, calculated as the reciprocal of the absolute difference in AER. Also shown is the relative rate ratio expressed as % difference in AER comparing triple vs dual therapy at either dose. AER was the primary outcome in TRIGGER/TRIMARAN and secondary in CAPTAIN and IRIDIUM.

ICS/LABA/LAMA vs ICS/LABA (AER)	CAPTAIN	TRIGGER/TRIMARAN	IRIDIUM
Medium doses: • Time to treat • Relative difference	5.3yr 22%	3.0yr 15%	11.1yr 13%
High doses: • Time to treat • Relative difference	50.0yr 3.0%	4.4yr 12%	12.5yr 15%

CAPTAIN: Fluticasone Furoate/Vilanterol/Umeclidinium vs Fluticasone Furoate/Vilanterol (Trelegy vs Breo Ellipta dry powder od).

TRIGGER/TRIMARAN: Beclometasone/Formoterol/Glycopyrronium vs Beclometasone/Formoterol (Trimbow vs Foster extra fine pMDI bid).

IRIDIUM: Mometasone Furoate/Indaceterol/Glycopyrronium vs Mometasone Furoate/Indaceterol (Enerzair vs Atecura Breezehaler dry powder od).