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Perspective

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

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Current Global Initiative for Asthma guidelines advocate the use of long-acting muscarinic antagonists (LAMAs) as add-on therapy to inhaled corticosteroid (ICS) combined with long-acting β-agonist (LABA) at steps 4 and 5 to improve control and reduce exacerbations in persistent adult asthma. Such triple therapy (ICS and LABA and LAMA) can either be open as 2 separate inhalers; ICS combined with LABA and a separate LAMA inhaler, or closed as a single triple inhaler. Muiser et al[1] recently provided an excellent overview on LAMAs in asthma as either open or closed therapies. Here, we will briefly critique the current evidence appertaining to pivotal phase 3 trials involving closed single inhaler triple therapy particularly focusing on exacerbations. Such trials allow for a valid head-to-head comparison of single triple vs dual therapy by the same inhaler platform. There are 3 currently available single triple and corresponding dual inhalers approved for asthma (Table 1). 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 summarized for effects on moderate-to-severe annualized exacerbation rates (AERs), with medium and high doses of each formulation, comparing triple vs dual inhalers (Table 1). The TRIGGER and TRIMARAN trials[2] differed from either the CAPTAIN[3] and IRIDIUM[4] trials in that the absolute AERs on treatment were approximately 2-fold higher, where AER was the primary outcome.

In TRIGGER and TRIMARAN[2] and in IRIDIUM trials[4] comparing triple vs 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 3-fold longer than in TRIGGER and TRIMARAN trials when comparing triple vs dual inhalers at either dose, in turn suggesting there is little benefit using the once-daily Enerzair (Novartis Pharmaceuticals UK Ltd, London W12 7FQ, UK) 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 IRIDIUM.[4]

The CAPTAIN trial[3] revealed a 10-fold longer TTT comparing the relative impact of high and medium doses of Trelegy (GlaxoSmithKline Ltd, Hertfordshire SG12 0DJ, UK) vs Breo (GlasxoSmithKline Ltd, Hertfordshire SG12 0DJ, UK), 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 more than or equal to 300 cells/μL and fractional exhaled nitric oxide more than 50 ppb reveals a clear dose-response effect for the FF moiety resulting in a 65% relative difference in exacerbations. This teaches the importance of first optimizing 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 the trials revealed that the addition of LAMA conferred no clinically meaningful impact on the asthma control questionnaire, whereas changes in forced expiratory volume in 1 second were also modest and less than the minimal clinical important difference of 230 mL. For example, in the CAPTAIN trial,[3] comparing medium and high doses of Trelegy vs Breo found that the mean differences in trough forced expiratory volume in 1 second were 100 mL and 92 mL, respectively.

This, therefore, begs the pertinent question as to where triple inhaler therapy should be best used. Perhaps patients with increased cholinergic drive such as smokers with asthma might benefit from

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Table 1
Triple vs dual therapy pivotal phase 3 trials comparisons

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

Abbreviations: AER, annualized exacerbation rate; ICS, inhaled corticosteroid; LABA, long-acting β-agonist; LAMA, long-acting muscarinic antagonist.
NOTE. Pivotal phase 3 trials comparing medium or high doses of ICS/LABA/LAMA vs ICS/LABA for effects on 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. Furthermore, the relative rate ratio expressed as % difference in AER comparing triple vs dual therapy at either dose, is illustrated. AER was the primary outcome in TRIGGER/TRIMARAN and secondary in CAPTAIN and IRIDIUM.
CAPTAIN: Fluticasone Furoate/Vilanterol/Umeclidinium vs Fluticasone Furoate/Vilanterol (Trelegy vs Breo Ellipta dry powder once a day).
TRIGGER/TRIMARAN: Beclometasone/Formoterol/Glycopyrronium vs Beclometasone/Formoeterol (Trimbow vs Foster extra-fine pMDI twice a day).
IRIDIUM: Mometasone Furoate/Indaceterol/Glycopyrronium vs Mometasone Furoate/Indaceterol (Enerzair vs Atectura Breezehaler dry powder once a day).

triple therapy akin to chronic obstructive pulmonary disease, 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 randomized crossover trial in smokers with asthma looked at open triple combinations revealing superiority over dual ICS and LABA at trough after chronic dosing for peripheral airway resistance and compliance measured by oscillometry.[5] 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 trial,[3] high-dose Breo vs medium-dose Trelegy had a relative TTT of 9.1 years and a 16% difference in AER in favor of the former, whereas 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 patients with type 2-low asthma 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 forward for open triple therapy given the potential inherent issues with regard to issues of inhaler technique and worse adherence associated with 2 different inhalers? One possible reason for choosing open triple therapy might be for those patients who prefer the inherent flexibility of a patient-centered variable dosing regimen using maintenance and reliever therapy with ICS and 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 do not seem to endorse a convincing argument for the wide-scale use of single triple inhaler therapy at step 4 and 5 of asthma guidelines. Prescribers should focus first on optimizing the dose of ICS and LABA, especially for patients with asthma with evidence of type 2 inflammation, to achieve better control and fewer exacerbations.

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