Iñigo Ojanguren[1,2,3], María Florencia Pilia[1]

iojanguren@vhebron.net
@InigoOjanguren
linkedin.com/in/iñigo-ojanguren-arranz-814863a1

Journal club

Efficacy and safety of once-daily single-inhaler triple therapy in patients with inadequately controlled asthma: the CAPTAIN trial

Commentary on:
Lee *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, randomized, phase 3A trial. *Lancet Respir Med* 2021; 9: 69–84.

Cite as: Ojanguren I, Pilia MF. Efficacy and safety of once-daily single-inhaler triple therapy in patients with inadequately controlled asthma: the CAPTAIN trial. *Breathe* 2021; 17: 200279.

Context

Inhaled corticosteroids (ICS) remain the cornerstone of treatment in asthmatic patients. In fact, many patients suffering from asthma are able to achieve good symptom control and avoid asthma exacerbations with a combination of moderate dose ICS and a long-acting β_2-agonist (LABA). However, a significant number of patients require stepping up from moderate dose ICS/LABA to achieve good asthma control. While LABA are effective bronchodilators primarily due to their ability to relax airway smooth muscle (ASM) by exerting their effects *via* binding to the active site of β_2-airway receptors, the mechanism of action of ICS in asthma is not well known, although they have shown to have a wide range of inhibitory effects on multiple cell types and mediators involved in inflammation and asthmatic response. The addition of tiotropium, a long-acting muscarinic antagonist (LAMA), which acts by blocking the bronchoconstriction effect of acetylcholine on M3 muscarinic receptors expressed in ASM, to the ICS/LABA combination has been shown to improve lung function and increase the time to first severe exacerbation in adult asthmatics [1].

Despite these advantages, adding the LAMA implies that patients must use two different inhalers with different dose regimens. This is an inconvenience which is not without relevance since it has an impact on treatment adherence and hampers the instructions of caregivers. In parallel, there is no study on whether the impact of increasing the ICS dose or adding LAMA varies depending on airway inflammatory status (type 2 or not type 2). Thus, the objectives of the CAPTAIN study were: 1) to analyse the safety and efficacy of single-inhaler fluticasone furoate (FF) plus umeclidinium (UMEC) plus vilanterol (VI) comparted with FF/VI; and 2) to analyse the effects of increasing FF or adding UMEC on lung function and exacerbations depending on the baseline inflammatory status.

Methods

The CAPTAIN trial was a randomised, double-blind, 24–52 week, active controlled, parallel group, phase 3A study, conducted across 15 countries,

@ERSpublications
Triple therapy with FF/UMEC/VI improved lung function in patients with moderate or severe uncontrolled asthma on ICS/LABA but did not lead to a reduction in moderate and/or severe exacerbations https://bit.ly/38UnuRW

encompassing 416 hospitals. Adults (aged ≥18 years) with inadequately controlled asthma symptoms (Asthma Control Questionnaire ≥1.5) despite maintenance therapy with daily ICS/LABA for at least 12 consecutive weeks before pre-screening were included. Patients were required to have a best pre-bronchodilator forced expiratory volume in 1 s (FEV_1) between 30% and 85% of predicted normal value and airway reversibility (defined as an increase in FEV_1 ≥12% and ≥200mL 20–60 min after four inhalations of albuterol or salbutamol) at screening. Patients were randomly assigned (1:1:1:1:1:1) to one of six treatment groups: FF/VI 100/25 µg or 200/25 µg; or FF/UMEC/VI 100/31.25/25 µg, 100/62.5/25 µg, 200/31.25/25 µg or 200/62.5/25 µg. The primary efficacy end-point was change from baseline FEV_1 at week 24. The key secondary end-point was the annualised rate of moderate and/or severe asthma exacerbations (up to week 52).

Main results

Out of 5185 patients screened, 2439 were recruited and randomly assigned to FF/VI (100/25 µg: n=407; 200/25 µg: n=406) or FF/UMEC/VI (100/31.25/25 µg: n=405; 100/62.5/25 µg: n=406; 200/31.25/25 µg: n=404; 200/62.5/25 µg: n=408). Baseline demographics were similar across all the treatment groups. The least squares mean (95% CI) improvement in FEV_1 change from baseline for FF/UMEC/VI 100/62.5/25 µg *versus* FF/VI 100/25 µg was 110mL (66–153 mL; p<0.0001), and for 200/62.5/25 µg *versus* 200/25 µg it was 92mL (49–135; p<0.0001). Adding UMEC 31.25 µg to FF/VI produced similar improvements (FF/UMEC/VI 100/31.25/25 µg *versus* FF/VI 100/25 µg: 96mL (52–139 mL; p<0.0001); and 200/31.25/25 µg *versus* 200/25 µg: 82mL (39–125 mL; p: 0.0002)) (table 1). No significant reductions in moderate and/or severe exacerbation rates were observed for FF/UMEC 62.5 µg/VI *versus* FF/VI (pooled analysis), with rates being lower in the FF 200 µg *versus* FF 100 µg containing treatment groups (table 2). A higher dose of FF had an impact on FEV_1 and annualised the moderate and/or severe exacerbations rate in patients with a higher baseline blood eosinophil count and exhaled nitric oxide fraction (F_{eNO}). The number of adverse events (ranging from 52% to 63% depending on the treatment group) and severe adverse events (ranging from <1% to 1% depending on the treatment group) was similar across treatment groups with nasopharyngitis, headache and upper respiratory tract infection being the most commonly reported adverse events. One death was considered to be related to the study drug (pulmonary embolism) in a patient in the FF/UMEC/VI 100/31.25/25 µg group.

Commentary

The CAPTAIN trial demonstrated that triple therapy with FF/UMEC/VI improves lung function in patients with moderate or severe uncontrolled asthma on ICS/LABA. Compared to FF/VI, FF/UMEC/VI also improved symptoms and asthma control in a dose-related manner. FF/UMEC/VI did not lead to a significant reduction in moderate and/or severe exacerbations when added to FF/VI 200/24 µg. High doses of FF were related to fewer exacerbations in patients with a higher baseline blood eosinophil count and F_{eNO}, but this was not observed with the addition of UMEC.

This study provides valuable information to the growing evidence that highlights the benefits of adding a LAMA to asthmatics that are not well-controlled on medium or high doses of ICS plus a LABA (table 3). In fact, in line with previous studies [1, 2] analysing the benefits of triple therapy in terms of lung function, symptoms and asthma control, adding UMEC to FF/VI showed a clinically relevant and statistically significant improvement in these outcomes.

Table 1 *Unpooled analysis of least squares mean change in FEV_1 from baseline to week 24*

	FF/VI 100/25 µg plus			FF/VI 200/25 µg plus		
	No UMEC	**UMEC 31.25 µg**	**UMEC 62.5 µg**	**No UMEC**	**UMEC 31.25 µg**	**UMEC 62.5 µg**
Subjects n	379	381	390	385	384	391
Changes from baseline in trough FEV_1 mL at week 24	24 (−6–55)	120 (89–151)	134 (104–165)	76 (45–106)	157 (127–188)	168 (137–198)
Changes in FEV_1 mL by adding UMEC at week 24	Ref.	+96 (52–139) p<0.0001	+110 (66–153) p<0.0001	Ref.	+82 (39–125) p<0.0002	+92 (49–135) p<0.0001

Data are presented as least squares mean (95% CI), unless otherwise stated. The p-values are not adjusted for multiplicity.

Table 2 *Analysis of mean annualised rate of moderate and/or severe exacerbations in the unpooled intention-to-treat population at weeks 1 to 52*

	FF/VI 100/25 µg plus			FF/VI 200/25 µg plus		
	No UMEC	**UMEC 31.25 µg**	**UMEC 62.5 µg**	**No UMEC**	**UMEC 31.25 µg**	**UMEC 62.5 µg**
Subjects n	407	405	406	406	404	408
Mean annualised moderate and/or severe exacerbations rate	0.87 (0.73–1.04)	0.76 (0.64–0.92)	0.68 (0.56–0.82)	0.57 (0.47–0.69)	0.61 (0.50–0.74)	0.55 (0.45–0.67)
FF/UMEC/VI *versus* FF/VI	Ref.	1.01 (0.72–1.42), p=0.96	1.07 (0.76–1.50), p=0.69	Ref.	0.98 (0.66–1.45), p=0.93	0.88 (0.60–1.31), p=0.54

Data are presented as rate ratio (95% CI), unless otherwise stated. The p-values are not adjusted for multiplicity.

A relevant strength of the CAPTAIN study consists in analysing the influence of baseline type 2 biomarkers on response to FF/UMEC/VI. The effect of increasing the FF dose on trough FEV_1 values and the rate of moderate and/or severe exacerbations were increased with the increasing blood eosinophil count and F_{eNO}. In this context, the proportion of patients on FF 100 µg who had a severe exacerbation was nearly three-fold higher in patients with baseline blood eosinophils of at least 300 cells·µL^{-1} and F_{eNO} >50 ppb compared to patients with baseline blood eosinophils <150 cells·µL^{-1} and F_{eNO} <20 ppb. This type of analysis makes it possible to take a step forward towards the implementation of treatable traits in current practice. Other positive aspects related to the CAPTAIN study consist of the 5-week pre-randomisation period during which standardised medication was provided, and both comparators (FF/VI and FF/UMEC/VI) were administered with the same dry powder inhaler.

However, there is an important difference between the present study and its predecessors in terms of asthma exacerbations [1–3]. While the TRIGGER and TRIMARAN tiotropium studies showed reductions in severe exacerbations with the addition of LAMA, these effects were not observed with the addition of UMEC to FF/VI. While adding UMEC to FF/VI 100/25 µg reduced moderate/severe exacerbations, no additional reduction was seen when added to FF/VI 200/24 µg. It should be kept in mind that the disparity in terms of the definitions of moderate exacerbations and the differences in study populations between studies could justify such discrepancies. In fact, the main limitation of the study is related to the low rate of exacerbations observed with respect to the lower risk population than was assumed in the calculations. This limitation could have had a relevant impact on the results observed and could, at least partially, explain the lack of efficacy of UMEC in reducing severe asthma exacerbations when added to high dose FF and VI. Another potential limitation could be related to the fact that during the run-in and stabilisation periods most patients received a lower ICS dose compared to their usual baseline dose. In this context, some patients requiring a higher ICS dose may have experienced exacerbations leading to study withdrawal. As a result, the efficacy of higher dose ICS may have been underestimated in the trial. Finally, it should be noted that no details were given regarding the proportion of participants receiving acceptable concomitant medications such as systemic steroids up to 5 mg·day^{-1}, anti-immunoglobulin E or anti-interleukin 5, and their potential impact on the results.

Implications for practice

Similar to previous triple therapy trials, the CAPTAIN study certifies that in general terms when asthma is not well-controlled with ICS/LABA, the ICS/LAMA/LABA combination is able to improve FEV_1 values. It also highlights the differential properties of each component of the triple combination. While adding LAMA translates into an improvement in FEV_1 values, increasing the ICS dose impacts the number of severe exacerbations. These findings favour the treatable treats approach that allows an individualised treatment strategy depending on the desired outcomes.

The CAPTAIN study also highlights the relevance of biomarker-based outcomes, since increasing the ICS dose could specially benefit asthmatics with high type 2 airway inflammation, while UMEC could have an important role particularly in patients with low type 2 inflammation.

Last but not least, the possibility of offering the combination of ICS/LAMA/LABA in a single inhaler could improve the low treatment adherence rates observed in asthmatics and could also ameliorate the inhaler instruction efforts of the caregivers.

In conclusion, this study could lead to a step-change in the asthma therapy paradigm in patients

Table 3 *Summary of the randomised controlled trials (RCTs) analysing triple therapy with LAMA, LABA and ICS in a single inhaler in asthma*

First author [ref.]	Study design	Primary outcome	Secondary outcome	Results	Limitations	Adverse events	Comments
Kerstjens [1]	Two replicates, RCTs	Change from baseline FEV_1 at week 24 Time to first severe asthma exacerbation	Peak and trough FEV_1 and FVC at each treatment visit Time to the first asthma exacerbation	Addition of tiotropium significantly increased the time to the first severe exacerbation and provided modest sustained bronchodilation	Inconsistency in the results between two trials	Most events were mild Dry mouth (<2% all patients, but was reported more frequently in the tiotropium group than in the placebo group)	
Virchow [2]	Two parallel-group, double-blind, randomised, active-controlled, phase 3 trials (TRIMARAN and TRIGGER)	Change from pre-dose FEV_1 at week 26 Annualised rate of moderate/severe exacerbations over 52 weeks	Change from baseline in peak FEV_1 at week 26 Average morning PEF over the first 26 weeks in each study Rate of severe exacerbations	Addition of a LAMA (glycopyrronium) improves lung function and reduces exacerbations	Much lower rate of severe exacerbations observed during the studies than reported in historical data	Similar across treatment groups Most events were mild	
Lee [3]	Double-blind, randomised, parallel-group, phase 3A study (CAPTAIN)	Change from the baseline FEV_1 at week 24	Annualised rate of moderate and/or severe asthma exacerbations Change from baseline in SGRQ Change from baseline in ACQ-7 total score	Adding UMEC improved lung function but did not lead to a significant reduction in moderate and/or severe exacerbations	Low rate of exacerbations compared to other studies Most patients received a lower ICS dose compared to their usual baseline dose during run-in/stabilisation period	Similar across treatment groups (dry mouth/drying of the airway secretions) Most events were mild	*Post-hoc* and prespecified subgroup analyses by biomarkers of type 2 inflammation

FVC: forced vital capacity; PEF: peak expiratory flow; SGRQ: St George's Respiratory Questionnaire; ACQ: Asthma Control Questionnaire.

on LABA/ICS based on the different properties of LABA, LAMA and ICS. While higher doses of ICS should be considered for exacerbating patients, LAMA should be added for those experiencing asthma symptoms. Nonetheless, given the discrepancy of recent trials on whether the addition of LAMA to LAMA/ICS reduces exacerbations in this subgroup of patients, further studies are needed to clarify these uncertainties.

Affiliations

Iñigo Ojanguren[1,2,3], María Florencia Pilia[1]

[1]Servei de Pneumología, Hospital Universitari Vall d´Hebron, Departament de Medicina, Universitat Autònoma de Barcelona (UAB), Barcelona, Spain. [2]Institut de Recerca (VHIR), Barcelona, Spain. [3]CIBER de Enfermedades Respiratorias (CIBERES), Barcelona, Spain.

Acknowledgements

I. Ojanguren is a researcher supported by the Pla Estratègic de Recerca i Innovació en salut (PERIS) 2016–2020 (SLT008/18/00108; G60594009).

Conflict of interest

I. Ojanguren reports personal fees from AstraZeneca, BIAL, Boehringer Ingelheim, MSD, Chiesi, GSK, Novartis and TEVA, grants from Menarini, grants and personal fees from Mundipharma, outside the submitted work. M.F. Pilia has nothing to disclose.

References

1. Kerstjens HA, Engel M, Dahl R, *et al.* Tiotropium in asthma poorly controlled with standard combination therapy. *N Engl J Med* 2012; 367: 1198–1207.
2. Virchow JC, Kuna P, Paggiaro P, *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, *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, randomized, phase 3A trial. *Lancet Respir Med* 2021; 9: 69–84.