



Manifesto on inhaled triple therapy in asthma: an Interasma (Global Asthma Association – GAA) document

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PHARMACOTHERAPY



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Fulvio Braidó, MD^{a,b,*} , Angelica Tiotiu, MD, PhD^{c,d,*} , Guillermo Guidos-Fogelbach, MD, PhD(C)^e , Ilaria Baiardini, MD^{b,f,g}, Filippo Cosini, MD^h, Jaime Correia de Sousa, MD, PhD^{i,j}, Andras Bikov, MD, PhD^{k,l}, Sylvia Novakova, MD, PhD^m, Marina Labor, MDⁿ , Igor Kaidashev, MD^o, Denislava Nedeva, MD, PhD^p, Krzysztof Kowal, MD, PhD^q, Stefan Mihaicuta, MD, PhD^r, Marilyn Urrutia Pereira, MD^s, Dirceu Solé, MD^t, Plamela Novakova, MD^u, Herberto Chong-Neto, MD, PhD^v, Laura Vrzy, MD^h, Ignacio J. Ansotegui, MD, PhD^w, Jonathan A. Bernstein, MD^x, Louis-Philippe Boulet, MD, PhD^y, Giorgio Walter Canonica, MD^{f,g,z}, Lawrence Dubuske, MD, PhD^{aa}, Carlos Nunes, MD, PhD^{bb}, Juan Carlos Ivancevich, MD, PhD^{cc}, Pierachille Santus, MD, PhD^{dd} , Nelson Rosario, MD, PhD^{ee}, Alexander Emelyanov, MD^{ff} and Paschalis Steiropoulos, MD, PhD^{gg}

^aIRCCS, Ospedale Policlinico San Martino, Genova, Italy; ^bDepartment of Internal Medicine, University of Genoa, Genova, Italy; ^cDepartment of Pulmonology, University Hospital of Nancy, Nancy, France; ^dEA 3450 DevAH - Development, Adaptation and Disadvantage, Cardiorespiratory Regulations and Motor Control, University of Lorraine, Nancy, France; ^eInstituto Politécnico Nacional, E.N.M.H/S.E.P.I, Laboratorio de Bioquímica Estructural, Ciudad de México, México; ^fDepartment of Biomedical Sciences, Humanitas University, Pieve Emanuele, Milan, Italy; ^gIRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; ^hUniversity of Genoa, Genova, Italy; ⁱLife and Health Sciences Research Institute (ICVS), School of Medicine, University of Minho, Braga, Portugal; ^jICVS/3B's, PT Government Associate Laboratory, Braga/Guimarães, Portugal; ^kManchester University NHS Foundation Trust, Manchester, UK; ^lDivision of Infection, Immunity and Respiratory Medicine, University of Manchester, Manchester, UK; ^mAllergy Unit of Internal Consulting Department, University Hospital "St. George", Plovdiv, Bulgaria; ⁿVärnamo Hospital, Värnamo, Sweden; ^oUkrainian Medical Stomatological Academy, Poltava, Ukraine; ^pMedical University Sofia, Sofia, Bulgaria; ^qDepartment of Allergology and Internal Medicine, Medical University of Białystok, Białystok, Poland; ^rPulmonology Department, Cardio Prevent Foundation, University of Medicine and Pharmacy "Dr Victor Babes", Timisoara, Romania; ^sFederal University of Pampa - Campus Uruguaiana, Pediatric Program of Asthma Prevention (PIPA), Pontificia Universidade Católica do Rio Grande do Sul, Universidad Nacional de Córdoba, Córdoba, Argentina; ^tAssociação Brasileira de Alergia e Imunologia, Sociedade Brasileira de Pediatria, Universidade Federal de São Paulo, São Paulo, Brazil; ^uClinic of Clinical Allergy, Medical University, Sofia, Bulgaria; ^vDivision of Allergy and Immunology, Department of Pediatrics, Federal University of Paraná, Curitiba, Brazil; ^wHospital Quirónsalud Bizkaia, Bilbao, Spain; ^xDivision of Immunology, Department of Internal Medicine, Allergy Section University of Cincinnati, Cincinnati, OH, USA; ^yQuébec Heart and Lung Institute-Laval University, Québec City, Canada; ^zPersonalized Medicine, Asthma and Allergy, IRCCS Humanitas Research Hospital, Rozzano, Milan, Italy; ^{aa}Division of Allergy and Immunology, Department of Internal Medicine, George Washington University School of Medicine and Health Sciences, George Washington University Medical Faculty Associates, Washington, DC, USA; ^{bb}Centro de ImunoAlergologia de Algarve, Porto, Portugal; ^{cc}Immunology Department, Faculty of Medicine, del Salvador University, Buenos Aires, Argentina; ^{dd}Department of Biomedical and Clinical Sciences, University of Milan, Division of Respiratory Diseases "L. Sacco" Hospital, ASST Fatebenefratelli Sacco, Milan, Italy; ^{ee}Federal University of Paraná (UFPR), Curitiba, Brazil; ^{ff}Department of Respiratory Medicine, North-Western Medical University named after I.I.Mechnikov, St-Petersburg, Russia; ^{gg}Department of Respiratory Medicine, Medical School, Democritus University of Thrace, University General Hospital Dragana, Alexandroupolis, Greece

ABSTRACT

Objective: The optimal use of drug combinations for the management of asthma is providing significant results. This has prompted Interasma (Global Asthma Association) to take a position on inhaled triple therapy in asthma.

Methods: We performed an extensive literature research to clinical trials, meta-analyses, randomized controlled trials and systematic reviews.

Results: Starting from an extensive literature review, Interasma executive committee discussed and approved this Manifesto, developed by Interasma scientific network (INES) members.

Conclusions: The manifesto describes the evidence gathered to date and states, advocates, and proposes issues on inhaled corticosteroid (ICS) plus long-acting beta 2 agonist (LABA) and long-acting muscarinic antagonists (LAMA) with the aim of challenging assumptions, fostering commitment, and bringing about change.

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CONTACT Guillermo Guidos-Fogelbach  guillermoguidos@yahoo.com  Instituto Politécnico Nacional, E.N.M.H/S.E.P.I, Laboratorio de Bioquímica Estructural, Ciudad de México, México.

*These authors contributed equally.

†These authors contributed equally.

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Background

The word “manifesto”, derived from the Latin noun “*manifestum*” (meaning clear or evident), refers to written statement declaring beliefs, opinions, intentions, aims, and policies as issued by a movement, group or organization. A manifesto usually starts from a published opinion or public consensus and creates a call-to-actions to implement changes in beliefs and behaviors. In the context of health care, a group of experts or a scientific organization usually develops a manifesto to attract attention to a specific topic (1), to highlight challenges faced by policymakers, health care professionals and patients (2), to set out standards for defining high-quality strategies (3), to provide a new perspective (4), and to arouse changes (5).

The optimal choice among combinations of molecules, treatment schedules, dosages and inhalers and the use of inhaled triple treatment (InTT) in asthma management are object of debate. This allows us to take a position on this timely issue in the light of available evidence

Methods

We performed a PubMed search using the MeSH terms “triple treatment and asthma”, “Long-Acting Muscarinic Antagonists (LAMA) and asthma”, “Tiotropium/Glycopyrronium/Umeclidinium and asthma.” The literature research has been limited to clinical trials, meta-analyses, randomized controlled trials and systematic reviews, involving adult patients, published until August 10th, 2021. A further search using as MESH terms “Tiotropium”, “asthma”, “real life”, “prospective”, “retrospective”, “observational”, “survey”, “audit”, “cross-sectional”, “adult”, has been also conducted. Selected papers were initially evaluated by a panel of experts, to assess their eligibility in contributing to the statements of the manifesto. There were considered only the trials in which the InTT, delivered by one or multiple devices, was compared with medium-high dose of ICS/LABA. In October 2021, the draft of the Manifesto was circulated among the Board of Officers of Interasma who appraised, discussed, modified, and approved the final version.

Results

We define

Inhaled triple therapy (ITT) refers to the concomitant administration of an ICS, a LABA and a LAMA. These drugs can be provided as multiple inhalers (Tiotropium+ICS/LABA) or as a fixed combination (‘triple’) inhaler for patients aged ≥ 18 years

(Beclometasone dipropionate-Formoterol fumarate dihydrate-Glycopyrronium; Fluticasone furoate-Vilanterol trifenate-Umeclidinium bromide; Mometasone furoate-Indacaterol-Glycopyrronium bromide; Budesonide-Formoterol fumarate dihydrate-Glycopyrronium). Global Initiative for Asthma (GINA) 2021 document (6) suggests the InTT among the “other step 4 options” and as preferred treatment at Step 5 in adults with not well controlled asthma with medium or high dose ICS-LABA. Although the step up from medium/high dose of ICS/LABA to InTT is a more usual approach in the real-life setting, the concomitant use of triple therapy with leukotriene receptor antagonists (LTRA), xanthine, biological drugs or oral steroids is frequent.

We know

Observational evidence

About 40% of patients with severe asthma are treated with InTT with or without concomitant use of biologics (7).

Data from the Severe Asthma Network Italy (SANI) registry showed that LAMAs are underused in severe asthma (35.9% were treated with LAMA). Patients on treatment with ICS/LABA/LAMA were characterized by higher age at asthma onset, significantly higher prevalence of former smokers and exacerbation rate, worse asthma control and disease-related quality of life and poorer lung function. Bronchiectasis was more frequently found in LAMA users (25.9%) (8,9).

The clinical pattern of patients initiating triple therapy is characterized also by a higher use of rescue oral corticosteroids (68%) and had high post-treatment ICS discontinuation rates at 6 months (44%) (9).

The persistence of exacerbations despite ICS/LABA treatment is a relevant driver to triple therapy initiation (10).

In a study enrolling elderly asthmatics, the incremental cost-effectiveness ratio of adding Tiotropium to ICS/LABA was \$60 074/quality-adjusted life-year (QALY), indicating that the addition of Tiotropium is not a cost-effective alternative. Nevertheless, a subgroup analyses showed that adding Tiotropium could be a cost-effective alternative for patients with poorly controlled symptoms and frequent short-acting beta-agonist users (\$4078/QALY) and frequent exacerbators (\$8332/QALY) (11).

Discussion

Multiple inhaler triple therapy

ICS/LABA plus tiotropium bromide RespiMat

Tiotropium bromide (TIO), 5 and 10 μ g daily administered through the RespiMat inhaler, as add-on

therapy in adult patients with uncontrolled severe asthma (Asthma Control Questionnaire - ACQ score ≥ 1.5 ; postbronchodilator FEV₁ $\leq 80\%$ of predicted value) despite maintenance treatment with at least a high-dose ICS/LABA, showed to significantly increase the peak FEV₁ after 8-weeks of treatment if compared with placebo (5 μg Δ 139 ml; 10 μg Δ 170 ml), without significant difference between the active doses. Trough FEV₁ was higher with TIO versus placebo (5 μg : 86 ml; 10 μg : 113 ml; both $p < 0.001$) as well as peak expiratory flow. No significant differences in Health-Related Quality of Life (HRQoL) scores and asthma symptoms between the treatment groups were shown. Adverse events were comparable across groups except for dry mouth, which was more common on 10 μg of TIO (12).

In a similar study ACQ-7 responders' rate was higher in the groups with TIO 5 μg and 2.5 μg (67.5%, respectively 69.3%) compared with the placebo (58.9%) at Week 24. However, at week 52, ACQ-7 responder rates were similar across treatment groups (13).

A *post hoc* analysis of five double-blind trials demonstrated the clinical benefits of tiotropium Respimat across GINA steps; FEV₁ response within 3 h post-dose, at week 24, after TIO Respimat 5 μg and 2.5 μg were respectively 111 ml and 181 ml in Step 4 and 164 ml in Step 5 for TIO 5 μg patients. Odds ratio (OR) for ACQ response to treatment versus placebo was 1.36 ($p < 0.05$) with TIO Respimat 5 μg at Step 4 (14).

Lung function improvements with TIO Respimat add-on to medium-dose ICS (with or without LABA) in adult patients with symptomatic asthma is sustained and similar for 5 μg once daily (158 ± 24 ml) and 2.5 μg twice-daily (149 ± 24 ml), both significant ($p < 0.01$) when compared with placebo (15).

In two replicated, randomized, controlled trials involving 912 patients with poorly controlled asthma treated with ICS/LABA, the administration of 5 μg of TIO o.d. significantly improved at 24 weeks the peak FEV₁ from baseline compared to placebo and increased the time to the first severe exacerbation (282 days vs. 226 days), with an overall reduction of 21% in the risk of a severe exacerbation (hazard ratio, HR 0.79; $p = 0.03$). The mean difference in ACQ-7 and Asthma Quality of Life Questionnaire (AQLQ) scores between the tiotropium group and the placebo group was significant only in trial 2 (-0.2 , $p = 0.003$; 0.18 units, $P = 0.02$) but minimal clinically important difference for the ACQ-7 and AQLQ score was not achieved in either trial (16).

TIO Respimat 5 μg o.d. add-on to ICS/LABA in patients with severe symptomatic asthma improved peak FEV₁, trough FEV₁ and ACQ-7 scores and

reduced the risk of exacerbations and worsening independently of a broad range of baseline characteristics including gender, age, allergic status, disease duration, age at asthma onset, and degree of airway obstruction at weeks 24 and 48. At Week 24, 53.9% of patients who received tiotropium 5 mg were responders compared with 46.9% of patients who received placebo (OR: 1.32) and the difference further increased at Week 48 (OR: 1.68) (17).

A post-hoc analysis of 4 randomized, double-blind, placebo-controlled studies in adults with asthma confirmed that age did not influence the effect of TIO Respimat 5 μg daily on mean ACQ total score (18).

A subgroup analysis from 5 clinical trials (12–48 weeks) demonstrated a comparable efficacy of TIO Respimat in the improvement of the FEV₁ in asthmatic patients across Body Mass Index (BMI) categories from 18.5 kg/m² to ≥ 30 kg/m² (19). Similarly, the efficacy of TIO Respimat as add-on to ICS $\pm$ LABA in patients with symptomatic asthma on peak FEV₁ and trough FEV₁ responses, risk of severe exacerbation, asthma worsening and ACQ-7 response rate is independent of T2 phenotype (serum IgE levels above or below 430 mg/L, blood eosinophil counts above or below 0.6 mg/L, and clinician judgment of allergic asthma) (20).

The addition of TIO 5 μg o.d. for 48 weeks to maintenance therapy with ICS/LABA in asthmatic patients significantly decreased airway wall area (WA) corrected for body surface area (BSA) (WA/BSA) ($p < 0.05$) and wall thickness (T) (T/BSA, $p < 0.05$) on the quantitative computed tomography. No significant difference in the change of fractional exhaled nitric oxide was observed. Changes in WA/BSA and T/BSA were significantly correlated with the change in FEV₁ ($r = 0.87$, $p < 0.001$, and $r = 0.82$, $p < 0.001$, respectively). Significantly better scores in the TIO group were found in two AQLQ domains: symptoms (mean differences 0.5 ± 1 , $p = 0.022$), and emotions (mean differences 0.4 ± 1.0 , $p = 0.050$), none in the group treated with ICS/LABA without TIO (21,22).

TIO dry powder inhaler (Handihaler). The inhalation of 18 μg of TIO o.d. improved the FEV₁ at 3 h from the baseline both in current smoker and nonsmoker asthmatics treated by ICS plus a second controller by 169 ml and 105 ml, respectively compared to placebo. The changes tended to be greater in smokers than in nonsmokers ($p = \text{ns}$) (23).

The effects TIO (18 μg o.d.) on lung function were investigated in patients with severe asthma with and without emphysematous changes treated with high-dose

ICS/LABA. At 60 min after TIO administration, the increase from baseline FEV1 was 12.6% higher than after placebo in patients with emphysema, and 5.4% in those without emphysema suggesting a comparable efficacy (24).

In patients with COPD and concomitant asthma, the administration of 18 µg of TIO o.d. significantly improved from baseline the pre-dose FEV1 (difference = 9.8 ± 23 ml vs placebo, $p < 0.001$) and forced vital capacity (FVC) (difference = 12.8 ± 34 ml vs placebo, $p < 0.001$) and FVC AUC 0–6 h (difference = 23.2 ± 35 ml, $p < 0.001$) at 12 weeks. Compared to baseline, the mean weekly number of daily puffs of prn salbutamol was reduced by 0.05 ± 0.12 puffs/day in the placebo group and by 0.50 ± 0.12 puffs/day in the TIO group at week 12 ($p < 0.05$) (25).

The comparison of a group of patients treated with TIO inhalation powder 18 µg o.d. combined with salmeterol-fluticasone propionate inhalant (50/250 µg b.i.d.) with the group receiving TIO combined with fluticasone propionate aerosol (250 µg b.i.d.) showed that after 8 weeks of treatment, the pulmonary function, asthma control and IL-13 levels in induced sputum were similar ($p > 0.05$). However, the use of rescue medication was significantly lower in the group treated by triple-therapy 1.20 ± 1.00 vs 2.20 ± 0.92 times of acute attacks/week, $p < 0.05$) (26).

No InTT with multiple inhalers exploring ICS/LABA plus Umeclidinium or Glycopyrronium are available.

Single inhaler triple therapy

Fluticasone furoate-umeclidinium bromide-vilanterol (FF/UMEC/VI)

The comparison of single-inhaler combination of FF/UMEC/VI (100/31.25/25 µg, 100/62.5/25 µg, 200/31.25/25 µg, or 200/62.5/25 µg) versus FF/VI 100/25 µg or 200/25 µg, in patients with inadequately controlled asthma (ACQ-6 score ≥ 1.5) despite at least medium dose of ICS/LABA, showed that the addition of UMEC 31.25 µg to FF/VI led to significant improvement in trough FEV1 at week 24 compared to baseline (FF/UMEC/VI 100/31.25/25 µg vs FF/VI 100/25 µg: Δ 96 ml; 200/31.25/25 µg vs 200/25 µg: Δ 82 ml; FF/UMEC/VI 100/62.5/25 µg vs FF/VI 100/25 µg: Δ 110 ml; 200/62.5/25 µg vs 200/25 µg: Δ 92 ml). The improvement in FEV1 was seen from week 4 and sustained over the course of the study.

The addition of UMEC to FF/VI resulted in small, dose-related improvements in ACQ-7 score compared to FF/VI alone. The decrease of ACQ-7 score was seen at week 4 and was maintained throughout the

study. The total Saint Georges's Respiratory Questionnaire (SGRQ) score was improved in all treatment groups at week 24, compared to baseline, but there were no differences between the different arms.

No reduction in the annualized rate of moderate and/or severe exacerbations was observed with the addition of UMEC 31.25 µg to FF/VI while the addition of UMEC 62.5 µg to FF/VI resulted in a 13% reduction ($p = 0.15$). The prespecified unpooled analyses showed numerically lower annualized rate of moderate and/or severe exacerbations in the FF/UMEC/VI 100/62.5/25 µg group than in both the FF/UMEC/VI 100/31.25/25 µg and FF/VI 100/25 µg groups while no numerical additional reductions were observed when UMEC 62.5 µg or 31.25 µg was added to FF/VI 200/25 µg. The time to the first moderate and/or severe exacerbation (and the times to the first severe exacerbation in pooled and unpooled treatment groups were consistent with corresponding annualized rate data. The addition of LAMA did not change the duration of moderate/severe exacerbations.

A reduction in moderate and/or severe exacerbations was observed when adding UMEC to FF/VI 100/25 µg therapy in the overall population suggesting that adding UMEC is an alternative strategy to increasing ICS dose.

Doubling the FF dose in FF/VI and FF/UMEC/VI groups resulted in substantial reductions in the annualized rate of both moderate and/or severe and severe exacerbations, and modest improvements in FEV1 and in Patient Reported Outcomes (PROs).

The addition of UMEC had no significant impact on the duration of exacerbations, neither on the time first moderate/severe event.

A prespecified and post-hoc analysis of the CAPTAIN study showed that in subject with high Type 2 inflammatory biomarkers (FENO > 50 ppb and blood eosinophils ≥ 300 cells/µL), FF 200 µg-containing groups had greater improvements in both trough FEV1 and annualized rates of moderate/severe exacerbation versus FF 100 µg containing groups. Conversely, the addition of UMEC 62.5 µg led to an improvement in FEV1 across the range of blood eosinophil and FENO levels without an impact on the moderate and/or severe exacerbations. The group of patients with FENO < 20 ppb and blood eosinophils < 150 cells/µL had a mean improvement from baseline in trough FEV1 of 23 ml and a 12.4% reduction in moderate and/or severe exacerbations (weeks 1–52) in the FF 200 µg-containing groups compared with FF 100 µg-containing groups; those with FENO > 50 ppb and blood eosinophils ≥ 300 cells/µL showed

a mean increase in FEV1 of 127 ml and a 65.2% reduction in moderate and/or severe exacerbations when comparing FF 200 µg- with FF 100 µg-containing groups. The adverse events occurrence was similar among all treatment groups (27).

The analysis of 229 patients of the Japanese cohort of the CAPTAIN confirmed the efficacy and safety showed in the overall population (28). Change from baseline in trough FEV1 for FF/UMEC/VI 100/62.5/25 µg compared to FF/VI 100/25 µg was 105 ml and 69 ml for 200/62.5/25 µg versus 200/25 µg. The incidence of moderate/severe exacerbation was low and similar across pooled treatment groups (FF/VI, FF/UMEC 31.25 µg/VI, FF/UMEC 62.5 µg/VI). In all pooled groups, clinically important improvements from baseline were achieved in ACQ-7, Saint George Respiratory Questionnaire (SGRQ) and respiratory symptoms. As well as for the overall ITT population, no safety concerns were found.

No new safety concerns with long-term (52 weeks) treatment with once-daily FF/UMEC/VI were observed in a Phase III, 52-week, multicenter, non-comparator, non-randomized, open-label study in Japanese adult patients receiving maintenance therapy with FF/UMEC/VI 100/62.5/25 µg or 200/62.5/25 µg (29).

The pharmacokinetic analysis showed no need for dose adjustments for FF, UMEC, or VI and no difference in FF or VI systemic exposure when administered either as a single-inhaler triple therapy (FF/UMEC/VI) or as the dual combination of FF/VI (30).

Beclometasone dipropionate (BDP), formoterol fumarate (FF) and glycopyrronium bromide (GLY)

In the TRIMARAN study, patients aged 18–75 years, with a documented history of asthma, diagnosed before age 40 years, with prebronchodilator FEV1 < 80% of predicted value and a significant bronchodilation, suffering from uncontrolled asthma (ACQ7 ≥ 1.5) and at least one exacerbation requiring treatment with systemic corticosteroids or an emergency department visit or inpatient admission to hospital in the previous 12 months despite receiving a stable dose of ICS/LABA, were randomized to 52 weeks of BDP/FF/GLY (100 µg BDP, 6 µg FF, and 10 µg GLY) or BDP/FF (100 µg BDP and 6 µg FF). Pre-dose FEV1 at week 26 (co-primary outcomes) showed a significant difference between the BDP/FF/G and BDP/FF groups of 57 ml (15 to 99; $p=0.0080$) and the rate of moderate and severe exacerbations (co-primary outcomes) in the BDP/FF/GLY group was significantly reduced by 15% compared with the BDP/FF group (RR 0.85, 95% CI 0.73–0.99; $p=0.033$).

Another concomitant clinical study (TRIGGER study) has been conducted. If the TRIMARAN study targeted patients taking medium doses of ICS (= 400 µg BDP/day) plus a LABA, the TRIGGER study included patients receiving high-dose ICS (= 800 µg BDP/day) plus a LABA. In TRIGGER study there was also an arm with open-label BDP/FF at 200 µg of BDP and 6 µg of FF at two inhalations twice daily via a pressurized metered-dose inhaler plus tiotropium 25 µg at two inhalations once daily.

Pre-dose FEV1 at week 26 (co-primary outcomes) showed a significant difference between the BDP/FF/G and BDP/FF groups of 73 ml (26 to 120; $p=0.0025$) while no difference between the BDP/FF/GLY and the BDP/FF plus tiotropium groups (−45 ml, −103 to 13; $p=0.13$) were found. There was a reduction of 12% (RR 0.88, 0.75–1.03; $p=0.11$) between the BDP/FF/G and BDP/FF groups and the Hazard ratio for the time to first moderate or severe exacerbation was 0.8 ($p=0.035$).

The change from baseline in peak FEV1 at week 26, average morning PEF predose FEV1, FEV1 AUC0–3h at all visits, PEF related secondary outcomes and FEV1 response at weeks 26 and 52 were higher in the BDP/FF/GLY group than in the BDP/FF group in both studies while no differences between the BDP/FF/GLY group and the BDP/FF plus tiotropium group were shown in TRIGGER.

In the pooled analysis of TRIGGER and TRIMARAN, patients in the BDP/FF/GLY groups had a reduced rate of moderate exacerbations (12%; $p=0.043$), and moderate/severe exacerbations (14%; $p=0.0083$) and reduced rate of severe exacerbations compared with those in the BDP/FF groups (23%; $p=0.0076$). This last point was a pre-specified secondary endpoint of the studies.

In the pooled analysis, time to first moderate or severe exacerbation was longer in the BDP/FF/GLY group than in the BDP/FF group (HR 0.82 $p=0.0002$), as was time to first moderate exacerbation (0.83, 0.74–0.93; $p=0.0010$), and time to first severe exacerbation (0.79, 0.66–0.95; $p=0.011$).

In the pooled analyses (therefore addressing both the dosages of the fixed triple combination), the numbers needed to treat for 1 year with BDP/FF/G rather than BDP/FF to prevent one moderate or severe exacerbation was 3, to prevent one severe exacerbation was 14, and to prevent one moderate exacerbation was 5.

The most common adverse event in all groups was asthma exacerbation, the occurrence of which was lower with triple therapy than with BDP/FF in both trials (31).

The post-hoc analysis showed that the relative efficacy of extra fine BDP/FF/GLY versus BDP/FF was not influenced by a range of clinical characteristics. However, some patient sub-groups gained additional benefit from BDP/FF/GLY for certain endpoints. Looking at exacerbations the relative efficacy of BDP/FF/G was greater in more reversible patients while blood eosinophil values did not influence relative efficacy on moderate-to-severe or severe exacerbations (32). Post-hoc analyses also showed that the addition of the LAMA to BDP/FF reduced seasonal peaks in moderate and severe exacerbations especially in the winter season (20.3% reduction; $p=0.0008$) (33).

Post-hoc analyses of TRIMARAN and TRIGGER evaluated the effect of BDP/FF/G versus BDP/FF on lung function and exacerbations in the subset of patients with persistent airways obstruction ($PAL=FEV_1/FVC$ post bronchodilator ≤ 0.7) and a who did not otherwise differ from the overall population. 658 (57.3%) of TRIMARAN and 880 (61.6%) of TRIGGER patients included in the intention-to-treat (ITT) population met this criterion. For pre-dose FEV₁, peak FEV₁ and PEF, BDP/FF/GLY consistently provided statistically superior efficacy vs BDP/FF and in the pooled analyses for severe exacerbations the reduction vs BDP/FF were 23.0% ($p=0.008$) overall and 33.5% ($p<0.001$) in the PAL subset with a prolonged time to first exacerbation in both analyses (overall: HR 0.79; $p=0.011$; PAL subset: 0.70; $p=0.003$) (34).

Mometasone furoate (MF), indacaterol acetate (IND), and glycopyrronium bromide (GLY)

In IRIDIUM study the addition of GLY to medium or high dose of MF-IND administered once daily showed statistically superior in improving trough FEV₁ versus corresponding doses of MF-IND at week 26 (medium-dose treatment difference Δ 76 ml; $p<0.001$; high-dose MF-IND Δ 65 ml; $p<0.001$). Compared with high-dose FLU-SAL twice daily, the improvements in trough FEV₁ at week 26 were greater for both medium-dose MF-IND-GLY once daily (99 ml [64–133]; $p<0.001$) and high-dose MF-IND-GLY once daily (119 ml [85–154]; $p<0.001$). The improvement showed at week 26 was maintained at week 52. In this study enrolling 3092 adult patients (18–75 years old; mean age 52) with a FEV₁ of less than 80% of the predicted normal, symptomatic at run-in ($ACQ-7 \geq 1.5$) and a documented history of one asthma exacerbation (20% more than one) that required medical care from a physician, emergency room visit, hospitalization, and systemic corticosteroid treatment in the 12 months before screening, the

improvement in post-dose FEV₁ was seen with both doses of MF-IND-GLY versus MF-IND and FLU-SAL (all $p<0.001$) as early as 5 min after the first study drug administration on day 1. The maximum effect on post-dose FEV₁, observed 1 h after dosing, was 277 ml with medium-dose and 283 ml with high-dose of MF-IND-GLY was 182 ml greater than that observed with medium-dose MF-IND ($p<0.001$) and 194 ml improvement observed with high-dose MF-IND ($p<0.001$) on day 1. Compared with both doses of MF-IND-GLY the improvement in FEV₁ with high-dose FLU-SAL was slower ($p<0.001$) and peaked at 157 ml 1 h post-dose. The difference in post-dose FEV₁ at 1 h was maintained throughout the 52 weeks of the study. All the 5 treatments showed a large (almost double the minimal clinically important difference [MCID]) improvements from baseline in ACQ-7 score, but the study did not meet the key secondary endpoint of superiority of either dose of MF-IND-GLY versus the respective dose of MF-IND in ACQ-7 score after 26 weeks. Differential improvements in ACQ-7 scores were observed for both doses of MF-IND-GLY versus high-dose FLU-SAL at week 26 (-0.084 [$p=0.038$] for medium-dose and -0.086 [$p=0.034$] for high-dose). There was no loss of effect of the treatments on ACQ-7 up to 52 weeks. A higher proportion of patients achieved the MCID with high-dose MF-IND-GLY versus high-dose FLU-SAL while a lower percentage of mild exacerbations was shown with medium-dose (13.5%) and high-dose (14.8%) MF-IND-GLY compared with high-dose FLU-SAL (19.4%) while no significant difference was shown in respect with similar doses of MF-IND. The study did not meet its key secondary endpoint of superiority in ACQ-7 score at week 26 for either dose of MF-IND-GLY versus the respective dose of MF-IND. Nevertheless, greater improvements in ACQ-7 score were observed with high-dose MF-IND-GLY versus high-dose FLU-SAL at week 52, accompanied by a greater proportion of patients achieving an MCID improvement in ACQ-7. Post-hoc analyses, for which the study was not powered, suggest that the rate of moderate-to-severe exacerbations was similar with medium-dose MF-IND-GLY and high-dose MF-IND, and was lower compared with high-dose FLU-SAL.

The improvements in FEV₁ and moderate-to-severe exacerbation rates shown with the addition of GLY to MF-IND were independent of the prespecified factors age, sex, race, pre-bronchodilator FEV₁% predicted, exacerbation history, previous asthma therapy, and baseline ACQ-7 (35).

A *post hoc* analysis of the IRIDIUM study to evaluate the efficacy of IND/GLY/MF medium- and

high-dose versus respective doses of IND/MF and SAL/FLU high-dose in the Asian subpopulation to understand whether there is an ethnic difference with the overall study population. The improvements in lung function, asthma control and exacerbation outcomes observed with IND/GLY/MF in the Asian population are consistent with the results in the overall population of the IRIDIUM study (36).

In the ARGON study, a partially-blinded, randomized, 24-weeks, parallel-group, non-inferiority, open-label, active-controlled Phase IIIb study once daily (o.d.) single-inhaler combination of MF/IND/GLY high- (156/150/50 µg) and medium-dose (80/150/50 µg) administered via Breezhaler compared to SAL/FLU high-dose (50/500 µg) twice daily (b.i.d.) via Accuhaler + TIO (5 µg) Respimat o.d. in patients with uncontrolled asthma (ACQ ≥ 1.5), MF/IND/GLY high- and medium-dose was non-inferior in AQLQ total score versus SAL/FLU high-dose + TIO. In this population (aged ≥ 18 years, with asthma for 6 months prior to screening treated with LABA/ICS medium- or high-dose and a history of ≥ 1 severe asthma exacerbation that required medical care from a physician, emergency room visit or hospitalization and systemic corticosteroid treatment for at least 3 days in the past 12 months) a higher percentage of responders achieved the MCID 0.5 in AQLQ with MF/IND/GLY high-dose versus SAL/FLU high-dose + TIO. These findings were substantiated by the improvements in SGRQ total score with MF/IND/GLY. The change from baseline in Asthma control (ACQ-7 total score) at weeks 24 was greater with MF/IND/GLY high-dose and comparable for MF/IND/GLY medium-dose o.d. versus SAL/FLU high-dose + TIO. A great improvement in trough FEV1 versus SAL/FLU high dose + TIO at week 24 (+96 ml $p < 0.001$) was shown. These improvements were observed as early as week 8 and were sustained until week 24. Furthermore, MF/IND/GLY high-dose showed greater improvements in FEF25–75 at week 24 and in both morning and evening PEF over 24 weeks versus SAL/FLU high-dose + TIO. Annualized rates of all (mild, moderate, and severe) and moderate or severe exacerbations were comparable between MF/IND/GLY high-dose versus SAL/FLU high-dose + TIO, while a greater reduction in the rate ratio of moderate exacerbations (43%), which met significance, was observed with MF/IND/GLY high-dose. MF/IND/GLY high- and medium-dose had acceptable safety profiles comparable with SAL/FLU high-dose + TIO. The incidence of pneumonia with IND/GLY/MF high-dose was 1.1% but not observed with MF/IND/GLY medium-dose or SAL/FLU high-dose + TIO all reported events were not

suspected to be study-drug related. Although allowed, no escalations or de-escalations of dosages occurred (37).

An analysis of the phase 3 trials did not find evidence of increased cardiovascular risk attributable to the addition of IND to MF or addition of GLY to MF/IND. Similarly, no evidence of increased cardiovascular risk was observed with an increase in the ICS-dose or relative to SAL/FLU $\pm$ TIO (38).

A phase II multi-center randomized, double-blind, double-dummy, active-comparator-controlled, crossover design with three consecutive study periods of 21 treatment days, investigated the superiority in peak bronchodilator effect of o.d. MF/IND/GLY 160/150/50 µg and 80/150/50 µg compared with twice-daily (b.i.d.) SFC (50/500 µg). The primary objective was met showing superiority of MF/IND/GLY at both ICS doses over SFC in peak FEV1 after 21 days of treatment. Both MF/IND/GLY doses also improved standardized FEV1 AUC 5 min–1h and FEV1 AUC 5 min–23h45 min versus SAL/FLU ($p < 0.0001$) and showed a superior treatment effect compared with SAL/FLU on mean PEF measurements (least square mean difference of 29 L/min with high-dose ICS and 24 L/min with medium-dose ICS versus SAL/FLU).

A higher percentage of patients did not need rescue medicine with MF/IND/GLY (high-dose ICS, 58%; medium-dose ICS, 52%) compared with SAL/FLU (45%). The odds of being free from rescue medication with MF/IND/GLY (high-dose ICS) was 2.4 times higher than with SFC (95% CI: 1.7, 5.0; $p = 0.018$). Similarly, the odds ratio (95% CI) was 1.7 (0.8, 3.4; $p = 0.153$) for MF/IND/GLY (medium-dose ICS) versus SAL/FLU (39). Lung function improvements with MF/IND/GLY over 24 h was irrespective of a.m. or p.m. dosing, in patients with mild-moderate asthma (40).

Budesonide/glycopyrrolate/formoterol fumarate

A small study investigating BUD/GLY/FOR compared to BUD/FOR in patients with asthma and COPD overlap reported an improvement in inspiratory capacity in the triple therapy compared to the dual therapy group without any difference in symptoms scores or FENO (41).

Systematic review and metanalysis

One systematic review, based on 4 double-blind, double-dummy trials, 1197 participants, found that adding Tiotropium to LABA-ICS reduced exacerbations compared with adding placebo, although the confidence interval included the possibility of no

difference (OR 0.76, 95% CI 0.57–1.02, moderate quality evidence). While lung function was improved, quality of life was not (42).

A subsequent systematic review (15 trials, 7122 participants) found that adding a LAMA (virtually always tiotropium) to ICS reduced exacerbations compared with adding placebo (RR 0.67, 95% CI 0.48–0.92; absolute risk reduction 2%), and adding a LAMA to ICS did not reduce exacerbation risk compared with adding a LABA (RR 0.87, 95% CI 0.53–1.42). Furthermore, adding a LAMA to a LABA-ICS regimen did not reduce exacerbation risk significantly compared with adding placebo (RR 0.84, 95% CI 0.57–1.22), but the trough FEV₁ was increased with triple therapy (mean difference 0.07 L [95% CI 0.01–0.14]) (43).

A metaanalysis of 20 RCTs, that enrolled 11 894 children and adults, on multiple or single inTT with 3 different LAMA, showed with high-certainty evidence, that triple therapy vs dual therapy was significantly associated with a reduction in severe exacerbation risk (risk ratio: 0.83) and an improvement in asthma control while no significant differences in asthma-related quality of life or mortality (44).

Conclusions

We state (that)

- Taking into consideration the overall available evidence, multiple and single inhalers triple therapy is a suitable option in asthmatic patients with residual symptoms, exacerbations, and impaired lung function despite medium/high dose of ICS/LABA.
- Use of inhaled triple therapy (InTT) is still limited in patients with uncontrolled severe asthma
- LAMA, as add on treatment to medium/high dose of ICS, is effective in improving lung function parameters independently from baseline characteristics including gender, age, allergic status, disease duration, age at asthma onset, and degree of airway obstruction; however previous smoking history or fixed airways obstruction might be predictive for a better therapeutic response.
- In some studies, adding LAMA to medium or high dose ICS-LABA reduces exacerbations compared with some medium or high dose ICS-LABA comparators.
- Available data related to the impact of InTT on PROs (HRQL, control) are conflicting
- The safety profile of adding LAMA to ICS/LABA is excellent.

- The improvement of lung function induced by adding LAMA to ICS/LAMA is sustained over time
- Single inhaler triple therapy and multiple inhaler triple therapy provide similar outcomes of lung function and exacerbation rate.
- The numbers needed to treat for 1 year with BDP/FF/G rather than BDP/FF to prevent one moderate or severe exacerbation was 3, to prevent one severe exacerbation was 14 (result conditioned by the low number of events recorded), and to prevent one moderate exacerbation was 5.
- The single inhaler triple therapy is cost effective compared to multiple inhalers triple therapy

We advocate

- to consider the addition of LAMA to at least a medium dose of ICS/LABA as alternative strategy to increasing ICS dose in patient adherent to treatment and with blood eosinophil counts without increase of blood eosinophils.
- to consider triple therapy before or independently from biologics.
- to tailor the prescription of InTT depending on the patient need and preferences
- to explore which different treatable traits may be addressed by different combinations of inhaled triple therapies (dose, posology, molecules, device, particle size)
- to consider the stepping down, in controlled patients, from high to medium dose triple therapy rather than to high dose of ICS/LABA if appropriate.

We propose

- To investigate, in real world setting, the impact of single versus multiple inhalers triple therapy on adherence.
- To assess the cost effectiveness of InTT in patients with poorly controlled asthma
- To explore the additive protective effects of InTT on bronchial remodeling.
- To develop further studies exploring the efficacy of InTT in different asthma endotype/phenotype
- To develop research to assess the relevance of measuring eosinophilic inflammation to determine the benefit of increasing ICS dose vs adding a LAMA in a subject with insufficient control of asthma".

- To assess the efficacy of LAMA to ICS/LABA in patient with different functional pattern (high or low reversibility, fixed obstruction, etc).
- Studies to compare adding LAMA to high ICS/LABA compared to initiation of biologics in difficult to treat asthma.

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ORCID

Fulvio Braido  <http://orcid.org/0000-0003-2460-4709>
 Angelica Tiotiu  <http://orcid.org/0000-0002-8038-9559>
 Guillermo Guidos-Fogelbach  <http://orcid.org/0000-0003-1675-3894>
 Marina Labor  <http://orcid.org/0000-0001-5216-8129>
 Pierachille Santus  <http://orcid.org/0000-0003-3462-8253>

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