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EDITORIAL

# Family increases: UPLIFT® first maintenance subgroup analysis

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In this issue of the *European Respiratory Journal*, TROOSTERS *et al.* [1] deliver another offspring to the numerous family [2–5] of analyses attempting to reinterpret the UPLIFT® study [5], a 4-yr trial specifically designed to test the reduction of decline in forced expiratory volume in 1 s ($FEV_1$). While UPLIFT® was well powered, it turned out to be a negative study in its main outcome, with differences in the rate of $FEV_1$ decline of 2 $mL \cdot yr^{-1}$ ($p=0.21$) when measured post-bronchodilator ($-40 \pm 1$ (mean $\pm$ SD) *versus* $-42 \pm 1$ $mL \cdot yr^{-1}$, respectively, for the treatment and control groups). Thus, the UPLIFT® conclusions were that ''in patients with COPD [chronic obstructive pulmonary disease], therapy with tiotropium was associated with improvements in lung function, quality of life, and exacerbations during a 4-yr period but did not significantly reduce the rate of decline in $FEV_1$'' [5].

It is possible that medications can only reduce the rate of decline to a certain ''floor'' value and therefore UPLIFT® was not able to detect differences because the comparison group was ''too active'', since it included a large proportion of patients treated with long-acting β-agonists and/or inhaled corticosteroids. There is evidence to suggest that this might be the case, *i.e.* the two treatment arms of the TORCH (TOwards a Revolution in COPD Health) study [6] had rates of decline of $-39 \pm 3$ $mL \cdot yr^{-1}$ for the salmeterol/fluticasone combination, $-42 \pm 3$ $mL \cdot yr^{-1}$ for salmeterol or fluticasone alone and $-55 \pm 3$ $mL \cdot yr^{-1}$ for the comparison group [6, 7], which was less actively treated than in the UPLIFT® (only short-acting β-agonists (SABA)). Rates of decline between -57 and -69 $mL \cdot yr^{-1}$ have been reported in other COPD studies with SABA-only comparison groups [8–10]. The best way to confirm that tiptropium reduces the $FEV_1$ decline rate would be to perform a study with a comparison group on SABA only in a mild to moderate COPD population in whom this would be ethically acceptable in light of the evidence of the UPLIFT® and TORCH studies; however, this will not be easy.

TROOSTERS *et al.* [1] performed a *post hoc* analysis of the subgroup of 810 subjects who were Global Initiative for Chronic Obstructive Lung Disease stage II or higher (403 on tiotropium and 407 in the comparison group) ''naïve'' to treatment (not receiving maintenance respiratory medications at baseline) from UPLIFT®. In this subgroup, different from the whole sample, the rate of $FEV_1$ decline was significantly slower in the treatment group, *i.e.* 11 $mL \cdot yr^{-1}$ ($p=0.026$) when measured post-bronchodilator ($-42 \pm 4$ *versus* $-53 \pm 4$ $mL \cdot yr^{-1}$, respectively, for the treatment and control groups). Compared with UPLIFT® this subgroup had a better baseline function, with similar responses to bronchodilators, a higher rate of current smokers (43% *versus* 27%) and showed striking differences in the geographical provenance of the participants, with proportionally many more subjects coming from the Americas (55% instead of 21%) than from Eastern and Western Europe (a potential confounder and in itself a topic for an editorial if the sociology of recruitment in these two geographic areas were distinct due to differences in healthcare that could make more appealing for very low-income subjects to participate in studies that provide medication). There were no differences in other potential confounders such us body mass index, age (1 yr younger than the UPLIFT®) or sex distribution. Potential biases of the study are that while both groups were the same at baseline the frequency of smoking cessation during the trial was not measured and there was a high dropout rate (38% and 43% in the treatment and control groups in this subgroup respectively), a shortcoming of most clinical trials in severely diseased populations. Withdrawals can be related to the investigated outcome (*i.e.* more frequent in patients with lower $FEV_1$, in whom it is known that the rate of $FEV_1$ decline is slower [11]), biasing estimates and treatment comparisons, particularly in the likely event of an imbalance [12]. While we focus this editorial on $FEV_1$ decline, in this subgroup of patients, different from UPLIFT®, neither significant differences between treatment and comparison groups in the rate of exacerbations (0.49 exacerbations per yr in the tiotropium group, 0.58 exacerbations per yr in comparison groups, $p=0.080$) nor in the time to the first exacerbation (27 *versus* 21.5 month, $p=0.24$) were seen and, as in UPLIFT®, more efficacy in the treatment group on health-related quality of life (-4.57 units in the total score of the Saint George's Respiratory Questionnaire after 4 yrs of treatment) and no differences in mortality (10.8 *versus* 13.9, $p=0.16$) were found.

Another more general issue introduced by this study and other subgroup analyses already published [3, 4] is the appropriateness of subgroup analysis. Medical research relies on randomised controlled trials to assess therapeutic benefits. Because of the effort and cost involved in these studies, investigators frequently use analyses of subgroups to extract as much information as possible. Such analyses may provide useful information for the care of patients and for future research;

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however, they also introduce analytic challenges that can lead to overstated and misleading results [13–16]. In general terms, subgroup findings should be considered exploratory. Investigators and readers should be particularly wary of subgroup rescues of otherwise negative trials, recognising that most subgroup claims are prone to exaggerate the truth [13–16]. The credibility of subgroup analyses, however, increases if they have enough statistical power, are confined to the primary outcome and to a few predefined subgroups defined on the basis of biologically plausible hypotheses specified before the analysis, statistical tests of interaction (that assess whether a treatment effect differs between different subgroups) are used rather than inspection of subgroup p-values (or at least p-values are corrected for the increased chance of finding spurious subgroup effects when performing multiple statistical tests, *i.e.* the increased chance of type I error) [13]. The study by TROOSTERS *et al.* [1] meets some but not all these requisites. Certainly, the analyses were confined to the same outcomes as UPLIFT®, and the hypothesis can be considered biologically plausible, since while no known mechanisms links anticholinergic drugs with the rate of $FEV_1$ decline, supposedly an inflammatory process [17], the evidence reviewed above suggests that several treatments, including tiotropium, can reduce the rate of decline in $FEV_1$ [6–10]. In contrast, it appears that in this case heterogeneities of the treatment were not specified ''*a priori*'', rather they were sought after UPLIFT® had concluded; the analysis is based on uncorrected p-values, thus increasing the chance of a false-positive effect, and no statistical test of interaction or other technique to strengthen the validity of the conclusions, such us randomly splitting the subsample, were performed. Lack of statistical power could justify the differences in exacerbation rate between this subanalysis and UPLIFT®.

In conclusion, this study adds further support to the theory that tiotropium, like other long-term treatments, can reduce the rate of decline in $FEV_1$; however, it cannot be taken as unquestionable evidence on whether tiotropium actually decreases the rate of $FEV_1$ decline or not, and certainly should not be used to support an indiscriminate use of tiotropium in non-symptomatic stage I or II COPD subjects to reduce their $FEV_1$ decline.

## STATEMENT OF INTEREST

Statements of interest for both authors of this manuscript can be found at www.erj.ersjournals.com/misc/statements.dtl

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