Regional differences in rate of FEV1 decline in COPD: lessons from SUMMIT

To the Editor:

A publication by Zhou *et al.* [1], who studied 841 patients from China with mild to moderate chronic obstructive pulmonary disease (COPD) (Global Initiative for Chronic Obstructive Lung Disease (GOLD) stage I and II) for 2 years, documented a 22 mL per year beneficial effect of tiotropium compared with placebo on rate of forced expiratory volume in 1 s (FEV_1). This effect was over three times larger than the 6 mL per year (95% CI 1 to 11 mL per year) reported by Decramer *et al.* [2] in the 2739 GOLD stage II patients from the 4-year UPLIFT trial. We hypothesised that the large difference in results in patients with COPD with similar degree of airflow limitation at study entry could be related to regional differences in response to similar pharmacological treatment. To test this hypothesis, we investigated the regional differences in FEV_1 decline in patients in the COPD Study to Understand Mortality and MorbidITy (SUMMIT), all of whom had spirometric GOLD stage II COPD at enrolment [3].

In SUMMIT, we investigated whether the inhaled corticosteroid fluticasone furoate 100 µg (FF), the long-acting beta-agonist vilanterol 25 µg (VI) or the combination (FF/VI) impacted on mortality. The results from this event-driven study failed to show a benefit of any of the medications on risk of death compared with placebo [3]. In addition, and as secondary pre-specified outcome, spirometry was measured every 12 weeks. Results of the effect of therapy on lung function decline for the whole SUMMIT cohort has been published [4], which included 15 457 patients with an average of seven spirometry assessments who were followed for an average of 1.7 years. This did not compare regional differences, so here we have performed a *post hoc* analysis using the same methods but with subjects divided into Asia and non-Asia subgroups. We present only patients taking placebo or FF/VI for brevity.

In SUMMIT, there were 1337 patients randomised to placebo or FF/VI in the Asia subgroup (China, Indonesia, India, Japan, Korea, Malaysia, Philippines, Taiwan, Thailand and Vietnam), of which 253 were from China. As shown in table 1, the rate of FEV_1 decline in this subgroup was 16 mL per year (95% CI −1 to 34 mL per year), slower on active FF/VI therapy than on placebo. This value is close to that reported by Zhou *et al.* [1] in their study, which was 22 mL per year (95% CI 6 to 37) favouring tiotropium over placebo. In contrast, in the 8232 patients that were not from Asia studied in SUMMIT, a 7 mL per year (95% CI −1 to 14 mL per year) difference was seen for FF/VI *versus* placebo.

Table 1 also shows that this regional effect remains when the values are expressed as per cent predicted FEV_1 in both the Zhou *et al.* [1] and SUMMIT Asia subpopulations. In the former study, a difference of 0.9% per year was seen for tiotropium *versus* placebo. In the SUMMIT Asia subgroup, this was 0.7% per year (95% CI −0.1 to 1.4% per year), whereas in the non-Asian SUMMIT patients taking FF/VI had a slower decline of 0.2% per year (95% CI 0.0 to 0.5% per year) compared with placebo.

To our knowledge, no study has reported the potential effect of regional response to medications as a possible determinant of lung function decline. The results observed suggests that there are regional differences in the response to pharmacotherapy. In the patients recruited in China by Zhou *et al.* [1] and in Asia in SUMMIT (table 1), the effect of pharmacotherapy, independent of the medication used, was at least double of that observed in non-Asian countries.

One potential explanation is that the patients had higher baseline FEV_1 value in mL in the Zhou *et al.* [1] cohort compared with the patients recruited in SUMMIT. However, the absolute rate of decline in the

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This analysis of FEV_1 decline in patients who enrolled with spirometric GOLD stage II COPD (SUMMIT) showed regional differences in therapeutic response. Such variation should be considered when comparing pharmacotherapies across different global areas. http://bit.ly/2YwMIgW

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TABLE 1 Clinical characteristics and lung function decline in Asians compared with non-Asians in two different pharmacological trials

	China population [1]		SUMMIT Asia subgroup [3]		SUMMIT non-Asia subgroup [3]	
	Placebo	Tiotropium	Placebo	FF/VI	Placebo	FF/VI
Subjects n	383	388	666	671	3445	3450
Age years	63.9±8.6	64.2±8.2	65.9±8.2	66.2±7.8	65.1±7.8	65.1±8.0
Males	330 (86%)	328 (85%)	607 (91%)	616 (92%)	2464 (72%)	2496 (72%)
Body mass index kg·m^{-2}	22.5±3.2	22.6±3.4	23.1±3.9	23.3±4.1	28.9±5.7	28.9±5.8
Baseline post-bronchodilator FEV$_1$ L	1.94±0.54	1.93±0.52	1.43±0.31	1.43±0.30	1.75±0.39	1.76±0.40
Post-bronchodilator FEV$_1$ % pred	78.1±17.1	77.9±15.8	60.7±6.4	60.9±6.3	59.5±6.0	59.5±6.1
Current smokers	154 (40%)	160 (41%)	231 (35%)	221 (33%)	1705 (49%)	1647 (48%)
Exacerbation rate per year	0.38	0.20	0.54	0.33	0.31	0.23
Hospitalised exacerbation rate per year	0.07	0.03	0.15	0.08	0.05	0.05
Post-bronchodilator rate of decline in FEV$_1$ mL per year, mean (SE)	51 (6)	29 (5)	56 (7)	40 (6)	44 (3)	37 (3)
Difference in active *versus* placebo mL per year (95% CI)	22 (6 to 37)		16 (−1 to 34)		7 (−1 to 14)	
Post-bronchodilator rate of decline in FEV$_1$$^{\#}$ % pred per year, mean (SE)	2.1 (0.2)	1.2 (0.2)	2.4 (0.3)	1.7 (0.3)	1.5 (0.1)	1.2 (0.1)
Difference in active *versus* placebo % pred per year (95% CI)	0.9 (0.2 to 1.5)		0.7 (−0.1 to 1.4)		0.2 (0.0 to 0.5)	

Data are presented as mean±SD or n (%), unless otherwise stated. FF/VI: combination fluticasone furoate 100 µg and vilanterol 25 µg; FEV$_1$: forced expiratory volume in 1 s. $^{\#}$: the National Health and Nutrition Examination Survey [5] was used to calculate % predicted FEV$_1$ in the SUMMIT study. Data on lung function decline for the SUMMIT cohort are from Calverley *et al.* [4].

placebo group in the SUMMIT Asian population (table 1) was, if anything, higher (56 mL per year) than that of the placebo group in the Zhou study (51 mL per year). Further, when expressed as a proportion of FEV$_1$ change (to normalise for baseline FEV$_1$ value) the difference still remained between the Asian and the non-Asian groups. It may also be that there were differences in the therapy that patients were receiving at baseline. However, the criteria for inclusion in SUMMIT was similar across regions. In addition, as was true for the study by Zhou *et al.* [1], the majority of patients had milder disease for which medications are least used. Other potential reasons such as differences in body mass index or environmental exposure remain to be explored.

We believe these findings are not only interesting but important because regional differences in response to therapy should be taken into account when comparing effects of therapeutic agents in different areas of the world. Why different populations behave in this way merits further study.

These analyses add to the growing evidence that pharmacotherapy does modify lung function progression in COPD and, as such, a nihilistic approach to the benefit of pharmacotherapy is not justified.

Bartolomé R. Celli[1], Julie A. Anderson[2], Robert D. Brook[3], Peter M.A. Calverley[4], Nicholas J. Cowans[5], Courtney Crim[6], Fernando Martinez[7], David E. Newby[8], Julie Yates[6] and Jørgen Vestbo[9]

[1]Pulmonary and Critical Care Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. [2]Research and Development, GlaxoSmithKline, Stockley Park, UK. [3]University of Michigan Health System, Ann Arbor, MI, USA. [4]Dept of Medicine, Clinical Sciences Centre, University of Liverpool, University Hospital Aintree, Liverpool, UK. [5]Statistics and Programming, Veramed Ltd, Twickenham, UK. [6]Research and Development, GlaxoSmithKline, Research Triangle Park, North Carolina, USA. [7]Division of Pulmonary and Critical Care Medicine, Weill Cornell Medicine, New York, NY, USA. [8]Centre for Cardiovascular Science, University of Edinburgh, Edinburgh, UK. [9]Division of Infection, Immunity and Respiratory Medicine, School of Biological Sciences, University of Manchester, and Manchester University NHS Foundation Trust, Manchester Academic Health Sciences Centre, Manchester, UK.

Correspondence: Bartolomé R. Celli, Pulmonary and Critical Care Division, Brigham and Women's Hospital, Harvard Medical School, Boston, MA, USA. E-mail: bcelli@copdnet.org

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The SUMMIT trial is a registered clinical trial (NCT01313676). Information on GSK's data sharing commitments and requesting access to anonymised individual participant data and associated documents can be found at www.clinicalstudydatarequest.com

References

1 Zhou Y, Zhong NS, Li X, *et al.* Tiotropium in early-stage chronic obstructive pulmonary disease. *N Engl J Med* 2017; 377: 923–935.
2 Decramer M, Celli B, Kesten S, *et al.* Effect of tiotropium on outcomes in patients with moderate chronic obstructive pulmonary disease (UPLIFT): a prespecified subgroup analysis of a randomised controlled trial. *Lancet* 2009; 374: 1171–1178.
3 Vestbo J, Anderson JA, Brook RD, *et al.* Fluticasone furoate and vilanterol and survival in chronic obstructive pulmonary disease with heightened cardiovascular risk (SUMMIT): a double-blind randomised controlled trial. *Lancet* 2016; 387: 1817–1826.
4 Calverley PMA, Anderson JA, Brook RD, *et al.* Fluticasone furoate, vilanterol and lung function decline in patients with moderate chronic obstructive pulmonary disease and heightened cardiovascular risk. *Am J Respir Crit Care Med* 2018; 197: 47–55.
5 Hankinson JL, Kawut SM, Shahar E, *et al.* Performance of American Thoracic Society-recommended spirometry reference values in a multiethnic sample of adults: the multi-ethnic study of atherosclerosis (MESA) lung study. *Chest* 2010; 137: 138–145.