



Rapid and Persistent 6-week Response to ICS/LABA/LAMA in Asthma



Western UNIVERSITY CANADA

M Sharma,^{1,2} HK Kooner,^{1,2} S Tchner,^{1,2} A Mozaffaripour,^{1,3} N Paul,⁴ C Yamashita,⁵ and G Parraga¹⁻⁵ ¹Robarts Research Institute; ²Department of Medical Biophysics; ³School of Biomedical Engineering; ⁴Department of Medical Imaging; ⁵Division of Respiriology, Department of Medicine, Western University, London, Canada

Introduction

- Despite inhaled corticosteroid (ICS)/long-acting β 2-agonist (LABA) therapy, 30-50% of asthma patients remain poorly controlled^{1,2}
- ICS/LABA in combination with a long-acting muscarinic antagonist (LAMA) showed significantly improved FEV₁ and symptom control after 24-weeks^{3,4}
- Mechanism of action on small airways dysfunction of ICS/LABA/LAMA is poorly understood

Hypothesis

Hyperpolarized ¹²⁹Xe MRI and oscillometry small airways measurements will be significantly improved in moderate-severe asthma patients after 6-weeks daily ICS/LABA/LAMA and will not significantly improve relative to 6-weeks after 12-weeks Rx

Objectives

To measure the effect of 6- and 12-weeks daily inhaled fluticasone furoate (FF), umeclidinium (UMEC), vilanterol (VI) in moderate-severe asthma

Methods

- 31 moderate-severe asthma, aged 18-70yr ACQ \geq 1.5, provided written informed consent (NCT04651777)
- Pre-post bronchodilator spirometry, oscillometry and ¹²⁹Xe MRI at baseline, 6-weeks and 12-weeks
- MRI performed using 3T Discovery MR750 (GEHC); CT performed using 320-slice Aquilion ONE/PRISM scanner (Canon)
- Semi-automated quantification of MRI ventilation defect percent (VDP)⁵
- Differences over time evaluated using repeated measures ANOVA; statistical significance level $p < .05$

Results

Figure 1. A 26 yo Female with Week 0: FEV₁=65%_{pred}; ACQ-6=4.3; AQLQ=2.7; SGRQ=75; VDP=18%; Week 6: FEV₁=97%_{pred}; ACQ-6=1.3; AQLQ=5.8; SGRQ=66; VDP=1%; Week 12 FEV₁=88%_{pred}; ACQ-6=1.3; AQLQ=5.9; SGRQ=50; VDP=2%.

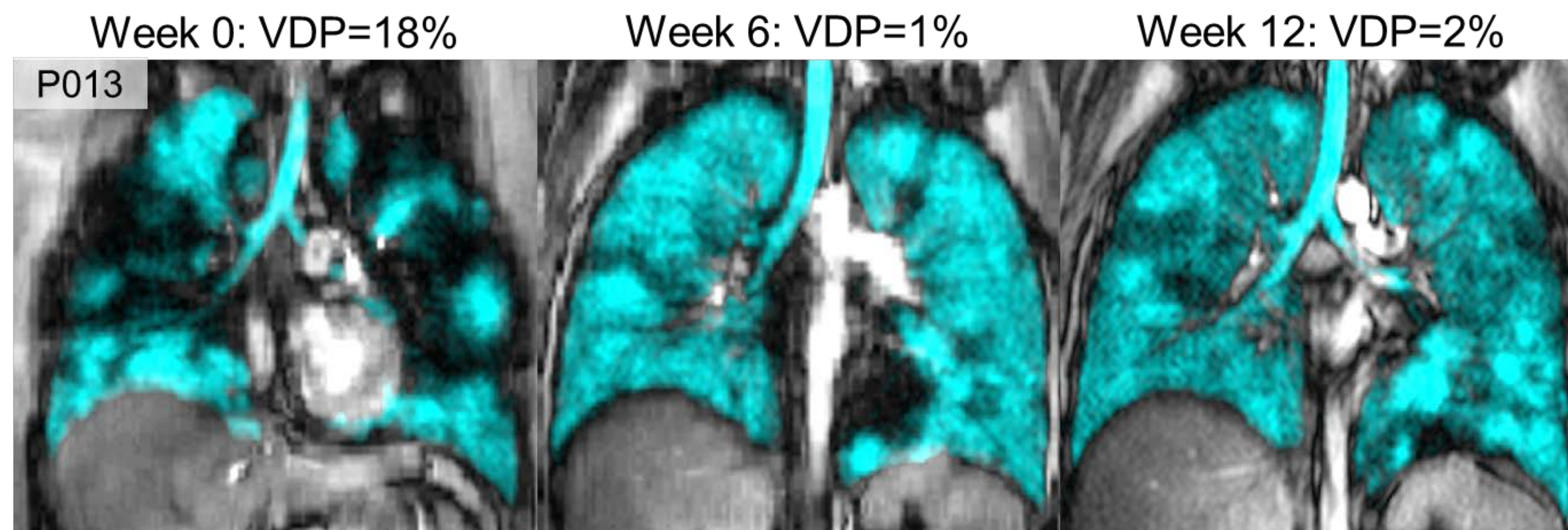


Table 1. Participant demographics and clinical measurements at baseline, 6-weeks and 12-weeks after daily FF/UMEC/VI

Parameter	Week 0 (n=31)	Week 6 (n=28)	Week 12 (n=17)	Weeks 0-6 p-val.*	Weeks 0-12 p-val.*	Weeks 6-12 p-val.*
Age years	54 (15)	55 (15)	58 (13)	-	-	-
BMI kg/m ²	31 (7)	30 (7)	30 (8)	-	-	-
Female n(%)	24 (77)	21 (75)	14 (82)	-	-	-
<i>Pulmonary function</i>						
FEV ₁ L	2.1 (0.7)	2.3 (0.8)	2.2 (0.8)	.053	.058	.2
FEV ₁ % _{pred}	72 (19)	78 (19)	76 (20)	.04	.056	.4
FVC L	3.3 (1.0)	3.4 (1.2)	3.2 (1.2)	.3	.1	.9
FVC % _{pred}	87 (13)	89 (15)	87 (14)	.4	.3	.7
FEV ₁ /FVC %	65 (12)	70 (11)	68 (10)	.01	.3	.09
RV/TLC %	44 (11)	42 (12)	43 (10)	.004	.4	.2
R ₅ cmH ₂ O·sec/L	5.7 (1.7)	4.5 (1.4)	4.8 (1.9)	.02	.1	.9
R ₁₉ cmH ₂ O·sec/L	3.7 (1.2)	3.3 (1.1)	3.6 (1.7)	.5	.6	.4
R ₅₋₁₉ cmH ₂ O·sec/L	2.0 (1.0)	1.2 (0.8)	1.2 (0.9)	.002	.002	.08
<i>Inflammatory markers</i>						
Eos cells/ μ L	342 (240)	-	-	-	-	-
FeNO ppb	43 (40)	29 (17)	45 (58)	.1	.9	.2
<i>Questionnaires and imaging</i>						
ACQ-6	2.1 (1.0)	1.4 (1.3)	1.2 (0.9)	.1	.002	.1
AQLQ	4.5 (1.2)	5.4 (1.2)	5.8 (0.7)	.07	.001	.1
SGRQ	49 (16)	35 (21)	30 (20)	.01	.001	.1
¹²⁹ Xe MRI VDP %	16 (13)	9 (9)	10 (9)	.03	.02	.9

*p=repeated measures ANOVA; BMI=body mass index; FEV₁=forced expiratory volume in 1 second; FVC=functional vital capacity; Eos=eosinophilic cell count; FeNO=fraction of exhaled nitric oxide; ACQ-6=Asthma Control Questionnaire; AQLQ=Asthma Quality-of-Life Questionnaire; SGRQ=St. George's Respiratory Questionnaire; VDP=ventilation defect percent.

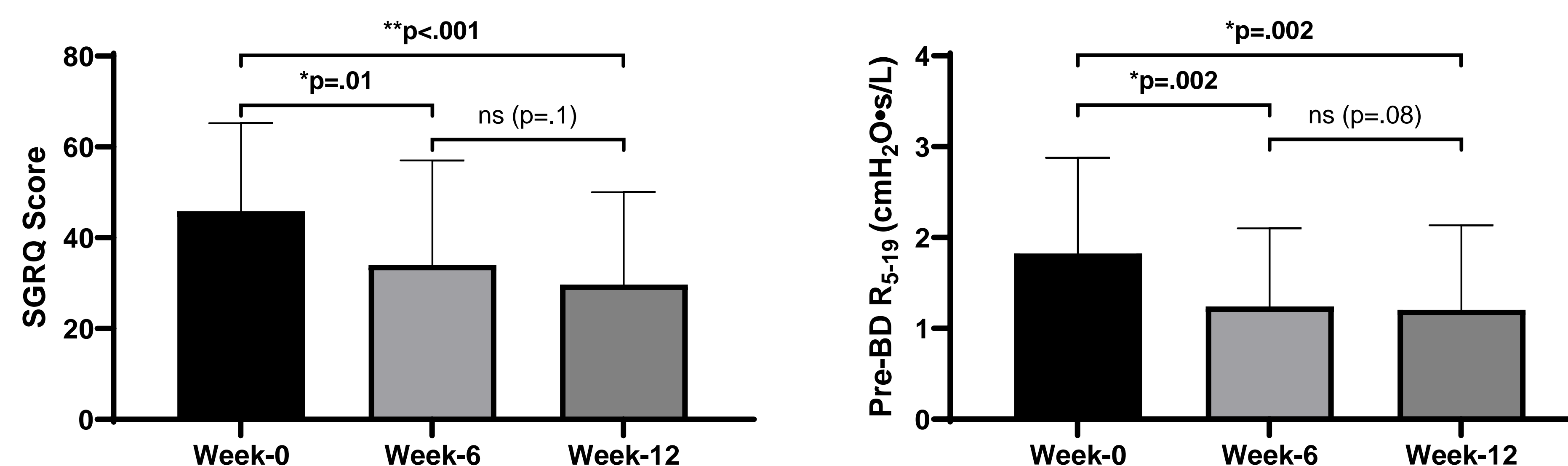


Figure 2. Rapid improvements in quality-of-life ($p=.01$) and small airways measurements ($p=.002$) after 6-weeks of daily FF/UMEC/VI, which persisted up to 12-weeks ($p=.1$ and $p=.08$, respectively).

Discussion

- First study to show ICS/LAMA/LABA therapy significantly improved FEV₁, R₅₋₁₉, SGRQ, MRI VDP after 6-weeks Rx which persisted after 12-weeks Rx
 - Sustained improvements after 12-weeks in R₅₋₁₉, ACQ-6, AQLQ, SGRQ and MRI VDP
- No significant differences between 6-weeks and 12-weeks time points (Table 1)
 - Indicative that the majority of the response occurs during the initial 6-weeks of treatment, extending previous findings^{3,4}
- Distal airway measurements (R₅₋₁₉, VDP) improved at 12-weeks, while central airway improvements trend towards significance at 12-weeks (FEV₁ %_{pred}; $p=.056$)
- In poorly-controlled asthma prescribed with ICS/LABA, improved small airways dysfunction likely stems from the contribution of the LAMA component which leverages different pathways to induce bronchodilation

Conclusion

Significantly improved ¹²⁹Xe MRI VDP at 6-weeks persisted after 12-weeks daily FF/UMEC/VI

References

1. Bernstein, et al. *J Asthma* (2015).
2. Dreher, et al. *TubercRespirDis* (2018).
3. Lee, et al. *LancetRespirMed* (2021).
4. Kerwin, et al. *Respir Res* (2020).
5. Kirby, et al. *Acad Radiol* (2012).

Acknowledgments

This investigator-initiated, investigator-sponsored study was funded in part by GlaxoSmithKline



CONTACT: mshar68@uwo.ca, gparraga@uwo.ca