

Responsiveness to leukotriene D₄ and methacholine for predicting efficacy of montelukast in asthma

Wei-Jie Guan¹, Jin-Ping Zheng¹, Yi Gao¹, Cai-Yu Jiang², Yan-Qing Xie¹, Xu Shi¹, Zheng Zhu¹, Jia-Ying An¹, Xin-Xin Yu¹, Wen-Ting Liu¹, Nan-Shan Zhong¹

¹State Key Laboratory of Respiratory Disease, First Affiliated Hospital of Guangzhou Medical University, Guangzhou 510120, China;

²Sichuan Provincial People's Hospital, Chengdu 610072, China

ABSTRACT

A lower responsiveness to leukotriene D₄ (LTD₄) or higher LTD₄/[methacholine (MCh)] potency ratio might suggest preferable outcomes of short-term montelukast monotherapy in terms of airway inflammation and lung function in asthmatic patients.

KEY WORDS

Asthma; leukotriene D₄ (LTD₄); leukotriene-responsive; leukotriene-unresponsive; methacholine (MCh); montelukast

J Thorac Dis 2013;5(3):298-301. doi: 10.3978/j.issn.2072-1439.2013.02.01

Introduction

Leukotrienes are pivotal inflammatory mediators of asthma (1) and potently elicit bronchoconstriction by combination with CysLT₁, the major leukotriene receptor (2). Despite that leukotriene receptor antagonists (LTRA) have been clinically applied for years, a considerable number of asthmatic patients did not respond preferentially. Although increased *in vivo* leukotriene release (3) has been linked to preferable response to montelukast, this appeared clinically complicated. Urinary LTE₄/exhaled nitric oxide ratio (4) reflected the efficacy in childhood asthma yet remained elusive in adults. We hypothesized that airway responsiveness to leukotriene D₄ (LTD₄) [cumulative dose of leukotriene D₄ causing a 20% fall in FEV₁ (PD₂₀FEV₁-LTD₄)] and LTD₄/[methacholine (MCh)] potency ratio could predict the efficacy of LTRA, based on the available methodology of LTD₄ bronchial provocation test (5,6) and the difference in responsiveness to LTD₄ and MCh (6).

Methods

Recruitment ran from March 2010 to August 2010. The inclusion and exclusion criteria have been described previously (6).

Asthmatic patients who tested positively to LTD₄ inhalation challenge were, in this open-label pilot trial, allocated to receive 28-day montelukast monotherapy (10 mg, once daily) followed by reassessment 3 to 5 days after montelukast withdrawal. Salbutamol was allowed as needed. Subjects were instructed to record the peak expiratory flow (PEF) thrice daily and as-needed use of salbutamol (puffs). Measurement of fractional exhaled nitric oxide (FENO) (7), airway responsiveness to LTD₄ and MCh, Asthma Quality of Life Questionnaire (AQLQ) score in the symptom dimension and asthma control test (ACT) score were performed prior to and after the treatment. Approval was obtained from Ethics Committee of First Affiliated Hospital of Guangzhou Medical University. All subjects gave informed consent prior to the study.

The methodology of LTD₄ and MCh inhalation challenge has been introduced previously (6). Both tests were performed at a 2- to 14-day interval. Measurement of FeNO was conducted by using NIOX MINO (Aerocrine Co, Sweden). All maneuvers met the guideline established by American Thoracic Society (7).

The geometric means of PD₂₀FEV₁-LTD₄ (0.533 nmol) and LTD₄/MCh potency ratio (3647), as determined by a previously conducted cross-sectional study, were adopted to identify leukotriene-responsive or leukotriene-unresponsive subjects (6). Subjects having a PD₂₀FEV₁-LTD₄ ≤ 0.533 nmol and LTD₄/MCh potency ratio ≥ 3,647 were deemed leukotriene-responsive, whilst those with PD₂₀FEV₁-LTD₄ > 0.533 nmol and LTD₄/MCh potency ratio < 3,647 were allocated to leukotriene-unresponsive group. The remaining were assigned to unclassified group. Data were expressed as mean ± standard deviation ($\chi \pm s$) for normal distribution, while median (interquartile range) [M(Q_R)] was otherwise applied. Analysis of variance (ANOVA) was conducted for among-group comparison on data with normal

Corresponding to: Jin-Ping Zheng, M.D. State Key Laboratory of Respiratory Disease, First Affiliated Hospital of Guangzhou Medical University, 151 Yanjiang Road, Guangzhou 510120, China. Email: jpzhenygy@163.com.

Submitted Jan 17, 2013. Accepted for publication Feb 21, 2013.

Available at www.jthoracdis.com

ISSN: 2072-1439

© Pioneer Bioscience Publishing Company. All rights reserved.

Table 1. Baseline levels.

Indices	Subgroup 1		Subgroup 2	
	PD ₂₀ FEV ₁ -LTD ₄ ≤0.533 nmol	PD ₂₀ FEV ₁ -LTD ₄ >0.533 nmol	LTD ₄ /MCh potency ratio <3,647	LTD ₄ /MCh potency ratio ≥3,647
No. of patients	18	5	13	10
Age (years)	38.11±11.71	40.00±8.12	39.69±11.92	37.00±10.53
Height (cm)	159.00 (11.50)	164.20±7.26	161.42±6.80	160.65±7.66
Weight (kg)	61.33±12.25	66.80±8.58	61.23±11.92	64.20±11.59
Male/female ratio	8/10	3/2	6/7	5/5
Controlled (No.)	3	0	2	1
Partly controlled (No.)	5	1	3	3
Uncontrolled (No.)	10	4	8	6
Pre-challenge FEV ₁ (pred%)	91.22±14.60	101.12 (15.97)	95.65±15.99	88.17±10.53
FeNO (ppb)	45.50 (47.00)	29.40±13.83	40.00 (52.00)	56.70±40.70
PD ₂₀ FEV ₁ -LTD ₄ (nmol)	0.25±0.12**	0.68 (0.86)	0.40 (0.29)	0.20 (0.26)
PD ₂₀ FEV ₁ -MCh (μmol)	1.12±0.79**	4.39±4.84	0.95±0.64**	1.71 (3.00)

*P<0.05, **P<0.01 for between-group comparison; FeNO, fractional exhaled nitric oxide; FEV₁, forced expiratory volume in one second; PD₂₀FEV₁-LTD₄, provocative dose of LTD₄ causing a 20% reduction in FEV₁; PD₂₀FEV₁-MCh, provocative dose of methacholine causing a 20% reduction in FEV₁.

distribution, whilst Kruskal-Wallis test was otherwise employed. Statistical analyses were performed using SPSS 16.0.

Results

Of 32 asthmatic patients allocated, 23 completed end-point reassessment. The 9 subjects dropped out owing to poor compliance (n=5, diary recording <50%), asthma exacerbation (n=3) and respiratory tract infection needing systemic therapy (n=1). All subgroups of subjects, mostly comprised of those with uncontrolled asthma, did not differ statistically (all P>0.05) in demography nor spirometry or FeNO (Table 1). Between-subgroup difference in pre- and post-treatment spirometry, quality of life, daily reliever use or airway hyperresponsiveness did not reach statistical significance (all P>0.05), except for that in PD₂₀FEV₁-LTD₄ and cumulative dose of methacholine causing a 20% fall in FEV₁ (PD₂₀FEV₁-MCh) (both P<0.05). There was a trend towards a favorable improvement in FeNO, FEV₁ and AQLQ scores in those with PD₂₀FEV₁-LTD₄ <0.533 nmol or LTD₄/MCh potency ≥3,647 (Table 2). Further comparison was conducted in leukotriene-responsive/-unresponsive asthmatic patients. As compared with leukotriene-unresponsive group, a similar trend towards preferentially improved FeNO and FEV₁ in leukotriene-responsive group was noted though the difference did not reach statistical significance (Table 3).

Discussion

A 3- to 5-day withdrawal period following 28-day montelukast

therapy was designed inasmuch that we aimed to determine the gross improvement in clinical indices and that all subjects might otherwise test negatively to LTD₄ challenge (unpublished data). This might, conceivably and inevitably, obscure the treatment effects of montelukast and lead to a relapse in some asthmatic patients. Interestingly, that subjects with PD₂₀FEV₁-LTD₄ <0.533 nmol or LTD₄/MCh potency ratio >3,647 showed significantly favorable improvement in FeNO and lung function indices seemed to suggest the roles that leukotrienes play in asthma. Our results were partly comparable to those of Athavale *et al.* (8), who reported markedly increased FEV₁, PEF and asthma symptom score and reduced salbutamol use in 148 clinically stable asthmatic patients receiving a 4-week open-labeled montelukast trial. The difference between these the two studies could have stemmed from the inclusion criteria, standards for allocation, concomitant use of medication and ethnicity.

Noticeably, several limitations must be addressed. Firstly, the subject enrollment might not be sufficient to warrant a clear-cut discrimination for between-group comparison, and hence, a sound conclusion. Secondly, the compelling results might be attributable to the lack of a placebo group. Thirdly, the comparatively short course of montelukast therapy appeared insufficient to clinical practice, particularly to those with uncontrolled asthma, who were expected to benefit more following a prolonged treatment. Finally, the different proportion of asthmatic patients with various levels of asthma control might have inevitably biased the results. However, subgroup analysis

Table 2. Comparison on pre- and post-treatment differences in lung function, FeNO, airway hyperresponsiveness and quality of life.

Indices	Subgroup 1		Subgroup 2	
	PD ₂₀ FEV ₁ -LTD ₄ <0.533 nmol	PD ₂₀ FEV ₁ -LTD ₄ ≥0.533 nmol	LTD ₄ /MCh potency ratio <3,647	LTD ₄ /MCh potency ratio ≥3,647
No. of patients	18	5	13	10
Difference in FeNO (ppb)	3.88±40.83	-1.00±30.68	-0.46±43.72	-1.00±30.38
28-day PEFr (%)	30.82 (17.83)	30.67±19.04	38.82±17.45	30.68±19.04
Difference in 28-day PEFr (%)	2.05 (17.70)	5.22 (9.13)	5.27±16.20	3.05 (9.13)
Difference in ACT	2.00 (6.00)	3.90±3.25	2.00 (6.00)	3.90±3.25
Difference in AQLQ symptom score	5.81±11.95	4.30±10.73	8.00±12.16	4.30±10.73
Difference in pre-challenge FEV ₁ (pred%)	0.54±11.42	-3.94±12.31	5.91 (7.93)	-3.94±12.31
Difference in weekly PEFmax (L/s)	-1.25±46.74	-7.00±40.29	-10.00 (20.00)	-7.00±40.29
Difference in weekly PEFmin (L/s)	8.75±41.61	12.00±34.58	10.00±49.80	12.00±34.58
Difference in PD ₂₀ FEV ₁ -LTD ₄ (nmol)	0.02 (0.51)	0.22 (0.74)	-0.07 (0.60) *	0.22 (0.74)
Difference in PD ₂₀ FEV ₁ -MCh (μmol)	0.00 (1.98)	-0.66±2.37	0.12 (2.80) *	-0.66±2.37
Daily use of salbutamol (puffs)	0.07 (1.77)	0.07 (1.56)	0.00 (1.64)	0.07 (1.56)

*P<0.05 for between-group comparison; FeNO, fractional exhaled nitric oxide; PEFr, peak expiratory flow variation (%); ACT, asthma control test; AQLQ, asthma quality of life questionnaire; PEFmax, maximal peak expiratory flow; PEFmin, minimal peak expiratory flow; All differences in clinical indices were obtained by subtracting post-treatment from pre-treatment level unless otherwise stated.

Table 3. Pre- and post-treatment difference in lung function, FeNO, airway hyperresponsiveness and quality of life in leukotriene-responsive/-unresponsive patients.

Indices	Leukotriene-responsive ^a	Leukotriene-unresponsive ^b
No. of patients	9	3
Difference in FeNO (ppb)	-1.11±32.72	-5.00 (37.00)
28-day PEFr (%)	33.05±19.04	38.05±9.31
Difference in 28-day PEFr (%)	1.09 (12.51)	7.93±13.61
Difference in ACT	3.56±3.25	4.67±3.79
Difference in AQLQ symptom score	2.33±9.27	5.67±8.39
Difference in pre-challenge FEV ₁ (pred%)	-4.54±12.92	-11.42±16.20
Difference in weekly PEFmax (L/s)	-11.11±44.85	-20.00 (10.00)
Difference in weekly PEFmin (L/s)	6.67±40.31	23.33±66.58
Difference in PD ₂₀ FEV ₁ -LTD ₄ (nmol)	0.09 (0.36)	0.76±1.81
Difference in PD ₂₀ FEV ₁ -MCh (μmol)	-0.74 (1.46)	3.93±5.22
Daily use of salbutamol (puffs)	0.07 (1.67)	0.00 (1.64)

^aAsthmatic patients with PD₂₀FEV₁-LTD₄ ≤0.533 nmol and LTD₄/MCh potency ratio ≥3,647; ^bAsthmatic patients with PD₂₀FEV₁-LTD₄ >0.533 nmol and LTD₄/MCh potency ratio <3,647; FeNO, fractional exhaled nitric oxide; PEFr, peak expiratory flow variation (%); ACT, asthma control test; AQLQ, asthma quality of life questionnaire; PEFmax, maximal peak expiratory flow; PEFmin, minimal peak expiratory flow; All differences in clinical indices were obtained by subtracting the post-treatment from pre-treatment level unless otherwise stated.

on the basis of asthma control level would be necessary when an adequate enrollment has been secured. Our hypothesis therefore urgently needs to be further tested in successive studies with a prolonged treatment course.

Conclusions

Lower PD₂₀FEV₁-LTD₄ or higher LTD₄/MCh potency ratio might suggest preferable outcomes of montelukast therapy in

terms of airway inflammation and spirometry, but not airway hyperresponsiveness or quality of life in asthmatic patients.

Acknowledgements

This study was supported by Provincial Natural Science Foundation of Guangdong 915280000100019 (to J. Zheng), Municipal science and technology plan of Guangzhou 2009J1-C321-1 (to Y. Gao), Guangzhou leading project for medicine and health 2009-YB-143 (to Y. Gao) and The Scientific Project of Guangzhou Medical University 2008A02 (to Y. Gao), Changjiang Scholars and Innovative Research Team in University ITR0961 (to J. Zheng) and The National Key Technology R&D Program of the 12th National Five-year Development Plan 2012BAI05B01 (to J. Zheng). None of these fundings had any influence on our study.

We thank Drs. Ke-fang Lai, Wei Luo and Ru-chong Chen (State Key Laboratory of Respiratory Disease, First Affiliated Hospital of Guangzhou Medical University) for their insightful suggestion.

Disclosure: The authors declare no conflict of interest.

References

1. Drazen JM. Leukotrienes as mediators of airway obstruction. *Am J Respir Crit Care Med* 1998;158:S193-200.
2. Suzuki M, Kato M, Kimura H, et al. Inhibition of human eosinophil activation by a cysteinyl leukotriene receptor antagonist (pranlukast; ONO-1078). *J Asthma* 2003;40:395-404.
3. Terashima T, Amakawa K, Matsumaru A, et al. Correlation between cysteinyl leukotriene release from leukocytes and clinical response to a leukotriene inhibitor. *Chest* 2002;122:1566-70.
4. Rabinovitch N, Graber NJ, Chinchilli VM, et al. Urinary leukotriene E4/exhaled nitric oxide ratio and montelukast response in childhood asthma. *J Allergy Clin Immunol* 2010;126:545-51.e1-4.
5. Guan W, Zheng J, Gao Y, et al. Leukotriene D4 bronchial provocation test: methodology and diagnostic value. *Curr Med Res Opin* 2012;28:797-803.
6. Guan W, Zheng J, Gao Y, et al. Leukotriene D(4) and methacholine bronchial provocation tests for identifying leukotriene-responsiveness subtypes. *J Allergy Clin Immunol* 2013;131:332-338.e4.
7. Recommendations for standardized procedures for the on-line and off-line measurement of exhaled lower respiratory nitric oxide and nasal nitric oxide in adults and children-1999. This official statement of the American Thoracic Society was adopted by the ATS Board of Directors, July 1999. *Am J Respir Crit Care Med* 1999;160:2104-17.
8. Athavale A, Souza GA, Avasthi R, et al. A clinical trial of the efficacy and safety of montelukast as monotherapy in patients with chronic stable bronchial asthma. *J Indian Med Assoc* 2004;102:109-11.



Cite this article as: Guan WJ, Zheng JP, Gao Y, Jiang CY, Xie YQ, Shi X, Zhu Z, An JY, Yu XX, Liu WT, Zhong NS. Responsiveness to leukotriene D₄ and methacholine for predicting efficacy of montelukast in asthma. *J Thorac Dis* 2013;5(3):298-301. doi: 10.3978/j.issn.2072-1439.2013.02.01