Responsiveness to leukotriene D_4 and methacholine for predicting efficacy of montelukast in asthma

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ABSTRACT A lower responsiveness to leukotriene D_4 (LTD_4) or higher LTD_4/[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 D_4 (LTD_4); leukotriene-responsive; leukotriene-unresponsive; methacholine (MCh); montelukast

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Introduction

Leukotrienes are pivotal inflammatory mediators of asthma (1) and potently elicit bronchoconstriction by combination with $CysLT_1$, 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 LTE_4/exhaled nitric oxide ratio (4) reflected the efficacy in childhood asthma yet remained elusive in adults. We hypothesized that airway responsiveness to leukotriene D_4 (LTD_4) [cumulative dose of leukotriene D_4 causing a 20% fall in FEV_1 ($PD_{20}FEV_1$-LTD_4)] and LTD_4/[methacholine (MCh)] potency ratio could predict the efficacy of LTRA, based on the available methodology of LTD_4 bronchial provocation test (5,6) and the difference in responsiveness to LTD_4 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 LTD_4 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 LTD_4 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 LTD_4 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 $PD_{20}FEV_1$-LTD_4 (0.533 nmol) and LTD_4/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 $PD_{20}FEV_1$-LTD_4 ≤0.533 nmol and LTD_4/MCh potency ratio ≥3,647 were deemed leukotriene-responsive, whilst those with $PD_{20}FEV_1$-LTD_4 >0.533 nmol and LTD_4/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

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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; FEV_1, forced expiratory volume in one second; $PD_{20}FEV_1$-LTD_4, provocative dose of LTD_4 causing a 20% reduction in FEV_1; $PD_{20}FEV_1$-MCh, provocative dose of methacholine causing a 20% reduction in FEV_1.

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 $PD_{20}FEV_1$-LTD_4 and cumulative dose of methacholine causing a 20% fall in FEV_1 ($PD_{20}FEV_1$-MCh) (both P<0.05). There was a trend towards a favorable improvement in FeNO, FEV_1 and AQLQ scores in those with $PD_{20}FEV_1$-LTD_4 <0.533 nmol or LTD_4/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 FEV_1 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 LTD_4 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 $PD_{20}FEV_1$-LTD_4 <0.533 nmol or LTD_4/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 FEV_1, 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)

[a]Asthmatic patients with $PD_{20}FEV_1$-LTD_4 ≤0.533 nmol and LTD_4/MCh potency ratio ≥3,647; [b]Asthmatic patients with $PD_{20}FEV_1$-LTD_4 >0.533 nmol and LTD_4/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 $PD_{20}FEV_1$-LTD_4 or higher LTD_4/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.

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