◆ ORIGINAL ARTICLE ◆

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Th2 cytokine inhibition and cough in asthmatic and bronchitic patients

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BACKGROUND: Activated T helper lymphocytes are present in the airway and their production of cytokines is important in the pathogenesis of asthma, however, the relationship between T helper lymphocyte-derived cytokines and airway cough reflex sensitivity remains unknown.

METHODS: The effect of the orally active Th2 cytokine inhibitor suplatast tosilate on cough response to inhaled capsaicin was examined in eleven patients with stable atopic asthma and compared with patients having non-atopic asthma and chronic bronchitis (the latter of which is not related to Th2 cytokines). Capsaicin cough threshold, defined as the lowest concentration of capsaicin eliciting five or more coughs, was measured as an index of airway cough reflex sensitivity. Concentration of serum total IgE level was also measured after treatment with suplatast tosilate.

RESULTS: The cough threshold after two weeks treatment with suplatast tosilate was significantly greater than the value with placebo accompanied by decrease of serum IgE level in atopic asthmatics. This significance was not observed in patients with non-atopic asthma or chronic bronchitis.

CONCLUSIONS: Th2 cytokines may be possible modulators augmenting airway cough reflex sensitivity in atopic asthmatic airways but not in non-atopic asthmatic or bronchitic airways.

Keywords: bronchial asthma; chronic bronchitis; cough reflex sensitivity; Th2 cytokines

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Introduction

Cough is one of the main symptoms in general practice and in the respiratory clinic, which can interfere with sleeping, studies and social activities. Thus, it is important to investigate the mechanism and factors involved in the cough reflex for specific therapy. However, the mechanism by which the cough reflex may be altered in humans remains unclear.

Activated T helper lymphocytes and their production of cytokines have been postulated to have an important role in chronic airway inflammation (1). Atopic bronchial asthma consists of chronic airway inflammation with eosinophils and Th2 dominant lymphocytes (2, 3); and neutrophils and Th1 dominant lymphocytes are involved in the airway of chronic bronchitis (4, 5). We have shown that inflammatory mediators are involved in airway cough reflex sensitivity in asthmatic and bronchitic airways (6–8). However, the role of Th2 cytokines as mediators of the airway inflammatory response in cough reflex sensitivity has not been defined.

We, therefore, conducted this study to examine the role of Th2 derived cytokines in cough reflex sensitivity to inhaled capsaicin in stable patients with bronchial asthma and chronic bronchitis using a novel Th2 inhibitor, suplatast tosilate ((±)-[2-[4-(3-ethoxy-2-hydroxypropoxy) phenylcarboxy]ethyl] dimethylsulfonium p-toluenesulfonate), which has been prescribed for allergic diseases since April 1995 in Japan (9).

Subjects and methods

Subjects

Twenty-two patients with bronchial asthma (12 men and 10 women) with a mean age of 52.9 ± 3.9 (±SEM) (range 25–72) years, and eleven patients

Abbreviations and acronyms

ATS	American Thoracic Society
BAL	broncho-alveolar lavage
CVA	cough variant asthma
ECP	eosinophil cationic protein
EG2	eosinophil granulocyte 2
FEV1	forced expiratory volume in one second
FVC	forced vital capacity
GM-CSF	granulocytes-macrophage colony stimulation factor
GSEM	geometric standard error of the mean
HLA	human leukocyte antigen
IgE	immunoglobulin E
IL	Interleukin
MBP	major basic protein
RIST	radioimmunosorbent test

Key messages

- **Th2-derived cytokines may be possible modulators augmenting airway cough reflex sensitivity in atopic asthmatics, but not in non-atopic asthmatics or bronchitic patients.**
- **Th2 inhibition should be considered to be one of the therapeutic options for the treatment of chronic non-productive cough in atopic patients.**

with chronic bronchitis (5 men and 6 women) with a mean age of 62.8 ± 3.6 (±SEM) (range 38–77) years, participated in this study. All patients were lifetime non-smokers or ex-smokers with no history of viral infection for at least 4 weeks prior to the study. Characteristics of individual patients are shown in Tables 1 and 2. Informed consent was obtained from all subjects. This study was approved by the Ethics Committee of our hospital.

Each asthmatic patient satisfied the American Thoracic Society definition of asthma, with symptoms of episodic wheezing, cough and shortness of breath responding to bronchodilators, and reversible airflow obstruction documented in at least one previous pulmonary function study (4). Reversibility was defined as greater than 12% increase in the forced expiratory volume in one second (FEV1) following a bronchodilator inhalation. All patients had bronchial hyperresponsiveness as shown in Table 1. The severity of asthmatic patients was classified according to the NIH/WHO guideline of global strategy for asthma management and prevention. We classified patients as mild when their symptoms were more than once a week but less than once a day. Asthmatic patients with symptoms daily were defined as moderate. Patients with bronchial asthma were divided into the two groups: atopic and non-atopic asthma. Patients with atopy were recognized as having a hereditary predilection to produce IgE antibodies against common environmental allergens (10). Eleven patients were labeled as atopic asthma because they showed increased specific IgE antibodies in the serum. The other eleven patients were classified as non-atopic asthma because they had no familial history of allergic diseases and no increased levels of specific IgE antibodies to 10 common allergens. This study was carried out when symptoms were mild and stable, while patients were taking oral theophylline, oral (short-acting clenbuterol) and/or aerosol β2-agonists (short-acting procaterol), inhaled steroids (beclomethasone dipropionate), inhaled anti-cholinergic agents (oxitropium bromide) and/or mucolytic agents (carbocysteine). They had not received oral steroid therapy for at least eight weeks.

Each patient diagnosed as chronic bronchitis satisfied the definition of chronic bronchitis recommended by the American Thoracic Society (ATS) (4). All patients were also diagnosed to have sinobronchial syndrome. Sinobronchial syndrome is a common chronic bronchial disorder in Japan, which is not related to smoking. We provide some details, as it is not recognized as a diagnostic category by the ATS. Sinobronchial syndrome is defined as a coexisting chronic sinusitis and non-specific chronic neutrophilic inflammation of the lower airways presenting with expectoration (e.g., chronic bronchitis, diffuse bronchiectasis and diffuse panbronchiolitis (11)). Suzaki et al. (12) reported that the sinobronchial syndrome was found in 10% of 309 patients with chronic sinusitis and in 55% of 74 patients with chronic lower respiratory tract infectious diseases. They suggested that there is a gene controlling the susceptibility to sinobronchial syndrome, especially diffuse panbronchiolitis, which is significantly associated with human leukocyte antigen (HLA)-BW54; this is found specifically in Japanese and not in Caucasians. The obstructive form of sinobronchial syndrome is known as 'diffuse panbronchiolitis' (11). Recognition of the sinobronchial syndrome is very important in Japan because long-term, low dose erythromycin therapy is as specifically effective (13, 14), as inhaled steroid therapy for bronchial asthma. In our patients, diagnosis of the sinobronchial syndrome was based on the following criteria: 1) productive cough on most days for at least 3 months for 2 consecutive years, 2) chronic sinusitis diagnosed, based on symptoms (postnasal drip, nasal discharge and nasal obstruction), physical examinations and plain roentgenogram as indicated by opacities or air-fluid levels of one or more paranasal sinuses, 3) no history suggesting to the attending physician that they had bronchial asthma, 4) no history of wheezing syndrome, and 5) no significant emphysema docu-

Table 1. Clinical characteristics of asthmatic patients.

Patient number	Age (yr)	Sex	Height (cm)	Type	Severity	Total IgE in serum (IU/ml)	Specific IgE in serum	Complication of allergic disease	FEV1% predicted (%)	PC 20-FEV1 (mg/ml)*	Treatment			
											BDP (μg/day)	Theophylline (μg/day)	Clenbuterol (μg/day)	Carbocystein (mg/day)
1	72	M	152	Int	Moderate	32	-	-	56.1	0.078	800	400	40	1500
2	74	M	160	Int	Mild	34	-	-	75.6	0.16	200	400	0	1500
3	60	F	156	Int	Mild	32	-	-	69.5	0.31	400	0	0	1500
4	65	M	165	Int	Mild	20	-	-	108.7	2.50	100	400	0	1500
5	45	F	164	Int	Mild	32	-	-	95.3	1.25	400	200	0	1500
6	40	F	164	Int	Mild	40	-	-	90.6	1.25	400	400	0	1500
7	70	F	148	Int	Moderate	2	-	-	81.5	0.31	800	200	40	1500
8	66	F	146	Int	Mild	78	-	-	94.3	1.25	400	400	0	0
9	42	M	176	Int	Mild	12	-	-	103.8	2.50	0	200	40	0
10	77	F	168	Int	Mild	80	-	-	105.3	0.31	400	400	40	0
11	79	M	155	Int	Moderate	88	-	-	95.1	0.31	800	400	20	1500
12	69	M	165	Ext	Mild	315	HD, Mite	-	95.7	1.25	0	200	20	0
13	70	M	156	Ext	Mild	146	HD	-	107.8	2.50	200	200	0	1000
14	29	M	168	Ext	Mild	263	Cedar, Mite	UR	84.6	0.16	200	0	20	1500
15	61	F	148	Ext	Mild	206	Mite	-	88.6	0.31	0	600	40	1500
16	25	F	165	Ext	Mild	178	HD, Mite	UR	79.0	2.50	0	400	40	0
17	39	M	173	Ext	Moderate	347	HD, Mite	-	104.1	1.25	800	0	0	1500
18	75	M	165	Ext	Mild	105	Cedar, HD, Mite	-	89.3	0.16	0	200	0	0
19	72	M	165	Ext	Mild	325	HD, Mite	-	79.5	1.25	0	600	30	0
20	42	M	173	Ext	Mild	100	HD, Mite	-	78.2	2.50	0	400	0	0
21	34	F	160	Ext	Mild	155	HD, Mite	AR, UR	101.6	0.31	200	200	0	1500
22	31	F	160	Ext	Mild	143	HD, Mite	-	103.0	1.25	0	400	20	0

Ext = extrinsic; Int = intrinsic; HD = house dust; AR = allergic rhinitis; UR = urticaria; BDP = beclomethasone diproprionate inhalation.
*PC20-FEV1 shows concentration of inhaled methacholine causing a 20% fall in FEV1.
All patients used inhaled β2-agonists (salbutamol or procaterol) on demand.

Table 2. Clinical characteristics of bronchitic patients.

Patient number	Age (yr)	Sex	Height (cm)	Total IgE in serum (IU/ml)	Total IgA in serum (IU/ml)	Sputum bacteria*	Bronchodilator response (%)**	Treatment***		
								Erythromycin (mg/day)	Carbocystein (mg/day)	Ambroxol (mg/day)
1	63	M	162	1	194	N	1.3	300	0	0
2	38	F	155	61	479	N	4.1	300	1500	45
3	75	M	159	88	722	K	4.3	200	0	0
4	61	F	146	84	274	N	2.4	300	1500	45
5	61	F	160	2	193	K	1.6	300	1500	45
6	65	M	154	13	248	St	3.8	300	0	0
7	57	F	161	1	155	N	4.8	200	0	0
8	57	F	154	11	44	N	0.8	200	0	0
9	50	M	167	75	230	N	2.4	0	1500	45
10	74	M	164	27	144	N	0.0	200	0	0
11	77	F	153	35	439	St	3.1	300	1500	45

* St = Streptcoccus pneumoniae; H = Haemophilus influenzae; N = no pathologic bacteria cultured from sputum.
** Bronchodilator response means percent increase in forced expiratory volume in 1sec (FEV1) from the baseline value after inhalation of 300 μg of salbutamol sulfate.
*** erythromycin, long-term low dose erythromycin.

mented by chest computed tomographic scan. A diagnosis of chronic sinusitis was based on symptoms (postnasal drip, nasal discharge and nasal obstruction), physical examination, and radiography. Clinical characteristics of each studied patient suffering from chronic bronchitis are shown in Table 2. None had perennial or vasomotor rhinitis. They were taking low-dose erythromycin and/or mucolytic agents, such as carbocysteine and ambroxol, but not taking theophylline, β2-adrenoceptor stimulants, or glucocorticosteroids. This study was carried out when their symptoms were mild and stable.

Assessment of cough reflex sensitivity to inhaled capsaicin

Cough reflex sensitivity was measured by capsaicin provocation test (15). Capsaicin (30.5 mg) was dissolved in Tween 80 (1 mL) and ethanol (1 mL) and then dissolved in physiological saline (8 mL) to make a stock solution of 1×10^{-2} M, which was stored at −20°C. This solution was diluted with physiological saline to make solutions starting at a concentration of 0.49 μM and increasing it by doubling concentrations up to 1000 μM. Each subject inhaled a control solution of physiological saline followed by progressively increasing concentrations of the capsaicin solution. Solutions were inhaled for 15 secs every 60 secs, by tidal mouth-breathing wearing a nose clip from a Bennett Twin nebulizer (3012-60cc, Puritan-Bennett Co., Carlsbad, California, USA). Increasing concentrations were inhaled until five or more coughs were elicited. The nebulizer output was 0.21 mL/min. The number of capsaicin-induced coughs was counted by a blinded medical technician in our pulmonary function laboratory. The cough threshold was defined as the lowest concentration of capsaicin that elicited five or more coughs.

Study protocol

The medication was stopped at 9.00 p.m. on the previous day to allow a washout time of 12 h or more before the measurements of cough threshold to inhaled capsaicin at 10.00 a.m. on each test day.

Each patient attended on five occasions separated by 14 days, at the same time each day. Control measurement of capsaicin cough threshold was carried out before the first treatment with test drugs. Then, treatment with suplatast tosilate and placebo was performed in a randomized, cross-over fashion. A suplatast tosilate tablet (100 mg) was taken orally three times a day for 14 days and at 8.00 a.m. on the test day. The dose tested in this study is the usual dose recommended for control of asthma, which has been proven by Phase II and III study for the treatment of bronchial asthma. FEV1 was measured on a dry wedge spirometer (Transfer Test, P K Morgan Ltd., UK) before capsaicin challenge to assess the bronchoactive effect of the treatment regimens. The serum was obtained after the suplatast tosilate treatment to measure the total IgE levels by the radioimmunosorbent test (RIST, Pharmacia, Uppsala, Sweden). Serum transaminases, lactic dehydrogenase, alkaline phosphatase, γ-glutamyltranspeptidase, leucine amoinopeptidase, total-bilirubin, blood urea, serum creatinine and serum uric acid were measured to assess adverse reactions caused by the suplatast tosilate treatment.

Data analysis

Capsaicin cough threshold values were expressed as

geometric means with the geometric standard error of the mean (GSEM). Forced vital capacity (FVC), FEV1 and total serum IgE levels were shown as arithmetic mean values ± SEM. The cough threshold values and the FEV1 values were compared between any pair of the three treatment regimens by the Wilcoxon signed-ranks test. To compare the changes in the cough threshold induced by suplatast tosilate and placebo as compared to the control value, the ratios of the cough threshold with suplatast tosilate and placebo to the control cough threshold were compared by the Wilcoxon signed-ranks test. A *P*-value of 0.05 or less was taken as significant.

Results

Geometric mean values of the cough threshold to inhaled capsaicin before treatment and after treatment with suplatast tosilate and placebo are shown in Table 3. The cough threshold after the suplatast tosilate treatment was significantly greater than the value after the placebo ($P < 0.05$) in patients with atopic asthma. FVC or FEV1 value was not significantly different between control and the other treatment regimens.

Figure 1 shows the changes in the serum total IgE levels by treatment with suplatast tosilate. In patients with atopic asthma, but not in patients suffering from non-atopic asthma or chronic bronchitis, there was significant decrease ($P < 0.01$) in the serum total IgE levels after suplatast tosilate treatment.

Changes in the cough threshold by treatment with suplatast tosilate or placebo in relation to the control value are shown in Figure 2. The change with the suplatast tosilate treatment was significantly ($P < 0.02$) greater than that with the placebo treatment in atopic asthmatics, but not in patients with non-atopic asthma or chronic bronchitis. Adverse reactions in serological findings were not detected in the present study.

Table 3. Pulmonary function and capsaicin cough threshold on suplatast tosilate and placebo treatments in patients with stable asthma and chronic bronchitis.

	Non-atopic asthmatics		
	Run-in	Placebo	Suplatast tosilate
FVC as % pred. (%)	95.1 ± 7.0	85.0 ± 10.5	97.9 ± 8.3
FEV1 as % pred. (%)	66.8 ± 5.1	80.1 ± 8.4	77.3 ± 7.2
Cough threshold (μM)	13.2 (1.7)	17.0 (1.8)	9.8 (1.7)
	Atopic asthmatics		
	Run-in	**Placebo**	**Suplatast tosilate**
FVC as % pred. (%)	106.9 ± 7.5	105.0 ± 8.4	101.0 ± 11.8
FEV1 as % pred. (%)	91.5 ± 8.7	90.8 ± 8.6	90.9 ± 8.7
Cough threshold (μM)	18.6 (1.8)	24.7 (1.8)	45.2 (1.8)**
	Chronic bronchitics		
	Run-in	**Placebo**	**Suplatast tosilate**
FVC as % pred. (%)	104.2 ± 5.1	105.3 ± 5.0	105.7 ± 5.2
FEV1 as % pred. (%)	104.2 ± 5.2	104.7 ± 5.3	106.7 ± 4.5
Cough threshold (μM)	10.5 (1.3)	10.2 (1.3)	10.9 (1.4)

Data are shown as standard error of the mean for FVC and FEV1 and as geometric mean value (geometric standard error of the mean) for capsaicin cough threshold.
**$P < 0.02$ compared with placebo treatment (Wilcoxon signed-ranks test).

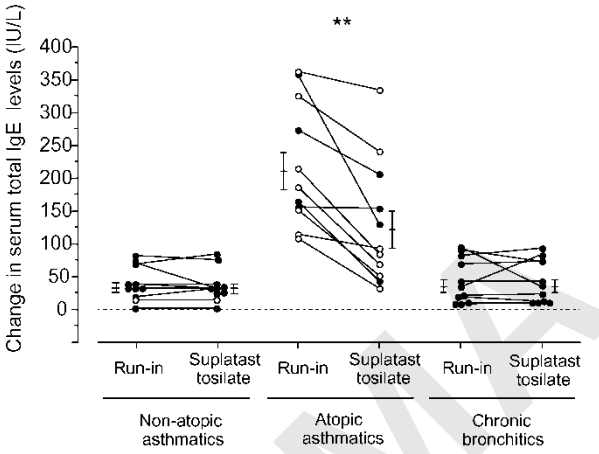

Figure 1. Change in serum total IgE levels with suplatast tosilate treatment in patients with atopic asthma, non-atopic asthma and chronic bronchitis. Closed circles and open circles represent patients undergoing steroid inhalation therapy and patients without steroid inhalation therapy, respectively. **$P < 0.02$ compared with run-in period by the Wilcoxon signed-ranks test.

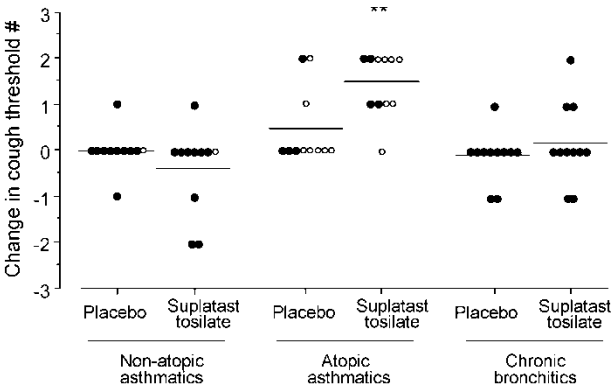

Figure 2. Change in capsaicin cough threshold with suplatast tosilate or placebo treatment from the control value in patients with stable atopic asthma, non-atopic asthma and chronic bronchitis. Closed circles and open circles represent patients undergoing steroid inhalation therapy and patients without steroid inhalation therapy, respectively. # Log 2 (capsaicin cough threshold with each treatment/control capsaicin cough threshold). **$P < 0.02$ compared with placebo treatment by the Wilcoxon signed-ranks test.

Discussion

The present study showed that two weeks' treatment with a novel Th2 cytokine inhibitor suplatast tosilate increased the cough threshold to inhaled capsaicin in patients with atopic asthma, but not in non-atopic asthma or chronic bronchitis. Suplatast tosilate also decreased the serum total IgE level in atopic asthmatics as shown in the past study administering inhaled steroids (16), indicating that this drug has actual activity to inhibit Th2 cytokine production, but did not change pulmonary function. These findings suggest that Th2-derived cytokines such as interleukin (IL)-4 and IL-5 may modulate to augment the airway cough reflex sensitivity in patients with atopic asthma, but not in non-atopic asthma or chronic bronchitis.

Chronic cough causes major functional limitation in a great number of people to seek medical service. It is well known that bronchial asthma and chronic bronchitis are the major disorders presenting with chronic persistent cough (17). Though specific therapy has been recommended, what mechanisms correlate to it remains obscure. We hypothesized that inflammatory mediators are involved in the airway cough reflex sensitivity in these diseases since inflammatory mediators have been shown to have an important role in the development of chronic airway inflammation (6–8) which exposes afferent receptors of the cough reflex to various stimuli (1, 18). Recently, it has been postulated that activated Th2 dominant lymphocytes in the airway have an important role in atopic bronchial asthma (2) and Th1 dominant lymphocytes in chronic bronchitis (4, 5). However, the relationship between airway cough reflex sensitivity and activated T helper lymphocytes remains unknown. Thus, we conducted this study to examine the effect of Th2 cytokine inhibition on airway cough reflex sensitivity in asthmatic and bronchitic patients and obtained the results described above.

Chronic eosinophilic inflammation of lower airways has been considered to be a fundamental feature of bronchial asthma (19). Azzawi et al. (3) studied the association between eosinophil infiltration into the airways and activated CD4 positive T cells in atopic asthmatic patients. Others have reported about the predominance of Th2 lymphocytes in BAL fluid with expression of mRNA for IL-3, IL-4, IL-5 and granulocytes-macrophage colony stimulation factor (GM-CSF) in patients with atopic asthma (20). Since the Th1 and Th2 types of reactions are reciprocally regulated *in vivo* (21, 22), it may be a rational therapy in allergic disorders in which Th2 cells are involved to modulate the Th1/Th2 balance shifting it from Th2 to Th1 dominant.

Suplatast tosilate is a novel antiallergic agent, which acts as a Th1/Th2 balance modulator having immuno-regulatory effect (9) through inhibiting IgE production and degranulation of basophils and mast cells induced by IgE, and suppressing production of IL-4 and IL-5 by Th2 cells (9). Tamaoki and colleagues (23) showed the efficacy of suplatast tosilate in controlling asthma symptoms, and decreasing diurnal variation in peak expiratory flow, serum eosinophil cationic protein (ECP) and IgE production. Other researchers (24) reported that suplatast tosilate attenuated bronchial hyperresponsiveness without affecting basal pulmonary functions, reduced sputum eosinophil count and decreased exhaled nitric oxide level in patients with mild and moderate asthma. These findings indicate the importance of Th2 inhibition in the asthmatic airway. Our previous study has shown that there is no relationship between cough reflex sensitivity to capsaicin and bronchial responsiveness to methacholine (25) and the attenuating effect of suplatast tosilate on bronchial hyperresponsiveness in asthma has been shown as described above (24). Therefore, the influence of Th2-derived cytokines for airway cough reflex sensitivity remains obscure. The results we obtained in this clinical trial indicate that Th2 derived cytokines may be possible modulators augmenting airway cough reflex sensitivity in atopic asthmatic airway, where Th2 dominant response operates, but not in non-atopic asthmatic or bronchitic airway; the latter is known to have Th1 dominant airway inflammation (5). Although we did not evaluate histological findings, a previous study revealed the reduction of eosinophil infiltration and eosinophil granulocyte 2 (EG2)-positive cells in bronchial epithelium in asthmatic airways after suplatast tosilate treatment (26). Since 2 weeks treatment with suplatast tosilate improved cough reflex sensitivity without affecting respiratory functions in this study, we can consider that clinical efficacy of suplatast tosilate for cough reflex sensitivity in atopic asthmatics may be a result from its Th2 suppression.

In conclusion, this study indicates that Th2 derived cytokines may be possible modulators augmenting airway cough reflex sensitivity in atopic asthmatics, but not in non-atopic asthmatics or bronchitic patients. Further studies may be required for determining individual Th2 cytokines actually involved in cough reflex sensitivity and for searching modulators of cough reflex sensitivity in non-atopic asthma and chronic bronchitis.

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