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Clinical Application of Histamine Prick Test for Food Challenge in Atopic Dermatitis

Determining positive food challenges are not easy as there is an absence of simple and objective tests. Histamine, an essential mediator for allergic reactions, is involved in the pathogenesis of atopic dermatitis (AD) and food challenges can change histamine levels. The significances of a prick test with histamine (histamine prick test, HPT) relating to the interpretation of food challenges in AD were evaluated. A total of 467 AD patients participated in this study. Skin prick tests, identification of specific IgE and open food challenge were conducted for the identification of food allergy. Elimination diet was performed with HPT. HPTs were conducted before and after food challenges. The wheal sizes by HPT were significantly decreased after an elimination diet. The relative changes of wheal sizes significantly correlated with those of clinical severity scores in AD patients (p<0.001). The wheal sizes in HPT were increased with a positive provocation in open food challenges. In conclusion, HPT may be a simple and objective test to interprete the results of food challenges in patients with AD. The exact mechanisms of the changes in skin reactivity by HPT need further investigation.

Key Words : *Dermatitis, Atopic; Histamine; Skin Test; Hypersensitivity*

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INTRODUCTION

Dietary manipulation is important in the management of atopic dermatitis (AD) (1) despite the basal immune dysregulation in pathogenesis (2). The avoidance of incriminated foods has been the mainstay of therapy. Compared with inhalant allergen, food allergen is easy to avoid. To identify food allergy in AD, many methods have been tried including detecting allergen-specific IgE (3-5) by RAST, skin prick test (6), patch test (7), lymphocyte transformation by antigen-stimulation (8, 9), and fecal eosinophil cationic protein and tumor necrosis factor-alpha as non-invasive indicators of food allergy in children with atopic eczema such as intestinal inflammation (10). However, it is difficult to identify and confirm food allergy in AD with these methods. For the identification of food allergy in patients with AD, many trials have been performed such as the combined test of RAST as well as skin prick test (11, 12), and skin prick test with patch test (13). Eventually, food challenge was essential in confirming food allergy (11, 14). Several methods have been tried for food challenges such as double-blind placebo-controlled food challenge (DBPCFC) (15), open food challenge (16), and labial food challenge (17) in children with food allergies. DBPCFC is difficult to perform in practice.

It is not easy to determine a positive food challenge. There is no simple and objective test for the food challenge as yet. Serum tryptase and urinary 1-methylhistamine were studied as parameters for monitoring oral food challenges in children (18). Measurements of plasma histamine, urinary N-methylhistamine, and peripheral eosinophil counts were also used for the interpretation of food challenges in infants and children with AD (19). In both reports, histamine levels were changed by food challenges.

Histamine is an essential mediator for an allergic reaction and is involved in the pathogenesis of allergic diseases including AD (20). Allergens penetrate through the skin by prick test and induce histamine release (21). Histamine, which mediates the whealing response through vasodilation and an increase of vascular permeability, is used as a positive control in allergen skin prick tests (22). Food challenges increase production, and enhance the plasma level of histamine. However, there has not been a detail report concerning the change of skin reactivity to histamine. The changes in skin reactivity to a prick test with histamine (histamine prick test, HPT) by elimination diet and by food challenge were investigated. Through these studies, we evaluated the possibility of

using HPT as a simple and useful method to predict the results of a food challenge.

MATERIAL AND METHODS

Study population and design

A total of 467 AD patients who visited the Allergy and Atopic Dermatitis Clinic of Samsung Cheil Hospital from May 1, 1997 to October 31, 1998 and Seoul Allergy Clinic from Jan 1, 2000 to July 30, 2000 participated in this study. They fulfilled the criteria of Hanifin and Rajzka (23). All the participants in this study had been suffering from AD for more than six months. A detailed history was obtained with special attention to food intake and possibly related AD exacerbations. The eventual positive history for aggravation of the disease by food was not considered in the selection of patients during open food challenge test. Any medication including systemic steroids and antihistamines were tapered and were withheld for at least 1 month before participating in this study. Topical steroid application (hydrocortisone 1%, Lacticare, Stiffel, Coral Gables, FL, U.S.A.) was permitted, except for the volar areas of both forearms to be tested. No patient had a convincing history of any major anaphylactic or anaphylactoid reaction.

Elimination diet was performed as described below. In the first step, the changes in skin reactivity to HPT were investigated according to the clinical changes following elimination diet in AD patients. The correlation between elimination diet and the changes in skin reactivity to HPT was evaluated. In the second step, open food challenge was performed by the indications described below in AD patients. HPT was performed to predict the result of the open food challenge.

MAST and FAST for specific IgE

All patients were tested by mutiple allergo-sorbent-test (MAST) and fluorescent allergo-sorbent-test (FAST) to identify the specific IgE for food allergens. The allergens which were not prepared by MAST were tested by FAST. The MAST assay was done according to the manufacturer's instructions (24). The MAST test chamber contained 35 threads coated with foods and inhaled allergens (baker's yeast, barley, beef, cheddar cheese, chicken, codfish, corn, garlic, onion mix, peanut, pork, rice, salmon, tuna, wheat, birch/alder, white oak, rye, mugwort, short ragweed, cat, cockroach mix, dog, house dust, *D. farinae*, *D. pteronysinussus*, cow's milk, crab, egg white, peach, shrimp, soybean, alternaria, *Aspergillus*, *Cladosporium*). FAST (BioWhittaker, Inc., Walkersville, MD, U.S.A.) was performed for specific IgE for rye, oatmeal, buckwheat, navy bean, lentil, chickpea, peas, chestnut, almond, walnut, hazelnut, egg yolk, parsley, celery, cabbage, spinach, potato, carrot, strawberry, banana, orange, kiwi, pear, tomato, grape, lemon, mango, pineapple, apple, chocolate, yeast, pepper, gluten, α lactalbumin, β lactalbumin, casein, and cocoa. The test was performed by the manufacturer's instructions (25).

Past history and skin prick test

Complete history takings were performed in all patients focusing on histories related to food ingestion, itching, skin rash, urticaria, and gastrointestinal symptoms. Skin prick tests were done on the back with commercially available allergens (Torii Pharm. Co., Ltd., Tokyo, Japan; Bencard, Brentford, England) (soybean, peach, almond, malt, hazelnut, parsley, pork, tomato, barley, clam, salmon, shrimp, tuna, chicken, beef, mushroom, sesame seeds, mackerel, celery, lettuce, baker's yeast, cheese, chocolate, egg, milk, rye grain, wheat grain, cod, lobster, mixed nuts, walnut, mixed flour, rice grain, mixed beans, plain flour, peas, potato, mutton lamb, apple, banana, orange, strawberry, grape, lemon, onion, cabbage, spinach, carrot, herring, sardine, plaice, crab, mussel, tea, oyster, coffee). A 1-mm single-peak lancet with shoulder (Allergopharma Joachim Ganzer KG, Hamburg, German) was used to prevent deeper penetration. Histamine hydrochloride 1 mg/mL (Bencard, l Brentford, England) was used as a positive control. Pricking with the vehicles (physiologic saline and distilled water) was used as a negative control. Reactions were read after 15 min and classified as negative (0: no reaction, 1+: reaction greater than control but smaller than half the size of histamine) or positive. Positive reactions were graded as follows: 2+: half, 3+: equal to, and 4+: twice the size of histamine. The minimum size of positive reaction was 3 mm.

Histamine prick test

HPT was performed on the volar aspects of the left forearms. Absolute wheal sizes were measured. Appearance of a pseudopod was regarded as absolutely positive.

One drop of histamine solution was quantified 92 times. The weight of each drop was measured. Each volume was calibrated by measuring the weights of 5 μL, 10 μL, and 30 μL of histamine solution. To clarify the quantitative effects of test reagent, 5, 10 and 30 μL of reagents such as histamine, normal saline and distilled water were introduced in HPT.

HPTs were conducted by two experts simultaneously on the volar aspects of both forearms to exclude bias by

different examiners and the different sites of examination. HPT and skin prick tests for allergens were interpreted three times at 15 min, 30 min, and 60 min to decide the most appropriate time for interpretation. As a result, 15 min was revealed to be optimal.

Clinical severity scoring and determination of the clinical results by open challenge test

Grading the clinical severity of AD was assessed by the scoring system of Hanifin and Rajka as described previously (23). The total clinical severity score (range from 0 to 15) was defined as the sum of individual scores, graded as 0 (none), 1 (mild), 2 (moderate), and 3 (severe) for each of five parameters: pruritus, erythema, edema/papulation, excoriation, and scaling/dryness. Food challenges were interpreted as positive with the new development or aggravation of itching, erythema, papulation, scaly change, excoriation which raised the severity score. The dietitian instructed patients on what or what not to eat.

Elimination diet and replacement diet

Elimination diet was performed as follows. At the beginning of the study, complete diet history, prick test, and determination of specific IgE were performed on suspected incriminated food allergens. All foods which showed positive results by skin prick test, by identification of the specific IgE, or by relation with obvious adverse reaction in past history were eliminated from every diet for two weeks during the first step. Elimination diet was guided by supplying a comparable replacement diet to substitute for the nutritional constitution of eliminated food considering a nutritional balance. A dietary diary was kept by all patients and examined by a special dietitian, allergy nurse, and physician on every visit. By this process, the incriminated foods were avoided and inadvertent exposures were prevented.

Open food challenge test

An initial open food challenge was performed on patients who fulfilled the following conditions: 1) Obvious clinical improvement was obtained by elimination diet for more than 2 weeks; 2) Patient's clinical status was stable for at least 2 weeks; and 3) Foods being tested had been eliminated during the past 2 weeks. These were monitored completely through the analysis of a dietary diary by a physician and a special dietitian.

Open food challenges were conducted in two steps. HPT were conducted just prior to the food challenge. Foods were challenged by adequate preparation in gradually increasing amount daily as 1/4, 1/4, 1/2, 1/2, 1, 1, and 1.5 portion size (1 portion size, an amount of food served for one person) for seven days. The clinical severity score and the result of food challenge were evaluated simultaneously with HPT three days after the food challenge. If the patient showed increased severity scores or obvious aggravation of clinical symptoms or signs, food challenges were regarded as positive and tests were discontinued. Otherwise, food challenges were continued with an increased amount of challenge food for another seven days. After the second challenge, a clinical result was evaluated simultaneously with HPT. If the patient showed a clinical aggravation during the test, the next challenge test was delayed until the severity scores returned to the pre-challenge levels, the clinical status was stabilized for more than a week, and the wheal size in HPT returned to the pre-challenge size. When the patients ate food to be eliminated during the study, the study was discontinued and the challenge tests were delayed for at least 1 week.

Statistical analysis

The data were shown as mean±standard deviation, range, and median. The sensitivity, specificity, positive predictive value and negative predictive value were calculated. To evaluate the significance of the test results, statistical analysis was performed. The correlation, linear regression, χ^2 test and paired t-test were used in this study. Differences associated with a p value less than 0.05 were considered significant. Correlation coefficients and statistical significance were determined by SPSS.

RESULTS

Histamine prick test (HPT)

One drop of histamine ranged from 5.4 to 29.1 μL (mean±SD, 9.9 μL±6.0 μL). To remove the quantitative bias of applied histamine solution in HPT, the skin reactivities to 5, 10, and 30 μL of histamine were tested in 67 AD patients (m:f, 46:21; age, 13.7±9.2 yr). The wheal sizes were 5.4±1.2 mm (median 5, ranged from 3 to 12) to histamine, 1.2±0.4 mm to normal saline and 1.0±0.2 to distilled water. The mean wheal sizes to 5, 10, and 30 μL of histamine were all the same, 5.4±1.2, and there were no statistical differences among the wheal sizes to three different volumes of histamine ($p>0.05$). There were no differences among the wheal sizes to normal saline and distilled water.

The skin reactivities to histamine were examined at 15 min, 30 min, and 60 min in 64 AD patients (m:f, 38:26;

age 13.7±7.98 yr). Maximal wheal sizes to histamine were obtained at 15 min in 32 subjects (50%) (7.1±2.8 mm) and at 30 min in 32 subjects (50%) (8.0±3.0 mm). Two subjects who showed the maximal wheal size at 30 min showed increased wheal sizes at 60 min (8.0±3.0). The mean wheal sizes were significantly increased at 30 min compared to those at 15 min ($p<0.001$), while those at 30 min were unchanged at 60 min ($p>0.1$). The wheal sizes ranged from 3 to 23 mm throughout this study. In the test of normal saline, maximal wheal sizes were obtained at 15 min in 50 subjects (87.1%) (3.5±1.7 mm). Fourteen subjects (22.9%) showed maximal wheal sizes at 30 min (3.8±1.8 mm). The mean wheal sizes were increased at 30 min compared to those at 15 min ($p=0.01$), while those at 30 min were unchanged at 60 min. For distilled water, skin prick tests showed maximal wheal sizes at 15 min in 62 subjects (96.9%) (1.0±1.2 mm) and two subjects (3.1%) showed maximal wheal sizes at 30 min (1.0±1.3 mm) ($p=0.182$). Those at 30 min were unchanged at 60 min ($p>0.1$). On the basis of these results, HPT were interpreted at 15 min in this study.

Two expert practitioners conducted HPT simultaneously in each patient on both volar aspect of left forearm. A total of 112 patients was enrolled in these examinations (male:female, 63:49; age, 15.8±12.7 yr). Mean differences of the wheal sizes to histamine were 0.0±0.2 mm ($p>0.05$) between left and right arms and 0.6±0.2 mm ($p>0.05$) between two observer. Consequently, there were no significant differences in wheal sizes measured by two practitioners or on different sites. There was no difference also among wheal sizes to normal saline and distilled water (data not shown).

Changes in skin reactivity changes to HPT in AD by elimination diet

Elimination diet was performed in 79 AD patients (m:f, 53:26; age, 11.7±8.9 yr) (Table 1). Sixty-four patients (81.0%) showed improvements with reduced wheal size 2.2±2.1 mm (food-responsive AD) (Fig. 1). Ten patients (12.7%) showed no significant changes with wheal size decrements by 1.2±2.0 mm. Five patients (6.3%) showed aggravation during an elimination diet with wheal size increments by 1.0±1.1 mm. Among 64 patients with improvements, 40 patients (50.6%) showed obvious clinical improvements by more than 20%, including 13 patients (16.5%) with a clinical remission. AD patients with improvements showed adverse reactions such as pruritus, scaly changes or papular eruption by open challenge test. A portion of AD patients was not controlled despite proper elimination diets.

The absolute wheal sizes to histamine in HPT were

Table 1. Clinical responses to elimination diet

Clinical response	Number
Response	64 (81%)
Complete remission*	13 (16.5%)
Improvement 20%>	27 (34.1%)
Improvement 20%<	24 (30.4%)
No response	10 (12.7%)
Aggravation	5 (6.3%)

*Complete remission: symptom-free state at the end point of elimination diet

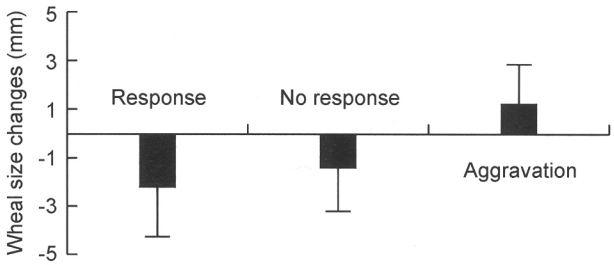

Fig. 1. The wheal size changes to histamine by elimination diet in atopic dermatitis. Response, patients who were improved by elimination diet; No response, patients who showed no clinical change by elimination diet; Aggravation, patients who were aggravation during elimination diet.

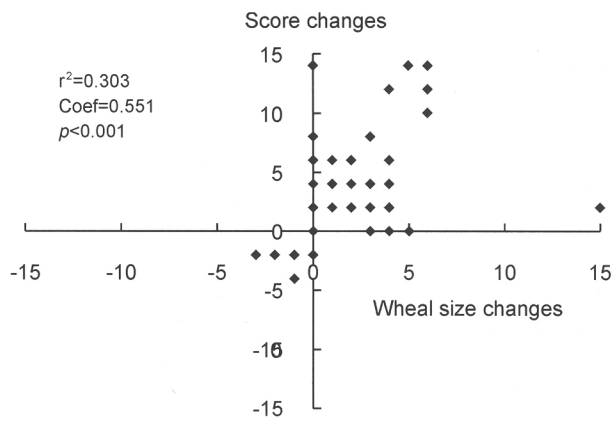

Fig. 2. The correlation between the changes of clinical severity scores and those of wheal sizes in histamine prick tests.

not correlated with the clinical severity scores in this study ($p=0.11$, Coef=0.133, $r^2=0.178$). However, the changes of wheal sizes were significantly correlated with the changes in clinical severity scores in AD patients ($p<0.001$, Coef 0.551, $r^2=0.303$) (Fig. 2).

Skin prick test results

The most frequent positive foods by skin prick test were tuna (68.3%), wheat (67.9%), shrimp (56.7%),

Table 2. Results of food open challenge test

Food	Total	Positive	Negative
Chicken	54	30 (55.6%)	24
Milk	43	25 (58.1%)	18
Pork	42	17 (40.5%)	25
Egg	38	19 (50%)	19
Wheat	18	7 (28.9%)	11
Beef	11	6 (54.5%)	5
Soybean	7	3 (42.9%)	4
Onion	2	0 (0%)	2
Sesame	2	0 (0%)	2
Potato	1	1 (100%)	0
Mackerel	1	1 (100%)	0
Herring	1	0 (0%)	1
Plaice	1	1 (100%)	0

mushroom (55.7%), milk (53.6%), lobster (52.3%), clam (51.5%), and beef (50.0%). By the identification of specific IgE, the most common allergenic foods were milk (29.4%), eggs (26.7%), soybean (22.7%), beef (19.1%), pork (18.7%), crab (16.2%), chicken (14.7%), shrimp (13.0%), and wheat (11.8%).

HPT in open food challenge test

HPTs were performed before and after open food challenge in 145 AD patients (m:f, 79:66; age 16.3± 15.5 yr). The results of open food challenges were interpreted by clinical changes as described above. By open food challenge, 110 (49.8%) of 221 tests showed positive results. Among the positive reactions, 62.7% of the tests showed obvious clinical symptoms and signs within 3 days while the remaining 37.3% between the 3rd and the 10th day. The food challenge results are described in Table 2.

Table 3. Statistical significance of wheal size change (positive cases/negative cases by open challenge test = 99/122)

Increment	1 mm	2 mm	3 mm
Positive cases/Negative cases	94/127	26/195	11/210
Sensitivity	95%	26.3%	11.1%
Specificity	100%	100%	100%
Positive predictive value	100%	100%	100%
Negative predictive value	96.1%	65.1%	60.7%
χ^2	201	25	0.916
p	<0.001	<0.001	0.025

The statistical significances of wheal size increment of 1 mm, 2 mm, and 3 mm were evaluated (Table 3). The 1-mm increment of wheal size was the most appropriate in determining the results of the food challenge. Typical changes in skin reactivity and open food challenge results are described in Fig. 3.

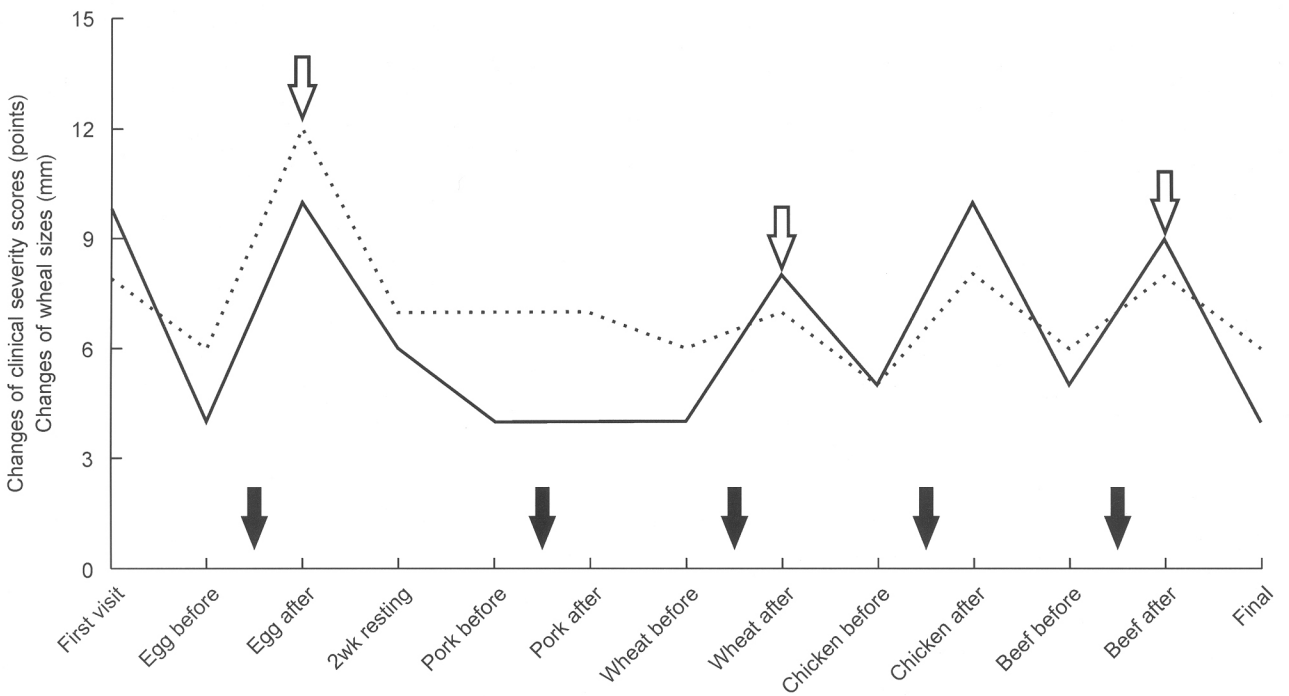

Fig. 3. A typical case which showed changes in the clinical severity simultaneously with those in the wheal size to histamine prick test by open food challenges. The solid line indicates clinical severity scores and the dotted line indicates the wheal sizes in histamine prick tests. Open arrows indicate pseudopod-positive cases with wheal by HPT and closed arrows indicate open food challenge tests.

DISCUSSION

The wheal sizes in HPT diminished simultaneously with clinical improvements by elimination diet in AD (Fig. 1). Technical bias for HPT was adequately controlled. The absolute wheal sizes had no significance related to the absolute clinical severities of AD. The changes of wheal size in HPT were reflective of the changes of clinical status (Fig. 2). These relative changes of skin reactivity to histamine was potentially useful as a supportive test to interpret the result of food challenge despite the individual differences of reactivity to histamine due to age, sex or other conditions. The skin reactivity to HPT was accentuated by a positive food challenge in this study. There have been several trials for the objective interpretation of the result of food challenges by laboratory methods. The histamine or related materials such as urinary 1-methylhistamine were measured after food challenges (18, 19). However, there has not yet been a report concerning the changes in skin reactivity to histamine by provocation with food allergen.

Most patients showed natural improvements after discontinuing the food challenge with continued elimination diet. Three patients showed respiratory symptoms (e.g., wheezing, rhinorrhea, sneezing, cough without upper respiratory infection) with skin manifestations, which were reconfirmed by repeated challenge tests. There were several reports that food allergens might be the causative factors for respiratory, skin, and gastrointestinal allergy confirmed by skin prick test and specific IgE and IgG4 FAST in children (26).

The characteristics of HPT as a test for the interpretation of a positive food challenge was specified as described in Table 3. The 1-mm increment of wheal size was an optimal value for the determination of food challenge in this study (Table 3). Although this change of 1 mm may be an error which occurred possibly during the examination process, it could also be a significant change as the HPT was performed by the same experienced examiner.

The changes in skin reactivity to histamine by positive food challenge mean the change of susceptibility to histamine after food allergy provocation in AD. Food challenge induces histamine release and increases plasma histamine concentrations in AD (27). The exact mechanisms for the changes in skin reactivity to histamine by food challenge need further investigation.

Histamine is used as a positive control in skin prick testing. The skin prick test is interpreted by comparing the wheal size to allergen with that to histamine. The result is used to determine the allergen concentration for the treatment of allergies such as hyposensitization. However, there was possible change in the wheal sizes to histamine by food allergy provocation in this study and it might be reconsidered to compare the wheal size to allergen with it to histamine.

Conclusively, the skin reactions were accentuated by positive food challenges in AD. HPT may be a simple and objective test for the interpretation of food challenge in food-responsive AD. The provocation of food allergy might be an important factor in affecting skin test results with histamine. The exact mechanisms of the changes in skin reactions by food challenge need further investigation.

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