

support the preventive effect of SLIT on asthma because we did not find any difference in the respiratory function (forced expiratory volume in 1 second) between the 2 groups.

In the former study, 6 patients in the active group and 5 patients in the placebo group were polysensitized, whereas all the others were monosensitized to *Parietaria* pollen. During the follow-up, monosensitized patients developed new sensitizations in both the SLIT and placebo groups, suggesting that SLIT for 2 years is ineffective in preventing new sensitizations.

Taken together, our data indicate that high-dose SLIT for 2 years is not sufficient to modify significantly the natural history of respiratory allergy to *Parietaria* pollen. When our first study was conducted from 1995 to 1997, the knowledge of the effects of SLIT was rather limited, and in particular it was not yet clarified that 3 to 5 years may represent an optimal duration.^{1,8} Furthermore, we can speculate that the prolonged exposure to *Parietaria* pollen (almost perennial in southern Italy) may lead to a greater degree of airway inflammation, which is likely to be associated with asthma onset. The data from our retrospective study indicate the need to perform new studies on SLIT in a larger number of patients with allergic rhinitis associated with *Parietaria* sensitization.

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METABOLIC PROFILE OF PLASMA FREE FATTY ACIDS IN PATIENTS WITH ASPIRIN-INTOLERANT URTICARIA

Acetylsalicylic acid (aspirin) and nonsteroidal anti-inflammatory drugs may act as an aggravating factor or augment urticaria after intake with a specific food.^{1–3} We speculated that aspirin-intolerant urticaria (AIU) may be related to altered fatty acid (FA) composition and investigated plasma FA composition during aspirin provocation.⁴

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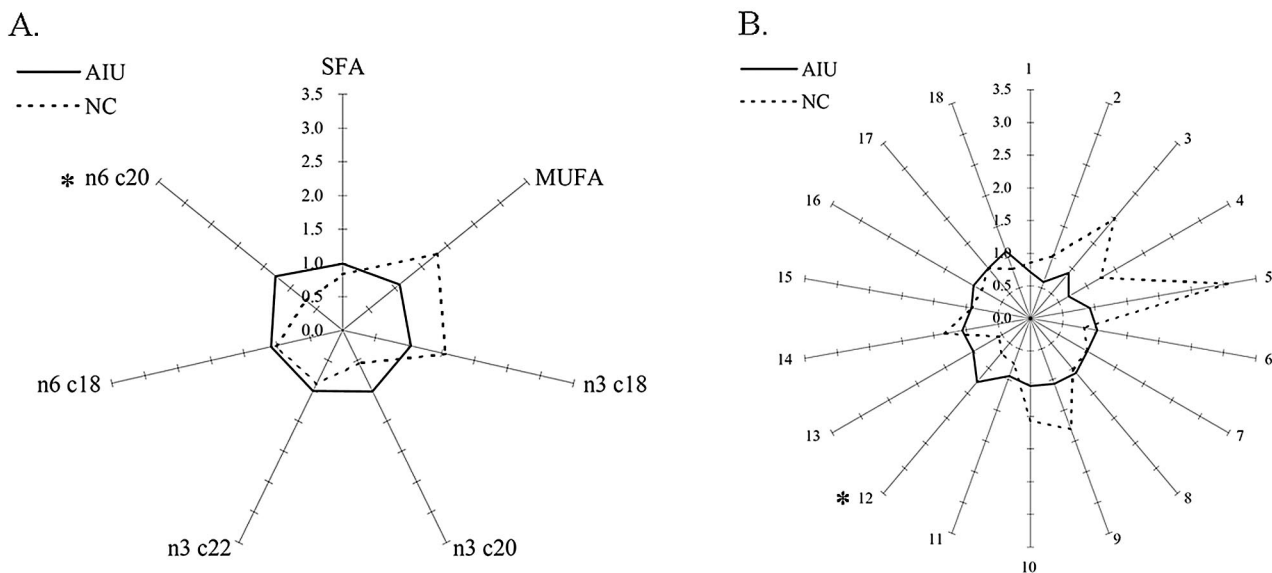


Figure 1. Aspirin-intolerant urticaria (AIU) and control (NC) groups based on the induction folds of the 18 fatty acid composition after normalization to the corresponding basal composition. A, Induction folds of saturated fatty acid (SFA), monounsaturated fatty acid (MUFA), and polyunsaturated fatty acid after aspirin provocation. B, Induction folds of free fatty acids after aspirin provocation. 1 indicates capric acid; 2, lauric acid; 3, myristoleic acid; 4, myristic acid; 5, palmitoleic acid; 6, palmitic acid; 7, γ -linolenic acid; 8, linoleic acid; 9, oleic acid; 10, α -linolenic acid; 11, stearic acid; 12, arachidonic acid; 13, eicosapentaenoic acid; 14, eicosanoic acid; 15, docosahexaenoic acid; 16, docosapentaenoic acid; 17, erucic acid; and 18, nervonic acid. * $P = .034$. Group comparison of fatty acid composition was performed with the Mann-Whitney test.

Patients with AIU, who ranged in age from 13 to 64 years (7 males and 2 females), were recruited from Ajou University Hospital in Suwon, Korea. Healthy controls (4 males and 5 females) of the same age range were recruited from volunteers. All study participants gave informed consent, and the protocol was approved by the institutional review board of Ajou University Hospital. The use of all medications, including antihistamines, was stopped 3 days before the procedure. After the placebo challenge, 500 mg of aspirin (KunWha Pharmaceutical Co, Seoul, Korea) in tablet form was administered orally, and cutaneous symptoms were observed for 4 hours with close monitoring. Venous blood was collected at 2 different times: basal status before aspirin provocation and symptom provocation status after aspirin provocation. Plasma free FAs were converted into their tert-butyldimethylsilyl derivatives according to our previous described method,⁵ and tert-butyldimethylsilyl derivatives were analyzed by gas chromatography-mass spectrometry (Agilent Technologies, Atlanta, Georgia) in selected ion monitoring mode. The FA values as a percentage of composition (mean [SD]) were calculated as follows: (each FA peak area ratio to internal standard) $\times$ 100/(total FA peak area ratio to internal standard).

The serum FA compositions for the AIU and control groups are given in Table 1. The data were normalized to the composition value of basal status before aspirin provocation and presented as the induction fold. To determine how FA changed during aspirin provocation, we

used star and symbol plotting considering the induction fold of FA after aspirin provocation for the AIU and control groups (Fig 1). The FA profiles of the AIU group showed patterns that differed from those of the control group (Fig 1A). The percentage of n-6 polyunsaturated FAs (C20) was significantly induced after aspirin provocation in the AIU group but was slightly reduced in the control group (Fig 1A; $P = .04$). The percentages of saturated FA and monounsaturated FA were induced after aspirin provocation in the control group but were unchanged in the AIU group. After aspirin provocation, the induction fold of arachidonic acid in the AIU group was significantly different from that in the control group (Fig 1B).

In the process of aspirin provocation, the percentage of arachidonic acid (C20:4) increased, and the induction fold in the AIU group showed significant variation from that in the control group. This means that the conversion of linoleic acid into arachidonic acid may be enhanced in urticaria with the intake of aspirin, especially in patients with AIU. This may be explained by the association between the provocation of cutaneous symptoms by aspirin in the AIU group and highly induced levels of arachidonic acid (C20:4), but not linoleic acid, in this study. It has been reported that plasma arachidonic acid levels are not correlated with dietary linoleic acid,⁶ so a dietary effect on altered arachidonic acid levels in patients with AIU during aspirin provocation is unlikely.

Table 1. Plasma Fatty Acid Composition of Patients With AIU and Controls (on Basal Status and Provocation Status)^a

Fatty acid	AIU patients			Controls			AIU patients vs controls <i>P</i> value ^c
	Basal status	Provocation	Induction fold ^b	Basal status	Provocation	Induction fold ^b	
SFA	68.401 (11.001)	67.998 (6.371)	1.0	71.746 (2.888)	62.473 (11.225)	0.8	.10
Capric acid (C10:0)	0.25 (0.208)	0.228 (0.159)	0.7	0.412 (0.319)	0.319 (0.231)	0.8	.90
Lauric acid (C12:0)	1.93 (1.106)	1.325 (0.878)	0.6	2.001 (1.427)	1.702 (1.048)	1.0	.35
Myristic acid (C14:0)	1.277 (0.288)	0.954 (0.336)	0.7	1.162 (0.436)	1.28 (0.258)	1.2	.05
Palmitic acid (C16:0)	47.783 (6.983)	48.085 (5.231)	1.0	51.979 (2.645)	45.632 (8.639)	0.8	.09
Stearic acid (C18:0)	17.161 (4.834)	17.406 (2.059)	0.9	16.192 (2.002)	13.54 (3.39)	0.7	.07
MUFA	20.756 (8.996)	19.717 (5.469)	1.1	15.722 (2.944)	24.259 (10.215)	1.8	.20
Myristoleic acid (C14:1)	0.058 (0.039)	0.043 (0.018)	0.9	0.039 (0.029)	0.076 (0.051)	2.0	.17
Palmitoleic acid (C16:1)	1.395 (1.082)	0.986 (0.418)	0.9	0.618 (0.281)	1.634 (1.32)	3.1	.09
Oleic acid (C18:1)	19.187 (8.098)	18.579 (5.111)	1.1	14.971 (2.835)	22.438 (9.039)	1.8	.23
Eicosanoic acid (C20:1)	0.081 (0.028)	0.077 (0.016)	1.1	0.063 (0.02)	0.084 (0.034)	1.3	.23
Erucic acid (C22:1)	0.011 (0.007)	0.008 (0.002)	1.0	0.009 (0.002)	0.009 (0.003)	1.0	.83
Nervonic acid (C24:1)	0.023 (0.011)	0.023 (0.006)	1.1	0.021 (0.009)	0.019 (0.007)	0.8	.38
PUFA	10.843 (2.457)	12.284 (1.782)	1.2	12.532 (1.923)	13.267 (1.911)	1.1	>.99
Total n-6	10.459 (2.396)	11.969 (1.740)	1.2	12.208 (1.824)	12.925 (1.898)	1.1	>.99
γ -Linolenic acid (C18:3n6)	0.007 (0.003)	0.006 (0.002)	1.0	0.006 (0.002)	0.006 (0.002)	1.0	.44
Linoleic acid (C18:2n6)	10.378 (2.414)	11.873 (1.734)	1.1	12.112 (1.828)	12.847 (1.912)	1.0	.51
Arachidonic acid (C20:4n6)	0.073 (0.031)	0.089 (0.024)	1.3	0.091 (0.029)	0.072 (0.034)	0.7	.04
Total n-3	0.384 (0.099)	0.316 (0.945)	0.9	0.324 (0.123)	0.342 (0.079)	1.2	.11
α -Linolenic acid (C18:3n3)	0.246 (0.131)	0.181 (0.06)	1.0	0.135 (0.038)	0.198 (0.09)	1.6	.09
Eicosapentaenoic acid (C20:5n3)	0.112 (0.06)	0.114 (0.065)	1.0	0.171 (0.119)	0.127 (0.082)	0.5	.83
Docosahexaenoic acid (C22:6n3)	0.019 (0.014)	0.014 (0.003)	0.9	0.012 (0.002)	0.013 (0.005)	0.9	.66
Docosapentaenoic acid (C22:5n3)	0.007 (0.003)	0.006 (0.001)	1.0	0.005 (0.002)	0.004 (0.002)	0.9	.54
n-6/n-3 PUFA	28.105 (6.497)	40.818 (13.915)	1.6	42.418 (16.52)	39.704 (11.799)	1.0	.09

Abbreviations: AIU, aspirin-intolerant urticaria; MUFA, monounsaturated fatty acid; PUFA, polyunsaturated fatty acid; SFA, saturated fatty acid.

^a Data are presented as mean (SD) fatty acid values as percentage of composition by (each fatty acid peak area ratio to IS) $\times$ 100/(total fatty acid peak area ratio to IS).

^b The data were normalized to the composition value of basal status before aspirin provocation.

^c Difference of the fatty acid induction fold between the AIU and control groups was analyzed by the Mann-Whitney test.

Eicosanoids derived from arachidonic acid are important mediators of allergic inflammation. Furthermore, in the mechanisms of AIU, a shift of arachidonic acid metabolism in favor of leukotrienes by aspirin has been suggested.¹ Therefore, our results of altered arachidonic acid levels in patients with AIU during aspirin provocation may support previous findings of altered arachidonic acid metabolism in patients with AIU. Aspirin-induced arachidonic acid may affect the formation of leukotrienes because the formation of leukotrienes depends on the deacylation of arachidonic acid. A relationship between AIU and arachidonic acid is suggested in this study, but further investigation into the relationship between plasma FA composition and leukotriene production is needed. In conclusion, our results suggest that aspirin ingestion may affect a specific pathway in FA metabolism and that arachidonic acid levels may be related to aspirin intolerance in patients with AIU.

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UPPER RESPIRATORY TRACT INFECTIONS AND SUBLINGUAL IMMUNOTHERAPY: PRELIMINARY EVIDENCE

Allergic rhinitis (AR) is characterized by T_H2 polarization with consequent defective interferon γ (IFN- γ) production.¹ Because IFN- γ is recruited to fight infections, it has been suggested that allergic patients may be more susceptible to upper respiratory tract infections (URIs) than nonallergic individuals.² URIs are frequent in the general population and constitute a demanding challenge for physicians.³ Recently, it has been evidenced that allergic children have more numerous and severe respiratory infections than nonallergic children.⁴ It has also been confirmed that adult patients with AR have more numerous and prolonged URIs than nonallergic adults.⁵

AR management includes, when appropriate, allergen-specific immunotherapy.⁶ The sublingual immunotherapy (SLIT) rationale is based on evidence that oral administration of high-dose allergens reduces and prevents IgE responses, achieving clinical tolerance to

the causal allergen. SLIT induces the appearance of allergen-specific tolerance, associated with restored allergen-specific IFN- γ production.⁷ However, no studies have evaluated the possible effect of SLIT on URIs. Therefore, this preliminary study was designed to evaluate whether a 2-year preseasonal SLIT might affect the number and the duration of URIs in AR patients.

Forty consecutive monosensitized patients (18 men and 22 women; mean age, 36.6 years) with AR due to pollen allergy were treated with SLIT. Forty consecutive well-matched patients (19 men and 21 women; mean age, 36.1 years) with pollen AR (16 of them were allergic only to *Betula alba*, 16 only to *Parietaria judaica*, and 8 only to Gramineae) were included in the study as controls because they refused SLIT. AR was diagnosed according to validated criteria provided by international guidelines.^{2,8} In addition, 40 healthy individuals (25 men and 15 women; mean age, 35.2 years; all of whom were US Navy soldiers) were enrolled as controls on the basis of a history negative for AR, clinical examination, nasal endoscopy, and skin prick test results.

This was a prospective, longitudinal, observational study conducted during a 3-year period. It was initiated after obtaining approval from the local ethics committee and written informed consent from all participants. SLIT-treated patients were evaluated the year before SLIT and during the 2-year preseasonal SLIT. All study participants, both allergic patients and healthy controls, were visited every 6 months for 3 years during the same period. In addition, a diary card was provided to each participant. At each visit, study participants had to report respiratory symptoms on a weekly basis.

Participants undergoing SLIT received either a *B alba* pollen allergen extract (Anallergo, Florence, Italy; 17 cases, cumulative dose was 60 μ g), *P judaica* (15 cases, cumulative dose was 24 μ g), or a mix of 3 Gramineae (7 cases, cumulative dose was 24 μ g) for at least 3 months before the 2 pollen seasons, as preseasonal immunotherapy, for 2 consecutive years. The dose during the maintenance phase was 5 drops 3 times per week. The diagnosis of URI was made according to previously validated studies.^{4,5} The primary end point was the comparison of the number of URI episodes recorded per year among groups during the study period. The secondary outcome was the comparison of the total duration of URI episodes (days per year).

Only SLIT-treated allergic patients had a significant reduction in incidence rate (IR) during the 3-year period ($P < .001$, Friedman test), whereas both untreated allergic patients and healthy controls did not show significant IR variation ($P = .60$ and $P = .90$, respectively) as reported in Figure 1A. With the group of untreated allergic patients as a reference, the IR for the treated group was 0.98 (95% confidence interval [CI], 0.73 to 1.33; $P = .94$) during the year before treatment, 0.81 (95% CI, 0.60 to 1.11; $P = .18$) during the first year of treatment, and 0.66 (95% CI, 0.47 to 0.90; $P = .01$) during the second year; this result indicates a significant decrease in the URI episode rate after 2 years of treatment.

Also regarding the mean duration of URI episodes, only SLIT-treated allergic patients had a significant reduction in IR during the 3-year period ($P < .001$, Friedman test), whereas no heterogeneities were found in the other 2 groups of patients ($P = .50$ and $P = .60$, respectively, Fig 1B). SLIT-treated patients had a mean difference in duration of -0.1 day compared with untreated patients during the year preceding treatment (95% CI, -2.1 to 1.92 ; $P = .92$), -3.5 days during the first year (95% CI, -5.1 to -1.7 ; $P < .001$), and -5.7 (95% CI, -7.1 to -4.2 ; $P < .001$) during the second year.

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