

Table 1. Studies Included in the Meta-analysis

	Yusuf et al, ² 2008	Malde et al, ⁵ 2007	Cicardi et al, ³ 2004	Granger et al, ⁴ 2003
Study design	Multicenter RCT	Single center Retrospective cohort	Single center Retrospective cohort	Multicenter RCT
Sex, M/F, %	57/43	40/60	59.4/40.6	68.2/31.8
Race, white/black, %	NR/NR	23/69	NR/NR	88.4/2.8
Follow-up, mean or median, mo	56	16.2	11	33.7
Patients in study, total No.	2,954	64	64	1,013
Patients with previous angioedema due to ACE-I switched to ARB, No.	38	6	26	39
Patients switched to ARB who developed angioedema, No.	0	0	5	3
Patients switched with angioedema confirmed due to ARB, No.	0	0	2	1

Abbreviations: ACE-I, angiotensin-converting enzyme inhibitor; ARB, angiotensin receptor blocker; NR, not reported; RCT, randomized controlled trial.

information to counsel their patients with a history of angioedema due to an ACE-I use if they have an indication for ARB use.

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LACK OF ASSOCIATION OF ALOX12 AND ALOX15 POLYMORPHISMS WITH ASPIRIN-EXACERBATED RESPIRATORY DISEASE IN KOREAN PATIENTS

The identification of genetic factors that confer susceptibility to the development of aspirin-exacerbated respiratory disease (AERD)

may contribute to our understanding of the disease. Aspirin-induced bronchoconstriction is thought to be caused by a shift in the arachidonic acid metabolism away from the cyclooxygenase (COX) pathway toward the lipoxygenase (LO) pathways, which include 5-LO, 12-LO, and 15-LO.¹ Previously, we suggested that arachidonate 5-LO (ALOX5 or 5-LO) genetic polymorphisms are associated with the phenotype of AERD.² This is the first study, to our knowledge, to investigate the genetic effects of ALOX12 (12-LO) and ALOX15 (15-LO) in patients with AERD.

A total of 139 patients with AERD and 176 with aspirin-tolerant asthma (ATA) were enrolled from Ajou University Hospital, Suwon, Korea; all the patients provided informed consent, and the protocol was approved by the ethics committee of Ajou University Hospital. The diagnosis of AERD was based on a positive response to lysine-aspirin bronchoprovocation tests with increasing doses of acetylsalicylic acid (75–300 mg/mL) (Altharyl; Arthromedica, Ilyang, Seoul, Korea), whereas negative responders were classified as having ATA.³ A total of 168 controls were randomly selected from the pool of healthy volunteers who come to the clinic without a known disease or who work at the clinic. Controls had no history of asthmatic symptoms, airway hyperresponsiveness to methacholine, or aspirin hyperresponsiveness. We used R.2.7.1 (<http://www.r-project.org/>) for random selection of participants. All the participants are of the same ethnic background.

Six genetic polymorphisms in the ALOX12 (–822 C > G, –540 G > A, –319 C > T, R261Q [G > A], and S322N [A > G]) and ALOX15 (–272 C > A) genes were genotyped by means of direct sequencing. Haplotype analysis of the genetic polymorphisms of ALOX12 was performed using Haploview 4.0 (<http://www.broad.mit.edu/mpg/haploview>).

Patients with AERD showed more severe asthmatic symptoms (a lower percentage of predicted forced expiratory volume in 1 second, a lower provocation concentration of methacholine that caused a decrease in forced expiratory volume in 1 second of 20%, a higher prevalence of rhinosinusitis, and nasal polyps, $P < .05$) compared with patients with ATA. The genetic polymorphisms of ALOX12 and ALOX15 were not significantly associated with the phenotype of AERD (Table 1), and, furthermore, there were no significant differences in the clinical variables according to the genetic polymorphisms with AERD (data not shown). Haplotype analysis of the ALOX12 genetic polymorphisms revealed that 3 single nucleotide

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Table 1. Distributions of Genotypes and Haplotypes of ALOX12 and ALOX15 in Korean Patients With AERD

		No. (%)			AERD vs ATA		AERD vs Controls	
		Patients with AERD (n = 139)	Patients with ATA (n = 176)	Controls (n = 168)	P value ^a	OR	P value ^a	OR
ALOX12								
-822 C > G	CC	29 (20.9)	37 (21.0)	29 (17.3)	.92	0.984	.80	0.943
	CG	71 (51.1)	92 (52.3)	88 (52.4)	.82	0.971	.74	0.943
	GG	39 (28.1)	47 (26.7)	51 (30.4)	.93	1.012	.97	0.993
	q.	0.536	0.528	0.565	.93	0.992	.81	0.974
-540 G > A	GG	103 (74.1)	119 (67.6)	126 (75.0)	.17	1.364	.75	0.905
	AG	33 (23.7)	51 (29)	38 (22.6)	.52	1.268	.35	0.653
	AA	3 (2.2)	6 (3.4)	4 (2.4)	.18	1.189	.97	0.994
	q.	0.140	0.179	0.137	.17	1.171	.75	0.950
-319 C > T	CC	51 (36.7)	76 (43.2)	52 (31.0)	.16	0.787	.40	0.825
	CT	65 (46.8)	78 (44.3)	92 (54.8)	.2	0.831	.16	0.745
	TT	23 (16.5)	22 (12.5)	24 (14.3)	.23	0.866	.91	0.981
	q.	0.399	0.347	0.417	.15	0.885	.41	0.910
R261Q (G > A)	GG	40 (28.8)	47 (26.7)	47 (28.0)	.98	1.005	.63	1.124
	AG	70 (50.4)	95 (54.0)	95 (56.5)	.76	0.957	.69	0.916
	AA	29 (20.9)	34 (19.3)	26 (15.5)	.75	1.042	.31	1.196
	q.	0.460	0.463	0.438	.98	1.002	.65	1.052
S322N (A > G)	AA	42 (30.2)	47 (26.7)	48 (28.6)	.88	1.025	.64	1.120
	AG	67 (48.2)	95 (54)	95 (56.5)	.68	0.942	.44	0.846
	GG	30 (21.6)	34 (19.3)	25 (14.9)	.55	1.080	.20	1.250
	q.	0.457	0.463	0.432	.89	1.012	.65	1.052
ht1: CGCag	+/+	25 (18.0)	30 (17.0)	25 (14.9)	.70	0.937	.40	0.818
	+/-	68 (48.9)	95 (54.0)	92 (54.8)	.45	0.909	.20	0.805
	-/-	46 (33.1)	51 (29.0)	51 (30.4)	.82	1.037	.87	1.037
	+	0.424	0.440	0.423	.71	0.970	.43	0.913
ht2: gGtga	+/+	19 (13.7)	22 (12.5)	23 (13.7)	.44	1.139	.79	1.064
	+/-	63 (45.3)	73 (41.5)	90 (53.6)	.42	1.099	.81	0.961
	-/-	57 (41.0)	81 (46.0)	55 (32.7)	.69	1.072	.40	1.202
	+	0.363	0.332	0.405	.43	1.071	.79	1.031
ht3: gaCGA	+/+	2 (1.4)	6 (3.4)	4 (2.4)	.06	0.639	>.99	1.000
	+/-	31 (22.3)	51 (29.0)	37 (22.0)	.08	0.789	.93	0.985
	-/-	106 (76.3)	119 (67.6)	127 (75.6)	.29	0.637	.78	1.167
	+	0.126	0.179	0.134	.06	0.798	>.99	1.000
ALOX15								
-272 C > A	CC	106 (76.3)	122 (69.3)	117 (69.6)	.36	1.253	.58	1.185
	AC	30 (21.6)	53 (30.1)	48 (28.6)	.19	0.459	.52	0.711
	AA	3 (2.2)	1 (0.6)	3 (1.8)	.18	1.193	.40	1.157
	q.	0.129	0.156	0.161	.38	1.110	.58	1.086

Abbreviations: AERD, aspirin-exacerbated respiratory disease; ATA, aspirin-tolerant asthma; OR, odds ratio; q., minor allele frequency.

^a Results of logistic regression with sex, age, and atopy.

polymorphisms in the promoter region (-822 C > G, -540 G > A, and -319 C > T) and 2 in the coding region (R261Q [G > A] and S322N [A > G]) showed strong linkage disequilibrium ($D' = 1$ and limit of detection ≥ 2) with each other, although the r^2 value was relatively low ($0.1 < r^2 < 0.96$). Three haplotypes derived from 5 genetic polymorphisms (Ht1: CGCag, Ht2: gGtga, and Ht3: gaCGA [lowercase letters indicate rare genotypes]) were not found to be significantly associated with the phenotype of AERD ($P > .05$) (Table 1).

Platelet-type 12-LO catalyzes the transformation of arachidonic acid into 12-hydroperoxyeicosatetraenoic acid (12-HETE), which is reduced by different mechanisms to 12(S)-HETE.⁴ The oxidation of arachidonic acid by leukocyte-type 15-LO leads to 15-HETE, which

activates peroxisome proliferator-activated receptor γ and suppresses leukotriene B₄-induced neutrophil chemotaxis.⁵

Kowalski et al⁶ reported that peripheral blood leukocytes from patients with AERD exposed to aspirin produce more 15(S)-HETE than do those from patients with ATA, and Heydeck et al⁷ showed that T_H2-derived cytokines upregulate murine macrophage 12-LO expression in vivo and in vitro. 12-HETE has been shown to induce COX-2 expression in pancreatic β cells.⁸ Therefore, it was speculated that increased expression of 12-LO may be partly responsible for increased COX-2 expression.

In this study, we did not find any association between AERD and genetic polymorphisms (ALOX12 to -822 C > G, -540 G > A,

–319 C > T, R261Q [C > G], and S322N [A > G] and ALOX15 to –272 C > A) or their haplotypes (Ht1: CGCag, Ht2: gGTga, and Ht3: gaCGA). These results suggested that the genetic effects of ALOX12 and ALOX15 for developing AERD may be minimal compared with those of ALOX5.

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INTENSE TACROLIMUS OINTMENT THERAPY IN CHILDREN WITH SERIOUS ATOPIC ECZEMA DERMATITIS SYNDROME

Atopic eczema dermatitis syndrome (AEDS)¹ can be considered a 2-faced disease characterized by the presence of early IgE-mediated and delayed T-lymphocyte-mediated allergy. Its pathogenesis is still not completely understood because many patients have an atopic profile with increased secretion of serum IgE and specific IgE sensitizations, but 10% to 30% of all patients have normal serum IgE levels and no specific IgE sensitization.² Topical tacrolimus ointment seems to be safe and effective,³ even in infants, and represents a widespread therapeutic approach for patients with AEDS because of its immunosuppressant action on T lymphocytes.

In this study, we evaluated the effect of intensive topical tacrolimus, 0.03% (Protopic; Astellas Pharma US Inc, Deerfield, Illinois), therapy on peripheral blood T-lymphocyte subsets in children with serious AEDS. All the patients were instructed to apply tacrolimus, 0.03%, ointment over affected skin areas according to the fingertip unit measure,⁴ approximately 12 hours apart, for 12 weeks (the total mean weighed quantity of applied ointment per patient was 193.5 g). Cleared areas were treated for an additional 7 days after clearance. The use of topical corticosteroids, nonsteroidal immunosuppressants, phototherapy, and topical antihistamines was stopped before the first application of tacrolimus and was not permitted in combination with tacrolimus during the study.

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Table 1. Immunologic, Hematologic, and Clinical Findings Across Time in Patients With AEDS

	Value, mean (SD)		P value ^a
	Baseline	End of treatment	
IgE total, U/mL	358 (488)	360 (482)	.98
IgG total, mg/dL	1,092 (168)	1,090 (189)	.97
IgG1, mg/dL	723 (144)	738 (139)	.73
IgG2, mg/dL	265 (143)	278 (165)	.78
IgG3, mg/dL	68 (38)	63 (31)	.64
IgG4, mg/dL	56 (50)	61 (63)	.77
IgM, mg/dL	110 (55)	112 (60)	.91
IgA, mg/dL	98 (45)	95 (43)	.82
RBCs, /mm	4,230,000 (630,000)	4,350,000 (570,000)	.52
Platelets, cell/mm	264,300 (82,440)	263,800 (76,120)	.98
Leukocytes, / μ L	8,760 (1,780)	8,543 (1,103)	.63
Neutrophils, / μ L	2,943 (1,126)	2,928 (1,500)	.97
Lymphocytes, / μ L	3,463 (1,089)	3,462 (1,052)	.99
Eosinophils, / μ L	423 (285)	429 (276)	.94
SCORAD score	37.2 (10.7)	10.3 (12.4)	<.001
SCORAD (atopic) score	36.59 (10.73)	9.5 (13.7)	<.001
SCORAD (nonatopic) score	36.52 (18.95)	10.3 (12.03)	<.006

Abbreviations: AEDS, atopic eczema dermatitis syndrome; RBC, red blood cell; SCORAD, SCORing Atopic Dermatitis.

^a Using the *t* test for paired data.

Data from patients with AEDS before and after 12 weeks of tacrolimus therapy are reported in Table 1. We found a significant improvement in mean (SD) SCORing Atopic Dermatitis scores (37.2 [10.7] vs 10.3 [12.4], $P < .001$), but total peripheral blood lymphocyte counts and serum IgG and serum IgG subclass values remained within the reference range after 12 weeks of therapy. When we compared SCORing Atopic Dermatitis scores between allergic and nonallergic patients, the change from before to after tacrolimus treatment was not statistically significant ($t = 0.136$, $P = .89$). We found no significant change in tested T-lymphocyte subsets in all patients with AEDS after the end of topical therapy (Table 2), and no difference was observed between the 2 subgroups. When we explored the distribution of T-lymphocyte subsets in allergic and nonallergic subgroups of patients with AEDS, we did not find significant modifications. As discussed previously herein for serum IgE levels, peripheral blood T-lymphocyte subsets also seem to have an unclear significance in AEDS. Some authors^{5,6} found an increase in CD4⁺ compared with CD8⁺ T cells, whereas others found a significant decrease in CD3⁺ and CD4⁺ T-lymphocyte levels.

We previously showed⁷ that untreated children with AEDS have decreased levels of CD8⁺ T cells, normal levels of CD3⁺ and CD4⁺ T cells, and a significantly higher CD4:CD8 ratio compared with healthy children in allergic and nonallergic subgroups. Until now, there have been no data on the effect of tacrolimus on peripheral blood T-lymphocyte subsets in children affected by serious AEDS, either allergic or nonallergic.

This study improves the understanding of the course of this disease in childhood, because we did not find any modifications in tested T-lymphocyte markers in patients with AEDS after 12 weeks of therapy. This result suggests that clinical improvement was ap-