



Figure 1. Urticarial lesions over areas of previous injection on buttocks after mecasermin injection.

reaction. The structure and activity of mecasermin are identical to endogenous IGF-1,⁷ which is homologous to insulin.⁸ IgE-mediated reactions to insulin have been well documented,⁹ making it likely that the reaction in this case is also IgE mediated. Although skin tests to mecasermin produced negative results, in the absence of a larger experience in skin testing with novel compounds, their validity in determining the mechanism of a reaction cannot be established. Local reactions to insulin may be due to an IgG-mediated event,¹⁰ which is also a plausible explanation in this case.

An IGF-1 deficiency registry shows that an additional 307 patients treated with mecasermin reported no skin or allergic reactions.¹¹ However, only approximately half of children currently treated with mecasermin are enrolled in this registry. Mecasermin is increasingly used for short stature patients with unclear forms of IGF-1 deficiency. Physicians must be aware of the potential for allergic reaction to mecasermin and caution patients appropriately.

KELLY ALLRED METZ, MD*

AMAL ASSA'AD, MD*

MICHELLE B. LIERL, MD*

PHILIPPE BACKELJAUW, MD†

*Division of Allergy and Immunology

†Division of Pediatric Endocrinology
Cincinnati Children's Hospital Medical Center
Cincinnati, Ohio
kelly.metz@cchmc.org

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USE OF ANGIOTENSIN RECEPTOR BLOCKERS AFTER ANGIOEDEMA WITH AN ANGIOTENSIN-CONVERTING ENZYME INHIBITOR

We recently published a meta-analysis¹ on the risk of angioedema associated with angiotensin receptor blocker (ARB) use in patients with previous angioedema from angiotensin-converting enzyme inhibitors (ACE-I). However, this study was limited by the few available trials. The recently published TRASCEND trial (Telmisartan Randomised AssessmeNt Study in ACE iNtolerant subjects with cardiovascular Disease)² would have qualified for our meta-analysis. Given these new data, we elected to update our meta-analysis to better define the risk.

We used the same search strategy as described previously¹ using the dates June 2007 to December 2008. The statistical analysis was the same, except that we added an additional step of calculating the odds ratio (OR) of ARB vs placebo using the Peto method because we now had 2 randomized controlled trials.

Of the 31 additional unique articles identified in this updated meta-analysis, only the TRASCEND trial,² which evaluated ACE-I-intolerant patients, met the inclusion criteria. In this study of nearly 3,000 individuals, 75 patients with a history of angioedema or anaphylaxis had a history of angioedema due to ACE-I use. Of these patients, none in the telmisartan group and 1 in the placebo group developed angioedema. Of all the study patients, 2 in telmisartan group and 3 in the placebo group developed angioedema.

Combining the data in the TRASCEND trial with those used in the previous meta-analysis (Table 1),³⁻⁵ the risk of angioedema secondary to ARB use is 2.5% (95% confidence interval [CI], 0%-6.6%), and for confirmed cases secondary to ARB use it is 1.5% (95% CI, 0%-5.1%). There was no statistical heterogeneity between trials ($P > .30$).

In addition, the Peto method was used for the 2 randomized controlled trials^{2,4} to compare the risk of angioedema between ARB and placebo. There is no statistically significant difference in the odds of angioedema between ARB and placebo, although the CI is broad (OR, 1.1; 95% CI, 0.07-17).

This information further narrows and refines the estimate of risk of recurrent angioedema with an ARB after having experienced this with an ACE-I. The risk of this event is low, with the top end of the 95% CI being 6.6%, but it seems to occur. There is also a risk of angioedema due to ARB use with no previous use of ACE-I, although this incidence also seems to be low. Physicians can use this

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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.

BRET R. HAYMORE, MD*

KENT J. DEZEE, MD, MPH†

*Department of Allergy-Immunology
Walter Reed Army Medical Center
Washington, DC

†Department of Internal Medicine
William Beaumont Army Medical Center
El Paso, Texas
bret.haymore@us.army.mil

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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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