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Development of food allergies in patients with Gastroesophageal Reflux Disease treated with gastric acid suppressive medications

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Abstract

Background—The prevalence of food allergy has steadily increased, especially in children. Reflux disease, a very common problem in children, is often treated with gastric acid suppressive (GAS) medications which may alter the processing of food allergens, thereby affecting oral mucosal tolerance.

Objective—The purpose of this study was to determine if use of GAS medications is associated with the occurrence of food allergies in children. **Methods:** Using a large national commercial insurance database, we identified 4724 children aged 0–18 years who were diagnosed with Gastroesophageal Reflux Disease (GERD) and treated with either GAS medications between (1/1/2008 and 9/30/2009). We then matched 4724 children with GERD not treated with GAS medications and 4724 children without GERD and not treated with GAS medications, at a 1 to 1 ratio, on age, gender and number of atopic risk factors. Patients were followed for 12 months.

Results—In comparison to the referent (children without GERD who received no GAS medications), children with GERD who were treated with GAS were more likely to be diagnosed with a food allergy (Hazard ratio (HR): 3.67, 95% CI 2.15–6.27), as were children with GERD diagnosis but who were not treated with GAS medications (HR: 2.15, 95% CI: 1.21–3.81). A direct comparison of the two GERD cohorts showed that children with GERD who were treated with GAS had a greater risk of food allergy than those with GERD who were untreated (HR, 1.68, 95%CI, 1.15–2.46).

Conclusion—Treatment with GAS medications is associated with the occurrence of food allergy, an effect not apparently related to a diagnosis of GERD alone.

Keywords

gastric acid suppression; GERD; food allergy

Introduction

Recent research indicates that the prevalence of food allergy is increasing, up 18% from 1997 to 2007 according to a survey of the US Centers for Disease Control and Prevention. [1] The estimated prevalence of clinical food allergy in the US population was 2.5% in an NHANES 2005–2006 study cohort and as high as 4.2% in children 1–5 years and 3.8% in those 6–19 years.[2] Food allergens are digested in the alimentary tract and sensitization is thought to be a result of presentation of undigested or improperly digested proteins by antigen-presenting cells in the intestinal epithelium.[3] Gastric acid digestion decreases the potential of food proteins to bind specific Immunoglobulin E (IgE).[4]

Medications such as proton pump inhibitors (PPIs) and Type 2 histamine receptor blockers (H2 blockers) that suppress gastric acid production are now commonly prescribed by physicians or self-prescribed, raising questions about the possible effect of increasing stomach pH on induction of food allergy, as the incidence of both has risen over the past several decades. One claims database study reported that the diagnosis of GERD more than tripled between 2000 and 2005 in North American infants less than one year of age and increased by up to 50% in other pediatric age groups, with an increase in the use of acid suppressive medications.[5] An Australian study showed an increase of 1318% in the use of PPIs in the general population over the course of the decade from 1995 to 2006.[6]

Murine model studies have demonstrated that mice treated with gastric acid suppressive (GAS) medications developed specific IgE and positive skin tests to caviar. This was not seen in those who did not receive acid suppression therapy.[7] Murine models have also demonstrated similar induction of IgE to diclofenac as well as hazelnut with gastric acid suppression.[8,9] Clinical studies have shown that 25% of patients given acid suppression for 3 months developed a boost in IgE towards constituents of the daily diet.[10] Studies measuring total as well as food-specific IgE have demonstrated elevated IgE levels in patients treated with GAS medications. One study calculated that the relative risk of developing food-specific IgE after anti-acid therapy was 10.5 (95% confidence interval[CI]: 1.44–76.48).[11] Additionally, studies have examined the relationship of the use of PPIs and the rise of eosinophilic esophagitis (EoE), thought to be a manifestation of food allergy.[12]

The relationship between EoE and PPI use is difficult to assess as often one of the reasons for further evaluation of a patient for EoE is the failure of PPIs to ameliorate symptoms. Concerns have also been raised of the predisposition of newborns with in utero exposure to PPIs toward T-helper 2 (Th2) immune responses.[10,13] In a population-based cohort study published in 2008, maternal acid suppressive medication use was associated with an odds ratio (OR) of 1.51 (95% CI 1.35–1.69) for developing asthma.[14] Kallen et al recently published a study assessing the effect of maternal drug use on asthma risk in offspring. It found that the use of medications for GERD was associated with an increased OR of 1.32 (95% CI 1.12–1.55) when they excluded women with prior use of anti-asthmatic medications.[15]

The purpose of this study is to determine the association between exposure to GAS medications and development of food allergy in children aged 0–18 years.

Methods

Data Sources

Data for this cohort study were obtained from a nationwide U.S. health claims database, consisting of electronic health insurance claims from an employed, commercially insured population with dependents. Medical claims from 2007 to 2010 were used. The subjects were selected from 2008–2009 data. The 2007 data were used to develop exclusion criteria and extract covariates. The 2010 data allowed for a 12 month follow-up period for all subjects. All three cohorts had a minimum of 24 months of continuous enrollment and were matched for age, state and number of atopic risk factors (see below). Prior to data being made available for research purposes, all patient identifiers were removed. The University of Texas Medical Branch institutional review board granted an exemption for this protocol.

Subjects

We selected three cohorts from enrollees between 0–18 years of age from January 1, 2008 through September 30, 2009. The cohorts of children were matched for age, gender and number of atopic risk factors (asthma, atopic dermatitis, allergic rhinitis, urticaria, drug allergy and eosinophil esophagitis). Children with any claims with diagnosis codes or V codes for food allergy within past 1 year (or going back as far as birth if they were younger than 1 year of age) prior to initiation of a study medication or reflux diagnosis were excluded. We included only children with at least 24 months of continuous enrollment. Children were excluded if there was an associated diagnosis code of eosinophilic esophagitis in the study period, with the intention to look back and ahead up 12 months each after inclusion into study.

Cohort 1 included children treated with a study defined medication during this time period AND with a claim indicating a diagnosis of gastroesophageal reflux within 3 months prior to the medication. A minimum of two consecutive prescriptions within a 120 day period of any listed gastric acid suppressive medication was a requirement for inclusion and defined exposure. Cohort 2 included a matched cohort of children with a diagnosis of reflux from

January 1, 2008 through September 30, 2009, but without any claims with an associated claim for medications of interest.

Cohort 3 included matched children (enrolled during the same time period with 24 months of continuous enrollment) who had no diagnosis of reflux and were never treated with a study medication. This resulted in 4724 successful matches of untreated children with a diagnosis of reflux (cohort 2) and 4724 untreated children without reflux disease (cohort 3) with 4724 children who were treated with a study medication and who had a diagnosis of reflux disease.

Outcome Measures

Food allergy was measured by whether a child with a diagnosis of reflux disease had a claim with a food allergy diagnosis code during 12 months of follow-up after initiating a study defined medication, or after index date for those who did not receive a study defined medication. The index date was defined as the first diagnosis date of reflux disease (for cohort 2) and the midpoint of enrollment period (for cohort 3). Patients were censored at 12 months of follow-up. To increase the predictive value positive of our algorithm for food allergy, only food allergy codes that had been entered by an allergist were counted. A diagnosis code for food allergy was included if it occurred at any time ≥ 90 days from initiation of medication or index date.

Drug exposure—During the 12 month period of follow-up, rates of incident cases of food allergy among GAS initiators were compared with rates of food allergy among untreated comparators. Covariates: Age at the beginning of treatment (cohorts 1) or at the first diagnosis of reflux (cohort 2) was calculated for each child and was treated as continuous variable in the multivariable analyses. We also included gender (female or male), geographic region (mid-west, north-west, south, or west) and whether the patient had had any previous diagnosis code of asthma, atopic dermatitis, allergic rhinitis, urticaria, drug allergy and eosinophilic esophagitis (Yes vs. No).

Appendix A lists the ICD-9-CM diagnosis codes and medication names that were used to construct the cohort and variables.

Statistical Analysis

Descriptive statistics were used for cohort characteristics. We estimated the incidence of food allergy across the three study cohorts using Kaplan-Meier analysis with log-rank tests. We also compared the three cohorts for each specific diagnosis code of food allergy. Cox proportional hazards models were used to evaluate the unadjusted treatment effects and effects adjusted for children's age, gender, and region, previous history of asthma, atopic dermatitis, urticaria, drug allergy and eosinophilic esophagitis.

To evaluate whether the type of medication is associated with food allergy, we compared the patients treated with H2 blockers to those treated with PPIs, using the PPI treated group as the reference and by repeating the analyses as described above.

SAS® 9.2 software (SAS institute, Cary, NC) was used for all the data extraction and statistical analysis.

RESULTS

Patient characteristics of the three cohorts are described in Table 1. The mean age of patients and the number of females in all cohorts were the same, which indicates matching on age was successful. Chi-square tests demonstrated a statistically significant difference across the three cohorts only in the proportion of patients with a prior diagnosis of asthma and atopic dermatitis. All cohorts had no patients with a diagnosis of EoE as was expected given that it was part of the exclusion criteria.

There was no significant interaction between age and group ($p=0.9232$) even when dichotomized as infant (Y/N) ($p=0.4987$). Although based on the Martingle residual plot, as might be expected, children aged 10+ had a 58% lower risk of food allergy, this also was not associated with a significant interaction ($p=0.8330$). Across the spectrum of food allergy-related diagnosis codes (entered by an allergist), there was a higher rate of occurrence of food allergy in those initiating GAS medication (Cohort 1), when compared to the untreated cohorts (see Table 2 and Appendix A for ICD-9 codes). The occurrence of food allergy in the comparison cohort (with no diagnosis of reflux and on no GAS medications) was 0.36%.

During 12 months of follow-up, 1.6% of those diagnosed with GERD who initiated treatment and 0.87% of those diagnosed with GERD but not treated with GAS medication were diagnosed with food allergy (Table II). After adjusting for age, gender, region and prior history of atopic disease (asthma, atopic dermatitis, urticaria, drug allergy and EoE), children with GERD who were treated with GAS medications were more likely to be diagnosed with a food allergy compared to a matched cohort without a diagnosis of GERD or treatment with GAS medications (Hazard ratio: 3.67, 95% CI 2.15–6.27). Interestingly, children with a GERD diagnosis but who were not treated with prescribed GAS medications were also more likely to be diagnosed with food allergy when compared to a matched cohort without a diagnosis of GERD or treatment with GAS medications (HR: 2.15, 95% CI: 1.21–3.81) (Table 3). A direct comparison of the two GERD cohorts showed that children with GERD who were treated with GAS had a greater risk of food allergy than those with GERD who were untreated (HR, 1.68, 95%CI, 1.15–2.46). Thus, patients with a diagnosis of GERD who were on GAS medications had a 1.7 fold increase in developing at least one food allergy at 1 year when compared to those without treatment (Table 4).

Table 3 also details the hazard ratios and covariates for both the samples (unrestricted and then restricted to allergist entered food allergy diagnosis). The risks for developing a food allergy were similar, regardless of type of GAS medication used (H2 blockers OR: 0.76[95% CI; 0.41–1.43] when compared to PPIs as a reference), after adjustment for the factors as identified in Table 1. Patients with a diagnosis of GERD had a two fold increase in the development of food allergy at 1 year when compared to the matched group without a diagnosis of GERD or treatment with GAS medications. Kaplan-Meier curves in Figure 1 illustrate the time to diagnosis of food allergy for each of the three groups. Based on a two

sided log rank test, all comparisons between pair combinations of the three groups were statistically significant ($p<0.001$).

DISCUSSION

The relationship between GAS and the increasing prevalence of food allergy has long been speculated upon. Gastric acid reflux disease is a common phenomenon in the pediatric population and the use of GAS medications to treat it has been rising. Animal studies suggest an association between the use of GAS medications and the development of IgE to specific foods [7]. Our study is the first large scale retrospective cohort study to further support a causative role of GAS medications in the development of food allergy. Restricting our analysis to children who had food allergy diagnosed by an allergist decreases the number of children included, but strengthens the accuracy of a food allergy diagnosis.

Our results indicate over a two-fold increase in the development of food allergy at 1 year in patients on GAS medications. This is a concern given the increase in use of GAS medications in children, especially when studies demonstrating efficacy are not clear.[16] The finding of an increase in the development of food allergy in the cohort with a diagnosis of reflux but no associated prescription for a GAS medication was unexpected. As several H2blockers and PPIs were available OTC during the study period, this finding may at least partly be explained by the use of over the counter (OTC) GAS medications. Although GER is often implicated in asthma (whether as causative or contributory), recent studies have shown that there is a different phenotype of non-allergic, GER related asthma.[17]

As this is a retrospective study looking at claims data, such an analysis contains some inherent issues. An algorithmic approach is limited in its ability to identify other variables and associations. For example, we looked at the association of other atopic disorders at the start of our cohort (i.e., asthma and EoE and were able to adjust for their presence, but were unable to reassess for the development of these same disorders during the course of the study. Adjusting for these factors at baseline effectively eliminates their influence during the follow-up period, which in this case is short (12 months).

We considered incorporating codes for skin testing, epinephrine pen prescription and immunocap testing into analysis, but given there are no results available in claims data, any of these simply being ordered would not help clarify or confirm the diagnosis of food allergy.

One limitation is the possibility of unmeasured residual confounding, especially confounding by indication remaining in the analysis. On the other hand, strengths of claims based studies are the size of the population available for study over time and the data reflects medicine as it is practiced in the population for which it is collected.

Another limitation of this type of study is that because pharmacy claims data capture only prescribed medications, many H2-blockers and PPIs now available over the counter (OTC) will not be included in claims-based studies. Assuming that those with a diagnosis of reflux and no treatment on the record were using OTC GAS medications, the data presented here would actually underestimate the relative risk of food allergy associated with GERD

medications. On the other hand, verifying compliance with prescribed medications can only be estimated by documenting the occurrence of obtaining refills, which was done by only including children who had evidence of at least one refill.

This study suggests the need for further evaluation of the role of gastric acid suppression in the development of food allergy as well as highlights the importance of the judicious use of these medications, especially in the pediatric population.

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Appendix A. ICD-9 codes and medications used

Reflux/Food Allergy defined by ICD 9 codes as below

ICD codes:

For Food Allergy:

- 995.60 – 995.69 (anaphylactic shock due to food)
- 995.7 (other adverse food reactions)
- 558.3 (allergic diarrhea and allergic gastroenteritis and colitis)
- 693.1 (dermatitis due to food)
- 477.1 (allergic rhinitis attributable to food)
- 692.5 (contact dermatitis attributable to food in contact with skin)
- V15.01-V15.05

EXCLUDE:

Eosinophilic Esophagitis ICD-9 code: 530.13 and 530.19

For Reflux:

- 536.8 (dyspepsia)
- 530.81 (esophageal reflux)
- 531 (Gastric Ulcer)
- 530.1 (Esophagitis)
- 530.11 (Reflux Esophagitis)
- 530.12 (acute esophagitis)
- 530.85 (barrett's)
- 533 (PUD NOS)
- 535 (Gastritis)

Medications

H2 blockers: Ranitidine, Cimetidine, Nizatidine, Famotidine

Proton Pump Inhibitors: Lansoprazole, Omeprazole, Esomeprazole, Pantoprazole, Rabeprazole

Figure 1.

Kaplan-Meier Curves: development of food allergy over study period including only patients that had Allergist Entered Food Allergy Diagnoses.

Cohort 1: blue line

Cohort 2: red line

Cohort 3: green line

Table 1

Baseline Characteristics of all patients on Gastric Acid Suppressive (GAS) Medication, with reflux and without as well as the comparison matched cohort with no reflux and on no GAS medication

Characteristics	All	Reflux dx treated with GAS medication	Reflux dx not treated with GAS medication	No reflux and never treated with GAS medication	p-value *
Age	3.06 ± 5.25	3.06 ± 5.25	3.06 ± 5.25	3.06 ± 5.25	1.0
Female	6853 (48.36)	2220 (46.99)	2327 (49.26)	2306 (48.81)	0.6
Region					1.0
North East	1017 (7.18)	339 (7.18)	340 (7.18)	341 (7.18)	
Middle West	4068 (28.70)	1356 (28.70)	1357 (28.70)	1358 (28.70)	
South	7332 (51.74)	2444 (51.74)	2445 (51.74)	2446 (51.74)	
West	1755 (12.38)	585 (12.38)	586 (12.38)	587 (12.38)	
Previous Dx					
Asthma	734 (5.18)	276 (5.84)	248 (5.25)	210 (4.45)	0.009
Atopic dermatitis	1043 (7.36)	300 (6.35)	340 (7.20)	403 (8.53)	0.0002
Allergic Rhinitis	984 (6.94)	345 (7.30)	331 (7.01)	308 (6.52)	0.32
Urticaria	15 (0.11)	6.00 (0.13)	5.00 (0.11)	4.00 (0.08)	0.82
Drug allergy	18 (0.13)	3.00 (0.06)	7.00 (0.15)	8.00 (0.17)	0.31
Esophageal Foreign Body	5.00 (0.04)	3.00 (0.06)	2.00 (0.04)	0.00 (0.00)	-
Eosinophilic Esophagitis	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	0.00 (0.00)	-
Total N	14172	4724	4724	4724	

* Using chi-square and one-way anova

Table 2
Rates of food allergy diagnosis in each of 3 cohorts, further categorized by specific food allergy diagnosis code

	N = 376						
Outcome	Reflux dx treated with GAS medication		Reflux dx not treated with GAS medication		No Reflux dx and not treated with GAS medication		
	N	%	N	%	N	%	
Food Allergy	76	1.61	41	0.87	17	0.36	
By FA diagnosis							
995.6 (Anaphylactic Shock due to food)	10	0.21	5	0.11	4	0.08	
995.7 (Other adverse food reactions)	12	0.25	3	0.06	2	0.04	
558.3 (Allergic diarrhea)	9	0.19	2	0.04	0	0.00	
693.1 (Dermatitis due to food)	47	1.00	26	0.55	8	0.17	
477.1 (allergic rhinitis)	0	0.00	3	0.06	2	0.04	
692.5 (topical food dermatitis)	0	0.00	3	0.06	0	0.00	
v1501 (allergy to peanuts)	7	0.15	2	0.04	2	0.04	
v1502 (allergy to milk products)	6	0.13	5	0.11	2	0.04	
v1503 (allergy to eggs)	5	0.11	2	0.04	1	0.02	
v1504 (allergy to seafood)	0	0.00	1	0.02	0	0.00	
v1505 (other food allergies)	8	0.17	5	0.11	4	0.08	

Table 3

Hazard Ratios comparing 3 cohorts: GAS compared to no GAS in patients with a diagnosis of GERD, using matched cohort without diagnosis of GERD and no GAS as reference

N = 376										Restricted to allergist confirmed dx (n = 134)									
Unadjusted Model					Adjusted Model					Unadjusted Model					Adjusted Model				
Hazard Ratio					95(%) Confidence Interval					Hazard Ratio					95(%) Confidence Interval				
															</				

N = 376										Restricted to allergist confirmed dx (n = 134)				
Unadjusted Model					Adjusted Model					Unadjusted Model				
	Hazard Ratio	95(%) Confidence Interval	Hazard Ratio	95(%) Confidence Interval	Hazard Ratio	95(%) Confidence Interval	Hazard Ratio	95(%) Confidence Interval	Hazard Ratio	95(%) Confidence Interval	Hazard Ratio	95(%) Confidence Interval		
	Yes	0.60	0.39	0.94	0.78	0.48	1.28		1.32	0.69	2.52			
	No		reference			reference		reference		reference				
Urticaria	Yes	1.95	0.27	13.89	3.28	0.46	23.70	0.00	0.00	.	0.00	.		
	No		reference			reference		reference		reference				
Drug allergies	Yes	0.00	0.00	.	0.00	0.00	.	0.00	0.00	.	0.00	.		
	No		reference			reference		reference		reference				
Esophageal foreign body	Yes	0.00	0.00	.	0.00	0.00	.	0.00	0.00	.	0.00	.		
	No		reference			reference		reference		reference				

Note: Initial N of 376 included patients with all food allergy diagnoses found with specified criteria; The second half of the table limited data analysis to patients who had a food allergy diagnosis code entered by an allergist.

Table 4

Hazard ratio of developing food allergy in cohort 1 (patients with history of GERD on GAS medications) compared to cohort 2 (patients with GERD with no history of prescribed GAS medications) as a reference

	Unadjusted Model			Adjusted Model		
	Hazard Ratio	95(%) Confidence Interval	P value	Hazard Ratio	95(%) Confidence Interval	P value
Treatment						
Dx of reflux with GAS	1.69	1.16	2.48	0.007	1.15	2.46
Dx of reflux with no GAS		reference			reference	0.007