Allergy immunotherapy: Reduced health care costs in adults and children with allergic rhinitis

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Background: Research demonstrates significant health care cost savings conferred by allergen-specific immunotherapy (AIT) to US children with allergic rhinitis (AR).

Objective: We sought to examine whether AIT-related cost benefits conferred to US children with AR similarly extend to adults.

Methods: A retrospective (1997-2009) Florida Medicaid claims analysis compared mean 18-month health care costs of patients with newly diagnosed AR who received *de novo* AIT and were continuously enrolled for 18 months or more versus matched control subjects not receiving AIT. Analyses were conducted for the total sample and separately for adults (age ≥18 years) and children (age <18 years).

Results: Matched were 4,967 patients receiving AIT (1,319 adults and 3,648 children) and 19,278 control subjects (4,815 adults and 14,463 children). AIT-treated enrollees incurred 38% ($6,637 vs $10,644, $P < .0001$) lower mean 18-month total health care costs than matched control subjects, with significant savings observed within 3 months of AIT initiation. Compared with control subjects, significantly lower 18-month mean health care costs were demonstrated overall (38%; $6,637 for patients receiving AIT vs $10,644 for control subjects, $P < .0001$), and for both AIT-treated adults (30%; $10,457 AIT vs $14,854 controls, $P < .0001$) and children (42%; $5,253 AIT vs $9,118 controls, $P < .0001$). The magnitude of 18-month health care cost savings realized by AIT-treated adults and children did not significantly differ ($4,397 vs $3,965, $P = .435$).

Conclusions: Patients with newly diagnosed AR initiating AIT incurred significantly lower health care costs than matched control subjects beginning 3 months after AIT initiation and continuing throughout the 18-month follow-up period. The significant cost benefits achieved by children with AR diagnoses who initiated AIT were also observed for adults with AR diagnoses who initiated AIT. (J Allergy Clin Immunol 2013;131:1084-91.)

Key words: *Allergic rhinitis, allergy immunotherapy, allergy immunotherapy, costs, health care use, Medicaid, matched cohort, retrospective, administrative claims*

Allergic rhinitis (AR), which affects approximately 1 in 5 persons in the United States, is associated with significant clinical and economic burden.[1] Those with AR can experience disturbed sleep, decreased energy, depressed mood, low frustration tolerance, poor concentration, decrements in performance at school and work, and millions of lost work and school days annually.[2,3] In 2005, estimated total direct US costs of AR exceeded $11 billion ($14 billion in 2011[1]), with 60% of expenditures for prescription medications (the cost of over-the-counter medications was not assessed).[4] Additional billions of dollars are reportedly spent to treat conditions for which AR is a predisposing risk factor, such as asthma, sinusitis, and otitis media.[5]

Subcutaneously administered allergen-specific immunotherapy (AIT), which has just commemorated its centennial anniversary since its first use to treat allergies,[6] is indicated in the US for the treatment of AR in patients with symptoms not adequately controlled by medications and avoidance measures, or those experiencing unacceptable adverse effects of medications, or who wish to reduce the long-term use of medications.[7] AIT is distinguished from symptomatic drug treatments by its unique potential to alter the course of allergic disease and thereby mitigate progression to asthma[8-11] and development of new allergen sensitivities,[12-18] as well as to maintain efficacy after discontinuation of treatment.[12,18-25]

The significant cost savings conferred by AIT to US children with AR are well documented.[26-28] In a 7-year (1997-2004) retrospective claims analysis of Florida Medicaid-enrolled children (age <18 years) who were given new diagnoses of AR (with or without asthma) and who were naive to AIT, use and costs of pharmacy, outpatient, and inpatient services were significantly reduced in the 6 months after versus preceding AIT initiation.[27] In a subsequent study, investigators examined 10 years (1997-2007) of Florida Medicaid claims data to compare health services use and costs between children with newly diagnosed AR who subsequently received AIT versus matched control subjects who did not receive AIT.[26] Compared with their matched counterparts, children who received AIT incurred significantly lower median total, outpatient, and pharmacy costs during the 18 months after AIT initiation. These significant health care savings were evident within the first 3 months of treatment initiation.

The present analysis examined whether AIT-related cost benefits demonstrated for children with AR extend to adults with AR diagnoses. To this effect, we examined 12 years of Florida Medicaid data as follows.

1. First, we compared health care use and costs of all targeted patients (adults and children) with newly diagnosed AR who received *de novo* AIT with matched control subjects with newly diagnosed AR who did not receive AIT.

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Abbreviations used
AIT: Allergen-specific immunotherapy
AR: Allergic rhinitis
CCI: Charlson Comorbidity Index
GEE: Generalized estimating equations
ICD-9: International Classification of Disease, ninth edition

2. Next, we conducted the same analyses described above for the adult (age ≥18 years) and child (age <18 years) subgroups to determine:
   A. whether previously reported AIT-related cost savings achieved by children with AR diagnoses (based on 10 years of data) held in this larger sample of children (based on 12 years of data);
   B. whether there were significant differences in health care use and costs between adults with newly diagnosed AR who received *de novo* AIT versus matched control subjects with newly diagnosed AR who did not receive AIT; and
   C. whether the magnitude of cost benefits differed between AIT-treated adults and children.

METHODS

Florida Medicaid dataset

To expound on the findings of our previous study in children enrolled in Florida Medicaid,[26] we examined Florida Medicaid claims data for both children and adults from July 1, 1997, to June 30, 2009. Florida Medicaid provides access to health care for more than 2 million low-income children and adults annually. The Florida Medicaid Bureau of Medicaid Program Analysis provides researchers with claims data that are patient deidentified and fully compliant with the Health Insurance Portability and Accountability Act Privacy Rule. Each patient-specific claim identifies the date and type of health service provided, such as prescription drug fills (per National Drug Codes) or medical, surgical, or diagnostic procedures (Current Procedural Terminology). Each claim also includes patients' demographics (eg, sex, age, and race/ethnicity) and clinical information (primary and secondary diagnoses according to the International Classification of Disease, ninth edition [ICD-9]). Because our research was restricted to the use of existing and Health Insurance Portability and Accountability Act–compliant patient-deidentified claims data, it was exempt from institutional board review.

Definition of terms

ICD-9 codes 477.X identified the diagnosis of AR. Current Procedural Terminology codes 95115, 95117, 95120, 95125, 95144, 95165, 95180, and 95199 identified the administration of AIT. Comorbid allergy-related illnesses were identified by the following ICD-9 codes: 493.X for asthma, 691.8 for atopic dermatitis, and 372.X for conjunctivitis. Patients with newly diagnosed AR were those who had no AR diagnoses in the year preceding their first ("index") AR diagnosis. Patients who received *de novo* AIT were characterized as those whose first documented AIT claim followed (rather than preceded) their index AR diagnosis and who received 2 or more administrations of AIT.

Identification of matched samples

Participants were Florida Medicaid enrollees who had a paid claim between July 1, 1997, and June 30, 2009. To identify the pool of eligible AIT-treated patients, we first selected subjects with a diagnosis of AR. In subsequent steps, we retained only those who had newly diagnosed AR, received at least 2 administrations of *de novo* AIT, and had at least 18 months of continuous enrollment after AIT initiation. To identify the pool of eligible control subjects, we selected subjects with newly diagnosed AR who had not received AIT at any time during the study. As described in greater detail below, each eligible AIT-treated patient was matched with up to 5 control subjects. We required that AIT-treated patients match to at least 1 control patient on all of the following 8 variables: demographics (age at first AR diagnosis ±6 months, sex, and race/ethnicity), comorbid illness burden (the Charlson Comorbidity Index),[29] date of AIT initiation ("match date"), and diagnoses of comorbid atopic conditions (asthma, atopic dermatitis, and conjunctivitis) during the year prior to AIT initiation (or match date). Matched control patients also were required to have at least 18 months of follow-up data from their match date. If an AIT-treated patient did not match to at least 1 control patient on all 8 matching variables, then that AIT-treated patient was excluded from further analysis. Because Florida Medicaid claims data do not provide information regarding the type of allergen or allergens to which patients had positive test results, we were not able to match on type of allergy.

To ensure that any observed differences in outcomes were unattributable to differences in disease burden not associated with AR, we matched patients on the Charlson Comorbidity Index (CCI) in the year before AR diagnosis.[29] The CCI has been widely used by researchers to measure burden of disease and has been adapted for use with ICD-9-CM administrative claims databases.[30] Although originally designed to predict risk of 1-year mortality in hospitalized patients,[29] the CCI also significantly predicts health care use and costs in primary care populations.[31,32] The CCI is comprised of 19 conditions that are assigned weights according to 1-year risk of mortality.[29] The total score (range, 0-37) is calculated as the sum of the weighted items.[29] A score of 0 denotes no comorbid illness burden.[29] The developers of the CCI noted that, in most clinical studies, it will not be possible to stratify patients into more than 2 comorbidity groups.[29] They further recommended that the selection of cut points should vary depending on the disease under investigation: if the disease investigated is associated with a low likelihood of mortality, a cut point of 1 or greater might be appropriate; if disease-related mortality is high, a cut point of 2 or greater or 3 or greater might be appropriate.[29] We used a score of 0 to 1 to characterize patients with no or mild comorbid disease burden and a score of 2 or greater for those with moderate-to-severe comorbid disease burden.

Because the CCI might not sufficiently assess the illness burden of IgE-mediated allergic illness, we further identified AIT-treated patients who had a diagnosis of other well-recognized atopic conditions (asthma, atopic dermatitis, and conjunctivitis) in the year before their first AIT administration. These AIT-treated patients were matched to control subjects with similar diagnoses of atopy during a comparable period, as follows. We first examined the AIT-treated patient sample to determine the date of each patient's index AR diagnosis and time elapsed until receiving administration of their index AIT. From the pool of matched control subjects, we established comparable periods from the dates of each control subject's index AR diagnosis. We then assessed for the presence of comorbid atopy in the year preceding this "match date." Excluded were control subjects who did not have at least 18 months of continuous enrollment after their match date and eligible AIT-treated patients who had no appropriate control group matches.

In summary, we required that each patient in the AIT-treated group match with at least 1 patient in the control group on all 8 of the following variables: age at index AR, sex, race/ethnicity, CCI 1 year prior to first AR diagnosis, date at AIT initiation, and comorbid atopic conditions (asthma, conjunctivitis, and atopic dermatitis) during the year prior to AIT initiation. Control patients who were matched on these variables also had to have at least 18 months of data after their match date. If an AIT-treated patient could not be matched on all 8 variables to at least 1 control patient, then that AIT-treated patient was excluded from further analysis. Overall, there were 3 matched cohorts of AIT-treated patients and control subjects: all patients, adults (age ≥18 years) only, and children (age <18 years) only.

Data analyses

The Florida Medicaid Program provided data in 36 compressed text files, which we decompressed and imported for analysis by using SAS/STAT (version 7; SAS Institute, Cary, NC). We compared groups on matching variables and health care use and outcomes by using pairwise comparisons

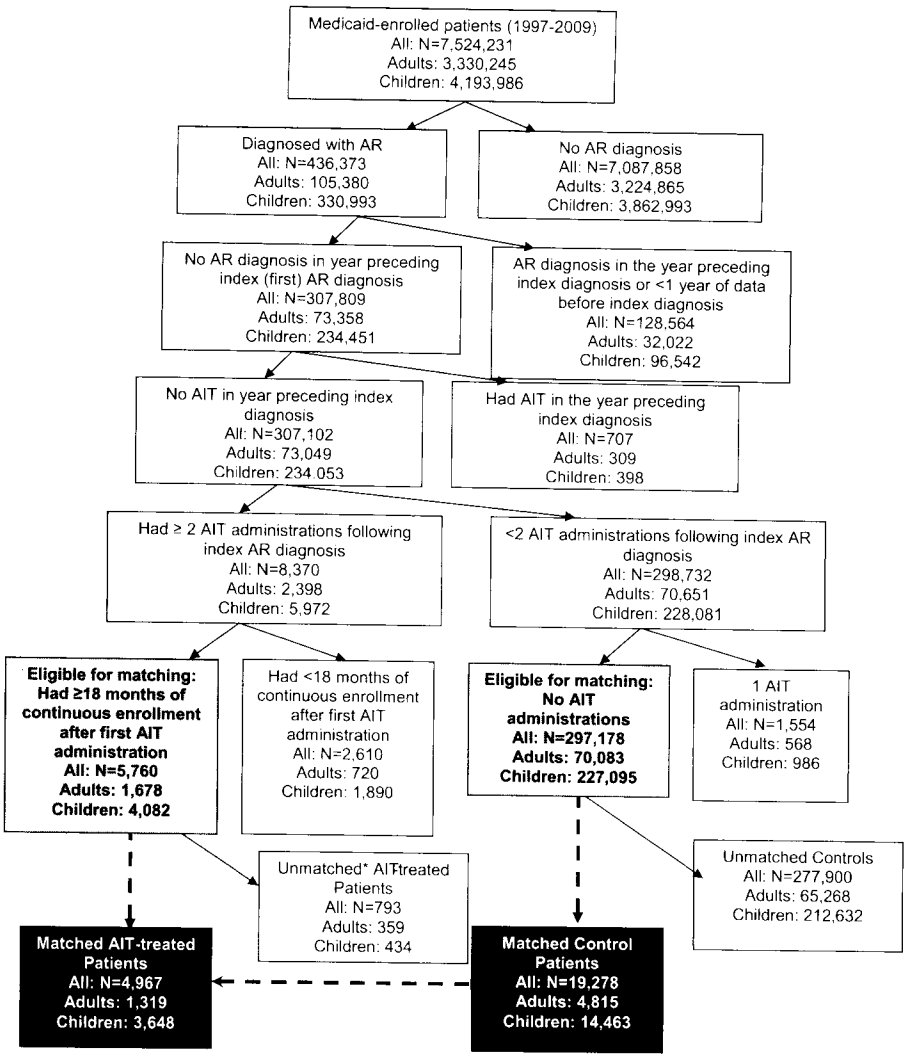

FIG 1. Identification of matched samples. *Seven hundred ninety-three AIT-treated patients (359 adults and 434 children) could not be matched on all 8 variables to at least 1 control patient and were therefore excluded from further analysis. Note: The 8 matching variables were: age at index AR diagnosis (±6 months), sex, race/ethnicity, CCI, date at AIT initiation, and 3 comorbid atopic conditions (asthma, atopic dermatitis, and conjunctivitis).

within cohorts. Components of total health care use and costs included inpatient care, outpatient visits (inclusive and exclusive of AIT-related care), and prescription medication use. In general, health care use data are not normally distributed and tend to be heavily skewed to the right (ie, a few patients might have unusually high rates of health care use and costs that skew the aggregated data). To withstand violations in normal distribution, we used the generalized linear model with log link and gamma variance functions to compare mean per-patient health care use and costs in patients with newly diagnosed AR who subsequently received *de novo* AIT and matched control subjects who did not receive AIT.[33] The SAS/STAT GENMOD procedure with generalized estimating equations (GEE) was used to fit the model, with correlated response for comparisons of health care outcomes between AIT-treated patients and matched control subjects. Because comparisons of the magnitude of cost savings for AIT-treated adults versus children did not involve correlated data, we used the GENMOD procedure without GEE for these analyses. Outcomes for AIT-treated patients and matched control subjects were compared for all patients, adults only, and children only. Generalized linear model with GEE also compared mean 18-month per-patient AIT-related cost savings (with positive values indicating lower mean costs for AIT-treated versus control patients) for adults versus children.

RESULTS

Characteristics of samples

Fig 1 displays the results of the sample identification procedures. Among all Florida Medicaid enrollees (n = 7,524,231), among whom there were 3,330,245 adults and 4,193,986 children, 5.8% (436,373/7,524,231) received a diagnosis of AR; among the 307,809 enrollees with newly diagnosed AR, 2.7% (8,370) received *de novo* AIT. Adult Medicaid enrollees were 62% less likely than child Medicaid enrollees to receive a diagnosis of AR (odds ratio, 0.38; 95% CI, 0.379-0.384; $P < .0001$) and 1.3 times more likely to initiate *de novo* AIT (odds ratio, 1.29; 95% CI, 1.23-1.36; $P < .0001$).

Overall, there were 5,760 AIT-treated patients and 297,178 control subjects eligible for matching; from this pool, 4,967 AIT-treated patients were matched to 19,278 control subjects (793 did not match to control subjects on all 8 of the requisite matching variables and were therefore excluded from further analysis). Among adults, 1,678 AIT-treated patients and 70,083 control

TABLE I. Comorbid disease and respiratory illness burden in the year before AIT initiation in AIT-treated adults and children and matched control subjects

Characteristic	Adults			Children		
	AIT group (n = 1,319)	Control group (n = 4,815)	*P* value	AIT group (n = 3,648)	Control group (n = 14,463)	*P* value
Comorbid disease burden: CCI, no. (%)*			.0007			<.0001
0-1 (none, mild)	1,244 (94.3)	4,404 (91.5)		3,622 (99.3)	14,125 (97.7)	
≥2 (moderate to severe)	75 (5.7)	411 (8.5)		26 (0.7)	338 (2.3)	
Respiratory illness burden, no. (%)						
Acute respiratory tract infections (ICD-9 460-466)	414 (31.4)	1,775 (36.9)	.0002	2,064 (56.6)	8,587 (59.4%)	.0022
Other diseases of the URT (ICD-9 codes 470, 472, 474-476, 478)	678 (51.4)	2,113 (43.9)	<.0001	2,915 (79.9)	9,662 (66.8%)	<.0001
Nasal polyps (ICD-9 code 471.0)	14 (1.1)	14 (0.3)	.0002	36 (1.0)	25 (0.2%)	<.0001
Chronic sinusitis (ICD-9 code 473)	208 (15.8)	437 (9.1)	<.0001	718 (19.7)	1,384 (9.6%)	<.0001
Pneumonia and influenza (ICD-9 code 480-488)	56 (4.3)	205 (4.3)	.985	349 (9.6)	1,417 (9.8%)	.675
COPD and allied conditions (ICD-9 codes 490-496)	424 (32.2)	1,334 (27.7)	.0016	1,983 (54.4)	7,223 (49.9%)	<.0001
Other respiratory system diseases (ICD-9 codes 510-519)	87 (6.6)	315 (6.5)	.944	483 (13.2)	1,345 (9.3%)	<.0001

COPD, Chronic obstructive pulmonary disease; *URT*, upper respiratory tract.
*The CCI includes 19 conditions assigned weights from 1 to 6, with a total score calculated by adding the weights.[30] A total score of 0 to 1 indicates no or mild comorbid disease burden, and a score of 2 or greater indicates moderate-to-severe comorbid disease burden.

subjects were eligible for matching, and 1,319 AIT-treated patients were matched to 4,815 control subjects (359 AIT-treated adults did not match to control subjects on all 8 of the requisite matching variables and were therefore excluded). Eligible children included 4,082 AIT-treated patients and 227,095 control subjects; of these 3,648 AIT-treated children were matched to 14,463 control subjects (434 did not match to control subjects on all 8 of the requisite matching variables and were therefore excluded).

The majority of the 1319 adults in the AIT-treated matched sample were female (86.2%) and of nonwhite race/ethnicity (53.7%); mean age at initial AR diagnosis was 47.3 (SD, 17.3) years. In the year before their initial AR diagnoses, most (96%) of these adults experienced no or mild comorbid disease burden, and rates of asthma, atopic dermatitis, and conjunctivitis were 23%, 0%, and 5.3%, respectively. The 3648 children in the AIT-treated matched sample were predominantly male (57.3%) and of nonwhite race/ethnicity (74.5%); mean age at initial AR diagnosis was 7.6 (SD, 3.9) years. In the year before their initial AR diagnoses, the majority (99.8%) of these children experienced no or mild comorbid disease burden, and rates of asthma, atopic dermatitis, and conjunctivitis were 51.1%, 5.7%, and 14.0%, respectively.

We conducted supplementary analyses to examine whether the demographic and comorbid illness characteristics of the 4967 matched AIT-treated adults and children differed from those of 793 AIT-treated patients for whom we found no matches and who were therefore excluded. Matched AIT-treated patients were significantly ($P < .0001$) more likely to be female and non-Hispanic white and to have less comorbid illness burden (CCI) in the year before their AR diagnosis and in the year before AIT initiation than unmatched subjects (data not shown). With regard to pre-existing atopy, although matched AIT-treated patients were significantly ($P < .0001$) less likely to receive a diagnosis of comorbid asthma, they were significantly more likely to receive diagnoses of atopic dermatitis or conjunctivitis compared with AIT-treated patients who could not be matched.

We returned to our primary research question to examine the overall comorbid disease burden (CCI) and specific respiratory illness burden experienced by the adult and child AIT-treated and matched control groups in the year before AIT initiation (or a comparable period for control subjects). As shown in Table I, compared with matched control subjects, adults and children who subsequently received AIT experienced significantly less overall comorbid disease burden in the year before AIT initiation. Whereas acute respiratory tract infections occurred significantly more frequently among matched controls, rates of other diseases of the upper respiratory tract, such as sinusitis, nasal polyps, chronic obstructive pulmonary disease, allied conditions, and other respiratory system diseases, such as pleurisy (in children), were significantly higher among AIT-treated patients.

TABLE II. Mean 18-month per-patient health care resource use and costs in AIT-treated patients and matched control subjects: all patients

	All patients			
	AIT group		Control group	
	No.	Mean ± SD	No.	Mean ± SD
Inpatient stays, no.	192	1.9 ± 2.3*	286	3.2 ± 8.2
Outpatient visits (including AIT), no.	4,954	40.5 ± 38.9	18,794	39.3 ± 46.0
Outpatient visits (excluding AIT), no.	4,777	23.6 ± 33.8§	18,145	39.9 ± 46.3
AIT visits, no.	4,967	21.3 ± 20.4	—	—
Pharmacy fills, no.	4,669	41.8 ± 48.4‡	17,000	39.7 ± 41.3
Inpatient cost ($)	192	8,834 ± 18,480*	286	13,372 ± 27,801
Outpatient (total) cost ($)	4,954	2,718 ± 5,216§	18,794	4,653 ± 11,951
Outpatient cost (excluding AIT [$])	4,777	2,252 ± 5,214§	18,145	4,728 ± 12,060
AIT cost ($)	4,967	547 ± 567	—	—
Pharmacy cost ($)	4,669	2,733 ± 4,312†	17,000	3,039 ± 5,167
Total health care cost ($)	4,960	6,637 ± 1,218§	18,952	10,644 ± 18,143

*$P < .05$.
†$P \leq .01$.
‡$P \leq .001$.
§$P < .0001$.

Patterns of AIT use (among patients receiving AIT)

Among all enrollees with newly diagnosed AR who initiated AIT, the median number of AIT administrations over 18 months

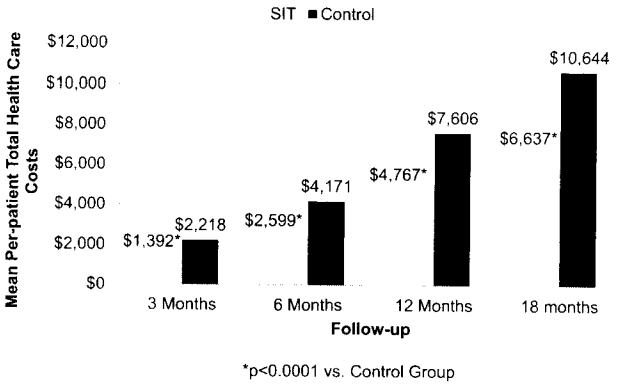

FIG 2. Mean total health care costs for AIT-treated patients and matched control subjects by duration of follow-up.

TABLE III. Mean 18-month per-patient health care use and costs in AIT-treated adults and matched control subjects

	Adults			
	AIT group		Control group	
	No.	Mean ± SD	No.	Mean ± SD
Inpatient stays, no.	121	2.0 ± 2.6	194	2.6 ± 3.5
Outpatient visits, no.	1,315	34.0 ± 39.3	4,765	34.0 ± 41.5
Outpatient visits (excluding AIT), no.	1,238	24.0 ± 34.5*	4,506	34.5 ± 41.9
AIT visits, no.	1,319	14.2 ± 18.3	—	—
Pharmacy fills, no.	1,203	83.8 ± 69.1	4,202	83.3 ± 55.3
Inpatient cost ($)	121	9,231 ± 21,899	194	13,152 ± 28,348
Outpatient (total) cost ($)	1,315	2,544 ± 4,298*	4,765	3,355 ± 5,144
Outpatient cost (excluding AIT [$])	1,238	2,372 ± 4,175*	4,506	3,439 ± 4,805
AIT cost ($)	1,319	311 ± 442	—	—
Pharmacy cost ($)	1,203	5,336 ± 5,921	4,202	5,395 ± 4,603
Total health care cost ($)	1,319	10,457 ± 1,649*	4,791	14,854 ± 16,557

*$P < .0001$.

was 13. Adults with newly diagnosed AR who initiated AIT received significantly fewer AIT administrations and experienced a shorter course of treatment than their child counterparts who initiated AIT (median number of AIT administrations was 6 for adults vs 18 for children, $P < .0001$; median duration of AIT [number of days between first and last AIT administration during 18-month follow-up] was 210 days for adults vs 271 days for children, $P < .0001$). The mean 18-month per-patient cost of AIT was $547 for the combined sample; these costs were significantly lower for adults than children ($311 vs $632, $P < .0001$) because of the higher number of AIT administrations received by children.

Health care use and costs: Combined sample

Table II shows the 18-month mean health care use and costs for the combined (adult and child) sample. Patients with newly diagnosed AR who initiated AIT had significantly fewer inpatient stays and outpatient visits excluding AIT but more pharmacy fills over 18 months. These patients also incurred 38% lower total 18-month health care costs ($6,637 vs $10,644, $P < .0001$), as well as significantly lower costs for inpatient, outpatient, and pharmacy services (34%, 52%, and 10%, respectively).

TABLE IV. Mean 18-month per-patient health care use and costs in AIT-treated children and matched control subjects

	Children			
	AIT group		Control group	
	No.	Mean ± SD	No.	Mean ± SD
Inpatient stays, no.	71	1.8 ± 1.7*	92	4.2 ± 12.6
Outpatient visits, no.	3,639	42.8 ± 38.5	14,029	41.2 ± 47.3
Outpatient visits (excluding AIT), no.	3,539	23.5 ± 33.5†	13,639	41.7 ± 47.6
AIT visits, no.	3,648	23.8 ± 20.5	—	—
Pharmacy fills, no.	3,466	27.3 ± 25.9†	12,798	24.5 ± 18.7
Inpatient cost ($)	71	8,157 ± 10,441	92	13,747 ± 27,038
Outpatient (total) cost ($)	3,639	2,781 ± 5,509†	14,029	5,123 ± 13,567
Outpatient cost (excluding AIT [$])	3,539	2,209 ± 5,506†	13,639	5,179 ± 13,632
AIT cost ($)	3,648	632 ± 583	—	—
Pharmacy cost ($)	3,466	1,829 ± 3,118†	12,798	2,221 ± 5,101
Total health care cost ($)	3,641	5,253 ± 9,818†	14,161	9,118 ± 18,451

*$P < .05$.
†$P < .0001$.

TABLE V. Magnitude of AIT-related cost savings in adults versus children

	Mean 18-month AIT-related cost savings*		
	Adults	Children	*P* value
Inpatient cost ($)	3,921 ± 35,014	5,590 ± 28,661	.745
Total outpatient cost ($)	811 ± 6,234	2,342 ± 14,231	<.0001
Outpatient cost excluding AIT ($)	1,066 ± 6,393	2,970 ± 14,298	<.0001
AIT cost ($)	−311 ± 442	−632 ± 583	<.0001
Pharmacy cost ($)	−59 ± 6,487	392 ± 5,868	.092
Total health care cost ($)	4,397 ± 21,426	3,965 ± 20,181	.435

*AIT-related cost savings calculated as the mean cost for matched control group minus the mean cost for the AIT-treated group. Positive numbers indicate that AIT resulted in cost savings.

Fig 2 compares the mean per-patient total health care costs for the combined sample of AIT-treated patients and their matched control subjects at 3-, 6-, 12-, and 18-month follow-up. Compared with matched control subjects, patients who received AIT incurred significantly lower mean per-patient total health care costs within 3 months of treatment initiation; this significant effect persisted over the 18-month follow-up period.

Health care use and costs: Adult and child samples

Tables III and IV provide the 18-month mean per-patient health care resource use and costs for adults and children separately. Relative to matched control subjects, AIT-treated adults and children incurred 30% ($10,457 vs $14,854, $P < .0001$) and 42% ($5,253 vs $9,118, $P < .0001$) lower mean 18-month total health care costs, respectively. Both AIT-treated adults and children had significantly fewer outpatient visits excluding AIT and lower overall outpatient costs compared with their respective matched control subjects. Although AIT-treated adults did not differ from control subjects in terms of the number of inpatient stays over the 18-month period, AIT-treated children had significantly fewer

inpatient stays than their matched counterparts. AIT-treated adults did not differ from control subjects in the number of pharmacy fills and costs, but AIT-treated children incurred significantly lower pharmacy costs (despite a significantly higher number of prescription fills) than their matched counterparts. Similar to findings noted for the combined sample, significant differences ($P < .0001$) in mean total health care costs among adults and children separately occurred at 3-, 6-, 12-, and 18-month follow-up.

Magnitude of cost savings: AIT-treated adults versus children

Table V compares mean 18-month AIT-related cost savings for adults and children. The mean 18-month total per-patient health care cost savings achieved by AIT-treated adults did not significantly differ from that observed for children ($4,397 vs $3,965, $P = .435$). The mean 18-month per-patient cost savings for outpatient visits achieved by AIT-treated children was almost 3 times greater ($2,342 vs $811, $P < .0001$) than that achieved by AIT-treated adults.

DISCUSSION

Recent research using retrospective administrative claims data to examine the real-world outcomes of AR has consistently documented the significant economic benefits of AIT for children. In the present study we sought to extend this research to US adults with AR. Most notably, we found compelling cost benefits for AIT among US adults with AR that paralleled the benefits seen in children. Significant AIT-related cost savings were observed within 3 months of treatment initiation and persisted throughout the 18-month follow-up for the combined sample, as well as for adults and children separately. Findings demonstrated at 3 months in our study are consistent with research showing significantly reduced allergy symptoms within 12 to 14 weeks of AIT initiation.[34-36]

As a well-established, effective, and safe treatment for AR, AIT offers the potential for long-term effectiveness and preventive effects. Notwithstanding these potential benefits and despite evidence of patient dissatisfaction with symptomatic drug treatments for AR,[2,37] only 2% to 9% of US patients with an AR diagnosis receive AIT,[27,37-39] and a preponderance of patients who initiate AIT are likely to prematurely discontinue treatment.[27,39-43] Such underuse of AIT might result in suboptimal health outcomes among patients with AR.

Barriers to AIT access, which likely contribute to its underuse, include the disinclination of primary care providers, who are usually the initial point of contact for adults and children with AR,[37] to refer potential AIT candidates to allergy specialists. Lack of training in allergy/immunology during residency[44] and concerns regarding the loss of autonomy of patient care[45] have been identified as barriers to generalists' use of allergy specialist referral. On the basis of the superior outcomes seen among patients with respiratory allergy treated by allergy specialists versus generalists,[46-53] interventions that encourage collaboration between generalists and specialists could foster wider use of AIT.

Several limitations of our research should be mentioned. First, despite the matching procedures used, groups might have differed in ways other than exposure to AIT that affected observed cost differences. Although we matched patients on the presence of allergy-related comorbid disease, including asthma, before AIT initiation, it is possible that patients who received AIT had more poorly controlled asthma, which might have increased costs because of more frequent use of asthma-related emergency visits and hospitalizations. However, this seems unlikely because poorly controlled asthma is a relative contraindication for AIT because of the risk of anaphylaxis.[7] In addition to our primary, matched cohort analysis, we subsequently examined whether the AIT-treated and control groups, each in aggregate, differed by overall disease and respiratory illness burden in the year preceding AIT initiation (or comparable period for controls). This supplementary analysis showed that, compared to the control group, the AIT-treated group experienced significantly less overall comorbid disease burden, but greater respiratory illness burden, in the year preceding AIT initiation. How these differences might have affected cost outcomes is unknown, but AIT might have indirectly improved clinical and cost outcomes because the regimen requires regular and ongoing health care visits, which afford opportunities to address other health issues, including nonallergic respiratory conditions. In addition, although the validity of the CCI has been more extensively studied than other comorbidity measures[54] and was used as a measure of comorbidity in a cost study of children's asthma,[55] it has not been validated in a pediatric population. Therefore despite attempts to control for illness burden, the health status of groups might have differed and influenced use and cost outcomes.

Second, the retrospective nature of this study prohibits definitive conclusions about causality and introduces the possibility of bias. Regarding the latter, patients who elect to engage in the demands of AIT might be a more compliant group than those who do not elect to receive AIT. Given this proclivity, AIT-treated patients who receive allergy medications or recommendations for allergen avoidance might have derived greater clinical benefit and incurred lower costs than their counterparts who do not elect to receive AIT. We are currently conducting follow-up research to examine these complex issues more fully. We also acknowledge that many AIT-treated patients received fewer administrations than required to achieve maximum and long-lasting clinical benefit. Studies have demonstrated significant reductions in allergy symptoms after only 12 to 14 weeks of AIT, even though the greatest benefits are seen after the maintenance dose is achieved and maintained for at least 1 year. We are currently conducting additional analyses to examine the relationship between the frequency and duration of AIT and health outcomes.

Third, there are limitations regarding the generalizability of findings. Because this study involved Medicaid enrollees, findings might not apply to broader patient populations. In addition, excluded unmatched cases had a greater comorbid illness burden and higher prevalence of comorbid asthma than matched cases. Therefore findings might not generalize to populations that are comprised of more seriously ill patients with AR who initiate AIT.

Fourth, although pollen seasons in southern states, such as Florida, tend to begin earlier and last longer than those in northern states, a recent study demonstrated that the ragweed pollen season has lengthened in northern states while remaining stable in southern states, most likely because of climate change.[56] Because of the longer pollen season in southern states, mean medical costs for patients with AR in this study might be higher than those for similar patients living in cooler climates; however, the length of the pollen season should not influence the magnitude of cost differences observed between AIT-treated and control patients.

Fifth, claims data might include missing, imprecise, or incorrect codes, although it is unlikely that such errors would systematically differ across cohorts.

Sixth, because the follow-up period was limited to 18 months, results might underestimate the long-term clinical and economic benefits associated with AIT, considering its potential to reduce the risk of asthma,[10,11,57] one of the most common and costly chronic US childhood and adult diseases.[58]

Finally, given the limitations of claims data, we were unable to estimate the societal burden of AR associated with lost productivity and patients' out-of-pocket expenditures (eg, for over-the-counter medications) to treat AR. In light of its high prevalence and significant effect on job and school performance, the indirect costs of AR are substantial and exceed those of other costly chronic diseases, including asthma, diabetes, and coronary heart disease.[59]

This study constitutes the first demonstration of significant cost benefits associated with AIT among US adults, who experienced comparable overall AIT-related cost savings compared with those seen in children. Our research approach is consistent with the call for comparative effectiveness research that reflects real-world interventions and provides public health guidance regarding the effective care of high-cost, widely prevalent, and preventable diseases.[60] Because new and likely more expensive symptomatic drug treatments for AR and asthma proliferate, it might be wise to first benchmark the clinical and cost benefits offered by AIT. On the basis of the growing evidence of the efficacy, safety, and cost benefits of AIT, implementation of coordinated efforts to remediate modifiable barriers to AIT access, adoption, and adherence could increase appropriate use of this disease-modifying treatment and ultimately reduce the public health burden of AR and AR-related disease progression.

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Clinical implications: Comparable, statistically significant health care cost benefits were achieved by children and adults with a diagnosis of AR who initiated AIT. Benefits appeared within 3 months of treatment initiation and continued through the 18-month follow-up.

REFERENCES

1. The American Academy of Allergy, Asthma & Immunology (AAAAI). The allergy report. Milwaukee (WI): AAAAI; 2000.
2. Meltzer EO, Blaiss MS, Derebery MJ, Mahr TA, Gordon BR, Sheth KK, et al. Burden of allergic rhinitis: results from the Pediatric Allergies in America survey. J Allergy Clin Immunol 2009;124(suppl):S43-70.
3. Long AA. Findings from a 1000-patient internet-based survey assessing the impact of morning symptoms on individuals with allergic rhinitis. Clin Ther 2007;29: 342-51.
4. Soni A. Allergic rhinitis: trends in use and expenditures, 2000 to 2005. Statistical Brief #204. Bethesda: Agency for Healthcare Research and Quality; 2008.
5. Blaiss MS. Allergic rhinitis: direct and indirect costs. Allergy Asthma Proc 2010; 31:375-80.
6. Noon L, Cantab BC. Prophylactic inoculation against hay fever. Lancet 1911;1: 1572-4.
7. Cox L, Nelson H, Lockey R, Calabria C, Chacko T, Finegold I, et al. Allergen immunotherapy: a practice parameter third update. J Allergy Clin Immunol 2011; 127(suppl):S1-55.
8. Moller C, Dreborg S, Ferdousi HA, Halken S, Host A, Jacobsen L, et al. Pollen immunotherapy reduces the development of asthma in children with seasonal rhinoconjunctivitis (the PAT-study). J Allergy Clin Immunol 2002;109:251-6.
9. Niggemann B, Jacobsen L, Dreborg S, Ferdousi HA, Halken S, Host A, et al. Five-year follow-up on the PAT study: specific immunotherapy and long-term prevention of asthma in children. Allergy 2006;61:855-9.
10. Jacobsen L, Niggemann B, Dreborg S, Ferdousi HA, Halken S, Host A, et al. Specific immunotherapy has long-term preventive effect of seasonal and perennial asthma: 10-year follow-up on the PAT study. Allergy 2007;62:943-8.
11. Novembre E, Galli E, Landi F, Caffarelli C, Pifferi M, De Marco E, et al. Coseasonal sublingual immunotherapy reduces the development of asthma in children with allergic rhinoconjunctivitis. J Allergy Clin Immunol 2004;114:851-7.
12. Des Roches A, Paradis L, Menardo JL, Bouges S, Daures JP, Bousquet J. Immunotherapy with a standardized *Dermatophagoides pteronyssinus* extract. VI. Specific immunotherapy prevents the onset of new sensitizations in children. J Allergy Clin Immunol 1997;99:450-3.
13. Pajno GB, Barberio G, De Luca F, Morabito L, Parmiani S. Prevention of new sensitizations in asthmatic children monosensitized to house dust mite by specific immunotherapy. A six-year follow-up study. Clin Exp Allergy 2001;31: 1392-7.
14. Marogna M, Spadolini I, Massolo A, Canonica GW, Passalacqua G. Randomized controlled open study of sublingual immunotherapy for respiratory allergy in real-life: clinical efficacy and more. Allergy 2004;59:1205-10.
15. Purello-D'Ambrosio F, Gangemi S, Merendino RA, Isola S, Puccinelli P, Parmiani S, et al. Prevention of new sensitizations in monosensitized subjects submitted to specific immunotherapy or not. A retrospective study. Clin Exp Allergy 2001;31: 1295-302.
16. Reha CM, Ebru A. Specific immunotherapy is effective in the prevention of new sensitivities. Allergol Immunopathol (Madr) 2007;35:44-51.
17. Inal A, Altintas DU, Yilmaz M, Karakoc GB, Kendirli SG, Sertdemir Y. Prevention of new sensitizations by specific immunotherapy in children with rhinitis and/or asthma monosensitized to house dust mite. J Investig Allergol Clin Immunol 2007;17:85-91.
18. Eng PA, Borer-Reinhold M, Heijnen IA, Gnehm HP. Twelve-year follow-up after discontinuation of preseasonal grass pollen immunotherapy in childhood. Allergy 2006;61:198-201.
19. Mosbech H, Osterballe O. Does the effect of immunotherapy last after termination of treatment? Follow-up study in patients with grass pollen rhinitis. Allergy 1988; 43:523-9.
20. Jacobsen L, Nuchel Petersen B, Wihl JA, Lowenstein H, Ipsen H. Immunotherapy with partially purified and standardized tree pollen extracts. IV. Results from long-term (6-year) follow-up. Allergy 1997;52:914-20.
21. Hedlin G, Heilborn H, Lilja G, Norrlind K, Pegelow KO, Schou C, et al. Long-term follow-up of patients treated with a three-year course of cat or dog immunotherapy. J Allergy Clin Immunol 1995;96:879-85.
22. Durham SR, Varney VA, Gaga M, Jacobson MR, Varga EM, Frew AJ, et al. Grass pollen immunotherapy decreases the number of mast cells in the skin. Clin Exp Allergy 1999;29:1490-6.
23. Di Rienzo V, Marcucci F, Puccinelli P, Parmiani S, Frati F, Sensi L, et al. Long-lasting effect of sublingual immunotherapy in children with asthma due to house dust mite: a 10-year prospective study. Clin Exp Allergy 2003;33:206-10.
24. Marogna M, Bruno M, Massolo A, Falagiani P. Long-lasting effects of sublingual immunotherapy for house dust mites in allergic rhinitis with bronchial hyperreactivity: a long-term (13-year) retrospective study in real life. Int Arch Allergy Immunol 2007;142:70-8.
25. Ariano R, Kroon AM, Augeri G, Canonica GW, Passalacqua G. Long-term treatment with allergoid immunotherapy with *Parietaria*. Clinical and immunologic effects in a randomized, controlled trial. Allergy 1999;54:313-9.
26. Hankin CS, Cox L, Lang D, Bronstone A, Fass P, Leatherman B, et al. Allergen immunotherapy and health care cost benefits for children with allergic rhinitis: a large-scale, retrospective, matched cohort study. Ann Allergy Asthma Immunol 2010;104:79-85.
27. Hankin CS, Cox L, Lang D, Levin A, Gross G, Eavy G, et al. Allergy immunotherapy among Medicaid-enrolled children with allergic rhinitis: patterns of care, resource use, and costs. J Allergy Clin Immunol 2008;121:227-32.
28. Lockey RF, Hankin CS. Health economics of allergen specific Immunotherapy in the United States of America. J Allergy Clin Immunol 2011;127:39-43.
29. Charlson ME, Pompei P, Ales KL, MacKenzie CR. A new method of classifying prognostic comorbidity in longitudinal studies: development and validation. J Chronic Dis 1987;40:373-83.
30. Deyo RA, Cherkin DC, Ciol MA. Adapting a clinical comorbidity index for use with ICD-9-CM administrative databases. J Clin Epidemiol 1992;45:613-9.
31. Perkins AJ, Kroenke K, Unutzer J, Katon W, Williams JW Jr, Hope C, et al. Common comorbidity scales were similar in their ability to predict health care costs and mortality. J Clin Epidemiol 2004;57:1040-8.
32. Dominick KL, Dudley TK, Coffman CJ, Bosworth HB. Comparison of three comorbidity measures for predicting health service use in patients with osteoarthritis. Arthritis Rheum 2005;53:666-72.
33. Manning WG, Basu A, Mullahy J. Generalized modeling approaches to risk adjustment of skewed outcomes data. J Health Econ 2005;24:465-88.