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Off-Label Topical Calcineurin Inhibitor Use in Children

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KEY WORDS

topical calcineurin inhibitors, pharmacoepidemiology, off-label drug use

ABBREVIATIONS

AD—atopic dermatitis
FDA—US Food and Drug Administration
TCI—topical calcineurin inhibitor

Dr Manthripragada conceptualized and designed the study and drafted the initial manuscript; Dr Pinheiro conceptualized and designed the study and reviewed and revised the manuscript; Dr MaCurdy oversaw the analysis and critically reviewed the manuscript; Mr Saneinejad and Mr Worrall carried out the analysis and critically reviewed the manuscript; Dr Kelman oversaw the analysis and critically reviewed the manuscript; Dr Graham conceptualized and designed the study and reviewed and revised the manuscript; and all authors approved the final manuscript as submitted.

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WHAT'S KNOWN ON THIS SUBJECT: In January 2006, a public health advisory and boxed warning for long-term safety and the risk of malignancies and a medication guide were issued for topical calcineurin inhibitors, tacrolimus and pimecrolimus.

WHAT THIS STUDY ADDS: Evaluation of off-label use of topical calcineurin inhibitors in children before and after regulatory action by the Food and Drug Administration is important to understand the impact of regulatory action.

abstract

OBJECTIVE: To assess off-label use of the topical calcineurin inhibitors (TCIs), tacrolimus and pimecrolimus, in children during periods before and after regulatory action by the US Food and Drug Administration (FDA) in 2005.

METHODS: We identified new pediatric (age <20 years) users of topical tacrolimus or pimecrolimus in US Medicaid from 2001 to 2009, and examined the annual rate of drug use (pre- and postregulatory action) by age. We assessed medical claims for diagnoses consistent with an indication for a TCI, and assessed prescriptions for evidence of first-line atopic dermatitis therapy use before TCI initiation.

RESULTS: There were 57 664 eligible pediatric tacrolimus users and 425 242 eligible pediatric pimecrolimus users at baseline. The rate of TCI use decreased substantially after FDA regulatory action. The proportion of new users younger than 2 years of age significantly decreased for both tacrolimus (36.7% to 22.5%, $P < .001$) and pimecrolimus (47.0% to 33.7%, $P < .001$) after regulatory actions. Previous use of topical corticosteroids increased by ~7% for both TCIs from the pre- to postregulatory period. However, after regulatory actions, there was only a small increase in the proportion of tacrolimus or pimecrolimus users with an atopic dermatitis or eczema diagnosis before drug initiation, and high strength use of tacrolimus was unchanged.

CONCLUSIONS: The rate of TCI use in children younger than 2 years of age fell substantially after FDA regulatory action in 2005. Off-label use of TCI as first-line therapy changed little. *Pediatrics* 2013;132:e1327–e1332

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The topical calcineurin inhibitors (TCIs), tacrolimus (Protopic [Astellas Pharma US, Inc, Northbrook, IL]) and pimecrolimus (Elidel [Meda Pharmaceuticals, Somerset, NJ]), are potent immunosuppressants that act by inhibiting T-lymphocyte activation and the release of proinflammatory cytokines via a calcineurin-mediated pathway.[1,2] Tacrolimus and pimecrolimus were approved by the US Food and Drug Administration (FDA) in December 2000 and 2001, respectively, as second-line therapies for the short and intermittent treatment of mild to moderate atopic dermatitis (AD). Pimecrolimus 1% and tacrolimus 0.03% ointment are indicated for adults and children ≥2 years of age, whereas tacrolimus 0.1% ointment is indicated for adults only.[1,2] Perhaps not unexpectedly, TCIs have been used off-label in children as first-line treatments for AD, and in children younger than the age of 2.[3]

One of the leading safety concerns with TCIs has been whether they might increase the risk of malignancy. During preclinical development, carcinogenicity signals were reported in both mice and monkeys.[3] Additionally, orally or intravenously administered tacrolimus is associated with an increased risk of lymphoproliferative disorders and skin cancer in transplant recipients.[4] Although TCIs are not administered systemically, systemic absorption after topical application has been reported, with increased absorption in AD resulting in greater systemic exposure.[3,5] Systemic absorption of TCIs is of particular concern in the pediatric age group, where the ratio of body surface area to weight is greatest. This may explain why detectable blood levels of these drugs are more frequently observed in children than in adults.[3]

In March 2005, the FDA issued a public health advisory warning of a potential malignancy risk with TCIs, and stated that TCIs should be used only as second-line agents, only for short periods of time, and only in children at least 2 years of age.[6] There was a general concern that TCIs were being used increasingly off-label, perhaps due in part to the heavy promotion for use in young children.[3] Supporting data revealed that from June 2003 through May 2004, the number of prescriptions dispensed for topical tacrolimus had increased by 16% and for pimecrolimus by 46%, compared with the previous year. In this same time period, patients aged 1 to 2 years accounted for 8% and 13% of topical tacrolimus and pimecrolimus prescriptions, respectively.[3] In January 2006, a boxed warning was added to TCI labeling, and a medication guide describing the potential malignancy risk with these products was issued. In March 2006, this warning was sent to prescribing physicians as a "Dear Health Care Provider" letter.

Despite heightened regulatory activity in 2005–2006, the impact of the FDA's actions on off-label use has not been carefully evaluated in a population-based study. The purpose of this study was to assess off-label use of TCIs in children during periods before and after the FDA's public health advisory and boxed warning. Specifically, we sought to determine whether off-label use in children <2 years of age and as a first-line therapy decreased after the FDA's labeling action. The impact of the boxed warning is especially important given that on May 16, 2011, the Pediatric Advisory Committee voted to leave the existing warning given currently available data on malignancy risk.[7]

METHODS

Study Population

Through the SafeRx Project, a collaboration between the Centers for Medicare & Medicaid Services and the FDA, a database containing all health care utilization and drug prescription claims for Medicaid recipients from the 50 states and the District of Columbia was created, covering the years 1999 to the present. We identified all pediatric (age <20 years) patients with a prescription for topical tacrolimus or pimecrolimus during the period January 1, 2001, through December 31, 2009. Children age 1 year or older were enrolled in a new-user study cohort if they had at least 183 days of previous continuous Medicaid enrollment and during which they did not have a prescription for a TCI. For children younger than 1 year of age, a minimum of 30 days of previous continuous Medicaid enrollment with no prescription for a TCI was required, thereby also permitting the inclusion of younger children in the study.

For each cohort member, demographic and claims data for all inpatient and outpatient medical encounters during the study period were collected, as were prescription data, including the name, strength, and dispensing date for all TCI prescriptions. We excluded children with a previous diagnosis of cancer, HIV/AIDS, or organ transplantation, or with previous chemotherapy, antiretroviral therapy, or systemic immunosuppressive prescriptions.

Statistical Analyses

We examined characteristics of tacrolimus and pimecrolimus users, including age and gender. Medical claims within the 183 days before filling of the first TCI prescription (or within 30 days before for children <1 year old) were analyzed for the presence of the AD (*International Classification of Diseases, Ninth Revision, Clinical Modification* code 691), eczema (code 692), other allergic dermatitis (code 693), psoriasis (code 696), allergic conjunctivitis (codes 372.0–372.3), allergic

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rhinitis (code 477), rash and other nonspecific skin eruptions (code 782.1), impetigo (code 684), and dermatophytosis of the body (code 110.5). We also assessed prescription claims for topical corticosteroid use during the period before TCI use and for use of medications that would not necessarily be expected to precede TCI use including oral corticosteroids, oral antihistamines, asthma inhalers (inhaled β-agonists), and asthma inhaled corticosteroids. Lastly, we determined the average number of refills per patient within a year, with patients followed until end of continuous fee for service (FFS) Medicaid enrollment, Dec 31, 2009, 1 year after medication initiation, or death.

We estimated the rate of new (incident) tacrolimus and pimecrolimus users per 100 000 children over time according to age category (ie, <1 year, 1 to <2 years, 2–19 years), by using Medicaid beneficiaries of the same age meeting the same enrollment requirements as the denominator.

We also evaluated the proportion of pimecrolimus and tacrolimus users with evidence of off-label use defined by age (<2 years) and initial treatment (no previous treatment with a topical corticosteroid) during the periods before the FDA's regulatory actions (2001–2004) and after (2007–2009). The mean number of refills per patient within a year after initiation during these time periods was also examined. The FDA regulatory actions included a public health advisory concerning a potential malignancy risk with TCI exposure issued on March of 2005, a boxed warning and a medication guide describing the potential malignancy risk issued on January of 2006, and a Dear Health Care Provider letter sent to prescribers on March of 2006. χ^2 tests were performed to identify statistically significant differences between these time periods.

RESULTS

From 2001 to 2009, we identified 58 648 and 429 495 children who initiated treatment with topical tacrolimus or pimecrolimus, respectively. Of these, 984 and 4253 were excluded due to other diagnoses (n = 772 and 3225) or being in pediatric nursing facilities (n = 212 and 1028). Thus we identified 57 664 eligible children who initiated treatment with topical tacrolimus and 425 242 with topical pimecrolimus. TCI use did not differ by gender, and the mean age of pediatric users was similar for both drugs (Table 1). The majority of users (64.3% of tacrolimus; 76.4% of pimecrolimus) did not have a diagnosis of AD or eczema during the preinitiation period. The presence of a diagnosis of psoriasis, allergic conjunctivitis, allergic rhinitis, and rash and other nonspecific skin eruptions was relatively infrequent across both cohorts. Use of topical corticosteroids before TCI initiation was low for both products (39.5% for tacrolimus; 21.2% for pimecrolimus). Mean tacrolimus refills within a year after initiation were slightly higher than mean pimecrolimus refills after initiation (tacrolimus: <2 years, 1.75 refills; ≥2 years, 1.87 refills; pimecrolimus: <2 years, 1.63 refills; ≥2 years, 1.62 refills). Average follow-up time ranged from 250.8 days to 296.7 days.

The rate of initiation of tacrolimus and pimecrolimus rapidly increased in children <2 years of age within a short time after drug approval (Figs 1 and 2). The rate of initiation of both products was higher among children <1 year and 1 to <2 years than among those age 2 to 19 years across the entire study period, with the exception of pimecrolimus use in children <1 year in 2009. For both tacrolimus and pimecrolimus, rates of initiation among <1 year and 1 to <2 year olds followed similar patterns over time. For both age groups, the rate of tacrolimus initiation peaked in 2003/2004 (<1 year: 368.9 per 100 000; 1 to <2 years: 383.5 per 100 000), and the rate of pimecrolimus initiation peaked in 2004 (<1 year: 5449.3 per 100 000; 1 to <2 years: 4601.8 per 100 000). The rates of initiation of both products in children age <1 year and age 1 to <2 years dropped markedly in 2005, the year of the public health advisory, and dropped again in 2006, the year the boxed warning was issued. Rates of tacrolimus and pimecrolimus initiation among children age 2 to 19 years also

TABLE 1 Characteristics of Pediatric Study Cohort, 2001–2009

	Tacrolimus, n = 57 664	Pimecrolimus, n = 425 242
Age, mean (SD), y	5 (5)	4 (5)
Girls, %	50.4	50.2
Medical conditions, %[a]		
AD or eczema	33.1	21.0
Other allergic dermatitis	0.7	0.4
Psoriasis	1.7	0.6
Allergic conjunctivitis	4.0	4.0
Allergic rhinitis	8.0	7.1
Rash and other nonspecific skin eruption	6.4	6.2
Impetigo	2.9	2.0
Dermatophytosis of the body	2.0	1.5
Medication use, %[a]		
Topical corticosteroids	33.7	16.5
Oral corticosteroids	12.1	9.1
Oral antihistamines	24.2	19.2
Inhaled β-agonists	17.4	14.6
Inhaled corticosteroids	7.8	6.0

[a] Within 183 d preceding study entry for children ≥1 y; within 30 d for children <1 y.

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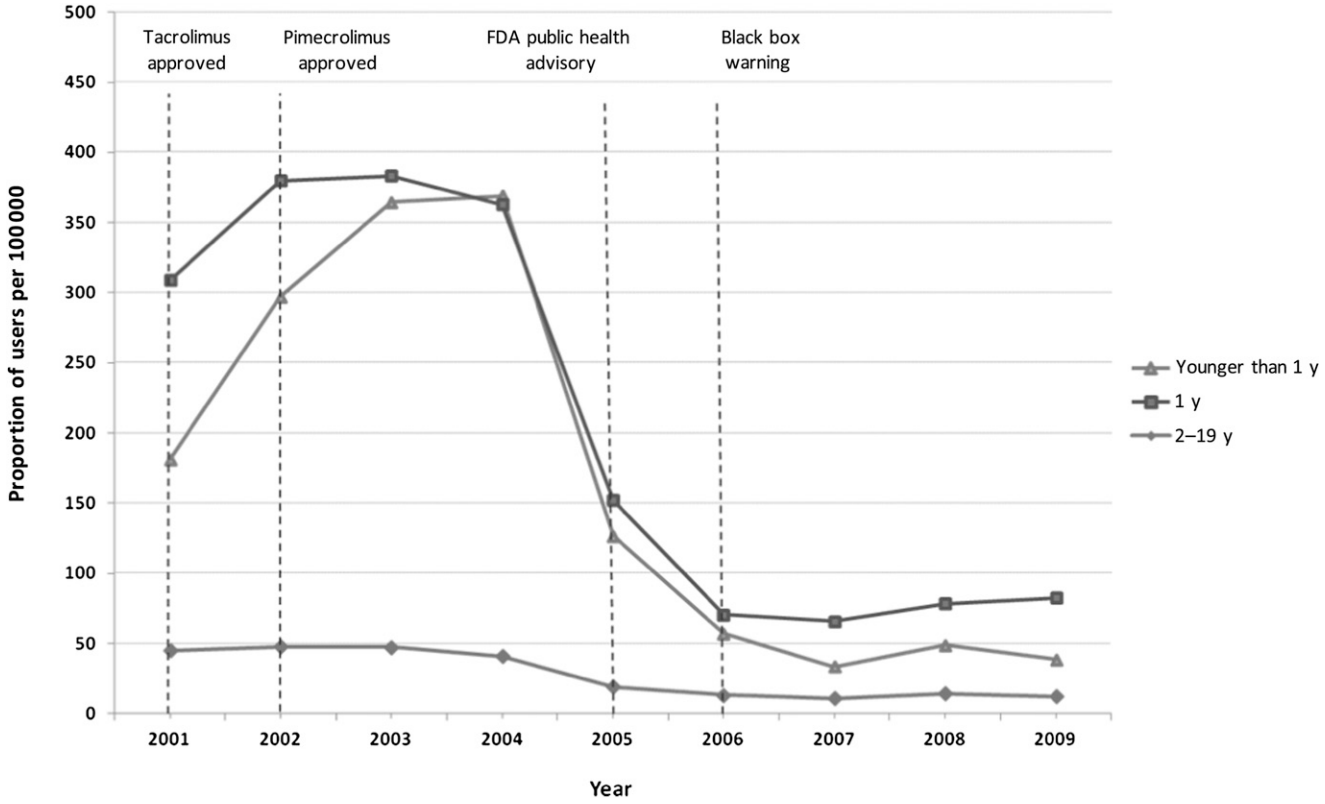


FIGURE 1
Rate of initiation of tacrolimus among beneficiaries <20 years by age and calendar year, Medicaid 2001–2009.

decreased post regulatory actions. Although the rate of initiation of both medications decreased post regulatory action, the mean number of prescriptions within a year after initiation appeared relatively stable for the pre- and postregulatory periods for both age groups (tacrolimus users: <2 years, 2.6 vs 2.3; 2+ years, 2.4 vs 2.2; pimecrolimus users: <2 years, 2.5 vs 2.1; 2+ years: 2.0 vs 1.9).

Table 2 reveals the characteristics of tacrolimus and pimecrolimus use before and after regulatory action. The proportion of tacrolimus users with a previous AD or eczema diagnosis increased little after regulatory action (33.2% to 34.5%), whereas for pimecrolimus there was a slightly larger increase (20.7% to 25.8%). A sensitivity analysis using a 365-day window revealed only a small increase in the percentage of AD or eczema diagnoses (data not shown). Previous use of a topical corticosteroid increased by ~7% for both tacrolimus and pimecrolimus from the pre- to postregulatory period. Nonetheless, during the period after regulatory actions, most children still did not receive topical corticosteroids before initiating a TCI. The proportion of users younger than 2 years of age significantly decreased for both tacrolimus (36.7% to 22.5%, $P < .001$) and pimecrolimus (47.0% to 33.7%, $P < .001$) after the regulatory actions. Of note, the contraindicated use of the higher strength tacrolimus ointment (0.03%) among children younger than age 2 years remained essentially unchanged.

DISCUSSION

We observed large decreases in the rate of new use of tacrolimus and pimecrolimus in the Medicaid pediatric population coincident with FDA regulatory actions in 2005 and 2006. In particular, there was an abrupt decrease in off-label use by children younger than 2 years of age. Although we cannot definitively attribute these decreases to specific FDA actions or publicity surrounding these actions, the decreases appear to coincide with the FDA's public health advisory and boxed warning, which emphasized the potential risk of malignancy and that use among children younger than 2 years of age was not an approved use.[6] Although off-label TCI use in children younger than 2 years of age decreased after FDA regulatory action, the rate of use remained slightly higher than or similar to the rate observed in children >2 years. Additionally, use of the higher strength tacrolimus (0.1%) ointment among children <2 years, which is indicated for patients >15 years only, did not change. The FDA's regulatory actions also did not lead to a marked reduction in off-label use of

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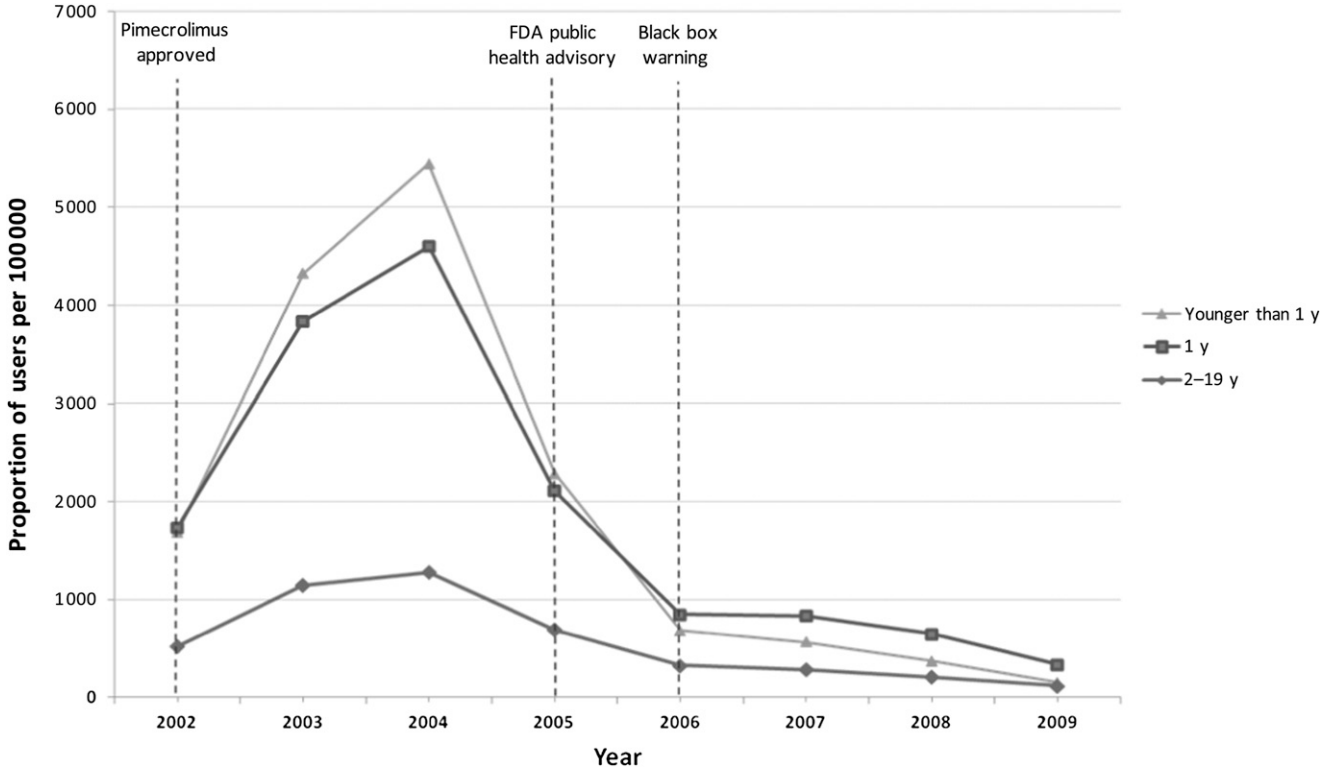


FIGURE 2
Rate of initiation of pimecrolimus among beneficiaries <20 years by age and calendar year, Medicaid 2001–2009.

TABLE 2 Characteristics of Tacrolimus and Pimecrolimus Use, Pre- (2001–2004) and Postregulatory (2007–2009) Action

	Tacrolimus			Pimecrolimus		
	% of Total Users		P^a	% of Total Users		P^a
	2001–2004	2007–2009		2001–2004	2007–2009	
All children <20 y[b]						
	N = 43 556	*N* = 6030		*N* = 297 853	*N* = 36 311	
Previous AD or eczema diagnosis	33.2	34.5	.04	20.7	25.8	<.001
Previous TCS use	33.2	41.5	<.001	16.1	22.8	<.001
Children <2 y[b]						
	N = 15 965	*N* = 1354		*N* = 140 047	*N* = 12 221	
Users <2 y	36.7	22.5	<.001	47.0	33.7	<.001
High strength use	27.4	27.2	.9	NA	NA	

NA, not available; TCS, topical corticosteroid.
[a] χ^2 *P* values comparing pre- and postintervention periods.
[b] 183-d clean period for children ≥1 y; 30-d clean period for children <1 y.

these products as first-line therapies. This is particularly concerning given that this type of off-label use could result in children not receiving the most effective and safest drug in an appropriate manner.[8] Although the increase in use of topical corticosteroids before TCI initiation in the period after FDA regulatory action was statistically significant, it is likely to have negligible public health impact, with most children not being treated with them before TCI therapy initiation. The magnitude of this off-label use was greater for pimecrolimus than tacrolimus. This could be explained by varying indications for the 2 drugs with pimecrolimus indicated for mild to moderate AD and tacrolimus indicated for moderate to severe AD. There was little or no increase in the proportion of children having a diagnosis of AD or eczema before starting tacrolimus or pimecrolimus after the FDA's regulatory action, and even then, most children did not have 1 of these diagnoses during the baseline period. Given the relatively short prior-use window of 183 days used in primary analyses, we may not have captured all diagnoses; a sensitivity analysis using a 365-day window only revealed a small increase in the percentage of AD or eczema diagnoses. Additionally, the sensitivity and the specificity of the *International Classification of Diseases, Ninth Revision, Clinical Modification* codes used to capture AD or eczema has not been established.

Two previous studies examined the use of TCIs in children. One study, published in abstract form only, revealed substantial declines in TCI use by children

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younger than the age of 2 in 2005 and again in 2007, using a pharmacy claims database.[9] The other was a cross-sectional study that examined the prescription of TCIs in visits for AD by children (0–18 years) by using the National Ambulatory Medical Care Survey and the National Hospital Ambulatory Care Survey databases.[10] The study revealed that topical tacrolimus was prescribed in 0.5 million (10%) and topical pimecrolimus was prescribed in 0.6 million (13%) of the 4.6 million AD visits in 2001 to 2004. The study also noted off-label use in children younger than 2 years, with TCIs prescribed in 22% of visits to office-based physicians or hospital outpatient departments in children younger than 2 years.

There were several important limitations to our study. Although we used a nation-wide cohort of pediatric patients from Medicaid, these differ from the general (non-Medicaid) population in terms of socioeconomic status and may carry a higher burden of medical comorbidities. Given the current AD treatment options, however, we do not expect that these differences would affect the TCI usage patterns we observed. There is also concern that the quality of medical care provided through Medicaid might be different than that available through the private sector, and that physicians who treat large numbers of Medicaid patients may differ in background and training from physicians treating privately insured patients. The potential impact of this concern on the generalizability of our results could be addressed by repeating this analysis in a privately insured population.

CONCLUSIONS

Off-label use of TCIs in children younger than 2 years of age decreased substantially in association with FDA regulatory actions, with the exception of the higher strength tacrolimus ointment. However, off-label use of TCIs as a first-line therapy in pediatric patients did not decrease and continues to remain a concern.

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