Healthcare utilization in Danish children with atopic dermatitis and parental topical corticosteroid phobia

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Comparing Prescribing Patterns for Topical Corticosteroids Based on their FDA Indication by Age

Megan E. Freeze¹, BS, Esther A. Balogh¹, MD, Abigail Cline¹, MD, PhD; Steven R. Feldman¹,²,³,⁴, MD, PhD; Alan B. Fleischer, Jr.⁵

¹ Center for Dermatology Research, Department of Dermatology, Wake Forest School of Medicine, Winston-Salem, North Carolina
² Department of Pathology, Wake Forest School of Medicine, Winston-Salem, North Carolina
³ Department of Social Sciences & Health Policy, Wake Forest School of Medicine, Winston-Salem, North Carolina
⁴ Department of Dermatology, University of Southern Denmark, Odense, Denmark
⁵ Department of Dermatology, University of Cincinnati

Address correspondence to:
Megan Freeze
Department of Dermatology, Wake Forest School of Medicine

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Megan Freeze, Esther A. Balogh and Abigail Cline have no conflicts to disclose.

Dr. Alan B. Fleischer is a consultant for Boehringer-Ingelheim, Dermavant, Incyte, Qurient, SCM Lifescience and Syneos. He is an investigator for Galderma, Menlo and Trevi.
Abstract

Background/Objectives: Atopic dermatitis (AD) affects up to 20% of the pediatric population, with a growing prevalence over the past 30 years. Topical corticosteroids (TCS) are commonly used as a first-line topical therapy for AD and are prescribed in 59% of all AD visits. However, some topical corticosteroids are prescribed outside of their age range indications. This paper aims to explore the frequency with which topical corticosteroids are prescribed for AD outside of their FDA-approved age range.

Methods: Data on prescribing patterns for AD were obtained from the National Ambulatory Medical Care Survey (NAMCS). We assessed the frequency of off-label use of topical corticosteroids with respect to age indications in four specific age groups, as delineated in the data (0-1 year, 2-7 years, 8-18 years, and 19+ years).

Results: All prescribed topical corticosteroids found in the NAMCS database have an indication for AD or other inflammatory dermatoses or pruritic dermatoses. However, some medications were prescribed outside of their FDA-approved age indications. These off-label prescription rates ranged from 52% for desoximetasone to 0% for halobetasol and alclometasone, or rates lower than could be detected by our study.

Conclusions: Much like other medications for AD treatment, TCS are sometimes used off-label. The off-label use of topical corticosteroids to treat pediatric AD highlights a gap between clinical practice and regulating guidelines. Additional pediatric studies would offer a greater body of evidence to maintain or expand label indications for the use of TCS in younger patients.

Introduction

Atopic dermatitis (AD) affects up to 20% of the pediatric population, with a two- to three-fold increase in prevalence over the past 30 years. With this increase in the number of AD patients, including infants and young children, providers require safe and efficacious medications to successfully treat these pediatric patients.
While TCS are commonly used as a first-line treatment for AD and prescribed in 59% of all AD visits, many are prescribed off-label.²⁻⁴ This is not isolated to TCS, as an estimated 21% of all drugs are prescribed off-label in the United States,⁵ with higher off-label use in pediatric populations (31%).⁶ Adverse events such as pruritus, skin burning, folliculitis and skin infection have occurred with use of TCS in pediatric populations even when used within label indications and age range.⁷⁻⁹ Off-label usage of TCS can also lead to adverse events. The FDA-approved age range indications of available TCS treatments vary (Table 1). This study explores the frequency with which topical corticosteroids are prescribed for AD outside of their FDA-approved age range and indication.

Methods

We obtained data from the National Ambulatory Medical Care Survey (NAMCS). The NAMCS is a national probability sample survey collected from ambulatory visits to emergency departments, outpatient departments, and ambulatory surgery locations of non-institutional, general and short-stay hospitals. Data is collected and submitted by physicians and their staff or Census Bureau field representatives from physician records. The NAMCS protocol has been approved by the NCHS Research Ethics Review Board annually since February 2003.¹⁰ We analyzed NAMCS weighted data on approximately 10.4 million pediatric AD patient visits collected from 2006 to 2015. Of these visits, 49% were for males, 51% were for females. Demographically, 71% were White, 19% were African American and 10% were Asian. 31% of visits were to pediatricians, 27% were to dermatologists, 11% were to family practitioners, and the remaining 31% were to other fields.² Prescriptions for each of these visits were tabulated and frequency of use was calculated.² Based on product label indications for use, we assessed the frequency of off-label use of TCS in the four specific age groups delineated in the NAMCS data (0-1 year, 2-7 years, 8-18 years, and 19+ years). Within each age group, we calculated an average prescription frequency by year or month for drugs whose age limit ended with an age category. Only those years/months outside of the labelled age range were included as off-label. Prescription data were not limited by provider type and therefore include data from providers in all fields of medicine, including pediatrics, dermatology, emergency medicine and family medicine. All potencies and preparations of the same drug were grouped together because the NAMCS data did not differentiate these. All TCS prescribed for AD in the NAMCS database

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were included in our off-label study except for triamcinolone, for which an age range indication is not specified on the FDA label.

**Results**

Only five of the TCS prescribed for AD in the NAMCS survey have an indication for AD specifically. All other TCS listed are indicated for either pruritic dermatoses or inflammatory dermatoses, of which AD could be considered a subset (Table 1). All TCS were prescribed in the 0 to 1-year cohort except clobetasol, alclometasone, beclomethasone and halobetasol. Halobetasol was the only TCS not prescribed in the 2 to 7-year cohort. Clobetasol, halobetasol, and alclometasone were not prescribed in the 8 to 18-year cohort. All TCS were prescribed in the 19+ age range.

TCS were prescribed for certain age groups despite not having an FDA indication for that age (Table 1 and 2). Desoximetasone had the greatest off-label prescription rate at 52%. Hydrocortisone and mometasone, despite having broad age indication of 2+ years, showed high values of off-label use at 43% and 30% respectively. Desonide and fluocinolone had low levels of off-label use. These two TCS are also labeled for use in children as young as 3 months, which may explain their low incidence of off-label use.

Alclometasone (approved for ages 1+ years) and halobetasol (approved for 19+ years) both had 0% off-label prescription use. Desoximetasone and clobetasol also had relatively high off-label rates at 52% and 34%, respectively.

**Discussion**

As a group, TCS are commonly used to treat pediatric patients with AD. Steroids range in potency from low to very high. Hydrocortisone is a low potency TCS that is one of the most commonly prescribed for pediatric AD patients (19%). However, hydrocortisone’s FDA-approved label only indicates use in patients two years or older, which offers some insight into the finding that in this dataset 43% of prescriptions for hydrocortisone are for age groups that are not listed in the labeling guidelines. Providers may choose this low-potency TCS as a first-line treatment for pediatric AD. Despite its low potency, hydrocortisone has been associated with adverse events such as erythema and skin infection even in patients within label indicated age groups. Given the widespread use, examining the rate of adverse events in patients younger than 3 years of age is critical for ensuring safe and effective use of these medications.
two years old may provide a basis for expanding the age label indications of some TCS to include this patient population. Alclometasone, desonide, and fluocinolone, prescribed at rates of 0.3%, 4.3% and 1.4% respectively, have low- to medium-potency and even lower age-range indications than hydrocortisone, likely explaining the lower rate of off-label use that was detected.

The off-label prescription rates of the higher potency TCS are less easily explained by their potency or age range indication. For example, both halobetasol and clobetasol, with prescriptions rates of 0.3% and 2.9%, are high- or very high-potency TCS with the same age indication (12+ years); yet we found that halobetasol was not prescribed off-label while the rate of off-label prescriptions for clobetasol was 34%. This difference could be explained by the earlier availability of a generic form of clobetasol. Alternatively, clobetasol’s high rate of off age label use could be due to clobetasol’s availability as a topical cream, lotion, solution foam, ointment, spray, gel and shampoo, whereas halobetasol is only available in ointment, cream and lotion formulations. Prescribers may prefer the mode of administration available for clobetasol or its price point over that of halobetasol. Mometasone, desoximetasone and betamethasone, with prescriptions rates of 4.3%, 1.0%, and 3.1%, are medium- to-high-potency TCS and come in formulations which can be less or equally as potent as halobetasol and clobetasol. In these cases, our lack of access to data on specific ester form, delivery vehicle, and concentration of the TCS limited our analysis of the correlation between TCS potency and off-label prescribing rates.

Triamcinolone, a medium-potency TCS with a prescription rate of 20.4%, does not specify an indicated age range on its FDA label, which by definition implies it is technically not used off-label in any age group. However, the label, along with other TCS drug labels, does caution prescribers to limit usage of the drug to the smallest necessary amount, as TCS drugs are more likely to disrupt the HPA axis in children, who have a different surface area to mass ratio than adults.

Some of the limitations of these results include a range of error in the off-label use rates, particularly for TCS whose labeled age limits fell between the age ranges of one of the four selected age cohorts in the NAMCS database. These drugs include desonide, fluocinolone, desoximetasone, clobetasol, and betamethasone. There is a margin of error in the off-age-label use rates due to the assumption that prescriptions for each age cohort were equally distributed.
among the years/months in that cohort. For example, if all desonide prescriptions for the 0-1 year cohort were actually prescribed in patients 3 months of age or older, then the true off-label rate would be 0%, and not 6%. This is the result of limitations in the granularity of our data. Additionally, our lack of access to data on specific ester form, delivery vehicle, and concentration of the TCS limited our analysis of the correlation between TCS potency and off-label prescribing rates.

Other limitations posed by the data include unrecorded information on the severity of AD in patients, the possible failure of prior treatments, and whether the patient encounter was an initial visit or follow-up. These limits are in part due to the cross-sectional nature of the NAMCS data, rather than a longitudinal design, which limits our ability to see the development of the disease in a particular patient. Understanding the severity of patients’ AD and the potential failure of prior treatments could offer a possible motivation for a provider using treatments outside of their FDA approved age ranges.

The use of evidence-based therapies for effective patient relief is a goal in medicine. Many of the TCS are labeled with a limited age range indication. Labeling changes are predicated on submission of substantial safety and efficacy data to the FDA for the proposed expansion of the age range indication, typically in the form of two or more well-controlled studies. The primary hurdle for age-label modification in pediatric drugs is the paucity of clinical trial data on children, leading to restricted age indications. Recent legislative changes including the Best Pharmaceuticals for Children Act in 2002 and the Pediatric Research Equity Act in 2003 have addressed some of these barriers by encouraging clinical studies in pediatric populations. Since their enactment, over 500 pediatric drug labelling changes have been made. Nevertheless, the frequent off-age-label use of TCS to treat pediatric AD highlights a gap between the realities of clinical practice and regulatory guidelines. Off-label TCS use in children is not necessarily dangerous and is currently within the standard of care for some dermatologic conditions such as AD, although adverse events have occurred. A systematic review of published trials addressing safety data on long-term use of TCS in children supported the use of low- to mid-potency TCS in pediatric populations based on multiple trials with patients whose ages were both within and outside drug label age indications. Physicians have a measure of liberty in their prescribing patterns based on widely accepted therapeutic value, proven efficacy.
through clinical trials, and believed potential benefit to the patient. While adult clinical trials have brought these TCS to market, additional pediatric studies, conducted and submitted to the FDA with the intention to update age label indications, would offer a greater body of evidence to maintain or expand label indications for the use of these topical drugs in younger patients.

Table 1: Product label indications and age range indications for topical corticosteroid preparations

<table>
<thead>
<tr>
<th>Topical Corticosteroid</th>
<th>Indication</th>
<th>Age Indications</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clobetasol</td>
<td>Atopic dermatitis</td>
<td>12+ years</td>
</tr>
<tr>
<td>Halobetasol</td>
<td>Pruritic dermatoses</td>
<td>12+ years</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>Pruritic dermatoses</td>
<td>13+ year</td>
</tr>
<tr>
<td>Desoximetasone</td>
<td>Atopic dermatitis</td>
<td>10+ years</td>
</tr>
<tr>
<td>Mometasone</td>
<td>Pruritic dermatoses</td>
<td>2+ years</td>
</tr>
<tr>
<td>Triamcinolone</td>
<td>Inflammatory dermatoses</td>
<td>No age specified</td>
</tr>
<tr>
<td>Fluocinolone</td>
<td>Atopic dermatitis</td>
<td>3 months+</td>
</tr>
<tr>
<td>Desonide</td>
<td>Atopic dermatitis</td>
<td>3 months+</td>
</tr>
<tr>
<td>Aleolometasone</td>
<td>Pruritic dermatoses</td>
<td>1+ years</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>Atopic dermatitis</td>
<td>2+ years</td>
</tr>
</tbody>
</table>

Table 2: Product label indications and frequency of off-label use for TCS
<table>
<thead>
<tr>
<th>Topical Corticosteroid</th>
<th>Total # of age-based off-label prescriptions</th>
<th>Ages prescribed</th>
<th>Percentage off-label use for AD</th>
</tr>
</thead>
<tbody>
<tr>
<td>Clobetasol</td>
<td>435,317</td>
<td>2 to 7 years; 19+ years</td>
<td>34%</td>
</tr>
<tr>
<td>Halobetasol</td>
<td>0</td>
<td>Only 19+ years</td>
<td>0%‡</td>
</tr>
<tr>
<td>Betamethasone</td>
<td>100,478</td>
<td>0 to 19+ years</td>
<td>18%</td>
</tr>
<tr>
<td>Desoximetasone</td>
<td>93,625</td>
<td>0 to 19+ years</td>
<td>52%</td>
</tr>
<tr>
<td>Mometasone</td>
<td>232,200</td>
<td>0 to 19+ years</td>
<td>30%</td>
</tr>
<tr>
<td>Fluocinolone</td>
<td>12,202</td>
<td>0 to 1 year; 19+ years</td>
<td>3%</td>
</tr>
<tr>
<td>Desonide</td>
<td>65,355</td>
<td>0 to 19+ years</td>
<td>6%</td>
</tr>
<tr>
<td>Alclometasone</td>
<td>0</td>
<td>2 to 7 years; 19+ years</td>
<td>0%‡</td>
</tr>
<tr>
<td>Hydrocortisone</td>
<td>1,559,704</td>
<td>0 to 19+ years</td>
<td>43%</td>
</tr>
</tbody>
</table>

†More detailed information regarding potency, formulation or preparation were not available. All formulations for each drug were combined.
‡This does not eliminate the possibility of these TCS being used off-label; the rates were not detected above this level in our study.
References


