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# Use of Systemic Immuno-Modulatory Medications in Children with Atopic Dermatitis

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## Abstract

**Objective:** Immuno-modulatory agents are increasingly discussed for the treatment of atopic dermatitis (AD) in children. We sought to understand patterns of systemic immuno-modulatory medication uses in children.

**Methods:** We used longitudinal patient data from an insurance claims database, IBM Market Scan, covering 185 million patients in the US between 2003 and 2016 to identify children with a diagnosis of AD (ICD-9 691.x or ICD-10 L20.9) associated with an outpatient or inpatient encounter. We computed the proportion of patients using systemic medications for the treatment of AD during the 6 months following the first office visit with a diagnosis of AD. Medications of interest include systemic non-biologic immuno-modulatory drugs and biologic immuno-modulatory drugs. We trended the use of systemic immuno-modulatory agents for the treatment of pediatric AD over a 10-year period, from 2005-2015, including for each agent separately.

**Results:** We identified 1.6 million children with AD and no other auto-immune or inflammatory conditions that would otherwise require immune-modulatory treatment. Across all age groups the use of biologic agents increased from 0.1 to 0.3 per 1,000 over the 10-year period from 2005-2015 and the use of non-biologic systemic immuno-modulatory drugs increased from 0.2 to 0.7 per 1,000. Among the non-biologic systemic agents' methotrexate was the one increasing fastest (0.1 to 0.3).

**Conclusion:** In children and adolescents diagnosed with atopic dermatitis and without other disease indication for their use, the new use of systemic immuno-modulatory agents was infrequent but steadily increasing over the past 10 years.

**Keywords:** Atopic dermatitis; Immuno-modulatory medications; Pediatric patients; Time trends; Epidemiology; Claims data

## Background

Atopic dermatitis (AD) is an inflammatory skin condition affecting 18 million adults, and 9.6 million children in the US, 3.2 million of those are estimated to suffer from severe AD [1]. In cases of more severe, refractory disease, treatment escalation to the off-label use of systemic immuno-modulatory agents is common Studies have shown promising results of biologic medications [2-4]. In cases of severe recalcitrant AD, refractory to lifestyle modification and topical agents, the next step in treatment escalation for many providers is the off-label use of systemic immune modulating agents. Case reports and some studies have shown promising results of both biologic and non-biologic systemic immune-modulatory medication use in the treatment of recalcitrant AD [2,5-10]. The biologic and non-biologic systemic drugs of choice for these patients are established treatments with indications in a number of other inflammatory and autoimmune conditions, such as psoriasis and rheumatoid arthritis [2-4,11,12].

Knowledge on the use of immuno-modulatory agents in the pediatric population has become increasingly more relevant as we enter into an era of biologics for atopic dermatitis. This study sought to understand patterns of systemic immuno-modulatory medication use in children.

## Methods

### Data source

We used longitudinal claims data from a large insurance claims database, IBM Market Scan covering approximately 185 million patients in the US between 2003 and 2016. The Patients in the databases are active employees, dependents, retirees, COBRA recipients, and Medicare or Medicaid enrollees. Data were drawn from large employers, health

plans, and public organizations in the United States. The database contains dated information on plan enrollment, healthcare utilization and expenditures, demographics, and integrated records for inpatient events, outpatient events, and pharmacy dispensing. All patient information was de-identified. The Brigham and Women's Hospital's institutional review board approved this study and signed data licensing agreements were in place.

## Patients

We identified children younger than 18 years with a diagnosis of AD (ICD-9 691.x or ICD-10 L20.9) associated with an outpatient or inpatient encounter between 2003 and 2016. Additionally, we required that these patients had been enrolled in their health plan during the 6 months prior to their diagnosis of AD. Key characteristics of interest were age, sex, region of residence, and prior topical corticosteroid use.

## Analysis

We tabulated patient characteristics and computed the proportion of patients using systemic medications for the treatment of AD during the 6 months following the first office visit with a diagnosis of AD (cohort entry). Medications of interest include systemic non-biologic immuno-modulatory drugs (cyclosporine, methotrexate, Mycophenolate and azathioprine) and biologic immuno-modulatory drugs (inflixumab, etanercept, ustekinumab, omalizumab, mepolizumab and rituximab), (e-appendix). Dupilumab, the only recently approved biologic for adults with AD, was not yet marketed in 2016. Analyses were stratified by age of the children. The non-biologic agents were selected for this study according to the 2014 American Academy of Dermatology recommendations for systemic treatments in AD [13]. Although there is less evidence demonstrating the efficacy of biologics in the treatment of AD, there is literature evaluating several biologic agents including ustekinumab, infliximab, omalizumab and others in the use of severe recalcitrant AD. These agents were therefore selected for inclusion in this analysis [3,5,6,8,14-24].

In addition, we computed the proportion of systemic immuno-modulatory drug use for each calendar year, from 2005 through 2015, individually and plotted a trend. Furthermore, we separated the data for cyclosporine, methotrexate, mycophenolate and azathioprine from the biologics. All analyses were conducted using the validated Action Evidence Platform [25].

# Results

Among 3.3 million patients with a diagnosis of AD, 1.6 million were younger than 18 years after all patients with inflammatory or autoimmune comorbidities that would be otherwise treated with systemic immuno-modulatory drugs had been excluded (**Table 1**).

**Table 1** Cohort of children diagnosed with AD and reasons for exclusions (CONSORT).

| | Less Excluded Patients | Remaining Patients |
|---|---|---|
| **All patients** | | 185,306,593 |
| Did not meet cohort entry criteria | -181,906,153 | 3,400,440 |
| Excluded due to insufficient enrollment | -23,025 | 3,377,415 |
| Excluded based on Transplantation | -321 | 3,377,094 |
| Excluded based on Congenital immunodeficiency | -3,672 | 3,373,422 |
| Excluded based on Occurrence of malignant cancer, any | -65,518 | 3,307,904 |
| Excluded based on Occurrence of Crohns disease | -5,145 | 3,302,759 |
| Excluded based on Occurrence of inflammatory bowel disease | -4,056 | 3,298,703 |
| Excluded based on Occurrence of ankylosing spondylitis | -825 | 3,297,878 |
| Excluded based on Occurrence of arthritis | -240,557 | 3,057,321 |
| Excluded based on Occurrence of autoimmune disorders* | -188,511 | 2,868,810 |
| Excluded based on Occurrence of connective tissue diseases | -8,068 | 2,860,742 |
| Excluded based on Occurrence of spondyloarthropathy | -3,520 | 2,857,222 |
| Excluded based on Occurrence of systemic vasculitis | -453 | 2,856,769 |
| Excluded based on Occurrence of HIV, AIDS, V | -2,066 | 2,854,703 |
| Excluded based on Age >= 18 years | -1,225,532 | 1,629,171 |
| Final cohort | | 1,629,171 |

Other autoimmune disorders including type-1-diabetes, psoriasis, psoriatic arthritis, lupus, lupus nephritis.

Most were infants (0-1 years: 18%), babies (1-2 years: 12%) and young children (2-4 years: 15%). 5% were in age the group 16-18 years. Among younger children 50% of patients were female, after the age of 14 about 60% were female (**Figure 1**).

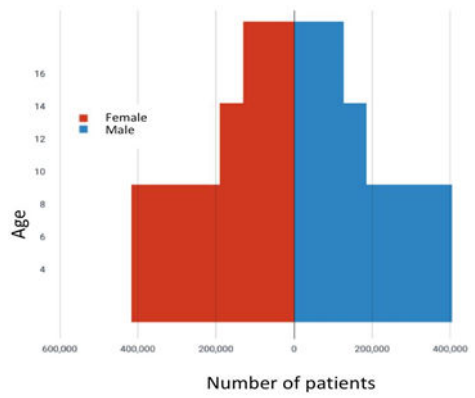


**Figure 1** Number of Patients with age.

Overall, 65% of patients used high-potency topical corticosteroids at least once during the 6 months after diagnosis. During this 6-month period, the use of systemic non-biologic immuno-modulators was 0.6 per 1,000 patients and use of biologics was 0.2 per 1,000 (**Table 2**).

**Table 2** Patient characteristics of 1.6 million children with atopic dermatitis.

| **Characteristic** | **N (%); risk (95% CI)** |
|---|---|
| Number of patients | 1,629,171 |
| Age, mean (sd) | 5.52 (5.06) |
| Age, median [IQR] | 4.00 [1.00, 9.00] |
| Male; n (%) | 824,883 (50.6%) |
| Region: Northeast; n (%) | 301,953 (18.8%) |
| Region: North Central; n (%) | 282,215 (17.6%) |
| Region: South; n (%) | 659,546 (41.1%)* |
| Region: West; n (%) | 310,376 (19.3%) |
| Age Categories | |
| ...< 1; n (%) | 286,476 (17.6%) |
| ...1 - 2; n (%) | 199,280 (12.2%) |
| ...2 - 4; n (%) | 250,218 (15.4%) |
| ...4 - 6; n (%) | 183.391 (11.3%) |
| ...6 - 8; n (%) | 157,038 (9.6%) |
| ...8 - 10; n (%) | 137,419 (8.4%) |
| ...10 - 12; n (%) | 118,804 (7.3%) |
| ...12 - 14; n (%) | 99,304 (6.1%) |
| ...14 - 16; n (%) | 84,786 (5.2%) |
| ...16 - 18; n (%) | 76,544 (4.7%) |
| High-potency topical corticosteroid use at time of AD diagnosis | 510/1,000 (509.3, 510.5) |
| Use of drugs during 6 months AFTER initial visit with a recorded diagnosis of AD | |
| Systemic Biologics | 0.19 (0.17, 0.21) |
| Systemic Non-Biologics** | 0.59 (0.55, 0.62) |
| Methotrexate | 0.26 (0.23, 0.28) |
| Cyclosporine | 0.21 (0.19, 0.23) |

| | |
|---|---|
| Mycophenolate | 0.11 (0.09, 0.13) |
| Azathioprine | 0.05 (0.04, 0.06) |
| *The southern states of the US are generally overrepresented by the insurance plans. **methotrexate, cyclosporine, mycophenolate, azathioprine. | |

In patients 0-5 years old, the new use of systemic non-biologics during 6 months after diagnosis was 0.23 per 1,000 patients and biologics was 0.02 per 1,000. Among the systemic non-biologics, new use of methotrexate was 0.11 per 1,000 patients, cyclosporine was 0.08 per 1,000, mycophenolate was 0.04 per 1,000 and azathioprine was 0.01 per 1,000 (**Table 3**).

**Table 3** Patient outcomes of 1.6 million children with atopic dermatitis, age stratified.

| | **Age: 0-5** | **Age: 6-12** | **Age: 13-17** |
|---|---|---|---|
| Characteristic | N (%); risk (95% CI) | N (%); risk (95% CI) | N (%); risk (95% CI) |
| Number of patients | 832,154 | 500,472 | 260,634 |
| Age, mean (sd) | 1.43 (1.38) | 7.72 (1.99) | 14.31 (1.71) |
| Age, median [IQR] | 1.00 [0.00, 2.00] | 8.00 [6.00, 9.00] | 14.00 [13.00, 16.00] |
| Male; n (%) | 449,236 (54.0%) | 244,999 (49.0%) | 110,569 (42.4%) |
| High-potency topical | 364,142 (43.8%) | 205,638 (41.1%) | 106,371 (40.8%) |
| corticosteroid use at time | | | |
| of AD diagnosis | | | |
| Use of drugs during 6 months AFTER initial visit with a recorded diagnosis of AD | | | |
| Systemic Biologics | 0.02 (0.01, 0.03) | 0.19 (0.15, 0.23) | 0.78 (0.67, 0.88) |
| Systemic Non-Biologics* | 0.23 (0.20, 0.26) | 0.75 (0.67, 0.83) | 1.47 (1.32, 1.62) |
| Methotrexate | 0.11 (0.09, 0.13) | 0.33 (0.28, 0.38) | 0.61 (0.52, 0.70) |
| Cyclosporine | 0.08 (0.06, 0.10) | 0.26 (0.22, 0.31) | 0.53 (0.44, 0.62) |
| Mycophenolate | 0.04 (0.03, 0.06) | 0.14 (0.10, 0.17) | 0.29 (0.23, 0.36) |
| Azathioprine | 0.01 (0.00, 0.01) | 0.07 (0.05, 0.10) | 0.17 (0.12, 0.22) |
| *methotrexate, cyclosporine, Mycophenolate, azathioprine. | | | |

In patients 6-12 years old, the new use of systemic non-biologics during 6 months after diagnosis was 0.75 per 1,000 patients and biologics was 0.19 per 1000 patients. Among the systemic non-biologics, new use of methotrexate was 0.33 per 1,000 patients, cyclosporine was 0.26 per 1,000, mycophenolate was 0.14 per 1,000 and azathioprine was 0.07 per 1,000 (**Table 3**).

In patients 13-17 years old, the new use of systemic non-biologics during 6 months after diagnosis was 1.47 (1.32, 1.62) per 1,000 patients and biologics was 0.78 (0.67, 0.88) per 1,000. Among the systemic non-biologics, new use of methotrexate was 0.61 per 1,000 patients, cyclosporine was 0.53 per 1,000, mycophenolate was 0.29 per 1,000 and azathioprine was 0.17 per 1,000 (**Table 3**).

Across all age groups the use of systemic non-biologic immuno-modulatory agents increased from 0.23 to 0.68 per 1,000 patients, over the 10-year period from 2005 to 2015, and the use of biologic immuno-modulatory agents increased from 0.08 to 0.29 per 1,000 (**Figure 2**).

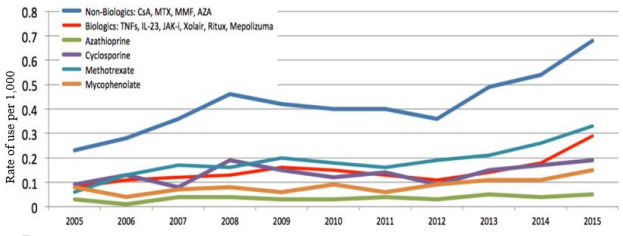


**Figure 2** Trends in the use of systemic non-biologic and biologic immune-modulatory drugs in children 2005 through 2015.

Among the non-biologic systemic agents methotrexate was the one increasing fastest (0.06 to 0.33), followed by cyclosporine (0.09 to 0.19), and then mycophenolate (0.08 to 0.15). Azathioprine had the least increase in use over the 10-year period (0.03 to 0.05).

## Discussion

In children and adolescents diagnosed with atopic dermatitis and without other disease indication for their use, the new use of systemic non-biologic and biologic immuno-modulatory agents was infrequent but steadily increasing over the past 10 years.

The increasing use of systemic immune-modulatory agents was likely influenced by a variety of factors. As we learn more about the burden of disease and comorbidities associated with atopic dermatitis, including psychological and metabolic, dermatologists may be treating severe disease earlier and more aggressively [26,27]. Successful systemic immuno-modulatory treatments in other pediatric inflammatory conditions, such as juvenile idiopathic arthritis, may have contributed to more aggressive treatment in AD [28,29]. Moreover, the commencing era of biologics for the treatment of inflammatory skin conditions, in particular psoriasis, likely lead to increased experience in the use of biologic immuno-modulatory agents. The observed time trends started in 2005, which marks the advent of biologics in the treatment of psoriasis. The FDA approved etanercept in 2004 for psoriasis followed by infliximab in 2006. Within a couple of years, biologics had a fast and steadily growing evidence base as highly effective treatments for psoriasis, which likely increased confidence in the use of these agents by dermatologists for treatment of other inflammatory skin conditions. We also see this as more data becomes available to support the efficacy and safety amongst non-biologic immuno-modulatory agents. For example, though cyclosporine has been an option for severe childhood atopic dermatitis since 2000, a large meta-analysis in 2007 found that cyclosporine was a particularly effective treatment and well tolerated in children [30,31]. This corresponds with the 2007 spike in cyclosporine use observed in our nationally representative data. Around this time, there was an increase in evidence and research showing the efficacy of mycophenolate as a treatment for recalcitrant atopic dermatitis in children and the overall use of systemic treatments for atopic dermatitis [32-34]. With few randomized clinical trials studying non-biologic immuno-modulators, the 2011 randomized clinical trial showing that methotrexate was clinically effective and safe when compared with azathioprine for patients with severe atopic dermatitis likely provided reassurance for its use and corresponds with the increase seen in our data [35,36]. In 2013 the guidelines for atopic dermatitis management of the American Academy of Dermatology (AAD) detailed the use of non-biologic immuno-modulatory agents in the pediatric population [37]. In particular, there had been no data supporting the use of methotrexate in pediatrics until a 2013 study showed children using methotrexate were less likely to relapse when compared to children using cyclosporine, and this was subsequently included in the AAD guidelines [38]. Azathioprine has shown efficacy for many years, but the associated risk for malignancy likely contributes to its lack of popularity in the pediatric population in particular.

## Conclusion

In this large population-based study in children diagnosed with atopic dermatitis and without other disease indication for their use, the new use of systemic immuno-modulatory agents was infrequent but steadily increasing over the past 10 years. More frequent initiation of systemic therapy for AD is also seen in older age groups. Among non-biologic systemic agents, methotrexate use has increased most over the past 10 years. Given the increasing off-label use of systemic immuno-modulatory agents in children it is important to better understand their safety profile.

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