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Comparative Safety of Systemic Immuno-modulatory Medications in Adults with Atopic Dermatitis

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Abstract:

Background: Severe atopic dermatitis (AD) is increasingly treated with systemic immunomodulatory drugs yet their safety is unclear.

Objective: We evaluated the comparative risk of serious bacterial and opportunistic infections among users of systemic immuno-modulatory medications in patients with severe AD in routine care.

Methods: In a population-based claims data study we identified adult patients with AD who were treated with systemic drugs. The incidence of serious bacterial and opportunistic infections leading to hospitalization was computed using ICD diagnosis codes. Relative risks were computed after 1:1 propensity score matching.

Results: Up to 232,611 patients with AD were eligible. The incidence of serious infections was 7.53 per 1,000 (7.18-7.89) among systemic non-biologics and 7.38 per 1,000 (5.68-9.57) among phototherapy treated patients, and 2.6 per 1,000 (0.45-14.3) dupilumab users. After matching, compared to methotrexate, cyclosporine had significantly reduced 6-month risk ($RR=0.87$), while prednisone, azathioprine and mycophenolate showed increased risks ($RR= 1.78, 1.89$ and 3.31 , respectively). Small numbers of dupilumab users showed no increase in risk ($RR=0.33; 0.03 - 3.20$).

Conclusion: In this population-based study of adult AD patients, cyclosporine and methotrexate have the lowest 6-month risks of serious infections. Increased risks were observed for prednisone, azathioprine, and mycophenolate relative to methotrexate.

Keywords: Atopic dermatitis; systemic medications; adult atopic dermatitis; safety; immunomodulating drugs; serious bacterial infections; opportunistic infections; epidemiology

Background

Atopic dermatitis (AD) affects 18 million adults in the U.S., 3.2 million of those suffer severe AD.¹⁻³ AD has a significant impact on the quality of life of individuals affected as well as on society in terms of healthcare utilization and absenteeism.⁴⁻⁷ In cases of severe recalcitrant AD, refractory to lifestyle modification and topical agents, the next step in treatment escalation for many providers is phototherapy or the off-label use of systemic immune modulating agents.⁸⁻¹⁵ Phototherapy is generally considered a safe treatment option for patients with recalcitrant AD with most of its safety evidence being derived from patients with psoriasis.¹⁶ The off-label use of systemic non-biologic immuno-modulatory agents is frequently considered after failure of topicals and several smaller studies have shown mixed results of biologic agents in the treatment of recalcitrant AD in the pre-dupilumab era.¹⁷⁻²⁰ Dupilumab is the only biologic specifically approved for atopic dermatitis and it was first marketed in the US on March 28, 2017. With an increasing number of systemic options available,¹⁸ few population-based studies exist on the comparative safety of systemic immuno-modulatory medication use in the treatment of recalcitrant AD.²¹ Increases in the risk of bacterial and opportunistic infections have been associated with non-biologic and biologic immuno-modulator use in patients with other inflammatory conditions such as rheumatoid arthritis and psoriasis.²²⁻²⁵ In patients with psoriasis, Kalb et al. found 14.5 per 1,000 patient-years incidence of serious infections in those who were treated with biologics.²⁶ Others found a 16 per 1,000 patient-years incidence of serious infection in patients with psoriasis treated with biologics and a 31% risk increase when compared with non-biologic agents.²⁷

This study sought to understand the comparative risk of serious bacterial and opportunistic infections among users of systemic non-biologic immuno-modulatory medications in patients with severe AD in routine care settings.

Methods

Data source

We used longitudinal claims data from a commercial insurance claims database, IBM MarketScan Database, covering 185 million patients in the US between January 1, 2003 and January 1, 2017. 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 patients aged 18 or older with a diagnosis of AD (ICD-9 691.x or ICD-10 L20.9) associated with an outpatient or inpatient encounter and who received treatment for AD. These patients had been enrolled in their health plan during the 6 months prior to initiation of the new drug of interest.

We compared five systemic non-biologic drugs that are frequently used in AD patients in ten pairwise contrasts (**Figure 1**): methotrexate, cyclosporine, azathioprine, prednisone, and mycophenolate. Cohort entry date was defined as the first use the non-biologic systemic drug of

interest, with first use additionally defined as no prior use of the comparator non-biologic systemic agents during 180 days before cohort entry.

We further compared two therapies that are reported in the treatment of moderate-severe AD with a focus on systemic non-biologic immuno-modulators and phototherapy. Cohort entry date was the first use of any of the two study treatment groups, including systemic non-biologic immuno-modulatory drugs (methotrexate, cyclosporine, azathioprine, prednisone, and mycophenolate), and phototherapy during any time after the diagnosis of AD (see **Figure 1**).²⁸ First use was defined as not having used any drug of the respective exposure and referent group during the 180 days before cohort entry. Patients were allowed to enter a cohort only once. In order to make these two patient groups more comparable we required prior topical treatment with medium/low potency corticosteroids. All patients had therefore been treated with the same group of medications before, had been evaluated by a dermatologist and their treatment was then escalated to any of the two therapies.

We excluded patients with less than 180 days of enrollment before cohort entry, per standard practice,²⁹ who had any pre-existing conditions that could increase the risk of serious infections, including congenital immunodeficiency, neutropenia (congenital, drug-induced, secondary to infection), other cytopenia, any malignant cancer and HIV or AIDS. To separate co-medications from treatments specific for AD, we further excluded patients with non-AD indications for being prescribed an immuno-modulatory medication, including: rheumatoid arthritis, rheumatologic disease, spondyloarthropathy, systemic vasculitis, psoriasis, psoriatic arthritis, vitiligo, pityriasis rubra pilaris, inflammatory bowel disease (ulcerative colitis, Crohn's disease), ankylosing spondylitis, autoimmune blistering diseases (bullous pemphigoid, pemphigus vulgaris), connective tissue diseases (including systemic lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis,

systemic sclerosis), organ transplantation, and other autoimmune conditions (Behçet's disease, autoimmune hepatitis, Sjögren's syndrome, myasthenia gravis, sarcoidosis). In a preliminary analysis of data through December 31, 2017, that was recently added, we identified new users of dupilumab with the same exclusion criteria as outlined, and compared them against non-biologic systemic immuno-modulatory agents.

Endpoints

Follow-up started the day after cohort entry and ended at 180 days after cohort entry, per standard practice.³⁰ All events of serious bacterial infections (cellulitis and abscess, septicemia or bacteremia, pneumonia, osteomyelitis, encephalitis, pyelonephritis, bacterial meningitis, endocarditis, septic arthritis) or opportunistic infections (pulmonary tuberculosis, listeriosis, leishmaniasis, pneumocystis jiroveci pneumonia, cryptococcus, histoplasmosis, atypical mycobacterium, necrotizing fasciitis) that led to hospital admissions were recorded as study endpoints (**e-appendix 1. Available at <https://data.mendeley.com/datasets/x3rp2pdg5c/draft?a=c872ea6f-0373-4df1-ad8f-ebbbaccc7493>**). In a secondary analysis we analyzed the incidence of inpatient cellulitis and pneumonia separately where numbers were large enough. These codes have been previously validated and shown positive predicted values of >80%.³¹ Patients were censored at the date of death, disenrollment, end of follow-up, end of data stream, whichever came first.

Patient characteristics

All patient characteristics were assessed during the 180 days before cohort entry, including the day of cohort entry. The following patient characteristics were considered: age at cohort entry, sex and

history of past serious bacterial infections / opportunistic infections that required an office visit or hospitalization as well as prior use of systemic or topical treatments for AD.

Statistical analysis

We tabulated baseline patient characteristics and follow-up, including reasons for censoring.

Balance in patient groups was largely achieved by restriction to patients without any risk factors for serious infections.

We computed the 6-month event risks carrying the exposure status at cohort entry forward for the 180 days of follow up. We analyzed multiple pair-wise contrasts: 10 among the individual systemic non-biologic agents and two among therapies including systemic non-biologic agents, phototherapy, and the AD-specific biologic, dupilumab. Relative risks (estimated as odds ratios including 95% confidence intervals)³² of the endpoint, serious infection, comparing each exposure pairs were estimated by fitting a logistic regression to the data adjusting for all baseline patient characteristics.

We further used propensity scores to achieve balance across covariates for each of the pair-wise comparisons. All confounders listed above were entered as independent variables without further variable selection.³³ Patients' propensity score values were estimated using the resulting logistic regression model.³⁴ Propensity scores were divided into deciles and indicators for decile of PS were entered into the outcome model, alongside exposure and age, sex. According to common practice the fifth decile was used as the reference category. Propensity score matching was performed using 1:1 nearest neighbor matching with a maximum matching caliper of 0.02.³⁵ In matched propensity score analyses, multivariate adjustment was achieved through the matching process. After matching, the treatment effect measures were directly derived from the balanced populations

without any further adjustment. Differences in the confounder distributions between exposure groups are displayed to inspect successful confounder balance in measured characteristics. A post-matching c-statistic is computed as a summary metric for confounder balance. C-statistics close to 0.5 represent good overall balance.³⁶

All analyses were conducted using the Aetion Evidence Platform v3.12 (including R version 3.10), which is validated^{37,38} and has successfully predicted RCT findings.³⁹

Results

Out of 185 million subjects, we identified 1,303,789 patients with AD 18 years or older. The number of patients reduced to 1,166,826 after excluding patients who may start systemic immunomodulatory drugs for reasons other than AD, including rheumatoid arthritis (9,415), connective tissue disease (1,354), psoriasis (10,146), Crohn's disease (3,866), colitis and other inflammatory bowel disease (3,290) etc., or had risk factors for serious infections due to immunodeficiency, including malignant cancer (40,622), congenital immunodeficiency (1,759), or HIV and AIDS (2,508). Cohort 1 had 232,611 new users of either non-biologic systemic immuno-modulators (225,023) or phototherapy (7,588). Cohort 2 had 23,908 new users of either dupilumab (391) or non-biologic systemic immuno-modulators (23,517) (**Table 1**). Although there was some imbalance in the proportion of prior bacterial infections, the 1:1 propensity score matching resulted in highly balanced patient groups. The absolute standardized differences between treatment groups were below 0.05 for all baseline characteristics.

Among comparisons within the systemic non-biologic agents, cyclosporine, methotrexate, mycophenolate, azathioprine and systemic prednisone, we found little differences in prior infection rates. The 6-month risk of serious infections among systemic non-biologics ranged from 6.9 per

1,000 to 37.2 per 1,000 (**Table 2**). The 10 pairwise 1:1 PS-matched comparisons yielded results that were sometimes based on very few events (**Figure 2**). Compared to methotrexate, cyclosporine had a 23% reduced 6-month risk (RR=0.87 [0.59 to 1.29]), while azathioprine and prednisone showed a doubling in risk (RR=1.78 [0.98 to 3.25] and 1.89 [1.05 to 3.42]), and mycophenolate tripling (RR=3.31 [1.94 to 5.64]) (**Table 3**).

An analysis comparing users of non-biologic systemic therapies against phototherapy demonstrated that patients initiating systemic non-biologics were similar in age, were equally likely female and had similar baseline prevalence of serious infections in the 180 days before cohort entry (**Table 1**). The baseline prevalence of non-biologic and biologic immuno-modulatory drug use was 0% due to the study exclusions. The median follow-up time was 180 days in the three treatment groups with similar reasons for censoring. Among the 225,023 systemic non-biologic initiators the incidence of serious infections was 7.53 per 1,000 patients and among 7,588 phototherapy initiators the 6-month risk was 7.38 per 1,000 patients (**Table 1**). Overall, the risk of serious infection with use of non-biologic systemic immuno-modulatory vs. phototherapy treatment was almost equal (RR=1.12 [0.79 to 1.61]) (**Table 1**).

The feasibility analysis of dupilumab users identified 1 event among 391 users (2.6 per 1,000). Patients initiating dupilumab were on average 10 years younger than non-biologic systemic users, were more likely male and had slightly higher prevalence of serious infections in the 180 days before cohort entry (**Table 1**). Prior use of systemic prednisone was higher in dupilumab patients. Prior use of methotrexate, cyclosporine, mycophenolate, azathioprine and non-dupilumab biologic immuno-modulatory drugs was 0% due to the study exclusions. After 1:1 PS-matching comparable non-biologics patients were identified and an analysis of 1 event among dupilumab users and 3

events among systemic non-biologic users in the treatment groups resulted in a RR of 0.33 (0.03 to 3.19) (Table 1).

Discussion

In commercially insured adults diagnosed with atopic dermatitis we found varying levels of risk to develop serious bacterial and opportunistic infections within 6 months of treatment that required hospitalization. Among five systemic non-biologic agents, our findings suggest that cyclosporine as used in the context of AD patients in the 'real-world' seems to have a similar risk of serious infection as methotrexate, while prednisone, azathioprine, and mycophenolate have higher risks compared to methotrexate. We observed no evidence of increased risk of non-biologic systemic immuno-modulatory drugs, compared to phototherapy treatment with a similar incidence of serious infection.

Although not approved for AD, systemic immuno-modulatory therapy is increasingly used to treat severe recalcitrant AD.^{8,9,40-49} It is therefore important to establish the relative safety of these products. Particularly relevant to clinical practice are the results of non-biologic systemic immuno-modulatory drugs regarding their 6-month risk of serious infections after PS risk adjustment. Our analysis suggests higher 6-month risks for prednisone, azathioprine, and mycophenolate relative to methotrexate. For these comparative analyses, the dosing patterns of these agents would be at their 'real world' use as captured in the routine care of patients with moderate-severe AD.⁵⁰ For this analysis, the only biologic approved for AD (dupilumab) was marketed in late March 2017 and could only be evaluated in a feasibility analysis of preliminary 2017 data.¹⁰ With one year of

data resulting in one event among 391 patients, this analysis is limited but does not show an obvious signal for increased risk.

Residual confounding remains a concern as an alternative explanation of the findings. We could not observe the underlying severity of AD in claims data although it will only be a meaningful confounder if severity of AD is a strong independent risk factor for serious infections. We included several measures to minimize confounding in the absence of baseline randomization. First, the 1:1 propensity score matched analysis restricted the analysis to a smaller number of very similar patients, yet the risk increase remained at a similar level as the logistic regression outcome model. Second, through extensive exclusions of conditions that have increased risk of infections (prior infections, malignancy, etc.) and of conditions that may lead to the use of systemic immunomodulatory agents other than for AD, the two comparison groups were made very homogeneous regarding confounding factors. Third, the new-user active comparator group cohort design is well-known to help make treatment groups more similar.⁵¹

The outcome of interest is severe enough to avoid differential surveillance bias since almost all serious infections that require hospitalization are captured in claims data.²³ The follow-up duration of a maximum of 180 days reduces the risk of differential dropout.⁵²

There are several limitations to be noted. Some analyses are based on few events resulting in wide confidence intervals. This analysis does not consider specific dosing schemes but is a reflection of how different clinical strategies lead to different levels of risk of serious infections. The preliminary data on dupilumab show no increase in risk but are not conclusive. Importantly, we do not have specific 6-month cumulative dose exposure over for these medications during the follow-up time,

most notably systemic prednisone and cyclosporine dosing regimens, which may vary along with relative risk of infection by dose. Along these lines, cyclosporine and systemic prednisone are more typically used for induction and flares than necessarily for long-term maintenance, which may limit the applicability of our data and results. Cyclosporine use duration may also be limited by other long-term toxicities considerations, such as nephrotoxicity.

Our findings on systemic non-biologics are highly plausible, given 1) the known risk of systemic immuno-modulators in patients treated for other indications, 2) the meaningful effect size, and 3) the methodologically robust approach with a new-user active-comparator design and propensity score matching.

In conclusion, this population-based propensity score-adjusted study represents a robust comparative safety evaluation in adult patients with severe AD. Among non-biologic systemic agents, cyclosporine and methotrexate appear to have better safety profiles than mycophenolate, azathioprine and systemic prednisone with regard to serious infections. These findings may help inform clinicians in their selection of medications for patients requiring systemic therapy for atopic dermatitis. Preliminary data on newer targeted biologic molecules such as dupilumab were encouragingly showing no increase in risk but need to be confirmed in larger user populations with longer use.^{54,55}

283 **Abbreviations and Acronyms**

284 AD - Atopic Dermatitis

285 IL - Interleukin

286 Immuno-mod. - Immuno-modulatory/ immuno-modulator

287 JAK - Janus Kinase

288 MTX - Methotrexate

289 PS - Propensity Score

290 PsA - Psoriatic Arthritis

291 RA - Rheumatoid Arthritis

292 RR - Relative Risk

Author Contributions

Dr(s) Schneeweiss, Perez-Chada, and Merola, had full access to all of the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis. Study concept and design: Dr(s) Schneeweiss, Perez-Chada, and Merola. Acquisition, analysis, and interpretation of data: Dr(s) Schneeweiss and Merola. Drafting of the manuscript: Dr(s) Schneeweiss and Merola. Critical revision of the manuscript for important intellectual content: Dr(s) Schneeweiss, Perez-Chada, and Merola. Statistical analysis: Dr. Schneeweiss. Obtained funding: Dr(s) Merola. Administrative, technical, or material support: Dr(s) Perez-Chada, Merola. Study supervision: Dr(s) Merola.

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Figure 1: Overview of study design

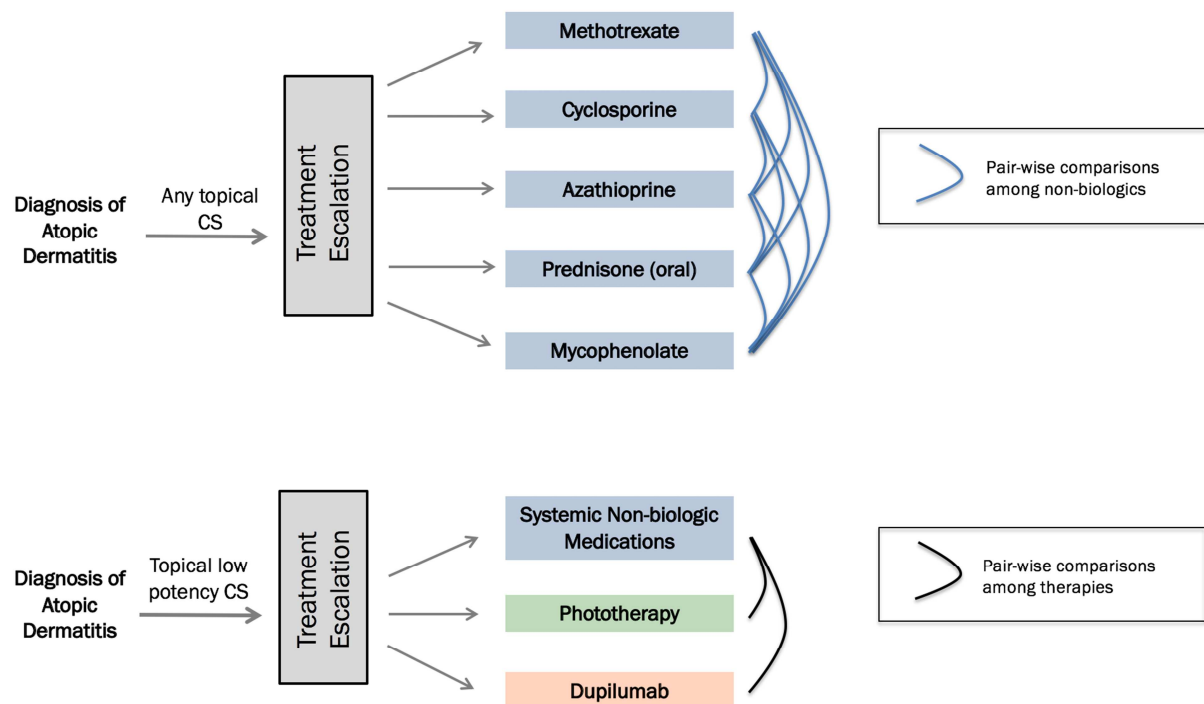
Figure 2: Relative risk (RR) estimates of developing serious infections within 6 months of treatment for 10 pairwise comparisons among non-biologic immuno-modulatory drugs

Table 1: Baseline patient characteristics and follow-up 6-month risks of serious bacterial infections in cohorts 1 and 2

Table 2: 6-month risks of serious bacterial infections among systemic non-biologic immuno-modulatory drug users

Table 3: Relative risk estimates of developing serious infections within 6 months of treatment

Figure 1: Overview of study design*



* Non-biologic systemic immuno-modulatory drugs included are: methotrexate, cyclosporine, azathioprine, prednisone, mycophenolate

Figure 2: Relative risk of developing serious infections within 6 months of treatment for 10 pairwise comparisons among non-biologic immuno-modulatory drugs.*

	Exposure agent				
	Methotrexate	Cyclosporine	Azathioprine	Prednisone	Mycophenolate
Referent agent	Methotrexate	0.87 (0.59, 1.29)	1.78 (0.98, 3.25)	1.89 (1.05, 3.42)	3.31 (1.94, 5.64)
	Cyclosporine	1.15 (0.78, 1.69)	1.57 (0.86, 2.85)	1.86 (1.33, 2.60)	2.68 (1.61, 4.45)
	Azathioprine	0.56 (0.31, 1.02)	0.63 (0.35, 1.16)	0.50 (0.05, 5.52)	1.31 (0.81, 2.12)
	Prednisone	0.52 (0.29, 0.95)	0.54 (0.38, 0.75)	2.00 (0.18, 20.0)	2.27 (0.70, 7.44)
	Mycophenolate	0.30 (0.18, 0.52)	0.37 (0.22, 0.62)	0.76 (0.47, 1.23)	0.44 (0.13, 1.43)

* 95% confidence intervals are in parentheses

Table 1: Baseline patient characteristics and follow-up 6-month risks of serious bacterial infections in cohorts 1 and 2

	Cohort 1: New users of Non-biologics vs. Phototherapy		Cohort 2: New users of Dupilumab vs. Non-biologics	
	Non-biologics	Phototherapy	Dupilumab	Non-biologics
Before PS matching				
Baseline Patient characteristics				
Number of patients	225,023	7,588	391	23,517
Age, mean (sd)	49.10 (16.18)	48.66 (16.63)	44.18 (14.47)	54.78 (14.86)
Female sex; n (%)	147,199 (65.4%)	4,705 (62.0%)	205 (52.4%)	17,674 (75.2%)
Prior Opportunistic infections with visit or inpatient stay; n (%)	171 (0.1%)	7 (0.1%)	0 (0.0%)	37 (0.2%)
Prior Bacterial infections with visit or inpatient stay; n (%)	11,149 (5.0%)	432 (5.7%)	25 (6.4%)	1,367 (5.8%)
Prior use of non-biologics; n (%)	0 (0.0%)	0 (0.0%)	148 (37.9%)*	5,780 (24.6%)*
Prior use of biologics; n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Follow-up 6-month risk of infection				
Number of events	1,695	56	1	235
Risk per 1,000 pts	7.53	7.38	2.56	9.99
After PS matching				
Baseline Patient Characteristics				
Number of patients	7,588	7,588	391	391
Age, mean (sd)	48.65 (16.63)	48.66 (16.63)	44.18 (14.47)	44.15 (14.49)
Female sex; n (%)	4,705 (62.0%)	4,705 (62.0%)	205 (52.4%)	205 (52.4%)
Prior Opportunistic infections with visit or inpatient stay; n (%)	5 (0.1%)	7 (0.1%)	0 (0.0%)	0 (0.0%)
Prior Bacterial infections with visit or inpatient stay; n (%)	434 (5.7%)	432 (5.7%)	25 (6.4%)	24 (6.1%)
Prior use of non-biologics; n (%)	0 (0.0%)	0 (0.0%)	148 (37.9%)	147 (37.6%)
Prior use of biologics; n (%)	0 (0.0%)	0 (0.0%)	0 (0.0%)	0 (0.0%)
Follow-up 6-month risk of infection				
Number of events	63	56	1	3
Risk per 1,000 pts	8.30	7.38	2.56	7.67
Risk Ratio (95% CI)	1.12 (0.79, 1.61)	Referent	0.33 (0.03, 3.19)	Referent
Risk difference per 1,000 pts	0.92 (-2.02, 3.86)	Referent	-5.12 (-17.67, 7.44)	Referent

* Patients with prior prednisone use were not excluded in this analysis.

Table 2: 6-month risks of serious bacterial infections among systemic non-biologic immuno-modulatory drug users

	New users of Cyclosporine vs. MTX**		New users of Prednisone vs. MTX		New users of Mycophenolate vs. MTX		New users of Azathioprine vs. MTX	
	Cyclosporine	MTX	Prednisone	MTX	Mycophenolate	MTX	Azathioprine	MTX
Before PS-matching *								
Number of patients	14,676	5,867	216,726	2,523	1,561	6,067	1,231	6,072
Number of events	101	64	1,698	17	58	64	30	65
Risk per 1,000 pts	6.88	10.91	7.83	6.74	37.16	10.55	24.37	10.70
Risk Ratio (95% CI)	0.63 (0.46, 0.86)	Referent	1.16 (0.72, 1.87)	Referent	3.52 (2.48, 5.00)	Referent	2.28 (1.48, 3.49)	Referent
Risk difference per 1,000 pts	-4.03 (-7.12, -0.93)	Referent	1.10 (-2.32, 4.51)	Referent	26.61 (16.5, 36.7)	Referent	13.67 (4.18, 23.2)	Referent
After PS-matching								
Number of patients	5,224	5,224	2,523	2,523	1,558	1,558	1,230	1,230
Number of events	47	54	32	17	58	18	30	17
Risk per 1,000 pts	9.00	10.34	12.68	6.74	37.23	11.55	24.39	13.82
Risk Ratio (95% CI)	0.87 (0.59, 1.28)	Referent	1.88 (1.05, 3.38)	Referent	3.22 (1.91, 5.44)	Referent	1.76 (0.98, 3.18)	Referent
Risk difference per 1,000 pts	-1.34 (-5.28, 2.60)	Referent	5.95 (0.14, 11.8)	Referent	25.7 (14.2, 37.1)	Referent	10.57 (-1.06, 22.2)	Referent

* PS, Propensity Score

** MTX, methotrexate

Table 3: Relative risk estimates of developing serious infections within 6 months of treatment

Contrast of interest	Odds ratios (95% confidence intervals)			
	Unadjusted	Adjusted by age, sex	Fully adjusted	1:1 propensity score matched
Cohort 1: Non-biologics vs. phototherapy	1.02 (0.78, 1.33)	1.02 (0.78, 1.33)	1.04 (0.79, 1.36)	1.13 (0.78, 1.62)
Cohort 2: Dupilumab vs. non-biologics	0.25 (0.04, 1.82)	0.25 (0.04, 1.82)	0.28 (0.04, 2.01)	0.33 (0.03, 3.20)
Among systemic non-biologics:				
<i>Cyclosporine vs. MTX *</i>	0.63 (0.46, 0.86)	0.63 (0.46, 0.86)	0.80 (0.56, 1.13)	0.87 (0.59, 1.29)
<i>Azathioprine vs. MTX</i>	2.31 (1.49, 3.57)	2.31 (1.49, 3.57)	1.95 (1.24, 3.06)	1.78 (0.98, 3.25)
<i>Prednisone vs. MTX</i>	1.16 (0.72, 1.88)	1.16 (0.72, 1.88)	1.30 (0.80, 2.11)	1.89 (1.05, 3.42)
<i>Mycophenolate vs. MTX</i>	3.62 (2.53, 5.19)	3.62 (2.53, 5.19)	3.06 (2.10, 4.46)	3.31 (1.94, 5.64)
<i>Azathioprine vs. cyclosporine</i>	3.24 (2.15, 4.87)	3.24 (2.15, 4.87)	1.87 (1.18, 2.97)	1.57 (0.86, 2.85)
<i>Prednisone vs. cyclosporine</i>	1.62 (1.23, 2.13)	1.62 (1.23, 2.13)	1.92 (1.45, 2.53)	1.86 (1.33, 2.60)
<i>Mycophenolate vs. cyclosporine</i>	5.62 (4.02, 7.84)	5.62 (4.02, 7.84)	3.76 (2.53, 5.60)	2.68 (1.61, 4.45)
<i>Prednisone vs. azathioprine</i>	1.39 (0.35, 5.56)	1.39 (0.35, 5.56)	1.93 (0.47, 7.84)	0.50 (0.05, 5.52)
<i>Mycophenolate vs. azathioprine</i>	1.54 (0.99, 2.40)	1.54 (0.99, 2.40)	1.42 (0.90, 2.24)	1.31 (0.81, 2.12)
<i>Mycophenolate vs. prednisone</i>	2.46 (1.27, 4.76)	2.46 (1.27, 4.76)	1.70 (0.86, 3.37)	2.27 (0.70, 7.44)

* MTX, methotrexate

Comparative Safety of Systemic Immuno-modulatory Medications in Adults with Atopic Dermatitis

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CAPSULE SUMMARY

- The risk of serious infections among users of systemic immuno-modulatory medications is not well understood in patients with atopic dermatitis.
- In adults with severe AD, cyclosporine and methotrexate have among the lowest 6-month risks of serious infections. Increased risks were observed for prednisone, azathioprine, and mycophenolate relative to methotrexate.