Comparative safety of systemic immunomodulatory medications in adults with atopic dermatitis

Maria C. Schneeweiss, MD,[a,b] Lourdes Perez-Chada, MD, MMSc,[a] and Joseph F. Merola, MD, MMSc[a]
Boston, Massachusetts

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 patients with severe AD using systemic immunomodulatory medications 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 by using International Classification of Disease diagnosis codes. Relative risks (RRs) were computed after 1-to-1 propensity score matching.

Results: Up to 232,611 patients with AD were eligible. The incidence of serious infections was 7.53 (7.18-7.89) risk per 1,000 patients among systemic nonbiologic—treated patients, 7.38 (5.68-9.57) risk per 1,000 patients among phototherapy-treated patients, and 2.6 (0.45-14.3) risk per 1,000 patients among dupilumab users. After matching, cyclosporine had a significantly reduced 6-month risk (RR 0.87) and prednisone (RR 1.78), azathioprine (RR 1.89), and mycophenolate (RR 3.31) showed increased risks compared with methotrexate. A small number of dupilumab users showed no increased risk (RR 0.33, 95% confidence interval 0.03-3.20).

Limitations: Some comparisons involved small population sizes.

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. (J Am Acad Dermatol 2021;85:321-9.)

Key words: adult atopic dermatitis; atopic dermatitis; epidemiology; immunomodulating drugs; opportunistic infections; safety; serious bacterial infections; systemic medications.

Atopic dermatitis (AD) affects 18 million adults in the United States, and 3.2 million of those have 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 health care utilization and absenteeism.[4-7]

In cases of severe, recalcitrant AD refractory to lifestyle modifications 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

From the Department of Dermatology, Brigham and Women's Hospital, Harvard Medical School;[a] and Department of Medicine, Division of Pharamacoepidemiology and Pharmacoeconomics, Brigham and Women's Hospital, Harvard Medical School.[b]

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Correspondence to: Joseph F. Merola, MD, MMSc, Department of Dermatology, Brigham and Women's Hospital, 221 Longwood Ave, Boston, MA 02215. E-mail: jfmerola@bwh.harvard.edu.

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patients with recalcitrant AD, with most of its safety evidence being derived from patients with psoriasis.[16] The off-label use of systemic nonbiologic immunomodulatory agents is frequently considered after failure of topicals; 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 AD, and the drug was first marketed in the United States on March 28, 2017.

With an increasing number of systemic options available,[18] few population-based studies exist on the comparative safety of systemic immunomodulatory medication use in the treatment of recalcitrant AD.[21] Increases in the risk of bacterial and opportunistic infections have been associated with nonbiologic and biologic immunomodulator use in patients with other inflammatory conditions, such as rheumatoid arthritis and psoriasis.[22-25] In patients with psoriasis, Kalb et al found an incidence of 14.5 cases of serious infection per 1000 patient-years among those treated with biologics.[26] Others found an incidence of 16 cases of serious infection per 1000 patient-years in patients with psoriasis treated with biologics, and a 31% risk increase compared with nonbiologic agents.[27]

In this study, we sought to determine the comparative risk of serious bacterial and opportunistic infections among patients with severe AD using systemic nonbiologic immunomodulatory medications in routine care settings.

CAPSULE SUMMARY

- The risk of serious infections among users of systemic immunomodulatory medications is not well understood in patients with atopic dermatitis.
- In adults with severe atopic dermatitis, 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.

METHODS

Data source

We used longitudinal claims data from a commercial insurance claims database, IBM MarketScan Database (Armonk, NY), covering 185 million patients in the United States during January 1, 2003-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, health care utilization and expenditures, demographics, and integrated records for inpatient events, outpatient events, and pharmacy dispensing. All patient information was deidentified. 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 >18 years of age with an AD diagnosis (International Classification of Disease, Ninth and Tenth Revision, codes 691.x and L20.9, respectively) associated with an outpatient or inpatient encounter and who received treatment for AD. These patients were also enrolled in their health plans 6 months before the initiation of the drug of interest.

We evaluated 5 systemic nonbiologic drugs frequently used in AD patients (methotrexate, cyclosporine, azathioprine, prednisone, and mycophenolate) in 10 pairwise comparisons (Fig 1). Cohort entry date was defined as the first use of the nonbiologic systemic drug of interest along with no prior use of the comparator nonbiologic systemic agents during the 180 days before cohort entry.

We further compared therapies that are reported in the treatment of moderate-severe AD, focusing on systemic nonbiologic immunomodulators and phototherapy. The cohort entry date was the first use of any of the 2 study treatments (systemic nonbiologic immunomodulatory drugs [methotrexate, cyclosporine, azathioprine, prednisone, and mycophenolate] and phototherapy) during any time after the diagnosis of AD (Fig 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. To make these 2 patient groups more comparable, we required prior topical treatment with medium-low potency corticosteroids. Therefore, all patients had been previously treated with the same group of medications, had been evaluated by a dermatologist, and had their treatment escalated to any of the 2 therapies.

We excluded patients with <180 days of enrollment before cohort entry, per standard practice,[29] with any pre-existing condition that could increase their risk of serious infection, including congenital immunodeficiency, neutropenia (congenital, drug-induced secondary to infection), other cytopenia, any malignant cancer,

Abbreviations used:

AD: atopic dermatitis
CI: confidence interval
PS: propensity score
RR: relative risk

and HIV or AIDS. We further excluded patients with comorbidities also treated for with immunomodulating therapies, 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 (systemic lupus erythematosus, lupus nephritis, dermatomyositis, polymyositis, systemic sclerosis), organ transplantation, and other autoimmune conditions (Behçet disease, autoimmune hepatitis, Sjögren syndrome, myasthenia gravis, sarcoidosis). In a preliminary analysis of data through December 31, 2017, we identified new users of dupilumab with the same exclusion criteria as outlined and compared them against nonbiologic systemic immunomodulatory 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 infection (cellulitis and abscess, septicemia or bacteremia, pneumonia, osteomyelitis, encephalitis, pyelonephritis, bacterial meningitis, endocarditis, septic arthritis) or opportunistic infection (pulmonary tuberculosis, listeriosis, leishmaniasis, pneumocystis jiroveci pneumonia, cryptococcus, histoplasmosis, atypical mycobacterium, necrotizing fasciitis) that led to hospital admission 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, when numbers were large enough. These codes have been previously validated and showed positive predicted values of >80%.[31] Patients were censored at the date of death, disenrollment, end of follow-up, or 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, history of past serious bacterial infections and opportunistic infections that required an office visit or hospitalization, and 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 pairwise contrasts: 10 among the individual systemic nonbiologic agents and 2 among therapy types (systemic nonbiologic agents, phototherapy, and AD-specific biologic dupilumab). For each exposure pair, we estimated the relative risks (RRs; estimated as odds ratios including 95% confidence intervals [CIs])[32] of the endpoint serious infection by fitting a logistic regression to the data and adjusting for all baseline patient characteristics.

We further used propensity scores (PSs) to achieve balance across covariates for each of the pairwise comparisons. All listed confounders were entered as independent variables without further variable selection.[33] Patients' PS values were estimated by using the resulting logistic regression model.[34] PSs were divided into deciles, and indicators for PS decile were entered into the outcome model, along with exposure, age, and sex. According to common practice, the fifth decile was used as the reference category. PS matching was performed by using 1-to-1 nearest-neighbor matching, with a maximum matching caliper of 0.02.[35] In matched PS 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 distributions of confounders and characteristics between exposure groups are displayed to enable measurement of balance. A postmatching c-statistic was computed as a summary metric for confounder balance. C-statistics close to 0.5 represent good overall balance.[36]

All analyses were conducted by using Aetion Evidence Platform version 3.12 (including R version 3.10), which is validated[37,38] and has been used to predict randomized controlled trial findings.[39]

RESULTS

Out of 185 million persons, we identified 1,303,789 patients with AD who were ≥18 years of age. The number of patients was reduced to

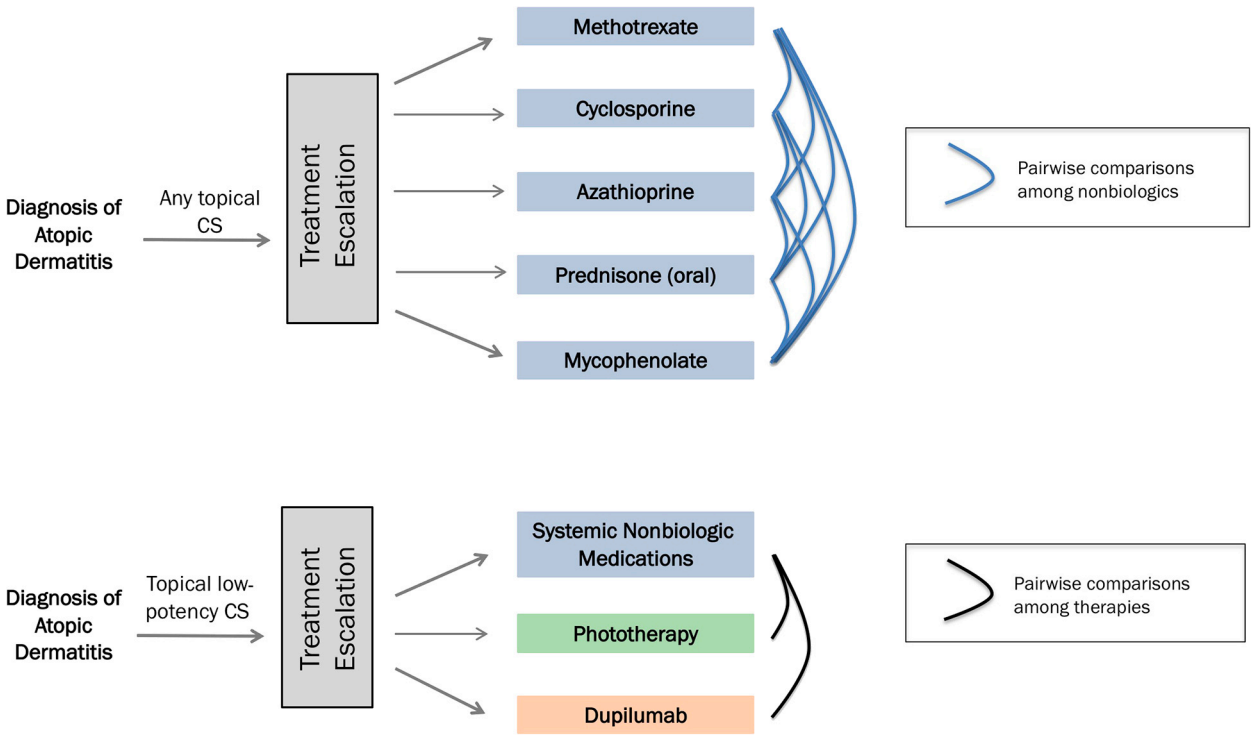

Fig 1. Overview of study design. Nonbiologic systemic immunomodulatory drugs included are methotrexate, cyclosporine, azathioprine, prednisone, and mycophenolate. *CS*, Corticosteroid.

1,166,826 after excluding patients who started systemic immunomodulatory drugs for reasons other than AD, including rheumatoid arthritis (n = 9415), connective tissue disease (n = 1354), psoriasis (n = 10,146), Crohn's disease (n = 3866), and colitis and other inflammatory bowel diseases (n = 3290) or had risk factors for serious infections because of immunodeficiency, such as having malignant cancer (n = 40,622), congenital immunodeficiency (n = 1759), or HIV or AIDS (n = 2508). Cohort 1 contained 232,611 new users of either nonbiologic systemic immunomodulators (n = 225,023) or phototherapy (n = 7588), and cohort 2 had 23,908 new users of either dupilumab (n = 391) or nonbiologic systemic immunomodulators (n = 23,517) (Table I). Although the proportion with previous bacterial infections was not balanced, 1-to-1 PS matching resulted in highly balanced patient groups. The absolute standardized differences between treatment groups were <0.05 for all baseline characteristics.

Among comparisons of the systemic nonbiologic agents cyclosporine, methotrexate, mycophenolate, azathioprine, and systemic prednisone, we found little differences in prior infection rates. The 6-month risk of serious infection among systemic nonbiologics ranged 6.9-37.2 per 1000 patients (Table II). The 10 pairwise 1-to-1 PS-matched comparisons yielded results that were based sometimes on very few events (Fig 2). Compared with methotrexate, cyclosporine had a 23% reduced 6-month risk (RR 0.87, 95% CI 0.59-1.29), while azathioprine (RR 1.78, 95% CI 0.98-3.25) and prednisone (RR 1.89, 95% CI 1.05-3.42) showed a doubling and mycophenolate a tripling (RR 3.31, 95% CI 1.94 to 5.64) of risk (Table III).

An analysis comparing users of nonbiologic systemic therapies with phototherapy demonstrated that patients initiating systemic nonbiologics were similar in age, were equally likely to be female, and had a similar baseline prevalence of serious infections in the 180 days before cohort entry (Table I). The baseline prevalence of nonbiologic and biologic immunomodulatory drug use was 0% because of the study exclusions. The median follow-up time was 180 days in the 3 treatment groups with similar reasons for censoring. Among the 225,023 systemic nonbiologic initiators, the incidence of serious infections was 7.53 cases/1000 patients, and among 7588 phototherapy initiators, the 6-month risk was 7.38 per 1000 patients (Table I). Overall, the risks of serious infection among users of nonbiologic systemic immunomodulatory therapy

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

	Cohort 1: new users of nonbiologics vs phototherapy		Cohort 2: new users of dupilumab vs nonbiologics	
Category	**Nonbiologics**	**Phototherapy**	**Dupilumab**	**Nonbiologics**
Before PS matching				
Baseline patient characteristic				
Patients, n	225,023	7588	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)	4705 (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)	37 (0.2)
Prior bacterial infections with visit or inpatient stay, n (%)	11,149 (5.0)	432 (5.7)	25 (6.4)	1367 (5.8)
Prior use of nonbiologic, n (%)	0 (0)	0 (0)	148 (37.9)*	5780 (24.6)*
Prior use of biologic, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Follow-up 6-month risk of infection				
Events, n	1695	56	1	235
Risk per 1000 patients	7.53	7.38	2.56	9.99
After PS matching				
Baseline patient characteristic				
Patients, n	7588	7588	391	391
Age, mean (SD)	48.65 (16.63)	48.66 (16.63)	44.18 (14.47)	44.15 (14.49)
Female sex, n (%)	4705 (62.0)	4705 (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)
Prior bacterial infection with visit or inpatient stay, n (%)	434 (5.7)	432 (5.7)	25 (6.4)	24 (6.1)
Prior use of nonbiologic, n (%)	0 (0)	0 (0)	148 (37.9)	147 (37.6)
Prior use of biologic, n (%)	0 (0)	0 (0)	0 (0)	0 (0)
Follow-up 6-month risk of infection				
Events, n	63	56	1	3
Risk per 1000 patients	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 1000 patients	0.92 (−2.02 to 3.86)	Referent	−5.12 (−17.67 to 7.44)	Referent

CI, Confidence interval; *SD*, standard deviation.
*Patients with prior prednisone use were not excluded in this analysis.

and phototherapy were almost equal (RR 1.12, 95% CI 0.79-1.61; Table I).

The feasibility analysis of dupilumab users identified 1 event among 391 users (2.6 events/1000 users). Patients initiating dupilumab were on average 10 years younger than nonbiologic systemic users, were more likely to be male, and had a slightly higher prevalence of serious infections in the 180 days before cohort entry (Table I). Prior use of systemic prednisone was higher in patients on dupilumab. Prior use of methotrexate, cyclosporine, mycophenolate, azathioprine, and nondupilumab biologic immunomodulatory drugs was 0% because of the study exclusions. After 1-to-1 PS matching, a comparable number of patients on nonbiologics were identified, and an analysis of 1 event among dupilumab users and 3 events among systemic nonbiologic users in the treatment groups resulted in an RR of 0.33 (95% CI 0.03-3.19) (Table I).

DISCUSSION

In commercially insured adults with AD diagnoses, we found varying levels of risk to develop serious bacterial and opportunistic infections that required hospitalization within 6 months of treatment. Among the 5 systemic nonbiologic agents evaluated, our findings suggest that cyclosporine use, in the context of treating AD patients in the real world, seems to be have a similar risk of serious infection as methotrexate use, while use of prednisone, azathioprine, and mycophenolate have higher risks compared with use of methotrexate. We observed a slight numerical increase in the risk of serious infections among users of non-biologics

Table II. The 6-month risks of serious bacterial infection among users of systemic nonbiologic immunomodulatory drugs

Category	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								
Patients, n	14,676	5867	216,726	2523	1561	6067	1231	6072
Events, n	101	64	1698	17	58	64	30	65
Risk per 1000 patients	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 1000 patients	−4.03 (−7.12 to −0.93)	Referent	1.10 (−2.32 to 4.51)	Referent	26.61 (16.5-36.7)	Referent	13.67 (4.18-23.2)	Referent
After PS matching								
Patients, n	5224	5224	2523	2523	1558	1558	1230	1230
Events, n	47	54	32	17	58	18	30	17
Risk per 1000 patients	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 1000 patients	−1.34 (−5.28 to 2.60)	Referent	5.95 (0.14-11.8)	Referent	25.7 (14.2-37.1)	Referent	10.57 (−1.06 to 22.2)	Referent

CI, Confidence interval; *MTX*, methotrexate; *PS*, propensity score.

compared to phototherapy with confidence limits overlapping the null and of no clinical consequence.

Although not approved for use in AD, systemic immunomodulatory therapy is increasingly used to treat severe, recalcitrant AD.[8,9,40-49] Therefore, establishing the relative safety of these products is needed. Particularly relevant to clinical practice are the results of nonbiologic systemic immunomodulatory 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 our comparative analyses, the dosing patterns of these agents were at their real-world use, as captured in routine care of patients with moderate-severe AD.[50]

For this analysis, the only biologic approved for treating AD (dupilumab) was marketed in late March 2017 and could only be evaluated in a feasibility analysis of preliminary 2017 data.[10] With 1 year of data resulting in 1 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; however, this characteristic is a meaningful confounder only if the 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-to-1 PS-matched analysis restricted the analysis to a smaller number of 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 (eg, prior infections, malignancy) and conditions other than AD that might lead to the use of systemic immunomodulatory agents, the 2 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 was severe enough to avoid differential surveillance bias because 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 were based on limited numbers of events, resulting in wide CIs. 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

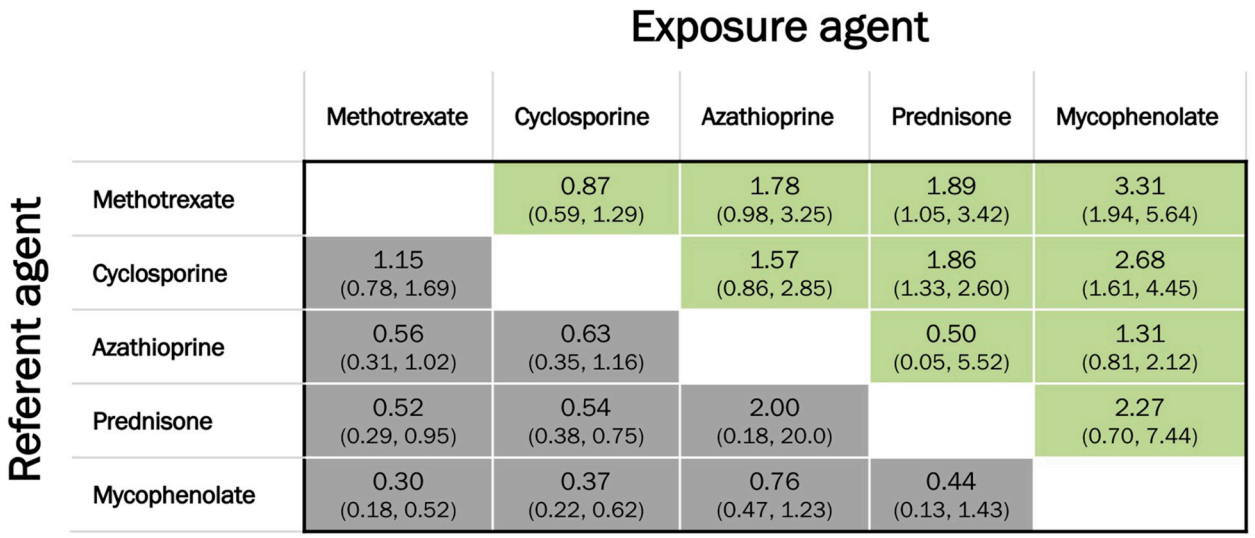

Fig 2. Relative risk of developing serious infections within 6 months of treatment in 10 pairwise comparisons among nonbiologic immunomodulatory drugs. The 95% confidence limits are in parentheses.

Table III. Relative risk estimates of developing serious infections within 6 months of treatment

	Odds ratio (95% confidence interval)			
Comparison of interest	**Unadjusted**	**Adjusted by age and sex**	**Fully adjusted**	**1-to-1 PS matched**
Cohort 1: nonbiologics 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 nonbiologics	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 nonbiologics				
Cyclosporine vs methotrexate	0.63 (0.46-0.86)	0.63 (0.46-0.86)	0.80 (0.56-1.13)	0.87 (0.59-1.29)
Azathioprine vs methotrexate	2.31 (1.49-3.57)	2.31 (1.49-3.57)	1.95 (1.24-3.06)	1.78 (0.98-3.25)
Prednisone vs methotrexate	1.16 (0.72-1.88)	1.16 (0.72-1.88)	1.30 (0.80-2.11)	1.89 (1.05-3.42)
Mycophenolate vs methotrexate	3.62 (2.53-5.19)	3.62 (2.53-5.19)	3.06 (2.10-4.46)	3.31 (1.94-5.64)
Azathioprine vs cyclosporine	3.24 (2.15-4.87)	3.24 (2.15-4.87)	1.87 (1.18-2.97)	1.57 (0.86-2.85)
Prednisone vs cyclosporine	1.62 (1.23-2.13)	1.62 (1.23-2.13)	1.92 (1.45-2.53)	1.86 (1.33-2.60)
Mycophenolate vs cyclosporine	5.62 (4.02-7.84)	5.62 (4.02-7.84)	3.76 (2.53-5.60)	2.68 (1.61-4.45)
Prednisone vs azathioprine	1.39 (0.35-5.56)	1.39 (0.35-5.56)	1.93 (0.47-7.84)	0.50 (0.05-5.52)
Mycophenolate vs azathioprine	1.54 (0.99-2.40)	1.54 (0.99-2.40)	1.42 (0.90-2.24)	1.31 (0.81-2.12)
Mycophenolate vs prednisone	2.46 (1.27-4.76)	2.46 (1.27-4.76)	1.70 (0.86-3.37)	2.27 (0.70-7.44)

PS, Propensity score.

dupilumab use showed no increase in risk but was not conclusive. Importantly, we do not have specific 6-month cumulative dose exposure for these medications, most notably systemic prednisone and cyclosporine, during the follow-up time, as the RR of infection might vary by dose. Along these lines, cyclosporine and systemic prednisone are more typically used for induction and flares than necessarily for long-term maintenance, which might limit the applicability of our data and results. Cyclosporine use duration might also be limited by other long-term toxicity considerations, such as nephrotoxicity.

Our findings on systemic nonbiologics are highly plausible, given the known risks associated with systemic immunomodulators in patients treated for other indications, the meaningful effect size, and our methodologically robust approach including a new user active-comparator design and PS matching.

In conclusion, this population-based PS-adjusted study represents a robust comparative safety evaluation in adult patients with severe AD. Among nonbiologic systemic agents, cyclosporine and methotrexate appear to have better safety profiles than mycophenolate, azathioprine, and systemic prednisone with regard to serious infections. These

findings can help inform clinicians in their selection of medications for patients requiring systemic therapy for AD. Preliminary data on newer targeted biologic molecules, such as dupilumab, were encouraging, showing no increase in risk, but our findings need to be confirmed in larger user populations with longer use.[53,54]

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