Dupilumab and the risk of conjunctivitis and serious infection in patients with atopic dermatitis: A propensity score–matched cohort study

Maria C. Schneeweiss, MD,[a,b,c] Seoyoung C. Kim, MD, ScD,[a,c,d] Richard Wyss, PhD,[a] Sebastian Schneeweiss, MD, ScD,[a] and Joseph F. Merola, MD, MMSc[b,c,d]
Boston, Massachusetts

Background: Dupilumab is an effective treatment for moderate to severe atopic dermatitis (AD) with limited safety data in clinical practice.

Objective: To assess the 6-month risk of conjunctivitis and serious infections in patients with AD who initiated dupilumab.

Methods: In a cohort study using US claims data, we compared the risk of conjunctivitis and serious infections in patients with AD who initiated either dupilumab, methotrexate (MTX), cyclosporine, or mycophenolate. Relative risks (RRs) were computed after 1:1 propensity score matching.

Results: We identified 1775 dupilumab, 1034 MTX, 186 cyclosporine, and 257 mycophenolate users. The 6-month risk for any conjunctivitis was 6.5% for dupilumab, 3.3% for MTX, 4.8% for cyclosporine, and 1.2% for mycophenolate initiators. After PS matching, the RR of any conjunctivitis was increased in dupilumab users versus MTX (RR, 2.45; 95% confidence interval [CI], 1.47-4.08), versus cyclosporine (RR, 1.56; 95% CI, 0.69-3.50), and versus mycophenolate (RR, 7.00; 95% CI, 2.12-23.2). The risk of serious infection was 0.6% in dupilumab and 1.0% in MTX initiators (RR, 0.90; 95% CI, 0.37-2.20).

Limitations: Analyses were based on few events, and differential surveillance is a concern.

Conclusions: Although dupilumab shows a low risk of serious infections, it is associated with a clinically meaningful increase in conjunctivitis that needs to be managed in practice. (J Am Acad Dermatol 2021;84:300-11.)

Key words: atopic dermatitis; conjunctivitis; dupilumab; epidemiology; immunomodulating drugs; methotrexate; opportunistic infections; real-world evidence; safety; serious bacterial infections.

From the Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, Boston[a]; Department of Dermatology, Brigham and Women's Hospital, Boston[b]; Harvard Medical School, Boston[c]; and Department of Medicine, Division of Rheumatology, Inflammation, and Immunity, Brigham and Women's Hospital, Boston.[d]

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Correspondence to: Maria Schneeweiss, MD, Division of Pharmacoepidemiology and Pharmacoeconomics, Department of Medicine, Brigham and Women's Hospital, 1 Brigham Circle, Suite 3030, Boston, MA 02120. E-mail: mschneeweiss@bwh.harvard.edu.

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Atopic dermatitis (AD) is a chronic inflammatory skin condition with significant impact on the quality of life in affected individuals. Dupilumab is a human monoclonal antibody that inhibits signaling of interleukin 4 and interleukin 13. It has shown marked efficacy in improving the signs and symptoms of AD in randomized controlled trials.[1-5]

Contrary to other biologic immunomodulating agents, dupilumab did not show an increase in serious infections, although the trials were not powered for infrequent events.[4,5] However, the US Food and Drug Administration label of dupilumab warns of an increased risk of conjunctivitis based on placebo-controlled trials (relative risk [RR], 4.2; 95% confidence interval [CI], 2.2-7.7) and against topical corticosteroids (RR, 1.9; 95% CI, 0.9-4.1). The etiology and actual risk in clinical practice of conjunctivitis remains unclear. The evaluation of conjunctivitis related to dupilumab has been limited to trials outside of clinical practice and smaller registry studies and case series.[6] This risk has not been systematically evaluated in a population-based study.[7-9]

CAPSULE SUMMARY

- Dupilumab is an effective treatment for atopic dermatitis. Limited data exist regarding its safety, including conjunctivitis and serious infection.
- Although dupilumab shows a low risk of serious infections compared to methotrexate, cyclosporine, or mycophenolate, it is associated with at least a doubling in the 6-month risk of conjunctivitis.

This study aimed to compare the risk of conjunctivitis and of serious bacterial and opportunistic infections in patients with AD who initiated dupilumab compared with methotrexate (MTX), cyclosporine, and mycophenolate in a population-based cohort study.

PATIENTS AND METHODS

Data source

We used longitudinal claims data from a commercial US-based insurance company, Optum Clinformatics, from March 1, 2017, through December 31, 2019. The database contains dated information on plan enrollment, health care use, demographics, and records for inpatient events, outpatient events, and pharmacy dispensing, which contains information on diagnoses, procedures, and the medication strength and quantity dispensed. The Brigham and Women's Hospital ethics board approved this study (#2011P002580) with a signed data use agreement in place.

Patients

We identified patients with a diagnosis of AD (International Classification of Diseases, 10th Revision (ICD-10): L20, L20.84, L20.82, or L20.83). Emulating a randomized controlled trial (RCT) design, we implemented 3 new-user, active-comparator cohorts[10,11]: Cohort 1 included new users of dupilumab versus MTX, cohort 2 included dupilumab versus cyclosporine, and cohort 3 included dupilumab versus mycophenolate. Cohort entry was the first use of any of these treatments. To identify new-user cohorts, *first use* was defined as no prior use of the exposure drug (dupilumab) and no prior use of the respective referent drug within each cohort within 180 days.[12] Patients were required to be continuously enrolled for 6 months before cohort entry. We excluded patients according to the following criteria: (1) pre-existing diagnosis of any conjunctivitis, uveitis, or Sjögren syndrome and (2) pre-existing conditions that could increase the risk of serious infections, including congenital or acquired immunodeficiency, neutropenia, leukopenia, any malignancy, and HIV/AIDS. To separate comedications from treatments specific for AD, we further excluded patients with concurrent immunomodulatory medication use for other indications, including psoriasis, psoriatic arthritis, systemic inflammatory disease, inflammatory bowel disease, autoimmune blistering diseases, organ transplantation, and other autoimmune conditions (Supplemental Fig 1; available via Mendeley at https://doi.org/10.17632/xhfzxp9nfp.1).

In a sensitivity analysis, we identified a cohort that included an additional 139 patients who had pre-existing conjunctivitis and a subgroup of patients with asthma.

Outcomes

We identified *any conjunctivitis* as the first visit with a diagnosis of conjunctivitis over 6 months (ICD-10 codes: H10, H10.0x, H10.1x, H10.2x, H10.3x, H10.5x, H10.89, H10.9x, B30.x, A54.31, A74.0, B00.53, B02.31, or H16.2x), because RCTs and clinical observations found a swift onset of conjunctivitis across all subtypes.[4,5,7] We defined *bacterial conjunctivitis* as the first outpatient visit with a diagnosis of conjunctivitis (H10.0x, H10.02x, H10.3x, H10.89, H10.9x, A36.86, A54.31, or A74.0) followed by the use of an ophthalmic antibiotic within 3 days of the diagnosis. We defined *allergic conjunctivitis* as a visit for allergic conjunctivitis

Abbreviations used:

AD:	atopic dermatitis
CI:	confidence interval
ICD-9:	International Classification of Diseases, Ninth Revision
ICD-10:	International Classification of Diseases, 10th Revision
MTX:	methotrexate
NNH:	number needed to harm
PS:	propensity score
RCT:	randomized controlled trial
RR:	relative risk

(H10.1x) that was not followed by an ophthalmic antibiotic within 3 days, and we defined *keratoconjunctivitis* a visit for keratoconjunctivitis (H16.2x, excluding H16.234x) (Supplemental Table I; available via Mendeley at https://doi.org/10.17632/xhfzxp9nfp.1). To our knowledge, no US-based International Classification of Disease, Ninth Revision (ICD-9) or ICD-10 validation study had been conducted for conjunctivitis. The current definitions were used by earlier studies.[13-16]

To address differential surveillance for conjunctivitis in dupilumab users, we included an analysis that limited the endpoint definition of *any conjunctivitis* to those recorded by an ophthalmologist. In another sensitivity analysis we identified eye examination without conjunctivitis as a negative tracer outcome, assuming that routine eye examinations should not depend on treatment choice. A null association would indicate equal access to eye care. Routine eye examination (Common Procedural Terminology: 92133, 92083, 92134, 92250, 92002, 92004, 92012, 92014, 92015, 99172, or 99173) excluded any eye examination encounters that had a diagnosis of conjunctivitis.

In the analysis evaluating the risk of serious infection, we included patients with pre-existing conjunctivitis. All events of serious bacterial infections (cellulitis and abscess, necrotizing fasciitis, septicemia or bacteremia, pneumonia, osteomyelitis, encephalitis, pyelonephritis, bacterial meningitis, endocarditis, septic arthritis) or opportunistic infections that led to hospital admissions were recorded as study endpoints (Supplemental Table I). Corresponding ICD-9 codes have been validated and shown positive predicted values of greater than 80%.[17] In the absence of a US-based ICD-10 validation study, we used recommended ICD-9 to ICD-10 conversion rules, and these ICD-10 codes were cross-checked against 2 European-based validation studies, which showed positive predictive values of larger than 90%.[18,19]

Follow-up started the day after cohort entry until the earliest occurrence of censoring events: occurrence of outcome, death, disenrollment, end of 180 days of follow-up, or end of the study period (Supplemental Fig 1).

The choice of comparator groups and the length of follow-up was informed by a use analysis of patients with AD who started a systemic treatment (Fig 1) and clinical observations.[7] Among 690 systemic naive patients with AD in 2017 to 2019, 61% started on dupilumab, 16% on MTX, 15% on cyclosporine, 5% on mycophenolate, 3% on azathioprine, and 0.2% on cyclosporine plus dupilumab (Fig 1). After 6 months, 49% had discontinued treatment, and 42% used dupilumab. After 1 year, 77% of patients had discontinued all systemic treatment.

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, year of cohort entry, history of past serious bacterial infections/opportunistic infections that required an office visit or hospitalization, prior use of other systemic nonbiologic immunomodulating agents (ie, cyclosporine, mycophenolate, or azathioprine), prior use of ophthalmic cyclosporine, prior use of other systemic biologic immunomodulating agents, ophthalmic medication use, and comorbidities (ie, asthma, allergic rhinitis, chronic sinusitis, or diabetes). Additional AD severity markers were considered: any and recent (<30 days) use of systemic glucocorticoids, cumulative sum of systemic prednisone equivalencies, and emergency department visits related to AD.

Statistical analysis

We tabulated baseline patient characteristics and computed the 6-month risk of the outcomes of interest with 95% CIs.

We used propensity score (PS) matching to achieve balance across covariates between the 2 treatment groups and reduce confounding.[20,21] The PS, defined as the probability that a patient initiated dupilumab versus the comparator conditional on all pre-exposure patient characteristics listed, was estimated with a logistic regression. PS matching was performed by using 1:1 nearest-neighbor matching with a maximum caliper of 0.02.[22] We examined standardized differences in the covariate distributions between treatment groups.[23,24]

We estimated RRs and 95% CIs after matching and computed risk differences and numbers needed to harm (NNH). We also conducted PS decile—stratified

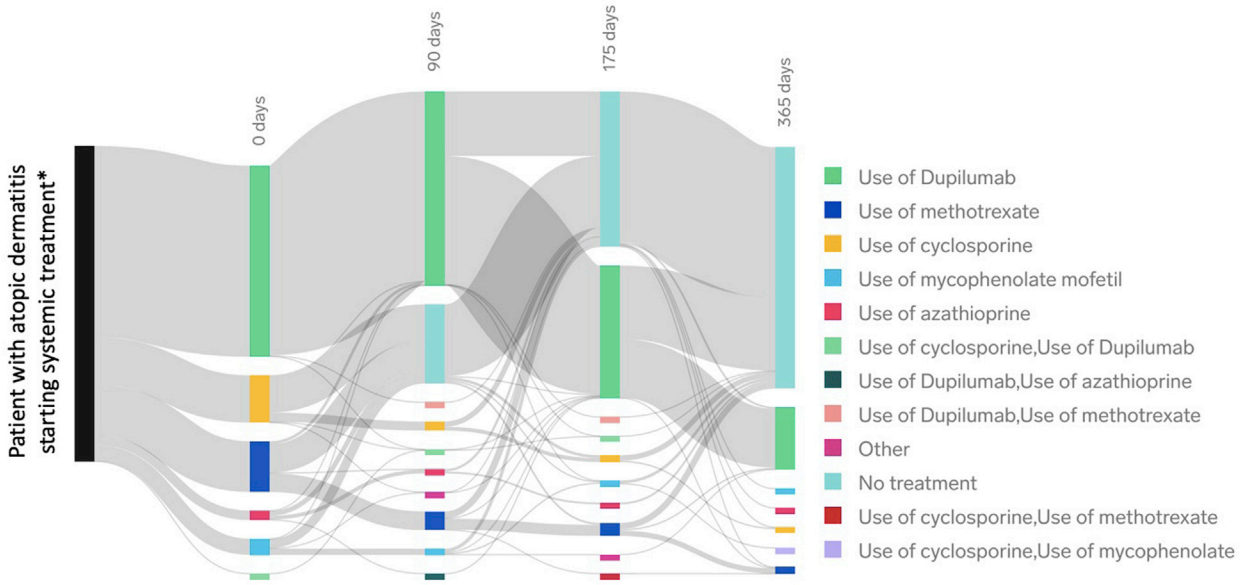

Fig 1. Treatment patterns after starting the first systemic treatment for atopic dermatitis. *Patients with atopic dermatitis starting systemic immunomodulatory treatment between March 2017 through June 2019: dupilumab, methotrexate, cyclosporine, mycophenolate mofetil, or azathioprine. **Patients are required to have at least 2 diagnoses of atopic dermatitis within the 180 days before initiation of the systemic agent (ie, cohort entry). Patients were excluded if they used any of these systemic agents within the 180 days before cohort entry.

analyses because they perform well in analyses with few events.[25] Some subgroup analyses were not conducted for the cyclosporine and mycophenolate comparators because the numbers were too small.

All analyses were conducted by using the Aetion Evidence Platform (New York, NY), version 4.3 (including R, version 4.0.2 [R Foundation for Statistical Computing, Vienna, Austria]), which has been validated and successfully predicted RCT findings.[26-28]

RESULTS

Study patients

We identified 1,419,113 patients with a diagnosis of AD (Table I). Embedded in this population, cohort 1 had 2814 new users of either dupilumab (n = 1775) or MTX (n = 1034), cohort 2 had 2011 new users of either dupilumab (1825) or cyclosporine (186), and cohort 3 had 2087 new users of either dupilumab (1826) or mycophenolate (257) (Table I and Supplemental Table II; available via Mendeley at https://doi.org/10.17632/xhfzxp9nfp.1). Some dupilumab patients did not meet cohort entry because of prior use of a comparator agent. After PS matching, all baseline characteristics, including age, were well balanced between treatment groups, and the absolute standardized differences between treatment groups were below 0.05 (Supplemental Tables II and III; available via Mendeley at https://doi.org/10.17632/xhfzxp9nfp.1). In the PS-matched analyses, cohort 1 had 774 pairs of patients initiating dupilumab versus MTX, cohort 2 had 186 pairs of patients initiating dupilumab versus cyclosporine, and cohort 3 had 238 pairs of patients initiating dupilumab versus mycophenolate (Table II).

Risk of conjunctivitis

Before PS matching, the 6-month risk for any conjunctivitis was 6.48% in dupilumab initiators and 3.29% in MTX, 4.87% in cyclosporine, and 1.17% in mycophenolate. When stratifying by conjunctivitis subtypes, the 6-month risk for bacterial conjunctivitis was 1.47% (vs 0.97% in MTX); for allergic conjunctivitis, it was 2.14% (vs 0.77% in MTX); and for keratoconjunctivitis, it was 1.07% (vs 0.97% in MTX) (Table III). Viral conjunctivitis occurred in only 2 dupilumab users.

After PS matching, we found that dupilumab initiators had a 2-fold increased risk of any conjunctivitis (RR, 2.45; [95% CI, 1.47-4.08]) compared to MTX (Table III), resulting in an NNH of 27 treated patients to harm 1. In dupilumab initiators vs cyclosporine, the RR was 1.56 (95% CI, 0.69-3.50),

Table I. CONSORT table of study populations

Reason for exclusion	Atopic dermatitis parent cohort: Excluded patients	Atopic dermatitis parent cohort: Remaining patients
All patients		75,894,642
Did not have at least 1 diagnosis of atopic dermatitis	−74,475,429	1,419,213
Excluded because of insufficient enrollment on cohort entry	−100	1,419,113
Final: atopic dermatitis cohort*		1,419,113

	Dupilumab versus methotrexate (referent)		Dupilumab versus cyclosporine (referent)		Dupilumab versus mycophenolate (referent)	
Atopic dermatitis cohort*		1,419,113		1,419,113		1,419,113
Did not use medication of interest between March 2017, and December 31, 2019	−1,412,504	6609	−1,415,717	3396	−1,415,161	3952
Excluded because of insufficient enrollment 180 days before cohort entry	−250	6359	−143	3253	−157	3795
Excluded because of prior use of referent†	−2255	4104	−169	3084	−607	3188
Excluded because of prior use of exposure (dupilumab)	−965	3139	−961	2123	−961	2227
Excluded because patient qualified in >1 exposure category	0	3139	0	2123	0	2227
Excluded based on history of any conjunctivitis	−60	3079	−40	2083	−37	2190
Excluded based on history of malignancy‡	−39	3040	−19	2064	−27	2163
Excluded based on other autoimmune disorders or connective tissue disorders§	−179	2861	−36	2028	−45	2118
Excluded based on other immune-compromising conditions‖	−12	2849	−9	2019	−23	2095
Excluded based on use of other systemic medications¶	−35	2814	−8	2011	−8	2087
Final: New user cohorts		2814		2011		2087

CONSORT, Consolidated Standards of Reporting Trials.

*We identified a parent cohort of patients with a diagnosis of atopic dermatitis (ie, atopic dermatitis cohort). From this parent cohort of patients with AD, we created 3 new-user, active-comparator cohorts for analysis: cohort 1, dupilumab vs methotrexate; cohort 2, dupilumab vs cyclosporine; and cohort 3, dupilumab vs mycophenolate.

†To identify new-user cohorts, we defined *first use* as no prior use of the exposure drug (dupilumab) and no prior use of the respective referent drug (methotrexate, cyclosporine, or mycophenolate) within each cohort during the 180 days before cohort entry.

‡Any malignant neoplasm, excluding nonmelanoma skin cancer.

§Other autoimmune disorders or connective tissue disorders include scleroderma, CREST syndrome (calcinosis, Raynaud's phenomenon, esophageal dysmotility, sclerodactyly, and telangiectasia), sicca (Sjögren), dermatomyositis, ulcerative colitis, Crohn's disease, rheumatoid arthritis, systemic lupus erythematosus, lupus nephritis, sarcoidosis, ankylosing spondylitis, psoriasis, psoriatic arthritis, uveitis, Behcet disease, vitiligo, bullous dermatoses, blistering diseases, pityriasis rubra pilaris, and idiopathic pulmonary fibrosis.

‖Other immune-compromising conditions include transplant, congenital immune deficiency, HIV or AIDs, cytopenias, humoral/cell-mediated immunodeficiencies, graft-versus-host disease, and end-stage renal disease.

¶Other systemic medications includes adalimumab, etanercept, infliximab, certolizumab, golimumab, ustekinumab, ixekizumab, secukinumab, guselkumab, tofacitinib, rituximab, omalizumab, tocilizumab, leflunomide, sulfasalazine.

with an NNH of 37, and the RR was 7.00 (95% CI, 2.12-23.15) versus mycophenolate, with an NNH of 13. The RR of bacterial conjunctivitis was 2.33 (95% CI, 0.90-6.04), of allergic conjunctivitis was 1.60 (95% CI, 0.53-4.87), and of keratoconjunctivitis was 1.57 (95% CI, 0.61-4.03) in dupilumab initiators compared to MTX (Table III). PS decile—stratified analyses showed similar findings (Table IV).

The RR of any conjunctivitis in patients with AD with comorbid asthma was 2.00 (95% CI, 0.78-5.13) in dupilumab compared to MTX (Table III). When including patients with pre-existing conjunctivitis, the RR of any conjunctivitis was 2.12 (95% CI, 1.42-3.15) in dupilumab versus MTX, 1.83 (95% CI, 0.93-3.60) in dupilumab versus cyclosporine, and 3.43 (95% CI, 1.50-7.82) in dupilumab versus mycophenolate (Table III).

Risk of serious infection

After PS matching, the 6-month risk of serious infection in dupilumab initiators was 1.10% and in MTX initiators was 1.22%, resulting in an RR of 0.90

Table II. Patient baseline characteristics after 1:1 propensity score matching

Characteristics, 180 days before cohort entry	1:1 Propensity-score matched patients					
	Dupilumab	Methotrexate	Dupilumab	Cyclosporine	Dupilumab	Mycophenolate
Number of patients	774	774	186	186	238	238
Year of cohort entry date, n (%)						
2017	187 (24.2)	176 (22.8)	66 (35.5)	66 (35.5)	74 (31.1)	64 (26.9)
2018	270 (34.9)	272 (35.2)	59 (31.7)	54 (29.0)	81 (34.0)	78 (32.8)
2019	316 (40.9)	325 (42.0)	61 (32.8)	66 (35.5)	83 (34.9)	96 (40.3)
Age, y						
Mean (SD)	51.93 (18.53)	51.34 (21.25)	44.65 (19.23)	42.69 (25.99)	51.94 (18.66)	52.29 (23.22)
Median (IQR)	54 (40-66)	55 (38-68)	46 (27-60)	47.50 (17-64)	54 (39-66)	56 (35-72)
Sex, n (%)						
Male	321 (41.5)	306 (39.6)	85 (45.7)	84 (45.2)	114 (47.9)	108 (45.4)
Female	452 (58.5)	467 (60.4)	101 (54.3)	102 (54.8)	124 (52.1)	130 (54.6)
Prior infection, opportunistic,* n (%)	1 (0.1)	2 (0.3)	0 (0.0)	0 (0.0)	0 (0.0)	0 (0.0)
Prior infection, bacterial,* n (%)	54 (7.0)	48 (6.2)	10 (5.4)	13 (7.0)	10 (4.2)	13 (5.5)
Prior conjunctivitis, n (%)	0 (0.0)†	0 (0.0)†	0 (0.0)†	0 (0.0)†	0 (0.0)†	0 (0.0)†
Asthma, n (%)	119 (15.4)	117 (15.1)	24 (12.9)	34 (18.3)	25 (10.5)	31 (13.0)
Allergic rhinitis, n (%)	123 (15.9)	122 (15.8)	39 (21.0)	43 (23.1)	32 (13.4)	29 (12.2)
Chronic sinusitis, n (%)	25 (3.2)	19 (2.5)	1 (0.5)	4 (2.2)	3 (1.3)	3 (1.3)
Diabetes, any, n (%)	92 (11.9)	86 (11.1)	11 (5.9)	11 (5.9)	30 (12.6)	35 (14.7)
Prior use of cyclosporine, oral, n (%)	20 (2.6)	10 (1.3)	0 (0.0)	0 (0.0)	14 (5.9)	13 (5.5)
Prior use of cyclosporine, ophthalmic, n (%)	6 (0.8)	6 (0.8)	0 (0.0)	0 (0.0)	0 (0.0)	1 (0.4)
Prior use of mycophenolate, n (%)	14 (1.8)	9 (1.2)	11 (5.9)	11 (5.9)	0 (0.0)	0 (0.0)
Prior use of azathioprine, n (%)	6 (0.8)	9 (1.2%)	0 (0.0%)	1 (0.5%)	8 (3.4%)	7 (2.9%)
Prior use of methotrexate, n (%)	0 (0.0)	0 (0.0%)	11 (5.9%)	15 (8.1%)	9 (3.8%)	16 (6.7%)
Prior use of other DMARDs,‡ n (%)	0 (0.0)§	0 (0.0)§	0 (0.0)§	0 (0.0)§	0 (0.0)§	0 (0.0)§
Ophthalmologist visit, n (%)	81 (10.5)	77 (10.0)	22 (11.8)	21 (11.3)	38 (16.0)	44 (18.5)
Ophthalmologist visit, number of visits						
Mean (SD)	0.39 (1.64)	0.43 (1.90)	0.41 (1.43)	0.35 (1.34)	0.44 (1.81)	0.49 (1.64)
Eye examination, routine, n (%)	125 (16.2)	119 (15.4)	35 (18.8)	31 (16.7)	38 (16.0)	44 (18.5)
Prior use of systemic glucocorticoids (180 days), n (%)	379 (49.0)	378 (48.9)	101 (54.3)	109 (58.6)	127 (53.4)	132 (55.5)
Recent use of systemic glucocorticoids (30 days), n (%)	163 (21.1)	160 (20.7)	50 (26.9)	48 (25.8)	67 (28.2)	64 (26.9)
Cumulative sum of systemic prednisone equivalencies, mean (SD)	340.9 (581.1)	331.2 (613.0)	439.7 (725.0)	478.3 (730.2)	530.4 (827.1)	546.4 (828.6)
Use of any ophthalmic treatments, ‖n (%)	34 (4.4)	33 (4.3)	9 (4.8)	6 (3.2)	12 (5.0)	11 (4.6)
Emergency department visit (atopic dermatitis related), n (%)	3 (0.4)	1 (0.1)	0 (0.0)	1 (0.5)	0 (0.0)	0 (0.0)

DMARD, Disease-modifying antirheumatic drug; *IQR*, interquartile range; *SD*, standard deviation.

*Inpatient and outpatient events of infection.

†The baseline prevalence of any prior conjunctivitis was 0% because it was a study exclusion criterion.

‡Other DMARD agents include adalimumab, etanercept, infliximab, certolizumab, golimumab, ustekinumab, ixekizumab, secukinumab, guselkumab, tofacitinib, rituximab, omalizumab, tocilizumab, leflunomide, sulfasalazine.

§The baseline prevalence of other DMARD agent use was 0% because it was a study exclusion criterion.

‖Prior use of ophthalmic corticosteroids, ophthalmic antihistamines, or ophthalmic mast cell inhibitors.

Table III. The 6-month risk of conjunctivitis or hospitalization for serious infections

		Unmatched patients					1:1 Propensity-score matched patients				
Outcome	Comparison	Patients, n	Events, n	6-month risk (%)	Risk ratio (95% CI)	Number needed to harm	Patients, n	Events, n	6-month risk (%)	Risk ratio (95% CI)	Number needed to harm
Serious infection*	Dupilumab	1982	12	0.61	0.61 (0.27-1.37)	−253	822	9	1.10	0.90 (0.37-2.20)	−820
	MTX	1100	11	1.00	R	R	822	10	1.22	R	R
	Dupilumab	2029	11	0.54	0.27 (0.09-0.83)	−67	196	3	1.53	0.75 (0.17-3.31)	−196
	CsA	196	4	2.04	R	R	196	4	2.04	R	R
	Dupilumab	2037	12	0.59	0.16 (0.07-0.38)	−33	259	2	0.77	0.20 (0.04-0.90)	−32
	MMF	279	10	3.58	R	R	259	10	3.86	R	R
Any conjunctivitis	Dupilumab	1775	115	6.48	1.97 (1.35-2.87)	31	774	49	6.34	2.45 (1.47-4.08)	27
	MTX	1034	34	3.29	R	R	774	20	2.59	R	R
	Dupilumab	1821	116	6.37	1.32 (0.68-2.55)	65	186	14	7.53	1.56 (0.69-3.50)	37
	CsA	186	9	4.84	R	R	186	9	4.84	R	R
	Dupilumab	1826	123	6.74	5.77 (1.85-18.00)	18	238	21	8.82	7.00 (2.12-23.15)	13
	MMF	257	3	1.17	R	R	238	3	1.26	R	R
Bacterial conjunctivitis	Dupilumab	1775	26	1.47	1.51 (0.73-3.13)	200	774	14	1.81	2.33 (0.90-6.04)	97
	MTX	1034	10	0.97	R	R	774	6	0.78	R	R
Allergic conjunctivitis	Dupilumab	1775	38	2.14	2.77 (1.30-5.91)	73	774	8	1.04	1.60 (0.53-4.87)	258
	MTX	1034	8	0.77	R	R	774	5	0.65	R	R
Keratoconjunctivitis	Dupilumab	1775	19	1.07	1.11 (0.52-2.37)	970	774	11	1.42	1.57 (0.61-4.03)	193
	MTX	1034	10	0.97	R	R	774	7	0.90	R	R
Any conjunctivitis (including patients with pre-existing conjunctivitis)	Dupilumab	1982	169	8.53	2.08 (1.51-2.87)	23	822	72	8.76	2.12 (1.42-3.15)	22
	MTX	1100	45	4.09	R	R	822	34	4.14	R	R
	Dupilumab	2029	170	8.38	1.37 (0.78-2.41)	44	196	22	11.22	1.83 (0.93-3.60)	20
	CsA	196	12	6.12	R	R	196	12	6.12	R	R
	Dupilumab	2037	179	8.79	3.50 (1.66-7.38)	16	259	24	9.27	3.43 (1.50-7.82)	15
	MMF	279	7	2.51	R	R	259	7	2.70	R	R

Any conjunctivitis (patients with AD and comorbid asthma)	Dupilumab	323	30	9.29	1.99 (0.89-4.43)	21	105	12	11.43	2.00 (0.78-5.13)	18
	MTX	150	7	4.67	R	R	105	6	5.71	R	R
Any conjunctivitis (diagnosed by an ophthalmologist)	Dupilumab	1775	30	1.69	1.75 (0.86-3.56)	138	774	14	1.81	2.80 (1.01-7.74)	86
	MTX	1034	10	0.97	R	R	774	5	0.65	R	R
	Dupilumab	1821	29	1.59	0.99 (0.30-3.21)	−5000	186	3	1.61	1.00 (0.20-4.89)	N/A
	CsA	186	3	1.61	R	R	186	3	1.61	R	R
	Dupilumab	1826	32	1.75	2.25 (0.54-9.34)	102	238	5	2.10	2.50 (0.49-12.76)	79
	MMF	257	2	0.78	R	R	238	2	0.84	R	R
Eye examination[†]	Dupilumab	1775	186	10.48	0.50 (0.42-0.60)	−10	774	115	14.88	0.93 (0.73-1.17)	−86
	MTX	1034	217	20.99	R	R	774	124	16.04	R	R
	Dupilumab	1821	186	10.21	0.83 (0.55-1.24)	−46	186	25	13.44	1.09 (0.64-1.84)	93
	CsA	186	23	12.37	R	R	186	23	12.37	R	R
	Dupilumab	1826	188	10.30	0.54 (0.41-0.72)	−11	238	41	17.23	0.91 (0.62-1.34)	−59
	MMF	257	49	19.07	R	R	238	45	18.91	R	R

AD, Atopic dermatitis; *CI*, confidence interval; *CsA*, cyclosporine; *MMF*, mycophenolate; *MTX*, methotrexate; *N/A*, not applicable; *R*, referent.
*For evaluation of serious infection, we did not exclude patients with pre-existing conjunctivitis.
[†]Eye examination, excluding eye examinations with a conjunctivitis diagnosis.

Table IV. Relative risk estimates of developing serious infections and conjunctivitis within 6 months of treatment initiation, with increasing levels of confounding adjustment

Outcome	Model	Odds Ratio* (95% Confidence interval)		
		Dupilumab versus methotrexate	Dupilumab versus cyclosporine	Dupilumab versus mycophenolate
Serious infection	Unadjusted	0.60 (0.27-1.37)	0.26 (0.08-0.83)	0.16 (0.07-0.37)
	Adjusted by basic confounders[†]	0.74 (0.30-1.82)	0.26 (0.08-0.84)	0.22 (0.09-0.54)
	Fully adjusted[‡]	0.74 (0.29-1.87)	0.26 (0.07-1.01)	0.22 (0.08-0.59)
	Adjusted by basic confounders and deciles of propensity score	0.69 (0.27-1.75)	0.34 (0.10-1.22)	0.27 (0.10-0.68)
Any conjunctivitis	Unadjusted	2.04 (1.38-3.01)	1.34 (0.67-2.68)	6.12 (1.93-19.37)
	Adjusted by basic confounders	2.39 (1.58-3.63)	1.51 (0.75-3.05)	7.19 (2.26-22.94)
	Fully adjusted	2.43 (1.59-3.72)	1.59 (0.78-3.26)	8.35 (2.48-28.10)
	Adjusted by basic confounders and deciles of propensity score	2.36 (1.54-3.63)	1.58 (0.78-3.21)	7.37 (2.30-23.66)
Any conjunctivitis (including patients with pre-existing conjunctivitis)	Unadjusted	2.19 (1.56-03.06)	1.40 (0.77-2.57)	3.74 (1.74-8.05)
	Adjusted by basic confounders	2.70 (1.88-3.87)	1.58 (0.86-2.92)	4.58 (2.11-9.92)
	Fully adjusted	2.57 (1.76-3.76)	1.40 (0.75-2.63)	4.88 (2.15-11.06)
	Adjusted by basic confounders and deciles of propensity score	2.40 (1.65-3.48)	1.43 (0.77-2.66)	4.21 (1.92-9.20)
Any conjunctivitis (diagnosed by an ophthalmologist)	Unadjusted	1.76 (0.86-3.62)	0.99 (0.30-3.27)	2.27 (0.54-9.55)
	Adjusted by basic confounders	2.13 (0.99-4.58)	1.15 (0.34-3.91)	3.13 (0.73-13.44)
	Fully adjusted	2.33 (1.05-5.18)	1.45 (0.40-5.25)	3.02 (0.68-13.39)
	Adjusted by basic confounders and deciles of propensity score	2.48 (1.11-5.51)	1.33 (0.38-4.60)	3.67 (0.84-15.98)
Eye examination[§]	Unadjusted	0.44 (0.36-0.55)	0.81 (0.51-1.28)	0.49 (0.3- 0.69)
	Adjusted by basic confounders	0.72 (0.57-0.91)	0.90 (0.56-1.47)	0.70 (0.48-1.00)
	Fully adjusted	0.73 (0.57-0.94)	0.94 (0.56-1.57)	0.82 (0.55-1.22)
	Adjusted by basic confounders and deciles of propensity score	0.82 (0.64-1.06)	0.99 (0.60-1.63)	0.82 (0.56-1.21)

CsA, Cyclosporine; *MMF*, mycophenolate; *MTX*, methotrexate.
*Odds ratios from logistic regression.
[†]Basic cofounders are defined as age and sex.
[‡]Confounder adjusted for the following patient characteristics in the 180 days before cohort entry: age; sex; year of cohort entry; any prior serious bacterial or opportunistic infections with an inpatient or outpatient encounter; prior conjunctivitis diagnosis; prior use of methotrexate; oral cyclosporine; ophthalmic cyclosporine mycophenolate, or azathioprine; prior use of ophthalmic corticosteroids, ophthalmic antihistamines, or ophthalmic mast cell inhibitors; comorbid diagnosis of asthma, allergic rhinitis, chronic sinusitis, or diabetes; any prior use of systemic glucocorticoids; recent use of systemic glucocorticoids (<30 days before cohort entry); cumulative sum of systemic prednisone equivalencies; and emergency department visits related to atopic dermatitis.
[§]Eye examination, excluding eye examinations with a conjunctivitis diagnosis.

(95% CI, 0.37-2.20) (Table III). These RRs, with wide CIs, were based on only 9 and 10 events, respectively. In PS decile–stratified analyses, the RR for serious infections was 0.69 (95% CI, 0.27-1.75) in dupilumab versus MTX, 0.34 (95% CI, 0.10-1.22) in dupilumab versus cyclosporine, and 0.27 (95% CI, 0.10-0.68) in dupilumab versus mycophenolate (Table IV).

Addressing the potential for differential surveillance for conjunctivitis

Given the increased conjunctivitis risk observed in RCTs, we were concerned that patients started on dupilumab were monitored more closely for the occurrence of conjunctivitis. To address differential surveillance, we evaluated the risk of conjunctivitis recorded by an ophthalmologist and found that the RR was 2.80 (95% CI, 1.01-7.74) in dupilumab versus MTX, 1.00 (95% CI, 0.20-4.89) in dupilumab versus cyclosporine, and 2.50 (95% CI, 0.49-12.76) in dupilumab versus mycophenolate (Table III). Additionally, we used a negative tracer outcome: routine eye examination without a diagnosis for conjunctivitis. The RR for a routine eye examination in PS decile—adjusted analyses was 0.82 (95% CI, 0.64-1.06) for dupilumab versus MTX, 0.99 (95% CI, 0.60-1.63) for dupilumab versus cyclosporine, and 0.82 (95% CI, 0.56-1.21) for dupilumab versus mycophenolate (Table IV), confirming equal access to eye care and making differential surveillance unlikely.

DISCUSSION

In this population-representative study of patients with AD, we observed that dupilumab initiators had at least twice the risk of developing conjunctivitis compared to patients who initiated MTX and similar findings compared against cyclosporine and mycophenolate. This was consistent across 3 conjunctivitis types. We found no increase in the 6-month risk of serious bacterial or opportunistic infections when starting dupilumab versus MTX, an analysis that is based on few events and is consistent across 3 comparators, dupilumab versus MTX, cyclosporine, or mycophenolate.

The clinical implications of this study are reassuring insofar as dupilumab does not increase the risk for serious bacterial or opportunistic infections. The consistently increased risk of conjunctivitis when treating patients with AD with dupilumab, however, may be an important decision factor when prescribing. Because more patients will be using dupilumab, future studies may identify specific risk factors for conjunctivitis and better guide prescribers.

The increased risk of developing conjunctivitis in patients with AD treated with dupilumab, as observed in this study, is in line with what we have observed in clinical trials. The SOLO 1 and SOLO 2 trials found a 3- to 5-fold increase in conjunctivitis among 465 patients with AD treated with dupilumab every other week versus 456 patients receiving placebo.[4] Similarly, the CHRONOS trial found a 1.7- to 2.5-fold increase among 425 patients with AD treated with dupilumab plus topical corticosteroids versus 315 patients treated with placebo plus topical corticosteroid.[4,5] A strength of our study using insurance claims data is that it represents the experience in clinical practice. The results add to the evidence from RCTs by including a broader patient population that dermatologists encounter in practice and the corresponding event rates.[29]

In an effort to overcome the absence of baseline randomization, we included several measures to minimize confounding, including 1:1 PS matching, extensive exclusions, and implementation of a new-user, active-comparator cohort design.[11,12] First, the use of 1:1 PS matching restricted our analysis to very similar patients, which balanced variation between treatment groups in our comparative analysis and minimized confounding.[30,31] Second, through clinically relevant exclusions at the design stage, our treatment groups were made very comparable regarding confounding factors.[32] Third, the implementation of a new-user, active-comparator cohort design is well known to reduce potential confounding and limiting the follow-up duration to 180 days of eliminated differential dropout.[33]

The use of insurance claims data allows for a population-representative cohort that captures safety in the real-world setting, but it is subject to limitations. First, the number of users that qualified for our study remain a limitation, despite the large source population. Because the numbers of users will increase quickly over time, we are confident that the increase in the risk of conjunctivitis in clinical practice will be confirmed. The differential increases in conjunctivitis risk among patients with comorbid asthma is a hypothesis worth testing with larger numbers, and it may serve as a clinical predictor of conjunctivitis risk. Equally, the different conjunctivitis subtypes raise interesting mechanistic hypotheses upon which to base future studies. Second, insurance claims data lack the clinical granularity to capture subtle distinctions in clinical diagnoses. In the absence of validated claims-based algorithms that differentiate the types of conjunctivitis, we combined diagnostic codes with typical treatments, like requiring the use of an ophthalmic antibiotic within 3 days of a bacterial conjunctivitis diagnosis. Third, this analysis reflects dosing patterns in clinical practice, and we did not categorize the referent agents or the dupilumab exposure into specific dose regimens, ie, weekly versus every 2 weeks. Fourth, the awareness of an increased conjunctivitis risk with dupilumab may introduce differential surveillance, leading to bias. We investigated for surveillance bias through sensitivity analyses and negative tracer outcomes and found no indication of differential

surveillance for conjunctivitis among users of dupilumab.

In conclusion, this population-based study adds further evidence that there is no increase in serious bacterial or opportunistic infections among patients treated with dupilumab compared to other systemic treatments and that a doubling in the risk of conjunctivitis needs to be managed in clinical practice.

REFERENCES

1. Beck LA, Thaci D, Hamilton JD, et al. Dupilumab treatment in adults with moderate-to-severe atopic dermatitis. *N Engl J Med*. 2014;371(2):130-139.
2. Simpson EL, Gadkari A, Worm M, et al. Dupilumab therapy provides clinically meaningful improvement in patient-reported outcomes (PROs): a phase IIb, randomized, placebo-controlled, clinical trial in adult patients with moderate to severe atopic dermatitis (AD). *J Am Acad Dermatol*. 2016;75(3):506-515.
3. Thaci D, Simpson EL, Beck LA, et al. Efficacy and safety of dupilumab in adults with moderate-to-severe atopic dermatitis inadequately controlled by topical treatments: a randomised, placebo-controlled, dose-ranging phase 2b trial. *Lancet*. 2016;387(10013):40-52.
4. Simpson EL, Bieber T, Guttman-Yassky E, et al. Two phase 3 trials of dupilumab versus placebo in atopic dermatitis. *N Engl J Med*. 2016;375(24):2335-2348.
5. Blauvelt A, de Bruin-Weller M, Gooderham M, et al. Long-term management of moderate-to-severe atopic dermatitis with dupilumab and concomitant topical corticosteroids (LIBERTY AD CHRONOS): a 1-year, randomised, double-blinded, placebo-controlled, phase 3 trial. *Lancet*. 2017;389(10086):2287-2303.
6. Ariens LFM, van der Schaft J, Bakker DS, et al. Dupilumab is very effective in a large cohort of difficult-to-treat adult atopic dermatitis patients: first clinical and biomarker results from the BioDay registry. *Allergy*. 2020;75(1):116-126.
7. Treister AD, Kraff-Cooper C, Lio PA. Risk factors for dupilumab-associated conjunctivitis in patients with atopic dermatitis. *JAMA Dermatol*. 2018;154(10):1208-1211.
8. Liberman P, Shifera AS, Berkenstock M. Dupilumab-associated conjunctivitis in patients with atopic dermatitis. *Cornea*. 2020;39:784-786.
9. Maudinet A, Law-Koune S, Duretz C, Lasek A, Modiano P, Tran THC. Ocular surface diseases induced by dupilumab in severe atopic dermatitis. *Ophthalmol Ther*. 2019;8(3):485-490.
10. Hernan MA, Sauer BC, Hernandez-Diaz S, Platt R, Shrier I. Specifying a target trial prevents immortal time bias and other self-inflicted injuries in observational analyses. *J Clin Epidemiol*. 2016;79:70-75.
11. Schneeweiss S. A basic study design for expedited safety signal evaluation based on electronic healthcare data. *Pharmacoepidemiol Drug Saf*. 2010;19(8):858-868.
12. Johnson ES, Bartman BA, Briesacher BA, et al. The incident user design in comparative effectiveness research. *Pharmacoepidemiol Drug Saf*. 2013;22(1):1-6.
13. Schwartz GF, Kotak S, Mardekian J, Fain JM. Incidence of new coding for dry eye and ocular infection in open-angle glaucoma and ocular hypertension patients treated with prostaglandin analogs: retrospective analysis of three medical/pharmacy claims databases. *BMC Ophthalmol*. 2011;11:14.
14. Suh DC, Sung J, Gause D, Raut M, Huang J, Choi IS. Economic burden of atopic manifestations in patients with atopic dermatitis—analysis of administrative claims. *J Manag Care Pharm*. 2007;13(9):778-789.
15. Smith AF, Waycaster C. Estimate of the direct and indirect annual cost of bacterial conjunctivitis in the United States. *BMC Ophthalmol*. 2009;9:13.
16. Chen YH, Lin CL, Bau DT, Hung YC. Risk of allergic conjunctivitis in patients with type 1 diabetes mellitus: a population-based retrospective cohort study. *BMJ Open*. 2017;7(6):e015795.
17. Schneeweiss S, Robicsek A, Scranton R, Zuckerman D, Solomon DH. Veteran's affairs hospital discharge databases coded serious bacterial infections accurately. *J Clin Epidemiol*. 2007;60(4):397-409.
18. Sahli L, Lapeyre-Mestre M, Derumeaux H, Moulis G. Positive predictive values of selected hospital discharge diagnoses to identify infections responsible for hospitalization in the French national hospital database. *Pharmacoepidemiol Drug Saf*. 2016;25(7):785-789.
19. Holland-Bill L, Xu H, Sorensen HT, et al. Positive predictive value of primary inpatient discharge diagnoses of infection among cancer patients in the Danish National Registry of Patients. *Ann Epidemiol*. 2014;24(8):593-597, 597.e1-18.
20. Brookhart MA, Schneeweiss S, Rothman KJ, Glynn RJ, Avorn J, Stürmer T. Variable selection for propensity score models. *Am J Epidemiol*. 2006;163(12):1149-1156.
21. Rosenbaum PR, Rubin DB. The central role of the propensity score in observational studies for causal effects. *Biometrika*. 1983;70:41-55.
22. Rassen JA, Shelat AA, Myers J, Glynn RJ, Rothman KJ, Schneeweiss S. One-to-many propensity score matching in cohort studies. *Pharmacoepidemiol Drug Saf*. 2012;21(Suppl 2):69-80.
23. Franklin JM, Rassen JA, Ackermann D, Bartels DB, Schneeweiss S. Metrics for covariate balance in cohort studies of causal effects. *Stat Med*. 2014;33(10):1685-1699.
24. Austin PC. Balance diagnostics for comparing the distribution of baseline covariates between treatment groups in propensity-score matched samples. *Stat Med*. 2009;28(25):3083-3107.
25. Desai RJ, Rothman KJ, Bateman BT, Hernandez-Diaz S, Huybrechts KF. A propensity-score-based fine stratification approach for confounding adjustment when exposure is infrequent. *Epidemiology*. 2017;28(2):249-257.
26. Wang SV, Verpillat P, Rassen JA, Patrick A, Garry EM, Bartels DB. Transparency and reproducibility of observational cohort studies using large healthcare databases. *Clin Pharmacol Ther*. 2016;99(3):325-332.
27. Kim SC, Solomon DH, Rogers JR, et al. Cardiovascular safety of tocilizumab versus tumor necrosis factor inhibitors in patients with rheumatoid arthritis: a multi-database cohort study. *Arthritis Rheumatol*. 2017;69(6):1154-1164.
28. Patorno E, Schneeweiss S, Gopalakrishnan C, Martin D, Franklin JM. Using real-world data to predict findings of an ongoing phase IV cardiovascular outcome trial: cardiovascular safety of linagliptin versus glimepiride. *Diabetes Care*. 2019;42(12):2204-2210.
29. Sherman RE, Anderson SA, Dal Pan GJ, et al. Real-world evidence—what is it and what can it tell us? *N Engl J Med*. 2016;375(23):2293-2297.
30. Austin PC, Mamdani MM, Stukel TA, Anderson GM, Tu JV. The use of the propensity score for estimating treatment effects: administrative versus clinical data. *Stat Med*. 2005;24(10):1563-1578.
31. Austin PC. Optimal caliper widths for propensity-score matching when estimating differences in means and differences in proportions in observational studies. *Pharm Stat*. 2011;10(2):150-161.

32. Schneeweiss S, Patrick AR, Stürmer T, et al. Increasing levels of restriction in pharmacoepidemiologic database studies of elderly and comparison with randomized trial results. *Med Care*. 2007;45(10 Suppl 2):S131-S142.

33. Suissa S, Garbe E. Primer: administrative health databases in observational studies of drug effects—advantages and disadvantages. *Nat Clin Pract Rheumatol*. 2007;3(12):725-732.