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## Immunosuppressive biologics did not increase the risk of COVID-19 or subsequent mortality: A retrospective matched cohort study from Massachusetts

*To the Editor:* The COVID-19 pandemic raised concerns about the management of patients with immune-mediated inflammatory diseases treated with immunosuppressive biologics. A third of patients with psoriasis who discontinued their medications had disease progression.<sup>1</sup> As population-level analyses of this patient group remain limited, we compared the incidence of COVID-19 and subsequent mortality in a large cohort of patients prescribed biologics and matched controls.

We identified all patients aged 18 years and older with at least 1 prescription for a biologic from July 1, 2019 to February 29, 2020 in the Massachusetts General Brigham Enterprise Data Warehouse. The primary and secondary outcomes for this study were risk of COVID-19 and subsequent mortality, respectively. A multivariable logistic regression was used on matched data to calculate the odds ratio (OR) for COVID-19 diagnosis between the 2 groups, adjusting for age, sex, race, Charlson Comorbidity Index severity grade, median income, and local infection rates. A multivariable Poisson regression was used to compare all-cause mortality among patients diagnosed with COVID-19, adjusting for age, sex, Charlson Comorbidity Index severity grade, median income, and local infection rates. Detailed methods and sensitivity analyses are included in the Supplemental Materials (available via Mendeley at https://data.mendeley.com/datasets/w4478kftkk/1).

We identified 7361 patients who received biologics and 74,910 matched controls. Patient baseline characteristics are presented in Table I. Tumor necrosis factor inhibitors (adalimumab [28.4%], infliximab [15.6%], and etanercept [11.9%]), CD20-directed antibody (rituximab [15.6%]), and interleukin-4A inhibitor (dupilumab [8.6%]) were the most frequently prescribed biologics. Rheumatoid arthritis (27.5%), psoriasis (27.3%), psoriatic arthritis (16.2%), Crohn's disease (24.9%), and ulcerative colitis (18.9%) were the most common indications for biologics in our study.

Overall, biologics were not associated with COVID-19 (OR, 0.88; 95% confidence interval [CI], 0.71-1.09; P = .25), adjusting for demographics, comorbidity burden, and local infection rates (Table II). Patients treated with tumor necrosis factor inhibitors were less likely to be diagnosed with SARS-CoV-2 infection compared to matched controls (OR, 0.69; 95% CI, 0.48-0.98; P = .04). Similarly, those treated with dupilumab had lower odds of diagnosis (OR, 0.38; 95% CI, 0.12-1.18), although this difference was not statistically significant (P = .10). Mortality rates were also similar between the 2 groups after adjusting for demographics, comorbidity burden, and local infection rates (OR, 1.13; 95% CI, 0.57-2.76; P = .57).

Despite the ongoing vaccination efforts, COVID-19 remains a top health concern. The major finding of our study is that biologics did not increase the risk of a positive COVID-19 diagnosis, which is consistent with published literature.<sup>2-4</sup> Additionally, distinct biologics classes are known to cause varying susceptibilities to other viral infections. In our study, tumor necrosis factor inhibitors were associated with lower odds of COVID-19 diagnosis, consistent with reports of this class of biologics being associated with less-severe disease among large cohorts of patients.<sup>2,4</sup> Furthermore, we did not identify an association between biologics and mortality.

Our results must be considered in light of the realworld data it is based upon, because these patients may have altered their behavior to decrease their risk of infection, as has been reported in surveys of patients with inflammatory bowel disease and rheumatic diseases.<sup>5</sup> Dermatologists and patients should prioritize the well-established risk factors for COVID-19 when making decisions to continue therapy.

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## Table I. Demographics and clinical characteristics of patients on biologics and matched controls

Demographic or clinical variable	Biologic group N = 7361	Matched controls N = 74,910	<i>P</i> value
Age group (years), N (%)	N - /301	N - /4,910	>.99
18-44	2783 (37.8%)	28,321 (37.8%)	/
45-64	2838 (38.6%)	28,881 (38.6%)	
65-74	1135 (15.4%)	11,550 (15.4%)	
≥75	605 (8.2%)	6157 (8.2%)	
Sex, female, N (%)	4124 (56.0%)	41,968 (56.0%)	>.99
Race and ethnicity, N (%)	4124 (30.070)	41,500 (50.070)	>.99
White non-Hispanic	6223 (84.5%)	63,329 (84.5%)	/
Asian or Pacific Islander non-Hispanic	263 (3.6%)	2676 (3.6%)	
Black non-Hispanic	332 (4.5%)	3379 (4.5%)	
Other non-Hispanic	139 (1.9%)	1415 (1.9%)	
Hispanic	223 (3.0%)	2269 (3.0%)	
Unknown	181 (2.5%)	1842 (2.5%)	
Charlson comorbidity index grade, N (%)	101 (21376)		>.99
Mild (1-2)	4050 (55.0%)	41,215 (55.0%)	
Moderate (3-4)	1591 (21.6%)	16,191 (21.6%)	
Severe ( $\geq$ 5)	1720 (23.4%)	17,504 (23.4%)	
Medical comorbidity, N (%)	1720 (2011/0)	17,551 (25.176)	
Hypertension	2147 (29.2%)	21,561 (28.8%)	.49
Congestive heart failure	355 (4.8%)	4867 (6.5%)	<.001
Diabetes	818 (11.1%)	11,234 (15.0%)	<.001
Chronic pulmonary disease	933 (12.7%)	10,738 (14.3%)	<.001
Other pulmonary disease	1529 (20.8%)	17,546 (23.4%)	<.001
Renal disease	561 (7.6%)	5797 (7.7%)	.72
Liver disease	1156 (15.7%)	11,821 (15.8%)	.86
Hematologic cancer	593 (8.1%)	3043 (4.1%)	<.001
Solid organ cancer, not metastatic	1270 (17.3%)	15,949 (21.3%)	<.001
Solid organ cancer, metastatic	145 (2.0%)	3592 (4.8%)	<.001
Indication			
Asthma	1428 (19.4%)	13,162 (17.6%)	<.001
Atopic dermatitis	2022 (27.5%)	15,112 (20.2%)	<.001
Chronic lymphocytic leukemia	65 (0.9%)	263 (0.4%)	<.001
Non-Hodgkin lymphoma	483 (6.7%)	1421 (1.9%)	<.001
Giant cell arteritis	186 (2.5%)	159 (0.2%)	<.001
Granulomatosis with polyangiitis	104 (1.4%)	105 (0.1%)	<.001
Microscopic polyangiitis	20 (0.3%)	6 (0.01%)	<.001
Systemic lupus erythematosus	233 (3.2%)	521 (0.7%)	<.001
Pemphigus	32 (0.4%)	59 (0.1%)	<.001
Hidradenitis suppurativa	166 (2.3%)	387 (0.5%)	<.001
Psoriasis	2012 (27.3%)	3054 (4.1%)	<.001
Psoriatic arthritis	1192 (16.2%)	369 (0.5%)	<.001
Rheumatoid arthritis	2027 (27.5%)	1930 (2.6%)	<.001
Ankylosing spondylitis	452 (6.1%)	183 (0.2%)	<.001
Uveitis	211 (2.9%)	594 (0.8%)	<.001
Crohn's disease	1829 (24.9%)	515 (0.7%)	<.001
Ulcerative colitis	1388 (18.9%)	1094 (1.5%)	<.001
COVID-19 positive, N (%)	87 (1.2%)	1063 (1.4%)	.10
Died, N (% of COVID-19-positive patients)	7 (8.0%)	71 (6.7%)	.79
COVID-19 town or county positivity rate per	1.4 (0.9)	1.6 (1.1)	<.001
100 mean (SD)			
	N = 7317	N = 74,389	
Median income in \$1000s mean (SD)	82.0 (29.2)	79.7 (29.2)	<.001

P values <0.05 appear in bold.

Table II. Multivariable logistic regression of the risk of COVID-19 infection and subsequent mortality for
patients treated with immunosuppressive biologics

Variable	OR	95% CI	P value
Risk of infection for all immunosuppressive biologics	5		
Biologic use	0.88	0.71-1.09	.25
Age group (years)			
18-44	ref*	ref*	ref*
45-64	0.92	0.79-1.07	.28
65-74	0.67	0.53-0.85	.001
≥75	1.22	0.96-1.56	.11
Sex, female	0.95	0.85-1.07	.43
Race and ethnicity			
White non-Hispanic	ref*	ref*	ref*
Asian or Pacific Islander non-Hispanic	0.36	0.21-0.62	<.001
Black non-Hispanic	2.10	1.73-2.56	<.001
Other non-Hispanic	1.36	1.04-1.79	.02
Hispanic	1.39	0.99-1.94	.06
Unknown	0.28	0.13-0.58	.001
CCI grade			
Mild (1-2)	ref*	ref*	ref*
Moderate (3-4)	1.32	1.11-1.56	<.01
Severe (≥5)	1.88	1.56-2.26	<.001
COVID-19 town or county positivity rate	1.24	1.19-1.29	<.001
Median income in \$1,000s	0.98	0.95-1.00	.06
Risk of infection by immunosuppressive biologic class	55		
Class			
B-cell activating factor inhibitor	0	0.00-Inf	.98
CD20-directed cytolytic antibody	1.16	0.73-1.83	.53
Integrin receptor antagonist	1.27	0.61-2.68	.52
Interleukin-1 receptor antagonist	2.23	0.31-15.82	.42
Interleukin-4A receptor antagonist	0.38	0.12-1.18	.10
Interleukin-6 receptor antagonist	1.35	0.60-3.02	.47
Interleukin-12/23 receptor antagonist	0.88	0.33-2.34	.79
Interleukin-17A receptor antagonist	1.75	0.83-3.69	.14
Interleukin-23 antagonist	1.60	0.23-11.40	.64
Selective T-cell costimulation modulator	1.63	0.61-4.36	.33
Tumor necrosis factor inhibitor	0.69	0.48-0.98	.04
Risk of subsequent all-cause mortality for all immune			
Biologic use	1.13	0.57-2.76	.57
Age	1.06	1.04-1.09	<.001
Sex, female	0.53	0.34-0.83	<.01
CCI grade			
Mild (1-2)	ref*	ref*	ref*
Moderate (3-4)	2.12	0.69-6.51	.19
Severe $(\geq 5)$	2.96	0.99-8.86	.05
Median income in \$1000s	0.90	0.80-1.00	.06
COVID-19 town or county positivity rate	0.93	0.78-1.11	.00

*CCI*, Charlson Comorbidity Index; *OR*, odds ratio; *ref*, reference. \*Reference variable. *P* values <0.05 appear in bold.

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## **Conflicts of interest**

None disclosed.

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