Antecedent immunosuppressive therapy for immune-mediated inflammatory diseases in the setting of a COVID-19 outbreak

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Background: Finite clinical data and understanding of COVID-19 immunopathology has led to limited, opinion-based recommendations for the management of patients with immune-mediated inflammatory disease (IMID) receiving immunosuppressive (IS) therapeutics.

Objective: To determine if IS therapeutic type affects COVID-19 risk among patients with IMID.

Methods: We conducted a retrospective cohort analysis of Henry Ford Health System patients tested for COVID-19 between February 1 and April 18, 2020, treated with IS medication for IMID. Therapeutic class of IS medication, comorbidities, and demographic factors were combined into multivariate models to determine predictors of COVID-19 infection, admission, ventilation, and mortality.

Results: Of 213 patients with IMID, 36.2% tested positive for COVID-19, and they had no greater odds of being hospitalized or requiring ventilation relative to the general population. No IS therapeutic worsened the course of disease after multivariate correction, although multidrug regimens and biologics predicted an increased and decreased rate of hospitalization, respectively, with the latter driven by tumor necrosis factor α inhibitors.

Limitations: A single-center study somewhat limits the generalization to community-based settings. Only patients tested for COVID-19 were analyzed.

Conclusion: IS therapies for IMIDs are not associated with a significantly greater risk of SARS-CoV-2 or severe sequelae when controlling for other factors, and tumor necrosis factor α inhibitors may decrease the odds of severe infection. (J Am Acad Dermatol 2020;83:1696-703.)

Key words: autoimmune disease; biologics; coronavirus; COVID-19; DMARDs; immune-mediated inflammatory diseases; immunosuppression; SARS-CoV-2.

The COVID-19 pandemic has sparked uncertainty throughout society and the medical community on how to best quell the spread of the virus, allocate critical resources, and care for high-risk populations, especially as new cases surge.[1-4] Concerns about potential increased risk for patients receiving immunosuppressive (IS) treatment for immune-mediated inflammatory disease (IMID) are warranted. Several professional societies suggest that clinicians should discontinue or reduce the use of IS agents in patients who test positive for severe acute respiratory syndrome coronavirus 2

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(SARS-CoV-2),[1,5,6] although there is insufficient evidence to recommend discontinuation of IS therapy in others. Although immunosuppression predisposes individuals to infection by influenza and rhinoviruses, it has not been reported as a risk factor in previous coronavirus outbreaks, and it did not appear as a frequent comorbidity in studies of the initial outbreak of SARS-CoV-2 in China.[7,8] Current guidance relies on expert opinion and incidences of infection from previous clinical trials for these therapies.[9,10] In the absence of a clinical or mechanistic understanding of SARS-CoV-2 immunopathology, this information may not be sufficient to guide clinical practice.

Discontinuation of IS treatment could lead to disease flares in patients with previously controlled IMID or to the development of antidrug antibodies, severely affecting quality of life.[2,11] Furthermore, the effect of perturbing a proinflammatory state in an already dysregulated immune system during a disease flare might provoke a cytokine storm in patients with mild or asymptomatic COVID-19, as has been seen in patients with cancer who contract COVID-19 soon after receiving immunotherapy.[12] Targeted immunomodulation may even prove beneficial, evidenced by data from previous coronaviruses and ongoing clinical trials.[13-15] Given this uncertainty, there is a great need for more data concerning patient outcomes in the early stages of the outbreak to guide clinical decision making.

During the COVID-19 pandemic, Detroit has had a high incidence of cases and is thus an excellent population from which to draw a single-center study, reducing the possible effect of confounding environmental factors. From February 1 to April 18, 2020, the Henry Ford Health System (HFHS) in Detroit, Michigan, tested a total of 15,345 individuals for SARS-CoV-2 using polymerase chain reaction (PCR), of whom 5881 (38.3%) had positive results. Of positive cases, 2650 (45.1%) patients were admitted, 522 (8.9%) required a ventilator, and 322 (5.5%) died (Supplemental Fig 1; all supplemental material available via Mendeley at https://doi.org/10.17632/hwf6mwdccj.1).

CAPSULE SUMMARY

- Little is known about the impact of systemic immunosuppressive (IS) medications common to dermatology on COVID-19 risk.
- IS medications for immune-mediated inflammatory disease were not associated with increased risk of SARS-CoV-2 infection or severe sequelae, and anti—tumor necrosis factor α monotherapy was associated with decreased admission rate. Patients can be reassured when continuing these medications during the COVID-19 pandemic.

METHODS

Study population

We performed a retrospective cohort study (Fig 1) using a chart review of patients tested for SARS-CoV-2 with laboratory PCR at HFHS between February 1 and April 18, 2020, who were being treated with IS drugs commonly used in dermatologic treatment and patients with IMID (Supplemental Table I) as documented in the electronic medical record. IS medications of interest included disease-modifying antirheumatic drugs (DMARDs) and biologics. DMARDs included apremilast, azathioprine, methotrexate, mycophenolate, cyclosporine, tofacitinib, and intravenous immunoglobulin. Biologics were subcategorized into tumor necrosis factor (TNF) α inhibitors (adalimumab, etanercept, infliximab, and certolizumab), interleukin (IL) 17 inhibitors (ixekizumab, secukinumab, and brodalumab), IL-12/23 inhibitors (ustekinumab, guselkumab, risankizumab, and tildrakizumab), and others (abatacept, dupilumab, omalizumab, belimumab, rituximab); no patients treated with IL-1 or IL-6 inhibitors were identified. For inclusion, patients were required to be treated with an IS medication at least 1 month before testing, which was validated through review of the treating physician notes and patient communications without reliance on autopopulated medication lists. Systemic corticosteroid use was not used as an independent identifying medication to avoid capturing patients on short-term corticosteroid regimens; however, some patients with IMID were concurrently treated with long-term corticosteroid regimens of at least 2 months in conjunction with another IS medication and were noted as such. Any patients receiving chemotherapy or those whose IS medication could not be verified as current were excluded. IMID status was verified via review of physician notes, and those taking IS medications for non-IMID indications, such as for the prevention of transplant rejection, were not included. A total of 213 patients with IMID treated with IS therapeutics were included and will be referred to as the IMID cohort (Table I). Individuals tested at HFHS during this time

Abbreviations used:

CI:	confidence interval
DMARD:	disease-modifying antirheumatic drug
HFHS:	Henry Ford Health System
IL:	interleukin
IMID:	immune-mediated inflammatory disease
IS:	immunosuppressive
OR:	odds ratio
PCR:	polymerase chain reaction
SARS-CoV-2:	severe acute respiratory syndrome coronavirus 2
TNF:	tumor necrosis factor

were under high suspicion for COVID-19, which included symptomatic patients or those with a known exposure presenting to the emergency department for testing, patients admitted, and HFHS health care providers seeking testing for concern of potential exposure. Asymptomatic patients without a verified exposure were not tested during this time. The policy for testing, admission, or ventilation did not vary based on comorbidities, demographics, or immunosuppressive treatments during this time. For patients tested multiple times, any positive result was considered a COVID-19–positive case. All research activities were conducted with approval of the HFHS institutional review board (no. 13768). We tracked outcomes for each patient via review of physician notes.

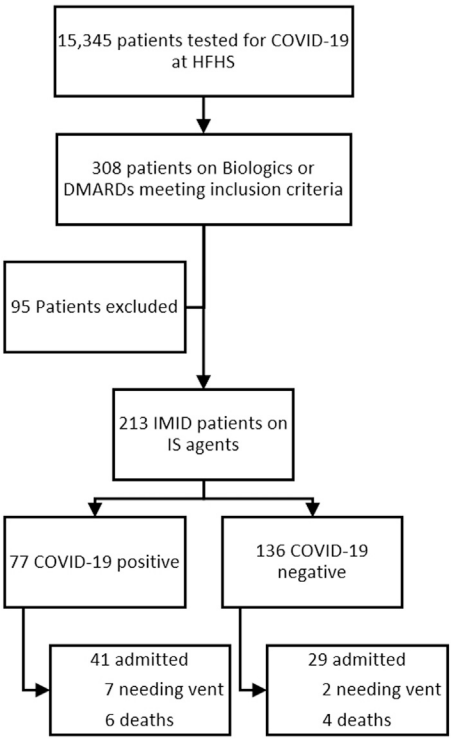

Fig 1. Flow diagram of the study. Patients were deemed to be positive for COVID-19 if any test result was positive for SARS-CoV-2 RNA and negative for COVID-19 if all test results were negative. *DMARD*, Disease-modifying antirheumatic drug; *HFHS*, Henry Ford Health System; *IMID*, immune-mediated inflammatory disease.

Analyses

The outcomes of interest were COVID-19 status (positive or negative) via PCR test, admission status (admitted or not admitted), ventilatory status (requiring or not requiring invasive mechanical ventilation), and vital status (living or deceased). We used 2-group comparisons to assess the overall outcomes for the IMID cohort against the general population tested at HFHS. For the purposes of this comparison, admission status, ventilator status, and mortality data were used only for those who tested positive for COVID-19. We then categorized IS medications into 2 primary groups—biologics and DMARDs, with hydroxychloroquine classified as an independent non-IS medication, given its potential use in both IMID and COVID-19. We subcategorized our cohort into those with rheumatoid arthritis/spondylitis, psoriasis/psoriatic arthritis, systemic lupus erythematosus/dermatomyositis/polymyositis/mixed connective tissue disorder/interstitial lung disease/scleroderma, inflammatory bowel disease, or others; others included autoimmune blistering conditions, autoimmune hepatitis, atopic conditions, hidradenitis suppurativa, myasthenia gravis, sarcoidosis, urticaria, and uveitis (Table I). We performed 2-group comparisons to assess the odds ratios of outcomes of interest as a function of IMID type or IS therapy present (Table II), with admission status, ventilator status, and mortality again being used only for those who tested positive for COVID-19. We additionally assessed admission status as a function of IS therapy class among the IMID cohort as a whole to determine if effects on admission rates were affected by COVID-19 status (Supplemental Table II). These comparisons were performed using chi-square testing, with Fisher's exact test used when expected counts were less than 5. Further investigation was performed by using multivariate logistic regression models while controlling for age, race, sex, COVID-19 status, IS medication, and comorbidities as documented in physician notes, including cardiac, pulmonary, renal, gastrointestinal, endocrine, and history of cancer (Supplemental Table III). For all analyses, statistical significance was determined if P was less than .05. All analyses were performed with SAS 9.4

Table I. Characteristics of the study population of patients tested for COVID-19

Characteristics	Patients with IMID on IS therapy (N = 213)
Age, y, mean ± SD	53 ± 15
Age >65 y, n (%)	50 (23.5)
Female sex, n (%)	155 (72.8)
Race or ethnic group, n (%)	
White	112 (52.6)
Black	74 (34.7)
Hispanic	3 (1.4)
Asian	2 (0.9)
Middle Eastern	3 (1.4)
Other/unknown	19 (8.9)
COVID-19 positive, n (%)	77 (36.2)
Hydroxychloroquine use, n (%)*	28 (13.1)
IS medication class, n (%)†	
Biologics	96 (45.1)
TNF-α inhibitors	56 (26.3)
TNF-α inhibitor monotherapy	45 (21.1)
IL-17 inhibitors	7 (3.3)
IL-12/23 inhibitors	7 (3.3)
Biologic monotherapy	73 (34.3)
DMARDs	138 (64.8)
Apremilast	10 (4.7)
Azathioprine	25 (11.7)
Methotrexate	65 (30.5)
Methotrexate monotherapy	45 (21.1)
Mycophenolate	23 (10.8)
DMARD monotherapy	100 (46.9)
Multidrug therapy‡	40 (18.8)
Systemic corticosteroids*	22 (10.3)
Comorbidity class, n (%)	
Cardiac	109 (51.2)
Pulmonary	75 (35.2)
Renal	11 (5.2)
Gastrointestinal	45 (21.1)
Endocrine	133 (62.4)
Cancer	11 (5.2)
IMID classification, n (%)	
Rheumatoid arthritis/spondylitis	72 (33.8)
Psoriasis/psoriatic arthritis	29 (13.6)
Inflammatory bowel disease	38 (17.8)
SLE/DM, PM/MCTD/ILD/Scl	33 (15.5)
Others§	45 (21.1)

DM, Dermatomyositis; *DMARD*, disease-modifying antirheumatic drug; *IL*, interleukin; *ILD*, interstitial lung disease; *IMID*, immune-mediated inflammatory disease; *IS*, immunosuppressive; *MCTD*, mixed connective tissue disease; *PM*, polymyositis; *Scl*, scleroderma and systemic sclerosis; *SD*, standard deviation; *SLE*, systemic lupus erythematosus; *TNF*, tumor necrosis factor.

*Concomitant use with IS medication.

†Any patient taking a medication from a therapeutic class (Supplemental Table I) was included in the respective group, regardless of additional medications taken. Biologics and DMARDs were further subcategorized as shown. Monotherapy designates a patient using a medication without an additional biologic or DMARD. Therapeutics with fewer than 5 patients treated are not shown.

‡Patients taking medications from both the biologics and DMARD groups or multiple DMARDs within the IMID cohort were also included in the multidrug therapy group.

§*Others* includes patients treated with IS therapy for autoimmune blistering conditions, autoimmune hepatitis, atopic conditions, hidradenitis suppurativa, myasthenia gravis, sarcoidosis, urticaria, and uveitis.

(SAS Institute Inc, Cary, NC) or GraphPad Prism software, version 8 (GraphPad Software, Inc, La Jolla, CA).

RESULTS

Of the 213 patients included in the IMID cohort, 77 (36.2%) tested positive for COVID-19 (Fig 1).

Table II. Outcomes by paired analysis among COVID-19–positive cases within the IMID cohort, OR (95% CI)*

Therapeutic class and IMID condition (COVID-19 cases, n)	COVID-19†	Admission	Ventilator	Mortality
Biologics (30)	0.94 (0.55-1.67)	**0.42 (0.16-1.09)**‡	1.06 (0.27-4.45)	0.61 (0.11-2.77)
TNF-α inhibitors (16)	0.63 (0.33-1.20)	**0.22 (0.07-0.73)**‡	0.61 (0.05-4.49)	0.75 (0.06-6.53)
TNF-α monotherapy (11)	0.50 (0.23-1.03)	**0.15 (0.03-0.70)**‡	0.00 (0.00-3.79)	0.00 (0.00-3.37)
Biologics monotherapy (23)	0.73 (0.41-1.32)	0.44 (0.17-1.21)	0.93 (0.18-5.72)	0.45 (0.04-3.73)
DMARDs (53)	1.33 (0.74-2.36)	2.54 (0.95-6.73)	1.15 (0.21-6.10)	2.40 (0.29-29.33)
Azathioprine (6)	0.52 (0.21-13.2)	0.87 (0.19-3.93)	**16.8 (2.90-84.4)**‡,§	2.64 (0.19-20.7)
Methotrexate (23)	0.95 (0.52-1.75)	0.94 (0.34-2.52)	0.93 (0.17-5.04)	1.19 (0.21-5.43)
Methotrexate monotherapy (15)	0.79 (0.40-1.58)	1.00 (0.34-2.93)	0.67 (0.055-4.96)	0.81 (0.065-7.2)
Mycophenolate (12)	2.10 (0.91-4.83)	1.94 (0.57-6.20)	0.89 (0.07-6.10)	3.05 (0.52-14.83)
DMARD monotherapy (34)	0.84 (0.49-1.48)	1.21 (0.50-2.87)	0.19 (0.02-1.29)	0.61 (0.11-2.77)
Systemic corticosteroids (12)	2.33 (1.01-5.73)	**5.48 (1.28-26.1)**‡	5.08 (1.10-20.9)	3.05 (0.52-14.8)
Multidrug therapy (21)	**2.31 (1.14-4.75)**‡	2.15 (0.73-5.59)	4.16 (1.01-17.41)	2.94 (0.63-13.29)
Hydroxychloroquine (7)	0.55 (0.21-1.38)	2.36 (0.45-12.4)	5.2 (0.83-26.8)	2.17 (0.16-15.5)
RA/spondylitis (26)	1.00 (0.56-1.78)	1.04 (0.41-2.73)	0.77 (0.14-4.10)	2.09 (0.45-9.39)
Psoriasis/PsA (13)	1.52 (0.69-3.47)	0.71 (0.20-2.26)	0.81 (0.07-6.16)	0.00 (0.00-2.69)
IBD (10)	0.58 (0.27-1.27)	0.54 (0.16-1.94)	0.00 (0.00-3.18)	1.38 (0.12-9.48)
SLE/DM/PM/MCTD/ILD/Scl (11)	0.77 (0.35-1.69)	1.65 (0.54-8.51)	1.13 (0.45-5.38)	0.00 (0.00-3.83)

Bold values represent significant values.

CI, Confidence interval; *DM*, dermatomyositis; *DMARD*, disease-modifying antirheumatic drug; *ILD*, interstitial lung disease; *IMID*, immune-mediated inflammatory disease; *MCTD*, mixed connective tissue disease; *OR*, odds ratio; *PM*, polymyositis; *PsA*, psoriatic arthritis; *RA*, rheumatoid arthritis; *Scl*, scleroderma and systemic sclerosis; *SLE*, systemic lupus erythematosus; *TNF*, tumor necrosis factor.

*The ORs and 95% CIs drawn from 2-group comparison have not been adjusted and should not be used to infer definitive effects.

†COVID-19 positivity among all patients with IMID.

‡$P < .05$.

§Three of 6 patients admitted requiring a ventilator.

Forty-one positive cases required admission (53.2% of positive cases), with 7 (9.1% of positive cases) necessitating ventilator use. Thirty-one patients with COVID-19–related admissions were subsequently discharged, 6 died, and 4 remained admitted and continued to receive care. Among 136 patients with IMID who tested negative for SARS-CoV-2, 29 (21.3% of negative cases) were admitted for continued suspicion of COVID-19 or reasons unrelated to COVID-19, and 2 (1.5% of negative cases) required a ventilator; any subsequent COVID-19 testing result was also negative. Twenty-five of these admitted patients were discharged, and 4 died of non–COVID-19–related reasons. Relevant additional information can be found in Supplemental Table IV. Relative to the general population, the IMID cohort did not have significantly greater odds of testing positive (odds ratio [OR], 0.91; 95% confidence interval [CI], 0.69-1.2), hospital admission after testing positive (OR, 1.39; 95% CI, 0.91-2.16), need for invasive mechanical ventilation after testing positive (OR, 1.03; 95% CI, 0.47-2.19), or COVID-19–related mortality (OR, 1.47; 95% CI, 0.68-3.25) (Supplemental Table V).

Although not corrected for additional variables, the following results from the 2-group comparison within the study cohort bear noting. The use of systemic corticosteroids compared to nonuse significantly increased the odds of admission within the cohort generally and among those who tested positive for COVID-19 (OR, 5.48; 95% CI, 1.28-26.1) (Table II). Receiving DMARD compared to non-DMARD therapy and multidrug therapy compared to monotherapy each led to increased odds of admission within the cohort generally, although this was not true when analysis was restricted to only those who tested positive for COVID-19 (Table II). Multidrug therapy compared to monotherapy also gave greater odds of a positive COVID-19 test result within the cohort (OR, 2.46; 95% CI, 1.20-5.06) (Supplemental Table II); no single medication among patients using multidrug therapy accounted for this result. Use of biologics compared to nonbiologic therapy was associated with lower odds of admission among patients with IMID generally as well as among those who tested positive (OR, 0.33; 95% CI, 0.14-0.82) (Supplemental Table II). No IMID type was associated with a particular outcome (Table II and Supplemental Table II).

When logistic regression was performed within the cohort to correct for contributing variables, significant positive predictors of admission status included age older than 65 years, SARS-CoV-2 status, multidrug therapy, and presence of a pulmonary

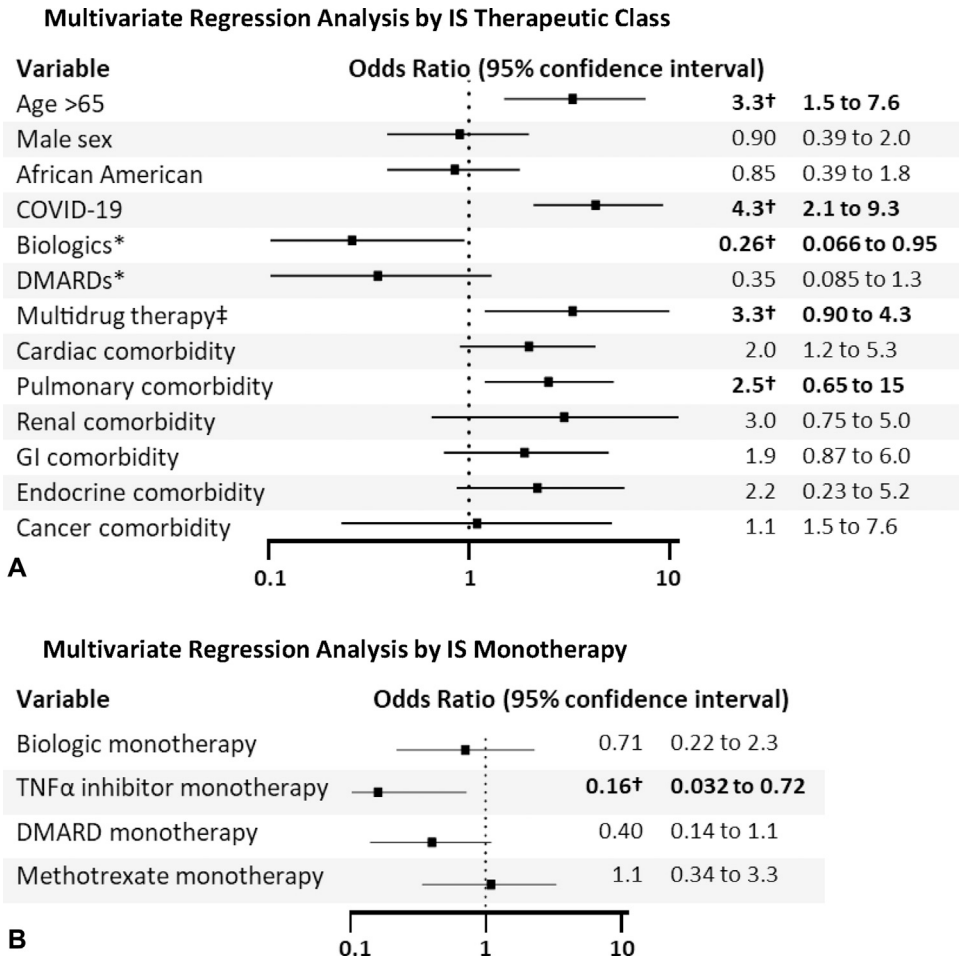

Fig 2. Multivariate analysis of factors associated with hospital admission among patients with IMID treated with IS medication tested for COVID-19 by (**A**) IS therapeutic class and (**B**) IS monotherapy. *Any patient taking a medication from a therapeutic class was included in the respective group, regardless of additional medications taken. Bold values indicate statistical significance. †$P < .05$. ‡Patients taking multiple biologics and/or DMARDs were included in the multidrug therapy group. *DMARD*, Disease-modifying antirheumatic drug; *GI*, gastrointestinal; *IS*, immunosuppressive; *TNF*, tumor necrosis factor.

comorbidity, whereas biologic therapy proved to be a negative predictor of admission (OR, 0.26; 95% CI, 0.066-0.95) (Fig 2, *A*). In turn, race was the only factor that proved able to predict COVID-19 status, with African American patients (OR, 2.8; 95% CI, 1.5-5.2) having greater odds of a positive test result (Supplemental Table VI, *A*). However, neither race nor any other factor besides age older than 65 years was a significant predictor of mortality (OR, 13; 95% CI, 2.3-122) for patients with IMID as a whole (Supplemental Table VI, *B*). When patients receiving monotherapy were compared to one another to remove the confounding effects of additional IS medications, patients treated with TNF-α inhibitor monotherapy had significantly lower odds of admission (OR, 0.16; 95% CI, 0.032-0.72) (Fig 2, *B*). There were no other significant effects on outcomes of interest due to IS medications after multivariate analysis.

DISCUSSION

Our study provides strong empirical evidence that the current perception of predisposition to contracting COVID-19 and developing associated sequelae among those receiving IS therapies common to dermatology may be overestimated. Among patients with IMID treated with IS therapy, those tested for COVID-19 had no greater odds of a positive test result or developing severe disease relative to the general population tested at HFHS. Additionally, biologic therapies led to decreased odds of admission after multivariate correction, an effect likely driven by TNF-α inhibitor therapies, which significantly lowered the odds of admission after correction

when used as a monotherapy. This finding mirrors the recent results found in convenience-based sampling from large databases of rheumatology patients.[16] A similar significant decrease was not shown with IL-17 or IL-12/23 inhibitors on paired comparison, although too few of such patients were present in the data set to allow for meaningful multivariate analysis. It has previously been postulated that certain biologic therapies might assist in the control of COVID-19, preventing the development of severe disease by acting to mitigate the development of cytokine storm,[17,18] and biologics including IL-17, IL-6, and TNF-α inhibitors are now currently under investigation for the treatment of COVID-19–related sequalae.[14]

In recently published cohorts of patients with IMID with COVID-19, those who were hospitalized as opposed to being treated on an outpatient basis tended to be older; had a greater number of comorbidities; and were more likely to use systemic corticosteroids, hydroxychloroquine, or methotrexate.[16,19] In our study, corticosteroids and multidrug therapy appeared on paired analysis to increase the odds of hospitalization among patients with IMID who were infected, but only multidrug therapy proved predictive of disease course when controlling for other contributing variables. A possible explanation for this seeming discrepancy is our accounting for a greater variety of contributing comorbidities than either prior study, including several thought to affect the course of COVID-19, such as kidney impairment,[20,21] chronic liver disease,[22,23] history of malignancy,[24,25] and pre-existing pulmonary compromise beyond chronic obstructive pulmonary disease. Each of these was present within our data set, and we have no reason to believe they would not be present among similar patient populations as well. Once these variables were accounted for, any negative contribution of individual classes of IS medications to the course of COVID-19 disappeared. Because significant comorbid conditions were grouped by organ system, we were unable to infer conclusions about any single comorbid disease.

Although multidrug therapy did portend a higher risk of hospitalization as compared to monotherapies, this result could be due to either additive immunosuppression or a greater burden of disease and overall lower functional status among patients receiving such combination regimens. However, the result remains instructive for dermatologists, who may want to consider abridging therapeutic regimens to monotherapy whenever possible or advising patients whose care necessitates multidrug regimens about their higher risk for hospitalization.

No other therapeutic or IMID condition showed an effect on outcomes from COVID-19 among those treated for IMIDs, including those with potentially more severe pre-existing pulmonary compromise, such as patients with connective tissue disease. This finding mirrors other recently published data[16] and suggests that those being treated in dermatology clinics for IMID conditions should not be considered high-risk for COVID-19 based on that IMID condition alone.

Several reports have suggested that IS therapy does not increase the prevalence of COVID-19 in patients with IMID.[26,27] However, these studies had the potential to miss many COVID-19 cases, because they surveyed patients with IMID for any history of a diagnosis, regardless of testing, and were unable to account for asymptomatic carriers or sheltering among patients with IMID. By restricting our study only to patients suspected of having and tested for SARS-CoV-2, we excluded asymptomatic or sheltered individuals entirely and gained a cohort of patients with both positive and negative test results, from which we are able to conclude that no IS therapy increased the odds of testing positive after controlling for other contributing factors. Although this strategy creates a selection bias and cannot be used to infer the absolute incidence of COVID-19 among this population, it does allow for important comparisons between COVID-19–negative and –positive patients as opposed to only analyzing positive cases. Only race predicted COVID-19 status on multivariate analysis, with African American individuals at greater odds of testing positive (Supplemental Table VI, *A*). This association was likely in part due to the epidemiology of SARS-CoV-2 in Detroit, which is roughly 78% African American and has had the greatest density of COVID-19 cases in Michigan,[28] although further expansion is beyond the scope of this article.

Performing a single-center retrospective chart review limits the total number of patients in our study and the number of patients using any given therapeutic, which somewhat limits the generalizability to community-based settings, yet also removes confounding variables such as the differences between hospital systems and environmental exposures that could affect disease course and outcome in larger databases involving multiple hospitals. The fact that HFHS is located in a SARS-CoV-2 hotspot allowed us to collect a substantial cohort of patients nonetheless and perform analysis from which to inform clinical care. Based on the available data from our study and others, there appears to be no need to discontinue use of particular IS medications in an attempt to reduce

risk of COVID-19 and related illness, although consideration should be given to reducing multidrug regimens to monotherapy wherever possible. Furthermore, TNF-α inhibitors may reduce the risk of more severe disease among patients with IMID requiring IS therapy.

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