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Clinical outcomes of COVID-19 in patients taking tumor necrosis factor inhibitors or methotrexate: A multicenter research network study

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Background: Data on the impact of biologics and immunomodulators on coronavirus disease 2019 (COVID-19)—related outcomes remain scarce.

Objective: We sought to determine whether patients taking tumor necrosis factor inhibitors (TNFis) or methotrexate are at increased risk of COVID-19—related outcomes.

Methods: In this large comparative cohort study, real-time searches and analyses were performed on adult patients who were diagnosed with COVID-19 and were treated with TNFis or methotrexate compared with those who were not treated. The likelihood of hospitalization and mortality were compared between groups with and without propensity score matching for confounding factors.

Results: More than 53 million (53,511,836) unique patient records were analyzed, of which 32,076 (0.06%) had a COVID-19—related diagnosis documented starting after January 20, 2020. Two hundred fourteen patients with COVID-19 were identified with recent TNFi or methotrexate exposure compared with 31,862 patients with COVID-19 without TNFi or methotrexate exposure. After propensity matching, the likelihood of hospitalization and mortality were not significantly different between the treatment and nontreatment groups (risk ratio = 0.91 [95% confidence interval, 0.68-1.22], P = .5260 and risk ratio = 0.87 [95% confidence interval, 0.42-1.78], P = .6958, respectively).

Limitations: All TNFis may not behave similarly.

Conclusion: Our study suggests that patients with recent TNFi or methotrexate exposure do not have increased hospitalization or mortality compared with patients with COVID-19 without recent TNFi or methotrexate exposure. (J Am Acad Dermatol 2021;84:70-5.)

Key words: coronavirus; COVID-19; methotrexate; TNF-alpha; tumor necrosis factor—alpha inhibitor.

Coronavirus disease 2019 (COVID-19) is a global pandemic caused by the respiratory droplet transmission of severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2). As of September 20, 2020, there have been more than 6.7 million cases and 199,000 deaths in the United States alone. Given lack of effective vaccines or highly efficacious medical therapy, a global strategy of social distancing and quarantining has been implemented. High-risk patient characteristics...
include advanced age and various underlying co-morbidities. The effect of immunosuppressive medications on COVID-19–related outcomes remains largely unknown. Tumor necrosis factor inhibitors (TNFis) and methotrexate (MTX) are used extensively in autoimmune inflammatory diseases, including rheumatoid arthritis, psoriasis, psoriatic arthritis, inflammatory bowel disease, ankylosing spondylitis, and others. Infliximab, adalimumab, etanercept, certolizumab, and golimumab are the 5 most commonly prescribed TNFis, and MTX is the most commonly prescribed disease-modifying antirheumatic drug (DMARD) in the United States. TNFis increase the risk of certain infections, such as upper respiratory infections, and cause flaring of pre-existing infectious diseases, such as tuberculosis. Likewise, MTX, a DMARD used as monotherapy or in conjunction with biologic agents, such as TNFi, can suppress immune function and increase infection risk. There are little data on SARS-CoV-2 risk in patients who are taking TNFis or MTX. The U.S. Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) did not issue guidelines regarding the usage of biologics including TNFis or immunomodulators including MTX during the COVID-19 pandemic. Medical societies such as the American College of Gastroenterology, American College of Rheumatology, and American Academy of Dermatology released guidelines on medication usage, although guidelines were based largely on expert opinion given the paucity of available information on SARS-CoV-2.

The effect of TNFi or MTX usage on COVID-19–related outcomes remains poorly characterized. We tested the hypothesis that TNFi or MTX usage increases the risk of report hospitalization and mortality from COVID-19 using data from a global health research network.

METHODS
Patient population
TriNetX (Cambridge, MA) is a global federated health research network providing access to statistics on electronic medical records, including diagnoses, procedures, medications, laboratory values, and genomic information. The COVID-19 research network includes approximately 53 million unique patient records from 2009 to 2020 across 42 large health care organizations, predominantly from the United States (91%) but including Italy, Spain, the United Kingdom, India, Malaysia, and Australia. TriNetX fast-tracked data inflow into the COVID-19 research network to add COVID-19 diagnoses and terminology following WHO and CDC guidelines. Importantly, TriNetX allows International Classification of Diseases, 10th Revision, Clinical Modification queries for comorbid diagnoses. As a federated network, TriNetX received a waiver from the Western Institutional Review Board (Olympia, WA) because only aggregated counts and statistical summaries of deidentified information are distributed, no protected health information is received, and no study-specific activities are performed in retrospective analyses.

COVID-19 patients ≥18 years of age were queried on June 11, 2020 using International Classification of Diseases, 10th Revision, Clinical Modification diagnoses and terminology recommended by the WHO and CDC (Supplementary Appendix available via Mendeley at https://data.mendeley.com/datasets/wgbv9mdv9x/1). Only patients diagnosed with a documented code after January 20, 2020 were included, following the first U.S. confirmed case. We captured patients with COVID-19 who were taking TNFis or MTX by requiring any instance of a documented TNFi (adalimumab, infliximab, etanercept, certolizumab, or golimumab) or MTX within 1 year of contracting COVID-19. Baseline characteristics were reported from documentation any time 6 months before the COVID-19 diagnosis. The index event was defined as contracting COVID-19.

Outcomes
The observation period for outcome analysis was defined as the date from the index event to 45 days after the index event. Primary outcomes studied were, from any cause, hospitalization and mortality. Outcomes analysis restricted the time window to capture primary outcomes related to COVID-19. TriNetX provided specific inclusion criteria defining each outcome (Supplementary Appendix).
A 1:1 propensity score match was performed for confounding variables previously found to be associated with COVID-19. Independent variables were chosen to assess for demographic disparities, including age at index event, gender, and race. Summary statistics were generated for all variables included in the propensity score match. A greedy nearest-neighbor matching algorithm was used with a caliper of 0.1 times the standard deviation. Chi-square analysis was conducted to determine significant differences between the TNFi or MTX cohort and the nontreatment cohort. Significance was set to an alpha level of 0.05 a priori. All statistical analyses were conducted on TriNetX.

### RESULTS

#### Patient population

More than 53 million (53,511,836) patient records were on the COVID-19 research network across 42 health care organizations, of which 32,076 (0.06%) had a COVID-19—related diagnosis documented starting after January 20, 2020. Among the COVID-19 population, 214 (0.7%) had either a documented TNFi or MTX exposure within 1 year of the COVID-19 diagnosis. One hundred and two (0.3%) patients were documented with a TNFi and 128 (0.4%) with methotrexate within 1 year before the COVID-19 diagnosis. (Patients with exposure to both TNFi and MTX were counted once in the combined TNFi or MTX group.)

#### Baseline characteristics

Patients in the TNFi/MTX group had a non-significant age difference (55.1 ± 15.8 years vs 53.2 ± 18.9 years, \( P = .1540 \)) when compared with the non-TNFi/MTX group (Tables I and II). Patients were more frequently female (66.4%) and white (42.5%) in the TNFi/MTX group compared with the non-TNFi/MTX group (54.6% and 34.4%, respectively). The TNFi/MTX group had substantially more comorbidities compared with the non-TNFi/MTX group. A greater proportion of the TNFi/MTX group was diabetic (20.6%) and obese (18.7%) compared with the non- TNFi/MTX group (12.5% and 9.1%, respectively).

Patients in the MTX subgroup were older than the non-MTX group (58.7 ± 14.9 years vs 53.2 ± 18.9 years, \( P = .0011 \)). In both TNFi and MTX subgroups, the demographic trends of more female and white patients remained, as did having substantially more comorbidities. Therefore, a 1:1 propensity score match was performed for all significant comorbidities, as well as age, gender, race, diabetes, and obesity.

#### 45-day outcomes

Propensity score matching in the TNFi/MTX group yielded \( n = 213 \) in both TNFi/MTX and non-TNFi/MTX groups. After matching, the groups were well balanced in age, gender, race, and all comorbidities. The likelihood of hospitalization was similar for the TNFi/MTX group and the non-TNFi/MTX group (risk ratio = 0.91 [95% confidence interval (CI) 0.68-1.22], \( P = .5260 \)). This trend remained when subgroup analysis was performed in the TNFi (risk ratio = 0.73 [95% CI 0.47-1.14], \( P = .1594 \)) and MTX (risk ratio = 0.87 [95% CI 0.62-1.23], \( P = .4272 \)) groups. Matching did not
change the overall outcome results for death, remaining nonsignificant in the TNFi/MTX group when compared with the non-TNFi/MTX group (risk ratio = 0.87 [95% CI 0.42-1.78], \( P = .6958 \), Tables III and IV).

**DISCUSSION**

Outcome-based data on the effect of recent anticytokine biologic or immunomodulator exposure in the setting of COVID-19 infection are limited. SARS-CoV-2 can induce a cytokine storm syndrome that worsens symptoms in the form of fevers, confusion, and coagulopathy.\(^6\) Initial hypotheses maintained that cytokine inhibition may worsen COVID-19 related outcomes via general immune suppression; however, more recent hypotheses suggest that inhibition of a cytokine storm may actually be beneficial. Anticytokine biologic therapies may prevent cytokine storm syndrome, which is the rationale for use of interleukin-6 inhibitors for treating COVID-19.\(^7,8\) Real-world evidence-based data are needed on COVID-19 related outcomes in the setting of TNFi or MTX exposure.

Two hundred fourteen of 32,076 patients with COVID-19 had TNFi or MTX treatment within 12 months of COVID-19 infection and comprised the treatment group. Thirty-one thousand eighty-two patients with COVID-19 infection had no TNFi or MTX exposure within the same time period and comprised the nontreatment group. The likelihood of hospitalization and mortality were compared between groups with and without propensity score matching for confounding factors. After propensity matching, the likelihood of hospitalization and mortality were not significantly different between the treatment and nontreatment group (risk ratio = 0.91 [95% CI 0.68-1.22], \( P = .5260 \) and risk ratio = 0.87 [95% CI 0.42-1.78], \( P = .6958 \), respectively). Subgroup analysis of TNFi exposure also showed no significant difference in likelihood of hospitalization compared with patients with COVID-19 without TNFi exposure (risk ratio = 0.73 [95% CI 0.47-1.14], \( P = .1594 \)). Likewise, MTX exposure alone showed no statistically significant difference in the likelihood of hospitalization compared with patients who were not exposed to MTX (risk ratio = 0.87 [95% CI 0.62-1.23], \( P = .4272 \)). There were insufficient data to calculate mortality for TNFi and MTX individually. In summary, our data showed similar likelihoods of hospitalization and mortality in the TNFi or MTX treatment group versus the nontreatment group. These results stood with and without propensity score matching for confounding factors.

Our study builds upon a case series from New York by Haberman et al\(^1\) that concluded that baseline anticytokine biologic use did not correlate with worse COVID-19 related outcomes. While hospitalization rates were similar in the anticytokine biologic treatment cohort compared with patients with COVID-19 in the general population of

| Characteristics | Before propensity matching | MTX (n = 128) | No MTX (n = 31982) | \( P \) value | \( P \) value |
|-----------------|---------------------------|--------------|------------------|--------------|--------------|
| Demographics    |                           |              |                  |              |              |
| Age at index, y ± SD | 49.7 ± 15.6 | 53.2 ± 18.9 | \( .0606 \) | 58.7 ± 14.9 | 53.2 ± 18.9 | \( .0011 \) |
| Female, n (%) | 62 (60.7) | 17540 (54.7) | \( .2189 \) | 93 (72.7) | 17461 (54.6) | \( <.0001 \) |
| White, n (%) | 46 (45.1) | 11040 (34.4) | \( .0237 \) | 53 (41.4) | 11011 (34.4) | \( .0974 \) |
| Comorbidities, n (%) |                   |              |                  |              |              |
| Diseases of the digestive system | 51 (50.0) | 5615 (17.5) | \( <.0001 \) | 62 (48.4) | 5599 (17.5) | \( <.0001 \) |
| Diseases of the musculoskeletal system and connective tissue | 58 (56.9) | 6490 (20.3) | \( <.0001 \) | 98 (76.6) | 6424 (20.1) | \( <.0001 \) |
| Diseases of the nervous system | 38 (37.3) | 5326 (16.6) | \( <.0001 \) | 63 (49.2) | 5286 (16.5) | \( <.0001 \) |
| Diseases of the blood and blood-forming organs | 37 (36.3) | 4115 (12.8) | \( <.0001 \) | 58 (45.3) | 4084 (12.8) | \( <.0001 \) |
| Diseases of the circulatory system | 50 (49.0) | 9644 (30.1) | \( <.0001 \) | 88 (68.8) | 9581 (30.0) | \( <.0001 \) |
| Diseases of the skin and subcutaneous tissue | 28 (27.5) | 2351 (7.3) | \( <.0001 \) | 36 (28.1) | 2339 (7.3) | \( <.0001 \) |
| Diabetes mellitus | 11 (10.8) | 4037 (12.6) | \( .5824 \) | 33 (25.8) | 4007 (12.5) | \( <.0001 \) |
| Body mass index 30-39.9 kg/m\(^2\) | 18 (17.6) | 2945 (9.2) | \( .0032 \) | 25 (19.5) | 2930 (9.2) | \( <.0001 \) |
| 45-day outcomes, n (%) |                   |              |                  |              |              |
| Hospitalization | 24 (23.5) | 6378 (19.9) | \( .3588 \) | 40 (31.3) | 6349 (19.9) | \( .0013 \) |
| Death | N/A* | 1979 (6.2) | - | 12 (9.4) | 1964 (6.1) | \( .1286 \) |

MTX, Methotrexate; N/A, not available; SD, standard deviation; TNFi, tumor necrosis factor inhibitor.

*TriNetX obfuscates patient counts ≥10 to safeguard protected health information.
New York City, their limited sample size made conclusions on mortality untenable. This study reviewed >55 million patients from 42 health care organizations, permitting a large enough sample size to conclude mortality likelihood differences and to control for confounding factors. Haberman et al included patients taking 5 different classes of anticytokine therapy (Janus kinase inhibitor, TNFi, interleukin-17 blocker, interleukin-23 blocker, and interleukin-12/23 blocker) with outcome data interpreted in aggregate. As a result, COVID-19–related outcomes related to a specific class of anticytokine biologics could not be evaluated. This study evaluated only 1 class of anticytokine biologics, the TNFis, and only 1 DMARD, MTX, to avoid influences of aggregating immunosuppressive medications. Nonetheless, the present study provides practical information to the clinician treating patients who are

| Table III. Matched characteristics and outcomes                                                                 |
|---------------------------------------------------------------|------------------|-----------------|-----------------|-----------------|-----------------|
| Demographics                                                  | After propensity matching                                      | TNFi plus MTX (n = 213) | No TNFi or MTX (n = 213) | P value |
| Age at index, y ± SD                                          | 55.1 ± 15.8      | 54.9 ± 16.2     | .9301            |
| Female, n (%)                                                 | 141 (66.2)       | 139 (65.3)      | .8382            |
| White, n (%)                                                  | 91 (42.7)        | 81 (38.0)       | .3234            |
| Comorbidities, n (%)                                          |                  |                 |                  |
| Diseases of the digestive system                              | 105 (49.3)       | 97 (45.5)       | .4376            |
| Diseases of the musculoskeletal system and connective tissue  | 142 (66.7)       | 149 (70.0)      | .4660            |
| Diseases of the nervous system                                | 93 (43.7)        | 81 (38.0)       | .2369            |
| Diseases of the blood and blood-forming organs                | 87 (40.9)        | 89 (41.8)       | .8440            |
| Diseases of the circulatory system                            | 130 (61.0)       | 123 (57.8)      | .4898            |
| Diseases of the skin and subcutaneous tissue                  | 58 (27.2)        | 50 (23.5)       | .3729            |
| Diabetes mellitus                                             | 44 (20.7)        | 39 (18.3)       | .5408            |
| Body mass index 30-39.9 kg/m²                                  | 40 (18.8)        | 32 (15.0)       | .5301            |
| 45-day outcomes, n (%)                                        | 61 (28.6)        | 67 (31.5)       | .5260            |
| Hospitalization                                               | 13 (6.1)         | 15 (7.0)        | .6958            |
| Death                                                         |                  |                 |                  |

MTX, Methotrexate; SD, standard deviation; TNFi, tumor necrosis factor inhibitor.

| Table IV. Subgroup analysis of matched baseline characteristics and outcomes                                      | After propensity matching                                      | TNFi (n = 101) | No TNFi (n = 101) | P value |
|---------------------------------------------------------------|------------------|-----------------|-----------------|-----------------|-----------------|
| Demographics                                                  |                  |                 |                 |
| Age at index, y ± SD                                          | 49.7 ± 15.7      | 52.0 ± 18.5     | .3304           |
| Female, n (%)                                                 | 61 (60.4)        | 67 (66.3)       | .3809           |
| White, n (%)                                                  | 46 (45.5)        | 48 (47.5)       | .7779           |
| Comorbidities, n (%)                                          |                  |                 |                 |
| Diseases of the digestive system                              | 50 (49.5)        | 51 (50.5)       | .8881           |
| Diseases of the musculoskeletal system and connective tissue  | 57 (56.4)        | 59 (58.4)       | .7760           |
| Diseases of the nervous system                                | 37 (36.6)        | 34 (33.7)       | .6584           |
| Diseases of the blood and blood-forming organs                | 36 (35.6)        | 35 (34.7)       | .8828           |
| Diseases of the circulatory system                            | 49 (48.5)        | 44 (43.6)       | .4803           |
| Diseases of the skin and subcutaneous tissue                  | 27 (26.7)        | 27 (26.7)       | 1.0000          |
| Diabetes mellitus                                             | 11 (10.9)        | N/A             | —               |
| Body mass index 30-39.9 kg/m²                                  | 18 (17.8)        | 12 (11.9)       | .2352           |
| 45-day outcomes, n (%)                                        | 24 (23.8)        | 33 (32.7)       | .1594           |
| Hospitalization                                               | N/A              | N/A             | 12 (9.4)        |
| Death                                                         |                  |                 |                 |

MTX, Methotrexate; N/A, not available; SD, standard deviation; TNFi, tumor necrosis factor inhibitor.

*TriNetX obfuscates patient counts ≤10 to safeguard protected health information.
taking these medications. Adalimumab, etanercept, infliximab, certolizumab, golimumab, and MTX were included in the study. This group includes 3 of the most commonly prescribed biologics (adalimumab, etanercept, and infliximab) and the most commonly prescribed DMARD (MTX) in the United States. Such a selection makes our study relevant to dermatologists, gastroenterologists, rheumatologists, and other specialists who routinely prescribe these medications. The large cohort is a strength of this study.

Limitations of our study include an inclusion criteria window for TNFi or MTX exposure within 12 months of COVID-19 infection that may have captured some patients who were no longer taking the medication of concern at the onset of COVID-19 infection. Some patients in the data set were taking a TNFi and MTX and therefore may have been included twice in the subgroup analysis. Diagnostic indication for TNFi and MTX prescription was not available for subgroup analyses. Furthermore, patients that took both TNFi and MTX may have taken both drugs concurrently or at different times during the 12-month window, and actual biologic exposure may differ from what is reflected in the electronic medical record. The present study did not control for the use of medications in other classes, which may affect the results of the study. In addition, all TNFis may not behave similarly and inclusion of multiple TNFis together may create bias; however, this bias is presumably to a lesser magnitude than studies that aggregate anticytokine biologics across multiple classes. COVID-19 infection may also have been misclassified in some patients given limitations of COVID-19 confirmatory testing, although COVID-19—specific diagnoses and terminology recommended by the WHO and CDC were used in our inclusion criteria. Finally, propensity score matching may not account for all possible confounders.

Because the COVID-19 pandemic is ongoing, there is desperate need for evidence-based data on biologic and immunomodulator exposure in the setting of COVID-19 infection. Current guidelines regarding COVID-19 and the use of biologics are largely based on expert opinion rather than rigorous statistical analysis. Our study supports the ongoing use of TNFi or MTX therapy and argues against the interruption of treatment because of the fear of possibly worse COVID-19—related outcomes.

REFERENCES
1. Haberman R, Axelrad J, Chen A, et al. Covid-19 in immune-mediated inflammatory diseases—case series from New York. N Engl J Med. 2020;383:85-88.
2. Bongartz T, Sutton AJ, Sweeting MJ, Buchan I, Matteson EL, Montori V. Anti-TNF antibody therapy in rheumatoid arthritis and the risk of serious infections and malignancies: systematic review and meta-analysis of rare harmful effects in randomized controlled trials. JAMA. 2006;295:2275-2285.
3. McLean-Tooke A, Aldridge C, Waugh S, Spickett GP, Kay L. Methotrexate, rheumatoid arthritis and infection risk—what is the evidence? Rheumatology. 2009;48:867-871.
4. Holshue ML, DeBolt C, Lindquist S, et al. First case of 2019 novel coronavirus in the United States. N Engl J Med. 2020;382:e53.
5. Jordan RE, Adab P, Cheng KK. Covid-19: risk factors for severe disease and death. BMJ. 2020;368:m1198.
6. Wang D, Hu B, Hu C, et al. Clinical characteristics of 138 hospitalized patients with 2019 novel coronavirus—infected pneumonia in Wuhan, China. JAMA. 2020;323:1061-1069.
7. Henriksen M. Anti-il6 treatment of serious COVID-19 disease with threatening respiratory failure (TOCIVD). Available at: https://www.clinicaltrials.gov/ct2/show/NCT04322773. Accessed September 20, 2020.
8. Regeneron Pharmaceuticals. Evaluation of the efficacy and safety of sarilumab in hospitalized patients with COVID-19. Available at: https://clinicaltrials.gov/ct2/show/NCT04315298. Accessed September 20, 2020.
9. Biologic drugs set to top 2012 sales. Nat Med. 2012;18:636.