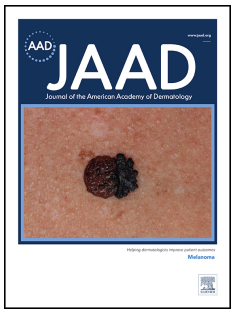
Journal Pre-proof



Clinical Outcomes of CoVid-19 in Patients Taking Tumor Necrosis Factor Inhibitors and/or Methotrexate: A Multi-Center Research Network Study

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PII: S0190-9622(20)32593-7

DOI: https://doi.org/10.1016/j.jaad.2020.09.009

Reference: YMJD 15198

To appear in: *Journal of the American Academy of Dermatology*

Received Date: 7 July 2020

Revised Date: 4 August 2020

Accepted Date: 3 September 2020

Please cite this article as: Yousaf A, Gayam S, Feldman S, Zinn Z, Kolodney M, Clinical Outcomes of CoVid-19 in Patients Taking Tumor Necrosis Factor Inhibitors and/or Methotrexate: A Multi-Center Research Network Study, *Journal of the American Academy of Dermatology* (2020), doi: https://doi.org/10.1016/j.jaad.2020.09.009.

Article type: Original article

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Funding sources: This article has no funding source.
Conflicts of interest: The authors have no conflict of interest to declare.
Prior presentations: None
Reprint request: Corresponding author

Manuscript word count: 1896 [excluding capsule summary, abstract, references, tables]
Abstract word count: 279
Capsule summary word count: 42
Tables: 4
Supplementary Tables:
Figures: 0
Supplementary Figures: 1 (https://data.mendeley.com/datasets/wgbv9mdv9x/1)
References: 9
Keywords: tumor necrosis factor alpha inhibitor, TNF-alpha, methotrexate, coronavirus, CoVid-19

Abstract

Background: Data on the impact of biologics and immunomodulators on CoVid-19 related outcomes remains scarce.

Objective: To determine whether patients on tumor necrosis factor inhibitor (TNFi) and/or methotrexate are at increased risk of CoVid-19 related outcomes.

Methods: In this large comparative cohort study, a real-time search and analysis were performed on adult patients diagnosed with CoVid-19 and treated with TNFi and/or methotrexate versus those not treated. Likelihood of hospitalization and mortality were compared between groups with and without propensity score matching for confounding factors.

Results: 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. 214 patients with CoVid-19 were identified with recent TNFi or methotrexate exposure compared to 31,862 patients with CoVid-19 without TNFi or methotrexate exposure. After propensity matching, likelihood of hospitalization and mortality were not significantly different between the treatment and non-treatment group (risk ratio 0.91, 95% confidence interval [CI] 0.68-1.22, p=0.5260; risk ratio 0.87, 95% CI 0.42-1.78, p=0.6958, respectively).

Limitations: All TNFi may not behave similarly.

Conclusion: Our study suggests that patients with recent TNFi and/or methotrexate exposure do not have increased hospitalization or mortality compared to CoVid-19 patients without recent TNFi and/or methotrexate exposure.

Capsule summary

- To date, there is insufficient real-world evidence to determine whether patients on tumor necrosis factor inhibitor (TNFi) and/or methotrexate are at increased risk of worse CoVid-19 related outcomes.
- This study supports the ongoing use of tumor necrosis factor inhibitors and/or methotrexate therapy.

Introduction

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). More than 2 million cases and 114,000 deaths have been reported 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 comorbidities. The effect of immunosuppressive medications on CoVid-19 related outcomes remains largely unknown.[1]

TNFi and 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 five most commonly prescribed TNFi, and MTX is the most commonly prescribed DMARD in the United States. Tumor necrosis factor inhibitors (TNFi) increase the risk of certain infections such as upper respiratory infections, and cause flaring of pre-existing infectious diseases such as tuberculosis.[2] Likewise methotrexate (MTX), a disease-modifying anti-rheumatic drug (DMARD) used as monotherapy or in conjunction with biologic agents such as TNFi, can suppress immune function and increase infection risk.[3] There is little data on SARS-CoV-2 risk in patients on TNFi and/or MTX. The Centers for Disease Control and Prevention (CDC) and the World Health Organization (WHO) did not issue guidelines regarding usage of biologics including TNFi, 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 paucity of available information on SARS-CoV-2.

The effect of TNFi and/or MTX usage on CoVid-19 related outcomes remains poorly characterized. We tested the hypothesis that TNFi and/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, USA) 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 2009-2020 across 42 large healthcare organization, predominantly from the United States (91%) but also 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 World Health Organization (WHO) and the Centers for Disease Control and Prevention (CDC) guidelines. Importantly, TriNetX allows International Classification of Diseases, Tenth Revision, Clinical Modification (ICD-10-CM) queries for comorbid diagnoses. As a federated network, TriNetX received a waiver from Western IRB since only aggregated counts and statistical summaries of de-identified information is distributed, no protected health information is received, and no study-specific activities are performed in retrospective analyses.

CoVid-19 patients age greater than or equal to 18 years old were queried on June 11, 2020 using ICD-10-CM diagnoses and terminology recommended by WHO and CDC (see Supplementary Appendix). Only patients diagnosed with a documented code after January 20, 2020 were included, following the first U.S. confirmed case.[4] We captured CoVid-19 patients on TNFi and/or MTX by requiring any instance of a documented TNFi (adalimumab, infliximab, etanercept,

certolizumab, golimumab) or MTX within one year of contracting CoVid-19. Baseline characteristics were reported from documentation any time 6 months prior to CoVid-19 diagnosis. The index event was defined as contracting CoVid-19.

Outcomes

The observation period for outcome analysis was defined as date from index event to 45 days after index event. Primary outcomes studied were, from any cause, hospitalization and mortality. Outcomes analysis restricted the time window in order to capture primary outcomes related to CoVid-19. TriNetX provided specific inclusion criteria defining each outcome (see Supplementary Appendix).

Statistical analysis

A 1:1 propensity score match was performed for confounding variables previously found to be associated with CoVid-19.[5] 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 and/or MTX cohort and the non-treatment cohort. Significance was set to an alpha level of 0.05 a priori. All statistical analyses were conducted on TriNetX.

Results

Patient population

53,511,836 patient records were on the CoVid-19 research network across 42 HCOs, of which 32,076 (0.06%) had a CoVid-19-related diagnosis documented starting after January 20, 2020. Amongst the CoVid-19 population, 214 (0.7%) had either a documented TNFi and/or MTX exposure within 1 year of CoVid-19 diagnosis. 102 (0.3%) patients were documented with a TNFi and 128 (0.4%) with methotrexate within 1 year prior to CoVid-19 diagnosis. [Note: Patients with exposure to both TNFi and MTX were counted once in combined TNFi and/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 = 0.1540) when compared to the non-TNFi/MTX group (Tables 1 and 2). Patients were more frequently female (66.4%) and white (42.5%) in the TNFi/MTX group compared to the non-TNFi/MTX group (54.6% and 34.4%, respectively). The TNFi/MTX group had substantially more comorbidities compared to the non-TNFi/MTX group. A greater proportion of the TNFi/MTX group was diabetic (20.6%) and obese (18.7%) compared to 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 = 0.0011). 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. Likelihood of hospitalization was similar for the TNFi/MTX group and non-TNF/MTX group (risk ratio 0.91, 95% confidence interval [CI] 0.68-1.22, p=0.5260). This trend remained when subgroup analysis was performed in the TNFi (risk ratio 0.73, 95% CI 0.47-1.14, p=0.1594) and MTX (risk ratio 0.87, 95% CI 0.62-1.23, p=0.4272) groups. Matching did not change the overall outcome results for death, remaining non-significant in the TNFi/MTX group when compared to the non-TNFi/MTX group (risk ratio 0.87, 95% CI 0.42-1.78, p=0.6958, Tables 3 and 4).

Discussion

Outcomes-based data on the effect of recent anti-cytokine biologic or immunomodulator exposure in the setting of CoVid-19 infection is limited. SARS-CoV-2 can induce a cytokine storm syndrome (CSS) 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 inhibition of a cytokine storm may actually be beneficial. Anti-cytokine biologic therapies may prevent the CSS, which is the rationale for use of interleukin--6 inhibitors for treating CoVid-19.[7, 8] Real-world evidence-based data is needed on CoVid-19 related outcomes in the setting of TNFi and/or MTX exposure.

214 of 32,076 CoVid-19 patients had TNFi and/or methotrexate treatment within 12 months of CoVid-19 infection and comprised the treatment group. 31,862 patients with CoVid-19 infection had no TNFi or methotrexate exposure within the same time period and comprised the non-treatment group. Likelihood of hospitalization and mortality were compared between groups with and without propensity score matching for confounding factors. After propensity matching, likelihood of hospitalization and mortality were not significantly different between the treatment and non-treatment group (risk ratio 0.91, 95% confidence interval [CI] 0.68-1.22, p=0.5260; risk ratio 0.87, 95% CI 0.42-1.78, p=0.6958, respectively). Subgroup analysis of TNFi exposure also showed no significant difference in likelihood of hospitalization compared to CoVid-19 patients without TNFi exposure (risk ratio 0.73, 95% CI 0.47-1.14, p=0.1594). Likewise methotrexate exposure

alone showed no statistically significant difference in likelihood of hospitalization compared to patients not exposed to methotrexate (risk ratio 0.87, 95% CI 0.62-1.23, p=0.4272). There was insufficient data to calculate mortality for TNFi and methotrexate individually. In summary, our data showed similar likelihoods of hospitalization and mortality in the TNFi and/or methotrexate treatment group versus the non-treatment group. These results stood with and without propensity score matching for confounding factors.

Our study builds upon a prior case series from New York by Haberman et al that concluded baseline anti-cytokine biologic use did not correlate with worse CoVid-19 related outcomes.[1] While hospitalization rates were similar in the anti-cytokine biologic treatment cohort compared to patients with CoVid-19 in the general population of New York City, their limited sample size made conclusions on mortality untenable. This study reviewed more than 53 million patients from 42 healthcare organizations (HCOs), permitting a large enough sample size to conclude mortality likelihood differences and control for confounding factors. Haberman et al included patients on five different classes of anti-cytokine 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 anti-cytokine biologics could not be evaluated. This study evaluated only one class of anti-cytokine biologics, the TNFi, and only one DMARD, methotrexate, to avoid influences of aggregating immunosuppressive medications. Nonetheless, the present study provides practical information to the clinician treating patients on these medications. Adalimumab,

etanercept, infliximab, certolizumab, golimumab and methotrexate were included in the study. This group includes three of the most commonly prescribed biologics (adalimumab, etanercept, and infliximab) and the most commonly prescribed DMARD (methotrexate) in the United States. Such a selection makes our study relevant to dermatologists, gastroenterologists, rheumatologists, and other specialists who routinely prescribe these medications.[9] The large cohort is a strength of this study.

Limitations of our study include an inclusion criteria window for TNFi and/or methotrexate exposure within 12 months of CoVid-19 infection that may have captured some patients who were no longer taking the medication of concern at onset of CoVid-19 infection. Some patients in the data set were taking a TNFi and methotrexate and therefore may have been included twice in the subgroup analysis. Diagnostic indication for TNFi and methotrexate prescription was not available for subgroup analyses. Furthermore, patients that took both TNFi and methotrexate 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 TNFi may not behave similarly and inclusion of multiple TNFi together may create bias, however presumably to a lesser magnitude than studies that aggregate anti-cytokine 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

WHO and CDC were utilized 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 and biologic use are largely based on expert opinion rather than rigorous statistical analysis. Our study supports the ongoing use of TNFi and/or methotrexate therapy and argues against interruption of treatment owing to fear of possibly worse CoVid-19 related outcomes.

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Table 1 Unmatched baseline characteristics and outcomes

Characteristics	Before Propensity Matching		
	TNFi + MTX (n = 214)	No TNFi or MTX (n = 31862)	P-value
Demographics			
Age at Index (± SD)	55.1 (± 15.8)	53.2 (± 18.9)	0.1540
Female	142 (66.4)	17393 (54.6)	0.0006
White	91 (42.5)	10958 (34.4)	0.0126
Comorbidities			
Diseases of the digestive system	106 (49.5)	5537 (17.4)	< 0.0001
Diseases of the musculoskeletal system and connective tissue	143 (66.8)	6366 (20.0)	< 0.0001
Diseases of the nervous system	94 (43.9)	5247 (16.5)	< 0.0001
Diseases of the blood and blood-forming organs	88 (41.1)	4037 (12.7)	< 0.0001
Diseases of the circulatory system	131 (61.2)	9526 (29.9)	< 0.0001
Diseases of the skin and subcutaneous tissue	59 (27.6)	2307 (7.2)	< 0.0001
Diabetes mellitus	44 (20.6)	3992 (12.5)	0.0004
BMI 30-39.9	40 (18.7)	2909 (9.1)	< 0.0001
45-Day Outcomes			
Hospitalization	61 (28.5)	6325 (19.9)	0.0016
Death	13 (6.1)	1963 (6.2)	0.9583

Table 2 Subgroup analysis of unmatched baseline characteristics and outcomes

	Before Propensity Matching					
Characteristics	**TNFi (n=102)**	**No TNFi (n=32057)**	**P-value**	**MTX (n=128)**	**No MTX (n=31982)**	**P-Value**
Demographics						
Age at Index (± SD)	49.7 (± 15.6)	53.2 (± 18.9)	0.0606	58.7 (± 14.9)	53.2 (± 18.9)	0.0011
Female	62 (60.7)	17540 (54.7)	0.2189	93 (72.7)	17461 (54.6)	< 0.0001
White	46 (45.1)	11040 (34.4)	0.0237	53 (41.4)	11011 (34.4)	0.0974
Comorbidities						
Diseases of the digestive system	51 (50.0)	5615 (17.5)	< 0.0001	62 (48.4)	5599 (17.5)	< 0.0001
Diseases of the musculoskeletal system and connective tissue	58 (56.9)	6490 (20.3)	< 0.0001	98 (76.6)	6424 (20.1)	< 0.0001
Diseases of the nervous system	38 (37.3)	5326 (16.6)	< 0.0001	63 (49.2)	5286 (16.5)	< 0.0001
Diseases of the blood and blood-forming organs	37 (36.3)	4115 (12.8)	< 0.0001	58 (45.3)	4084 (12.8)	< 0.0001
Diseases of the circulatory system	50 (49.0)	9644 (30.1)	< 0.0001	88 (68.8)	9581 (30.0)	< 0.0001
Diseases of the skin and subcutaneous tissue	28 (27.5)	2351 (7.3)	< 0.0001	36 (28.1)	2339 (7.3)	< 0.0001
Diabetes mellitus	11 (10.8)	4037 (12.6)	0.5824	33 (25.8)	4007 (12.5)	< 0.0001
BMI 30-39.9	18 (17.6)	2945 (9.2)	0.0032	25 (19.5)	2930 (9.2)	< 0.0001
45-Day Outcomes						
Hospitalization	24 (23.5)	6378 (19.9)	0.3588	40 (31.3)	6349 (19.9)	0.0013
Death	n/a*	1979 (6.2)	-	12 (9.4)	1964 (6.1)	0.1286

*TriNetX obfuscates patient counts less than or equal to 10 to safeguard protected health information

Table 3 Matched characteristics and outcomes

Characteristics	After Propensity Matching		P-value
	TNFi + MTX (n = 213)	No TNFi or MTX (n = 213)	
Demographics			
Age at Index (± SD)	55.1 (± 15.8)	54.9 (± 16.2)	0.9301
Female	141 (66.2)	139 (65.3)	0.8382
White	91 (42.7)	81 (38.0)	0.3234
Comorbidities			
Diseases of the digestive system	105 (49.3)	97 (45.5)	0.4376
Diseases of the musculoskeletal system and connective tissue	142 (66.7)	149 (70.0)	0.4660
Diseases of the nervous system	93 (43.7)	81 (38.0)	0.2369
Diseases of the blood and blood-forming organs	87 (40.9)	89 (41.8)	0.8440
Diseases of the circulatory system	130 (61.0)	123 (57.8)	0.4898
Diseases of the skin and subcutaneous tissue	58 (27.2)	50 (23.5)	0.3729
Diabetes mellitus	44 (20.7)	39 (18.3)	0.5408
BMI 30-39.9	40 (18.8)	32 (15.0)	0.3010
45-Day Outcomes			
Hospitalization	61 (28.6)	67 (31.5)	0.5260
Death	13 (6.1)	15 (7.0)	0.6958

Table 4 Subgroup analysis of matched baseline characteristics and outcomes

	After Propensity Matching					
Characteristics	**TNFi (n=101)**	**No TNFi (n=101)**	**P-value**	**MTX (n=128)**	**No MTX (n=128)**	**P-Value**
Demographics						
Age at Index (± SD)	49.7 (± 15.7)	52.0 (± 18.5)	0.3304	58.7 (± 14.9)	58.7 (± 16.7)	0.9968
Female	61 (60.4)	67 (66.3)	0.3809	94 (73.4)	94 (73.4)	0.8880
White	46 (45.5)	48 (47.5)	0.7779	53 (41.4)	53 (41.4)	1.0000
Comorbidities						
Diseases of the digestive system	50 (49.5)	51 (50.5)	0.8881	62 (48.4)	62 (48.4)	1.0000
Diseases of the musculoskeletal system and connective tissue	57 (56.4)	59 (58.4)	0.7760	98 (76.6)	99 (77.3)	0.8820
Diseases of the nervous system	37 (36.6)	34 (33.7)	0.6584	63 (49.2)	55 (43.0)	0.3158
Diseases of the blood and blood-forming organs	36 (35.6)	35 (34.7)	0.8828	58 (45.3)	53 (41.4)	0.5283
Diseases of the circulatory system	49 (48.5)	44 (43.6)	0.4803	88 (68.8)	96 (75.0)	0.2661
Diseases of the skin and subcutaneous tissue	27 (26.7)	27 (26.7)	1.0000	36 (28.1)	32 (25)	0.5714
Diabetes mellitus	11 (10.9)	n/a*	-	33 (25.8)	32 (25)	0.8858
BMI 30-39.9	18 (17.8)	12 (11.9)	0.2352	25 (19.5)	24 (18.8)	0.8738
45-Day Outcomes						
Hospitalization	24 (23.8)	33 (32.7)	0.1594	40 (31.3)	46 (35.9)	0.4272
Death	n/a*	n/a*	-	12 (9.4)	n/a*	-

*TriNetX obfuscates patient counts less than or equal to 10 to safeguard protected health information

Capsule summary

- To date, there is insufficient real-world evidence to determine whether patients on tumor necrosis factor inhibitor (TNFi) and/or methotrexate are at increased risk of worse CoVid-19 related outcomes.
- This study supports the ongoing use of tumor necrosis factor inhibitors and/or methotrexate therapy.