Characteristics and Outcomes of IBD Patients with COVID-19 on Tofacitinib Therapy in the SECURE-IBD Registry

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INTRODUCTION

The coronavirus disease 2019 (COVID-19) pandemic due to the severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) has led to unprecedented loss of life and health on a global scale.1 COVID-19 outcomes are more severe among those with comorbid conditions,1 which raises concerns for patients with inflammatory bowel disease (IBD), especially given the increased infection risk with immunosuppression used for IBD therapy.

Tofacitinib is a Janus kinase inhibitor (JAKi) approved for the treatment of ulcerative colitis (UC)2 and other immune-mediated diseases. Tofacitinib is associated with higher risk of herpes zoster (HZ) infection.2 Although HZ is a DNA virus, little is known regarding risks and outcomes of RNA viral infections such as SARS-CoV-2 with JAKi. Type 1 interferons, central to anti-SARS-CoV-2 activity and induced by the JAK-STAT pathway, were found to be impaired in severe COVID-19 in some studies and conversely upregulated in others, possibly reflecting heterogeneity in COVID-19 severity.3 Emerging data in non-IBD patients suggest that JAKi may blunt the cytokine storm that characterizes severe COVID-19 and potentially improve outcomes.4 In fact, a number of JAKi such as tofacitinib, baricitinib and ruxolitinib are being studied in clinical trials for COVID-19 treatment.

Moreover, hospitalized COVID-19 patients are at a greater risk of thromboembolic events. This is important because findings from an interim analysis of a rheumatoid arthritis study for tofacitinib in older patients with ≥1 cardiovascular risk factor, alongside data from other JAKi clinical programs, suggest a higher risk of venous thromboembolic events.3

Emerging data on COVID-19 outcomes in patients with immune-mediated diseases treated with JAKi do not indicate worse outcomes compared with other immunosuppressive therapies; prior studies have been limited by very small sample sizes of fewer than 10 patients.** To address this critical knowledge gap, we analyzed characteristics and outcomes of tofacitinib-treated IBD patients with COVID-19 compared with those on other medications in a global registry.

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| Characteristic | All Patients on ≥1 Medication | Tofacitinib | Other IBD Therapy | P<sup>c</sup> |
|---------------|-----------------------------|-------------|------------------|-------------|
| | N (Mean) | % (SD) | N (Mean) | % (SD) | N (Mean) | % (SD) | |
| Total number of patients | 2326 | 37 | 2289 | 0.747 |
| Mean age | 41.5 | 18.1 | 42.4 | 17.18 | 41.5 | 18.08 | 0.670 |
| Median age (IQR) | 39 | 27.0, 54.0 | 41 | 30.5, 55.0 | 39 | 27.0, 54.0 |
| Female sex | 1150 | 49.4% | 15 | 40.5% | 1135 | 49.6% | 0.275 |
| Race | | | | | | | |
| White | 1840 | 79.1% | 29 | 78.4% | 1811 | 79.1% | 0.913 |
| Black or African American | 158 | 6.8% | 1 | 2.7% | 157 | 6.9% | 0.512 |
| American Indian/Native Alaskan | 4 | 0.2% | 0 | 0.0% | 4 | 0.2% | >0.999 |
| Asian | 132 | 5.7% | 2 | 5.4% | 130 | 5.7% | >0.999 |
| Native Hawaiian/Pacific Islander | 0 | 0.0% | 0 | 0.0% | 0 | 0.0% | — |
| Other | 175 | 7.5% | 3 | 8.1% | 172 | 7.5% | 0.755 |
| Unknown | 96 | 4.1% | 3 | 8.1% | 93 | 4.1% | 0.194 |
| Hispanic/Latinx | 407 | 17.5% | 4 | 10.8% | 403 | 17.6% | 0.480 |
| Yes | | | | | | | |
| No | 1484 | 63.8% | 27 | 73.0% | 1457 | 63.7% | 0.148 |
| Reporting Country | | | | | | | |
| United States | 926 | 39.8% | 19 | 51.4% | 907 | 39.6% | 0.148 |
| Spain | 247 | 10.6% | 6 | 16.2% | 241 | 10.3% | 0.276 |
| Russian Federation | 140 | 6.0% | 3 | 8.1% | 137 | 5.9% | 0.485 |
| United Kingdom | 95 | 4.1% | 0 | 0.0% | 95 | 4.2% | 0.401 |
| France | 102 | 4.4% | 1 | 2.7% | 101 | 4.4% | >0.999 |
| Italy | 81 | 3.5% | 0 | 0.0% | 81 | 3.5% | 0.638 |
| Brazil | 85 | 3.7% | 1 | 2.7% | 84 | 3.7% | >0.999 |
| Iran, Islamic Republic of | 53 | 2.3% | 1 | 2.7% | 52 | 2.3% | 0.577 |
| Belgium | 48 | 2.1% | 1 | 2.7% | 47 | 2.1% | 0.541 |
| Argentina | 49 | 2.1% | 0 | 0.0% | 49 | 2.1% | >0.999 |
| Germany | 46 | 2.0% | 1 | 2.7% | 45 | 2.0% | 0.596 |
| Turkey | 41 | 1.8% | 0 | 0.0% | 41 | 1.8% | >0.999 |
| Netherlands | 32 | 1.4% | 1 | 2.7% | 31 | 1.4% | 0.403 |
| Canada | 33 | 1.4% | 1 | 2.7% | 32 | 1.4% | 0.413 |
| Other | 348 | 15.0% | 2 | 5.4% | 346 | 15.1% | 0.100 |
| Disease Type* | | | | | | | |
| Crohn’s Disease | 1299 | 55.8% | 6 | 16.2% | 1293 | 56.5% | <0.001 |
| Ulcerative Colitis | 976 | 42.0% | 30 | 81.1% | 946 | 41.3% | |
| IBD-unspecified | 45 | 1.9% | 1 | 2.7% | 44 | 1.9% | |
| Characteristic $^{ab}$ | All Patients on ≥1 Medication | Tofacitinib | Other IBD Therapy | $P^c$ |
|------------------------|-------------------------------|-------------|-------------------|------|
|                        | N (Mean) % (SD) | N (Mean) % (SD) | N (Mean) % (SD) |      |
| IBD disease activity $^{d,*}$ | | | | 0.031 |
| Remission | 1290 55.5% | 12 32.4% | 1278 55.8% | |
| Mild | 454 19.5% | 12 32.4% | 442 19.3% | |
| Moderate/Severe | 496 21.3% | 12 32.4% | 484 21.1% | |
| Concomitant systemic corticosteroids | 192 8.3% | 5 13.5% | 187 8.2% | 0.106 |
| Comorbidity summary score | | | | >0.999 |
| 0 | 1541 66.3% | 23 62.2% | 1518 66.3% | |
| 1 | 513 22.1% | 9 24.3% | 504 22.0% | |
| 2 | 150 6.4% | 3 8.1% | 147 6.4% | |
| ≥3 | 122 5.2% | 2 5.4% | 120 5.2% | |
| Comorbid conditions | | | | |
| Cardiovascular disease | 153 6.6% | 3 8.1% | 150 6.6% | 0.732 |
| Diabetes | 130 5.6% | 2 5.4% | 128 5.6% | >0.999 |
| Asthma | 115 4.9% | 2 5.4% | 113 4.9% | 0.705 |
| COPD | 40 1.7% | 0 0.0% | 40 1.7% | >0.999 |
| Other chronic lung disease | 33 1.4% | 1 2.7% | 32 1.4% | 0.413 |
| Hypertension | 272 11.7% | 6 16.2% | 266 11.6% | 0.433 |
| Cancer | 39 1.7% | 1 2.7% | 38 1.7% | 0.468 |
| History of stroke | 30 1.3% | 1 2.7% | 29 1.3% | 0.384 |
| Chronic renal disease | 54 2.3% | 1 2.7% | 53 2.3% | 0.584 |
| Chronic liver disease | 80 3.4% | 1 2.7% | 79 3.5% | >0.999 |
| Other comorbidity | 293 12.6% | 3 8.1% | 290 12.7% | 0.616 |
| Current smoker | 88 3.8% | 0 0.0% | 88 3.8% | 0.400 |
| BMI | | | | 0.122 |
| BMI <30 | 1524 65.5% | 23 62.2% | 1501 65.6% | |
| BMI ≥30 | 370 15.9% | 10 27.0% | 360 15.7% | |
| Missing | 432 18.6% | 4 10.8% | 428 18.7% | |

$^a$Unless otherwise specified, percentages do not include missing values or “unknown.” For all characteristics, unless noted above, less than 4% of data were missing and unknown, respectively, for each category.

$^b$Percentages and n from each subcategory may not add up to the exact number of total reported cases due to missing values and/or non-mutually exclusive variables.

$^cP$-values for tests comparing variables between tofacitinib and other medications groups.

$^d$By physician global assessment (PGA) at time of COVID-19 infection.

$^e$Statistically significant association.

Abbreviations: CAD, coronary artery disease; COPD, chronic obstructive pulmonary disease.
METHODS

The Surveillance Epidemiology of Coronavirus Under Research Exclusion for Inflammatory Bowel Disease (SECURE-IBD) is a global, web-based, collaborative registry established in March 2020 to understand COVID-19 outcomes in IBD patients, including the impact of immunosuppression.6 The collection and categorization of data have been reported previously.6

Using data reported though September 2020, we compared characteristics and COVID-19 outcomes of IBD patients on tofacitinib and those on other medications. We determined the proportion of patients with severe COVID-19, defined as a composite of intensive care unit (ICU) admission, mechanical ventilation, and/or death. In June 2020, we added the SECURE-IBD data collection form to include questions pertaining to thrombotic complications. We compared the proportion of patients with thrombotic complications who were on tofacitinib with those on other IBD therapies. We performed bivariate analyses using χ² or Fisher exact test for categorical variables and Wilcoxon rank-sum or t test for continuous variables. P values ≤0.05 were considered statistically significant for all analyses. SAS version 9.3 (SAS Institute, Cary, North Carolina) was used for data preparation and analyses.

As SECURE-IBD collects only de-identified data, the UNC-Chapel Hill Office for Human Research Ethics has determined that the storage and analysis of de-identified data for this project does not constitute human subjects research.

RESULTS

Of 2326 patients who were on ≥1 IBD medication in the SECURE-IBD registry, 37 (1.6%) were treated with tofacitinib; 17 (45.9%) and 20 (54.1%) patients were on ≥20 and <20 mg total daily dose of tofacitinib, respectively. Baseline demographic and clinical characteristics of patients on tofacitinib compared with those on other medications are reported in the Table 1. Thirty (81.1%) patients in the tofacitinib group had UC compared with 946 (41.3%) patients on other IBD medications (P < 0.001). Significantly fewer patients were in remission in the tofacitinib group compared with those on other medications (32.4% vs 55.8%, P = 0.03). All other baseline demographic and clinical characteristics were comparable between the 2 groups.

With respect to COVID-19 outcomes, there were no significant differences between tofacitinib-treated patients and other patients in the occurrence of hospitalization (21.6% vs 23.3%), admission to the ICU (5.4% vs 4.5%), and severe COVID-19 (6.2% in both groups, Table 2). In the subgroup of patients on tofacitinib for whom information on thrombotic events were available (n = 19), none experienced a thrombotic event. Among those on other IBD medications, thrombotic events occurred in 9 of 1270 (0.7%).

DISCUSSION

We describe characteristics and outcomes of COVID-19 in 37 patients with IBD treated with tofacitinib compared with other medications in the SECURE-IBD registry. Overall, we found no difference in COVID-19 outcomes between the 2 groups.

Our findings are consistent with previous descriptive reports of patients on JAKi for UC and other immune-mediated disease; although in each of these studies, COVID-19 outcomes are reported jointly among the few patients on JAKi along with other immunosuppression.6–9 In a case report of a 33-year-old woman with UC on tofacitinib, respiratory symptoms resolved in 5 days, and the patient recovered completely in 2 weeks with no change to tofacitinib treatment.10

In addition, although patients with COVID-19 may experience thrombotic complications, and tofacitinib at the higher dose has been associated with venous thromboembolism,2 none of the tofacitinib-treated patients in SECURE-IBD experienced thrombotic complications. Overall, these early data should be viewed as cautiously reassuring to patients and providers while we await larger studies and more granular analyses to parse out the impact of JAKi on COVID-19 outcomes.

### TABLE 2. COVID-19 Outcomes Among IBD Patients on Tofacitinib Compared With Other IBD Therapies in the SECURE-IBD Registry

| Outcome               | All Patients on ≥1 Medication n (%) | Tofacitinib, n (%) | Other IBD therapy, n (%) | P |
|-----------------------|-------------------------------------|--------------------|--------------------------|---|
| Outpatient care       | 1753 (75.4%)                        | 29 (78.4%)         | 1724 (75.3%)             | 0.668 |
| Hospitalization       | 542 (23.3%)                         | 8 (21.6%)          | 534 (23.3%)              | 0.807 |
| ICU admission         | 106 (4.6%)                          | 2 (5.4%)           | 104 (4.5%)               | 0.685 |
| Mechanical ventilation| 77 (3.3%)                           | 1 (2.7%)           | 76 (3.3%)                | >0.999 |
| Death                 | 61 (2.6%)                           | 1 (2.7%)           | 60 (2.6%)                | >0.999 |
| Severe COVID-19 outcomesa | 144 (6.2%)                        | 2 (5.4%)           | 142 (6.2%)               | >0.999 |

*aIncludes composite of ICU admission, mechanical ventilation, and death.*
Strengths of this study include the use of a large, international registry of adult and pediatric IBD patients with diverse characteristics and outcomes. Limitations include the small number of patients on tofacitinib and even fewer outcomes precluding adjusted analyses; however, most demographic and clinical characteristics were comparable between tofacitinib-treated and other IBD patients. The only notable differences were the higher proportion of tofacitinib-treated patients with UC and active IBD. This is likely due to the real-world use of tofacitinib in moderate-severely active UC refractory to tumor necrosis factor antagonists. There are also risks of reporting bias and missing data in this voluntary registry.

In summary, in our descriptive analysis, characteristics and COVID-19 outcomes among IBD patients on tofacitinib were comparable to those on other IBD medications. Future larger studies of patients on tofacitinib are needed to understand clinical implications.

Data Availability: The data underlying this article are available in the article and in its online supplementary material.

REFERENCES
1. Richardson S, Hirsch JS, Narasimhan M, et al.; the Northwell COVID-19 Research Consortium. Presenting characteristics, comorbidities, and outcomes among 5700 patients hospitalized with COVID-19 in the New York city area. Jama. 2020;323:2052–2059.
2. Sandborn WJ, Su C, Sands BE, et al.; OCTAVE Induction 1, OCTAVE Induction 2, and OCTAVE Sustain Investigators. Tofacitinib as induction and maintenance therapy for ulcerative colitis. N Engl J Med. 2017;376:1723–1736.
3. Lee JS, Shin EC. The type I interferon response in COVID-19: implications for treatment. Nat Rev Immunol. 2020;20:585–586.
4. Bronte V, Ugol S, Tinazzi E, et al. Baricitinib restraints the immune dysregulation in severe COVID-19 patients. J Clin Invest. 2020.
5. Pfizer. XELJANZ (Tofacitinib): Increased Risk of Pulmonary Embolism and Mortality in Rheumatoid Arthritis Patients Receiving 10 mg Twice Daily in a Clinical Trial. 2019.
6. Brenner EJ, Ungaro RC, Geary RB, et al. Corticosteroids, but not TNF antagonists, are associated with adverse COVID-19 outcomes in patients with inflammatory bowel diseases: results from an international registry. Gastroenterology. 2020.
7. Lukin DJ, Kumar A, Hajifathalian K, et al.; Jill Roberts Center Study Group Study Group; Weill Cornell Medicine-Gastrointestinal Study Group. Baseline disease activity and steroid therapy stratify risk of COVID-19 in patients with inflammatory bowel disease. Gastroenterology. 2020;159:1541–1544.e2.
8. Gianfrancesco M, Hyrich KL, Al-Adely S, et al.; COVID-19 Global Rheumatology Alliance. Characteristics associated with hospitalisation for COVID-19 in people with rheumatic disease: data from the COVID-19 Global Rheumatology Alliance physician-reported registry. Ann Rheum Dis. 2020;79:859–866.
9. Remisch W, Rubin D, Zhou X, et al. Evaluation of patient characteristics and clinical outcomes among SARS-CoV-2 diagnosed patients with and without UC treated with systemic therapies: a retrospective cohort study using US Optum® COVID-19 EHR data. Am J Gastroenterol. 2020.
10. Jacobs J, Clark-Snustad K, Lee S. Case report of a SARS-CoV-2 infection in a patient with ulcerative colitis on tofacitinib. Inflamm Bowel Dis. 2020;26:e64.