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Tofacitinib Use in Adults with Chronic Inflammatory Disease During the Severe Acute Respiratory Syndrome Coronavirus 2 Pandemic: What Is Known So Far?

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ARTICLE INFO

Article history:

Received 1 June 2021

Accepted 13 July 2021

Keywords:

gastroenterology
immunosuppressive treatment
rheumatology
virology

ABSTRACT

Background: Concerns have been raised that the risk of severe acute respiratory syndrome coronavirus 2 infection, or more severe or critical coronavirus disease 2019 (COVID-19), may be higher in immunocompromised individuals receiving immunomodulatory therapies compared with immunocompetent individuals. Tofacitinib is an oral Janus kinase inhibitor for the treatment of rheumatoid arthritis, psoriatic arthritis, ulcerative colitis, and polyarticular course juvenile idiopathic arthritis. To date, data on tofacitinib treatment during the COVID-19 pandemic are limited.

Objectives: To summarize current understanding of the use of tofacitinib in adults during the COVID-19 pandemic, and discuss research questions that are yet to be addressed, to further inform the safe and effective use of tofacitinib in clinical practice.

Methods: We conducted a review of the literature (as of February 2021), to summarize the expert recommendations for the management of rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis in the context of COVID-19, and to assess the current data regarding the use of tofacitinib in adult patients during the pandemic.

Results: Current recommendations for rheumatoid arthritis, psoriatic arthritis, and ulcerative colitis state that tofacitinib treatment should be continued during the pandemic, except in cases of positive or presumed severe acute respiratory syndrome coronavirus 2 infection. However, limited data are available; analyses of data from international rheumatology and gastroenterology registries have suggested that tofacitinib may not be associated with an increased risk of hospitalization or treatment switching in adults with COVID-19.

Conclusions: Further assessment of tofacitinib use in patients with rheumatoid arthritis, psoriatic arthritis, or ulcerative colitis will be required to elucidate and establish the benefit:risk profile of tofacitinib during the current COVID-19 pandemic.

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Introduction

Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) is responsible for the current coronavirus disease 2019 (COVID-19) pandemic. The course of COVID-19 can range from asymptomatic

disease to severe multisystem complications, including hyperinflammatory responses that can lead to death.¹ The underlying reasons for this variance have not yet been fully resolved. Particular concern has been raised that immunocompromised individuals may have an increased risk of SARS-CoV-2 infection, compared with immunocompetent individuals²; in addition, there is conflicting evidence regarding the risk of COVID-19-related complications, including mortality, in immunosuppressed patients compared with immunocompetent individuals.

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Use of immunomodulatory therapies is common in patients with chronic inflammatory diseases.³⁻⁷ One class of immunomodulatory drugs used in the treatment of some of these diseases is Janus kinase (JAK) inhibitors, which modulate cytokine signaling during activation of the immune response.⁸ Similar to other immunomodulatory therapies, an increased risk of infection has been reported in patients receiving JAK inhibitors.⁸

In this report, we summarize the expert recommendations currently available for the management of rheumatoid disease (including rheumatoid arthritis [RA] and psoriatic arthritis [PsA]), and inflammatory bowel disease (IBD; including Crohn's disease and ulcerative colitis [UC]), in adult patients, in relation to COVID-19 infection, and discuss what is currently known about the use of the JAK inhibitor tofacitinib⁸ in these patient populations during the COVID-19 pandemic, as well as highlighting research questions that are yet to be addressed.

Methods

A review of the literature was conducted in February 2021, using the search terms *COVID-19*, *SARS-CoV-2*, *rheumatology*, and *gastroenterology*, to determine the current expert recommendations for the management of RA, PsA, and UC in the context of COVID-19. A second search, conducted in February 2021, included *JAK inhibitor* and *tofacitinib* as search terms in addition to those above, to assess the current data regarding the use of tofacitinib in adult patients with RA, PsA, or UC during the COVID-19 pandemic.

International recommendations on managing adult patients with RA, PsA, or UC during the COVID-19 pandemic

When the COVID-19 pandemic began to unfold, recommendations for the treatment of patients with chronic inflammatory disease in the context of the pandemic were developed, based on expert opinion. As new data emerge and knowledge of COVID-19 evolves, these recommendations are being continuously reviewed and updated. The influence of COVID-19 in pediatric patients is not yet fully understood. For adult patients, the American College of Rheumatology (ACR) and the European Alliance of Associations for Rheumatology (EULAR) state that adults with rheumatic disease do not appear to be at greater risk of SARS-CoV-2 infection than the general population,^{3,4} and the risk of poorer outcomes for adults with rheumatic disease appears to be primarily related to other factors, such as older age and preexisting comorbidities (eg, hypertension, cardiovascular disease, chronic lung or kidney disease, obesity, and diabetes mellitus).³ Likewise, the International Organization for the Study of IBD (IOIBD) and the American College of Gastroenterology state that adults with IBD are unlikely to have a greater risk of infection with SARS-CoV-2 than the general population.^{5,6}

ACR recommends that, in adults with rheumatic disease, ongoing treatments such as conventional synthetic disease-modifying antirheumatic drugs (csDMARDs) or biologic disease-modifying antirheumatic drugs (bDMARDs) and JAK inhibitors, should continue in the absence of SARS-CoV-2 infection. However, in patients with documented or presumptive COVID-19, immunosuppressive treatments (eg, tacrolimus, cyclosporin A, mycophenolate mofetil, and azathioprine), csDMARDs (eg, methotrexate, leflunomide, and sulfasalazine), noninterleukin-6 bDMARDs, and JAK inhibitors, should be withheld temporarily. The precise duration of temporary discontinuation is not defined, and the effects of withholding treatment following SARS-CoV-2 exposure are uncertain.³ In contrast, EULAR recommends that potential changes in DMARD therapy for patients with rheumatic and musculoskeletal disease should be assessed on a case-by-case basis, due to the wide variability in patient response to SARS-CoV-2 infection.⁴ For patients with

IBD, in line with IOIBD recommendations, prednisone use (≥ 20 mg/d) may increase the risk of more severe outcomes due to SARS-CoV-2 infection.⁷ The effects of other therapies for UC, including azathioprine/6-mercaptopurine, methotrexate, tumor necrosis factor inhibitors, and tofacitinib, in the context of SARS-CoV-2 infection, were determined to be unclear at the time of the IOIBD consensus statements; however, it was recommended that prednisone, azathioprine/6-mercaptopurine, methotrexate, and tofacitinib should be withheld from patients who test positive for SARS-CoV-2, regardless of the presence of COVID-19 symptoms.⁷

In summary, the currently available guidelines for adult patients with chronic inflammatory disease during the pandemic recommend that treatment should be withheld from patients who test positive for SARS-CoV-2, but that patients not infected with, nor presumed to have, SARS-CoV-2, should continue to receive their existing therapy, including tofacitinib.

Use of tofacitinib during the COVID-19 pandemic

To date, data on tofacitinib treatment in adults with RA, PsA, or UC during the pandemic are limited. International registries have been created expeditiously by rheumatology and gastroenterology experts to monitor outcomes in patients with rheumatic disease or IBD with confirmed COVID-19. An analysis of patients with rheumatic disease, which used real-world data from the COVID-19 Global Rheumatology Alliance registry, found that glucocorticoid use (doses of ≥ 10 mg/d) was associated with higher odds of hospitalization.⁹ The number of patients with COVID-19 in this analysis receiving JAK inhibitors, either as monotherapy or in combination with csDMARDs, was too low for separate assessment; instead, JAK inhibitors were included in a combined analysis of bDMARDs and targeted synthetic (ts)DMARDs, which found that bDMARD/tsDMARD treatment was associated with a decreased risk of hospitalization.⁹ An analysis of medication and clinical care changes by patients with RA carried out during the first 3 months of the pandemic demonstrated that, whereas JAK inhibitor use was associated with medication changes, only glucocorticoid use was identified as a strong factor for treatment switching.¹⁰

A study in patients with rheumatic disease receiving JAK inhibitors (including tofacitinib) with symptomatic COVID-19 found that patients with RA were more likely to be hospitalized than patients with PsA; however, overall, only glucocorticoid use and hypertension were significant risk factors for hospitalization of patients with rheumatic disease after adjusting for age and sex.¹¹

Risk factors for severe COVID-19 in the Surveillance Epidemiology of Coronavirus Under Research Exclusion for IBD (SECURE-IBD) registry included increasing age, presence of ≥ 2 comorbidities, and treatment with either systemic glucocorticoids, sulfasalazine, or 5-aminosalicylates. In this analysis, use of tumor necrosis factor inhibitors was not associated with increased risk of severe COVID-19, and the proportion of patients receiving tofacitinib was too low for meaningful evaluation.¹² In a subsequent analysis, assessment of the characteristics and outcomes of COVID-19 in patients with IBD in the SECURE-IBD registry receiving tofacitinib, compared with other medications, showed that, overall, no significant differences in COVID-19 outcomes (eg, occurrence of severe COVID-19 symptoms, hospitalization, or intensive care unit admission due to COVID-19) were identified between the 2 groups (all $P > 0.05$).¹³ However, this analysis was limited by the small number of patients receiving tofacitinib, and the risks of reporting and treatment biases. There has been 1 published case report of continuous tofacitinib in a patient with UC who had contracted SARS-CoV-2; in this case, respiratory symptoms resolved after 5 days, and there were no major complications related to COVID-19.¹⁴

Pharmacovigilance of treatments used in clinical care is of paramount importance during the COVID-19 pandemic,¹⁵ and

pharmaceutical manufacturers and regulatory agencies continue to scrutinize all reported adverse events. For example, as of February 25, 2021, of 7832 relevant cases of COVID-19 reported to Pfizer, 4355 cases reported COVID-19 during treatment with Pfizer pharmaceutical products, including 945 patients receiving tofacitinib (unpublished data).

Further assessment of tofacitinib use in patients with RA, PsA, or UC during the current COVID-19 pandemic is ongoing.

Vaccination for SARS-CoV-2 in adult patients with RA, PsA, and UC receiving tofacitinib

The safety and efficacy of vaccines against herpes zoster (administered before tofacitinib treatment), and influenza and pneumococcal vaccines (administered during tofacitinib treatment), have previously been demonstrated in patients with RA, and vaccination is recommended for patients with rheumatic disease.¹⁶

Vaccines targeted against SARS-CoV-2 have now been approved for use in many countries, having been shown to protect against COVID-19 in the general population in Phase I to III clinical trials with a favorable safety profile. However, it should be noted that the trials conducted to date excluded patients taking immunosuppressive therapies,¹⁷ and investigations of SARS-CoV-2 vaccine efficacy in children have not yet been published.

As governments commence rollout of SARS-CoV-2 vaccination programs, with priority given to frontline healthcare workers and vulnerable populations, adult patients with chronic inflammatory disease receiving tofacitinib or other immunomodulatory therapies may be among these priority cohorts; therefore, close monitoring of these patient populations is warranted.

In line with recent guidelines from ACR and IOIBD, patients with rheumatic disease or IBD should be vaccinated against SARS-CoV-2 at the earliest possible opportunity,^{6,18} and vaccination should not be deferred in patients receiving immunosuppressive therapy. The ACR guidelines state no preference regarding the use of 1 COVID-19 vaccine over another. The lack of direct evidence concerning the safety and efficacy of COVID-19 messenger RNA vaccines in patients with rheumatic disease was highlighted, and the authors concluded that there was no evidence to support concerns regarding the use/timing of immunomodulatory therapies with respect to messenger RNA vaccine safety.¹⁸ However, ACR provisionally recommended that some treatments should be withheld, either before vaccination (eg, subcutaneous abatacept), or following vaccination (eg, methotrexate, JAK inhibitors, or subcutaneous abatacept [first vaccination dose only]); in the case of infusion treatments such as intravenous abatacept, intravenous cyclophosphamide, or rituximab, scheduling of vaccination should be amended to allow vaccine administration to take place without disruption to treatment cycles.¹⁸ It is likely that further investigation will be required to elucidate whether or not withdrawal is necessary, or even beneficial, for all treatments, and ACR recommendations on treatment withdrawal could be updated when more evidence becomes available. Of note, a prior investigation into the use of tofacitinib with influenza and pneumococcal vaccines found that temporary (2-week) withdrawal of tofacitinib had little influence on vaccine efficacy, based on the observation that the majority of patients were able to mount satisfactory responses to either vaccine.¹⁹ Moreover, a steady increase in disease activity measures was observed in those patients who experienced an interruption in tofacitinib treatment, compared with patients receiving continuous treatment.²⁰ ACR does not recommend modification to corticosteroid use in patients with rheumatic disease; in contrast, IOIBD recommends that patients with IBD should be counseled that vaccine efficacy could be reduced by use of systemic corticosteroids.^{5,18}

Factors for future consideration

The long-term influence of SARS-CoV-2 in patients with chronic inflammatory disease treated with tofacitinib has yet to be established. Continued surveillance of patients with RA, PsA, or UC who contract COVID-19 will be required to determine the efficacy and safety profiles of pharmacotherapies, including, but not limited to, tofacitinib, during the COVID-19 pandemic and beyond. Of note, risk of thromboembolic events has been highlighted as a particular concern in patients with severe COVID-19,¹ and local labeling of JAK inhibitors, including tofacitinib, identifies venous thromboembolism as an important safety risk.⁸ The potential effect of tofacitinib treatment on the risk of thromboembolic events in patients with COVID-19 is, as yet, unknown. Ultimately, clinical studies investigating the effects of tofacitinib on SARS-CoV-2 vaccine response and, conversely, the effects of vaccine administration on tofacitinib response, are required.

The efficacy and safety of tofacitinib as a treatment for moderate to severe COVID-19 is currently under investigation. A recently completed multicenter, randomized, double-blind, placebo-controlled study conducted in Brazil demonstrated that tofacitinib led to a lower risk of death or respiratory failure through day 28 than placebo, among adult patients hospitalized with COVID-19 pneumonia who were not receiving noninvasive or invasive ventilation. All the patients were treated according to local standards of care for COVID-19.²¹ Additional studies are ongoing.

Conclusions

Current recommendations for RA, PsA, and UC state that tofacitinib treatment should be continued during the pandemic, except in cases of positive or presumed SARS-CoV-2 infection. Although, to date, data on tofacitinib use in the context of COVID-19 are limited, no apparent increase in the risk of SARS-CoV-2 infection, and no treatment-related COVID-19 manifestations, have been observed in patients receiving tofacitinib. Despite the initiation of SARS-CoV-2 vaccination programs, further assessment of tofacitinib use in patients with chronic inflammatory disease will be required to help elucidate and establish the benefit:risk profile of tofacitinib in patients with RA, PsA, or UC during the COVID-19 pandemic.

Conflicts of Interest

This work was sponsored by Pfizer Inc. S. Howland, J. Deuring, X. Zhou, and Y. Chen are employees and shareholders of Pfizer Inc. L. M. H. Mota has received personal or institutional support from AbbVie, Janssen, Pfizer Inc, and Roche, and has received speaker's fees from AbbVie, Eli Lilly, Janssen, Pfizer Inc, Roche, Sandoz, and UCB. R. C. Ungaro has served as a consultant and/or advisory board member for Bristol-Myers Squibb, Eli Lilly, Janssen, Pfizer Inc, and Takeda, has received research support from AbbVie, Boehringer Ingelheim, and Pfizer Inc, and is supported by a Career Development Award from the National Institutes of Health (K23KD111995-01A1). The authors have indicated that they have no other conflicts of interest regarding the content of this article.

Acknowledgments

Medical writing support, under the guidance of the authors, was provided by Anthony McCluskey, PhD, CMC Connect, McCann Health Medical Communications and was funded by Pfizer Inc, New York, NY, in accordance with Good Publication Practice guidelines (*Ann Intern Med.* 2015; 163: 461–464). All authors contributed equally.

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