DOI: 10.1002/jmv.26528

LETTER TO THE EDITOR

JOURNAL OF MEDICAL VIROLOGY WILEY

Safety of nontumor necrosis factor-targeted biologics in the COVID-19 pandemic

To the Editor,

Coronavirus disease 2019 (COVID-19) is a respiratory tract infection (RTI) caused by novel severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2), which has been spreading worldwide.[1] SARS-CoV-2-induced pneumonia is a commonly reported event and caused by hyperactivation of effector T cells and excessive production of inflammatory cytokines (i.e., tumor necrosis factor [TNF], interferon-γ, and interleukin 6 [IL-6]), known as a cytokine storm.[2] Hence, anticytokine therapies have become of keen interest for physicians because these drugs might be preventive for SARS-CoV-2-induced pneumonia.[3,4]

Anticytokine therapies have been widely used for autoimmune diseases including psoriasis, rheumatoid arthritis, and inflammatory bowel disease. However, these therapies have known adverse events. In clinical trials of TNF, IL-12/23, IL-23, IL-17, and Janus kinase (JAK) inhibitors for autoimmune diseases, the most commonly reported adverse events included upper RTIs (URTIs).[5–8] JAK inhibitors are also known to increase the risk of herpes zoster infection.[8] Although under usual circumstances patients on these therapies are closely monitored for these events, the COVID-19 pandemic has raised concern among physicians and patients on the safety of continuing these therapies; furthermore, their safety must be considered if they are being explored for the treatment for COVID-19.

Although previous studies demonstrated that TNF inhibitors increased the risk of serious infections including RTIs,[5] it is still unclear whether newer non-TNF-targeted biologics, including IL inhibitors and JAK inhibitors, would increase the risk of RTIs. This information is essential in making treatment decisions for patients with autoimmune diseases during this pandemic, especially in patients who are experiencing increased disease activity and who may be at risk of infection with SARS-CoV-2.

Here, we studied the risk of RTIs with IL-12/23, IL-23, IL-17, and JAK inhibitors in patients with autoimmune diseases. We reviewed studies published on PubMed/MEDLINE from 2007 to 2019 and included randomized placebo-controlled trials (RCTs) of autoimmune diseases reporting the incidence of adverse events including RTIs (Supporting Information References). We performed a pooled analysis to assess the risk of RTIs with IL-12/23 (ustekinumab), IL-23 (guselkumab, risankizumab, tildrakizumab), IL-17 (brodalumab, secukinumab, ixekizumab), and JAK inhibitors (tofacitinib, baricitinib; Table S1). Incidence of RTIs included influenza, nasopharyngitis, pneumonia, URTIs, and viral URTIs were pooled for each drug and placebo to obtain the odds ratio (OR).

We included 106 RCTs for a total of 27,340 patients treated with non-TNF-targeted biologics and 11,347 treated with placebo. The mean placebo-controlled period was 16.2 ± 8.7 weeks. The pooled data of IL-12/23 and IL-23 inhibitors showed that there was no increased risk of RTIs (Figure 1). No IL-17 inhibitors showed an increased risk of RTIs except for secukinumab, which increased the risk of nasopharyngitis (OR, 1.48; 95% confidence interval [CI], 1.20–1.83; $p < .001$; Figure 1). The analysis of JAK inhibitors revealed that baricitinib significantly increased the risk of influenza (OR, 2.41; 95% CI, 1.11–5.26; $p = .027$) and viral URTIs (OR, 3.10; 95% CI, 1.06–9.10; $p = .039$), while tofacitinib was not associated with an increased risk of RTIs (Figure 1).

In this pooled analysis, we demonstrated that tofacitinib, IL-12/23, IL-23, and IL-17 inhibitors did not increase the risk of RTIs, particularly viral RTIs, in patients with autoimmune diseases. Baricitinib, however, significantly increased the risk of viral RTIs including influenza and viral URTIs. Notably, several studies suggested that baricitinib can be a potential drug to treat COVID-19 because it inhibits the viral assembly by the prevention of AP-2 associated protein kinase 1,[9] and a recent pilot study demonstrated its efficacy and safety for COVID-19 pneumonia.[10] However, given baricitinib has a significant risk of viral RTIs, caution should be exercised to continue it during the pandemic or to use it as an antiviral therapy against SARS-CoV-2.

Several limitations of our studies should be acknowledged. First, this study did not evaluate the long-term effect of non-TNF-targeted biologics on RTIs. Second, our study may not reflect the risk in patients at high risk for RTIs due to the possible exclusion of patients with recent RTIs or chronic lung disease in the setting of clinical trials. Third, our results do not provide evidence of whether non-TNF-targeted biologics can be continued after a diagnosis of RTIs.

In conclusion, this analysis suggests that the benefit of using these non-TNF-targeted biologics, particularly baricitinib, should be weighed against the risk of viral RTIs and other risks presented on a patient-by-patient basis.

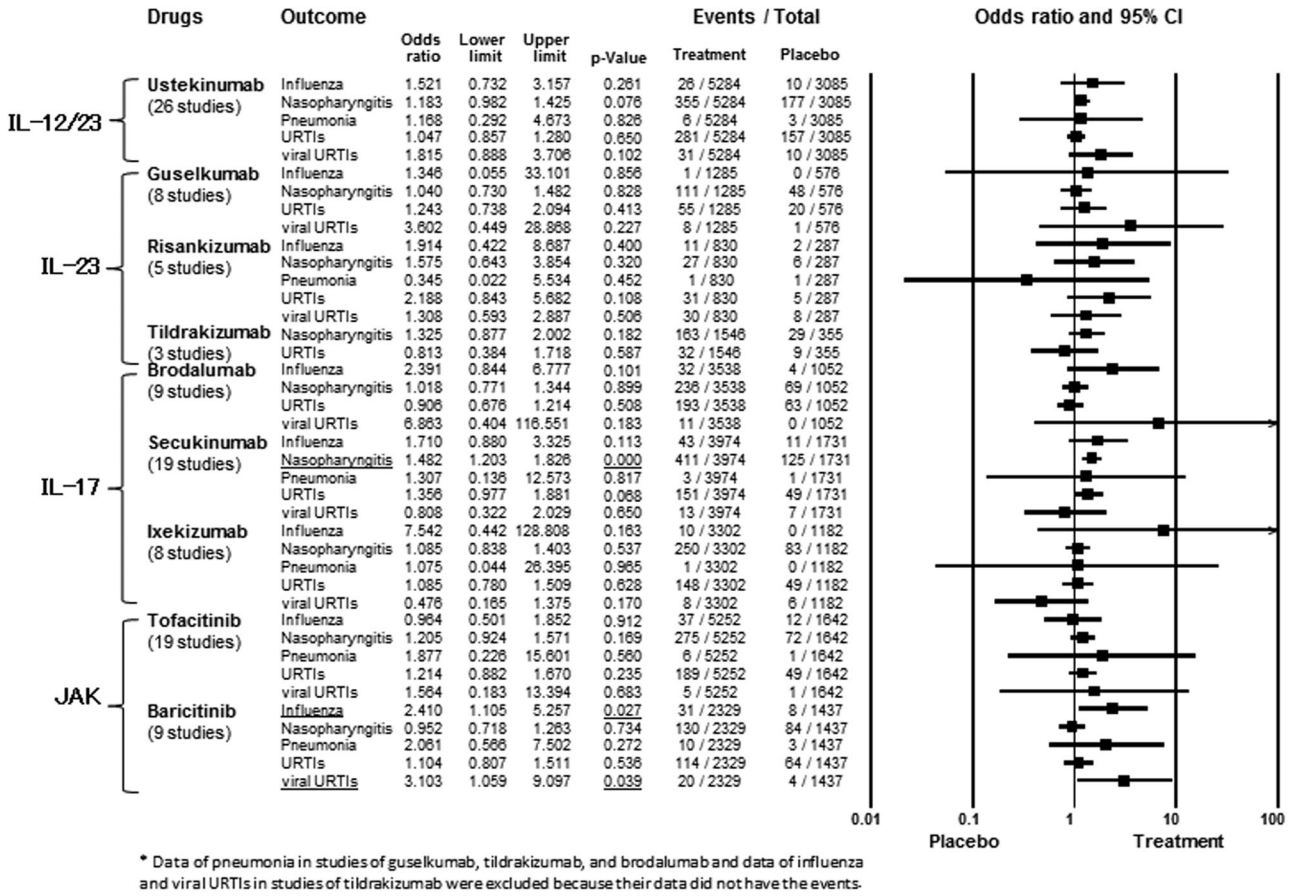

FIGURE 1 A pooled analysis of OR of RTIs with IL-12/23, IL-23, IL-17, and JAK inhibitors. Incidence of RTIs included influenza, nasopharyngitis, pneumonia, URTIs, and viral URTIs were extracted and were pooled among each drug and placebo to obtain OR. Data of pneumonia in studies of guselkumab, tildrakizumab, and brodalumab and data of influenza and viral URTIs in studies of tildrakizumab were excluded because their data did not have the events. IL, interleukin; JAK, Janus kinase; OR, odds ratio; RTI, respiratory tract infection; URTI, upper RTI

CONFLICTS OF INTERESTS

The authors declare that there are no conflict of interests.

AUTHOR CONTRIBUTIONS

Literature search and data collection: Shintaro Akiyama and Akihiro Yamada. *Figures*: Shintaro Akiyama. *Study design, data analysis and interpretation, and drafting of manuscript*: Shintaro Akiyama and Atsushi Sakuraba.

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SUPPORTING INFORMATION

Additional Supporting Information may be found online in the supporting information tab for this article.