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Infectious side effects of baricitinib: A big data analysis based on VigiBase

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Dear Editor,

Baricitinib (known as "Olumiant"), is an inhibitor of Janus-associated kinase 1 and 2 (JAK1 and JAK2) initially introduced for the treatment of rheumatoid arthritis (RA), and later for systemic lupus erythematosus (SLE), and atopic dermatitis [1]. The first approval of baricitinib was from the European Medicines Agency (EMA) as a monotherapy or combination therapy with methotrexate for patients with RA unresponsive to disease-modifying anti-rheumatic drugs (DMARDs) [2]. Later on, baricitinib was approved by the Food and Drug Administration (FDA) for RA with inadequate response to TNF antagonists [3]. Recently, under the Emergency Use Authorization (EUA) of the FDA, baricitinib was approved for patients with severe SARS-CoV-2 infection requiring mechanical ventilation [4]. In fact, JAK inhibitors have a variety of regulatory mechanisms due to their effects on several signaling functions of JAK/STAT (Signal Transducer and Activator of Transcription) pathway (Fig. 1). In terms of baricitinib use in RA, randomized controlled trials showed that 2 mg or 4 mg doses of baricitinib was significantly associated with remission in refractory RA, with admissible safety profile [1]. However, the recommended dose of baricitinib in RA patients is 2 mg, whereas the 4 mg dose was suggested for patients with severe COVID-19 [5] following the use of immunosuppressive agents in patients with severe SARS-CoV-2 infection [6]. Randomized controlled trials of baricitinib and remdesivir therapy for patients with COVID-19 demonstrated greater effectiveness in terms of improvement and reducing time to recovery compared to remdesivir alone [7]. In terms of side effects, the known adverse effects of baricitinib include upper respiratory tract infections, nausea, headache, and gastrointestinal perforations [1]. The occurrence of side effects seemingly depends on the dosage of the drug [5]. The infectious side effects encountered are hypothesized to be related to the immunomodulatory effects of baricitinib [8]. Based on the World Health Organization (WHO) VigiBase data, we aimed to present the profile of infectious side effects of baricitinib treatment in RA.

The VigiBase is a global pharmacovigilance database recording around 20 million individual case safety reports (ICSRs) of suspected adverse drug reactions (ADRs) from more than 135 countries around the globe. The odds-ratio (OR) and the information component (IC) are the most commonly used measurement methods to report ADRs of drugs. With the calculated 95% credible interval (CrI) of the disproportionality measures, the IC0.25 represents the lower bound values, whereas the IC97.5 represents the upper bound values. That to say, IC is interpreted as statistically significant when IC0.25 is a positive figure, which is the statistical figure used in the VigiBase. Therefore, the IC0.25 values were used in our analysis of the infectious side effects of approximately 300 RA patients treated with baricitinib. Among the infectious side effects, the most significant infections were oral herpes and herpes zoster infections, with IC025 values of 4.36 and 4.15 respectively. Other infectious ADRs such as urinary tract infections and lower respiratory tract infections were also documented with IC025 values of 2.70 and 3.91, respectively. The lowest prevalence rate of infectious side effects was measured in regard to gastric infections with an IC025 value of 0.006, followed by infectious pleural effusion with values of 0.09.

Discussion

According to our data, oral herpes was the most common infectious side effect of baricitinib in terms of the rate of occurrence. In fact, while primary HSV-1 infection occurs in childhood as an asymptomatic or mild skin disease; HSV-1 infection may cause recurrent infections later in life, particularly in immunocompromised patients. Interestingly, both herpes simplex and herpes zoster infections are known side effects of JAK inhibitors [9]. Bieber et al. [10] showed that oral herpes cases had a steep increase of prevalence in baricitinib treated group (4 mg) when compared with placebo (6.1%vs 2.7%). In addition, a large scale case-control study including more than 86,000 patients with RA, demonstrated an increase in overall infections including herpes zoster in patients with RA compared to controls [11]. Similarly, Winthrop et al. [12] reported a high over all infectious side effects in patients treated with baricitinib alongside a significantly higher rate of herpes zoster infections in participants receiving 4 mg. The latter finding suggests a probable dose dependent effect. Likewise, Bechman et al. [13] showed that in RA population, herpes zoster infection was higher than expected in patients treated with JAK inhibitors. The risk was statistically significant in patients treated with baricitinib. In parallel with the previous studies, our data showed that herpes zoster is the second most common

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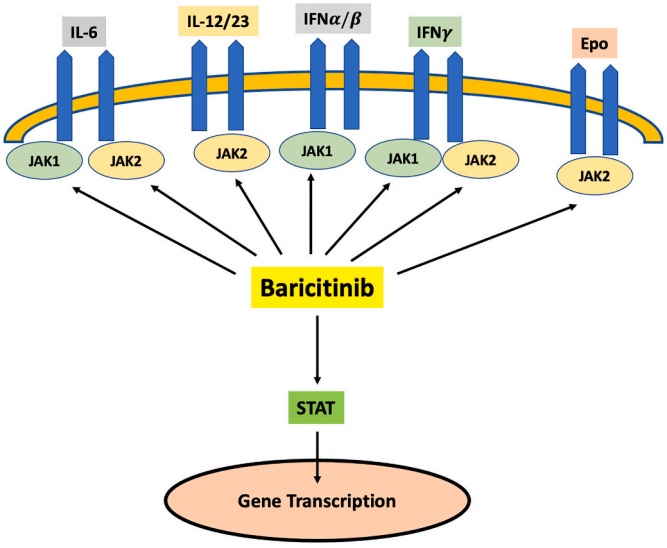

Fig. 1. The JAK and STAT pathways affected by baricitinib. STAT: signal transducer and activator of transcription.

adverse effect after oral herpes (IC025 = 4.15). Interestingly, urinary tract infections were also reported as part of the infectious side effects of JAK inhibitors. In a Chinese cohort of RA patients treated with baricitinib, the prevalence of UTI was 9.5% compared to 4.3% in the placebo [14]. UTIs, according to the same study, were the most common infectious side effects of baricitinib use. Correspondingly, in a phase 3 study of more than 500 RA patients with inadequate response to TNF-inhibitors or other DMARDs, the prevalence of infections including UTIs were higher for patients treated with baricitinib 2 mg and 4 mg than for patients receiving placebo [15]. Our data illustrated an IC025 value of 2.70 pointing to the risk of UTI events during baricitinib treatment.

Conclusion

Oral herpes and herpes zoster were the most common infectious side effects of baricitinib treatment in RA patients. Rheumatologists considering baricitinib treatment for RA should take the profile of these side effects into consideration. Preventive measures, such as vaccination against herpes zoster prior to the initiation of treatment should be warranted. The same could be applied for oral herpes in terms of early treatment initiation, as oral herpes might carry severe discomfort and risk of complications particularly in immunocompromised individuals. Of note, the studies pointed out a dose dependent pattern of side effects particularly with the higher dose of 4 mg recommended for patients severe COVID-19.

Declaration of Competing Interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

Data availability

The data that has been used is confidential.

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