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Nicolas Massart, Pierre Fillatre, Florian Lemaitre, Arnaud Mari, Camille Tron

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**Pharmacokinetics of baricitinib in critically ill COVID-19 patients****Running title:** Baricitinib pharmacokinetics in COVID-19Nicolas MASSART, M.D.<sup>a</sup>, Pierre FILLATRE, M.D.<sup>a</sup>, Florian LEMAITRE PharmD, PhD.<sup>b</sup>, Arnaud MARI, M.D.<sup>a</sup>, Camille TRON, PharmD, PhD.<sup>b</sup><sup>a</sup>Service de Réanimation, CH de St BRIEUC, 10, rue Marcel Proust 22000 Saint-Brieuc, France.<sup>b</sup>Laboratoire de Pharmacologie, CHU de rennes, 2, rue Henri le Guilloux 35000 rennes, France.**Corresponding author:** Camille TRON, Laboratoire de pharmacologie, CHU de Rennes, 2 rue Henri Le Guilloux, 35000 Rennes, France. [camille.tron@chu-rennes.fr](mailto:camille.tron@chu-rennes.fr), +33 2 99 28 42 80**Word count :** 1544 words**Competing interests**

The author have no competing interest do declare.

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NM, PF and AM participated to acquisition of data, NM, PF, FL and CT participated to the conception and design of the study, NM and CT performed the analysis and interpretation of data and drafted the article, all authors finally approved the submitted version

**ABSTRACT****BACKGROUND**

The use of the selective Janus Kinase 1/2 inhibitor baricitinib has shown a survival benefit in mechanically ventilated COVID-19 patients but this is not without adverse drug reactions. Although critically ill patients are at risk of altered drug exposure, data on baricitinib pharmacokinetics (PK) are scarce. This study describes real-life baricitinib plasma exposure in critically ill COVID-19 patients.

**METHODS**

This retrospective observational study was conducted in critically ill patients with COVID-19 treated with baricitinib 4 mg/day. Plasma concentrations were measured at predose (C0), 1 h (C1) and 3 h (C3) after the drug intake. PK and area under the curve (AUC) were estimated using non-compartmental pharmacokinetic analysis.

**RESULTS**

Seven patients contributed to 22 baricitinib plasma concentration measurements after a median [range] of 3 days [2-3] of treatment. Median baricitinib plasma concentrations were 2.2 ng/mL [1.4-8.0], 24.0 ng/mL [4.9-37.3] and

14.1 ng/mL [8.3-15.1] for trough (C0), C1 and C3 concentrations respectively. The median AUC 0-24h was 188.8 ng.h/mL [141.3-236.3]. No difference was observed in C0 and C1 when comparing patients according to body mass index < or > 30. The patient with the lowest glomerular filtration rate (74 mL/min) had the highest baricitinib trough concentration. Overall, 2 patients had liver function test perturbation and both of them had atypical PK with delayed time to reach maximum concentration.

## CONCLUSION

High inter-patient variability and relatively low baricitinib trough concentrations and AUC were observed in critically ill COVID-19 patients receiving the usual dosage of 4 mg/day. This preliminary study encourages further exploration of the concentration-effect relationship of baricitinib in this clinical context.

**Keywords:** Critical care; baricitinib; pharmacokinetics; COVID-19

## BACKGROUND

Despite tremendous improvements in severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) infectious disease (COVID-19) management, few treatments improve survival in critically ill patients. Among them, the oral selective Janus Kinase 1/2 (JAK1/2) inhibitor baricitinib has shown a survival benefit in mechanically ventilated COVID-19 patients [1,2] but is not without adverse drug reactions [3]. Surprisingly, data regarding baricitinib pharmacokinetics (PK) are scarce even in usual rheumatology indications and do not exist in the COVID-19 setting. However, some variables may modify baricitinib PK such as weight and renal function [4,5], both parameters being highly dynamic in critically ill patients. The pharmacokinetic pathway of baricitinib is characterized by a rapid absorption orally, with a median time to peak concentrations of 1 hour and bioavailability around 79%. Baricitinib is widely distributed in tissues (Vd 76 L) and is mainly excreted unchanged in urine and feces. Renal elimination is the main mechanism of baricitinib clearance, with less than 10% eliminated by hepatic metabolism. Baricitinib is a substrate of drug transporters which may impact its PK profile and may be involved in drug-drug interactions [6].

As baricitinib is a life-saving therapy of a severe acute infection, it is crucial to further study its PK in this context. The aim of our study is to describe real-life baricitinib plasma exposure in critically ill COVID-19 patients.

## METHODS

We performed a retrospective observational study in patients treated in a polyvalent intensive care unit (ICU) in western France. Critically ill COVID-19 patients, as assessed by a SARS-CoV 2 positive retro-transcription polymerase chain reaction (RT-PCR), admitted between October 2021 and May 2022 were eligible. Only those who received baricitinib as a COVID-19 therapeutic and for whom blood concentration measurements were performed were included. Patients were informed of the study and were offered the option of declining to participate. However, as we performed a retrospective analysis of previously collected data, written informed consent was not required. The study protocol received approval from the local Ethics Committee (n° 22-137).

The therapeutic COVID-19 protocol consisted of 6 to 12 mg/day of dexamethasone (depending on inflammatory parameters) for 10 days following admission, and baricitinib was prescribed after a collegial discussion between critical care and infectious disease physicians. In this case, 4 mg of baricitinib was administered daily for 14 days, orally or in the gastric tube for intubated patients. Other medications included 3<sup>rd</sup> generation cephalosporin in case of suspicion of co-infection, proton pump inhibitor when clinically indicated and respiratory organ support with facial mask, high flow nasal cannula or tracheal intubation when indicated.

Baricitinib plasma concentrations were measured at trough (C0), 1 hour (C1) and when possible, 3 hours (C3) after the drug intake. After centrifugation (10 min, 2000 g, 10°C) of heparinized blood samples, the plasma samples were sent (frozen) to the Rennes University Hospital pharmacology laboratory for analysis. Concentrations were measured using a validated liquid-chromatography tandem mass spectrometry method (LC-MS/MS) adapted from [7]. Briefly, 100 µL of plasma were mixed with 300 µL of precipitant solution (acetonitrile-zinc sulphate in water (0.05 M), 1:1 v/v) and 100 µL of internal standard diluted in acetonitrile ( $H^8$  deuterated imatinib). Samples were vortexed for 1 min and centrifuged for 5 min at 3000g 4°C. A volume of 5µL of the supernatant was injected in a LC-MS/MS system composed of an Acquity UPLC-H-Class and a Xevo TQ-XS (Waters, Milford, USA). The quantification range was 0.5 to 100 ng/mL. When three concentration time-points were available between two administrations, AUC was estimated using non-compartmental pharmacokinetic analysis (PK Solver). Non-parametric descriptive statistics (median, range) were used to describe the data, and the Mann Whitney test was used to compare groups.

## RESULTS

During the study period, 56 patients were admitted for COVID-19 confirmed by RT-PCR. Of these, 12 received baricitinib but for organizational reasons, only 7 had drug concentrations measurements. The baseline characteristics, co-medication, and outcomes are reported in Table 1. The median age was 65 years [range 63-72], the median SAPS II was 44 [range 38-48], the median PaO<sub>2</sub>/FiO<sub>2</sub> ratio was 172 mmHg [range 160-190]; 3 patients were mechanically ventilated and the others had high flow nasal cannula support. The median body mass index (BMI) was 28.6 kg/m<sup>2</sup> [28.1-33.9] and the median glomerular filtration rate (GFR) was 108 mL/min [105-127] (Cockcroft formula). None of the patients died. Baricitinib blood measurements were performed at steady state after a median of 3 days [2-3] of treatment.

The median baricitinib plasma concentrations were 2.2 ng/mL [1.4-8.0], 24.0 ng/mL [4.9-37.3] and 14.1 ng/mL [8.3-15.1] for the trough (C0), C1 and C3 concentrations, respectively. High inter-patient variability was observed especially for C0 and C1 (coefficient of variation of 62.5% and 47.7% respectively) (Figure 1). Overall exposure between two administrations could be estimated by calculating the AUCs for 4 patients. The median AUC<sub>0-24h</sub> was 188.8 ng.h/mL [141.3-236.3]. Overall, 2 patients who received baricitinib had liver function test perturbation that eventually led to baricitinib cessation. Both had baricitinib trough concentrations higher than the median and appeared to have atypical pharmacokinetic profiles with similar C1 and C3 concentrations, although no difference in plasma concentrations was observed between patients with or without liver cytolysis (p=0.32 for C0 and 0.19 for C1) (Table 1). Liver function tests subsequently corrected without other implications for patient management. The only patient with altered renal function (GFR of 74 mL/min) had the highest baricitinib trough concentration (Table 1).

## DISCUSSION

Baricitinib is approved for chronic inflammatory disease such as rheumatoid arthritis, alopecia areata and atopic dermatitis, and PK data are available for rheumatology indications. Since the pandemic, baricitinib has been approved to treat severe forms of COVID-19, however, no real life PK data are available in the case of acute inflammation such as COVID-19. While the pandemic situation is currently improving, the drug still helpful in case of severe forms that still exist in vulnerable patients that are at high risk of PK variability [8].

To the best of our knowledge, this is the first description of baricitinib plasma exposure in critically ill COVID-19 patients. All patients received the same drug dosage (4 mg daily) that is the usual dosage used in the context of rheumatology indications. However, baricitinib PK may be different in critically ill COVID-19 patients. In our cohort, we observed high interpatient variability in C0, C1 and C3 plasma concentrations and to a lesser extent in AUC<sub>0-24h</sub>. Median C1, trough concentrations and AUC, were lower than values observed in rheumatoid arthritis (RA) patients (i.e. 6.9 ng/mL, 53.4 ng/mL, 477.6 ng.h/mL for C0, C<sub>max</sub>, and AUC<sub>0-24h</sub> respectively in RA [6]). This may be explained by a higher

distribution volume in critically ill patients (e.g. due to vascular filling) and to the high median BMI of our patient population. However, the small size of our cohort does not allow verifying this hypothesis and no association was found between BMI and exposure. Influence of body weight on baricitinib PK was suggested by Kim et al. in pediatrics. They reported that weight and renal function significantly influenced volume of distribution and clearance, and that higher body weight was associated with lower exposure, which is consistent with our hypothesis [4]. In healthy volunteers, C<sub>max</sub> and AUC lower than in RA were reported suggesting an impact of chronic but not acute inflammation (COVID-19) on the exposure [9,10]. The only patient of our cohort with significant renal failure had the highest trough concentration which is consistent with a lower clearance and the elimination pathway of the drug.

Interestingly, PK of ruxolitinib, which is also a JAK1/2 inhibitor, is well described in hematological patients. Noteworthy, ruxolitinib exposure is highly increased in patients with renal or hepatic impairment or when co-administrated with CYP3A4 inhibitors [11,12]. In opposition to baricitinib, this treatment failed to demonstrate mortality reduction in mechanically ventilated COVID-19 patients [13]. Comparative PK studies of baricitinib and ruxolitinib in a critical-care setting would be of interest. Contrary to ruxolitinib, baricitinib is not extensively metabolized by the liver, so less exposure variability due to liver impairment or CYP450-mediated drug-drug interactions is expected. Nevertheless, our data suggest that PK variability and atypical PK profiles still occur with baricitinib and that one drug dosage is unlikely to fit all patients.

The main limitation of our study is the small number of patients for whom the AUC could be calculated due to the small number of sampling time-points available for each patient. In addition, the non-compartmental method used to estimate AUC could overestimate the actual value due to lack of concentration time points in the terminal elimination phase of the PK profile. Moreover, no population PK modeling was available in this population as an alternative to estimate the patients' individual PK parameters. The size of our cohort did not allow assessing accurately the exposure/effect relationship of baricitinib in critically ill COVID-19 patients but despite relatively low plasma concentrations, all patient had positive evolution of the disease. Further studies are needed to determine whether a threshold of plasma exposure is associated with clinical outcomes in COVID-19 and whether therapeutic drug monitoring of baricitinib could contribute to optimize the drug response.

## CONCLUSION

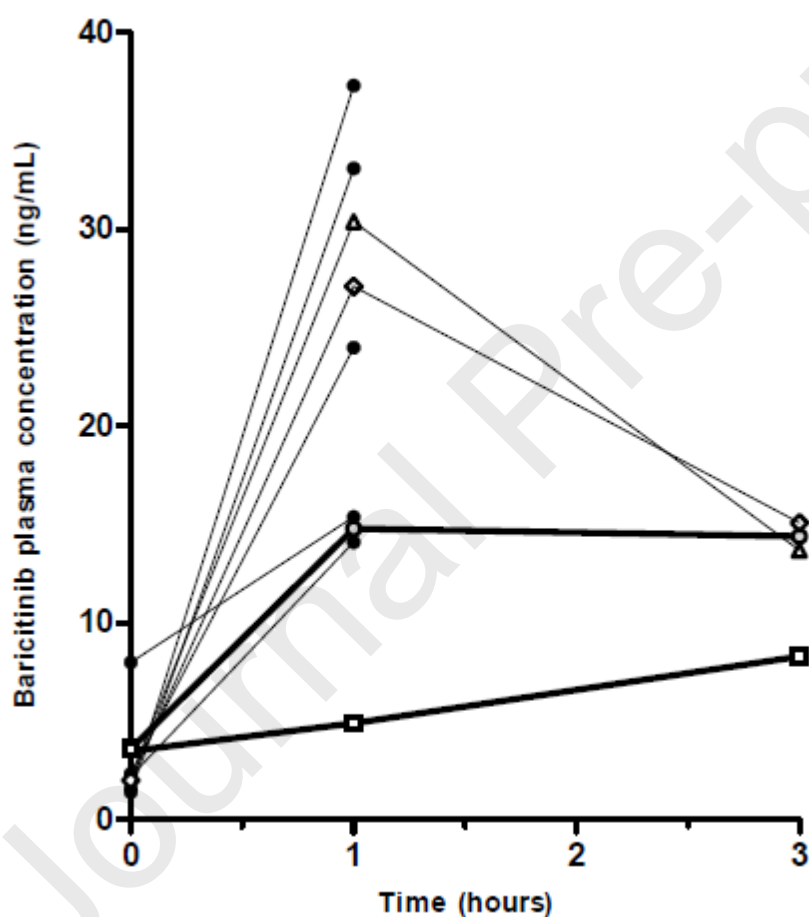
In conclusion, we observed a high inter-patient PK variability as well as relatively low trough concentrations and AUCs of baricitinib in critically ill COVID-19 patients. Further concentration-controlled studies of baricitinib in the critical care setting should be performed to decipher the exposure-effect relationship in the COVID-19 indication.

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**Figure** : Plasma concentrations of baricitinib in critically ill COVID-19 patients (n=7). The four patients with three baricitinib concentrations available are displayed with empty forms. Patients with delayed Tmax are displayed in bold lines.

## Pharmacokinetics of baricitinib in critically ill COVID-19 patients

**Running title:** Baricitinib pharmacokinetics in COVID-19

Nicolas MASSART, M.D.<sup>a</sup>, Pierre FILLATRE, M.D.<sup>a</sup>, Florian LEMAITRE PharmD, PhD.<sup>b</sup>, Arnaud MARI, M.D.<sup>a</sup>, Camille TRON, PharmD, PhD.<sup>b</sup>

<sup>a</sup> Service de Réanimation, CH de St Brieuc, 10, rue Marcel Proust 22000 Saint-Brieuc, France.

<sup>b</sup> Laboratoire de Pharmacologie, CHU de rennes, 2, rue Henri le Guilloux 35000 rennes, France.

- This study provides original data on baricitinib plasma concentrations observed in critically ill patients with COVID-19
- High inter-patient variability of baricitinib plasma exposure was observed
- The results of this observational study incite to further investigate the use of therapeutic drug monitoring to optimize the drug response

Table. Patients characteristics and baricitinib measurements

| Pa<br>tie<br>nt | Sam<br>pl<br>e<br>n° | Days<br>betw<br>een<br>admi<br>ssion<br>and<br>1st<br>admi<br>nistr<br>ation | Days<br>since<br>1 <sup>st</sup><br>admi<br>nistr<br>ation | A<br>ge<br>(y<br>ea<br>rs) | He<br>igh<br>t<br>(m<br>)<br><br>/w<br>eigh<br>t<br>(Kg<br>) | B<br>MI<br>(k<br>g/<br>m <sup>2</sup><br>) | SA<br>II<br>PS<br>at<br>ad<br>mis<br>sion | SO<br>FA<br>sco<br>re<br>at<br>ad<br>mis<br>sion | Pa<br>O <sub>2</sub> /<br>FIO <sub>2</sub> | Me<br>cha<br>nica<br>l<br>ven<br>tilat<br>ion | Glo<br>mer<br>ular<br>filtra<br>tion<br>(mL<br>/mi<br>n –<br>Coc<br>kroft<br>For<br>mula) | Bilir<br>ubin<br>emia<br>(μM<br>/L) | AS<br>T/<br>AL<br>T<br>(IU<br>/L) | Albu<br>min<br>emia<br>(g/L) | Dexa<br>meth<br>asone<br>daily<br>dose<br>(mg) | Co-<br>medicatio<br>ns     | Baricitinib<br>plasma<br>concentratio<br>n<br>(ng/mL) | Liver<br>pert<br>urba<br>tions | Le<br>ng<br>th<br>of<br>IC<br>U<br>stay<br><br>(d<br>ay<br>s) |    |
|-----------------|----------------------|--|--|----------------------------|--|--|---|--|--|---|---|-------------------------------------|-----------------------------------|------------------------------|--|----------------------------|---|--------------------------------|---|----|
|                 |                      |  |  |                            |  |  |   |  |  |   |   |                                     |                                   |                              |  |                            | H<br>0  | H<br>1                         | H<br>3  |    |
| A               | 1                    | 8  | 2  | 65                         | 1.8<br>/9<br>1   | 28   | 38  | 3  | 110  | No  | 127   | 7                                   | 37<br>/3<br>5                     | 42                           | 12   | No                         | 1<br>3<br>4<br>1                                      | -                              | -   |    |
| A               | 2                    | 8  | 7  | -                          | -  | -  | -   | -  | -  | -   | -   | -                                   | -                                 | -                            | -  | -                          | 2<br>7<br>1   | 2<br>5<br>1                    | No  | 14 |
| B               | 1                    | 10   | 3  | 72                         | 1.7<br>2/<br>71  | 23   | 55  | 5  | 190  | Yes   | 89  | 12                                  | 13<br>7/<br>38                    |                              | 12   | Ronaprev<br>e<br>/Atorvast | 1<br>3<br>7<br>6                                      | -                              | -   |    |



