Use of Janus kinase inhibitors in COVID-19: a prospective observational series in 522 individuals

Janus kinase (JAK) inhibitors for the treatment of hospitalised patients with COVID-19 have been extensively studied. Initially, at the start of the pandemic outside of China, baricitinib was shown using artificial intelligence to have a potential dual anti-cytokine and antiviral effect, computer predictions that were then supported by mechanistic data.[1–3] This included kinase assays demonstrating inhibition of host numb-associated kinases, notably AP-2-associated protein kinase 1 (AAK1) and cyclin G-associated kinase (GAK), responsible for activating protein-1 (AP-1)-mediated viral propagation and super-resolution microscopy which showed inhibition of SARS-CoV-2 entry into primary human liver spheroids.[4] Based on double-blind randomised data from the Adaptive COVID-19 Treatment Trial-II (ACTT-II) under the National Institutes of Allergy and Infectious Diseases,[5] it received an Emergency Use Authorisation from the United States Food and Drug Administration in November 2020, in combination with remdesevir for the treatment of hospitalised individuals with COVID-19.

We implemented an institutional review board approved multicentre observational cohort study in four hospitals in Moscow, Russia, to both administer and collect clinical data on individuals treated with this class of drug. Data were prospectively obtained, focusing on the primary outcome of death. Secondary variables include duration of hospitalisation, severity of COVID-19 at admission, severity of pneumonia at imaging (CT0–CT4), requirement for mechanical ventilation, intensive care unit admission, thrombotic events, pulmonary emboli and secondary infectious complications. A total of 522 individuals between May and September 2020 were treated with either baricitinib or tofactinib, orally for 7–14 days. All the patients were hospitalised COVID-19 cases. Individuals with rheumatic or inflammatory bowel disease treated with JAK inhibitors were excluded.

All patients hospitalised from May to September 2020 were analysed for the purposes of the study. In those individuals treated with tofacitinib (n=320: 10 mg n=44; 20 mg n=276), 293 patients (91.6%) recovered, and 27 (8.4%) died. The mortality rate was 2.4% in patients younger than 65 years (5/210 patients) and 20% in patients of 65 years and older (22/110 patients), as shown in table 1. In those who received baricitinib (n=202: 4 mg n=52, 8 mg n=150), 193 patients (95.5%) recovered, and 9 (4.5%) died. The mortality rate measured 2.1% in patients younger than 65 years (3/146) and 10.7% in patients of 65 years and older (6/56) (table 2). With regards to imbalance in dexamethasone treatment, we may suppose that baricitinib was administered to patients with less severe disease (98% mild and moderate) than tofacitinib (84%). No tests was applied to evaluate the statistical significance of difference for 'COVID-19 severity' and 'lung involvement' because to compare baricitinib and tofacitinib treatments was not the objective of the study.

Table 1 Clinical outcomes in patients with COVID-19 treated with tofacitinib

	All cases	<65 years old	≥65 years old
Population			
Number of patents, n (%)	320 (100)	210 (66)	110 (34)
Female, %	50	46	57
Mean age (range), years	59 (22–96)	52 (22–64)	74 (65–96)
Mean treatment duration (range), days	7 (1–18)	6 (1–17)	7 (1–18)
Dexamethasone, %	30.0	30.0	30.0
Disease (on admission)			
Clinical severity, %			
Mild	4.7	3.8	6.4
Moderate	79.7	83.3	72.7
Severe	15.0	11.9	20.9
Critical	0.6	1.0	0.0
Lung involvement, %			
CT 0	0.0	0.0	0.0
CT 1	10.9	10.0	12.7
CT 2	65.0	68.6	58.2
CT 3	22.8	20.0	28.2
CT 4	1.3	1.4	0.9
C reactive protein: clinically significant abnormality, %	73	74	71
Outcomes			
Death, n (%)	27 (8.4)	5 (2.4)	22 (20.0)
Mean days from hospitalisation till death (range), days	13 (4–60)	17 (9–34)	12 (0–33)
ICU admission, n (%)	65 (20)	28 (13)	37 (34)
Mean stay in ICU (range), days	7 (1–28)	7 (1–28)	7 (1–24)
Mechanical ventilation, n (%)	28 (8.8)	11 (5.2)	17 (15.5)
Mean duration of mechanical vent. (range), days	5 (1–26)	9 (1–26)	3 (1–6)
Safety			
Thromboses, n (%)	7 (2.2)	2 (1.0)	5 (4.6)
Pulmonary embolism, n (%)	3 (0.9)	0 (0.0)	3 (2.7)
Infectious complications, n (%)	22 (6.9)	9 (4.3)	13 (11.8)

ICU, intensive care unit.

In general, we observed that JAK inhibitors were well tolerated with a low rate of complications. Clot risk during infection with SARS-CoV-2 is well described and mechanisms include activation of platelet-associated genes.[4] Concerns regarding a prothrombotic tendency based on these data and previous studies[5] appear unfounded in the context of SARS-CoV-2 infection, despite some concerns from previous trials in rheumatoid arthritis; real-world data outside the setting of COVID-19 have not suggested an increased clot incidence.[6] As these data are not randomised and lack a comparator arm, we cannot draw conclusions regarding the efficacy of these drugs, but their oral use, lack of drug–drug interactions, short half-life with excretion via the renal system largely unchanged and dosing flexibility supports the use of these medicines in resource constrained or out-patient settings. As recently highlighted,[7] drugs such as baricitinib appear to fulfil an unmet clinical need in the treatment of

Table 2 Clinical outcomes in COVID-19 patients treated with baricitinib

	All cases	<65 years old	≥65 years old
Population			
Number of patents	202	146	56
Female, %	48	47	52
Mean age (range), years	58 (25–92)	52 (25–64)	75 (65–92)
Mean treatment duration (range), days	6 (1–35)	6 (1–11)	7 (1–35)
Dexamethasone, %	7.4	7.5	7.1
Disease (on admission)			
Clinical severity, %			
Mild	3.0	3.4	1.8
Moderate	95.0	95.2	94.6
Severe	2.0	1.4	3.6
Critical	0	1.0	0
Lung involvement, %			
CT 0	0	0	0
CT 1	8.0	7.5	19.0
CT 2	71.2	68.5	78.5
CT 3	20.8	24.0	12.5
CT 4	0	0	0
C reactive protein: clinically significant abnormality, %	95	92	100
Outcomes			
Death, n (%)	9 (4.5)	3 (2.1)	6 (10.7)
Mean from hospitalisation till death (range), days	12 (2–32)	14 (2–32)	12 (5–20)
ICU admission, n (%)	19 (9.4)	10 (6.9)	9 (16.1)
Mean stay in ICU (range), days	7 (1–30)	9 (1–30)	5 (1–13)
Mechanical ventilation, n (%)	8 (4.0)	4 (2.8)	4 (7.1)
Mean duration of mechanical vent. (range), days	7 (2–22)	9 (3–22)	6 (2–13)
Safety			
Thromboses, n (%)	1 (0.5)	0 (0)	1 (1.8)
Pulmonary embolism, n (%)	1 (0.5)	0 (0)	1 (1.8)
Infectious complications, n (%)	7 (3.5)	4 (2.8)	3 (5.4)

ICU, intensive care unit.

COVID-19 pneumonia. Ongoing studies such as ACTT-IV will help delineate its role versus dexamethasone.

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Supplementary materials
The use of Janus kinase inhibitors in COVID-19: a prospective observational series in 522 individuals

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Methods

Study design and participants. Multicentre observational study performed at four clinical hospitals, Moscow, Russian Federation (City Hospital №4; City Hospital №24; City Hospital №50; City Hospital №52) from May to September 2020. The data from original patient healthcare records were collected after death or discharge. Due to pandemic, both on and off-label drug administration was permitted by the Russian Ministry of Health. [1]

Enrolment criteria: i) adults above 18 year old able to consent; ii) diagnosed and hospitalised with COVID-19; iii) treated for COVID-19 according to respective hospital specific and national COVID-19 guidelines; iv) received at least one dose of tofactinib or baricitinib

COVID-19 was diagnosed as per a standard positive SARS-CoV-2 RNA test. [2]

Procedures. All patients received standard of care treatment in the settings of routine medical practice in accordance with Russian official guidelines for management of patients with COVID-19. [2]

Variables and outcomes. General information was taken including socio-demographic and laboratory parameters. Severity of lung impairment was assessed by CT at the day of hospitalization. Each of the five lung lobes was assessed for degree of parenchymal involvement and classified as none CT0 (0%), mild CT1 (1%–25%), moderate CT2 (26%–50%), severe CT3 (51%–75%), or critical CT4 (76%–100%). [2,3]

Laboratory. C-reactive protein, leucocytes, thrombocytes, lymphocytes, fibrinogen in blood were measured at hospitalization.

Safety. All safety events were collected.

Analyses. Descriptive statistics was used for data presentation. No comparative analysis was performed for this study.

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