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ARTICLE

Immunotherapy

JAK-inhibitors for coronavirus disease-2019 (COVID-19): a meta-analysis

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Abstract

We analyzed reports on safety and efficacy of *JAK*-inhibitors in patients with coronavirus infectious disease-2019 (COVID-19) published between January 1st and March 6th 2021 using the Newcastle-Ottawa and Jadad scales for quality assessment. We used disease severity as a proxy for time when *JAK*-inhibitor therapy was started. We identified 6 cohort studies and 5 clinical trials involving 2367 subjects treated with ruxolitinib ($N = 3$) or baricitinib 45 ($N = 8$). Use of *JAK*-inhibitors decreased use of invasive mechanical ventilation (RR = 0.63; [95% Confidence Interval (CI), 0.47, 0.84]; $P = 0.002$) and had borderline impact on rates of intensive care unit (ICU) admission (RR = 0.24 [0.06, 1.02]; $P = 0.05$) and acute respiratory distress syndrome (ARDS; RR = 0.50 [0.19, 1.33]; $P = 0.16$). *JAK*-inhibitors did not decrease length of hospitalization (mean difference (MD) –0.18 [–4.54, 4.18]; $P = 0.94$). Relative risks of death for both drugs were 0.42 [0.30, 0.59] ($P < 0.001$), for ruxolitinib, RR = 0.33 (0.13, 0.88; $P = 0.03$) and for baricitinib RR = 0.44 (0.31, 0.63; $P < 0.001$). Timing of *JAK*-inhibitor treatment during the course of COVID-19 treatment may be important in determining impact on outcome. However, these data are not consistently reported.

Introduction

Infection with severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2) causes coronavirus disease-2019 (COVID-19), an important feature of which is dysregulated immune responses resulting in so-called cytokine release syndrome (CRS). There are several reports of using *JAK*-inhibitors in persons with COVID-19 [1–3]. These data are from small uncontrolled, non-randomized, open-label trials which mostly conclude *JAK*-inhibitors are safe and effective. However, with appropriate controls these conclusions are unconvincing. We analyzed 11 studies of safety and efficacy of ruxolitinib and baricitinib in persons with COVID-19. We found these drugs decreased the use of invasive mechanical ventilation, had borderline effects on rates of intensive care unit (ICU) admission and acute respiratory distress syndrome (ARDS) and did not decrease interval of hospitalization. The risk of death was decreased, most convincingly for baricitinib.

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Methods

Search strategy and selection criteria

We conducted a systematic review and meta-analysis focused on effects of *JAK*-inhibitors on diverse outcomes in persons with SARS-CoV-2-infection and/or COVID-19. We searched on PubMed, Web of Science and Medline with search terms using the Boolean operators including *coronavirus* OR *COVID-19* OR *2019-nCoV* OR *SARS-CoV-2* AND *ruxolitinib* OR *baricitinib* OR *Janus kinase* OR *JAK*. Inclusion dates were 1st January 2020 to 6th March 2021. Two investigators independently reviewed the identified abstracts and selected articles for full reviewing. Discordances were resolved by a 3rd reviewer. Review Manager 5.4 was used for the meta-analysis and modified Newcastle-Ottawa scale (NOS) and Jadad scale for quality assessment. Our focus was on clinically relevant outcomes including rates of ICU admission, ARDS and invasive mechanical ventilation, interval of hospital stay, and death. We also considered relevant laboratory co-variates including blood C-reactive protein (CRP) procalcitonin concentrations, pulse oxygen saturation (SP_{O2}) and $Pa_{O2}/Fi_{O2.}$

We identified 823 articles excluding 516 duplicates. Next, we identified 96 relevant articles by reviewing the title and abstract. After further review 11 studies were included in the meta-analysis [1–11] (Supplementary Fig. 1).

Inclusion and exclusion criteria

We included all English language clinical trials and observational dataset of *JAK*-inhibitors used singly or with other therapies in persons with COVID-19. We excluded reviews and case reports. Studies had to report outcomes including data of survival, ICU admission, or invasive mechanical ventilation.

Data extraction

Two authors independently reviewed identified abstracts and selected articles for full review and a third reviewer resolved discordances. For each selected article we extracted baseline and study co-variates including 1st author, publication year, country, number subjects, subject co-variates, and therapy details (Table 1, Supplementary Table 1). Outcomes measures included rates of ICU admission, ARDS and use of invasive mechanical ventilation, interval of hospitalization, and survival. We used anonymized, published data without a need of Ethics Committee approval.

Risk of bias assessment

The risk of bias was assessed according to the Jadad scale in the domains of random sequence generation, allocation concealment, blinding of participants and personnel, and completed withdrawals and dropouts. The methodological quality of retrospective studies was assessed by the modified NOS consisting of subject selection, comparability of the study groups, and assessment of outcome. A score of 0–9 was allocated to each observational study. Studies with ≥6 score were judged high quality.

Statistical analyses

We pooled data and used relative risks (RRs) and confidence intervals (CIs) to describe dichotomized outcomes including rates of ICU admission and ARDS, use of invasive mechanical ventilation, and death. We used mean difference (MD) and 95% CIs for continuous outcomes including interval of hospitalization, blood CRP and procalcitonin concentrations, $SP_{O2,}$ and Pa_{O2}/Fi_{O2}. A fixed-effect model was used if there the heterogeneity test statistic between studies was $I^2 \leq 50\%$ and a random-effects model was used if I^2 statistic was >50%. Funnel plots were used to screen for publication bias. Statistical analyses were carried out with Review Manager 5.4 (The Cochrane Collaboration).

Results

We included 6 observational studies and 5 clinical trials comprising 2367 subjects [1–11]. Studies were conducted in Italy [1, 2, 4, 6, 8, 9], China [5], USA [7], UK [11], and Spain [3, 10]. NOS scores of the observational studies ranged from 7 to 9. Jadad scales of the clinical trials were 1, 1, 1, 7, and 7.

Surrogate outcomes

To test the impact of *JAK*-inhibitors on ICU admission, we included 5 studies of 706 subjects [2–4, 8, 10]. RR of ICU admissions = 0.24 (95% CI, 0.06, 1.02; $P = 0.05$; $I^2 = 65\%$; Fig. 1A). To test the impact of *JAK*-inhibitors on the rate of ARDS, we included 2 studies of 93 subjects [1, 6]. RR = 0.50 (0.19, 1.33; $P = 0.16$; $I^2 = 0\%$; Fig. 1B). To test the impact of *JAK*-inhibitors on the rate of invasive mechanical ventilation, we included 5 studies of 1604 subjects [3, 5, 7, 8, 11]. RR = 0.63 (0.47, 0.84; $P = 0.002$; $I^2 = 0$). RRs for $Pa_{O2}/Fi_{O2} < 300$ mmHg and any Pa_{O2}/Fi_{O2} based on the study protocols were RR = 0.50 (0.26, 0.95, $P = 0.03$;

Table 1 Studies included.

Ref.	Study-type	Jadad scale/NOS scale	Drug	Deaths
1	Observational	NOS scale: 9	Baricitinib	1/20 vs. 25/56
2	Clinical trial	Jadad scale: 1	Baricitinib	NE
3	Observational	NOS scale: 7	Baricitinib	5/117 vs. 11/270
4	Observational	NOS scale: 9	Baricitinib	0/113 vs. 5/78
7	RCT	Jadad scale: 7	Baricitinib	24/515 vs. 37/518
9	Observational	NOS scale: 7	Baricitinib	5/40 vs. 65/275
10	Observational	NOS scale: 8	Baricitinib	2/12 vs. 6/17
11	Observational	NOS scale:7	Baricitinib	1/37 vs. 47/142
5	RCT	Jadad scale: 7	Ruxolitinib	0/20 vs. 3/21
6	Clinical trial	Jadad scale: 1	Ruxolitinib	1/7 vs. 1/10
8	Clinical trial	Jadad scale: 1	Ruxolitinib	3/32 vs. 13/43

RCT randomized controlled trial, *NOS* Newcastle-Ottawa scale.

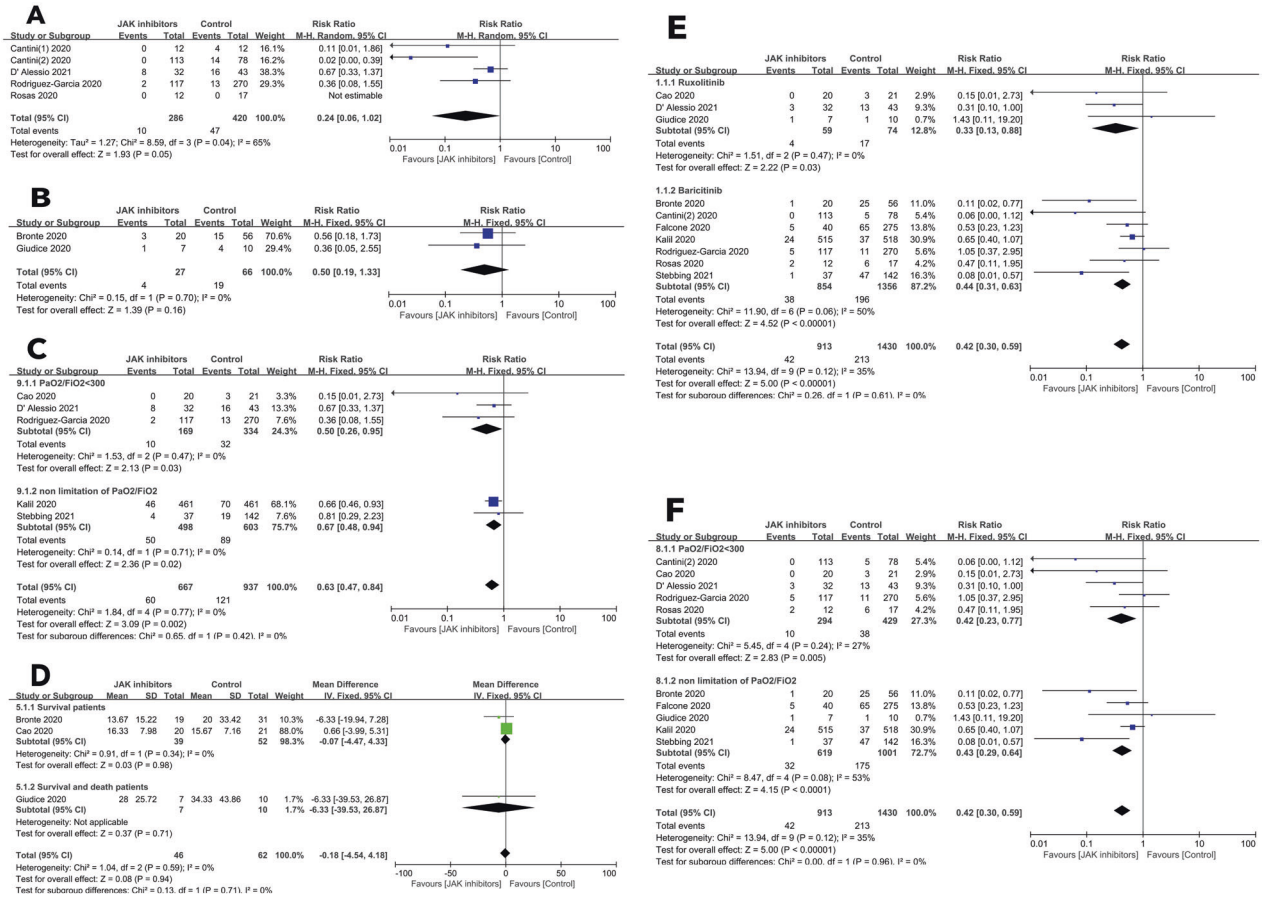

Fig. 1 The effect of *JAK*-inhibitors on COVID-19 related outcomes. Risks of **A** ICU admission; **B** ARDS; **C** invasive mechanical ventilation; **D** interval of hospitalization; **E** risk of death grouped by agents; **F** risk of death grouped by the study protocol.

$I^2 = 0$) and RR = 0.67 (0.48, 0.94, $P = 0.02$; $I^2 = 0$; Fig. 1C). To test the impact of *JAK*-inhibitors on hospitalization interval, we included 3 studies of 108 subjects [1, 5, 6]. MD was −0.18 (−4.54, 4.18, $P = 0.94$; $I^2 = 0$). In subjects discharged from hospital, MD was −0.07 (−4.47, 4.33; $P = 0.98$; $I^2 = 0$; Fig. 1D).

Survival

To test the impact of *JAK*-inhibitors on survival we included 10 studies of 2343 subjects [1, 3–11]. RR in a fixed-effects model = 0.42 (0.30, 0.59; $P < 0.001$; $I^2 = 35\%$). RRs for ruxolitinib and baricitinib were RR = 0.33, (0.13, 0.88;

$P = 0.03$; $I^2 = 0\%$) and RR = 0.44 (0.31, 0.63; $P < 0.001$; $I^2 = 50\%$; Fig. 1E). RRs for survival for $Pa_{O2}/Fi_{O2} < 300$ mmHg and any Pa_{O2}/Fi_{O2} based on the study protocol were RR = 0.42 (0.23, 0.77, $P = 0.005$; $I^2 = 27$) and RR = 0.43 (0.29, 0.64, $P < 0.001$; $I^2 = 53$; Fig. 1F).

Secondary endpoints

To test the impact of *JAK*-inhibitors on CRP concentration we used 4 studies of 293 subjects [1, 2, 4, 10]. MD was −25 (−49, −1; $P < 0.001$; $I^2 = 96\%$). To test the impacts of *JAK*-inhibitors on procalcitonin concentration, SP_{O2}, and Pa_{O2}/Fi_{O2}, we included 2 studies of 215 subjects [2, 4]. MD = −0.06 (−0.24, 0.12; $P = 0.54$; $I^2 = 0\%$), 2 studies of 215 subjects [2, 4] MD = 5.49 (4.25, 6.72; $P < 0.001$; $I^2 = 0\%$) and 5 studies of 393 subjects [1–4, 6] MD = 81 (15, 147; $P = 0.02$; $I^2 = 86\%$; Supplementary Table 2).

Publication bias

We found no convincing evidence of publication bias in survival studies in subjects receiving or not receiving *JAK-inhibitors* with no study falling outside the 95% CI of the funnel plot (Supplementary Fig. 2).

Discussion

The use of *JAK*-inhibitors in persons with COVID-19 decreased the use of invasive mechanical ventilation and increased survival, most convincingly for baricitinib. Estimates of RRs of surrogate endpoints of ICU admission and ARDS favored a substantial reduction but the 95% CI included 1. Changes in other surrogate co-variates were not significantly altered by *JAK*-inhibitor therapy except Pa_{O2}/Fi_{O2}.

JAK-inhibitors target *JAK1, JAK2, JAK3,* and *TYK2* whose inhibition should downregulate the JAK/STAT signaling pathway decreasing cytokine concentrations and thereby reducing CRS. Given this hypothesis, it's not surprising that CRP concentrations were decreased.

When persons with COVID-19 receive *JAK*-inhibitors may be important in determining safety and efficacy. Some data suggest a start time for *JAK*-inhibitors based on an estimation of inflammation severity. For example, La Roseé et al. based the decision to start *JAK*-inhibitors on a COVID-19 inflammation score [12, 13]. Other data support this suggestion [14, 15]. There were no data on a score or measure of inflammation in the studies we analyzed. As a surrogate, we performed subgroup analyses of disease severity based on Pa_{O2}/Fi_{O2} data. Our data suggest *JAK*-inhibitors may be more effective in subjects with a $Pa_{O2}/Fi_{O2} < 300$ mmHg compared efficacy in all subjects. Because we used a surrogate for inflammation severity this conclusion should be viewed cautiously.

Our study has limitations. First, although there are >2000 subjects in the combined analyses, some co-variate analyses had substantially fewer subjects. Second, some studies we analyzed were observational and subject to selection biases. Third, *JAK*-inhibitor therapy was likely confounded by other interventions. Fourth, there was substantial heterogeneity between studies but no evidence of publication bias. Fifth, one large study gave concurrent remdesivir confounding our evaluation of baricitinib. Lastly, we could not analyze data on diverse blood cytokine concentrations, presumptive target of *JAK*-inhibitors.

In conclusion, we found a potential role for *JAK*-inhibitors in reducing the risk of death in persons with COVID-19. The mechanism(s) underlying this benefit is unknown and when therapy is begun may be important. Because the available dataset was limited and our conclusion should be viewed cautiously.

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Author contributions YL, RPG, and CXC designed study. CXC and JJW searched databases and processed analysis. CXC, JJW, HL, LTY, YL, and RPG drafted the typescript. YL, RPG, CXC, JJW, and LTY revised the final typescript. YL and RPG are responsible for the paper.

Compliance with ethical standards

Conflict of interest RPG is a consultant to BeiGene Ltd, Fusion Pharma LLC, LaJolla NanoMedical Inc., Mingsight Parmaceuticals Inc., and CStone Pharmaceuticals. Advisor: Antegene Biotech LLC, Medical Director: FFF Enterprises Inc. Partner: AZACA Inc. Board of Directors: RakFond Foundation for Cancer Research Support. Scientific Advisory Board, StemRad Ltd. All other authors declare no competing interests.

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