A Systematic Review and Meta-Analysis of the Janus Kinase Inhibitors Safety Profile in Relation to the Risks of Secondary Bacterial Infections

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Introduction

- An overactive inflammatory response to SARS-CoV-2 infection plays a central role in the pathogenesis of acute respiratory distress syndrome (ARDS) and is one of the leading causes of death in COVID-19. As a pathogenetic therapy for ARDS, immunomodulatory drugs are widely used. These agents include glucocorticosteroids, blockers of interleukin-6 (IL6) or IL6 receptors, as well as selective reversible inhibitors of Janus kinase (JAK).

Aim

- Evaluation of the safety of drugs for preventive pathogenetic therapy of a new coronavirus infection COVID-19 with the of Janus kinase inhibitors.

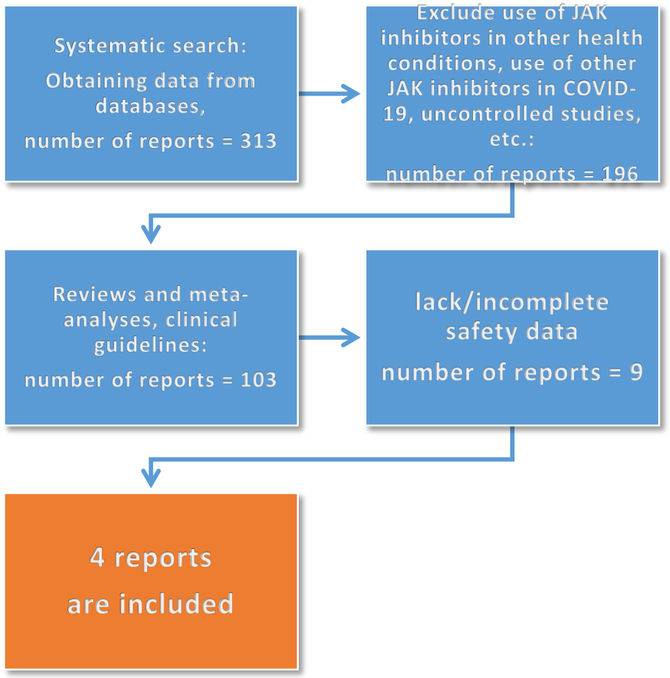
Materials and methods

- A systematic review with a meta-analysis was conducted based on search queries in international databases. Search strategy included queries for controlled studies on the use of baricitinib and tofacitinib recommended for use as a preventive therapy for mild and moderate cases of a new coronavirus infection.

Results

- When assessing the quality of selected studies, adapted questionnaires were used to assess the quality of randomized and non-randomized studies. When conducting a meta-analysis, a relative risk indicator (RR) was used with 95% confidence intervals (CI) to describe dichotomous results. The threshold value of the χ^2-test for assessing the statistical significance of the results was taken equal to 0.1. A fixed effect model was used if the heterogeneity index was $I^2 \leq 40\%$, and a random effects model was used if the heterogeneity index was $I^2 > 40\%$.

Fig. 1. *Algorithm of data search queries in international databases*



Tab.1. Information on the safety reports of JAK inhibitors in the treatment of novel coronavirus infection included in the meta-analysis

Title	Design	Number of patients	Patient population characteristics	Evaluated safety criteria	Serious adverse events, total	MedDRA classification «Infections and infestations»
Baricitinib						
Kalil AC, 2021 ACTT-2 Study	Double-blind, randomized, placebo-controlled study	1033: 515 - baricitinib 4 mg + remdesivir; 518 - placebo + remdesivir	706 – moderate course of the disease, 327 – severe course Age of patients 55.4±15.7 Women – 36.9% BMI – 32.2±8.3 kg/m² Without concomitant pathology – 15.6%, 1 comorbidity – 27.2%, 2 or more comorbidities – 57.2%	AE grades 3 and 4, clinically significant changes in laboratory parameters	Baricitinib + remdesivir: 81 out of 508 Control: 107 out of 509	AE stage 3-4 Baricitinib + remdesivir: 56 out of 508 Control: 81 out of 509
Marconi VC, 2021 COV-BARRIER Study	Double-blind, randomized, placebo-controlled, phase III in parallel groups	1525: 764 - baricitinib 4mg + standard therapy 761 - placebo control + standard therapy	1148 – moderate course of the disease, 370 – severe course. Age of patients 57.6±14.1 Women – 36.9% BMI – 30.4±6.4 (baricitinib group) and 30.6±6.6 (control) 99.7% had at least 1 comorbidity	AE grades 3 and 4, clinically significant changes in laboratory parameters	Baricitinib - 110 out of 750 Control - 135 out of 752	Baricitinib: 64 out of 750 Control: 74 out of 752
García-García JA, 2021	Retrospective cohort study	342 patients: Baricitinib - 125 Anakinra - 217	Age (median) 69.4 Women – 42.4% More than two comorbid diseases – 54.7%	AE grades 3 and 4	No data	Baricitinib: 22 out of 125 Anakinra: 42 out of 217
Tofacitinib						
Guimarães PO, 2021 STOP-COVID Trial	Multicenter, randomized, placebo-controlled, in parallel groups	284 patients: Tofacitinib - 142 Placebo - 142	Age (median) 56±14 years Women – 34.9% BMI – 29.7 (26.7-32.9)	AE grades 3 and 4, clinically significant changes in laboratory parameters	Tofacitinib 20 of 142 Control - 17 out of 142	Tofacitinib: 7 out of 142 Control: 8 out of 142

Data were obtained from three randomized clinical trials. A meta-analysis of the results regarding the total number of serious adverse events (AEs) and adverse events belonging to the class "Infections and infestations" showed statistically significant evidence on the greater safety of baricitinib and tofacitinib in relation to the risks of these events compared with standard therapy: the risk ratio (RR) of serious adverse events in the comparison groups was 0.82 [95%, CI 0.69; 0.96] (p=0.02), the risk ratio of "Infections and invasions" was 0.78 [95% CI 0.63; 0.97] (p=0.03). In both cases RR was in favor of the use of Janus kinase inhibitors.

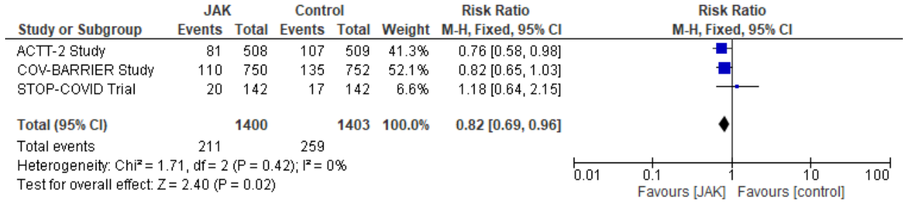


Fig. 2*. Meta-analysis of RCTs on the hazard ratio of serious adverse events outcome*

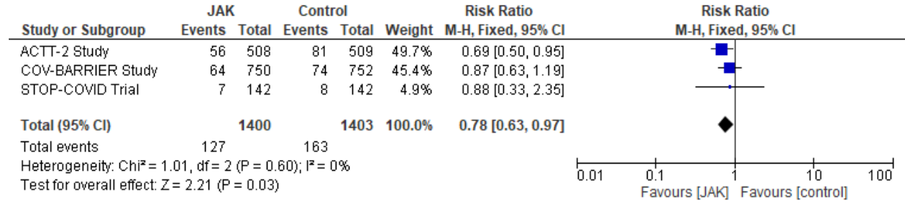


Fig. 3*. Meta-analysis of RCTs on the outcome "Ratio of risks of infections and infestations"*

Conclusion

The results of the meta-analysis demonstrated a favorable safety profile of baricitinib and tofacitinib when used in patients with COVID-19 in relation to the risks of developing serious AEs, as well as infections. Conducting studies of various designs in a wider patient population will allow more accurate assessment of the risks of developing secondary bacterial infections against the background of short-term use of Janus kinase inhibitors as part of their use as a preventive pathogenetic therapy during the COVID-19 pandemic..