A Systematic Review of the Safety of COVID-19 Anti-Interleukin Therapy

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Introduction

- Hypoxic respiratory failure in patients with COVID-19 is associated with signs of systemic inflammation, including the release of pro-inflammatory cytokines such as interleukin (IL)-1, IL-6, and tumor necrosis factor α, as well as higher concentrations of D-dimer, ferritin, and C-reactive protein. It is believed that the immune response plays a key role in the development of an acute inflammatory pneumonia process with diffuse damage to the alveoli, the formation of myeloid cell infiltrates, and microvascular thrombosis. The demonstrated efficacy of glucocorticosteroids in patients with severe COVID-19 suggests that other, more specific immunomodulatory agents may be clinically effective.

Aim

- Assessment of the safety of anti-interleukin drugs used as a part of the COVID-19 pathogenetic therapy in relation to the risks of developing infectious complications.

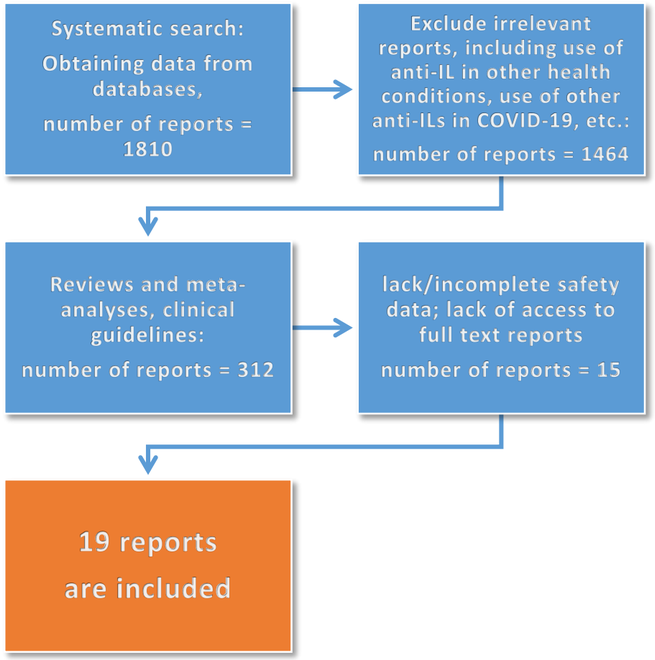
Materials and methods

- A systematic review of publications relating to the safety assessment in terms of the incidence of serious adverse events (AEs), as well as adverse events related to the class "Infections and invasions" of anti-interleukin drugs recommended for use as pathogenetic therapy for COVID-19 was carried out.

Results

- 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



The resulting meta-analysis included 16 randomized clinical trials (9 with IIA evidence level and 7 with IIC evidence level), and 3 non-randomized trials (1 with high risk of bias and 2 with moderate risk of bias).

In order to assess the publication bias, the method of constructing funnel-shaped scatterplots was applied.

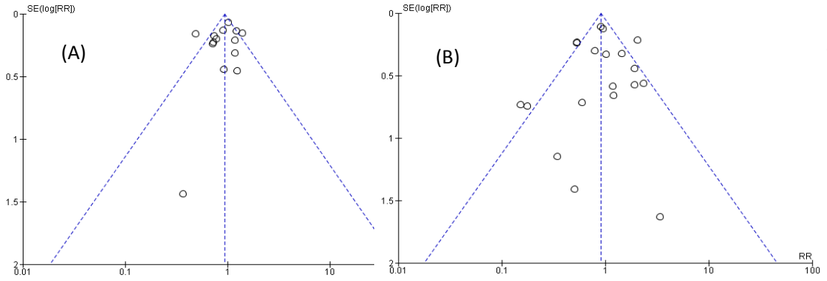


Fig. 2. Funnel-shaped scatter plots for outcomes studied:
(A) RRs of developing SAEs; (B) RRs of developing infections and infestations.

As can be seen from the data in Fig. 2A and 2B a publication bias exists in the results of clinical studies with a small number of patients (asymmetry about the central tendency axis). At the same time, the results of large clinical trials were distributed relatively symmetrically, which indicates the absence of publication bias in the corresponding results. In this regard, it was not possible to unambiguously judge the presence of publication bias among the studies included in the meta-analysis for both outcomes.

The results of the meta-analysis are presented in fig. 3-4.

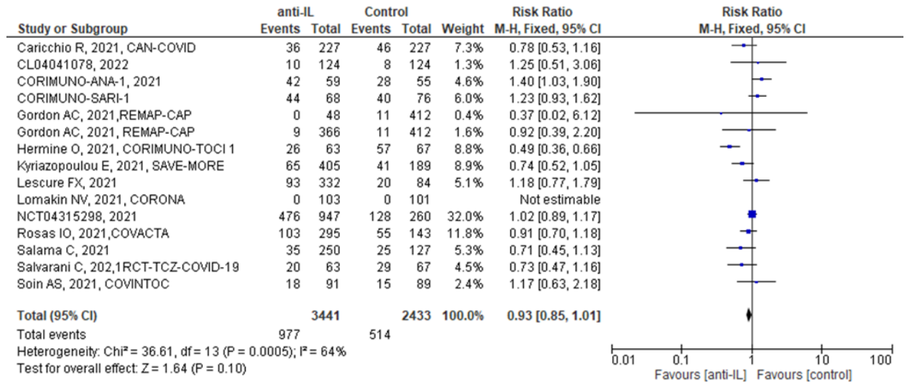


Fig. 3. Meta-analysis of RCTs on the outcome "hazard ratio of serious AEs".

The risk ratio (RR) for developing serious adverse events in the comparison groups was 0.93 [95% CI 0.85; 1.01] (p=0.1), the risk ratio of "Infections and invasions" was 0.9 [95% CI 0.8; 1.02] (p=0.09), which indicated no differences in the frequency of these events between the groups.

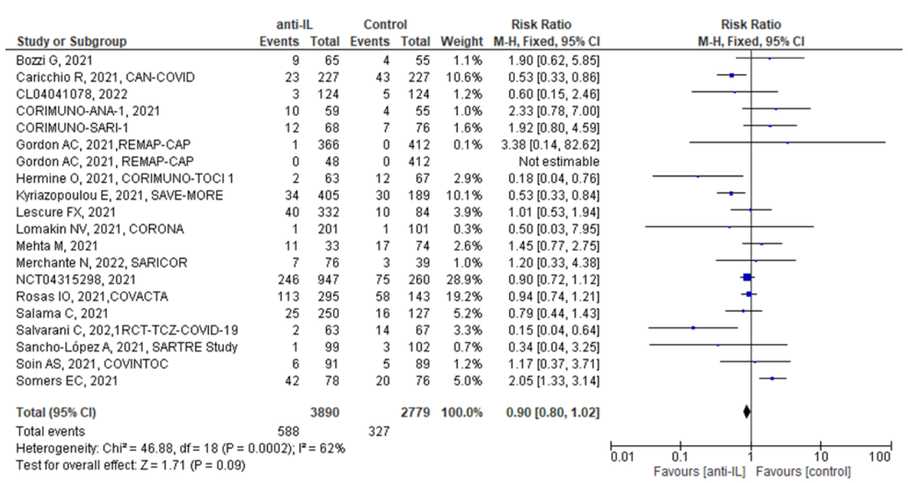


Fig. 4. Meta-analysis of RCTs on the outcome "Ratio of risks of infections and infestations".

Conclusion

A meta-analysis of the results of a systematic review did not show statistically significant differences in the relative risks of developing serious adverse events and adverse events belonging to the class "Infections and infestations" when using anti-interleukin drugs in the treatment of COVID-19. Given the known data on the unsafety of this class of drugs when used in chronic non-communicable diseases in relation to the risks of reactivation of chronic infections, and due to the masking of secondary infectious complications against the background of COVID-19, further epidemiological studies are required to identify and clarify the risks of secondary bacterial infection complications in the COVID-19 patient population.