JAK Antagonists and IL-6 Inhibitors for Management of SARS-CoV-2: A Meta-Analysis of RCTs

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INTRODUCTION

COVID-19 has ravaged the healthcare system since May 2020, and treatments and recommendations for patients are rapidly changing as we understand more about the pathophysiology of the disease. IL-6 inhibitors and JAK antagonists have both recently been used for critically ill COVID-19 patients in an attempt to reduce the severe immune response.

DESCRIPTION

Janus kinase (JAK) antagonists and IL-6 inhibitors are both clinically used to treat Rheumatoid arthritis and other auto-inflammatory conditions [1-2]. IL-6 inhibitors include Siltuximab, Sarilumab, and Tocilizumab. JAK antagonists include Ruxolitinib, Baricitinib, and Tofacitinib.

NEED

Selection between the two drug classes has largely been attributed to local availability and physician comfort. Presently, no randomized controlled trial exists to compare the mortality and progression rates of COVID treatments using JAK Inhibitors and IL-6 inhibitors, specifically in conjunction with corticosteroids and Remdesivir.

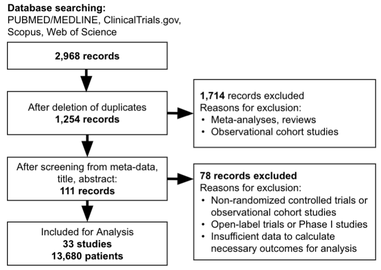
GOAL

This study seeks to provide an indirect-estimate comparing the two drugs of choice in efficacy in managing patients in the hospital using results from recent randomized trials.

METHOD

This study included 33 randomized controlled trials (RCT) evaluating IL-6 inhibitors and JAK-antagonists. The outcomes were 28-day mortality and progression, defined to be advancement of a patient to mechanical ventilation or ECMO. This study also conducted a subgroup analysis investigating concomitant steroid and Remdesivir usage. P-scores were used to hierarchically rank the treatment groups in their class-specific and drug-specific classifications.

PRISMA DIAGRAM



RESULTS

CLASS- SPECIFIC COMPARISONS

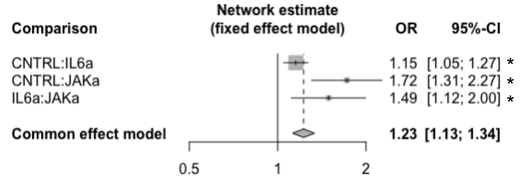


Figure 1: *Aggregate Impact of Drug Choice on 28-Day Mortality. JAKa associated with minimized mortality*

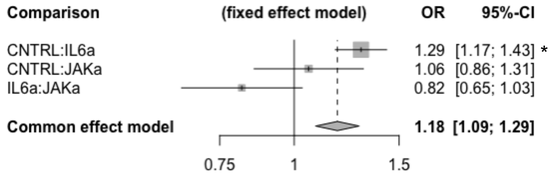


Figure 2: *Aggregate Impact of Drug Choice on 28-Day Progression. IL-6 antagonists reduce mortality (vs control), but JAK-a is not associated with reduction in progression*

DRUG- SPECIFIC COMPARISONS

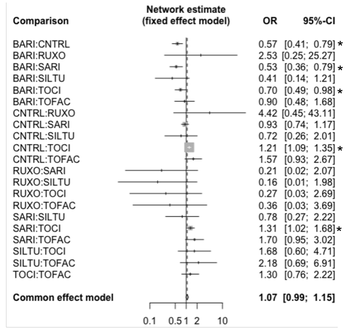


Figure 3: *Baricitinib is the only JAKa to show a significant decrease in mortality compared to control and Tocilizumab is the only IL-6 inhibitor. Baricitinib os associated with a significant 30% reduction in mortality compared to Tocilizumab.*

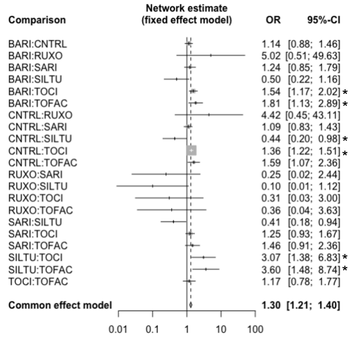


Figure 4: *Only IL-6 inhibitors, Tocilizumab and Siltuximab, showed an improvement in progression when compared to the control. Tocilizumab performed better in regards to progression compared to Siltuximab.*

HIERARCHICAL RANKING

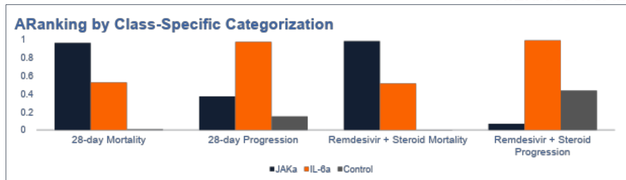


Figure 5: *Ranking between class specific categorization. Graph indicates IL-6a's association with lower 28-day mortality but higher 28-day progression in comparison to control and JAK antagonists.*

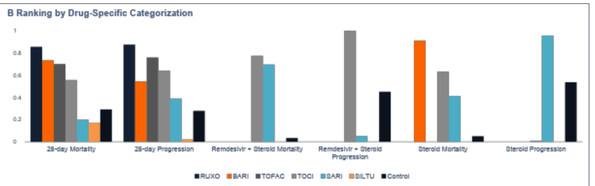


Figure 6: *Ranking between drug specific categorization. Graph indicates TOCI presenting with a consistently high mortality and progression outcome.*

DISCUSSION

This meta-analysis study details the difference between IL-6 inhibitors and JAK antagonists in the treatment of severe COVID-19 cases. Both JAK-a and IL-6 inhibitors decreased mortality but JAKs did so at a greater rate. Similarly, for drug specific comparisons, Baricitinib reduced mortality by the greatest amount. Only IL-6 inhibitors seemed to have a significant effect on preventing progression. Siltuximab and Tocilizumab were both effective against control but Tocilizumab reduced progression the best.

As a secondary goal, a sub-group analysis on concomitant steroid and Remdesivir usage demonstrated that for drug specific comparisons, Baricitinib (JAKa) performed better for reducing mortality and only IL-6 inhibitors decreased progression. Tocilizumab continued to be the most effective in preventing progression This confirmed the findings of the primary aim. However, with Remdesivir and steroids, there was no significant difference between Baricitinib and Tocilizumab in decreasing mortality. This is contrary to the findings without steroids.

Several studies in the field also indicate barticnib, a JAK antagonist, and combination therapy demonstrated 28 day mortality benefit [3-4]. A group in Italy concluded there were no serious side effects for either therapy option for COVID-19 treatment [5].

CONCLUSIONS

We identified 33 RCTs with 13,680 patients that met our selection criteria. We hope to use this data to help clinical decision making between JAK-s and IL-6 inhibitors which are currently being used interchangeably for the management of COVID-19 in hospitalized patients.

Through our study results and analysis, we recommend that Tocilizumab be used to decrease mortality rates and disease progression for the treatment of COVID-19 with concomitant therapy corticosteroids and Remdesivir. Moving forward with this data, we aim to help restructure COVID-19 treatment algorithms regarding IL-6 and JAK antagonists. .

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