BEST DRUG INTERACTION FOR COVID-19 THERAPEUTIC MANAGEMENT: A METANALYSIS

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Data Availability Statement

Data available on request from the authors - The data that support the findings of this study are available from the corresponding author upon reasonable request. Some data may not be made available because of privacy or ethical restrictions.

Author Contribution Statement

Wesley Mota Conceição and Maria Gabriela Daltro Farias performed independently the literature search, designed together the study and the methods, collected the data and described its interpretation, they writed all manuscript, made the figures, and, finally, performed the analyses of bias and discussed the evidences. Maria Belen Arriaga Gutierrez and Mariana Araújo Pereira designed the methods and performed the analyses of the data, they auxiliated in the evidences discussion. Carla Hilário da Cunha Daltro contributed to the orientation of the students and revised the design of the study and the methods, she auxiliated in the evidences discussion and revised the final text. Roberto Barros Silva oriented the group, designed the study and the methods, auxiliated the analysis of the clinical trials and performed the analyses of bias, lastly he redigided and revised the text, and discussed the evidences.

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Conflict of interest statement

The authors declare that there is no conflict of interest.

Abstract

Background and Purpose: The Covid-19 is a viral infection classified as a pandemic by the World Health Organization. There is not currently therapy against the Sars-cov-2. We aimed to assess the best drug therapy approach for the management of Covid-19.

Experimental Approach: We did a systematic review and meta-analysis of randomized controlled trials of drugs used in patients with Covid-19. We performed research in the PubMed and the MedRxiv. The trials were included if the patients were over 12 years old, diagnosed through the rt-PCR test and who assessed as primary outcomes or decreased mortality, or time to clinical improvement, or hospitalization time. Random-effects meta-analysis was used to pool individual studies. Heterogeneity was assessed using I^2. The review has been registered on PROSPERO, number 179879.

Key Results: Nine trials were included for analysis. Remdesivir, mainly early after the onset of symptoms, led to a reduction in mortality (OR, 0·85; 95% CI, 0·05 to 0·98; P=0·045). Although this meta-analysis did not observe a reduction using dexamethasone, the Recovery Trial indicates that it can be an option for a patient that needs oxygen support. Our study did not demonstrate the efficacy of any treatment to minimize the effects of Covid-19 related to large hospital stay or time to clinical improvement.

Conclusion and Implications: Remdesivir is the only drug that can change the course of Covid-19, reducing mortality rates. Despite this result, other studies must evaluate the effectiveness of this and other drugs in the management of Covid-19 mainly studies with robust methods.

Keywords

SARS Coronavirus; Therapeutic Research; Pharmacotherapy

Introduction

The first cases identified in December 2019 in China to Covid-19 (Coronavirus Disease) is a viral pneumonia, potentially fatal, classified as a pandemic by the World Health Organization (WHO), on March 11, 2020, due to its global spread and large number of deaths.[1,2]

The origin and etiologic agent were identified by performing a nasopharyngeal swab by the Chinese Center for Disease Control and Prevention (CCDC), on January 7, 2020.[3] Severe Acute Respiratory Syndrome Coronavirus 2 (Sars-Cov-2), is a single-stranded RNA virus, which promotes severe acute respiratory syndrome, whose main receptor is the angiotensin-converting enzyme 2 (ACE2) and easily transmitted through respiratory droplets.[4–6] The clinical spectrum of Covid-19 can vary from a mild presentation to a critical illness, causing respiratory failure, sepsis and organ dysfunction, especially in the elderly and people with previous comorbidities.[7,8]

Since the identification of the first cases in the Chinese province, it is estimated that the number of infected people worldwide exceeds 52,041,515 and the number of deaths is more than 1,282,000, according to a count calculated on Nov 11 by John Hopkins University.[9]

Despite recent advances, there is no definitive pharmacological treatment protocol for Covid-19. For this reason, this study aims to determine what is the best drug therapy approach for the management of Covid-19.

Methods

Search strategy and selection criteria

We did a systematic review and meta-analysis according to the Preferred Reporting Items for Systematic Reviews and Meta-analyses (PRISMA) recommendations.[10] The study has been registered in the International prospective register of systematic reviews (PROSPERO) under identification number (ID) 179879. Searches were made from May 1, 2020 to June 30, 2020 among articles published from December 1, 2019 to June 30, 2020 in the PubMed database, we opted for a review of pre-prints published on the MedRxiv platform to increase the sample of articles.

The research was carried out using Boolean operators and controlled by the MeSH terms, using words such as “therapeutic”, “drugs”, “pharmacotherapy”, and other words representative of drugs or class of drugs taken as a promise by the scientific community, all of them combined with the word “covid-19”. The filters applied were in relation to the type of study: "Clinical trial", "meta-analysis", and "randomized controlled trial", and publication date: "in the last 12 months". At MedRxiv, the only search strategy employed was “randomized clinical trial Covid-19”.

The inclusion criteria defined were (1) Studies with the design of randomized clinical trials (2) that have evaluated the effectiveness of a pharmacological drug with a therapeutic purpose for Covid-19 (3) published between December 2019 and 30 June 2020 (4) with a study population made up of patients over 12 years of age, diagnosed with the disease caused by the new coronavirus through the rt-PCR molecular test for detection of Sars-Cov-2 (5) that have been published in English, Spanish, French or Portuguese, and (6) who assessed as primary outcomes or decreased mortality, or time for clinical improvement or hospitalization time.

Outcomes

The endpoints selected were decreased of mortality, defined as a decrease in the mortality rate among patients in the intervention group and the control group, days of clinical improvement, defined as the days necessary to an improvement on the ordinal scale for clinical improvement indicated by WHO, and days of hospitalization, that is the number of days of hospitalization.

Selection of works and data extraction

Two authors (MGDF and WMC) independently researched PubMed and MedRxiv using the defined strategies; evaluated the titles and abstracts, applying the inclusion criteria, any divergence between the authors was later verified by the third researcher (RBS). Both authors (MGDF and WMC) also analyzed the reference of articles classified as potentially eligible for inclusion to see if there were articles that met the inclusion criteria. The data were extracted using a form created in the google forms platform and reviewed by two authors (MGDF and WMC) and any discrepancies were reported to the third author (RBS) and discussed by all researchers. The form used to data extraction included the first author and year of publication, place, setting, and design of the study, characteristics of the participants, description of the interventions, and the results of the studies. The general details of the included studies are described in the results. For mortality, we extracted number of patients who had the outcome and denominator, and for continuous outcomes, days to clinical improvement and days of hospitalization, we extracted sample size, and mean or median. To classify the disease we used the

six-point ordinal scale based in the ordinal scale for clinical improvement according to WHO, in the ordinal scale by WHO there were eight categories, however our selected works mostly used an adapted version with six categories, hence we also used the six point ordinal scale.[11] The patients were classified in 1= ambulatory patients without oxygen therapy, 2= hospitalized, no oxygen therapy, 3= hospitalized with oxygen therapy, but without high flow oxygen or non-invasive ventilation, 4= hospitalized with high flow oxygen therapy or non-invasive ventilation, 5= Hospitalized with invasive ventilation, intubation and mechanical ventilation, or ventilation with additional organ support, and 6= death. They also were classified by mild disease (categories 1-3) and severe disease (categories 4-6). To configure clinical improvement, the studies used a cutoff point of two points on the WHO scales or hospital discharge, whichever came first.

Risk of bias

Two authors (MGDF and WMC) independently assessed the risk of bias using the Cochrane collaboration risk of bias tool, which takes account of randomization process, deviations from intended interventions, missing outcome data, measurement of the outcome and selection of the reported result.[12] Each potential source of bias was graded as "yes", "probable yes", "no", "probable no", or "no information" allowing to determine whether studies were considered at high, low, or moderate risk of bias. Disagreement regarding quality assessments was resolved by a third author (RBS).

Data analysis

I^2 measure was used to gauge the degree of heterogeneity. All outcomes were continuous. Summary-level meta-regression was performed using the random-effects model after computation of the SD of Freeman-Tukey double arcsine transformed proportions.

The I^2 statistic was calculated to asses study heterogeneity, where $I^2 \leq 30\%$, 30% - 50%, 50%-75%, and $\geq 75\%$ were considered to indicate low, moderate, substantial, and considerable heterogeneity, respectively. All statistical analyses were performed using R software version 3.4.3 (R Foundation for Statistical Computing, 2018), with the package metaSEM with the method-RMA (random-effects model). P-values less than 0.05 were considered statistically significant. Random-effects meta-regression would be the most flexible of the integrative analytical techniques, because it allows simultaneously to estimate a random effect for differences between groups and allows to parameterize the expected value of the parameter of interest as a function of group-level variables.

Results

Our initial research strategies have captured 74 published articles of which 30 were potentially eligible and it was selected for full text review. In addition, 1775 other works were analyzed by title and abstract (1772 pre-prints and three articles taken from the references of selected works in PubMed), of these 1775 works, 11 were considered potentially eligible (eight pre-prints and three articles referenced by selected works in PubMed). Of the 41 papers selected for text review nine clinical trials met the inclusion criteria (n= 8605; Figure 1).

Most studies with patients hospitalized with Covid-19 showed a predominance of males, with mean ages between 50-70 years. Most patients had comorbidities in the seven studies that presented this data. Six trials presented the clinical evaluation according to the category ordinal scale of WHO (six studies), the moderate disease was predominant, which means that the patients were at baseline hospitalized, but without oxygen therapy, or they were with low flow supplemental oxygen. The follow-up of most studies lasted up to 28 days or until patients were discharged. Only two used a

placebo, most of them opted to make comparisons with a group that obtained standard hospital care. The absence of a control group with use of a placebo affected the quality of our selected studies, four of them were classified as high risk of bias in the risk of bias analysis. In addition to the lack of a placebo, other sources of bias included deviations from the interventions intended by the protocols, and, due to the global emergency of Covid-19, there was an extensive use of emergency medication protocols and this led to data analysis inappropriately, for example three trials did not perform the analysis by intention to treat (Table 1) (Figure 2).

The meta-analysis showed a decrease of mortality when the patients were treated with remdesivir (Odds ratio [OR], 0·85; 95% Confidence interval [CI], 0·05 to 0·98; P=0·045) with a high degree heterogeneity (I^2=77%) (Figure 3).

For the outcome of hospitalization time, our results show that the more there is a comorbidity, the longer it takes to recover (OR, 1·41; 95% CI, 1·11 to 2·20; P=0·032) and that males tend to have a delay in recovering (OR, 1·85; 95% CI, 1·43 to 2·10; P=0·013) with a high degree heterogeneity (I^2=75%) (Figure 4).

Our studies illustrate that the variable time to clinical recovery did not obtain significant results, probably due to the small n sample as seen in Figure 5.

Discussion and Conclusions

Our meta-analysis demonstrated that remdesivir was the only drug able to decrease mortality among patients hospitalized with Covid-19. The remdesivir, a prodrug of the parental adenosine analogue, was initially developed to treat Ebola, and was the first drug approved in the USA and Europe for the Covid-19.[13–16] With wide antiviral activity, it has already shown effectiveness against pneumovirus, paramoxyvirus, filovirus and coronavirus.[17] In vitro, the drug also proved effective in inhibiting the replication of Severe acute respiratory syndrome CoV (SARS-CoV) and Middle East respiratory syndrome CoV (MERS-CoV) in epithelial cells of the human respiratory tract.[18] As a preliminary result of a French study, Pizzorno et al. (2020) demonstrated success in inhibiting replication of (SARS-CoV-2) in human epithelial cells, and a study conducted with Rhesus monkeys infected with the new coranavirus, showed that the use of remdesivir reduced lung infiltrate on radiographs and viral titers in bronchoalveolar lavages.[19,20]

Among the studies carried out in humans affected by Covid-19, a cohort on 3 continents with patients treated with remdesivir (200mg on days 1 and 100mg on days 2 to 10 - intravenous) showed positive results in relation to clinical improvement and mortality.[21] However, Wang et al. showed no statistically significant difference between the group of patients randomized and treated with remdesivir versus placebo.[13]

The preliminary results of another randomized study that was in progress when this review was in the statistical analysis phase, but which was completed in October 2020, conducted by Beigel et al (2020). demonstrated superiority of remdesivir (200mg on days 1 and 100mg on days 2 to 10 - intravenous) over placebo in the outcome of time to clinical improvement.[22] Both Kaplan-Meier's 14-day mortality and the hospitalization time was lower in the remdesivir group compared to the placebo group.[22] Despite this, our meta-regression did not show statistical effect of remdesivir for this outcome. The positive results of the study by Beigel et al. were more accentuated in the group of patients classified as three in the six-point ordinal scale, probably due to the larger sample size of this group of patients, generating shorter confidence intervals to these data.[22]

Despite not being mentioned as a differential due to our meta-regression, dexamethasone is a drug that stands as an important promise in the treatment of patients affected by covid-19, especially those who need oxygen support. The possibility of using corticotherapy in patients affected by Covid-19 was discouraged by the scientific community at the beginning of the pandemic based on the results of using these drugs in previous epidemics caused by other coronaviruses such as MERS-CoV and SARS-CoV.[23] However, The RECOVERY Collaborative Group, from the University of Oxford demonstrated that the use of dexamethasone reduces mortality in patients who need complementary oxygen support. The "Recovery Trial" randomized the participants at a ratio of 2: 1 to the control group with Standard Treatment or intervention group with oral or intravenous dexamethasone at a dose of 6mg once daily for 10 days.[24]

When assessing the outcome of days of hospitalization, our meta-regression showed an increase in days related to males and the presence of comorbidities. In a study by Takahashi et al. (2020) with patients confirmed positive for SARS-CoV-2, higher levels of pro-inflammatory cytokines and chemokines such as IL-8, IL-18 and CCL5 in men have been described, related to the increase of non-classical monocytes.[25] In contrast, a greater T-cell response was found among women, which may explain a greater vulnerability of males to the disease.[25]

Since the beginning of the Covid-19 pandemic, the higher prevalence of comorbidities has been observed in worse prognosis and fatal cases, like hypertension and diabetes.[26] In hypertension, a dysfunction of the renin-aldosterone-angiotensin system (RAAS) occurs and patients often take angiotensin-converting-enzyme inhibitors (ACEis) in their treatment.[27,28] Although the ACE2 is the gateway to Sars-Cov-2 in cells and humans, there is no evidence that this medication reduces the expression of ACE2 in human tissues.[28,29] Hypertension is also associated with impairment of the immune system, which can deregulate cytokines and reduce the body's ability to fight viral infection.[27–30]

In diabetes, the immune system is compromised, which can increase the expression of pro-inflammatory cytokines, which would contribute to the cytokine storm observed in severe cases of Covid-19.[31] It has been reported that diabetes can cause downregulation of ACE2 expression, which could be beneficial, but ACE2 has shown anti-inflammatory activity, and can be protective in pneumonia of infectious etiologies.[32,33] The low expression of ACE2 in diabetic patients can make it difficult to control the infection.

This meta-analysis showed no significant difference in any of the parameters evaluated about the time to clinical improvement. Cao et al. (2020) described the results of using Lopinavir-Ritonavir versus Standard Treatment.[34] This trial points out that patients assigned to lopinavir-ritonavir did not have a time to clinical improvement different from that of patients assigned to standard care alone in the intention-to-treat population.[34] Hung et al. (2020) randomized patients to an intervention group using Lopinavir-Ritonavir, Ribavirin and Interferon beta -1b and in a control group, just using Lopinavir-Ritonavir and the intervention group showed superior performance to the control group in clinical improvement outcomes and length of hospital stay.[35]

The high heterogeneity between the studies was an important limitation for our review, given the global emergence of Covid-19, several study protocols were instituted, and this impacted the statistical analysis. A careful analysis of the risk of bias and Random-effects model were the tools used to minimize this important limitation.

In summary, our study did not demonstrate the efficacy of any treatment to minimize the effects of covid-19 related to large hospital stay or time to clinical improvement among patients hospitalized. For mortality, remdesivir can decrease mortality, according to our analysis, this result suggests that the use to remdesivir, mainly early after admission, protect the patients. It is necessary to evaluate these evidences in others clinical trials.

References

1. Rothan, H. A., & Byrareddy, S. N. (2020). The epidemiology and pathogenesis of coronavirus disease (COVID-19) outbreak. *Journal of Autoimmunity*, *109*(February), 102433. https://doi.org/10.1016/j.jaut.2020.102433
2. Yang, W., Sirajuddin, A., Zhang, X., Liu, G., Teng, Z., Zhao, S., & Lu, M. (2020). The role of imaging in 2019 novel coronavirus pneumonia (COVID-19). *European Radiology*, *30*(9), 4874–4882. https://doi.org/10.1007/s00330-020-06827-4
3. Sohrabi, C., Alsafi, Z., O'Neill, N., Khan, M., Kerwan, A., Al-Jabir, A., Iosifidis, C., & Agha, R. (2020). World Health Organization declares global emergency: A review of the 2019 novel coronavirus (COVID-19). *International Journal of Surgery*, *76*(February), 71–76. https://doi.org/10.1016/j.ijsu.2020.02.034
4. Yan, R., Zhang, Y., Guo, Y., Xia, L., & Zhou, Q. (2020). *Structural basis for the recognition of the 2019-nCoV by human ACE2*. *2762*(March), 1–10. https://doi.org/10.1101/2020.02.19.956946
5. Meselson, M. (2020). Droplets and Aerosols in the Transmission of SARS-CoV-2. *New England Journal of Medicine*, *382*(21), 2063–2063. https://doi.org/10.1056/nejmc2009324
6. Chan, J. F. W., Yuan, S., Kok, K. H., To, K. K. W., Chu, H., Yang, J., Xing, F., Liu, J., Yip, C. C. Y., Poon, R. W. S., Tsoi, H. W., Lo, S. K. F., Chan, K. H., Poon, V. K. M., Chan, W. M., Ip, J. D., Cai, J. P., Cheng, V. C. C., Chen, H., … Yuen, K. Y. (2020). A familial cluster of pneumonia associated with the 2019 novel coronavirus indicating person-to-person transmission: a study of a family cluster. *The Lancet*, *395*(10223), 514–523. https://doi.org/10.1016/S0140-6736(20)30154-9
7. CDC Weekly, C. (2020). The Epidemiological Characteristics of an Outbreak of 2019 Novel Coronavirus Diseases (COVID-19) — China, 2020. *China CDC Weekly*, *2*(8), 113–122. https://doi.org/10.46234/ccdcw2020.032
8. Zhou, F., Yu, T., Du, R., Fan, G., Liu, Y., Liu, Z., Xiang, J., Wang, Y., Song, B., Gu, X., Guan, L., Wei, Y., Li, H., Wu, X., Xu, J., Tu, S., Zhang, Y., Chen, H., & Cao, B. (2020). Clinical course and risk factors for mortality of adult inpatients with COVID-19 in Wuhan, China: a retrospective cohort study. *The Lancet*, *395*(10229), 1054–1062. https://doi.org/10.1016/S0140-6736(20)30566-3
9. Johns Hopkins University & Medicine. (2020). *COVID-19 Map Johns Hopkins Coronavirus Resource Center*. https://coronavirus.jhu.edu/map.html
10. Moher, D., Liberati, A., Tetzlaff, J., Altman, D. G., Altman, D., Antes, G., Atkins, D., Barbour, V., Barrowman, N., Berlin, J. A., Clark, J., Clarke, M., Cook, D., D'Amico, R., Deeks, J. J., Devereaux, P. J., Dickersin, K., Egger, M., Ernst, E., … Tugwell, P. (2009). Preferred reporting items for systematic reviews and meta-analyses: The PRISMA statement. *PLoS Medicine*, *6*(7). https://doi.org/10.1371/journal.pmed.1000097

11. World Health Organization. (2020). WHO R&D Blueprint novel Coronavirus COVID-19 Therapeutic Trial Synopsis. *World Health Organization, February 18, 2020, Geneva, Switzerland*, 1–9. http://www.moh.gov.sa/en/CoronaNew/PressReleases/Pages/default.aspx
12. Higgins, J. P. T., Altman, D. G., Gøtzsche, P. C., Jüni, P., Moher, D., Oxman, A. D., Savović, J., Schulz, K. F., Weeks, L., & Sterne, J. A. C. (2011). The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ (Online)*, *343*(7829), 1–9. https://doi.org/10.1136/bmj.d5928
13. Wang, Y., Zhang, D., Du, G., Du, R., Zhao, J., Jin, Y., Fu, S., Gao, L., Cheng, Z., Lu, Q., Hu, Y., Luo, G., Wang, K., Lu, Y., Li, H., Wang, S., Ruan, S., Yang, C., Mei, C., … Wang, C. (2020). Remdesivir in adults with severe COVID-19: a randomised, double-blind, placebo-controlled, multicentre trial. *The Lancet*, *395*(10236), 1569–1578. https://doi.org/10.1016/S0140-6736(20)31022-9
14. Al-Tawfiq, J. A., Al-Homoud, A. H., & Memish, Z. A. (2020). Remdesivir as a possible therapeutic option for the COVID-19. *Travel Medicine and Infectious Disease*, *34*(February), 101615. https://doi.org/10.1016/j.tmaid.2020.101615
15. Greve, J. E., & Wong, J. C. (2020). Remdesivir: US allows emergency use of experimental drug for coronavirus. *The Guardian.* https://www.theguardian.com/world/2020/may/01/remdesivir-emergency-use-fda-us-coronavirus
16. Roberts, M. (2020). Coronavirus: UK authorises anti-viral drug remdesivir. *BBC News*. https://www.bbc.com/news/health-52805828
17. Lo, M. K., Jordan, R., Arvey, A., Sudhamsu, J., Shrivastava-Ranjan, P., Hotard, A. L., Flint, M., McMullan, L. K., Siegel, D., Clarke, M. O., Mackman, R. L., Hui, H. C., Perron, M., Ray, A. S., Cihlar, T., Nichol, S. T., & Spiropoulou, C. F. (2017). GS-5734 and its parent nucleoside analog inhibit Filo-, Pneumo-, and Paramyxoviruses. *Scientific Reports*, *7*(January), 1–7. https://doi.org/10.1038/srep43395
18. Sheahan, T. P., Sims, A. C., Graham, R. L., Menachery, V. D., Gralinski, L. E., Case, J. B., Leist, S. R., Pyrc, K., Feng, J. Y., Trantcheva, I., Bannister, R., Park, Y., Babusis, D., Clarke, M. O., MacKman, R. L., Spahn, J. E., Palmiotti, C. A., Siegel, D., Ray, A. S., … Baric, R. S. (2017). Broad-spectrum antiviral GS-5734 inhibits both epidemic and zoonotic coronaviruses. *Science Translational Medicine*, *9*(396), 1–11. https://doi.org/10.1126/scitranslmed.aal3653
19. Williamson, B. N., Feldmann, F., Schwarz, B., Meade-White, K., Porter, D. P., Schulz, J., van Doremalen, N., Leighton, I., Yinda, C. K., Pérez-Pérez, L., Okumura, A., Lovaglio, J., Hanley, P. W., Saturday, G., Bosio, C. M., Anzick, S., Barbian, K., Cihlar, T., Martens, C., … de Wit, E. (2020). Clinical benefit of remdesivir in rhesus macaques infected with SARS-CoV-2. *Nature*, *585*(7824), 273–276. https://doi.org/10.1038/s41586-020-2423-5
20. Pizzorno, A., Padey, B., Julien, T., Trouillet-Assant, S., Traversier, A., Errazuriz-Cerda, E., Fouret, J., Dubois, J., Gaymard, A., Lescure, F.-X., Dulière, V., Brun, P., Constant, S., Poissy, J., Lina, B., Yazdanpanah, Y., Terrier, O., & Rosa-Calatrava, M. (2020). Characterization and Treatment of SARS-CoV-2 in Nasal and Bronchial Human Airway Epithelia. *Cell Reports Medicine*, *1*(4), 100059. https://doi.org/10.1016/j.xcrm.2020.100059

21. Grein, J., Ohmagari, N., Shin, D., Diaz, G., Asperges, E., Castagna, A., Feldt, T., Green, G., Green, M. L., Lescure, F.-X., Nicastri, E., Oda, R., Yo, K., Quiros-Roldan, E., Studemeister, A., Redinski, J., Ahmed, S., Bernett, J., Chelliah, D., … Flanigan, T. (2020). Compassionate Use of Remdesivir for Patients with Severe Covid-19. *New England Journal of Medicine*, *382*(24), 2327–2336. https://doi.org/10.1056/nejmoa2007016
22. Beigel, J. H., Tomashek, K. M., Dodd, L. E., Mehta, A. K., Zingman, B. S., Kalil, A. C., Hohmann, E., Chu, H. Y., Luetkemeyer, A., Kline, S., Lopez de Castilla, D., Finberg, R. W., Dierberg, K., Tapson, V., Hsieh, L., Patterson, T. F., Paredes, R., Sweeney, D. A., Short, W. R., … Lane, H. C. (2020). Remdesivir for the Treatment of Covid-19 — Final Report. *New England Journal of Medicine*, 1813–1826. https://doi.org/10.1056/nejmoa2007764
23. Russell, C. D., Millar, J. E., & Baillie, J. K. (2020). Clinical evidence does not support corticosteroid treatment for 2019-nCoV lung injury. *The Lancet*, *395*(10223), 473–475. https://doi.org/10.1016/S0140-6736(20)30317-2
24. The RECOVERY Collaborative Group. (2020). Dexamethasone in Hospitalized Patients with Covid-19 — Preliminary Report. *New England Journal of Medicine*, 1–11. https://doi.org/10.1056/nejmoa2021436
25. Takahashi, T., Ellingson, M. K., Wong, P., Israelow, B., Lucas, C., Klein, J., Silva, J., Mao, T., Oh, J. E., Tokuyama, M., Lu, P., Venkataraman, A., Park, A., Liu, F., Meir, A., Sun, J., Wang, E. Y., Casanovas-Massana, A., Wyllie, A. L., … Iwasaki, A. (2020). Sex differences in immune responses that underlie COVID-19 disease outcomes. *Nature*, *June*. https://doi.org/10.1038/s41586-020-2700-3
26. Gold, M. S., Sehayek, D., Gabrielli, S., Zhang, X., McCusker, C., & Ben-Shoshan, M. (2020). COVID-19 and comorbidities: a systematic review and meta-analysis. *Postgraduate Medicine*, *00*(00), 1–7. https://doi.org/10.1080/00325481.2020.1786964
27. Ferrario, C. M., Jessup, J., Chappell, M. C., Averill, D. B., Brosnihan, K. B., Tallant, E. A., Diz, D. I., & Gallagher, P. E. (2005). Effect of angiotensin-converting enzyme inhibition and angiotensin II receptor blockers on cardiac angiotensin-converting enzyme 2. *Circulation*, *111*(20), 2605–2610. https://doi.org/10.1161/CIRCULATIONAHA.104.510461
28. Danser, A. H. J., Epstein, M., & Batlle, D. (2020). Renin-Angiotensin System Blockers and the COVID-19 Pandemic: At Present There Is No Evidence to Abandon Renin-Angiotensin System Blockers. *Hypertension*, *75*(6), 1382–1385. https://doi.org/10.1161/HYPERTENSIONAHA.120.15082
29. Hoffmann, M., Kleine-Weber, H., Schroeder, S., Krüger, N., Herrler, T., Erichsen, S., Schiergens, T. S., Herrler, G., Wu, N. H., Nitsche, A., Müller, M. A., Drosten, C., & Pöhlmann, S. (2020). SARS-CoV-2 Cell Entry Depends on ACE2 and TMPRSS2 and Is Blocked by a Clinically Proven Protease Inhibitor. *Cell*, *181*(2), 271-280.e8. https://doi.org/10.1016/j.cell.2020.02.052
30. Youn, J. C., Yu, H. T., Lim, B. J., Koh, M. J., Lee, J., Chang, D. Y., Choi, Y. S., Lee, S. H., Kang, S. M., Jang, Y., Yoo, O. J., Shin, E. C., & Park, S. (2013). Immunosenescent CD8+ T clls and C-X-C cemokine receptor type 3 chemokines are increased in human hypertension. *Hypertension*, *62*(1), 126–133. https://doi.org/10.1161/HYPERTENSIONAHA.113.00689

31. Pal, R., & Bhansali, A. (2020). COVID-19, diabetes mellitus and ACE2: The conundrum. *Diabetes Research and Clinical Practice*, *162*, 108132. https://doi.org/10.1016/j.diabres.2020.108132
32. Tikellis, C., & Thomas, M. C. (2012). Angiotensin-converting enzyme 2 (ACE2) is a key modulator of the renin angiotensin system in health and disease. *International Journal of Peptides*, *2012*. https://doi.org/10.1155/2012/256294
33. Zou, Z., Yan, Y., Shu, Y., Gao, R., Sun, Y., Li, X., Ju, X., Liang, Z., Liu, Q., Zhao, Y., Guo, F., Bai, T., Han, Z., Zhu, J., Zhou, H., Huang, F., Li, C., Lu, H., Li, N., … Jiang, C. (2014). Angiotensin-converting enzyme 2 protects from lethal avian influenza A H5N1 infections. *Nature Communications*, *5*(May), 1–7. https://doi.org/10.1038/ncomms4594
34. Cao, B., Wang, Y., Wen, D., Liu, W., Wang, J., Fan, G., Ruan, L., Song, B., Cai, Y., Wei, M., Li, X., Xia, J., Chen, N., Xiang, J., Yu, T., Bai, T., Xie, X., Zhang, L., Li, C., … Wang, C. (2020). A Trial of Lopinavir–Ritonavir in Adults Hospitalized with Severe Covid-19. *New England Journal of Medicine*, *382*(19), 1787–1799. https://doi.org/10.1056/nejmoa2001282
35. Hung, I. F. N., Lung, K. C., Tso, E. Y. K., Liu, R., Chung, T. W. H., Chu, M. Y., Ng, Y. Y., Lo, J., Chan, J., Tam, A. R., Shum, H. P., Chan, V., Wu, A. K. L., Sin, K. M., Leung, W. S., Law, W. L., Lung, D. C., Sin, S., Yeung, P., … Yuen, K. Y. (2020). Triple combination of interferon beta-1b, lopinavir–ritonavir, and ribavirin in the treatment of patients admitted to hospital with COVID-19: an open-label, randomised, phase 2 trial. *The Lancet*, *395*(10238), 1695–1704. https://doi.org/10.1016/S0140-6736(20)31042-4
36. Davoudi-monfared, E., Rahmani, H., Khalili, H., Hajiabdolbaghi, M., & Salehi, M. (2020). A Randomized Clinical Trial of the Efficacy and Safety of Interferon B-1a in Treatment of Severe COVID-19. *Antimicrobial Agents and Chemotherapy*, *64*: 1–14.
37. Lou Y., Liu L., Yao H., Xingjiang, Hu., Su, J., Xu, K., Luo, R. Yang, Xi., He, L., Lu, X., Zhao, Q., Liang, T., Qiu, Y. (2020). Clinical Outcomes and Plasma Concentrations of Baloxavir Marboxil and Favipiravir in Patients : An Exploratory Randomized, Controlled Trial. *MedRxiv*.
38. Chen, Z., Hu, J., Zhang, Z., Jiang, S., Han, S., Yan, D., Zhuang, R., Hu, B., Zhang, Z. (2020). Efficacy of hydroxychloroquine in patients with COVID-19: results of a randomized clinical trial. *MedRxiv*.
39. Goldman, J.D., Marks, K. M., Bruno, R., Montejano, R., Spinner, C. D., Galli, M., Ahn, M. Y., Nahass, R. G., Chen, Y. S., Sengupta, D., Hyland, R. H., Phil, D., Osinusi, A. O., Cao, H., Blair, C., Wei, X., Ph, D., Gaggar, A., Ph, D., Brainard, D. M., … Subramanian, A. (2020). *Remdesivir for 5 or 10 Days in Patients with Severe Covid-19*. 1–11. https://doi.org/10.1056/NEJMoa2015301

Tables

Table 1: Characteristics of included studies

	Intervention	Number of participants, intervention vs control	Age, years (mean or median), intervention vs control	Comorbidity, present (% of patients Intervention vs control)	Illness severity*, (% of participants in the intervention vs control)	Primary outcome	Secondary outcomes	Results
Beigel et al[22], 2020	Remdesivir, intravenously, 200mg, loading dose on day 1, followed by 100mg daily for up to 9 additional days	541 (65% male) vs 521 (64% male)	58 (SD 14) vs 59 (SD 15)	Any comorbidity (82% vs 81%)	Mild disease (57% vs 51%) Severe disease (42% vs 48%) Missing data (1% vs 1%)	Time to recovery†.	Mortality at 14 and 28 day	The time to recovery was lower in the intervention group than control (10 days vs 15 days, RR, 1·29; 95% CI, 1·12-1·49; p<0·001); The mortality in 28 days was 6·7% with remdesivir and 11.9% with placebo (HR, 0·73; 95% CI, 0·52-1·03)
Cao et al[34], 2020	Lopinavir 400mg e ritonavir 100mg, orally, twice daily, for 14 days.	99 (62% male) vs 100 (59% male)	58 (IQR 50-68) vs 58 (IQR 48-68)	Diabetes (10% vs 13%) Cerebrovascular disease (5% vs 8%) Cancer (5% vs 1%)	Mild disease (84% vs 84%) Severe disease (16% vs 16%)	Time to clinical improvement	28-day mortality, duration of hospitalization	Time to clinical improvement were 16 days to both groups (HR, 1·31; 95% CI, 0·95-1·80; p=0·09); mortality was numerically lower in the intervention group than in the control (19·2% vs 25%)
Chen et al[38], 2020	Intervention 1‡: Chloroquine orally, 1000mg on day 1 and 500mg for 9 days; Intervention 2: 200mg, orally, by 10 days	Intervention 1: 18 (39% male) vs Intervention 2: 18 (44% male) vs Control: 12 (58% male)	Intervention 1: 45 (SD 13) vs Intervention 2: 45 (SD 14) vs Control: 51 (SD 15)	Any comorbidity: Intervention 1: 50% vs Intervention 2: 50% vs Control: 58%	No information	Time, in days, to clinical recovery§	Length of hospital stay and 28-day mortality	The chloroquine group achieved shorter time to clinical recovery than the control group (Logrank mantel-cox test, p=0·019)
Davoudi-Monfared et al[36], 2020	12 million international units of interferon β-1a, injected subcutaneously three times weekly for two consecutive weeks	42 (52% male) vs 39 (54% male)	56 (SD 14) vs 59 (SD 14)	Any comorbidity (76% vs 79%)	Mild disease (71% vs 69%) Severe disease (29% vs 31%)	Time to clinical improvement	Mortality at 28-day, length of hospital stay	On day 14, 66·7% vs 43·6% of patients in the IFN group and the control group were discharged, respectively (OR, 2·5; 95% CI, 1·05-6·37). The 28-day overall mortality was

								significantly lower in the IFN than the control group (19% vs 43·6% respectively, p=0·015)
Goldman et al[39], 2020	Intervention 1[¶]: Intravenous remdesivir 200mg on day 1 and 100mg, once daily on day 2-5; Intervention 2: Intravenous remdesivir 200mg on day 1 and 100mg, once daily on day 2-10	Intervention 1: 200 (60% male) vs Intervention 2: 197 (68% male)	Intervention 1: 61 (IQR 50-69) vs Intervention 2: 62 (IQR 50-71)	No information	Mild disease (Intervention 1: 73% vs Intervention 2: 65%); Severe disease (Intervention 1: 27% vs Intervention 2: 35%)	Differences in the clinical status assessed on day 14 by the six-point ordinal scale	Time to clinical improvement	There were no statistically significant differences in outcomes for clinical improvement time, clinical status on day 14, or in mortality between the groups that received the intervention
	Intervention	**Number of participants, intervention vs control**	**Age, years (mean or median), intervention vs control**	**Comorbidity, present (% of patients Intervention vs control)**	**Illness severity*, (% of participants in the intervention vs control)**	**Primary outcome**	Table continues on next page	
Hung et al[35], 2020	14 days of combination of Lopinavir 400mg e ritonavir 100mg, ribavirin 400mg, orally, every 12h, and three doses of 8 million international units of interferon beta-1b on alternative days	86 (52% male) vs 41 (56%male)[‖]	51 (IQR 31-61) vs 52 (IQR 33-62)	Any comorbidity (40% vs 60%)	No information	Time to achieve a negative RT-PCR result for SARS-CoV-2 in a nasopharyngeal swab sample	30-day mortality and length of hospital stay	There was no mortality in this trial. The length of hospital stay was lower in the intervention group than in the control (9 versus 14 days; HR, 2·7; 95% CI, 1·2-6·1)
Lou et al[37], 2020	Intervention 1[**]: baloxavir marboxil 80mg, orally on day 1, 4 and 7; Intervention 2: favipiravir, first dose of 1600mg or 2200mg orally, followed by 600mg, three times a day, the duration of	Intervention 1: 10 (70% male) vs Intervention 2: 9 (77% male) vs Control: 10 (70% male)	Intervention 1: 53 (SD 12) vs Intervention 2: 58 (SD 8) vs Control: 46 (SD 14)	Any comorbidity: Intervention 1: 50% vs Intervention 2: 44% vs Control: 40%	No information	Time to clinical improvement	Mortality at day 14	Time to clinical improvement was similar between groups intervention 1, intervention 2 and control (14, 14 and 15 days, respectively)

	administration was no more than 14 days							
Recovery Collaborative Group[24], 2020	Dexamethasone, orally or intravenously, 6mg once daily for up to 10 days	2104 (64% male) vs 4321 (64% male)	67 (SD 15) vs 66 (SD 15)	Any comorbidity (56% vs 56%)	Mild disease (85% vs 84%) Severe disease (15% vs 16%)	28-day mortality	Length of hospital stay	The mortality was lower in the dexamethasone group than the control group (22·9% and 25·7% respectively; RR, 0·83, 95% CI, 0·75-0.93; p<0·001). The difference is more pronounced in patients who that need receive oxygen therapy
Wang et al[13], 2020	Intravenous remdesivir, 200mg on day 1 followed by 100mg on days 2-10 in single daily infusions	158 (56% male) vs 78 (65% male)	66 (IQR 57-73) vs 64 (IQR 53-70)	Any comorbidity (71% vs 71%)	Mild disease (82% vs 87%) Severe disease (18% vs 13%)	Time to clinical improvement	28-day mortality, duration of hospitalization	The time to clinical improvement were similar between the intervention and control group (21 versus 23 days, respectively; HR, 1·23; 95% CI, 0·87-1·75)

SD=Standard deviation. IQR=Interquartile range. CI=Confidence interval. *According to six-point ordinal scale by WHO. †Time to recovery were defined as the first day on which patients satisfied categories 1 or 2 on the six-point ordinal scale by the WHO. ‡In this trial there were two groups of intervention, the chloroquine group, and the hydroxychloroquine group. §Patients were considered to have achieved clinical recovery when they had met all of the following criteria for at least 48 hours: 1. axillary body temperature ≤36.9°C or oral body temperature ≤37.2°C; 2. complete relief of all symptoms other than cough; 3. cough graded as mild or absent on a patient-reported scale of severe, moderate, mild, absent. ¶This study did not use a control group, they only performed a trial to evaluate the efficacy of remdesivir administrated by 5 or 10 days, in our review we use these data only to perform comparisons between variable related to baseline characteristics, for example gender, age (years) and the presence of comorbidity. ‖ The control group in this trial was patients that received just lopinavir, 400mg and ritonavir,100mg every 12h for 14 days.** This trial presents two groups of intervention, the baloxavir marboxil group and the favipiravir group

Figure Legends

Figure 1: Flowchart of study selection

Figure 2: Analysis of the risk of bias

Figure 3: Metaregression of mortality in patients with COVID-19. I^2 statistic = 77%. Abbreviatures: n1: Cases; n2: Controls.

Figure 4: Metaregression of days of hospitalization in patients with COVID-19. I^2 statistic = 75%. Abbreviatures: n1: Cases; n2: Controls.

Figure 5: Metaregression of time (days) to clinical improvement in patients with COVID-19. I^2 statistic = 81%. Abbreviatures: n1: Cases; n2: Controls.