Clinical outcomes of the drugs repurposed for the treatment of COVID-19

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Abstract

SARS-CoV-2 infections are the most contagious among the three coronavirus infections the world has witnessed till date which have affected almost all parts of the world in millions of population till date since its outbreak in china in Dec. 2019. Moreover, it has severely hit the world economy and therefore there is a dire need to develop the treatment of this deadly disease. Numbers of potential vaccines are in the early or advanced stage of clinical trials. But the development of a vaccine is a very tedious and time consuming task. Therefore, numbers of groups are working on the repurposing of drugs with already known safety and efficacy profile to shorten the time of development of the potential treatment. The main aim of this review article is to summarize the clinical outcomes of the various drugs which have been repurposed for the treatment of COVID-19 associated with SARS-CoV-2.

Keywords: SARS-CoV-2, COVID-19, cytokine storm, non-invasive mechanical ventilation, standard of care

Contents

1. Introduction

Since the beginning of 21st century, world has witnessed three types of deadly coronaviruses which have led to significant number of deaths. The first being severe acute respiratory syndrome (SARS-CoV) which outbreak in 2003 where 8098 cases were reported globally with 774 deaths [1]. Second being middle east respiratory syndrome coronavirus (MERS-CoV) having higher fatality rate than SARS-CoV which was emerged during 2012 with total of 2494 cases and 858 deaths [2]. Third type which is severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) which spread from Wuhan City, China in Dec. 2019 followed by sequencing and isolation in Jan. 2020 [3-4] and is competitively lesser fatal than the previously known SARS-CoV and MERS-CoV but is highly contagious. SARS-CoV and SARS-CoV-2 shares much of the resemblance and has been known to be originated from bats [5]. However, it is believed that transmission of SARS-CoV-2 from bat to humans occurred through raccoon dogs and palm civets [6-7]. Its entry into the host cell is a complex process which is facilitated by the spike (S) glycoprotein on the virus surface [8]. Further, in a similar fashion to SARS-CoV, SARS-CoV-2 also utilizes ACE2 to enter into the host cell and both the viruses bind with ACE2 with similar energies [9]. Studies on clinical characteristics of 1420 patients suggested that headache, loss of smell, cough, nasal obstruction, gustatory dysfunction, rhinorrhea, sore throat and myalgia were the main symptoms of COVID-19 associated with SARS-CoV-2 infections [10].

Since its outbreak in Dec. 2019, total of 37704153 confirmed cases with 1079029 deaths have been reported till date across all part of globe [11]. On 30th Jan. 2020, World Health Organization (WHO) declared COVID-19, a disease associated with SARS-CoV-2, a public health emergency of international concern followed by declaration of this disease as pandemic on 11th March 2020 [12]. Apart from the health crisis, this disease has made the world stand still and has badly affected the world economy in every sector like aviation, oil, stock market,

transport, restaurant, bars, entertainment, manufacturing etc. by decreasing the productivity, slowing down the supply chain due to change in the spending behavior of the consumers [13-17]. Therefore, there is an urgent need for the treatment of this disease as till date no approved treatment is available to stop this outbreak although 2 medications has been approved with emergency use authorization (EUA) from FDA which is remdesivir and other drug used to sedate the patients on ventilator. Many vaccines are at different stages of development for the treatment of COVID-19 [18-25]. But the development of new vaccine is a tedious and time consuming process which includes many steps like exploratory stage, pre-clinical stage, clinical development (which involves Phase I-IV studies), regulatory review and approval, manufacturing and quality control [26]. Normal process of vaccine from idea generation to licensure takes around 15 years which can be reduced to 8-10 years in case of accelerating vaccine development [27]. The fastest efforts till date have been made in case of vaccine development for the treatment of Ebola where time period from Phase I till its approval was 5 years [28]. By considering these facts, there is another group of researchers who are exploring the repurposing the drugs already available in markets for the treatment of SARS-CoV-2 infections. There are many advantages of drug repurposing. For example safety, efficacy profile of the existing drugs have already been studied extensively which helps in gaining the fast approval from regulatory bodies like United States Food and Drug Administration (USFDA) and European Medical Agency (EMA) and therefore it saves time and money. Also, the repurposed drugs get approval in a very shorter time (3-12 years) with 50-60% reduction in the cost of the drug, making it affordable for the patients [29-30]. There are many drugs which have been repurposed for the treatment of COVID-19 and various review articles have been published for the repurposing of existing drugs for the treatment of COVID-19 but either they are not updated till date or cover only a limited number of treatments/ therapies available [31-47]. Moreover, these articles do not give the complete information about the dose regimen, the demographic characteristics of patients, design of the trials etc. The main aim of this review article is to give holistic approach to the clinical outcomes of the current therapies available which will be important to the researchers in move faster for the development of drug candidate.

2. Use of antivirals as a treatment for COVID-19

2.1 Remdesivir

Remdesivir (**1**) is an antiviral drug originally developed for the treatment of Ebola and Marburg viruses. It possesses broad spectrum activity against SARS and MERS *viz.*, SHC014, HKU3, WIV1, HKU5 etc. [48].
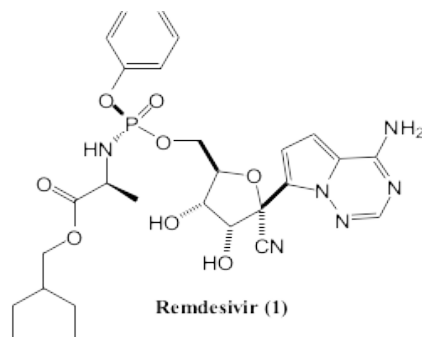
Remdesivir (1)

Beigel *et al.* presented preliminary report for double-blind, randomized, placebo-controlled trial of remdesivir by intravenous administration on 1063 adult patients [49]. The patients were chosen from 60 trial sites and 13 subsites in 10 countries. About 541 patients were assigned remdesivir treatment out of which 49 patients were discontinued from the treatment either because of adverse effects or the patients withdrew the consent whereas 522 patients were given placebo out of which 53 patients were discontinued from the treatment because of the same reasons (**Figure 1**).
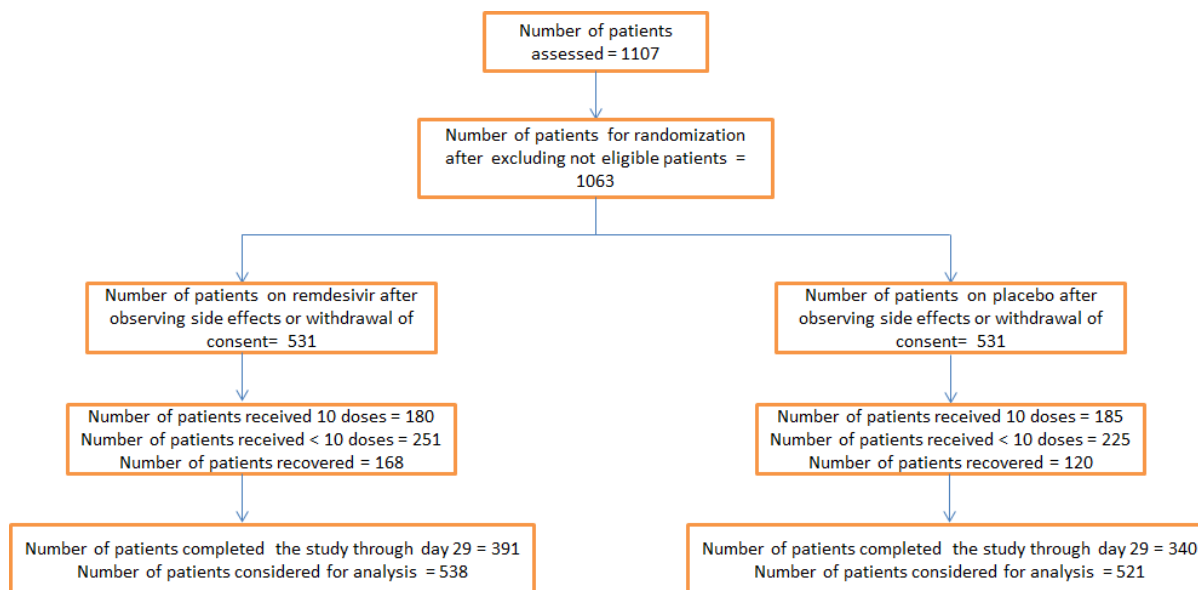

Figure 1: Details of patients under study

The mean age of the enrolled patients was 58.9 years and almost 64% of the enrolled patients were male. The patients were administered 200 mg of remdesivir by intravenous route for day 1 followed by maintenance dose of 100 mg for next 9 days or till the discharge of the patients from the hospital. Placebo administration was also done in the same way and volume. Further, the patients were assessed daily on the fixed parameters from day 1 to day 29. The studies suggested that the patients under remdesivir treatment had better mean recovery rate of 11 days as compared to the patients under placebo treatment with mean recovery rate of 15 days. In addition, the patients underwent randomization during the 10 days of onset of symptoms of COVID-19 and showed higher recovery rate of 1.28 as compared to 1.38 recovery rate for the patient underwent randomization after 10 days of onset of symptoms. The mortality rate of patients after 14 days under remdesivir treatment was found to be lower (7.1%) than that for the patients under placebo treatment (11.9%) (**Figure 2**). In terms of safety, 21.1% of the patients suffered with severe adverse effects in remdesivir group where as 27% of the patients under placebo treatment observed serious adverse events (**Figure 3**).
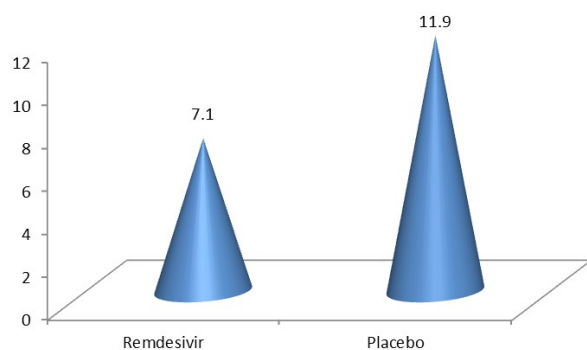
Figure 2: Rate of mortality (% age) after 14 days of administration of remdesivir and placebo
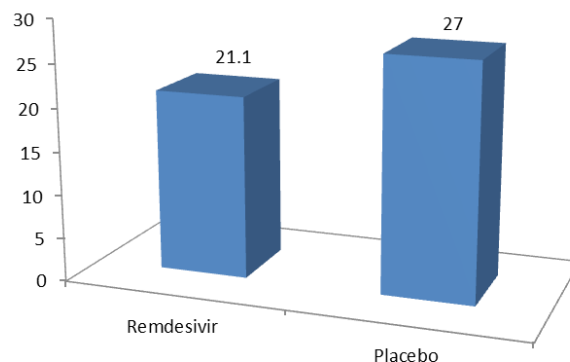
Figure 3: Percentage of patients observed severe adverse effect after administration of remdesivir and placebo

Wang *et al.* have reported randomized, double-blind, placebo-controlled, multicenter clinical trial of remdesivir (**1**) on 237 adult patients of the age of greater than 17 years including men and non-pregnant women across ten hospitals in Wuhan and Hubei in China, having laboratory confirmed COVID-19 infection [50]. The mean age of the patients was 65 years. Out of 237 patients, 158 patients were enrolled for remdesivir treatment (56% men and 44% women)

whereas 79 patients (65% men and 35% women) were observed under placebo conditions (**Figure 4**).
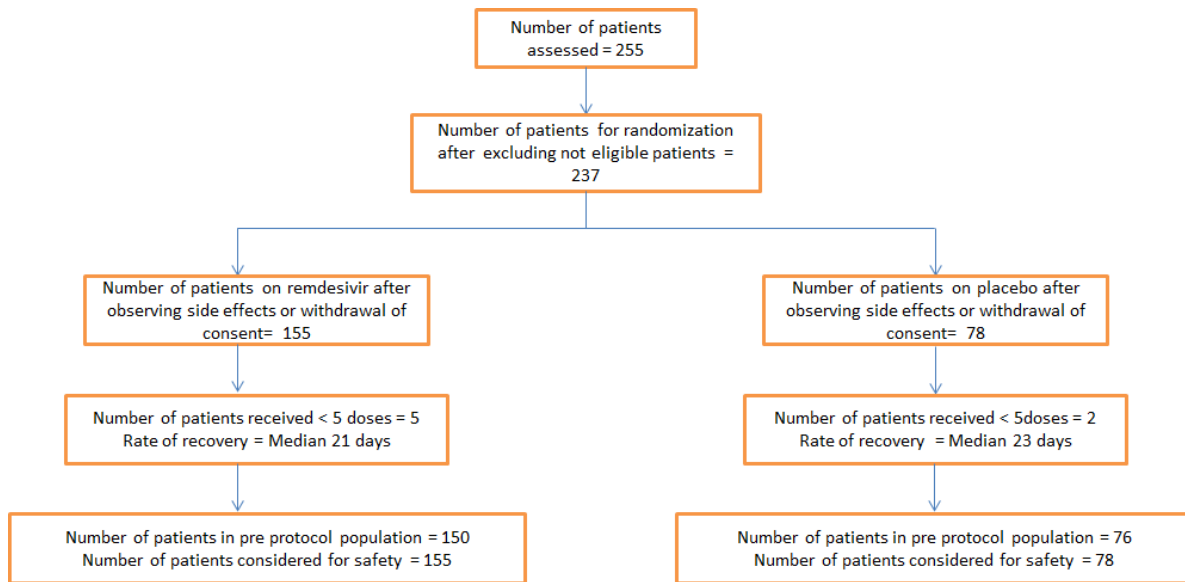
Figure 4: Details of patients under study

Further, patients under remdesivir treatment were administered 200 mg of the intravenous drug for day 1 followed by administration with 100 mg of remdesivir for next 9 days. Infusion at same volume was given to patients treated with placebo for 10 days. In addition, 18% of the patients were also given lopinavir/ritonavir treatment whereas 66% patients received corticosteroids treatment. The patients under the study were tested on the selected parameters for 28 days or till death. Although there was no significant change in the rate of recovery of the patients under remdesivir treatment (median = 21 days) as compared with the placebo group (median = 23 days), the time to clinical improvement was found greater in remdesivir group (18 days) as compared to placebo group (23 days). Moreover, mortality rate after 28 days was found to be similar in remdesivir (14%) and placebo group (13%). Also, the adverse events observed by the patients in remdesivir group (66%) and placebo group (64%) were almost of the same extent (**Table 1**).

Table 1: Clinical outcomes of the patients under remdesivir and placebo treatment

Clinical outcomes	Remdesivir group	Placebo group
Rate of recovery	Median = 21 days	Median = 23 days
Time for clinical improvement (Days)	18	23

Mortality rate (%age)	14	13
Patients observed adverse events (% age)	66	64

2.2 Favipiravir

Favipiravir (**2**) selectively inhibits RNA-dependent RNA polymerase of RNA viruses. In addition to its activity against influenza viruses, it possesses inhibitory action against number of RNA viruses like bunya, filo, arena and flavi causing fevers [51-52]. The genome sequencing of SARS-CoV-2 has disclosed its structure as single stranded RNA β-coronavirus with RNA-dependent RNA polymerase [53]. Therefore, favipiravir could be a possible candidate for the treatment of COVID-19 associated infections.
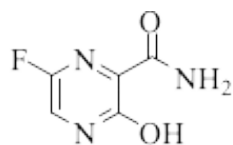
Favipiravir (2)

Cai *et al*. have reported an open label non-randomized control study of favipiravir against COVID-19 as compared to lopinavir/ ritonavir treatment at Third People's Hospital of Shenzhen, China [54]. Patients under favipiravir treatment were of the age between 16-75 years. Patients having chronic liver or kidney diseases were excluded from the study. About 56 confirmed patients of COVID-19 were screened for favipiravir treatment out of which 35 were considered for further studies. On the other hand, 45 patients were chosen from 91 screened patients for lopinavir/ ritonavir (LPV/RTV) treatment (**Figure 5**).
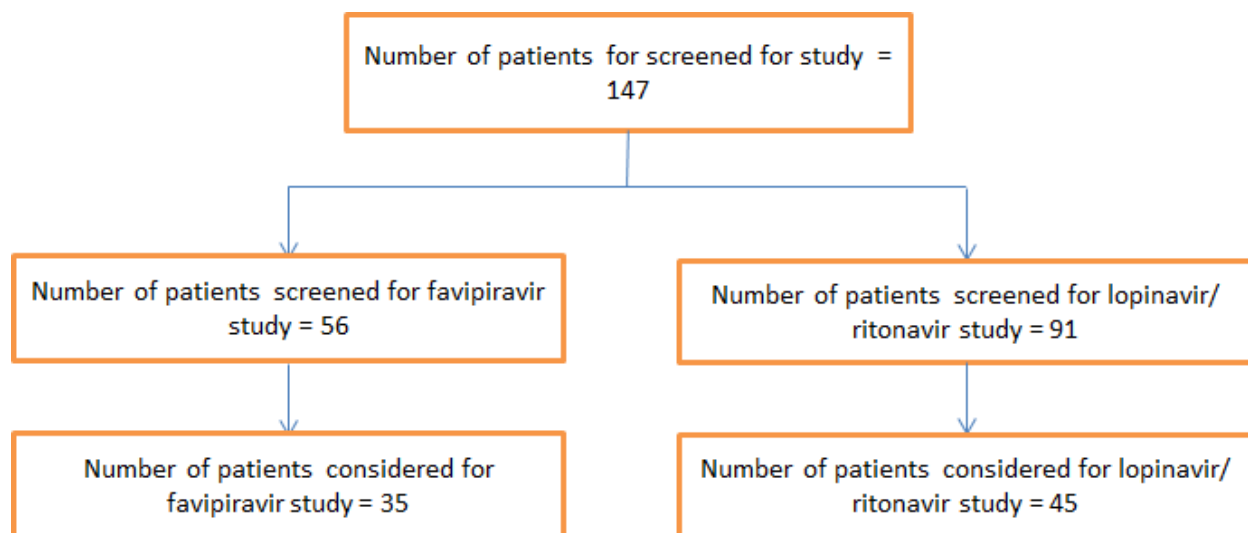
Figure 5: Randomization of patients in favipiravir and lopinavir/ ritonavir treatment

Favipiravir was given to patients at 1600 mg twice daily for day 1 followed by 600 mg daily from day 2 to day 14. On the other hand, the control arm consisted of patients who were given lopinavir/ ritonavir treatment at 400 mg/ 100 mg twice daily. The treatment in both the groups was continued till the viral clearance or till 14 days whichever was earlier. Further, the efficacy study of the given treatment was done by time required for viral clearance and significant improvement in the CT scan. The data suggested that median time of clearance of the viral load in case of favipiravir group was 4 days which was significantly lesser than 11 days in lopinavir/ ritonavir group. In addition, the chest CT scan of the patients after 14 days in favipiravir group showed almost 91% improvement as compared to almost 62% improvement in lopinavir/ ritonavir group. Also, favipiravir was found to be safer than the lopinavir/ ritonavir treatment as shown by the lesser number of adverse events (11% in case of favipiravir versus 55% in case of lopinavir/ ritonavir treatment) (**Figure 6**).
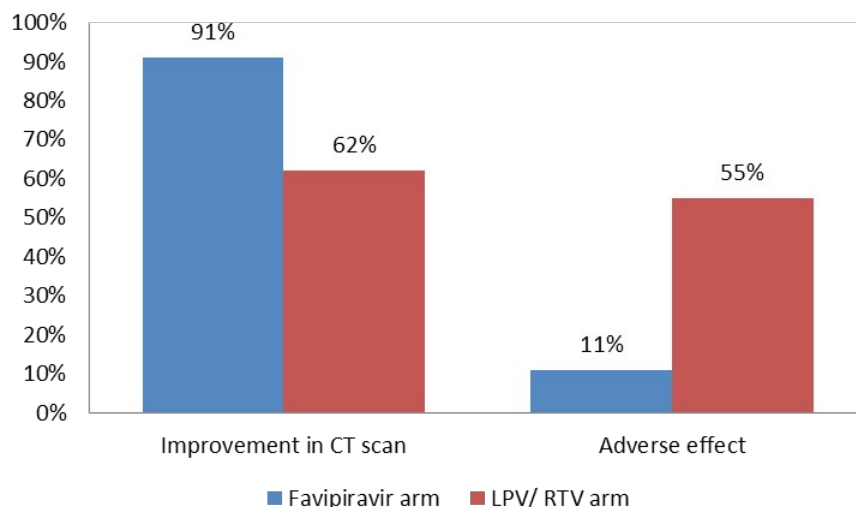
Figure 6: Comparison of clinical outcomes of COVID-19 patients in favipiravir and LPV/ RTV arm

2.3 Oseltamivir

Oseltamivir (**3**) is used for the treatment of influenza infections including influenza A and B [55]. It binds reversibly to neuraminidase thereby preventing it from cleaving the sialic acid residues which are found on the surface of the host cell [56]. This results in prevention of virus into the host cell and reduction in viral load and infections [57].

Oseltamavir (3)
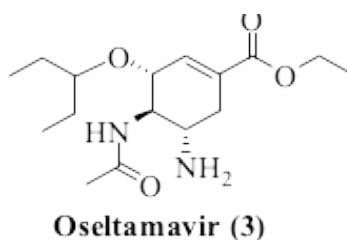
Chiba *et al.* have reported the effect of early oseltamivir treatment on thirteen COVID-19 suspected patients with hypoxia which were the hospital staff members of Sapporo Suzuki Hospital [58]. The suspected patients were adopted peak temperature greater than or equal to 37.5 °C and suffering from one of the respiratory symptoms like cough, sore throat etc. About 21 medical staff and their families were administered in the hospital out of which 7 patients were excluded because of low fever and 1 patient was excluded because of hypoxia. The clinical outcomes were compared for the patients (7, 54%) who were given early treatment of oseltamivir

(within 24 hrs) and for the patients (6, 48%) who were given late treatment (after 24 hrs) (**Figure 7**).
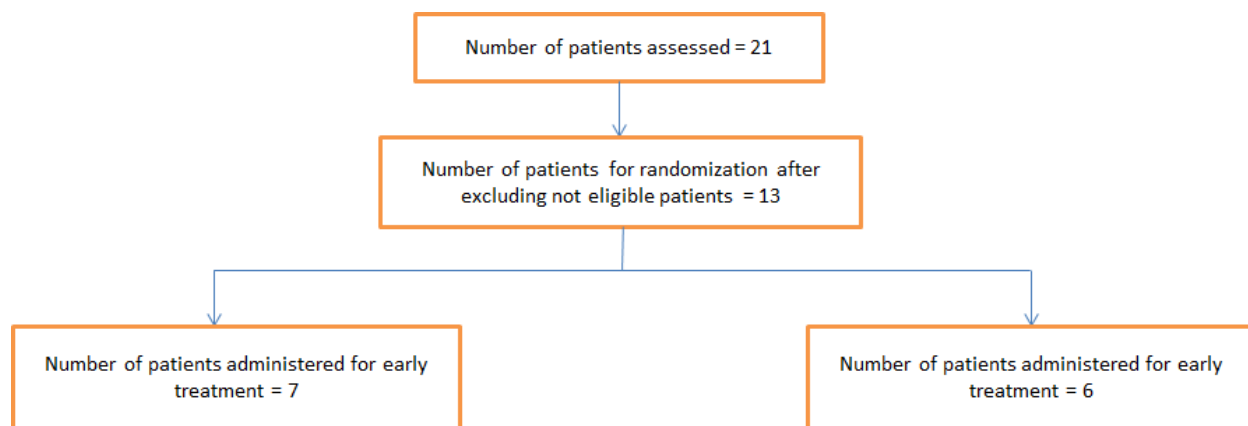
Figure 7: Randomization of COVID-19 patients in early and late treatment group for oseltamivir treatment

Patients were given 75 mg of oseltamivir twice daily for 5 days along with antibacterial agents like 500 mg of levofloxacin for 7 days, 400 mg of garenoxacin for 7 days, 750 mg of amoxicillin/ clavulanic acid for day 1 and 700 mg for next 6 days. The treatment with oseltamivir resulted into lowering down of the temperature to normal value of less than 37 °C within first 24 hrs for 8 (62%) patients and for 11 (85%) patients in 48 hrs. All the patients observed the normalization of temperature after 4 days of oseltamivir treatment. In addition, the patients under early treatment group observed shorter duration of fever than those in late treatment group.

Muralidharan *et al.* have reported the docking study of combination of oseltamivir, lopinavir and ritonavir against SARS-CoV-2 protease to study the synergic effect of these drugs against the virus and have concluded that the binding energies of these three drugs in combination with the SARS-CoV-2 virus is greater than those of individual drugs supporting the fact that these drugs can be used for drug repurposing against COVID-19 using AutoDock 4.2 [59]. The results suggested the binding energies of -4.65 Kcal/mol, -4.1 Kcal/mol and -5.11 Kcal/mol for oseltamivir, lopinavir and ritonavir, respectively. Interestingly, high binding energy of -8.32 Kcal/mol was observed on simultaneously sequential docking study of these three drugs with SARS-CoV-2 protease. In sequential docking studies, it was observed that the formation of salt bridge was the dominant factor in case of oseltamivir whereas π-interactions were observed in

case of ritonavir. Although some deviations were found in case of lopinavir and ritonavir while oseltamivir complex was found to be stable throughout the simulations at 1 Å and did not affect the protein flexibility.

2.4 Chloroquine and hydroxychloroquine

Chloroquine (**4**) and hydroxychloroquine (**5**) have been used extensively against autoimmune diseases since long time. Along with their use as antimalarial drugs, these are also responsible for the inhibition of some cellular functions which may trigger immune activation. In addition, these drugs can inhibit the production of proinflammatory cytokines like IL-1, TNF, IFNα leading to anti-inflammatory responses [60]. Recent studies have also shown that these drugs can interfere with glycosylation of ACE-2 receptor resulting into the prevention of SARS-CoV-2 receptor binding [61].

Chloroquine (4)

Hydroxychloroquine (5)
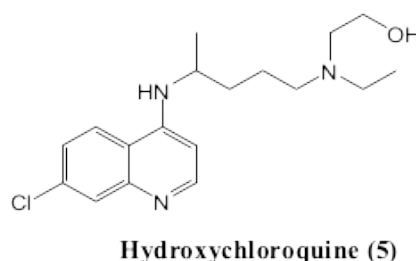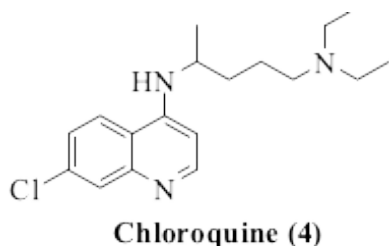
Gao *et al.* have reported the *in vitro* activity of chloroquine against SARS-CoV-2 and found that chloroquine was able to block COVID-19 infections with $EC_{50} = 1.13$ μM and $CC_{50} > 100$ μM [62]. Further, early results of trials on 100 patients lead to conclusion that use of chloroquine is better than the control treatment in treating the pneumonia associated with COVID-19 and reducing the time of viral load in patients. These encouraging results of chloroquine were attributed to its antiviral and anti-inflammatory properties.

Borba *et al.* have reported the use of chloroquine diphosphate as an adjunct therapy to treat the COVID-19 patients with respiratory syndrome in a parallel, double-blinded, randomized, phase IIb clinical trial in Manaus, Brazilian Amazon [63]. Total of 440 patients were enrolled for the trial and 81 patients came across the eligibility criteria. All the patients were of 18 years in age. Further 41 patients were randomized for high dose of chloroquine whereas 40 patents were randomized for low dose of chloroquine. In addition, the older patients of age greater than 75 years were enrolled only in high dose group (**Figure 8**).
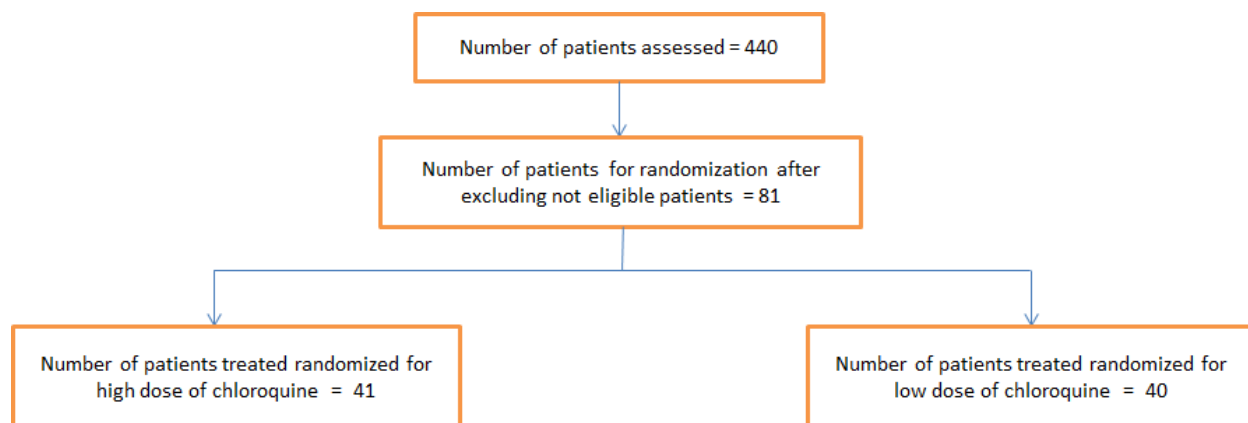
Figure 8: Randomization of COVID-19 patients in high dose and low dose chloroquine group

These patients were given either a dose of 600 mg of chloroquine twice daily for 10 days or 450 mg twice daily for 1 day followed by once daily for next 4 days. The patients were also given azithromycin and ceftriaxone therapy along with hydroxychloroquine treatment. The data suggested that the patients enrolled for high dose of chloroquine witnessed prolonged QTc of the value greater than 500 ms (18.9%). However until day 13, 16 (39%) patients died in high dose chloroquine group as compared to 6 (15%) patients in low dose chloroquine group pointing out the serious concerns about the safety of the drug at the higher concentrations (**Figure 9**). These findings did not support the treatment with high dose of chloroquine because of safety issues.
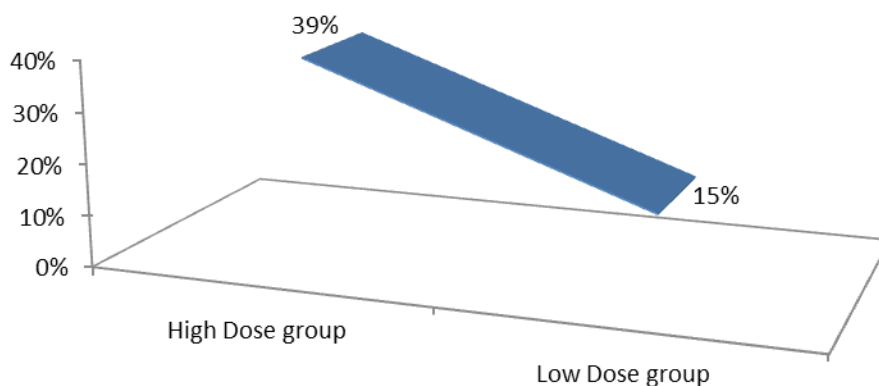
Figure 9: Mortality rate in the high dose and low dose group of COVID-19 patients

Mehra *et al.* have reported the use of either chloroquine or hydroxychloroquine with or without the use of macrolide for the treatment of COVID-19 patients across 671 hospitals in 6 continents [64]. Total of 98,262 patients were assessed for the study out of which 96,032 were

treated further. These screened COVID-19 patients were distributed among chloroquine (CQ group, 1868 patients), chloroquine and macrolide (CQ+ML, 3783 patients), hydroxychloroquine (HCQ, 3016 patients) and hydroxychloroquine and macrolide groups (HCQ+ML, 6221 patients) (**Figure 10**). The mean age of the randomized patients was 53.8 years and 4446 (46.3%) patients were women.
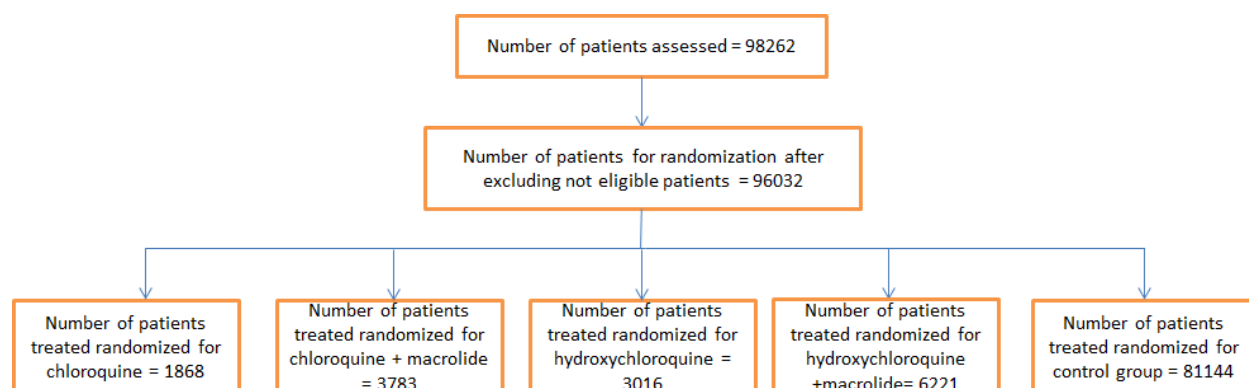
Figure 10: Randomization of COVID-19 patients in different group of treatments

The patients were given chloroquine at a dose of 765 mg (SD 308) and 6·6 days (2·4), chloroquine and macrolide, 790 mg (320) and 6.8 days (2.5), hydroxychloroquine at 596 mg (126) and 4.2 days (1.9) and hydroxychloroquine with macrolide at 597 mg (128) and 4·3 days (2·0). The primary outcome of study was association between the different treatments with the hospital mortality rate whereas the secondary outcomes involved the association of the adverse events with the different treatment groups. The study suggested that old and obese men were the major patients among the non-survivor group and majority of patients among this group had history of diabetes, heart failure, coronary artery disease, smoking etc. Ventricular arrhythmias were more prevalent in treatment groups as compared to control group. The mortality rate was found higher in all the treatment groups as compared to control group (9.3%). Within the different treatment groups, mortality rate was found higher in HCQ+ML group (23.8%) followed by CQ+ML group (22.2%) , HCQ group (18%) and was minimum in CQ group (16.4%) (**Figure 11**). These finding suggested no beneficial effects of early use of hydroxychloroquine or chloroquine either used in combination or absence of macrolides in patients of clinical outcomes.
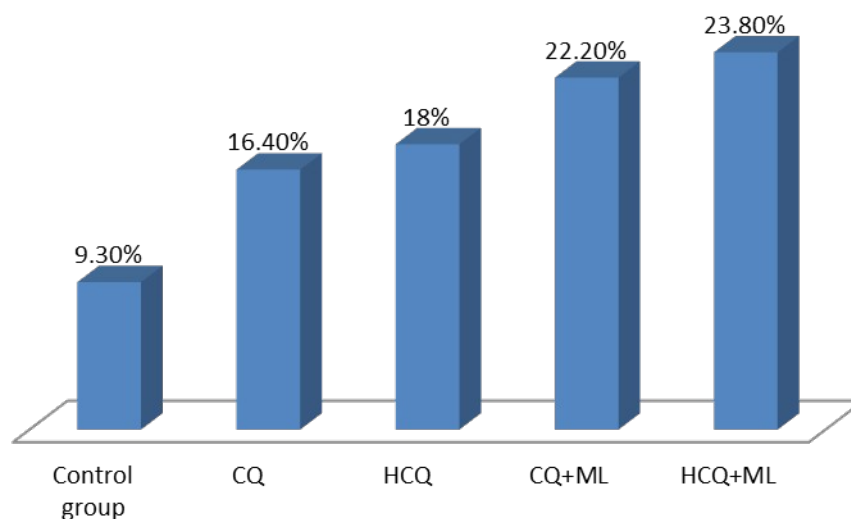
Figure 11: Mortality rate of COVID-19 patients under different treatment groups.

Wang and co-workers have examined the effect of 7 drugs which included 5 FDA approved drugs *viz.*, ribavirin, penciclovir, nitazoxanide, nafamostat and chloroquine along with two other antiviral drugs such as remdesivir and favipiravir on ATCC-1586 cell line which were infected by nCoV-2019BetaCoV/Wuhan/WIV04/2019 virus [65]. The studies suggested that high concentrations of ribavirin (EC_{50} = 109.50 μM, CC_{50} > 400 μM, SI > 3.65), penciclovir (EC_{50} = 95.96 μM, CC_{50} > 400 μM and SI > 4.17) and favipiravir (EC_{50} = 61.88 μM, CC_{50} > 400 μM and SI > 6.46) were required to reduce the viral infection. However, no encouraging results were obtained for nafamostat. Interestingly, nitazoxanide inhibited the virus at lower concentration (EC_{50} = 2.12 μM, CC_{50} > 35.53 μM and SI > 16.76). Best results were observed for remdesivir (EC_{50} = 0.77 μM, CC_{50} > 100 μM and SI > 129.87) and chloroquine (EC_{50} = 1.13 μM, CC_{50} > 100 μM and SI > 88.50). Remdesivir was also found to inhibit the Hyh-7 cell lines infected with virus. On the other hand, chloroquine was found to act at entry level as well as post entry levels of COVID-19. Chloroquine also improved the immune response of the COVID-19 patients which further supported its synergetic effect to its antiviral activity.

Boulware *et al.* have reported a randomized, double-blind, placebo-controlled trial of hydroxychloroquine in USA and Canada for its use as postexposure prophylaxis [66]. Participants for the study were taken who had either household or occupational exposure to confirmed COVID-19 patients and are asymptomatic and were of the age at least 18 years. Total

of 821 asymptomatic patients were enrolled for the study out of which 414 patients were assigned hydroxychloroquine treatment whereas 407 patients were placed in placebo group. The median age of the patients was 40 years and women participants were 51.6% (**Figure 12**).
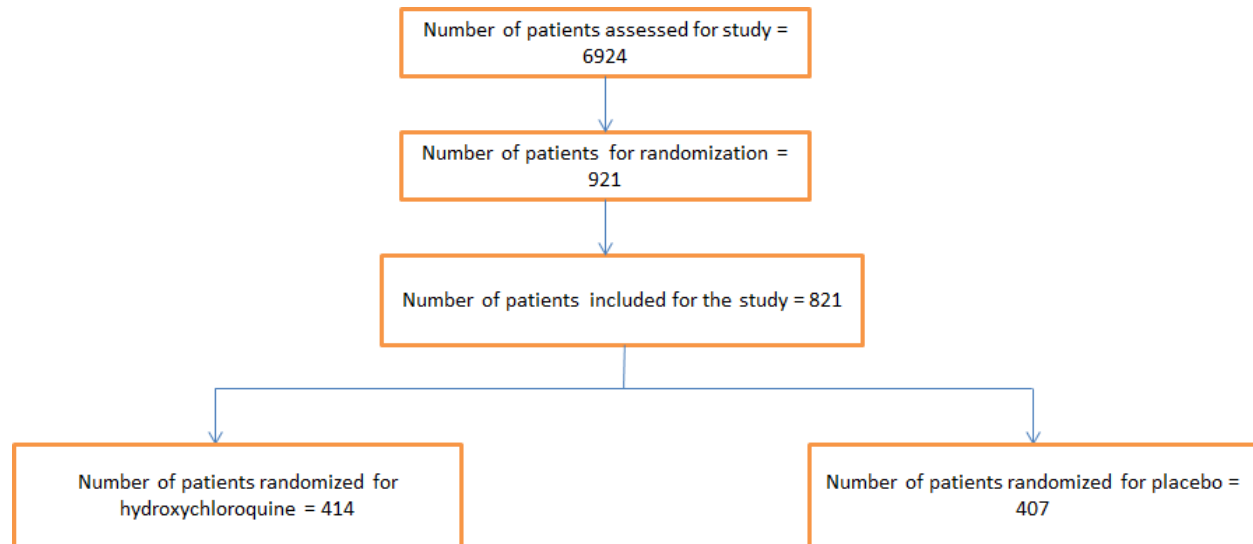
Figure 12: Randomization of asymptomatic patients for hydroxychloroquine and placebo treatment

The participants were given 800 mg of hydroxychloroquine as an initial dose followed by 600 mg in 6-8 hrs after the initial dose at day 1. Further, they were given 600 mg of hydroxychloroquine daily for next 4 days. In addition, the participants in the placebo group were given folate tablets with same regimen. The primary outcome of the study was the confirmation of the symptomatic illness associated with COVID-19 whereas the secondary output was associated with the incidence of hospitalization or deaths because of COVID-19. The data suggested that 107 (13%) participants developed COVID-19 during 14 days of study. The main symptoms found in these patients were cough, high body temperature, shortness of breath, fatigue etc. In terms of safety, 40.1% of the patients in the hydroxychloroquine group observed side effects as compared to 16.8% patients in the placebo group by day 5 (**Figure 13**). Moreover, more number of patients in hydroxychloroquine (17, 4.1%) stopped taking the treatments because of side effects than the placebo group (1.9%).
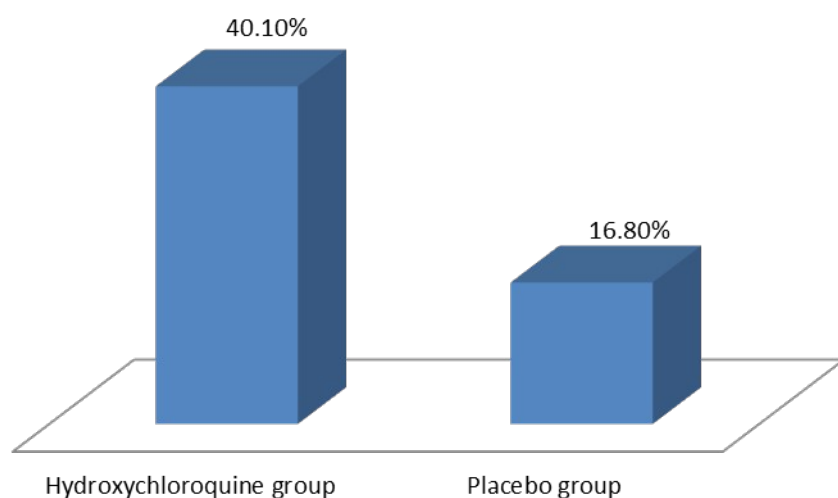
Figure 13: Percentage of patients observed side effects in different treatment groups by day 5 of the treatment

Chen *et al.* have reported a pilot study of the use of hydroxychloroquine for the treatment of patients with moderate COVID-19 [67]. The study was conducted on 30 patients at Shanghai Public Health Clinic Center. The included patients were randomized in hydroxychloroquine arm and control arm in the ratio of 1:1. The patients in hydroxychloroquine arm were given 400 mg of hydroxychloroquine once daily for 5 days along with the conventional treatments. Further, the primary end point of the study was the negative conversion rate of SARS-CoV-2 nucleic acid test after 7 days of randomization. The outcomes of the trial suggested that 1 (1%) patient from the hydroxychloroquine arm observed severe COVID-19 during the treatment. Interestingly lesser number of patients observed negative SARS-CoV-2 tests in hydroxychloroquine arm (13, 86.7%) as compared to control arm (14, 93.3%). In terms of adverse events, the patients in the hydroxychloroquine arm (4, 26.7%) were more prone to adverse events like abnormal liver functions and diarrhea as compared to control arm (3, 20%) (**Table 2**). It was very clear from the study that the use of hydroxychloroquine did not result into any significant improvements as compared to control arm.

Table 2: Clinical outcomes of the patients with moderate COVID-19 in different treatment groups

Clinical Outcomes	Patients observing negative SARS-CoV-2 test (% age)	Median duration for viral clearance (days)	Patients witnessing the improvement in CT scan (% age)	Patients observing the adverse events (% age)
Control group	93.3	2	46.7	20
Hydroxychloroquine group	86.7	4	33.3	26.7

In a similar study, Chen *et al.* have reported the results of a randomized clinical trial of hydroxychloroquine for COVID-19 patients at Renmin Hospital in Wuhan University, China [68]. Patients of at least 18 years in age were included in the study whereas the patients with severe renal or liver problems and breast feeding and pregnant women were excluded from the trial. Out of 142 patients, 62 eligible patients as per inclusion criteria were randomized in control (31 patients) and hydroxychloroquine group (31 patients). Along with the standard therapy, the patients in hydroxychloroquine group received additional 400 mg of hydroxychloroquine once a day for 5 days. The patient outcomes were monitored in terms of time to clinical recovery (TTCR) which corresponded to normalization of fever and cough for more than 3 days. In addition, 4 (13%) patients in the control group observed adverse events as compared to 0% patients in the hydroxychloroquine group. Also, the patients in hydroxychloroquine group (80.6%) observed improvement in pneumonia as compared to control group (54.8%) (**Table 3**).

Table 3: Clinical outcomes of the COVID-19 patients under different treatment regimens

Clinical Outcomes	Time taken for normalization of body temperature (in days)	Patients observing the adverse events (%age)	Patients witnessing the improvement in pneumonia
Control group	3.2	13	54.8
Hydroxychloroquine group	2.2	0	80.6

Gonzalez *et al.* have reported the design for a randomized placebo controlled trial of hydroxychloroquine to study its safety and efficacy to treat mild COVID-19 in women during pregnancy [69]. The primary outcomes of the study were the effect of hydroxychloroquine in reducing the viral load or preventing the development of COVID-19 and to study its efficacy whereas the secondary outcomes of the study involved the effect of hydroxychloroquine treatment on the clinical outcomes of the patients like risk of hospitalization, mortality rate, risk of transmission and to study its safety and tolerability. Pregnant women of more than 12 weeks

of gestation having mild symptoms of COVID-19 were included for the study whereas the women having sensitivity of hydroxychloroquine, with history of retinopathy, cardiac pathology etc. was excluded from the study. The patients in the hydroxychloroquine group were to be given 400 mg of hydroxychloroquine once daily for 3 days followed by 200 mg for 11 days whereas the participants in control group were to be given 2 tablets for 3 days followed by 1 tablet for 11 days.

Barnabas *et al.* have reported the design of randomized controlled trial of hydroxychloroquine for post-exposure prophylaxis for the treatment of severe SARS-CoV-2 infections in adults [70]. The main objectives of the study were to check the efficacy of hydroxychloroquine regimen at 400 mg dose once daily for 3 days followed by 200 mg for next 11 days as compared to the use of ascorbic acid for the treatment of COVID-19. On the other hand, the secondary outcomes of the study were to study the safety and tolerability of hydroxychloroquine to prevent incidences of COVID-19, shortening of the duration of viral clearance etc. The number of asymptomatic patients enrolled for this study was 2000 adults at least 18 years of age and the trial was planned to be conducted across 7 different sites of New Orleans, Seattle, New York City, Baltimore, Los Angeles, Boston and Syracuse. Further, these patients would be randomized in 1:1 ratio in different treatment groups (**Figure 14**).
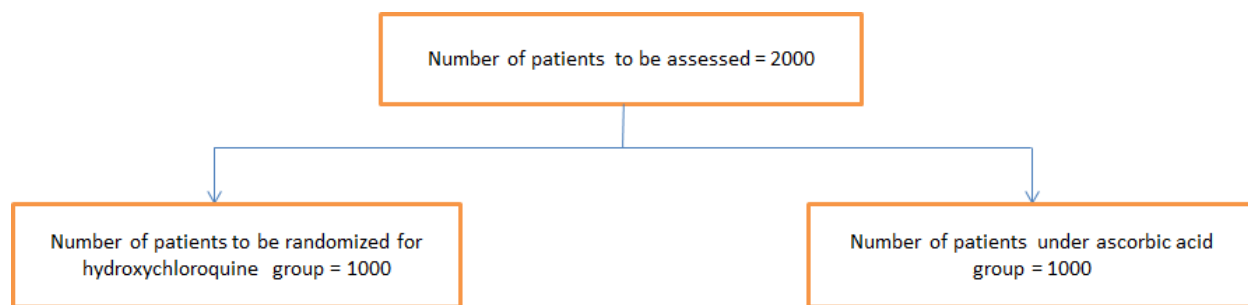
Figure 14: Study protocol for the proposed randomised controlled trial of hydroxychloroquine for postexposure prophylaxis for the treatment of severe SARS-CoV-2 infections in adults

Wright *et al.* have reported protocol of randomized placebo-controlled multisite trial in Toronto, Canada to study whether pre-exposure prophylaxis (PrEP) with 400 mg of hydroxychloroquine once daily for 90 days resulted in the treatment of COVID-19 in front line health care workers who are at high risk of viral infections [71]. The study was also focused on the secondary outcomes like adverse events, risk of hospitalization, respiratory dysfunctioning,

psychological distress etc. Further, the participants were patients of at least 18 years in age and were placed in control and hydroxychloroquine arm in 1:1 ratio. The participants under different treatment groups were assessed on the set clinical parameters at 30th, 60th, 90th and 120th day.

Mitja *et al.* have reported a randomized controlled trial of hydroxychloroquine for the early treatment of mild COVID-19 patients in Catalonia, Spain [72]. The patients enrolled for this study were recently diagnosed non hospitalized COVID-19 patients having symptoms from less than 5 days. A total of 293 patients were enrolled for the study after screening of 753 patients, out of which 157 patients were placed in control arm whereas 136 patients were placed in hydroxychloroquine arm. The median time from the symptoms onset to randomization was 3 days (**Figure 15**).
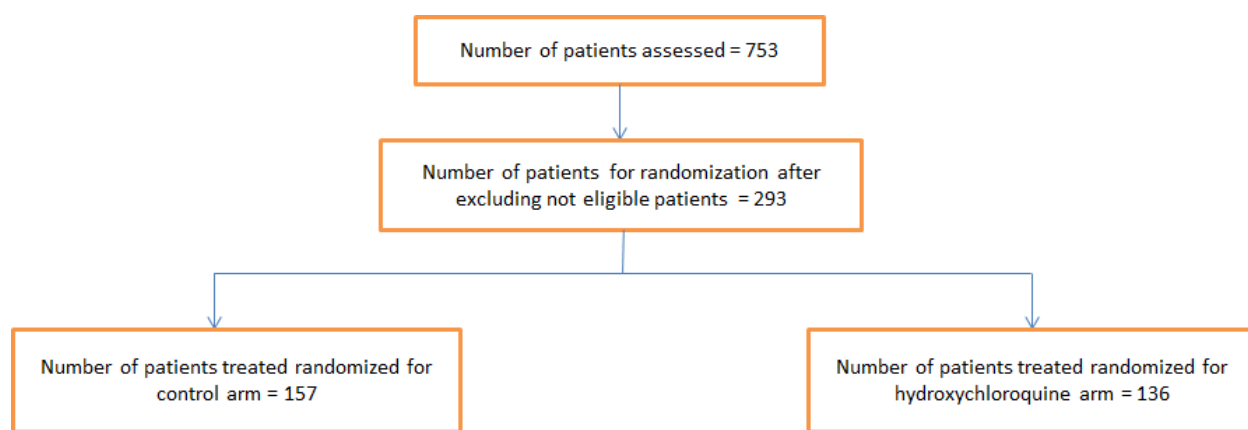
Figure 15: Randomization of the COVID-19 patients in different treatment groups

Further, the patients were given 800 mg of hydroxychloroquine once daily on day 1 followed by 400 mg once daily for next 6 days. The outcomes of the study were the reduction in the viral load up to 7 days after the start of treatment, disease progression along with adverse events up to 28 days. The data suggested that no significance improvement was observed in the hydroxychloroquine arm as compared to control arm during the study. For example, reduction in the viral load at day 3 and day 5 were observed to be same in both the arms. Also, the risk of hospitalization of the patients in control arm was found to be lesser (5.9%) than the control arm (7.1%) but that difference was not of significance.

The clinical data received from the clinical trials of chloroquine and hydroxychloroquine puts a question on the use of these drugs as a drug candidate for the treatment of COVID-19 as these drugs did not show much of the encouraging results as compared to the control group.

Chloroquine has been reported to be lethal at high doses whereas it showed high mortality rate as compared to the control group. Similar results have been observed for hydroxychloroquine where almost 40% of the patients observed side effects. Also in another study, it did not give the significant results as compared to the control group. However, other antiviral drugs like remdesivir, favipiravir and oseltamivir have shown some encouraging effects. The use of remdesivir has been associated with lower mortality rate whereas favipiravir is associated with lesser number of adverse events. On the other hand, rate of recovery has been found in shorter time in case of oseltamivir. Disclosure of more clinical data on the trials of these drugs with time would ponder a deep insight to their use against COVID-19 in future.

3. Use of antiretrovirals as a treatment for COVID-19

3.1 Lopinavir/ Ritonavir

Lopinavir (**6**) along with ritonavir (**7**) as a booster is used for the treatment of HIV infections. It is an inhibitor of protease which is a key enzyme in polyprotein processing of coronavirus cycle [73].

Lopinavir (6)   Ritonavir (7)
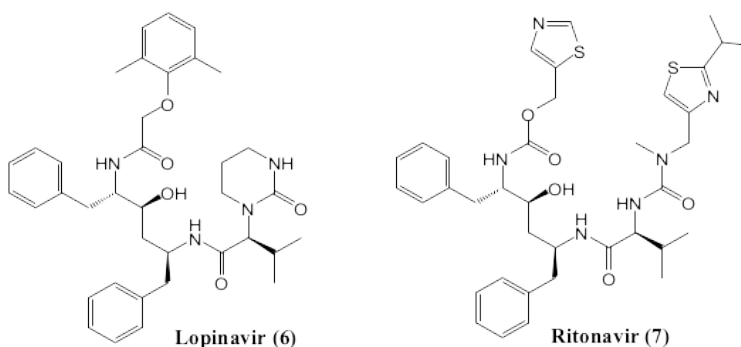
Bhatnagar *et al.* have reported the protocols of emergency use of Lopinavir/ ritonavir therapy for the treatment of symptomatic patients of COVID-19 in India [74]. The patients considered for treatment were adults of the age greater than 18 years. Patients having hepatic impairment, HIV positive patients and on the treatment of drugs which may create complications with lopinavir/ ritonavir were excluded from the study. 400 mg of lopinavir and 100 mg of ritonavir can be given to the symptomatic patients orally or in the form of suspension via nasogastric tube, twice a day after interval of 12 hrs for 14 days or for 7 days after the patients get asymptomatic, whichever is earlier. The patients were clinically assessed daily till the discharge from the hospital which was done only after 2 successive negative RT-PCR tests for

COVID-19. The clinical outcomes were studied in terms of time of stay in hospital, requirement of ventilators and mortality rate whereas safety outcomes were recorded in terms of occurrence of adverse events like acute pancreatitis, abdominal pain, elevation in ALT etc.

Cao *et al.* have conducted a randomized, controlled, open-label trial of lopinavir/ ritonavir (LPV/RTV) treatment on severe COVID-19 patients at Jin Yin-Tan Hospital, Wuhan, China and have reported that no significant improvement was observed in the patients with the treatment as compared to standard of care [75]. The study was done on total of 199 patients out of which 99 patients were given LPV/ RTV treatment whereas 100 patients received standard of care treatment. The number of patients included for intention to treat population after excluding the mortality was 96 and 100 for LPV/ RTV and standard of care group. Finally, 95 patients from LPV/ RTV group and 99 patients from standard of care group were considered for safety studies (**Figure 16**)
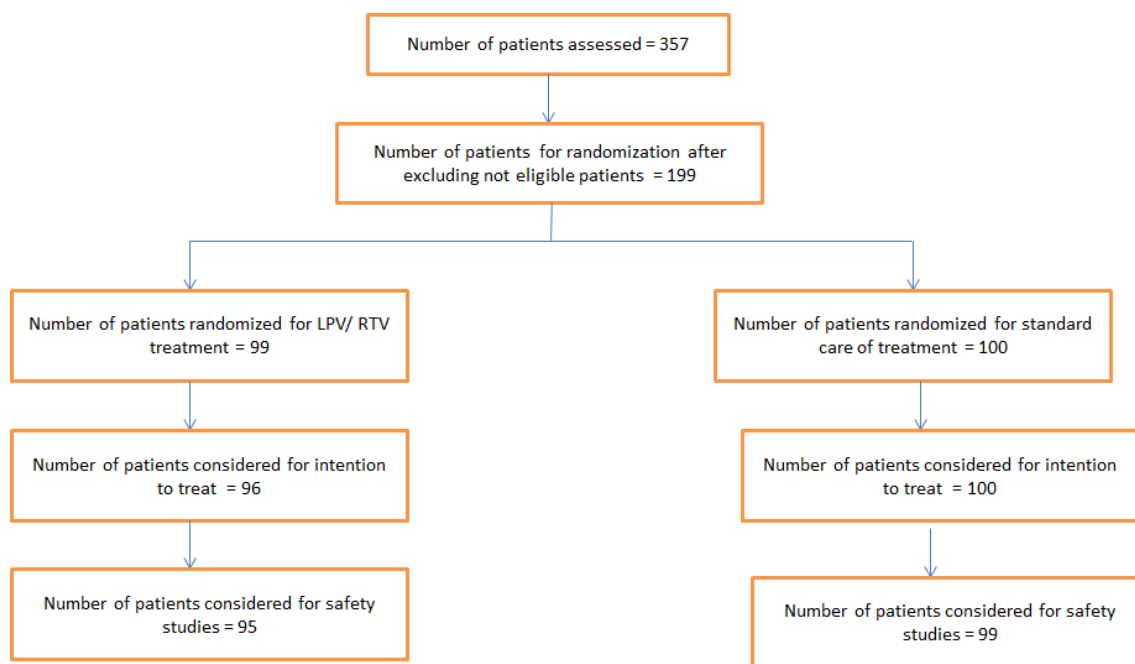
Figure 16: Randomization of severe COVID-19 patients for LPV/ RTV and standard of care treatment

The patients under the LPV/ RTV treatment were given 400 mg of lopinavir and 100 mg of ritonavir twice daily along with the standard of care for 14 days whereas the patients under standard of care were given supplement oxygen, ventilation, antibiotics, renal replacement

therapy etc. The end point of patient was the time taken from the randomization to the improvement to at least 2 points on a 7 category ordinal scale or discharge from the hospital. Clinical outcomes included mortality rate, need for ventilators etc. whereas safety outcomes were monitored in terms of adverse events occurred during the treatment. The data suggested no significant difference in the mean-time to improvement for the patients in both the groups which was 16 days. In addition, the time to clinical deterioration was also similar for both the groups. Further, 28 days mortality rate was found lower in case of LPV/ RTV group as compared to standard of care group which were 19.2% and 25%, respectively and 16.7% *vs* 25% in intention to treatment group. The virology studies showed that the percentage of patients having viral load after treatment in both the groups were found similar in both the cases (60.3% *vs* 58.3% in LPV/ RTV and standard of care group after day 28). Also, the percentage of the patients observing the adverse events in both the groups were found same (48.4% in LPV/ RTV group Vs 49.5% in standard of care group) questioning the beneficial effect of LPV/ RTV treatment over the standard of care treatment (**Figure 17**). The same point has been discussed by Doggrell *et al.* in a separate publication [76-78].
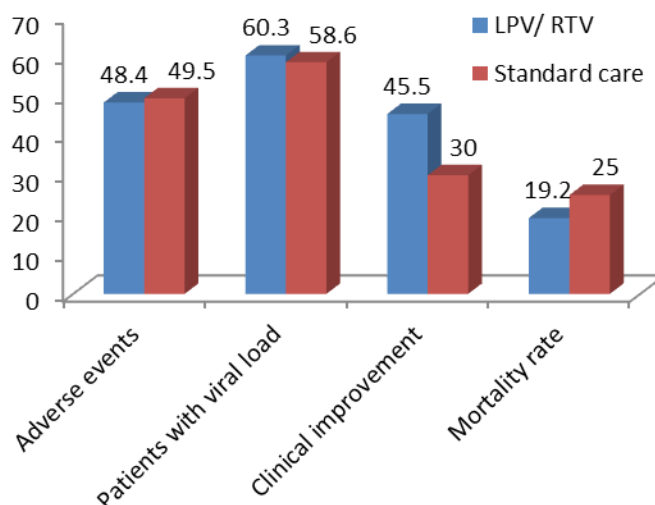
Figure 17: Comparison of clinical outcome of the COVID-19 patients in LPV/ RTV and standard of care group (Values are presented in percentage)

Hung *et al.* have reported an open-label, multicenter, randomized phase 2 trial of combination of LPV/ RTV along with ribavirin and interferon β-1b on 127 COVID-19 patients of age at least 18 years who were admitted across six hospitals in Hong Kong [79]. Total 144

patients were enrolled for the study out of which 127 patients were randomized for combination therapy group and control group in 2:1 ratio. In addition, the patients who were administered to hospitals within 7 days of onset of symptoms were given LPV/ RTV, ribavirin and interferon β-1b whereas the patients who were administered to hospitals after 7 days of onset of symptoms were given only LPV/ RTV and ribavirin (**Figure 18**). The median age of the patients was 52 years with 54% patients as men and 46% patients as women. The patients under combination therapy group were given 400 mg/ 100 mg of LPV/ RTV twice daily after 12 hrs, 400 mg of ribavirin twice daily after 12 hrs and 1-3 doses of 8 million IU of interferon β-1b on alternate days for 14 days. On the other hand, the patients in the control group received only 400 mg/ 100 mg of LPV/ RTV every 12 hrs for 14 days. The primary outcome of the trial was the time to achieve negative RT-PCR test for COVID-19 which was found to be much shorter (7 days) in combination therapy as compared to the control group (12 days). Also, the clinical outcomes in terms of alleviation of the symptoms was achieved in much shorter days (4 days with 9 days of average time in hospital) in case of combination therapy group as compared to the standard of care (8 days with average time in hospital of 14.5 days) (**Figure 19)**.
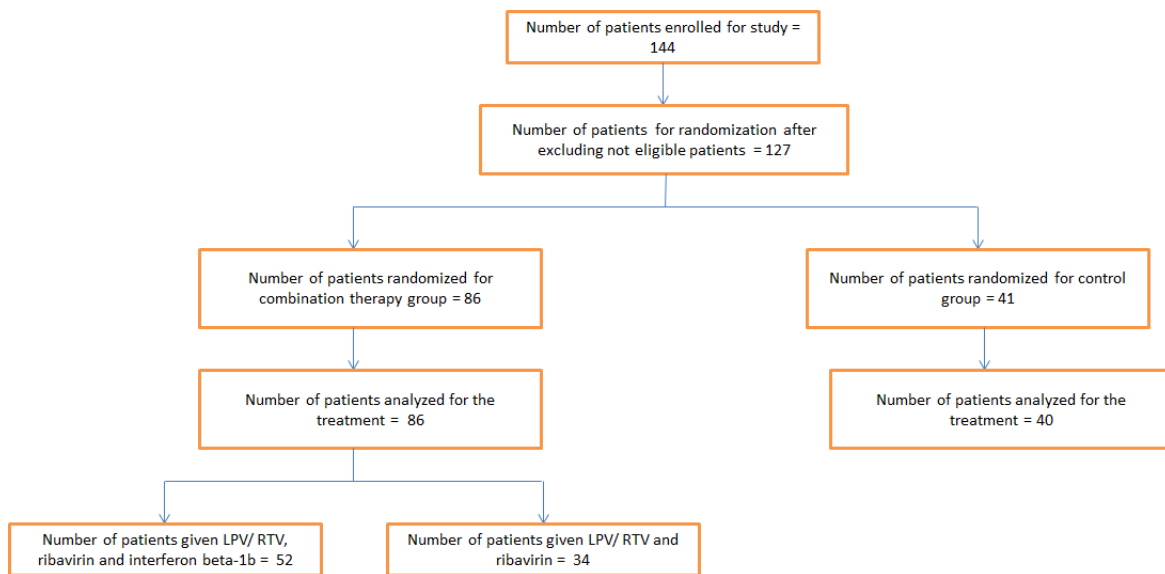
Figure 18: Randomization of the COVID-19 patients for combination and standard of care group

Moreover, negative viral load was observed faster in combination group as compared to control group. Interestingly, the patients in combination therapy group who were given treatment before

the 7 days of onset of symptoms observed better clinical and virological outcome supporting the early treatment with the combination therapy. However, the patients under both the groups observed similar adverse events.
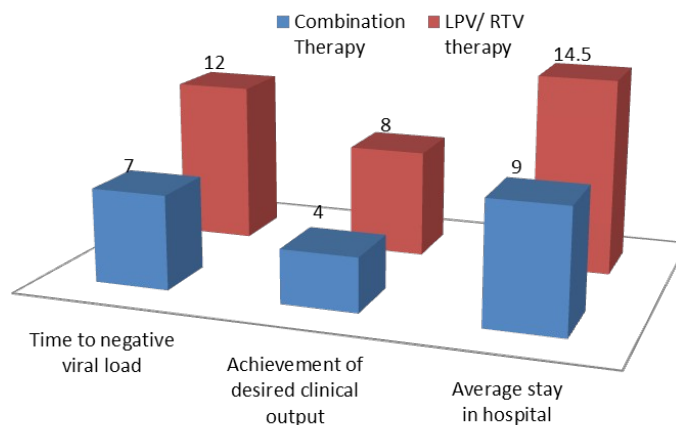
Figure 19: Comparison of clinical outcomes of COVID-19 patients in combination and LPV/RTV therapy (Values are presented in days)

Liu *et al.* have reported a study protocol of prospective, open-label, multicenter, randomized controlled clinical study to compare the efficacy of LPV/ RTV treatment in comparison to chloroquine treatment [80]. The proposed trial was planned to be conducted in three different hospitals in China wherein the patients were divided into control arm which was planned to be given 800 mg of lopinavir and 200 mg of ritonavir daily for 10 days and investigation are, which was to be given 1000 mg of chloroquine phosphate daily for 10 days. Further, the randomization was planned in 1:1 ratio containing 56 participants in each arm and was planned for 90 days and follow up for 28 days (**Figure 20**). The inclusion criteria for the prosed study was COVID-19 patients of at least 18 years of age with symptoms of cough, fever, decrease in respiratory functions and had lower levels of white-blood-cell counts or lymphocyte counts. However, the patients who were allergic to lopinavir had hematological diseases with liver, kidney, heart or renal disease and the female patients in pregnancy were excluded from the study.
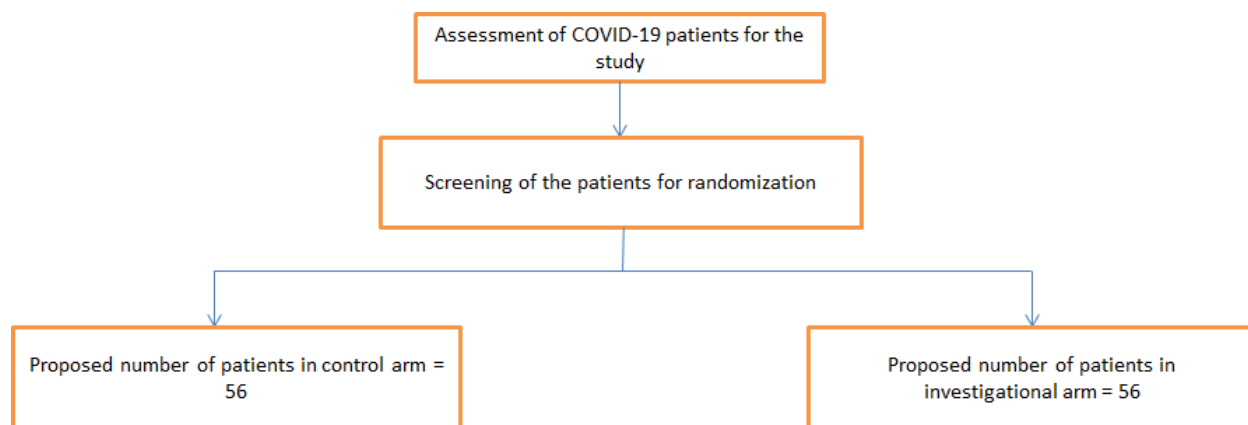
Figure 20: The proposed design of randomization of COVID-19 patients in control and investigational arm

Ye *et al.* have reported the clinical efficacy of lopinavir/ ritonavir for the treatment of 47 COVID-19 patients at Ruian People's Hospital, China [81]. About 42 patients were randomized for lopinavir/ritonavir treatment whereas 5 patients were placed in control group. The patients in control group were given interferron, arbidol, asmeton, moxifloxacin, eucalyptol limonene and pinene enteric soft capsules whereas the patients registered in the investigation were given 400/100 mg of lopinavir/ritonavir twice daily or 800/200 mg once daily. The data suggested that the patients in the investigation group observed the normalization of the body temperature in shorter time span (4.8 days) as compared to control group (7.3 days). Further the time required for the negative viral load was 7.8 days for investigation group as compared to 12 days in control group. The studies suggested the use of the lopinavir/ritonavir treatment lead to improvement in the clinical outcomes of the COVID-19 patients at a significant level as compared to control group.

Significant improvement in the clinical parameters have been observed by using lopinavir/ritonavir treatment like mortality rate, risk of hospitalization, percentage of patients observed improvement during the study, recovery rate etc. as compared to the control group. However, no significant differences in certain parameters like mean time for improvement, adverse events were observed in some of the clinical trials. The treatment with lopinavir/ritonavir looks encouraging but more data on the use of this drug would further give an idea about the efficacy and safety of this drug combination.

4. Use of antibiotics as a treatment for COVID-19

4.1 Azithromycin

Azithromycin (**8**) is commonly used for the treatment of bacterial respiratory infections and might also have antiviral activity against some of the RNA viruses like rhino and Zika viruses [82-83]. It is also known to possess immune-modulatory effects [84] and therefore can be a potential treatment for the improvement of immune response and viral infections associated with COVID-19.
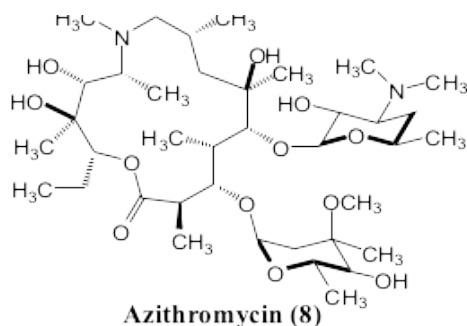
Azithromycin (8)

Arshad *et al.* have reported Multi-center retrospective observational trial treatment of adult COVID-19 patients at least of the age of 18 years with hydroxychloroquine, azithromycin and combination of both the drugs [85]. Total of 2948 patients in Southeast Michigan, USA, were screened for the trial, out of which 2541 were considered for the further studies. Out of 2541 patients, 1202 patients were given hydroxychloroquine, 783 patients were given azithromycin and hydroxychloroquine, 147 patients were given azithromycin and 409 patients were given neither of the drugs (**Figure 21**).
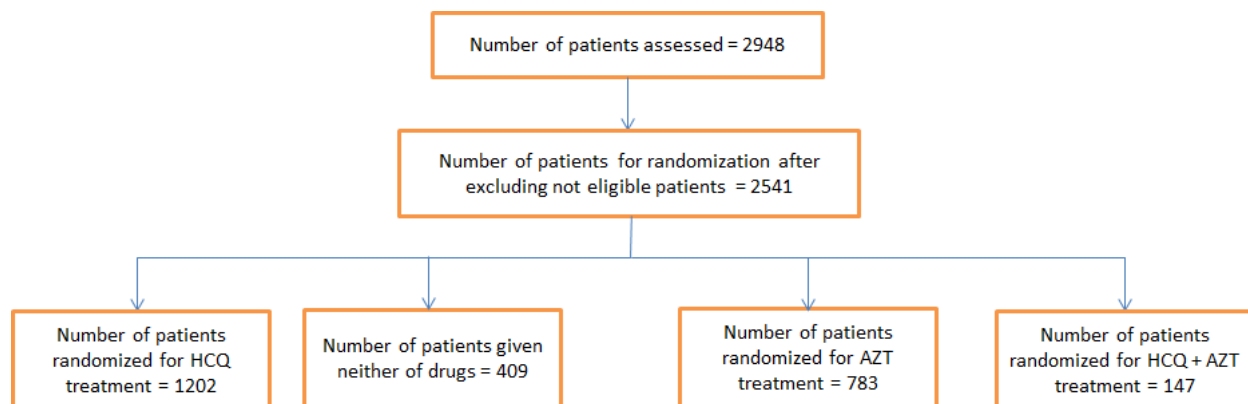
Figure 21: Randomization of COVID-19 patients

The patients under study were given 400 mg of hydroxychloroquine twice on day 1 followed by 200 mg from day 2 to day 5. Azithromycin was given at dose of 500 mg for day 1 followed by 250 mg for next 4 days. The data suggested that lower crude mortality rate (13.5%) was observed in hydroxychloroquine (HCQ) as compared to the azithromycin (AZT) (22.4%), combination (HCQ +AZT) receiving hydroxychloroquine and azithromycin (20.4%) and (NT) receiving neither of the group (26.4%) (**Figure 22**), indicating the fact that the survival rate of the COVID-19 patients was more in case of patients receiving azithromycin or combination of azithromycin and hydroxychloroquine as compared to azithromycin alone. However, the main limitation of the trial was its retrospective, non-randomized, non-blinded study design and non-availability of the duration of the symptoms of the patients before hospitalization.
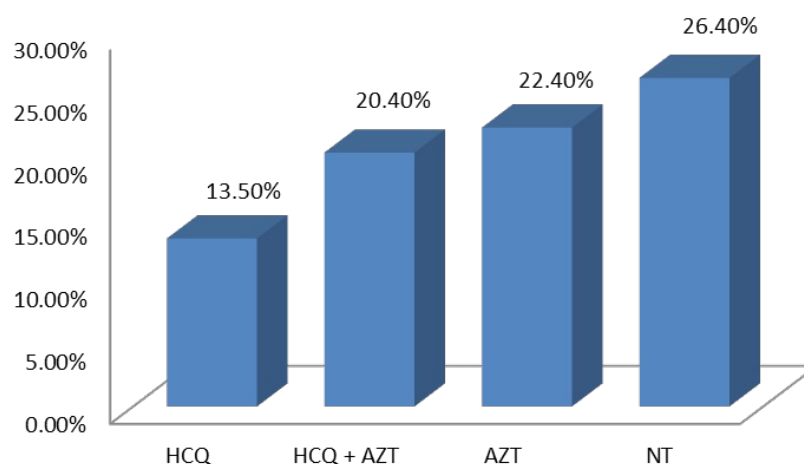
Figure 22: Mortality rate of COVID-19 patients receiving different treatments

Cavalcanti *et al.* have reported the multicenter, randomized, open-label, three-group, controlled trial of hydroxychloroquine and its combination with azithromycin for the treatment of mild to moderate COVID-19 across 55 hospitals in Brazil [86]. The study was done on 667 adult patients including 504 confirmed cases. Out of the registered patients, 217 patients received 400 mg of hydroxychloroquine twice daily and 500 mg of azithromycin once a day for 7 days (HCQ+AZT), 221 patients received 400 mg of hydroxychloroquine (HCQ) twice daily for 7 days and 229 received standard of care therapy. The mean age of the patients was 50 years and 58% of the patients were men (**Figure 23**).
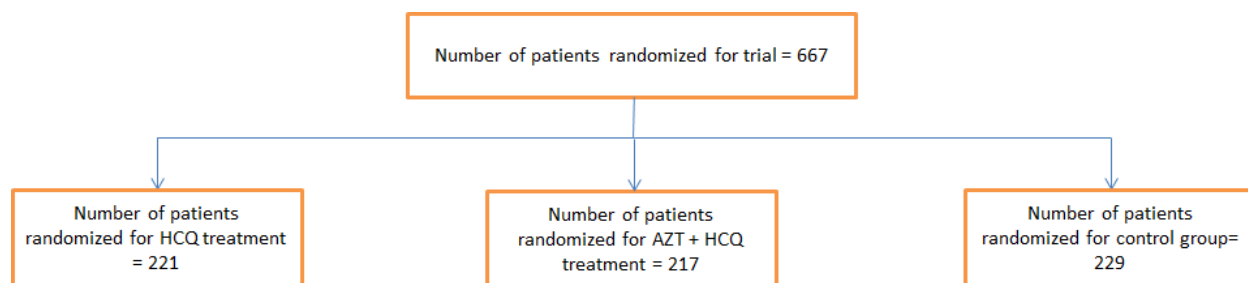
Figure 23: Randomization of COVID-19 patients

The clinical outcomes of the patients were analyzed till 15 days from the randomization on a seven level ordinal scale whereas the secondary outcome as the clinical outcomes at 6 level ordinal scale. The results of the trial suggested no significant difference in primary or secondary outcome of the patients between two groups. Also, no significant rate of mortality was observed between three groups. Total of 18 patients died during the treatment which corresponded to 5 patients in HCQ+AZT group (0.7%), 7 (1%) patients in HCQ group and 6 (0.9%) patients in control group. However, in terms of safety measurements, the number of adverse events observed for AZT group was significantly lesser (18%) than HCQ group (33.7%), HCQ+AZT group (39.3%) and control group (22.6%) (**Figure 24**).
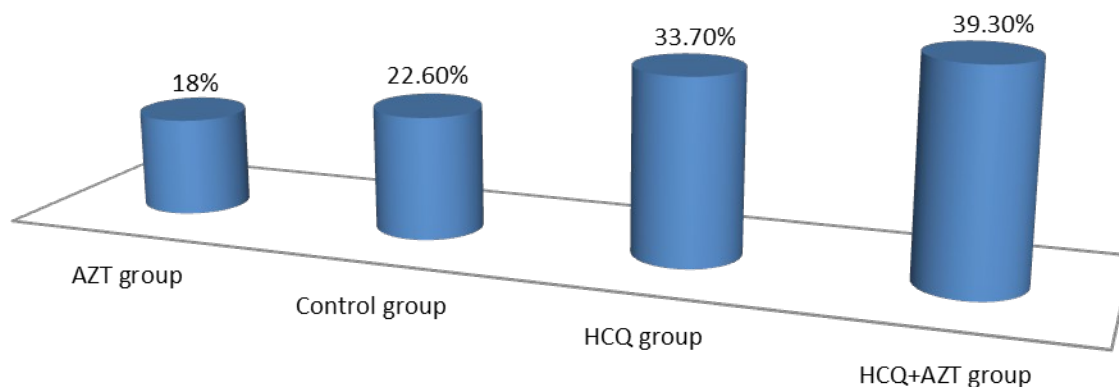
Figure 24: Percentage of adverse events witnessed by different therapy groups for COVID-19 patients

O'Connell *et al.* have reported a retrospective cohort study of the QT prolongation of COVID-19 patients with the use of combination of hydroxychloroquine and azithromycin in Beaumont Hospital – Royal Oak and Beaumont Hospital, Dublin, Ireland [87]. Total of 586

patients were enrolled for the study, out of which 171 patients were excluded on the basis of age, shorter baseline QRS duration and shorter QT intervals etc. About 415 patients including 178 (43%) female patients were further considered for the study for which the baseline QT interval was 443(+/-) 25 msec. The enrolled patients were given 400 mg of hydroxychloroquine twice daily for day 1 followed by 200 mg twice daily for next 4 days and 500 mg of azithromycin for day 1 followed by 250 mg for next 4 days. The results suggested the prolongation of the QT interval with the administration of hydroxychloroquine/ azithromycin therapy reaching the maximum value of 473(+/-) 40. 87 (21%) patients observed QT levels of greater than 500 msec over 5 days treatment. In a subset of 137 patients, the average to maximum QT was 2.9(+/-) 1.4 days. Further, 85 (21%) of the patients died during the treatment, out of which 32 (38%) patients had either pulseless bradycardia or electrical activity at the initiation of resuscitation and 53 (62%) patients had no resuscitation (**Figure 25-26**).
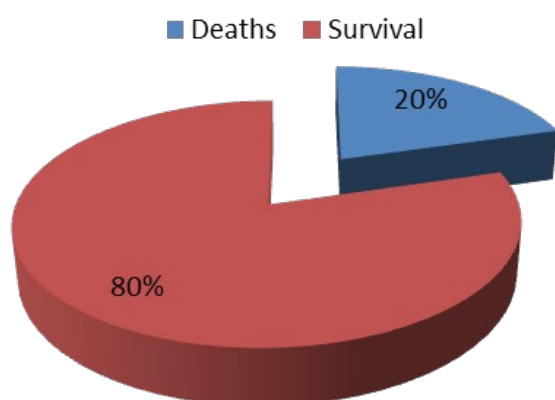
Figure 25: Mortality rate of the registered COVID-19 patients during the trial
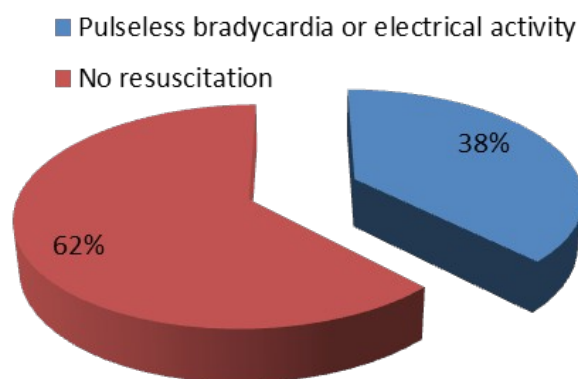
Figure 26: Clinical history of the dead COVID-19 patients

Gautret *et al.* have reported the results of an open label non-randomized clinical trial of hydroxychloroquine and azithromycin for the treatment of 20 patients of COVID-19 in France [88]. Total of 42 patients were screened for the study out of which 36 patients met the inclusion criteria and were promoted for trial. The patients were further classified as asymptomatic, lower respiratory tract infection (LTRI) and upper respiratory tract infection (UTRI). Out of 36 patients, 6 (16.7%) of the patients were asymptomatic, 22 (61.1%) patients were UTRI and 8 (22.2%) patients were LTRI. Further, 26 patients received hydroxychloroquine therapy while 16

patients were placed in control group. The patients in hydroxychloroquine group were given 200 mg of hydroxychloroquine thrice a day for 10 days and were assessed on the set clinical parameters for duration for 14 days during the treatment. However, 6 patients under hydroxychloroquine treatment were lost during the study and hence 36 patients (30 in hydroxychloroquine and 6 in control group) were analyzed for data collection. Also, 6 patients from hydroxychloroquine group received 500 mg of azithromycin for day 1 followed by 250 mg of azithromycin for next 4 days (**Figure 27**).
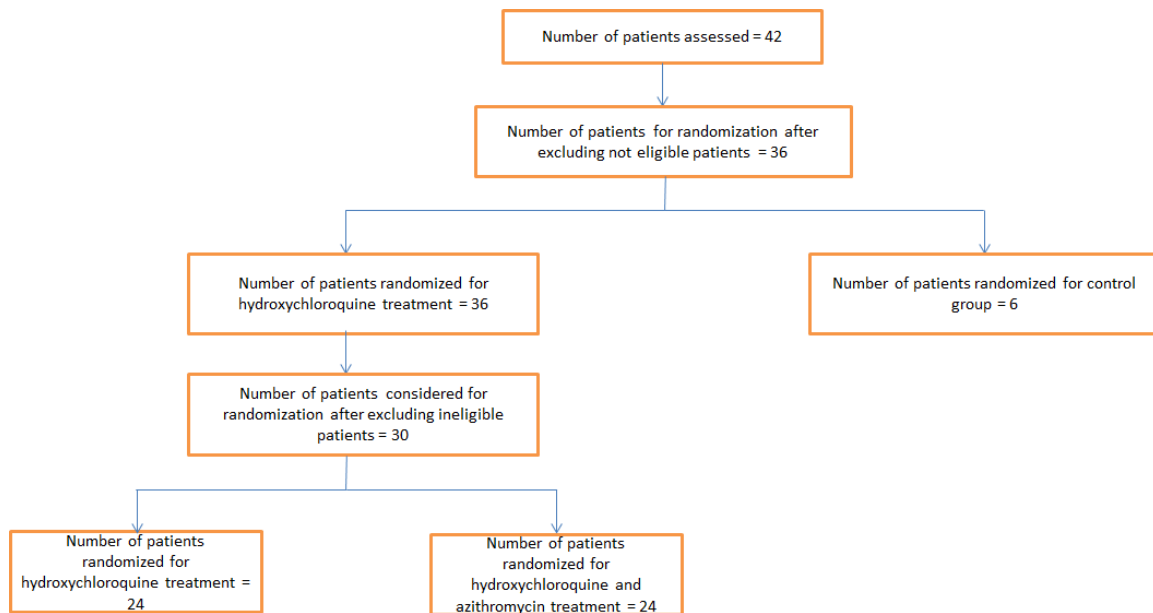
Figure 27: Randomization of COVID-19 patients in control group, hydroxychloroquine group and combination group

The data suggested that after 6 days of treatment, 100% of the patients in combination of hydroxychloroquine and azithromycin group (HCQ +AZT) observed viral clearance as compared to 57.1% patients in hydroxychloroquine group (HCQ) and 12.5% patients in the control group (**Figure 28**). Interestingly, the patients in hydroxychloroquine group who were positive on day 6 of inclusion for COVID-19 test were given azithromycin and were found negative on day 9. This clearly supported the positive synergic effect of the azithromycin with hydroxychloroquine for the treatment of COVID-19 patients.
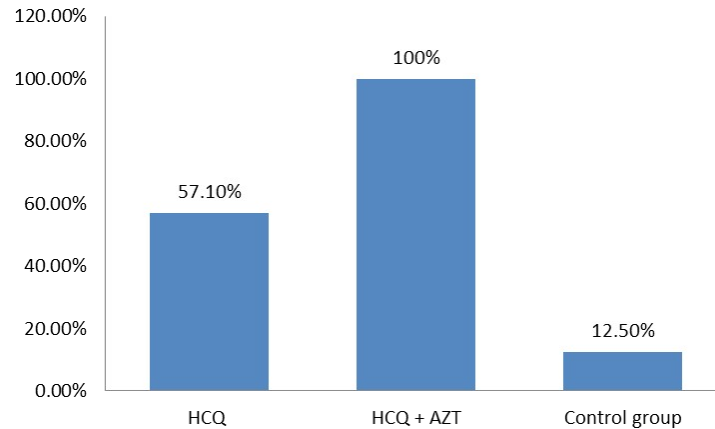
Figure 28: Percentage clearance of viral load of COVID-19 patients on day 6 post inclusion

Rosenberg *et al.* have reported a retrospective multicenter cohort study of hydroxychloroquine with or without in combination with azithromycin to treat COVID-19 patients among 25 hospitals in New York, USA [89]. Total of 7914 patients were screened for the trial out of which 2362 patients were selected randomly and finally 1438 patients were considered for further study for data collection. These 1438 patients were further categorized in four groups. Group 1 included 735 patients and was given hydroxychloroquine and azithromycin (HCQ+AZT), group 2 containing 271 patients received only hydroxychloroquine (HCQ), group 3 containing 211 patients received only azithromycin (AZT) whereas 221 patients in group 4 received neither of the drugs (ND) (**Figure 29**).
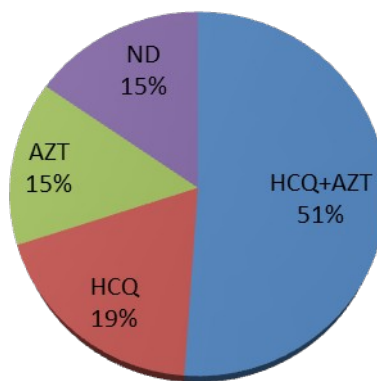
Figure 29: Distribution of COVID-19 patients among different treatments

Primary outcome of the patients was taken as mortality and the secondary output was taken as abnormal ECG level and cardiac arrest. The data suggested that 22.5% of the mortality rate

was observed in HCQ+AZT group which was higher than the overall mortality rate of 20.3% whereas patients in other groups witnessed lower mortality rate with lowest being observed in AZT group (10.9%) followed by ND (17.8%) and HCQ group (18.9%). Also, abnormal ECG patterns and cardiac arrests were observed more common in HCQ+AZT (27.1% and 15.5% respectively) group and HCQ group 27.3% and 13.6%, respectively) which were further found to be of similar magnitude. Whereas these values were found lowest in case of AZT group (16.1% and 6.2 %) followed by ND group (14.0% and 6.8%). The data clearly suggested that the clinical outcomes of the patients in AZT group were encouraging as compared to the other groups (**Table 4**).

Table 4: Clinical outcomes of the COVID-19 patients in different groups of treatments

	Mortality rate	Cardiac Arrest	Abnormality in ECG patterns
HCQ+AZT group	22.5	15.5	27.1
HCQ group	18.9	13.6	27.3
AZT group	10.9	6.2	16.1
ND group	7.8	14.0	6.8

Million *et al.* have reported the clinical outcome of 1061 COVID-19 patients in Marseille, France on early treatment with combination of hydroxychloroquine and azithromycin [90]. Total of 1411 patients were screened for the study, out of which 350 patients were excluded on the basis of age lesser than 14 years and pregnancy. Remaining 1061 screened patients were treated with hydroxychloroquine and azithromycin for at least 3 days (**Figure 30**).
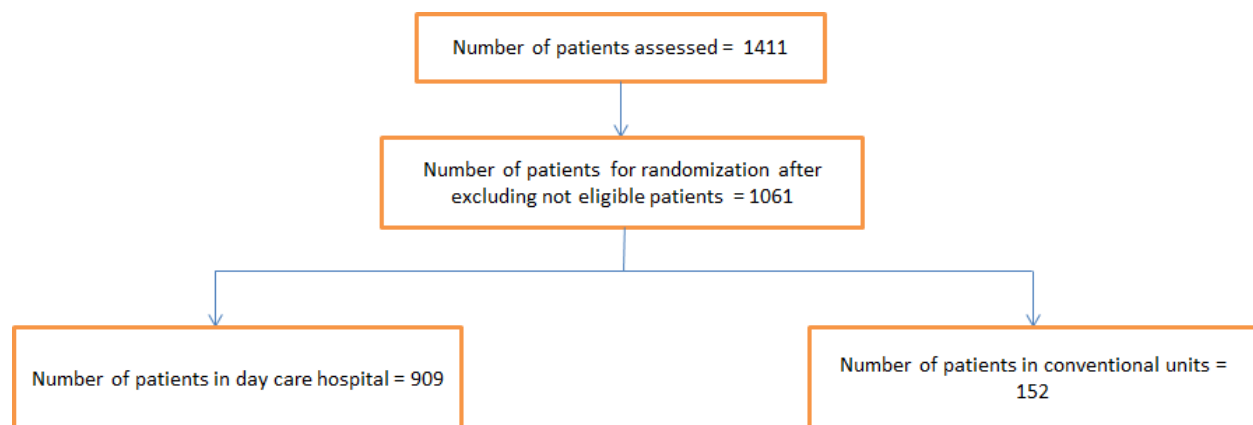
Figure 30: Randomization of the COVID-19 patients for combination of `hydroxychloroquine and azithromycin therapy

The patients were given 200 mg of hydroxychloroquine thrice a day for 10 days along with 500 mg of azithromycin for day 1 followed by 250 mg daily for next 4 days. These patients were further classified between PClino (Poor clinical outcome), PViro (poor virological outcome) and GO (Good clinical outcome) groups. The time between onset on the symptoms and start of the treatment was 6.4 days. Almost 95% of the patients were having only mild disease at the time of admission to hospitals. The data suggested that the treatment was found to be well tolerated with only 10 (0.9%) of the patients observed adverse events and were transferred to ICU with only 8 (0.75%) patients died during the treatment. Surprisingly, 32.4% of the patients in PClino group were found to have blood HCQ level lower than the therapeutic target. Overall, 973 (91.7%) patients observed good clinical and virological outcome within ten days of treatment. Although prolonged viral carriage was observed for 47 (4.4%) patients, but viral load was found to be negative for all patients at day 15.

Sivapalan *et al.* have reported a design for a randomized controlled trial to study if treatment with hydroxychloroquine and azithromycin could lead to shortening of the hospitalization time for COVID-19 patients [91]. Further, this trial would be multi-centred, randomized, Placebo-controlled, 2-armed ratio 1:1, double-blinded in which 226 patients were recruited in Denmark. The inclusion criteria for the patients for this study was the patients of age at least 18 years with hospitalization time of less than 48 hrs who have been diagnosed with COVID-19. The patients would be categorized in control group which would receive standard of care along with placebo and intervention group. These patients would receive standard of care treatment along with 500 mg of azithromycin from day 1 to day 3 and 250 mg from day 4 to day 15 along with hydroxychloroquine treatment at 200 mg dose twice a day for 15 days. The main outcomes of this study would be number of days during which the patients would be alive and discharged from the hospital during 14 days.

The data suggested that azithromycin has been used mostly in combination with hydroxychloroquine as an add-on therapy for the treatment of the viral infections associated with SARS-CoV-2 which resulted in significant clinical outcomes of COVID-19 patients. In an early study, treatments with combination of these 2 drugs have resulted into viral clearance of up to 100% patients within 10 days. Data from some of the clinical trials have suggested high mortality rate of COVID-19 patients if they are administered only azithromycin as compared to combination of azithromycin and hydroxychloroquine or only hydroxychloroquine, supporting

the fact that the azithromycin should be given as an add-on therapy to hydroxychloroquine. However, the use of combination of these 2 drugs have resulted into more number of adverse events in some cases as compared to the drugs used individually which is a matter of concern. Many of the clinical trials are still under progress which will give more insight for the use of these 2 drugs as potential treatment for COVID-19.

5. Use of avermectins as a treatment for COVID-19

5.1 Ivermectin

Ivermectin (**9**) is a broad spectrum antiparasitic agent that has also shown to possess antiviral against broad range of viruses in vitro [92-93]. It is known to inhibit the nuclear import of the viral and host protein. It is also known to inhibit the infections caused by RNA viruses which include influenza, west nile virus and dengue virus [94]. In addition to antiparasitic and antiviral activities, ivermectin is also known to cause immunomodulation effects in the host cell [95]. SARS-CoV-2 is also a single stranded RNA which depreciates the immunological response in the patients.

Ivermectin B$_{1a}$ (a)   Ivermectin B$_{1b}$ (9b)
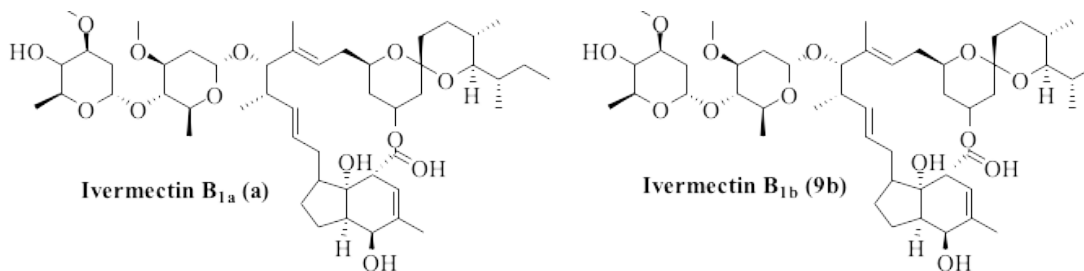
Caly *et al.* have reported the *in vitro* inhibition of the SARS-CoV-2 by ivermectin with almost 5000 fold reduction in the viral RNA load at 48 hrs [96]. The method included infecting of Vero/hSLAM with SARS-CoV-2 isolate Australia/VIC01/2020 and then adding 5 μg of ivermectin. Cell pallets and supernatant were harvested for 3 days and were analyzed by RT-PCR for the presence of SARS-CoV-2. Data supported the remarkable activity of ivermectin against SARS-CoV-2 as 93% of the reduction in the viral load was observed after 24 hrs for the supernatant samples along with 99.8% reduction in the cell-associated viral load. Surprisingly, the reduction in the viral load approached to almost 5000 fold in 48 hrs and no further reduction in the viral load was observed at 72 hrs. Similar results were obtained when cells infected with

SARS-CoV-2 were treated with different dilution of ivermectin. The observed IC_{50} value of ivermectin under these conditions was 2.5 μM. In addition, no toxicity of ivermectin was observed at the tested dilutions.

In continuation with the findings by Caly *et al*., Momekov *et al*. have pointed out a question on possibility of achieving the desired level of ivermectin in human dosingto, examine its possibility of repurposing this drug to treat COVID-19 patients [97]. The study suggested that the 5 μg/L level mentioned by Caly *et al*. for the inhibition of SARS-CoV-2 were virtually not achievable in case of known dosing regimen of ivermectin. It was almost 50 times higher than the maximum attainable level at 700 μg/kg and almost 17 times higher than the maximum attainable level at 247.8 ng/ml dose. Massive overdose is required to attain the required level of ivermectin which could trigger adverse events like abdominal pain, eosinophilia, fever or tachycardia, CNS effects etc. Also at overdose, ivermectin could penetrate through blood-brain barrier which could result in GABA-ergic transmission and potentiation of the effects of benzodiazepines.

Chaccour *et al*. have reported the design of double-blind, randomized, placebo-controlled, superiority trial with two parallel arms to investigate the effect of ivermectin on low risk, non-severe COVID-19 patients in first 48 hrs after the onset of the symptoms [98].
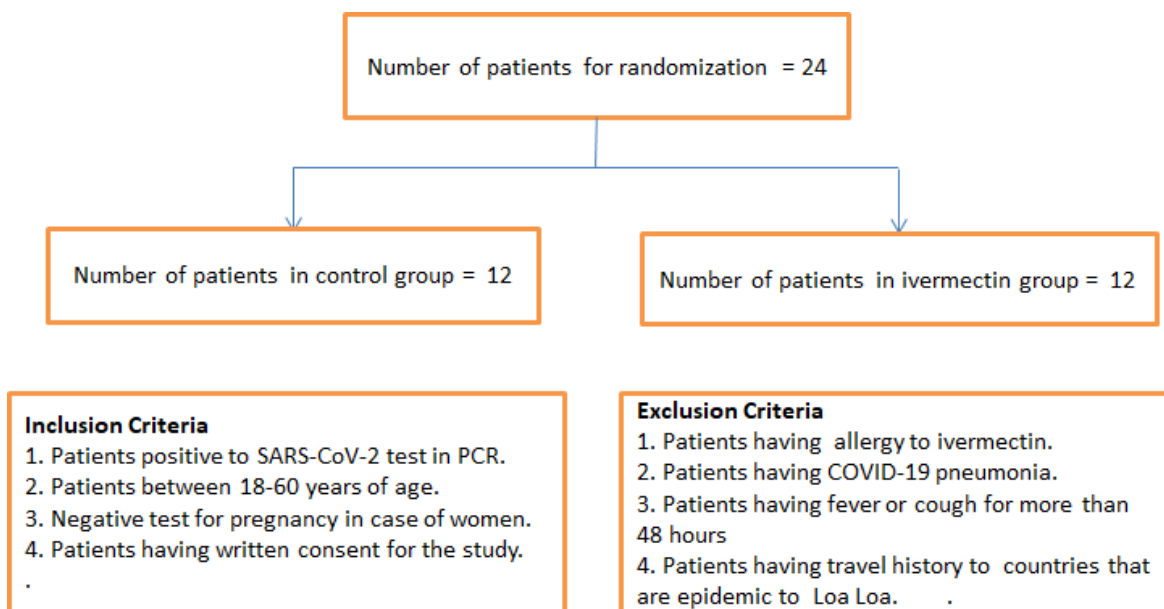
Figure 31: Proposed design of double-blind, randomized, placebo-controlled, superiority trial with two parallel arms for ivermectin

The patients of age between 18 to 60 years would be taken from Pamplona basin, Cuenca de Pamplona. The eligible patients would be distributed in 1:1 ratio of ivermectin and control group. 12 patients would be taken in ivermectin group while another 12 patients would be taken in control group (**Figure 31**). Ivermectin will be given at a dose of 400 μg/ Kg whereas control group will be given placebo. Primary outcome of the study would be the number of patients having positive COVID-19 tests at day 7. The secondary outcome would be to study the safety and efficacy of ivermectin along with other clinical parameters.

Chowdhury *et al.* have reported a randomized trial of ivermectin-doxycycline on COVID-19 patients in Chakoria Upazilla Health Complex, Cox's Bazar; Bangladesh which was found comparable to hydroxychloroquine-azithromycin treatment [99]. The study was done on 116 patients, out of which 60 patients were enrolled in group A which were given 200 μg/ Kg of single dose of ivermectin along with 100 mg BID of doxycycline for 10 days. Other 56 patients were enrolled in group B which were given hydroxychloroquine (400 mg on the first day followed by 200 mg BID for 9 days) and azithromycin (500 mg for 5 days) (**Figure 32**).
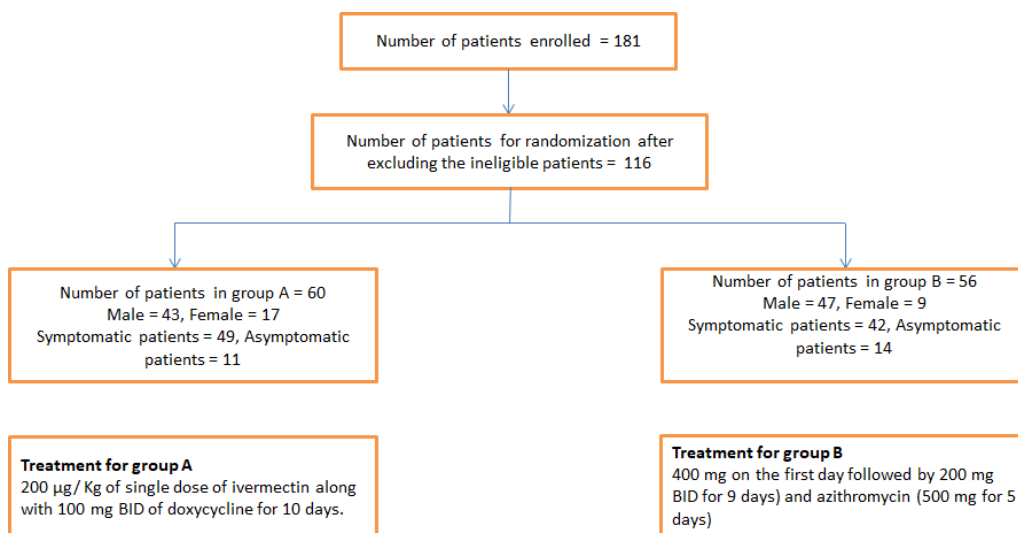
Figure 32: Randomization of COVID-19 patients in group A and Group B

In addition, all the enrolled patients were also given standard treatment for fever, cough, headache etc. The patients were subjected to PCT test for COVID-19 each day after the start of the treatment until it is negative. The results showed that the mean recovery time to negative PCR test was almost 9 days for group A with all the patients showing recovery. Further, 41 (63%) patients did not observe any new adverse effect whereas 14 (23%) patients observed

lethargy, 11 (18%) patients observed nausea and 7 (12%) patients observed occasional vertigo. In comparison the patients in group B witnessed lesser recovery rate of 96% with 54 out of 56 patients, showing the negative PCR test with mean recovery time of 9 days which is almost same in case of group A. Further, 30 (53%) patients were observed no new symptoms whereas 13 (23%) patients observed blurred vision, 22 (39%) patients observed lethargy, 10 (18%) patients observed palpitation and 9 (10%) patients observed nausea (**Table 5**).

Table 5: Clinical outcomes of group A and group B patients

	Recovery rate (% age)	Mean recovery time (Days)	Patients with no new symptoms (% age)	Number of patients observed Lethargy (% age)	Number of patients observed Nausea (% age)	Number of patients observed occasional vertigo (% age)	Number of patients observed blurred vision (% age)	Number of patients observed palpitation (% age)
Group A	100	8.93	63.3	23.3	18.3	11.66	NA	NA
Group B	96.36	9.33	53.57	39.2	16.07	NA	23.21	17.85

Gorial *et al.* have discussed the use of ivermectin as an add-on therapy to azithromycin and hydroxychloroquine in adult patients to treat mild to moderate COVID-19 patients at Al-Shifa'a Hospital [100]. Patients suffering from severe COVID-19 were excluded from this study. The trial was done on 85 patients wherein 16 patients were randomized for ivermectin therapy and 69 patients were taken in synthetic control arm (**Figure 33**).
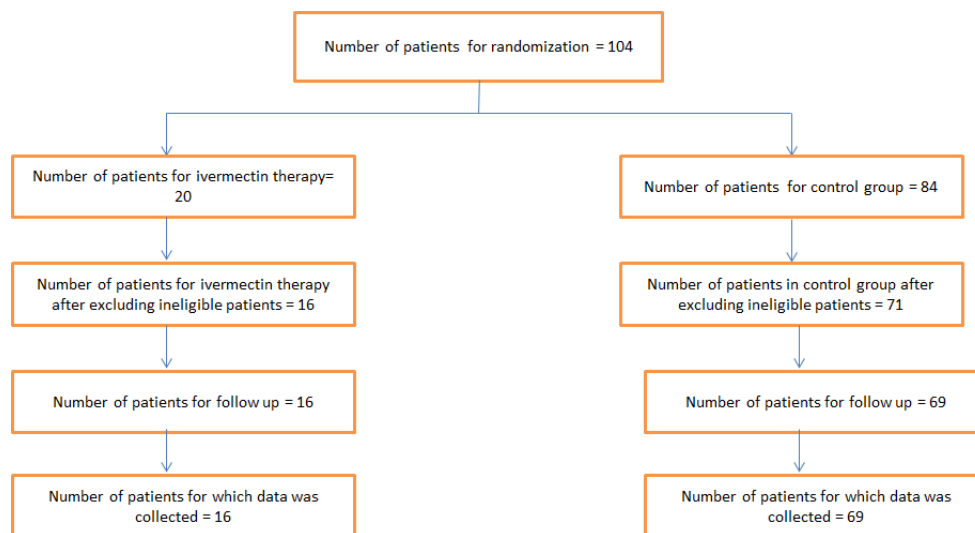
Figure 33: Randomization of COVID-19 patients in ivermectin and synthetic control group

Primary outcome of the study was the percentage of the patients cured within 23 days whereas the secondary outcome was the time taken to cure the patients. Further, the patients were given 200 μg of ivermectin as an add-on therapy to the standard of care which included 400 mg BID for day 1 followed by 200 mg BID for 5 days along with 500 mg of azithromycin on day 1 followed by 250 mg for 5 days. The data suggested the encouraging results for the add-on ivermectin therapy wherein 100% of the patients got cured as compared to the cure rate of 97.2% in case of synthetic control arm. Interestingly, the mean time to stay in the hospital was significantly lesser in ivermectin group (7.62 days) as compared to the synthetic control arm (13.22 days) (**Figure 34**). Also, the mortality rate in ivermectin group was zero as compared to 2.8% in synthetic control group.
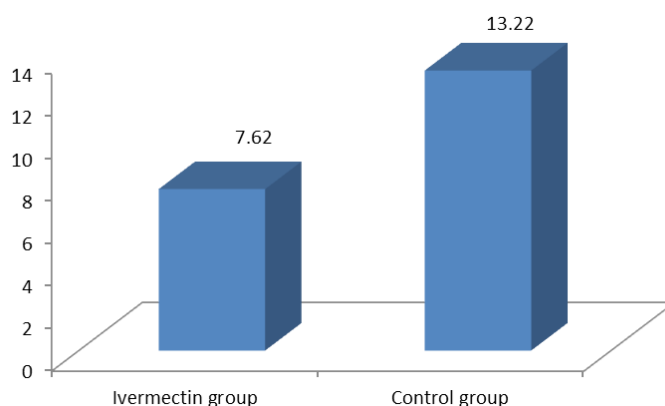
Figure 34: Mean time (days) to stay in hospital for COVID-19 patients for ivermectin and synthetic control group

Although invermectin has been reported to reduce the viral load to 5000 fold at 48 hrs but question of achieving the desired level of the drug in the human body still remains the challenge. Even if it is somehow achievable, the dose at such a high level (17 times higher than the maximum attainable level at 247.8 ng/ml dose) could be lethal. Moreover, at a dose regimen of 200 μg/ Kg for 10 days, the dug did not show significant improvement in the clinical parameters as compared to combined treatment with hydroxychloroquine and azithromycin. Interestingly, in one of the trial, the use of ivermectin as an add-on therapy to combined regimen of hydroxychloroquine and azithromycin that leads to improvement in the clinical outcomes of the 100% patients under study.

6. Us of Bruton's tyrosine kinase inhibitors as a treatment for COVID-19

6.1 Acalabrutinib

Acalabrutinib is a Bruton's tyrosine kinase inhibitors class of drug which has been used for the treatment of mantle cell lymphoma. Bruton's tyrosine kinase inhibitors are well known to modulate human inflammatory responses which are dominated by macrophages [101-102]. Further, the deficiency of BTK in mice is associated with the increased events of infections [103-105]. Thus the acalabrutinib may be used for the treatment of cytolkine storms and the immune responses associated with COVID-19.
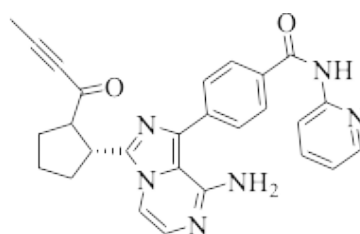
Acalabrutinib (10)

Roschewski *et al.* have reported the use of acalabrutinib, Bruton Tyrosine Kinase (BTK) inhibitor, to treat COVID-19 patients in off–label trial on 19 patients suffering from severe hypoxia and inflammation [106]. About 13 (68%) patients were men with median age of 61 years. Further, 11 patients (58%) were on supporting supplement of oxygen out of which 7 patients were on high flow nasal therapy and 8 (42%) patients were on invasive mechanical ventilation (**Figure 35**).
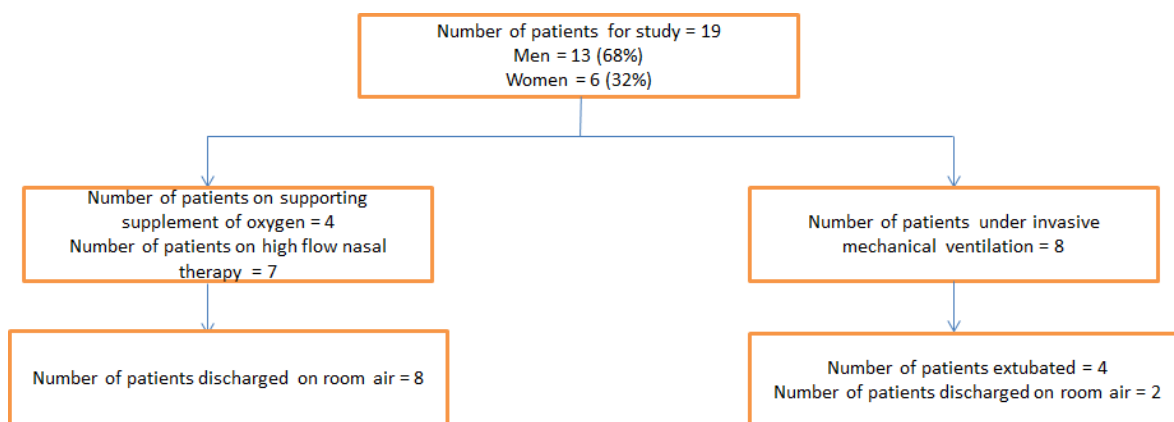
Figure 35: Enrollment details of the COVID-19 patients under study

Acalabrutinib (100 mg) was given to the patients orally once or twice daily for 10 days for the group under oxygen supplement and for 14 days for the group under invasive mechanical ventilation. The patients under study were also on concomitant drugs which included steroids or/ and hydroxychloroquine. Data indicated that 8 (73%) out of 11 patients who were of oxygen supplement did not require the oxygen and they were discharged from the hospital. Other 3 patients who were either on cannula or ventilation required less oxygen as supplement after the treatment with acalabrutinib. Further, out of 8 patients who were on invasive mechanical ventilation, 2 patients died during the study. At the end of the treatment, 8 (73%) patients from the supplement oxygen cohort group were discharged on room air whereas from the invasive mechanical ventilation cohort, 4 patients were extubated out of which 2 patients were discharged on room air. In terms of improvement of the inflammation, CRP level of 10 (91%) patients from the oxygen supplement group came to normal after the treatment and decreased for 1 patient. On the other hand, only 1 (37%) patient was discharged on room air from the invasive mechanical ventilation group (**Table 6**). Moreover, the oxygen uptake efficiency was found to be higher in oxygen supplement group as compared to invasive mechanical ventilation group.

Table 6: Clinical outcomes of the COVID-19 patients after 12 days

Clinical outcomes	Oxygen supplement group	Invasive mechanical ventilation group
Number of patients discharged on room air (% age)	73	25
Patients with normalization of CRP level (% age)	91	37
p-value	1.82E-3	1.46E-2

The data suggested that acalabrutinib treatment was found to be encouraging for the COVID-19 patients suffering from the mild to moderate respiratory dysfunctions whereas the treatment was not found encouraging for the patients who were on invasive ventilation group. However, very less data has been reported for its use and therefore more trials are needed to comment on the safety and efficacy for the treatments on the basis of clinical outcomes.

7. Use of corticosteroids as a treatment for COVID-19

7.1 Dexamethasone

Dexamethasone (**11**) is a potent corticosteroid medication which is used for the treatment of number of skin diseases, lung diseases, rheumatic problems etc. It is very well known to activate histone deacetylase [107]. 3C-like proteinase on SARS-CoV-2 virus can inhibit HDAC2 transport into the nucleus resulting in the impairment of the inflammation and cytokine responses [108]. Therefore activation of to activate histone deacetylase by dexamethasone may counter the action of the SARS-CoV-2 virus.
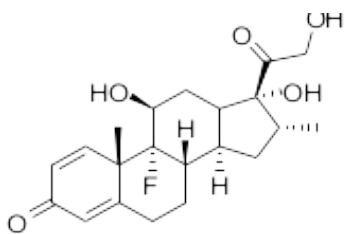
Dexamethasone (11)

Horby *et al*. reported the preliminary report for the controlled, open-label trial of dexamethasone (**2**) at an intravenous dose of 6 mg once daily for 10 days and the study was compared with the patients on usual care group which included 8% patients receiving dexamethasone, another 8% of the patients receiving azithromycin and 0-3% of the patients receiving lopinavir/ ritonavir, hydroxychloroquinine or interleukin-6 antagonists [109]. Total of 11,303 patients were screened including pregnant and breast feeding women in United Kingdom, out of which 2105 patients were assigned dexamethasone treatment and 4321 patients were assigned usual care (**Figure 36**).

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│  Number of patients assessed = 11303 │
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│  Number of patients for randomization for │
│  dexamethasone and other treatments after │
│  excluding not eligible patients = 9355   │
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│  Number of patients for randomization for │
│  dexamethasone and usual care= 6425       │
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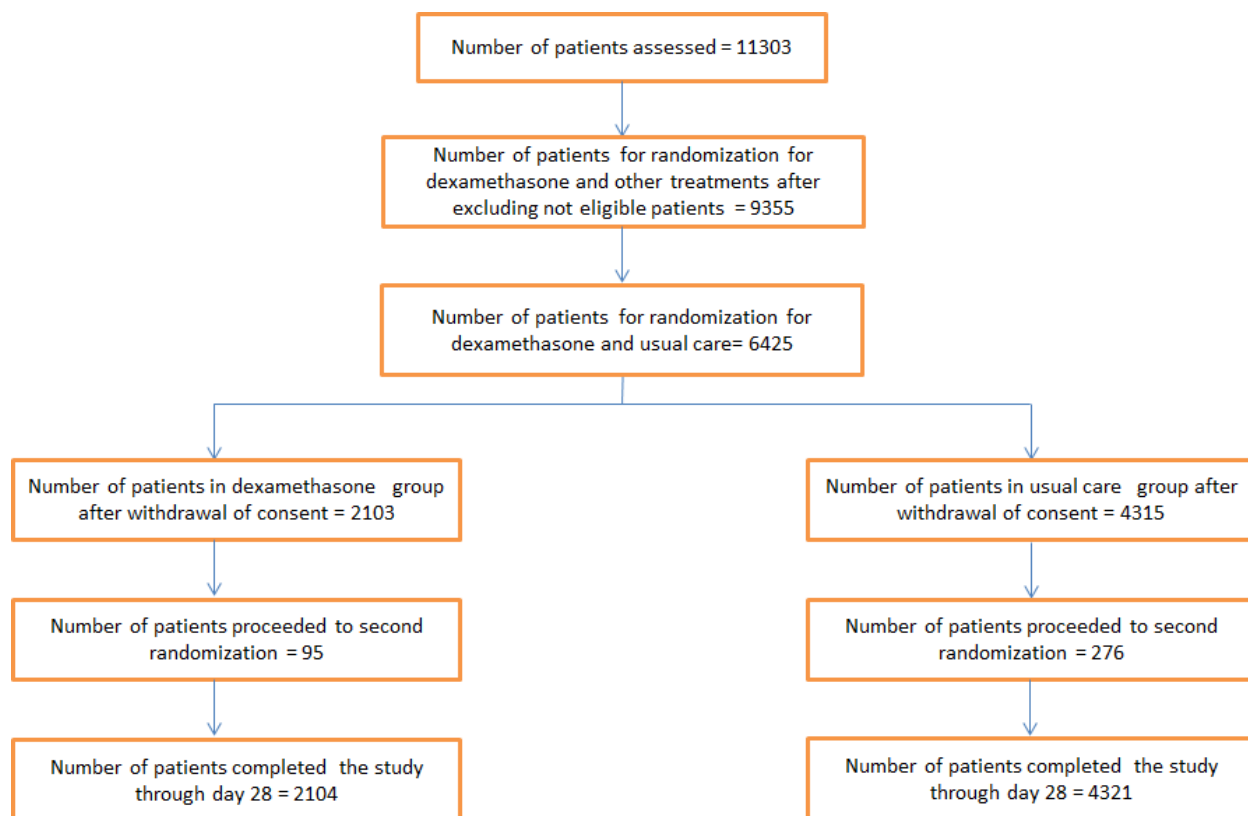
Figure 36: Details of patients under study

The mean age of the patients under dexamethasone group was 1.1 years which is greater than that of usual care group and the sex ratio of the women and men patients were 36% and 64%, respectively. Primary outcomes of trial suggested lower mortality rate of 22.9% for the patients in dexamethasone group as compared to mortality rate of 25.7% in usual care group at day 28. Interestingly, most promising results were obtained for patients who were under invasive mechanical ventilation. In addition, the reduction in the mortality after 28 days for the patients in dexamethasone group on invasive mechanical ventilation was found to be 12.3 percentage points as compared to 4.2 percentage points for the patients receiving oxygen only (**Figure 37**). Moreover, the duration of hospitalization was shorter for the patients under dexamethasone treatment (median 12 days) as compared to the patients in usual care group (median 13 days). In addition, the patients in dexamethasone group were found to have lesser risk for the progression to invasive mechanical ventilation than the usual care group.
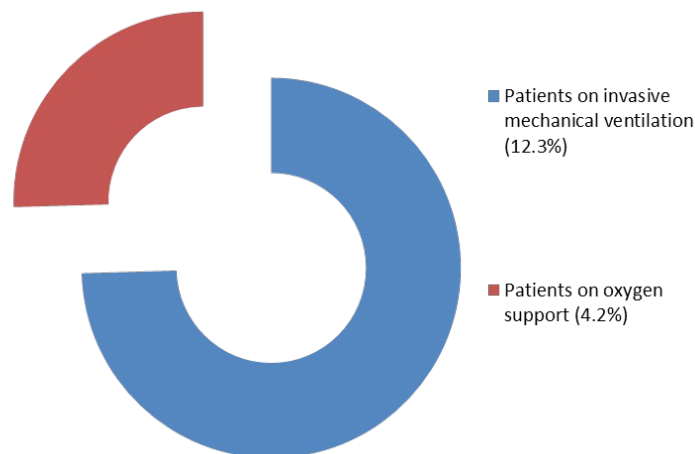
Figure 37: Reduction in the mortality rate among dexamethasone group with patients on invasive mechanical ventilation versus oxygen support

7.2 Methylprednisolone

Methylprednisolone (**12**) is a class of glucocorticoid medication which is used as autoimmune suppressant and for imparting inflammatory responses in rheumatic diseases [110]. It has also been used for the treatment of complications associated with SARS and MERS, however the results found were controversial [111-113]. ARDS is the leading cause of deaths in case of COVID-19 and it is proposed that glucocorticoids having immunosuppressant properties can treat the cytokine storm and eventually ARDS [114].
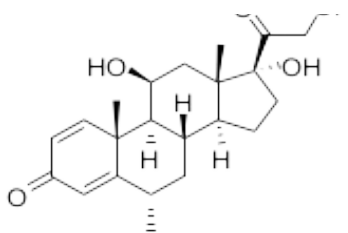
Methylperdnisolone (12)

Corral-Gudinol *et al*. have reported a multicentric, partially randomized, preference, open-label trial of methylprednisolone on 85 adult COVID-19 patients in Spain [115]. In this case, 34 patients were given methylprednisolone treatment, 22 patients were given methylprednisolone on clinician's choice and 29 patients were placed in control group (**Figure 38**). Further, the patients in methylprednisolone group were given standard of care alongwith 40 mg of

44

methylprednisolone after each 12 hrs for first 3 days followed by 20 mg after each 12 hrs for next three days whereas the patients in control group were given standard of care including oxygen therapy, antibiotics, acetaminophen, hydroxychloroquine, lopinavir/ritonavir and azythromycin. The data suggested the 45% risk reduction (24% absolute risk reduction) in the methylprednisolone group. Also, the CRP levels were found to be lower in methylprednisolone group as compared to control group. However, more number of patients (21%) in the methylprednisolone group observed side effects as hyperglycemia.
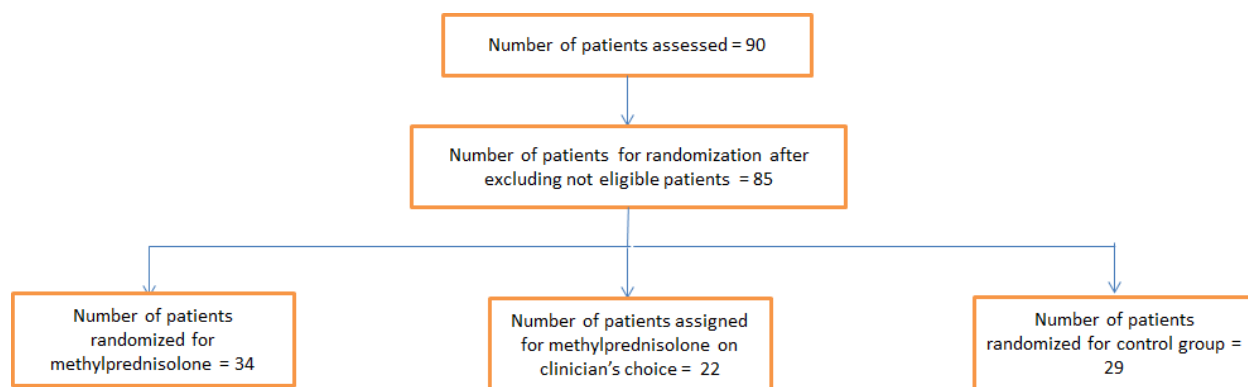
Figure 38: Randomization of adult COVID-19 patients for the trial

In a letter to editor, Liu *et al.* have reported the early use of methylprednisolone on 101 hospitalized patients in Zhuhai, China [116]. Out of 26 critical patients, methylprednisolone treatment (upto highest dose of 1000 mg) was given to 15 patients which resulted into significant improvement in the requirement of supplement oxygen. Also, the pulmonary functions were found to improve with these patients. Also, the mean time for viral clearance was found same (10 days) in the patient group treated with or without methylprednisolone dispelling the worry that use of methylprednisolone would affect negatively on viral clearance. All the patients were recovered during the methylprednisolone treatment. In term of efficacy, no adverse events were observed for the patients on methylprednisolone even after 1 month of follow ups.

Edalatifard *et al*. have reported the results from a randomized controlled clinical trial of intravenously administered methylprednisolone on patients with severe COVID-19 [117]. The study was performed on 68 patients from Tehran out of which 34 patients were placed in methylprednisolone group and other 34 patients were given standard of care treatment. However, 6 patients from control group were given methylprednisolone on clinician's choice and were

therefore excluded from the group (**Figure 39**). The methylprednisolone group was given 250 mg intravenous methylprednisolone for three days whereas the patients in control group were given hydroxychloroquine sulfate, naproxen and lopinavir. The end point of the study was taken as the clinical improvement or death. The collected data from the trial suggested high rate of clinical improvement (94%) in methylprednisolone group as compared to control group (57%).
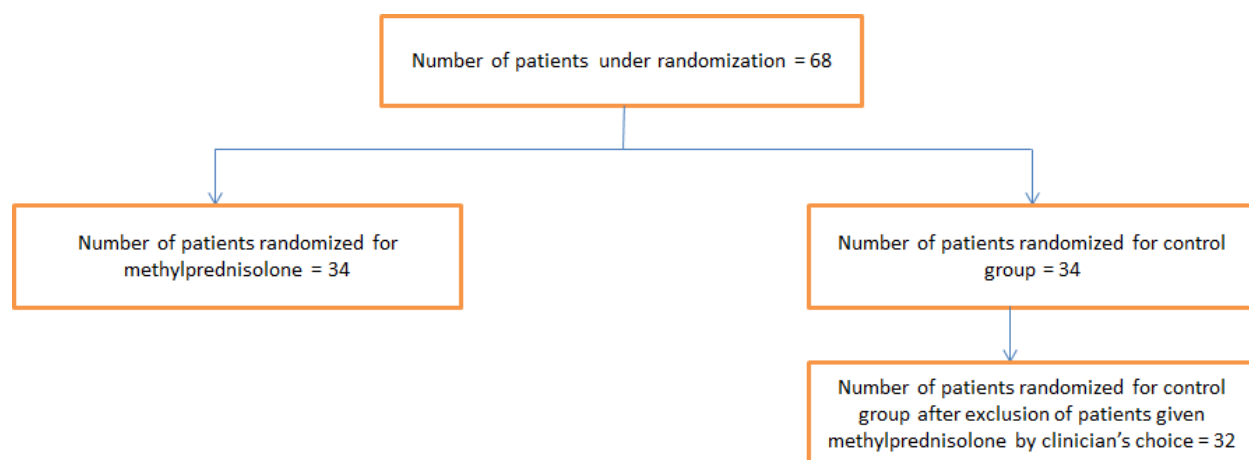
Figure 39: Randomization of COVID-19 patients for control and methylprednisolone treatment

In addition, the mortality rate in methylprednisolone group was found remarkably lower (5.9%) as compared to control group (43%). Further, the mortality rate was found lower in case of patients with non-invasive ventilation as compared to the patients on supplement oxygen. Also, time to improvement in the methylprednisolone group was found lower (11.62 days) as compared to control group (17.61 days). Although no significant difference in the adverse events were found in both the group, but the patients in methylprednisolone group were at lower adverse events (5.8%) than the control group (7.1%). However, cough was observed in both the groups as a common side effect. In terms of secondary outcomes, blood SO_2 levels, heart rate and normalization of body temperature of patients in methylprednisolone group were improved significantly after 3 days as compared to the control group where no significant improvements were observed (**Table-7**).

Table 7: Clinical outcome of COVID-19 patients under different treatment groups

	Time to end point (Days) (Discharge/	Time to improvement (Days)	Improvement (% age)	Mortality rate (% age)	Patients do not need supplement

	death)				oxygen at discharge (% age)
Methylprednisolone group	11.62	11.84	94.1	5.9	81
Control Group	17.61	6.93	57.1	42.9	62

Liu *et al.* have reported the use of methylprednisolone on COVID-19 patients in Beijing, China at different levels of severity and from different demography [118]. Total of 65 COVID-19 patients as confirmed by RT-PCR method were included for the study out of which 10 (16%) patients were mild, 32 (49%) patients were general, 8 (12%) patients were severe and 15 (23%) patients were critical (**Figure 40**). Further, 36 (55%) patients were having history of travelling to Wuhan, 17 patients were in close contact with clinically confirmed COVID-19 patients and 5 (7.69%) patients were in contact with people from Wuhan. The patients were treated commonly with interferon and lopinavir/ritonavir treatment along with the oxygen supplement as per the conditions of the patients. 31 (48%) patients were treated with median dose of prednisolone at 1-5 mg/ Kg per day with 1-2 mg/Kg for general, 1-5 mg/Kg for severe and 1-4 mg/Kg for critical patients. Further, the patients were categorized into lower dose (less than or equal to 2 mg/ Kg per day; 20 (64.52%)) and high dose (> 2 mg/ kg per day; 11 (35.48%)) (**Figure 41**).
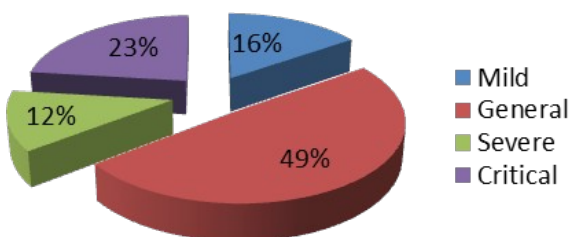
Figure 40: Clinical conditions of COVID-19 patients in methylprednisolone group
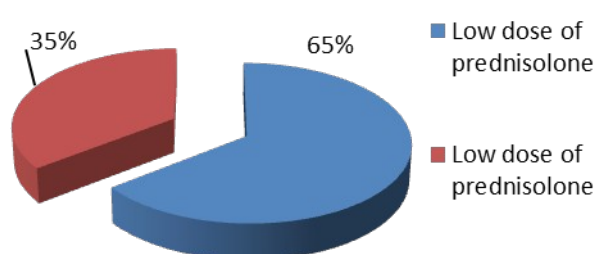
Figure 41: Grouping of COVID-19 patients on the basis of methylprednisolone dose

The data suggested that 30 (96.77%) patients were observed improvement in the pneumonia on CT scan. However, 2 (6%) patients died during the treatment. The median time for viral clearance was found shorter (12.5 days) in methylprednisolone group as compared to the control group (19 days). Further, IL-6 levels were found to increase more in case of patients with severe and critical COVID-19 as compared to mild patients (**Figure 42**).
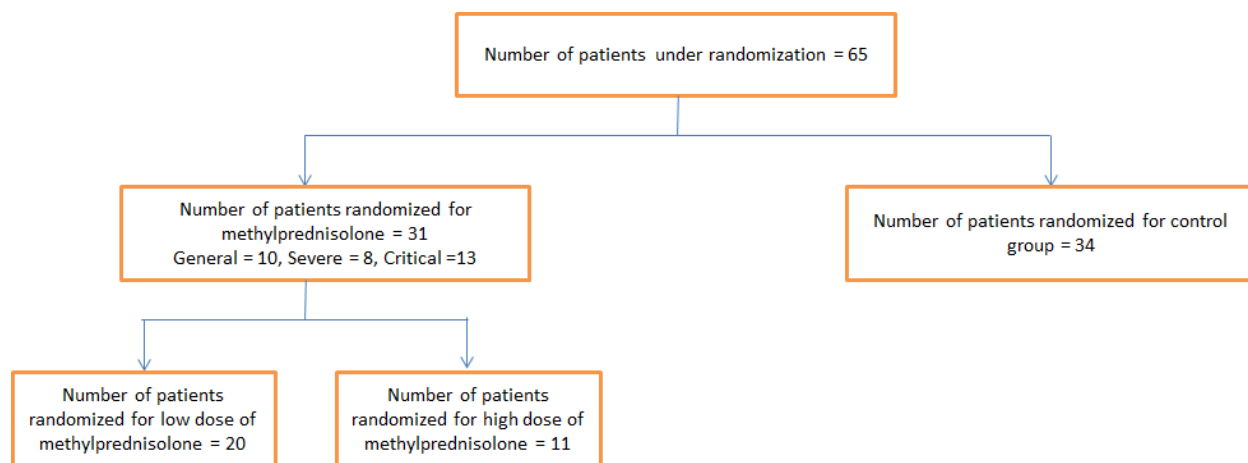
Figure 42: Randomization of COVID-19 patients

The use of corticosteroids for the treatment of COVID-19 patients has been controversial due their potential side effects. The use of glucocorticoid is recommended to be avoided by WHO for the management of COVID-19 [119]. But at the same time, they are known to inhibit the inflammatory storm by the suppression of cytokine storm [120]. Moreover, the initial clinical studies by using these drugs have resulted in remarkable decrease in the mortality rate with low adverse events. Also, these drugs have been proven to be more efficient in case of severe and critical COVID-19 patients in the clinical trials supporting their potential to be used as emergency medicine to treat COVID-19.

8. Use of Phosphodiesterase 4 (PDE4) inhibitors as a treatment for COVID-19

8.1 Apremilast

Apremilast is a class of Phosphodiesterase 4 (PDE4) inhibitors used for the treatment of psoriatic arthritis. The most severe case of COVID-19 is associated with hyperinflammatory state which can be attributed to cytokine storm which results in multiple organ failure such as ARDS [121-122]. Cyclic adenosine monophosphate is known to hold a key role in modulating the cytokine release by suppressing the pro-inflammatory cytokines such as TN-α and IL-10 [123]. Further, intracellular levels of cyclic adenosine monophosphate depend upon the activity of 4(PDE4) and therefore the inhibition of 4(PDE4) could lead to the improvement in the inflammatory response [124-125].
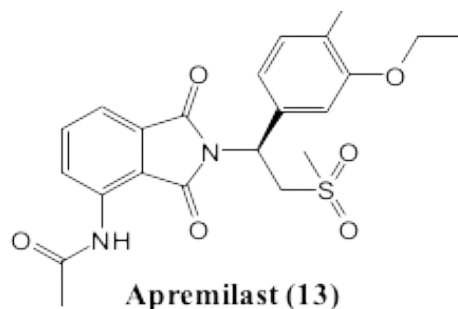
Apremilast (13)

Olisova *et al.* have reported a case study of apremilast on 61 years old male suffering from psoriasis from almost last 15 years and had a history of being treated with 30 mg of apremilast twice daily since September 2020 [126]. In mid April 2020, his family members were diagnosed with COVID-19 with severe cough, fever and COVID-19 associated infections. But to the surprise, although he was also tested positive with COVID-19, no sign of infections were observed. It was assumed that due to the accumulation of apremilast in the body as a result of the apremilast treatment from the past 8 months, the patients under study had developed some kind of immune system against COVID-19 in terms of increase in intracellular cyclic adenosine monophosphate levels, phosphodiesterase inhibition and a decrease in the expression of TNF-α which is found to increase during COVID-19 (**Figure 43**).

In an another letter to editor Mugheddu *et al.* have reported a case of apremilast on 45 years old man having a history of severe psoriasis and arthritis and have been treated with all traditional drugs and eventually underwent chemotherapy with emozolomide [127]. The patient was initially treated with 30 mg of apremilast twice daily which was reduced to 12.5 mg per day on observing the gradual improvement. On confirmation with COVID-19, treatment with lopinavir/ ritonavir (400 mg/ 100 mg twice daily) was started along with ceftriaxone (2 gm/ day). Apremilast therapy was continued during the COVID-19 treatment. Interestingly, the patient was discharged within a week from the hospital after negative test for COVID-19.
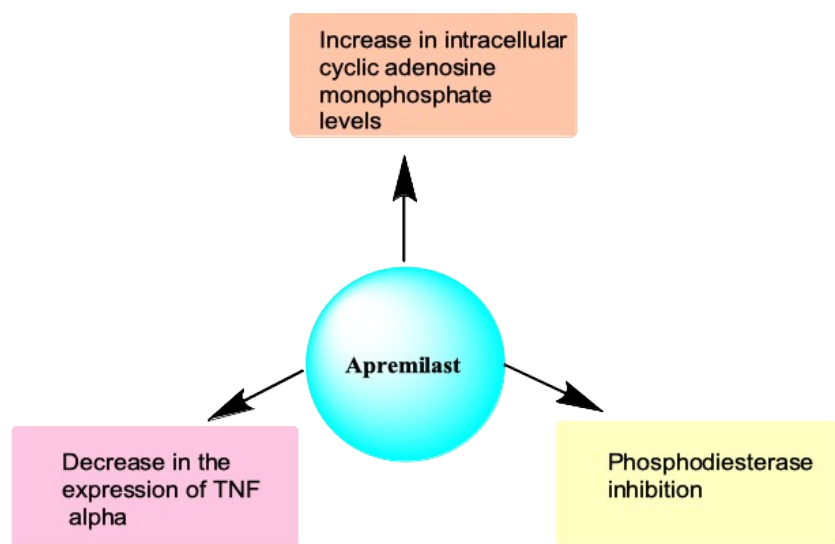
Figure 43: Probable development of defense system against COVID-19 due to apremilast

Very less data has been collected for the use of apremilast for the treatment of the COVID-19 patients and more data is required to comment on the safety and efficacy of this drug. Moreover, it is very hard to comment on the potential of this drug on the basis of only 2 cases.

9. Use of Human granulocyte macrophage colony-stimulating factor receptor (GM-CSF-R) inhibitors as a treatment for COVID-19

9.1 Mavrilimumab

Human granulocyte macrophage colony-stimulating factor (GM-CSF) is a cytokine having role in modulating the inflammation responses. Therefore, receptors which bind GM-CSF can activate multiple pro-inflammatory pathways by increasing the levels of IL-1, IL-1, IL-23, IL-12 etc. [128]. Mavrilimumab is a monoclonal antibody that binds to GM-CSF-R and disrupts downstream signaling [129].

Luca *et al.* have reported a single-centre, prospective cohort study of 13 patients who were given mavrilimumab, an anti-granulocyte–macrophage colony-stimulating factor receptor-α monoclonal antibody, with their standard therapy in San Raffaele Hospital (Milan, Italy) [130]. The patients under study did not require mechanical ventilation and were of the age greater than or equal to 18 years. A cohort of control group consisting 26 patients was also designed for the patients who were on standard of care excluding the treatment with mavrilimumab. The patients

under study were on hydroxychloroquine, azithromycin, lopinavir/ ritonavir and supplement oxygen as a standard of care. Mavrilimumab was given to the patients at a dose of 6 mg/ Kg and the clinical outcomes of the patients were assessed on a seven point ordinal scale. The main outcome was the improvement of at least 2 points on the ordinal scale. **Table 8** depicts the status of the patients in mavrilimumab and control group.

Table 8: Status of the patients in mavrilimumab and control group.

	Number of febrile patients	Number of patients on supplemental low-flow oxygen	Number of patients on high flow oxygen	Number of patients on non-invasive ventilation
Mavrilimumab group (n = 13)	11 (85%)	4 (31%)	6 (46%)	3 (23%)
Control group (n = 26)	18 (69%)	11 (42%)	9 (35%)	6 (23%)

The patients under both the groups were studied for their clinical outcomes for 28 days. The data supported the positive impact of mavrilimumab where no mortality was observed as compared to control group where 7 (27%) patients died during the treatment (**Figure 44**). Further, 13 (100%) patients in the mavrilimumab group observed improvement in the clinical outcomes as compared to 17 (65%) patients in control group (**Figure 45**). In addition, only 1 (8%) patient in mavrilimumab group required mechanical ventilation as compared to 9 (35%) patients in control group. Also, 11 (85%) of the patients in mavrilimumab group observed normalization of CRP levels as compared to 11 (44%) patients in control group. The data further suggested that the mavrilimumab treatment was well tolerated in the patients under study without occurrence of any infusion reactions. However for one patient, an increase in the CRP level, serum procalcitonin and white blood cells was observed who was therefore shifted to ICU after 3 days of infusion.
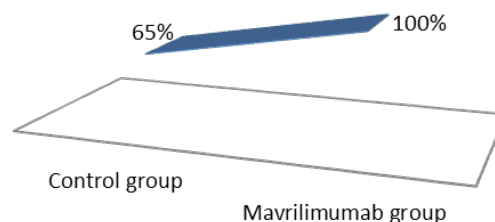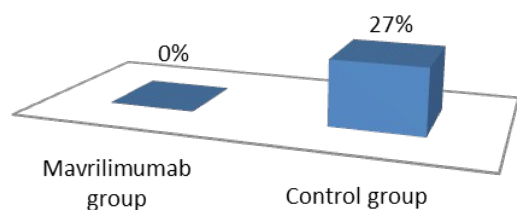
Figure 44: Mortality rate of COVID-19   **Figure 45:** Percentage of patients observing

patients   clinical improvement

The use of mavrilimumab resulted in the improvement of the respiratory functions of COVID-19 patients as compared to control group. This may be attributed to the activation of the pro-inflammatory as well as downstream pathways.

10. Use of Interleukin 1 receptor antagonists as a treatment for COVID-19

10.1 Anakinra

Anakinra is IL-1 receptor antagonist which is used for the treatment of rheumatoid arthritis. IL-1 is a pro-inflammatory mediator which is produced in response to the infections and is central to hyperinflammation associated with cytokine syndromes. It can cross the blood brain barrier on intravenous administration and therefore, it has been used for the treatment of the range of cytokine storms [131]. Association between the systemic inflammation, adverse outcome and severity of COVID-19 has been well reported in literature [132-133]. The use of anakinra may results into the management of the ARDS and immunological responses in COVID-19 patients.

Aouba et al. have reported the use of IL-1 blocker anakinra for the treatment of 9 patients of age greater than or equal to 18 years which were suffering from severe COVID-19 pneumonia [134]. Anakinra was administered to the COVID-19 patients subcutaneously at 100 mg dose after 12 hrs from day 1 to day 3 followed by 100 mg after 24 hrs from day 4 to day 10. One patient of age 45 years witnessed acute respiratory failure after first dose of anakinra and therefore the treatment was stopped for that patient. On the other hand, 8 patients under study observed improvement in their clinical and biological parameters. 5 (62%) patients showed normalization of CRP levels at day 11 with improvement in the chest lesion. Mortality rate of this treatment was zero showing the negative toxicity of this drug.

Cauchois et al. have reported the trial of anakinra over 30 patients from Avignon and Toulon which were on standard treatment including antibiotics and hydroxychloroquine [135]. All the patients were having moderate to severe COVID-19. Along with that, 2 patients were also on lopinavir/ ritonavir treatment. After satisfying the inclusion criteria, 12 patients were taken on anakinra treatment while 10 patients were taken in control group (**Figure 46**).
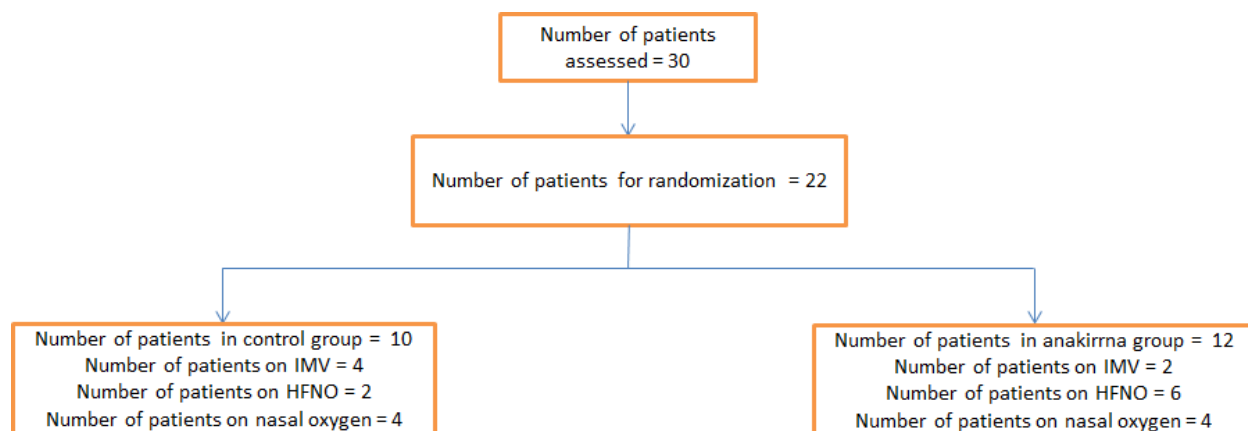
Figure 46: Randomization of the patients having moderate to severe COVID-19

The patients were given anakinra intravenously at 300 mg from day 1 to day 5 followed by 200 mg from day 7 and finally at 100 mg for day 8. The clinical and biological outcomes of the patients were monitored for 20 days. The patients under anakinra group showed rapid response to fever within 48 hrs of administration of the drug whereas the patients under control group had fever symptoms even after taking the paracetamol. In addition, the patients under anakinra group showed rapid stabilization of CRP as compared to the control group.

Cavalli *et al*. have reported a cohort study of interleukin-1 blockade in patients suffering from ARDS and hyperinflammation associated with COVID-19 with the use of high dose of anakinra at the San Raffaele Hospital in Milan, Italy [136]. Duration of the treatment was taken as time to achieve 75% reduction in CRP for at least 2 days or until adverse side effects were observed or until death of the patient. The clinical outcomes of the patients were monitored for 21 days. High dose of anakinra was administered intravenously at 5 mg/ Kg twice daily in group 29 patients having median age of 62 years out of which 24 (38%) patients were male. 21 (72%) patients observed improvement in the respiratory function. Moreover, at the end of the anakinra therapy, 13 (45%) patients were discharged from the hospital, 3 (10%) patients were in no need of supplement oxygen, 3 (10%) patients were requiring low supplement of oxygen and 2 (7%) patients were recovered from ARDS. However, 3 (10%) patients died and 5 (17%) patients were on mechanical ventilation during the anakinra treatment. On the other hand in control group containing 16 patients on standard of care treatment (**Figure 47**), 8 (50%) patients showed improvement in the respiratory function out of which 7 (44%) patients were discharged from the hospital, 1 (6%) patient needed low supplement of oxygen.
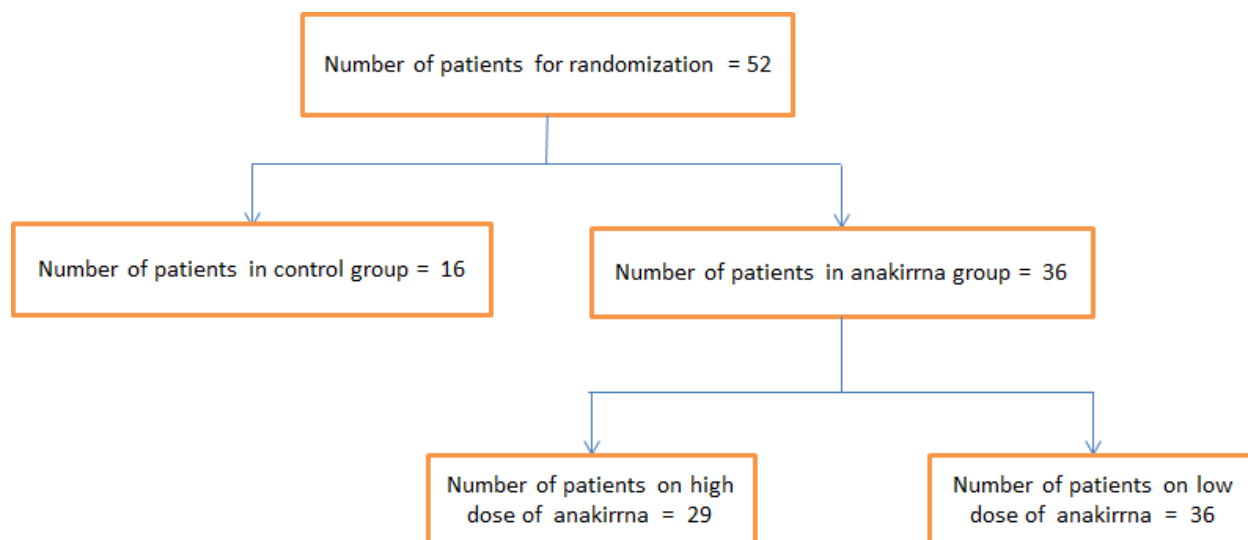
Figure 47: Randomization of the COVID-19 patients

However, 7 (44%) patients died and 1 (6%) patient was on mechanical ventilation during the treatment (**Table 9**). The data clearly suggested that remarkable results were obtained in the patients in anakinra group with very less mortality rate of 55% as compared to 44% of mortality rate in control group.

Table 9: Clinical outcome of the COVID-19 patients under control group and anakinra treatment

	Total patients enrolled	Patients recovered from respiratory functions	Patients discharged from the hospital	Patients requiring no supplement of oxygen	Patients requiring low supplement of oxygen	Patients requiring mechanical ventilation	Mortality rate
Anakinra group*	29	72	45	10	10	10	5
Control Group*	16	50	7	NA	6	6	44

* The data is given in percentage values

Interestingly, anakinra was found to be efficacious even at high dose with 7 (24%) patients observing the adverse events after mean duration of 9 days. In contrast, the trial of anakinra in 7 patients with low dose of 100 mg twice daily did not give any significant improvement in their clinical outcomes and therefore it was discontinued after 7 days.

Dimopoulos *et al*. have reported the significant improvement in the clinical parameters with the use of anakinra in severe COVID-19 patients with Secondary Hemophagocytic Lymphohistiocytosis (SHL) [137]. The study was done of 7 male patients in Greece who were given intravenous administration of 200 mg of anakinra after each 8 hrs for 7 days along with azithromycin, hydroxychloroquine and broad spectrum antibiotics. The treatments led to improvement in the clinical outcomes of all the 7 patients, especially in the respiratory function. However, 3 (43%) patients died within 28 days of treatment. Similarly, in another study on 71 years old female patient at Radboud University Medical Center treated with chemotherapy and hydroxychloroquine, the treatment with anakinra led to rapid and remarkable improvement in the respiratory function.

Filocamo *et al*. have reported a successful trial with anakinra on healthy 50 years old man in Crema, Lombardy, which was confirmed COVID-19 positive [138]. The patient was initially treated with hydroxycholoroquine, lopinavir/ ritonavir and was put on non-invasive ventilation. The health of the patient was deteriorated by day 10 of administration with the patient being shifted to ICU and was put on invasive mechanical ventilation. This led to start of off-label anakinra treatment which was started with initial dose of 200 mg of anakinra followed by 100 mg subcutaneously after each 6 hrs which resulted in remarkable decrease in the inflammatory markers and ferritin. In addition, significant reduction in liver enzymes was also observed. Considering the significant improvement in the clinical parameters and remarkable response to respiratory functions, anakinra treatment was discontinued and antibiotic treatment was started. The patient was discharged from the hospital on day 29.

Huet *et al*. have reported a cohort study of anakinra for severe COVID-19 cases in Groupe Hospitalier, Paris [139]. The study was done on 52 patients registered in anakinra group and 44 patients in historical group. The patients in anakinra group were given subcutaneous dose of 100 mg anakinra twice daily followed by 100 mg for 7 days whereas the patients under historical group were given standard of care of 600 mg/ day of hydroxychloroquine for 10 days, 250 mg/ day of azithromycin for 5 days and either 1 gm of ceftriaxone or 3 gm of amoxicillin for 7 days. The study suggested that the lower number of patients (13, 25%) in the anakinra group needed invasive mechanical ventilation as compared to historical group (32, 73%) (**Figure 48**). In terms of safety, the increase in the liver aminotransferase was observed at a greater value of 13%

patients in anakinra group as compared to 9% in historic group. In addition, 19% patients in anakinra group witnessed thromboembolic events as compared to 11% in historic group.
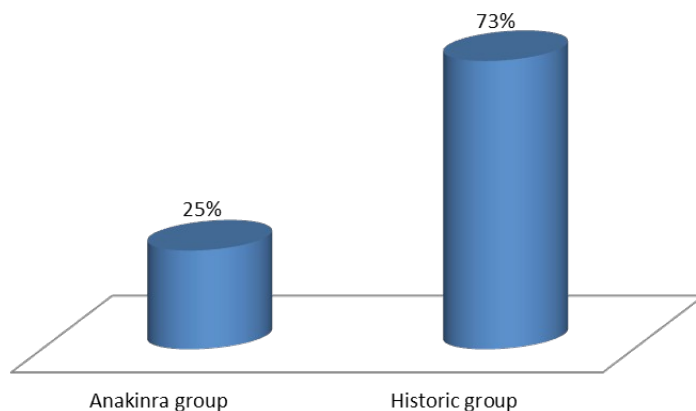
Figure 48: Percentage of COVID-19 patients requiring invasive mechanical ventilation in anakinra and historic group

10.2 Canakinumab

Canakinumab is a monoclonal antibody which is IL-1β blocker and is used for the treatment of the rheumatologic disorders. IL-1β is known to induce inflammation during infections and autoimmunity [140]. Based upon its mechanism of action, canakinumab has been under investigation for its potential use to treat COVID-19.

Caracciolo *et al*. have reported the case study of another IL-1β inhibitor for the treatment of 85 years old male patient suffering from COVID-19 [141]. The patient was first treated with hydroxychloroquine, antibiotics and with supplement oxygen. The patient did not respond to therapy and severe lung injury was observed on day 3. Although his fever was somehow subsided in day 4 but constant deterioration of the respiratory function was observed along with the need of non-invasive ventilation. The patient was subjected to azithromycin, lopinavir/ ritonavir and enoxaparin sodium. The patient was further given 8 mg/ kg of tocilizumab intravenously on day 5 which was repeated after 12 hrs. On day 23, the patient was shifted to ICU because of severe arterial hypertension. The patient was finally given 300 mg of canakinumab subcutaneously on day 25 and day 31. The patient responded remarkably to canakinumab with improvement in the diuresis and renal functions. In addition, improvement in IL-6 and NK cells expressing CD56. However, the patient did not recovered from the infections

during the treatment and the patient died finally died on day 58 but the positive result of canakinumab on respiratory and diuresis cannot be ignored.

Sheng *et al*. have reported the design for double-blind, randomized controlled trial for the study of canakinumab treatment to reduce cardiac and respiratory functions in COVID-19 patients of age either equal to or greater than 18 years in hospitals across the Cleveland Clinic Health System [142]. The enrolled patients must be positive for COVID-19 for the upper respiratory tract specimen. Total of 45 patients have been enrolled for this study for 7 months and the first patient have been randomized on 28th April 2020. The patients are to be randomized in 1:1:1 ratio wherein 15 patients are planned to be given 600 mg of canakinumab and other 15 patients are to be given 300 mg of canakinumab intravenously whereas 15 additional patients are to be randomized for placebo studies. The enrolled patients are also to be allowed for the standard of care of treatment for COVID-19 (**Figure 49**).
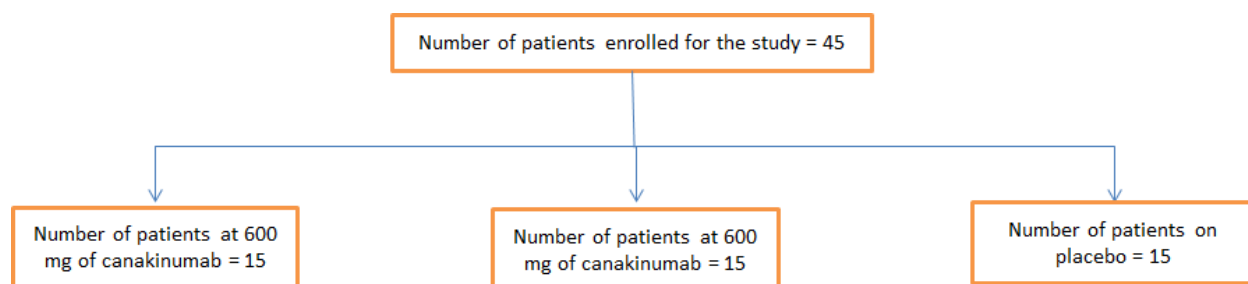
Figure 49: Proposed 1:1:1 randomization of COVID-19 patients for canakinumab study

In a correspondence to editor, Ucciferri *et al*. have reported analysis of treatment of 10 clinically confirmed COVID-19 patients (9 men and 1 woman) in Annunziata Hospital in Chieti, Italy on administration of 300 mg of canakinumab subcutaneously [143]. The patients were also on other treatment like 200 mg twice daily of hydroxychloroquine and 400/100 mg of lopinavir/ ritonavir twice daily. The study suggested that the canakinumab was well tolerated in patients without observing any significant adverse events. The patients observed improvement in the CRP level at day 1 and day 3 along with the reduction in the demand for oxygen supplement at day 3 and day 7. Interestingly, all the 10 patients were discharged from the hospital after 45 days of treatment.

The uses of anakinra in different clinical trials have been proven to be beneficial for the treatment of the ARDS and cytokine storm associated with COVID-19. The drug has been found

to be safe as low mortality rate was observed by the patients as compared to control group. However, high dose of anakinra is needed to achieve the desired clinical outcomes as the drug did not give positive results in one of the clinical trial at low dose. However, only few cases for the use of canakinumab wherein alongwith this drug, the patients were also given the other established treatments like lopinavir/ ritonavir, hydroxychloroquine, tocilizumab etc. which may have the synergic effect with canakinumab. More clinical data on large set of population of these 2 drugs can give the idea about the safety and efficacy parameters.

11. Use of Interleukin-6 receptor antagonists as a treatment for COVID-19

11.1 Tocilizumab

Tocilizumab is IL-6 receptor antagonist used for the treatment of severe rheumatoid arthritis, giant cell artheritis and to treat cytokine release syndrome. In the biopsy sample of COVID-19, patient inflammatory lymphocytes were seen in both the lings which suggested that cytokine storm might have occurred [144]. Also, on analyzing the immune factors of COVID-19 patient, aberrant pathogenic T cells along with inflammatory monocytes with large number of cytokine factors were observed [145]. Therefore, tocilizumab which is a IL-6 receptor antagonist and well known to manage cytokine storm has been explored for its potential use for the management of COVID-19.

Guaraldi *et al.* have reported the retrospective, observational cohort study of tocilizumab on 544 laboratories, confirmed COVID-19 patients from tertiary care center Reggio Emilia and Bolonga, Modena in Italy [146]. The study was aimed to investigate the role of tocilizumab in reducing the risk of invasive mechanical ventilation or death in patients suffering with severe pneumonia associated with COVID-19 who were given the standard of care. All the patients were given standard of care with supplement oxygen, azithromycin, hydroxychloroquine, low molecular weight heparin and antiretrovirals. Out of 544 patients under study, 359 (66%) patients were male with median age of 67 years. 365 (67%) patients were subjected to the standard of care group whereas 179 (33%) patients were given tocilizumab (**Figure 50**).
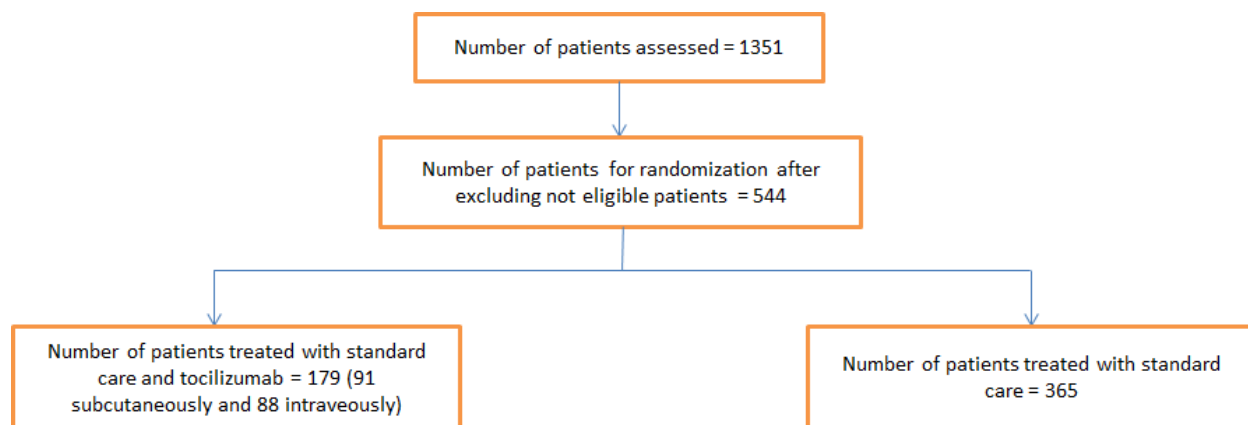
Figure 50: Overview of patients for retrospective, observational cohort study of tocilizumab

About 53 (30%) patients from tocilizumab group started glucocorticoids as compared to 61 (17%) patients in standard of care group. Further, patients treated with tocilizumab observed worst inflammatory profile and higher lactate dehydrogenase at baseline. 86 (16%) patients died during the treatment out of which patients treated with tocilizumab showed reduced mortality rate of 7% (13 patients) as compared to the patients in standard of care group where 20% (73 patients) of mortality rate was observed (**Figure 51**). In terms of safety, 1 patient was found to have injection site reaction and 1 patient suffered from severe neutropenia in tocilizumab group.
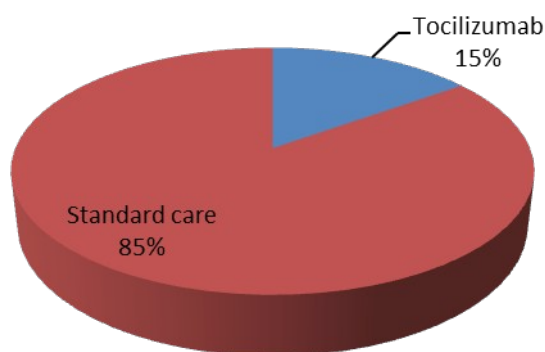
Figure 51: Percentage of mortality rate for COVID-19 patients treated with tocilizumab and standard of care

In addition, the patients receiving tocilizumab were found at reduced risk of invasive mechanical ventilation as compared to standard of care group and this effect was same irrespective of route of administration of tocilizumab. In terms of safety, one patient was found

to have injection site reaction and 1 patient suffered from severe neutropenia in tocilizumab group.

Klopfenstein *et al*. have reported a retrospective case-control study of 45 patients in France to study the effect of tocilizumab on the mortality rate and risk of requirement of ICU for severe COVID-19 patients [147]. Total of 45 patients were registered for the study out of which 20 patients received tocilizumab along with standard of care whereas 25 patients were placed in the control group who received standard of care only (**Figure 52**).
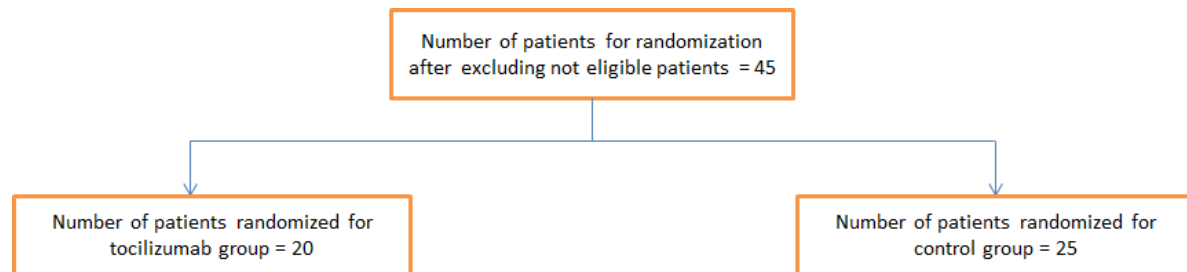
Figure 52: Randomization of severe COVID-19 patients for tocilizumab and control group

Further, tocilizumab was given to the patients after 13 days of onset of symptoms. The data suggested that the use of tocilizumab along with the standard of care resulted in the significant lesser number of deaths (25%) as compared to control group (48%). Moreover, none of the patient in tocilizumab group was in need of ICU or invasive mechanical ventilation after the treatment as compared to control group where 44% of the patients still needed ICU and 32% of patients needed invasive mechanical ventilation (**Figure 53**). The data suggested that the tocilizumab can be a potential treatment for the management of the severe COVID-19 patients.
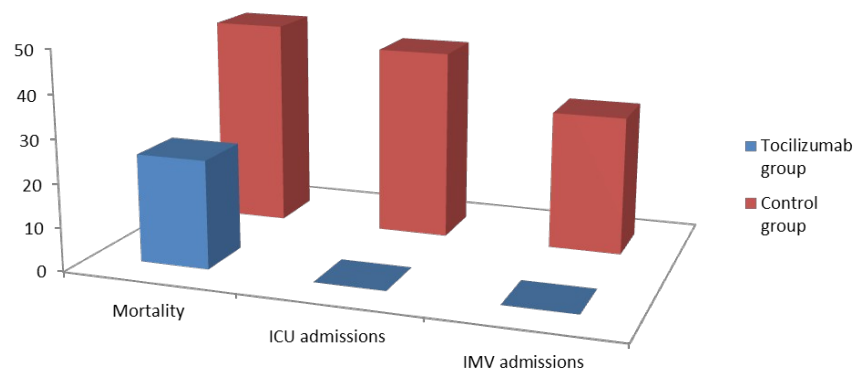
Figure 53: Clinical outcomes of the severe COVID-19 patients under different treatment groups (values presented are in percentage).

Luo *et al.* have reported single center study of tocilizumab on 15 patients (12 males and 3 females) in Tongji Hospital in Wuhan, China [148]. Out of 15 patients, 2 (13.3%) patients were moderately ill, 6 (40%) were seriously ill and 7 (46.7%) were critically ill (**Figure 54**).
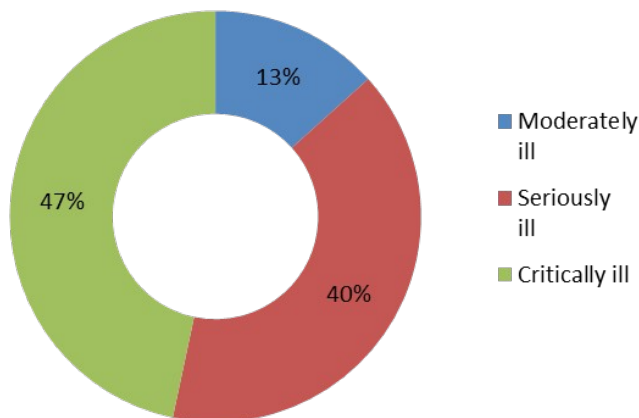
Figure 54: Distribution of the COVID-19 patients for tocilizumab treatment

Further, 8 (53.3%) patients received tocilizumab along with methylprednisolone whereas 5 (33.3%) patients received tocilizumab twice or more. The tocilizumab was given to the patients at dose of 80-600 mg per time. Interestingly, out of 4 patients who were given only one dose of tocilizumab, three patients were dead whereas no improvement in CRP level was observed for the 4th patient. In addition, 10 (66.7%) patients were observed normalization of IL-6 levels with tocilizumab therapy. This decrease was more persistent for the patients who received tocilizumab and methylprednisolone therapy. The data suggested that the repeated dose of tocilizumab is more effective than the single dose or methylprednisolone which is required at higher dose to achieve desired clinical outcomes.

Michot *et al.* have reported a case study for the use of tocilizumab for the treatment of respiratory failure associated with COVID-19 [149]. A 42 years old man having history of cancer observed elevated fever on 12th March 2020 and was recommended ceftriaxone. On day 6, he witnessed cough along with high temperature and was tested positive for COVID-19 test. On day 7, he was given lopinavir/ ritonavir treatment for 5 days. On day 8, his respiratory functions deteriorated and supplement oxygen was given. He received 2 doses of tocilizumab at 8 mg/ Kg at interval of 8 hrs after which improvement in the respiratory functions were observed. On day 12, the patient supplement oxygen was discontinued. In addition, the patient observed significant

improvement in CT scan on day 19 along with the decrease in the CRP levels 225 mg/L to 33 mg/L. The patient was found to recover completely from COVID-19.

Mihai *et al.* have reported a case study of 57 years old woman with systemic sclerosis associated interstitial lung disease (SSc-ILD) who was found positive for COVID-19 test [150]. On treatment with intravenous dose of 8 mg/ kg after every 4 weeks resulted in the improvement of arthritis and SSc-ILD and respiratory functions which were also confirmed in CT-scan. He did not observe any adverse symptoms and was advised to quarantine at home. Her mild symptoms were recovered after 10 days and she was found negative for the COVID-19 test.

Radbel *et al*. have reported two case studies of COVID-19 patients treated tocilizumab [151]. The first case was of 40 years old man with no medical history who was confirmed for COVID-19 test on PCR. He was started with hydroxychloroquine and azithromycin but he started observing sever adverse events after 2 days and was shifted to ICU where he also observed ARDS and was given bumetanide. On deterioration of inflammatory responses, tocilizumab treatment was started at 400 mg intravenously. Although the CRP levels were decreased after tocilizumab treatment but the patient could not survive and died. Second case was for 69 years old woman with history of type 2 diabetes, aplastic anemia and rheumatoid arthritis. The patient was given combined treatment of hydroxychloroquine and azithromycin on conformation of COVID-19 test. After 7 days from the onset of the symptoms, she observed septic shock with failure of respiratory functions and therefore was given norepinephrine and 560 mg of intravenous tocilizumab. On the next day, her shock worsened and she observed acute kidney injury. She was given second dose of 700 mg of tocilizumab after 9 days of symptoms onset after observing increase in inflammatory markers. But the patient did not recover and passed away.

Sciascia *et al*. have reported the Pilot prospective open, single-arm multicenter study of use of tocilizumab on 63 hospitalized patients with confirmed COVID-19 across 4 hospitals in Italy [152]. Total 34 (54%) patients were received intravenous dose of tocilizumab at 8 mg/ kg out of which 31(49%) patients received second dose of tocilizumab. Rest 29 patients received 324 mg of subcutaneous dose of tocilizumab with 21 patients receiving the second dose of 162 mg (**Figure 55**).

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│ Number of patients randomized for│
│        tocilizumab= 63           │
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        │                    │
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│ Number of        │  │ Number of        │
│ patients         │  │ patients         │
│ randomized for   │  │ randomized for   │
│ intravenous      │  │ subcutaneous     │
│ tocilizumab      │  │ tocilizumab = 29 │
│ group = 34       │  │                  │
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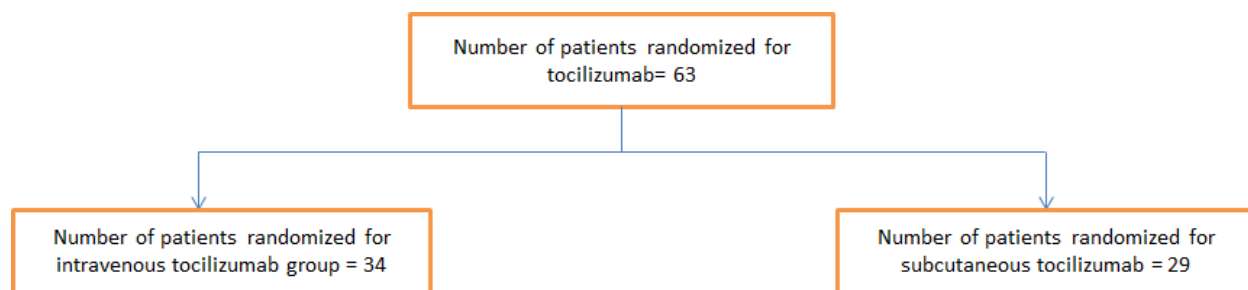
Figure 55: Randomization of COVID-19 patients for subcutaneous and intravenous tocilizumab treatment

The patients were kept under observation for 14 days after admission. Out of which 7 (11%) patients died during the treatment with no significant difference of mortality rate in both the arm (4 patients in intravenous group and 3 patients in subcutaneous group). In addition, significant improvement in the CRP, D-dimer and ferritin levels were observed. Also, the survival rate of the patients was increased after 6 days from the admission.

Toniati *et al*. have reported a single center study for the use of tocilizumab for severe COVID-19 patients with acute respiratory failure and hyperinflammatory syndrome in Brescia, Italy [153]. Total of 100 patients were considered for the study out of which majority of the patients were male (88%). Out of which 46% of the patients suffered from hypertension, 31% of the patients were having obesity, 17% of the patients having diabetes and 16% of the patients were suffered cardiovascular disease. Standard of care treatment involving lopinavir/ ritonavir 400 mg/100 mg twice a day or 100 mg of remdesivir twice a day, 400 mg of hydroxychloroquine per day, 30 mg of dexamethasone per day and antibiotics was also given to the patients along with the tocilizumab treatment. All the patients received 8 mg/Kg of tocilizumab in 2 doses 12 hrs a part. 87% of the patients received 2 doses of tocilizumab whereas 13% patients received 3 doses (**Figure 56**).


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┌─────────────────────────────────┐
│ Number of patients randomized for│
│        tocilizumab= 100          │
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│ Number of        │  │ Number of        │
│ patients         │  │ patients         │
│ randomized for 2 │  │ randomized for 3 │
│ doses of         │  │ doses of         │
│ tocilizumab      │  │ tocilizumab = 13 │
│ group = 87       │  │                  │
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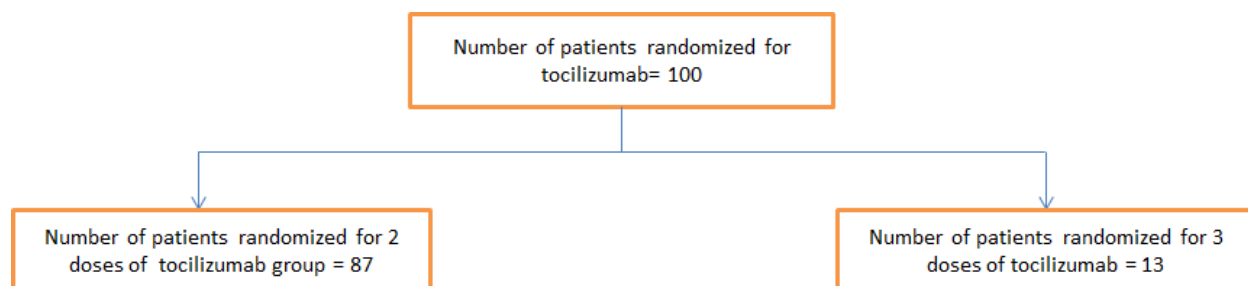
Figure 56: Randomization of COVID-19 patients for 2 and 3 doses of tocilizumab

After 72 hrs of tocilizumab treatment, 58% patients observed rapid improvement in their clinical outcomes, 37% patients stabilized and 5% patients observed worsening of the clinical outcomes out of which 4 patients died. After 10 days of tocilizumab treatment, 77% of the patients observed either improvement or stabilized whereas 23% of the patients observed worsening of the situations out of which 20 patients died (**Figure 57**). In terms of safety, 3% of the patients observed adverse events of septic shock and gastrointestinal perforation.
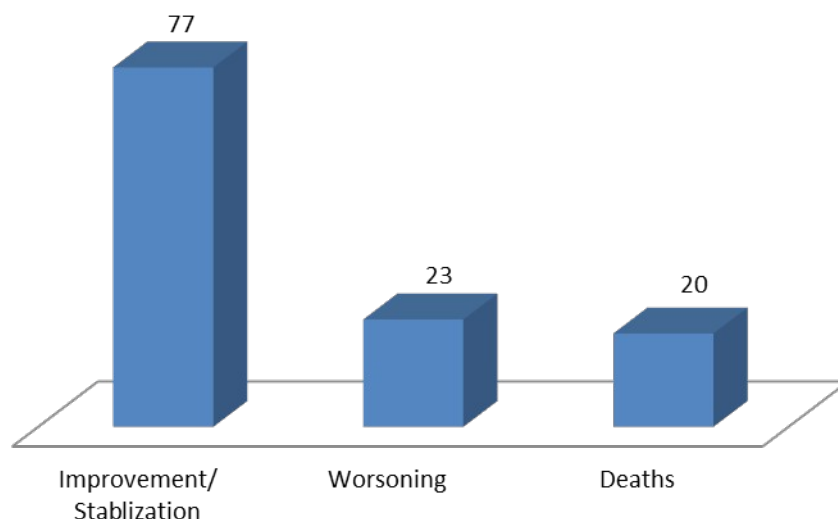
Figure 57: Status of the COVID-19 patients after 10 days of tocilizumab treatment

Xua *et al*. have studied the efficacy of the tocilizumab to treat severe COVID-19 patients [154]. The study was done on 21 patients in China out of which 18 patients were male and 3 patients were female (**Figure 58**).
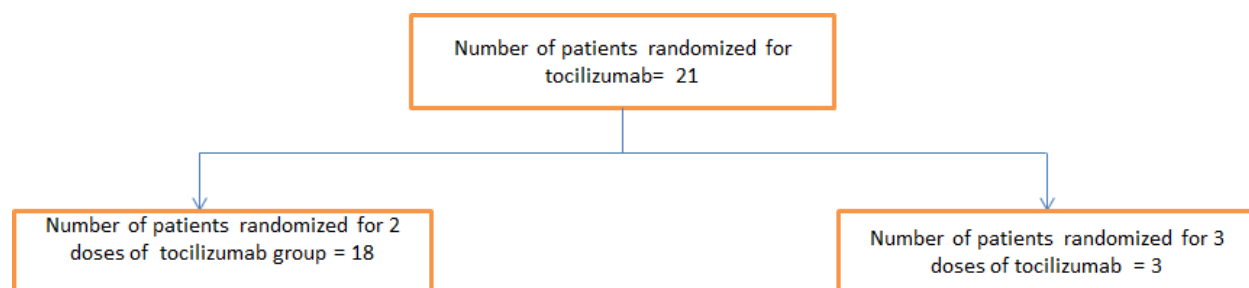
Figure 58: Randomization of sever COVID-19 patients

Further, 17 patients were severe and 4 patients were critical. Further, 18 patients received one dose of tocilizumab whereas 3 patients needed another dose within 12 hrs due to fever. [154].

The body temperature of all the patients returned to normal level on the first day after receiving the tocilizumab along with the improvement in the clinical outcomes in the following days. Remarkable improvement in the respiratory functions of the patients was observed within 5 days of treatment Only 10.5% patients were having abnormal levels of white blood cells whereas 52.6% patients observed normalization of lymphocytes. No significant decrease in IL-6 levels was observed in short treatment. In terms of safety, no serious adverse events were observed during the treatment (**Figure 59**).
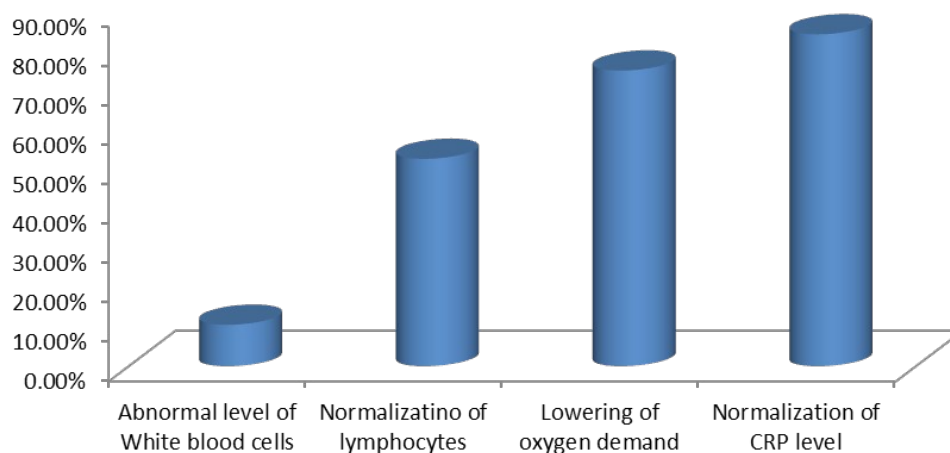
Figure 59: Clinical outcomes of the severe COVID-19 patients

Zhang *et al*. have reported a case study of 60 years old man suffering from COVID-19 who had history of multiple myeloma since 2015 and had received 2 cycles of chemotherapy consisting dexamethasone, bortezomib, and thalidomide [155]. The patient was admitted to hospital on 16 Feb. 2020 due to tightness in chest and shortness of breath. The patient was given 40 mg of methylprednisolone from day 2 to day 6. On day 8, the patient observed improvement in shortness of breath but still felt tightness of chest. Considering the situation of the patient, 8 mg/ kg of tocilizumab was given intravenously to the patient one time in day 9. Interestingly, the tightness in the chest was disappeared on day 12 and his IL-6 levels were found to decrease within 10 days of treatment. The achievement of the peak value of IL-6 was attributed to normalization of levels of T cells. The patient was finally recovered from COVID-19 after the treatment.

11.2 Sarilumab

Sarilumab is another IL-6 receptor antagonist used for the treatment of rheumatoid arthritis. Rapid exhaustion of tocilizumab resulted into exploration of sarilizumab as a potential treatment for COVID-19 patients.

Benucci *et al*. have reported a clinical trial of sarilumab, which is an IL-6 inhibitor, on eight patients to treat the pneumonia associated with COVID-19 [156]. The mean age of the patients was 62 years and the trial was done on 6 men and 2 women in Florence, Italy which were tested positive for COVID-19 in RT-PCR test. Sarilumab was added to the standard therapy of the patients which included 500 mg of azithromycin, 400 mg of hydroxychloroquine, 800 mg of darunavir, enaoxaparin 100 U/Kg and 150 mg of cobicistat. Sarilumab was given twice as 200 mg dose administered intravenously after 24 hrs of hospitalization and 200 mg dose subsequently after 2 and 4 days, respectively. Interestingly, the use of sarilizumab with the standard treatment resulted in the early discharge of the patients within 14 days of hospitalization. However, one patients of age 83 years died after 13 days of hospitalization.

Della-Torre *et al*. have reported an open label cohort study of sarilumab on 28 patients with severe COVID-19 pneumonia and systemic hyperinflammation at San Raffaele Hospital, Milan, Italy [157]. The inclusion criteria of the patients included the confirmed COVID-19 infections by PCR on nasal-pharyngeal swab, pneumonia confirmed by radiology. In addition, the clinical outcomes of the patients were compared with the controlled group of another 28 patients which were on standard of care alone (**Figure 60**).
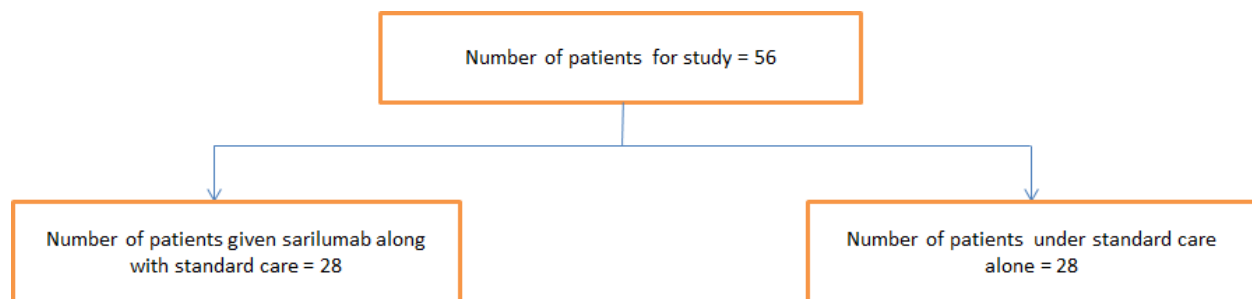
Figure 60: Enrollment details of the COVID-19 patients under study

All the patients under study were taking standard therapy which included lopinavir/ritonavir, azithromycin and hydroxychloroquine along with the supportive care like supplement oxygen, non-invasive ventilation. The patients were given 200 mg of sarilumab twice after 1 hr

interval administered intravenously. The clinical outcomes of two groups were compared after 28 days which suggested that the group treated with sarilumab witnessed higher survival rate of 93% as compared to 82% of survival rate of the group taking standard therapy (**Figure 61**).
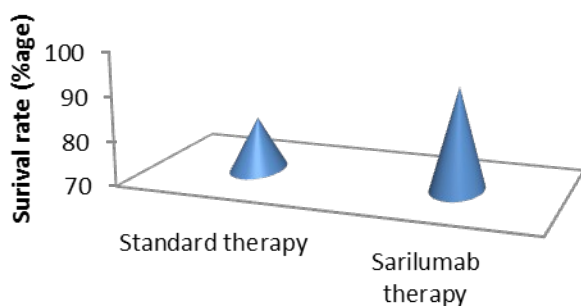
Figure 61: Survival rate of the COVID-19 patients treated with standard therapy and sarilumab
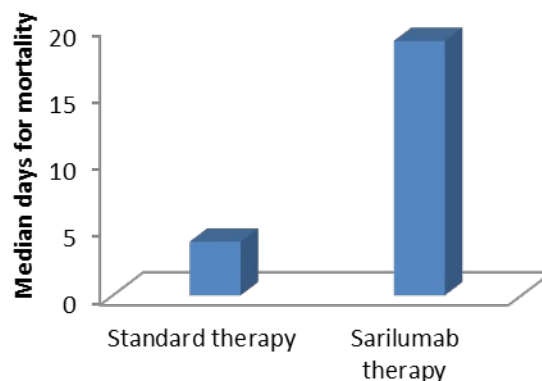
Figure 62: Median time to martality of the COVID-19 patients treated with standard therapy and sarilumab

The median time for mortality was 19 days in sarilumab group as compared to 4 days in standard therapy group (**Figure 62**). In addition, CRP normalization was witnessed 86% patients in sarilumab group *vs* 61% patients in standard therapy group. Further study of the safety data revealed that 43% of the patients in the sarilumab group reported the adverse events with 21% of the patients reported with bacterial infections as compared to 36% of patients with adverse events including 18% patients confirmed with bacterial infections in standard therapy unit (**Table 10**).

Table 10: Clinical outcomes of the COVID-19 patients after 28 days of administration

Clinical outcomes	Sarlumab group	Standard therapy group
Survival rate (% age)	93	82
Median time mortality (days)	19	4
Patients with CRP normalization after 28 days (% age)	86	61
Patients with adverse events (% age)	43	36
Patients with bacterial infections (% age)	21	18

Tocilizumab has been found to treat the cytokine storm and ADRS in severe and critical COVID-19 cases. Moreover, the dug is found to be safe in the initial trials as supported by less mortality rate as compared to control group. However, multiple doses of tocilizumab at high dose were needed to attain the required clinical outcomes in some trials as lower dose, high mortality rate was observed. Also, the recovery rate and time to recovery was significantly lesser in tocilizumab group as compared to control group. Some of the case studies have suggested further use of tocilizumab for COVID-19 patients who have history of cancer or multiple myeloma during which patients have more probability of infections which supported the safety of this drug. The results from the clinical trials at lower population size are promising suggesting its potential use for the management of deadly COVID-19 disease. On the other hand, lesser data has been collected for sarilumab where the drug has shown its potential for the management of COVID-19 with high survival rate of the treated patients. However, more incidences of adverse events have been observed in case of sarilumab as compared to tocilizumab. More data needs to be collected on sarilumab to comment on the safety and efficacy of this drug.

12. Use of IL-17 inhibitor as a treatment for COVID-19

12.1 Ixekizumab

Ixekizumab is IL-17 inhibitor which is used for the treatment of autoimmune disease. It has also been reported that ixekizumab is implicated in ARDS which is the severe condition of COVID-19 [158].

In a letter to editor, Balestri *et al*. have reported a case study of 55 years old general practitioner having 4 years history of psoriasis who was treated with ixekizumab [159]. The patient had the history of being treated with the conventional drugs and adalimumab. He was shifted to ixekizumab therapy of 160 mg for week 0 followed by 80 mg for weeks 2, 4, 6, 8, 10 and 12. He was tested for COVID-19 test on March 3, 2020 but the current therapy with ixekizumab was continued. The patient was observed negative for COVID-19 test on April 2, 2020. Interestingly, the patient did not observe any symptoms associated with COVID-19 infections.

11.2 Secukinumab

Secukinumab is a monoclonal antibody that binds to IL-17A and used for the treatment of psoriasis, psoriatic arthritis and ankylosing spondylitis. Conti *et al.* have reported a case study of 66 years old man who had history of being treated with ecukinumab since Oct 2019. He was in constant touch with his wife since 17th March 2020 who was tested positive with COVID-19. But, he did not observe any symptoms during the quarantine of 15 days [160].

Although the case study suggested that the use of ixekizumab and secukinumab may have resulted in the treatment of COVID-19 due to its ability to improve immune responses and ARDS. It is important to gather more data to study its beneficial effect for future use to treat the viral load.

13. Use of IL-23 inhibitors as a treatment for COVID-19

13.1 Guselkumab

It is a class of IL-23 inhibitors which is used for the treatment of plaque psoriasis and is associated with the side effect of lowering of immune response which may eventually increase the risk of infections in the patients under treatment.

Messina *et al.* have reported a case study of 32 years old woman who had a history of psoriatic arthritis and psoriasis since 18 years [161]. Further, the patient was treated with conventional and biology drugs like infliximab, adalimumab, methotrexate, etanercept, cyclosporine, ixekizumab and secukinumab. The patient was switched to ustekinumab therapy during April 2019 which was again shifted to guselkumab to which he observed marked improvement in arthritis and psoriasis. On 5th March 2020, she was tested positive for COVID-19 test. Interestingly, next day, the patient observed normal body temperature. Also, the patient never developed cough, sore throat, respiratory problem or any infections.

In another letter to editor, Benhadou *et al.* have reported a case study of 40 years old woman having history of psoriasis since 2000 and was on treatment with guselkumab since 2019 [162]. She was also treated previously with cyclosporine and methotrexate. On 9th March 2020, she was tested positive for COVID-19 and observed rapid worsening of her respiratory functions along with severe cough and fever. Her fever did not drop even with the treatment of paracetamol. She was given guselkumab on 16th March 2020 as scheduled injection for psoriasis. Interestingly, the patients observed remarkable improvement to body temperature and fatigue symptoms day after the guselkumab injection.

In a similar case study reported by Conti *et al*. for a 62 years old man having history of diabetes, overweight, renal failure who was receiving guselkumab since Nov. 2019 [160]. The patient was discharged from the hospital after 1 month of hospitalization including 2 weeks of treatment in ICU.

13.2 Ustekinuma

Ustekinuma is used for the treatment of psoriasis by inhibiting IL-1 and IL-23 which is a cytokine involved in inflammatory and immune responses [163]. Therefore, this drug can also be explored for the improvement in the cytokine and immune response in the COVID-19 patients.

Conti *et al*. have reported a case study of 66 years old man who received ustekinuma treatment on15th March 2020 and was found positive for COVID-19 test. Interestingly, the patient was recovered from the viral infection without undergoing any therapeutic treatment and was found negative for COVID-19 test on 15th April 2020 [160].

Although the use of guselkumab and ustekinuma is associated with the depreciation of the immune system leading to increase the probability of infections, the data collected from the case studies suggested that the use of these drugs is not detrimental in setting up COVID-19 infections. However, it was also assumed that these drugs did not help in viral clearance. Rather, it helps in the treatment of cytokine storm and immune responses associated with COVID-19. More data is required to be collected to support these assumptions.

14. Use of TNF-α inhibitors as a treatment for COVID-19

During the inflammatory response to pneumonia associated with COVID-19, levels of TNF-α were found to increase [164]. Therefore, the drugs inhibiting TNF-α can be a potential candidates for the management of ARDS and cytokine storm associated with COVID-19 [165].

14.1 Adalimumab

Adalimumab is TNF inhibitor which is used for the treatment of arthritis, ulcerative colitis and ankylosing spondylitis. Conti *et al*. have reported a case study of 67 years old woman who was on adalimumab treatment since Sept 2019 and were in close contact with 3 of her COVID-19 positive family members Since Feb 2020 end. She did not observe any symptoms of COVID-19 during her quarantine time [160].

Initial data collected from the case studies of the COVID-19 patients having history of being treated TNF-α inhibitors is encouraging but it represents only a very small population. More clinical trials on large population need to be performed to understand how this drugs can be utilized in the management of the COVID-19 patients.

15. Use of Janus kinase (JAK) inhibitors as a treatment for COVID-19

An elevated level of proinflammatory cytokines have been observed in COVID-19 patients which includes IL-2, IL-4, IL-6, IL-7, IL-10, TNF and IFN levels [166-168]. Among these cytokines, many employ distinct intercellular signaling pathway mediated by JAK [169]. For example IL-6 which is known to play important role in cytokine response syndrome activates JAK-STAT signaling pathway for various biological functioning which includes immune regulation and lymphocyte growth. [170-171]. Therefore, researchers are exploring the need of JAK-inhibitors for the potential uses in COVID-19 management.

15.1 Tofacitinib

Tofacitinib (**14**) is a class of Janus Kinase (JAK) inhibitor used for the treatment of various types of arthritis which is an autoimmune and inflammatory disease wherein the cytokines play an important role in disease progression [172]. It blocks IL-2, IL-4, IL-6 and IL-7 and there the use of this drug in COVID-19 patients can lead to effective management of the inflammatory responses and ARDS.
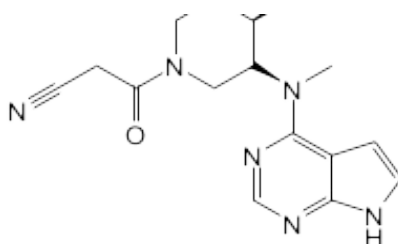
Tofacitinib (14)

Jacobs *et al*. have recently reported a case study of tofacitinib on 33 years of woman in case of COVID-19 infection [173]. The patients had a history of ulcerative colitis from the last 13 years. She became non-responsive to other medications like vedolizumab, infliximab and adalimumab and thus was under treatment with 10 mg of tofacitinib twice daily which resulted in

clinical remission after 5 months. She was discontinued from tofacitinib therapy afterwards. On confirmation of the COVID-19 positive test, she was again given tofacitinib therapy of 10 mg twice daily by keeping in mind her old history of poor response to multiple therapies. Her respiratory symptoms were found to be resolved after 5 days and no residual symptoms were visible after 2 weeks. However, the main reason for the recovery of patients remained undiscovered.

15.2 Ruxolitinib

Ruxolitinib is another drug of JAK inhibitors which has been used for the treatment of neoplastic disease. Its use is associated with therapeutic implications like sHLH and cytokine related inflammatory syndromes which is the measure of the disease progression in COVID-19 patients [174]. Therefore, many trials have been reported in literature regarding the use of this drug as a potential candidate for COVID-19.
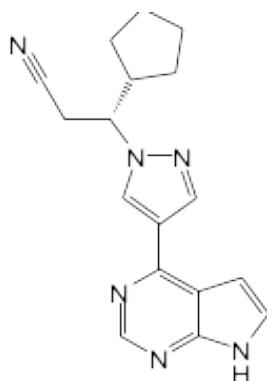
Ruxolitinib (15)

In a letter to editor, Gaspari *et al*. have reported the side effects of ruxolitinib on 2 patients [175]. The patients was 74 years old clinically confirmed COVID-19 male patient who was given non- invasive ventilation 20 mg dexamethasone, 6000 IU of enoxaparin, lopinavir (200 mg)/ ritonavir (50 mg) and 400 mg of hydroxychloroquine twice a day. The patients were showing adverse events and persistent deterioration of the health after 5 weeks of hospitalization after which he was given 162 mg of tocilizumab which resulted in clinically improvement to certain extent. Again after 6 weeks, the patient started showing the adverse effects due to which he was shifted to ruxolitinib treatment with 2 tablets of 5 mg each per day for 2 days followed by

4 tablets per day for next 3 days. Deep tissue infection on the left arm was observed due to which the ruxolitinib treatment was suspended.

Second case of COVID-19 was reported for a 63 years old woman who had a history of hypothyroidism which was treated with levothyroxine. On confirmation of COVID-19, she was given 200 mg of hydroxychloroquine, 6000 IU of enoxaparin and 200 mg of lopinavir/ 50 mg ritonavir twice daily along with low volume of supplement oxygen. On the 12th day of administration, treatment with 50 mg of ruxolitinib twice daily for the first 3 days after which the dose of ruxolitinib was doubled. The patient showed negative test of COVID-19 on 4th day of the start of ruxolitinib treatment. The dose of ruxolitinib was reduced to 50 mg per day along with the introduction of acyclovir therapy. After 4 days, the patient started observing reduction in hemoglobin value and erythrodermic rashes on whole body surface due to which ruxolitinib therapy was stopped and steroid therapy was started. The mode of action of ruxolitinib was attributed to its ability to reduce the cytokine storm associated with COVID-19.

Cao et al. have evaluated safety and efficacy of ruxolitinib in a multicenter, single-blind, randomized controlled phase II clinical trial across three hospitals in China [176]. Total of 58 patients were screened for the study out of which 43 patients were randomized for the study and 15 patients were excluded for the study. Out of 43 randomized patients, 22 patients were given ruxolitinib treatment along with the standard of care of placebo treatment whereas 21 patients were given placebo based upon standard of care. After further exclusion, 20 patients were considered for ruxolitinib group and 21 patients were considered for standard of care (**Figure 63**).
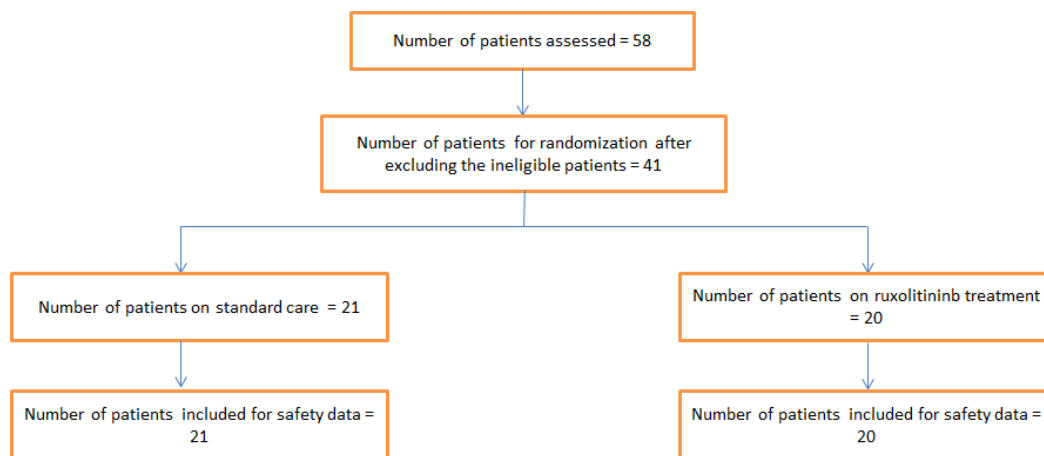
Figure 63: Randomization of the COVID-19 patients for the phase II clinical trial

Patients in ruxolitinib group who were given 5 mg of ruxolitinib twice daily along with the standard of care group which included antiviral therapy, non-invasive and invasive ventilation, supplement oxygen, antibiotic agents, renal placement therapy, vasopressor support and extracorporeal membrane oxygenation. The data suggested that 90% of the patients in the ruxolitinib group experienced significant improvement in the CT scan on day 15 as compared to 61.9% patients in control group. Moreover, 4 patients in the controlled group experienced adverse events during the study out of which 3 patients were died due to respiratory failure leading to overall mortality rate of 14.3% in control group as compared to no mortality in case of ruxilitinib group. However, there was no significant difference in the days from the randomization to discharge between the two groups and percentage of patients observing adverse events after 29th day of randomization for ruxilitinib group and control group was 80% and 71.4%, respectively. Interestingly, median time of recovery from lymphopenia for ruxolitinib group was shorter (5 days) than the control group (8 days) (**Table 11**). Further studies showed that ruxolitinib was also responsible to reduce the cytokine storm associated with COVID-19 for the mitigation of inflammation.

Table 11: Comparison of the clinical outcomes of the COVID-19 patients under ruxolitinib and control group

Clinical outcomes	Control group	Ruxolitinib group
Improvement in CT scan after 15 days of andomization (% age of patients)	90	61.9
Mortality rate (% age)	14.3	0
Adverse events after 29th day from randomization (% age of patients)	71.4	80
Median time for virus clearance (Days)	12	13
Median time of recovery from lymphopenia (Days)	8	5

Capochiani *et al.* have reported the effect of using ruxolitinib to treat the acute respiratory distress syndrome in eighteen COVID-19 patients in Livorno, Viareggio, Siena [177]. The data set included 12 male and 6 female patients with median age of 62.5 years and age limit of 28 years to 86 years (**Figure 64**).
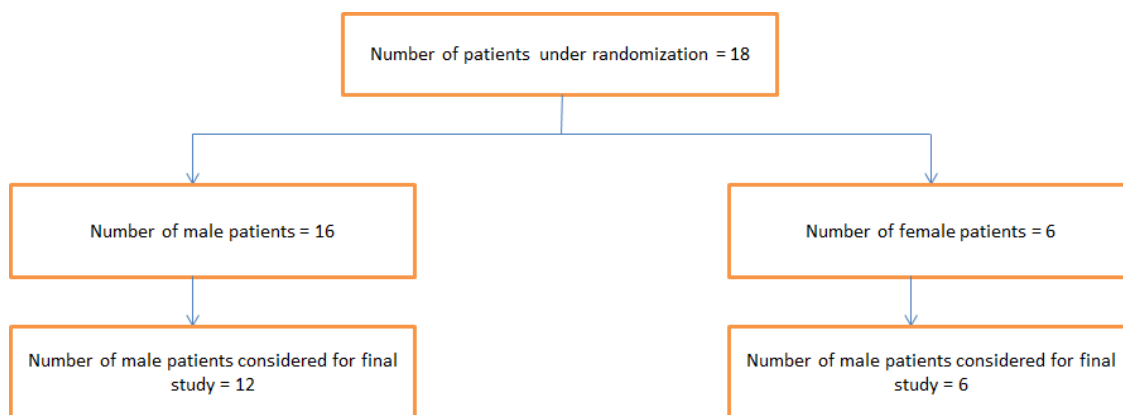
Figure 64: Randomization of the patients for ruxolitinib treatment

The patients were given 20 mg of ruxolitinib for the first 48 hrs which was reduced to 10 mg or 5 mg of dose as per the response of the patients within 14 days of start of treatment. In case where the patients were found to suffer from adverse effect with 20 mg of dose of ruxolitinib, the reduction of dose to 10 mg was done for the next 24 hrs. Ruxolitinib was given along with the standard of care which included azithromycin, heparin or steroids etc. Data suggested that 16 (89%) patients showed improvement in the respiratory response along with the reduction of IL-6 levels within 48 hrs of administration of ruxolitinib whereas 2 (11%) patients were found non-responsive to the treatment and increase in the IL-6 levels were observed. Interestingly, 11 (61%) of the patients were totally recovered from the respiratory syndrome after 7 days while 4 (22%) patients had minimal oxygen requirement. In addition, 1 (56%) patient were having stable while other 2 (11%) patients showed progressive disease (**Figure 65**).
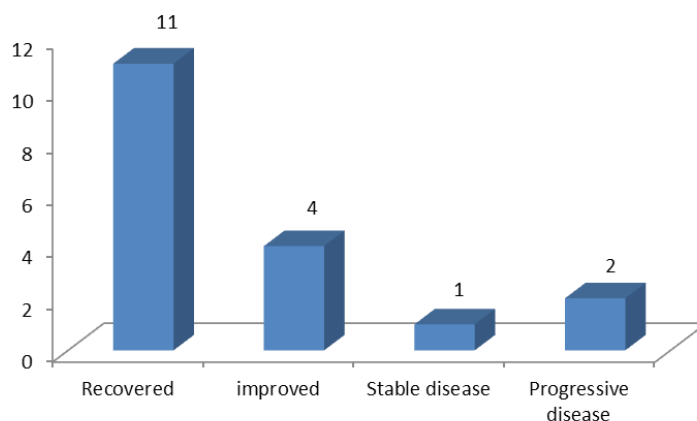
Figure 65: Status of the COVID-19 patients against Acute Distress Respiratory Syndrome after 7 days of treatment with ruxolitinib.

Rosee *et al*. have reported the use of ruxolitinib for the treatment of severe systemic hyperinflammation associated with COVID-19 using a newly developed COVID-19 inflammation score (CIS) by monocentric retrospective chart analysis [178]. Out of 105 patients administered in hospital, 66 patients were treated with standard of care treatment.
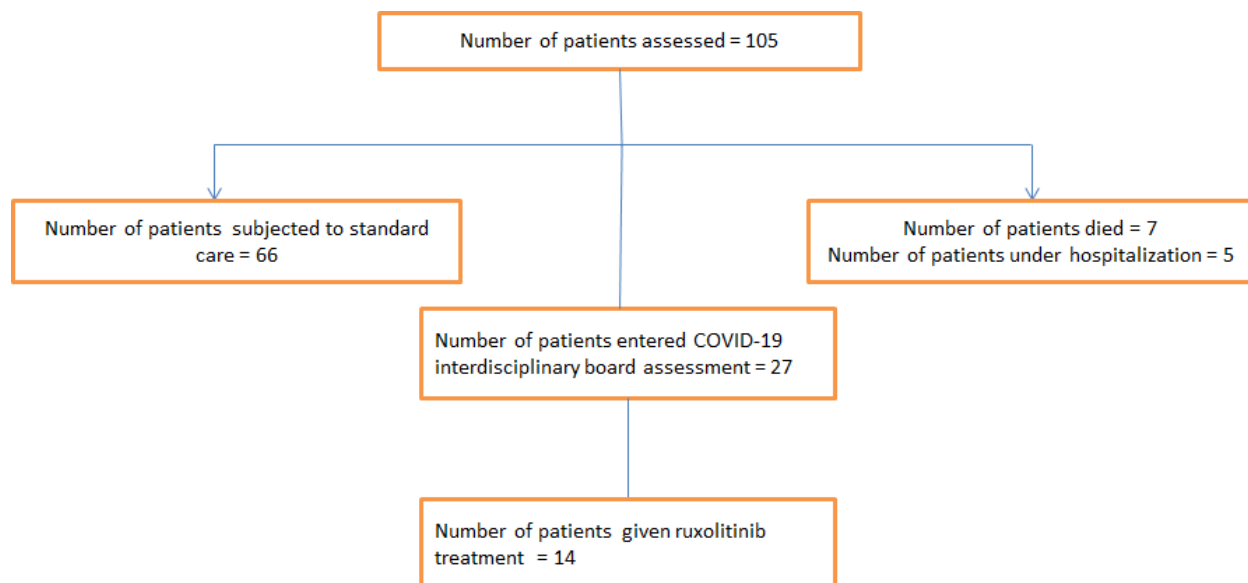
Figure 66: Randomization of COVID-19 patients

Total 27 patients were considered for COVID-19 interdisciplinary board assessment out of which 14 patients were given ruxolitinib treatment (**Figure 66**). Patients having prior infections and having survival probability of less than 6 months were excluded from the study. Further, majority of the patients were on non-invasive ventilation. The patients having CIS of greater than or equal to 10/16 were taken as high risk of inflammation. Ruxolitininb treatment was started with 7.5 mg which was increased stepwise to 15 mg. Patients under study were given 1000 mg of ascorbic acid, 500 mg of acetylsalicylic acid, 600 mg of hydroxychloroquine on day 1 followed by 200 mg from 2-5 days, heparin and antibiotic treatment. In addition, prednisone at dose of 2 mg/ Kg from day 1-3 was also given depending upon the condition of the patients. Further, patients having greater value of IL-6 levels were also given single dose of 400 mg of tocilizumab. The study showed that the treatment with ruxolitinib resulted in the reduction of CIS within days along with the reduction of the necessity of supplement oxygen. The study suggested the acceptable side effects with the use of ruxolitinib.

15.3 Barcitinib

Baricitinib is an inhibitor of JAK1 and JAK2 and is used for the treatment of rheumatoid arthritis in adults. It may possess inhibitory effects on regulators of endocytosis like AAKI and GAK due to which it may affect the cellular viral entry of SARS-CoV-2 [179]. It can also be used in combination with remdesivir which has been used for the treatment of COVID-19 because of its minimal interaction with CYP enzymes [180].
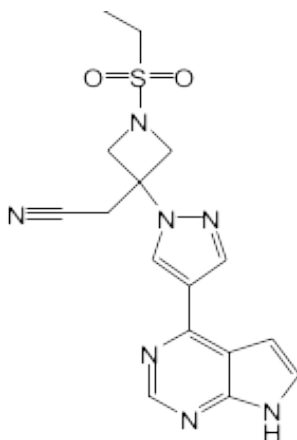
Baricitinib (16)

Bronte *et al*. have studied the effect of barcitinib to restrain the dysregulation of immune system witnessed by twenty COVID-19 patients who were admitted in University Hospital of Verona and Pederzoli Hospital of Peschiera [181]. Total of 88 patients in 1:1 sex ratio of male and female were administered in the hospitals which were kept on either hydroxychloroquine or lopinavir/ ritonavir therapy individually or in combination. In addition, the patients were also given supportive therapy like prophylaxis, anticoagulant treatment or antibiotic treatment. Rest 76 patients were distributed among control group with 56 patients and barcitinib group with 20 patients (**Figure 67**).
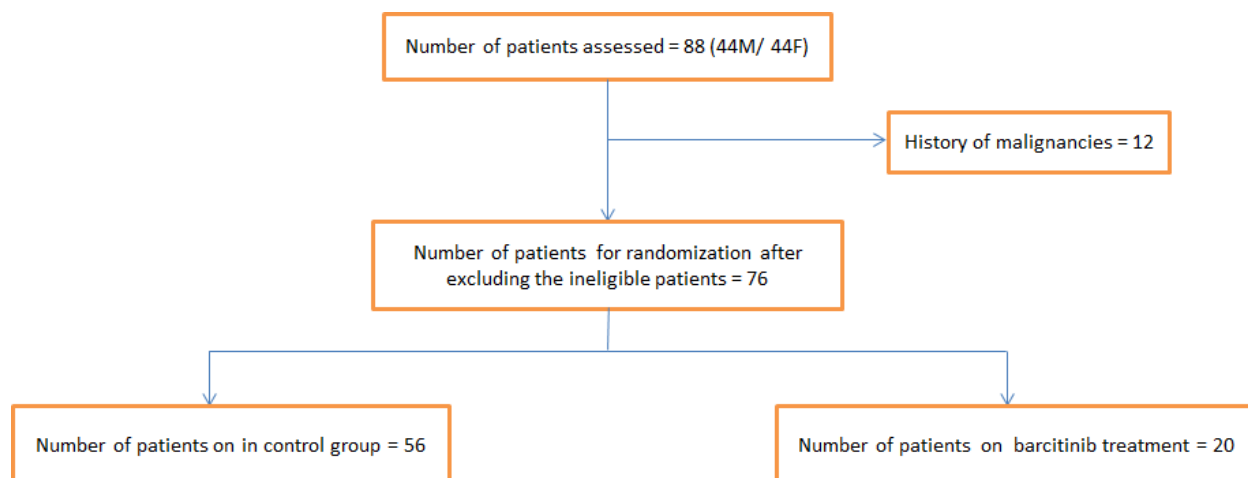
Figure 67: Randomization of the COVID-19 patients under control group and barcitinib group

The barcitinib group was treated with 4 mg of baricitinib twice daily for 2 days followed by 4 mg of barcitinib once daily for next 7 days. The dose was decreased in certain cases depending upon the adverse effects observed by the patients. Interestingly, the mortality rate of barcitinib group was only 1 (5%) patient out of 20 as compared to 25 (45%) patients died in control group (**Figure 68**). In addition the patients in barcitinib group experienced reduction in the need of supplement oxygen as compared to the control group. The use of barcitinib resulted in the normalization of the plasma concentration of abnormal level of pro-inflammatory cytokines which are associated with COVID-19 in short span of 7 days as compared to the control group. Further studies suggested that the use of baricitinib resulted in the modification of immune suppressive characteristic of myeloid cells.
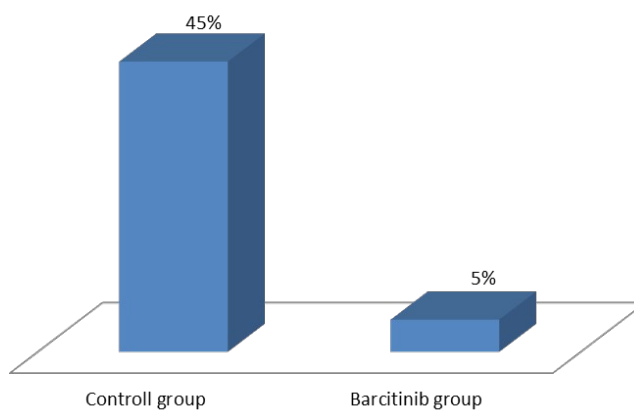
Figure 68: Percentage of mortality in control group *vs* Barcitinb group

In a letter to editor, Cantini *et al.* and coworkers have reported the use of combined therapy of barcitinib and lopinavir/ ritonavir in patients suffering from moderate pneumonia associated with COVID-19 [182]. The study was performed on 12 patients including 10 men and 2 women of age greater than 18 years admitted in hospital of Pratoand Alessandria after confirmation of COVID-19 (**Figure 69**). The patients were treated with 2 mg of barcitinib along with lopinavir/ ritonavir therapy for 2 weeks.
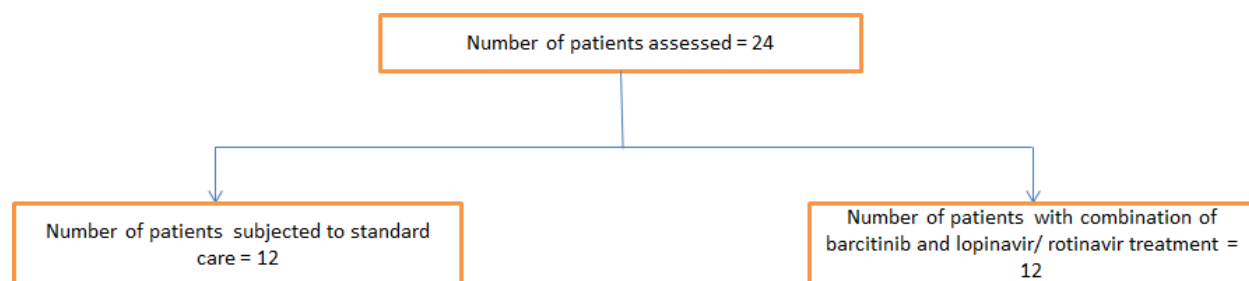
Figure 69: Randomization of the COVID-19 patients

One patient was withdrawn from the barcitinib therapy due to consistent transaminases elevation. The results showed that the use of barcitinib led to improvement in the clinical parameters and respiratory functions at week 1 and week 2 as compared to the baseline. However, no such significant changes were observed in case of standard COVID-19 treatment. Moreover, 7 (52%) patients were discharged from the hospital from the barcitinib group as compared to 1 (8%) patient in standard of care group after 2nd week (**Figure 70**).
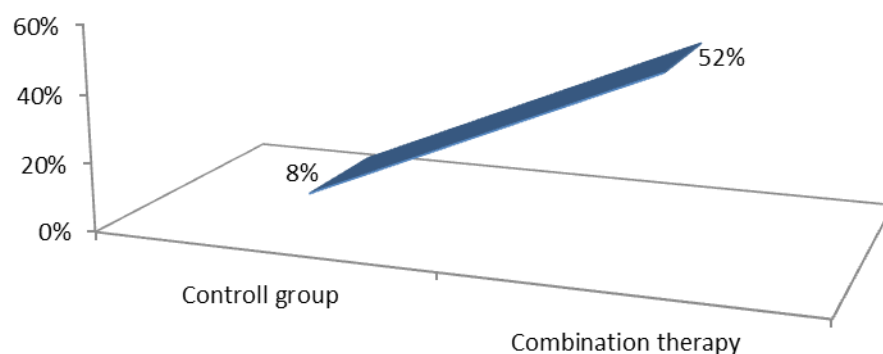
Figure 70: Percentage discharge of COVID-19 patients after 2 weeks

In another study, Cingolani *et al.* have reported a case of 71 years old male patient suffering from respiratory failure associated with COVID-19 [183]. In addition, the patient was suffering from high level of IL-6, IL-8 and TNFα. Treatment was started with lopinavir/ ritonavir (800 mg/ 100 mg once daily), azithromycin (500 mg once daily) and hydroxychloroquine (400 mg once daily) along with supplement oxygen. In addition, the patient was given 400 mg of sarilumab intravenously with repeated dose after 3 days. The CT scan of the patient confirmed centrolobular and paraseptal emphysema. Considering the continuously deteriorating condition of the patient, it was decided to start the barcitinib treatment of 4 mg per day for 2 weeks after which the patients showed remarkable improvements in multiple areas of increased parenchymal density in CT scan along with significant improvement of the IL-6 and CRP levels.

Sodani *et al.* have reported a case study of 50 years old man having history of being treated with chemotherapy because of Follicular non-Hodgkin lymphoma [184]. The patient was diagnosed with severe COVID-19 pneumonia along with moderated ADRS and was placed in isolation. He was treated with initial therapy of azithromycin, large spectrum antibiotics and hydroxychloroquine. The patient showed very mild response to barcitinib treatment at 4 mg/ day and the clinical outcomes of the patient worsened further. The patient was further given steroids at 1 mg/ kg and tocilizumab at 8 mg/ kg intravenously. The patient started witnessing the improvement in the respiratory symptoms and fever was come at normal level after 4 days of administration of tocilizumab. However, the patient's IL-6 and ferritin response increased to critical level. Remdesivir treatment was started with the administration of 200 mg of the drug followed by 100 mg dose daily for next 9 days which led to remarkable improvement for the recovery of the patient. The dry cough and shortness of breath were totally cured and the demand for supplement oxygen was negative.

Titanji *et al.* have reported the study of the effect of barcitinib along with hydroxychloroquine on a small uncontrolled cohort of 15 patients with moderate or severe COVID-19 at Atlanta Veterans Affairs Medical Center [185]. The patients under study were given 2-4 mg of barcitinib along with 200-400 mg of hydroxychloroquine once daily. The data suggested that 13 (87%) out of 15 patients witnessed significant reduction in the CRP levels as well as body temperature after the barcitinib treatment. In addition, 12 (80%) out of 15 patients observed clinical improvements leading to 80% survival rate at the end of study but 3 (20%) patients were died during the study (**Figure 71**). This study was not able to confirm that if the

patients would have shown improvement without barcitinib as hydroxychloroquine alone is also known to impart similar results. Also, the chances of possible synergic effect of barcitinib with antiviral drug have not been studied.
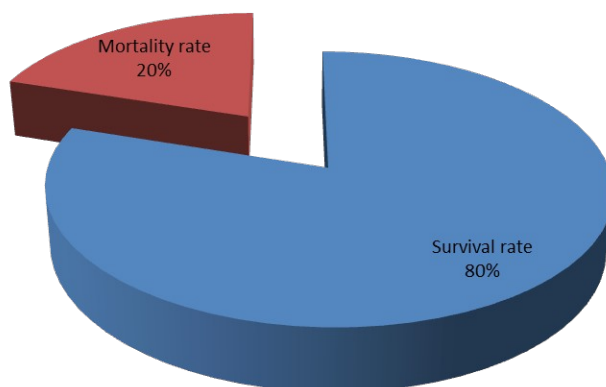
Figure 71: Survival and mortality rate of COVID-19 patients treated with barcitinib and hydroxychloroquine

Interestingly, Praveen *et al*. have reported the limitations of barcitinib therapy for COVID-19 patients [186]. They have observed that the barcitinib therapy cannot be given to the COVID-19 patients having lower values of absolute neutrophil count (Less than 1×10^9 cells/L) or absolute lymphocyte count (less than 0.5×10^9 cells /L) [187]. Moreover, barcitinib therapy is well known to be associated with anemia [188] which may further led to anemic incidence in COVID-19 patients. Studies suggested that almost 26% incidence of anemia [189] and 46% of the elevated level of creatine kinase [190] have been found in non survivors of COVID-19 patients. The study of barcitinib therapy has not been explored much on elderly patients and associated with secondary infections (**Figure 72**).
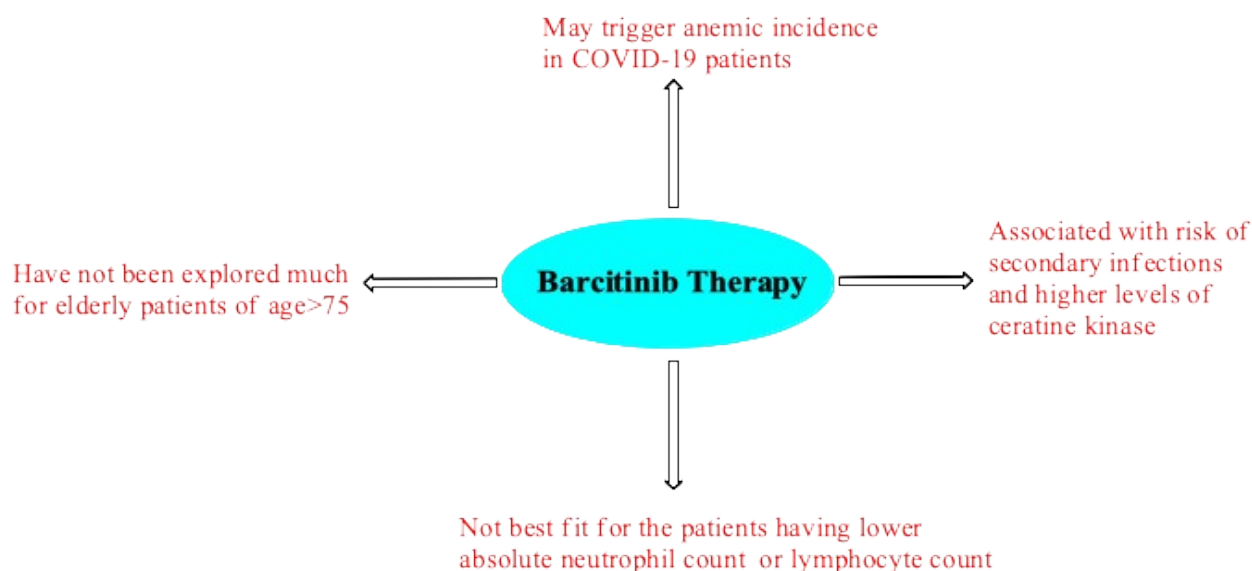
Figure 72: Limitations of the barcitinib therapy in COVID-19 patients

Stebbing *et al*. have reported the pilot study for the use of barcitinib in 4 patients with severe COVID-19 in Milan, Italy [191]. The patients were given 4 mg once daily from 10-12 days. All the 4 patients showed improvement in their clinical parameters during the treatment with barcitinib including improvement in the levels of viral load. Two patients showed negative viral load at the end of the study. In addition, all the 4 patients achieved sero conversion after barcitinib treatment. All patients under study observed the improvement in their D-dimer levels, CRP and ferritin level. At the end of the study, the data suggested that the barcitinib treatment resulted in the improvement in the clinical, virologic, radiologic, cytokines and inflammatory response in diverse group of patients.

Although the case study has presented that the use of tofacitinib has resulted in the recovery of COVID-19 patient but the history of using other drugs like vedolizumab, infliximab and adalimumab cannot be ruled out which may also play important role in the disease management. On the other hand, the use of baricitinib is associated with the low mortality rate and improvement in the respiratory functions of COVID-19 patients. In addition, this drug has been used in combination with other drugs like lopinavir/ ritonavir, remdesivir and hydroxychloroquine to attain the desired clinical outcomes. However, baricitinib treatment did not give the significant results and hence was found of no use for the patients having lesser values of absolute neutrophile count or absolute lymphocyte count. Although few case studies

have been reported for associated side effects in case of ruxolitinib, the trials of this drug over small population has resulted in improvement of inflammation and respiratory functions associated with cytokine storm in case of COVID-19 patients.

16. Use of Proinflammatory mechanisms inhibitors as a treatment for COVID-19

16.1 Colchicine

Colchicine (**17**) is a tricyclic alkaloid which is used to treat the gout. It affects the chemotaxis of inflammatory cells like monocytes and neutrophils. It is responsible for the reduction of neutrophil production [192] and also known to disrupt inflammasome activation by reducing the release of IL-1β and IL-18 [193]. Therefore, it can be used for the management of COVID-19 which is associated with inflammasome activation [194].
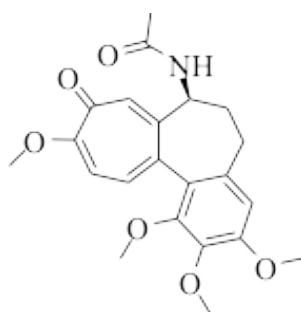
Colchicine (17)

In continuation of disclosure of the design for trial [195], Deftereos *et al.* have reported the benefits of using colchicine for the improvement in clinical outcomes of 55 COVID-19 patients across 16 hospitals in Greece in an open-label, randomized trial [196]. A total of 105 patients fulfilled the eligibility criteria out of which more than 90% of the patients had received hydroxychloroquine or azithromycin treatment (**Figure 73**).
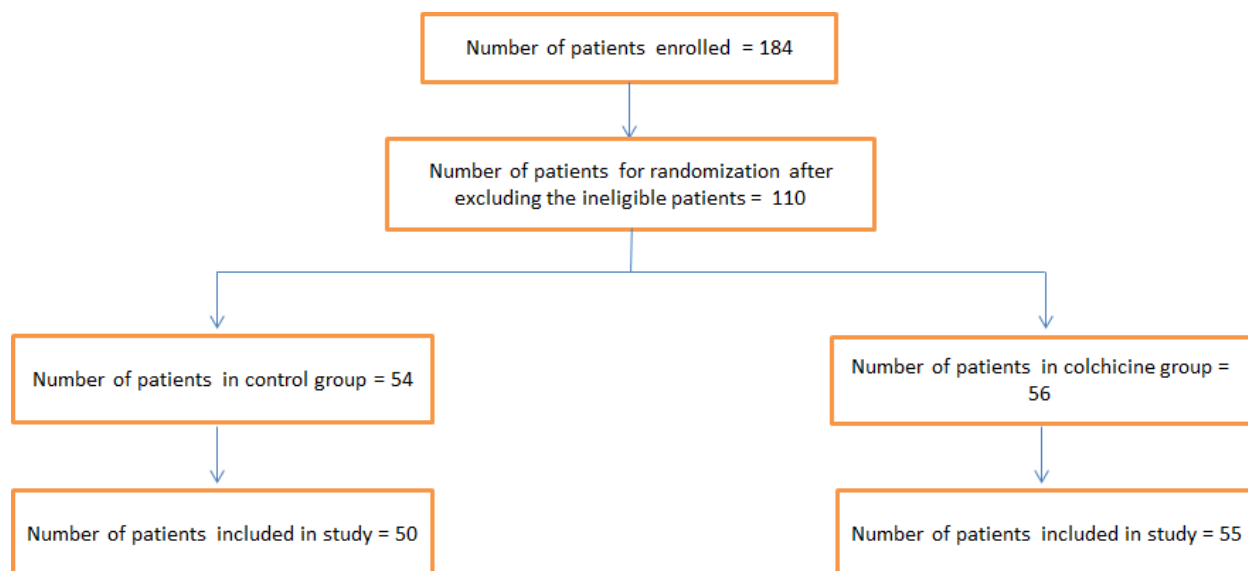
Figure 73: Randomization of COVID-19 patients under colchicine and control group

The patients under colchicine group were given loading dose of 1.5 mg of colchicine followed by administration of another 0.5 mg of colchicine after 60 minutes for day 1. In addition, a maintenance dose of 0.5 mg twice daily was given to the patients till day 21 or till hospital discharge. The findings suggested 97% survival rate of colchicine group after 10 days of treatment as compared to 83% survival rate in case of control group. Further, 14% of the patients in control group witnessed clinical primary end point as compared to 1.8% patients reaching the same in colchicine group. The change in CRP levels, electrolyte levels and hs cTn levels were almost same in both the groups. Moreover, both the groups witnessed similar adverse events. However, colchicine group (45%) witnessed more instances of diarrhea than control group (18%). Further, no serious adverse events were witnessed by both the groups.

Mansouri *et al*. have reported a case study of successful treatment of cytokine release syndrome of 42 years COVID-19 patient with no medical history [197]. On confirmation of the COVID-19, he was given 75 mg of oseltamivir and 200 mg of hydroxychloroquine twice a day from day 1 to day 5 which led to improvement of his respiratory functions but fever, loss of appetite and fatigue were still observed. Further, his clinical outcomes associated with inflammation like IL-6, ferritin, CRP, fibrinogen, D-dimer, liver enzymes etc. levels were found to elevate due to which the patient was given colchicine as 1 mg dose intravenously twice a day which resulted into significant improvement in his appetite, pain and urine output only after 48 hrs of administration. The colchicine therapy of 1 mg daily was maintained for 14 days, resulted

in normalization of his ferritin, LDH, D-dimer and IL-6 levels. Moreover, the patient was tested negative for viral load twice during the treatment. Thus, the colchicine therapy led to treatment of the cytokine storm of the patients which was associated with COVID-19.

Although the use of colchicine in the treatment of COVID-19 patients has resulted in the reduction in the level of proinflammatory cytokines like IL-6 and improvement in other clinical parameters, but whether the results achieved are due to the treatment of colchicine or due to the other drugs like hydroxychloroquine or azithromycin used in trials which have also been used for the COVID-19 management which can be entertained by collecting more clinical data in future.

17. Conclusion and future perspectives

It has been estimated that for every dollar spent on the research and development of ta new molecule, a value of less than a dollar is returned which makes pharmaceutical sector a comparatively less desirable option for investors in terms of novel drug discovery [198]. Repurposing or repositioning of the already available drugs for new therapeutic indication is not a new approach and has been used in past also. Best example is the sildenafil which was developed as an antihypertensive drug but was repurposed as a drug to treat erectile dysfunction by Pfizer. Owing to the escalating cost involved and lengthy time required for the development of a novel therapy for the treatment of COVID-19, various researchers are hoping on drug repurposing as a cost effective and time saving approaching which is what is exactly required in this pandemic situation. The initial results are encouraging in the cases of drugs like antivirals, IL inhibitors, JAK inhibitors, Burton Kinase inhibitors which target the cytokine storm, trigger autoimmune functions in the body and improve the ARDS. Interestingly, the use of corticosteroids which are associated with side effects have been proven to be safe in initial studies with reduction of the mortality rate. However, the results are not encouraging in certain cases like in the case of chloroquine which was found to be lethal at lower dose regimen and hydroxychloroquine which did not give significant results as compared to the control group. In addition, certain drugs like ivermectin have been found to possess remarkable activity against SARS-CoV-2 but at a dose which is practically impossible to achieve in human body. More data is required on the use of these drugs over larger population to establish their safety and efficacy profile. There are many other strategies like high nasal oxygenation, plasma therapy and development of novel vaccines which are at various stages of development and initial results are

encouraging in many cases. Drug repositioning will remain an initial strategy to mitigate the spread of COVID-19 and to reduce the mortality rate associated with this disease till the time an effective vaccine is available

Table 12: Summary of the clinical trials of the drugs

Drug repurposed for the treatment of COVID-19	Design of the trial	Number of Patients involved	Patient's demography	Dose regimen	Reference
Antivirals					
Remdesivir	Double-blind, randomized, placebo-controlled phase III trial	1063	United Kingdom, United States, Denmark, Korea, Germany, Mexico, Greece, Singapore, Japan and Spain	200 mg for day 1 followed by maintenance dose of 100 mg for next 9 days or till the discharge of the patients from the hospital	49
	Randomized, double-blind, placebo-controlled, multicentre clinical trial	237	Wuhan, Hubei, China	200 mg for the day 1 followed by 100 mg for next 9 days	50
Favipiravir	Open label, non-randomized, controlled study	147	Third People's Hospital of Shenzhen, China	1600 mg twice daily for day 1 followed by 600 mg daily from day 2 to day 14.	54
Oseltamivir	To study the effect of early oseltamivir treatment on COVID-19 suspected patients with hypoxia or their family	13	Sapporo Suzuki Hospital, Japan	75 mg twice daily for 5 days	58
Chloroquine	Double-blinded, randomized, phase IIb clinical trial	81	Manaus, Brazilian Amazon	600 mg twice daily for 10 days or 450 mg twice daily for day 1 followed by once daily for next 4 days	63
	Multinational registry analysis	96032	6 continents	765 mg (SD 308) and 6.6 days (2.4)	64
Hydroxychloroquine	Randomized, double-blind, placebo-	921	USA and Canada	800 mg as an initial dose followed by 600	66

				mg for 6-8 hrs after the initial dose at day 1 and 600 mg once daily for next 4 days	
	Treatment of patients with moderate COVID-19	30	Shanghai Public Health Clinic Center, China	400 mg once daily for 5 days	67
	Randomized clinical trial	62	Renmin Hospital in Wuhan University, China	400 mg once daily for 5 days	68
	Randomized controlled trial	293	Catalonia, Spain	800 mg once daily on day 1 followed by 400 mg once daily for next 6 days	72
Antiretrovirals					
Lopinavir/ Ritonavir	Randomized, controlled, open-label trial	199	Jin Yin-Tan Hospital, Wuhan, China	400 mg of lopinavir and 100 mg of ritonavir twice daily along with the standard of care for 14 days	75
	Open-label, multicenter, randomized, phase II trial	127	Hong Kong	400 mg/ 100 mg of LPV/ RTV twice daily after 12 hrs on alternate days for 14 days	79
	Clinical efficacy of Lopinavir/ Ritonavir against COVID-19	47	Ruian People's Hospital, China	400/100 mg of lopinavir/ritonavir twice daily or 800/200 mg once daily for 10 days	81
Antibiotics					
Azithromycin	Multi-center retrospective observational trial	2541	Southeast Michigan, USA,	500 mg for day 1 followed by 250 mg for next 4 days	85
	Multicenter, randomized, open-label, three-group, controlled trial	667	55 hospitals in Brazil	400 mg of hydroxychloroquine twice daily and 500 mg of azithromycin once a day for 7 days	86
	Retrospective cohort study of COVID-19 patients	415	Beaumont Hospital, Dublin, Ireland	400 mg of hydroxychloroquine twice daily for day 1 followed by 200 mg twice daily for next 4 days and 500 mg of	87

				azithromycin for day 1 followed by 250 mg for next 4 days	
	Open label non-randomized clinical trial	36	France	200 mg of hydroxychloroquine thrice a day for 10 days along with 500 mg of azithromycin for day 1 followed by 250 mg for next 4 days	88
	Retrospective multicenter cohort study	1438	New York metropolitan region.	From 200 mg to 500 mg in different regimens	89
	Early treatment of COVID-19 patients with hydroxychloroquine and azithromycin	1061	Marseille, France	200 mg of hydroxychloroquine thrice a day for 10 days alongwith 500 mg of azithromycin for day 1 followed by 250 mg daily for next 4 days	90
Avermectins					
Ivermectin	Randomized trial	116	Cox's Bazar, Bangladesh	200 μg/ Kg for 10 days	99
	Use of ivermectin as an add on therapy to hydroxychloroquine and azithromycin	104	Al-Shifa'a Hospital, Saudi Arabia	200 μg of ivermectin as an add-on therapy to the standard of care which included hydroxychloroquine, 400 mg BID for day1 followed by 200 mg BID for 5 days alongwith 500 mg of azithromycin on day1 followed by 250 mg for 5 days	100
Bruton's tyrosine kinase inhibitors					
Acalabrutinib	Off –label trial	19	United States	100 mg once or twice daily	106
Corticosteroids					
Dexamethasone	Open-label trial	6425	United Kingdom	6 mg once daily for 10 days	109
Methylprednisolone	Multicentric, partially randomized, preference, open-	85	Spain	40 mg after each 12 hrs for first 3 days followed by 20 mg	115

	label trial			after each 12 hrs for next three days	
	Early use of methylprednisolone for COVID-19 patients	101	Zhuhai, China	Up to maximum of 1000 mg	116
	Randomized controlled clinical trial	68	Tehran	250 mg intravenously for three days	117
	Use of methyl prednisolone on COVID-19 patients of different demography and clinical status	65	China	Median dose of 1-5 mg/ Kg per day	118
Phosphodiesterase 4 (PDE4) inhibitors					
Apremilast	Case study on 61 years old male	1		30 mg of apremilast twice daily	126
	Case study of 45 years old obese man	1		30 mg twice daily	127
Human granulocyte macrophage colony-stimulating factor receptor (GM-CSF-R) inhibitors					
Mavrilimumab	Single-centre, prospective cohort study	13	Milan, Italy	6 mg/ Kg	130
Interleukin 1 receptor antagonists					
Anakinra	Use of anakinra for severe pneumonia associated with COVID-19	9	France	100 mg dose after 12 hrs from day 1 to day 3 followed by 100 mg after 24 hrs from day 4 to day 10	134
	Early blockade of IL-1 receptor by anakinra	30	France	300 mg from day 1 to day 5 followed by 200 mg from day 7 to day 8 and finally at 100 mg for day 8	135
	Cohort study by using high dose of anakinra	52	Milan, Italy	5 mg/ Kg twice daily	136
	Salvage treatment with Anakinra	7	Greece	200 mg after each 8 hrs for 7 days	137
	Case study on 50 years old man	1	Lombardy, Italy	200 mg of anakinra followed by 100 mg subcutaneously after each 6 hrs	138
	Cohort study of	52	Paris	100 mg anakinra twice	139

	anakinra for severe COVID-19			daily followed by 100 mg for 7 days	
Canakinumab	Case study of 85 years old man	1	Italy	300 mg in day 25 and day 31	141
	Treatment of 10 clinically confirmed COVID-19 patients	10	Annunziata Hospital , Chieti, Italy	300 mg injection	143
Interleukin 6 receptor antagonists					
Tocilizumab	Retrospective, observational cohort study	544	Italy	Intravenous- 8mg/ Kg with subject to maximum 800 mg of dose in 2 infusions after an interval of 12 Subcutaneous - 324 mg twice	146
	Retrospective case-control study	45	France	Single dose	147
	Single center study	15	Tongji Hospital in Wuhan, China	Single to multiple doses	148
	Case study of 42 years old male	1	France	Two doses of 8 mg/kg	149
	Case study of 57 years old woman	1	Zurich, Switzerland	8 mg/Kg after 4 weeks	150
	Case study on 2 patients	2		400 mg to 700 mg of single or multiple doses	151
	Pilot prospective open, single-arm multicentre study	63	Italy	8 mg/Kg intravenously or 324 mg subcutaneously	152
	Single center study	100	Brescia, Italy	8 mg/ kg twice after interval of 12 hrs	153
	To study the efficacy of tocilizumab against severe COVID-19 patients	21	China	One to two doses within 12 hrs of interval	154
	Case study of COVID-19 patient with multiple myeloma	1	Wuhan, China	One dose of 8 mg/Kg	155
Sarilimab	Early use of sarilumab along with standard of care therapy	8	Florence, Italy	200 mg dose administered intravenously after 24 hrs of hospitalization	156

				and 200 mg dose subsequently after 2 and 4 days, respectively	
	Open label cohort study	28	Milan, Italy	200 mg twice after 1 hr interval administered intravenously	157
IL-17 inhibitors					
ixekizumab	Case study on 55 years old general practitioner	1		160 mg for week 0 followed by 80 mg for weeks 2, 4, 6, 8, 10 and 12	159
Secukinumab	Case study of 66 years old man	1		History of treatment with secukinumab	160
IL-23 inhibitor					
Guselkumab	Case study on 32 years old woman	1		2 injections of guselkumab	161
	Case study of 40 years old woman	1		1 injection of guselkumab	162
	Case study of 62 years old man	1		History of treatment with guselkumab	160
Ustekinuma	Case study of 62 years old man	1		History of treatment with ustekinuma	160
TNF-α inhibitors					
Adalimumab	Case study of 67 years old woman	1		History of treatment with adalimumab	160
Janus kinase (JAK) inhibitors					
Tofacitinib	Case study of 33 years old woman	1	USA	10 mg twice daily	173
Ruxolitinib	Case study of 2 COVID-19 patients for side effects	2	Italy	2 tablets of 5 mg each per day for 2 days followed by 4 tablets per day for next 3 days	175
	Multicenter, single-blind, randomized controlled phase II clinical trial	41	China	5 mg twice daily along with the standard of care group	176
	Use of ruxolitinib to treat ARDS	18	Siena, Italy	20 mg for the first 48 hrs which was reduced to 10 mg or 5 mg of dose as per the response of the patients	177
	Monocentric retrospective chart analysis	105	Germany	7.5 mg which was increased stepwise to 15 mg	178

Barcitinib	Observational longitudinal trial	76	Verona, Italy	4 mg twice daily for 2 days followed by 4 mg of barcitinib once daily for next 7 days	181
	Use of combined therapy of barcitinib and lopinavir/ ritonavir	24	Italy	2 mg of barcitinib along with lopinavir/ ritonavir therapy for 2 weeks	`182
	Case study of 71 years old male patient	1	Italy	4 mg per day for 2 weeks	183
	Case history of 50 years old man	1	Italy	4 mg per day	184
	Small uncontrolled cohort study of baricitinib and hydroxychloroquine	15	USA	2-4 mg of baricitinib along with 200-400 mg of hydroxychloroquine once daily	185
	Pilot study	4	Milan, Italy	4 mg once daily from 10-12 days	191
Proinflammatory mechanisms inhibitors					
Colchicine	Open-label, randomized trial	110	Greece	1.5 mg followed by administration of another 0.5 mg after 60 minutes. A maintenance dose of 0.5 mg twice daily was given to the patients till day 21	196
	Case study of 42 years old man	1		1 mg daily was maintained for 14 days	197

Abbreviations

ARDS: Acute respiratory distress syndrome, CT scan: Computerized tomography scan, ICU: Intensice care unit, SARS: Severe Acute Respiratory Syndrome, MERS: Middle east respiratory syndrome, SNS: Central nervous system, LTRI: Lower respiratory tract infection, UTRI: Upper respiratory tract infection, RT-PCR: Real-time polymerase chain reaction, TNF: tumor necrosis factor, INF: Interferon, JAK: Janus kinase, ACE: Angiotensin-converting enzyme, IL: Interleukin, USFDA: United States Food and Drug Administration, EMA: European Medical Agency

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Conflicts of interest

There are no conflicts to declare.

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