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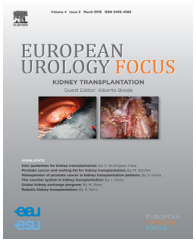

Clinical Studies Update

Investigational Therapies for the Treatment of COVID-19: Updates from Ongoing Clinical Trials

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1. Introduction

Currently there are no therapeutics approved by the US Food and Drug Administration (FDA) for the treatment of COVID-19. Traditionally, the development of novel therapeutics takes years, including rigorous randomized controlled trials (RCTs), the gold standard of clinical research. However, the urgency of the COVID-19 pandemic has led to widespread use of unproven treatments, supported largely by observational studies. As outlined in the National Institute of Allergy and Infectious Diseases strategic plan for COVID-19 research [1], it is essential to identify promising candidates with activity against SARS-CoV-2 and conduct treatment studies to advance high-priority therapeutic candidates.

In this review we discuss investigational treatments (Supplementary Table 1), both repurposed and novel, early data regarding their use in the treatment of COVID-19, and key clinical trials that are currently under way (Table 1).

2. Antiviral therapy

2.1. Chloroquine and hydroxychloroquine

Chloroquine and hydroxychloroquine are antimalarial agents with immunomodulatory properties that exhibit antiviral activity in vitro against SARS-CoV-2 [2,3]. Early series from China revealed earlier viral clearance, improved radiologic findings, and shortened disease course among patients diagnosed with COVID-19 when treated with chloroquine [4]. In a small study from France, hydroxychloroquine, which has a more tolerable safety profile [5], reduced SARS-CoV-2 viral burden, although the clinical significance was unclear [6]. With these limited data, on March 28, 2020, the FDA issued an emergency use authorization of hydroxychloroquine for the treatment of COVID-19.

Several subsequent studies have not shown a benefit with hydroxychloroquine [7–10] but rather a trend towards potential harm, including QTC prolongation [11,12]. An open-label RCT of 150 patients did not find a significantly higher probability of viral clearance in the hydroxychloroquine group, and the risk of adverse events was greater compared to standard of care [13]. The ORCHID trial (NCT04332991) is a multicenter, blinded RCT that aims to compare the effect of hydroxychloroquine versus placebo on clinical outcomes among adults hospitalized with COVID-19 [14].

2.2. Remdesivir

Remdesivir is a novel broad-spectrum antiviral that disrupts viral replication by inhibiting the RNA polymerase of RNA viruses such as coronaviruses [15,16]. Remdesivir has demonstrated antiviral and clinical effects in animal model studies of SARS COV-1, MERS-COV [17,18], and most recently against SARS COV-2 [19].

Early studies of remdesivir in COVID-19 have been inconclusive because of non-RCT designs and an inability to achieve target enrollment [20,21]. On February 21, 2020, the National Institutes of Health launched the Adaptive COVID-19 Treatment Trial (ACTT - NCT04280705), a double-blind randomized, placebo-controlled trial. After the study team released independent data safety monitoring board (DSMB) recommendations for early unblinding due to an interim analysis which demonstrated 31% faster time to

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Table 1 – Key clinical trials for COVID-19 treatments that are currently under way.

	ACTT [44]	Convalescent Plasma EAP [33]	CORIMUNO-TOCI [39]	Regeneron [40]
Trial ID	NCT04280705	NCT0433860	NCT0433180839	NCT04315298
Study agent	Remdesivir (RDV)	Convalescent plasma	Tocilizumab	Sarilumab
Study location	International	USA	France	USA
Study design	Adaptive, double-blind, placebo RCT	Open-label expanded access program	Open-label RCT	Adaptive, phase 2/3, randomized, double-blind, placebo-controlled
Patients	1063 randomized (1059 included in preliminary analysis)	5000	129	457
Median age, yr (range)	58.9	62.3 (18.5–97.8)	Not reported	Not reported
Male patients	RDV: 352 (65.1%); Placebo: 332 (63.6%)	3153 (63.1%)	Not reported	Not reported
Disease status	RDV: 352 (65.1%); Placebo: 332 (63.6%)	Severe or life-threatening: 4051 (81%) High risk of disease progression: 949 (19%)	Moderate or severe (number not reported)	Severe: 28% Critical: 49% MOD: 23%
Baseline clinical status	127 (11.9%) RA; 421 (39.6%) supplemental oxygen; 197 (18.5%) NIV/HFNC; 272 (25.6%) MV/ECMO	Total ICU admissions: 3316 (66%) Respiratory failure: 2912 (72%) MOD/failure: 745 (18.4%) Septic shock: 600 (14.8%)	All patients required O_2 supplementation, but levels not specified	Not reported
Clinical improvement	Median Time to recovery: RDV: 11 days; Placebo: 15 days ($p < 0.001$); Rate ratio for recovery 1.32 (95% CI 1.12-1.55)	Not reported	Significantly lower proportion of patients in tocilizumab arm met primary outcome (need for NIV or MV) at day 14	All patients met primary endpoint (% change in CRP): −21% placebo vs −77% sarilumab 200 mg vs −79% sarilumab 400 mg Clinical improvement (critical): 18 (41%) placebo vs 48 (51%) sarilumab 200 mg vs 52 (59%) sarilumab 400 mg
Death	Mortality at 14 days: RDV: 7.1% (95% CI, 5-9.9); Placebo: 11.9% (95% CI, 9.2-15.4)	7-d mortality rate: 14.9%	Significantly lower proportion of patients in tocilizumab arm met primary outcome (death) at day 14	Critical: 12 (27%) placebo vs 34 (36%) sarilumab 200 mg vs 20 (23%) sarilumab 400 mg
Serious adverse events	RDV: 114 (21.1%); Placebo: 141 (27.0%); Most common SAEs - respiratory failure, hypotension, viral pneumonia, AKI	4 h after transfusion: 36 (<1%) including transfusion-associated circulatory overload (7); transfusion-related acute lung injury (11); severe allergic transfusion reactions	Not reported	No new safety signals
Limitations	Complete statistical analysis needed to determine efficacy and safety	No control group; study not designed to assess efficacy of convalescent plasma	Press release with limited preliminary data; not peer-reviewed	Press release with limited preliminary data; not peer-reviewed

ACTT: Adaptive COVID-19 Treatment Trial AKI: Acute Kidney Injury CI: Confidence Interval EAP: Expanded access program ECMO: Extracorporeal membrane oxygenation HFNC: High-flow nasal cannula ICU: Intensive Care Unit MV: Mechanical Ventilation NIV: Non-invasive Ventilation RA: Room Air RCT: Randomized controlled trial RDV: Remdesivir SAE: Serious Adverse Event.

recovery (primary endpoint) among patients who received remdesvir compared to placebo ($p < 0.001$) [22], the US FDA issued an emergency use authorization (EUA) on 1 May 2020 for remdesivir for hospitalized patients with confirmed COVID-19 with SpO_2 94% and eGFR > 30 ml/min [23]. After the EUA, a preliminary report of the ACTT results was published on 22 May 2020. Initial data suggest that compared to placebo, patients in the remdesivir arm had a shorter time to recovery (median 11 days vs 15 days, $p < 0.001$) and reduced mortality at 14 days (7.1% vs 11.9%). Patients with critical disease (requiring non-invasive or mechanical ventilation) appeared to have a lower recovery rate than those with less severe disease, however, it is important to note that follow-up data collection and analysis are not yet complete [44]. Additional Phase 3 clinical trials (NCT04292730, NCT0429899) to determine the safety and efficacy of remdesivir in the treatment of moderate and severe COVID-19 remain ongoing and plan to enroll over 7000 patients.

3. Immune-based therapy

3.1. *Convalescent plasma*

Convalescent plasma (CP) contains antibodies directed against specific pathogens and is used for passive

immunization in the treatment of infections. CP has been used since the 19th century in infectious disease outbreaks including diphtheria, influenza, and, more recently, SARS, MERS, and Ebola [24–28]. Some limited studies demonstrate a reduction in mortality, with the greatest benefit when CP is administered early in the disease course. However, there are no data that clearly demonstrate the value of CP for the treatment of any infectious disease [29].

While case series from early in the SARS-CoV-2 pandemic demonstrate a possible role for CP in COVID-19 [30–32], no RCT data are available. As an investigational agent, CP is currently available via clinical trials, single-patient emergency use, or expanded access protocols (EAPs). On March 30, 2020, the FDA identified the Mayo Clinic as sponsor of the national EAP. In a preprint publication of the first safety EAP study communications, CP was found to be safe among 5000 recipients with no signal of toxicity beyond what is expected from plasma use in severely ill patients [33]. Ongoing RCTs are investigating the use of CP in hospitalized patients and in ambulatory settings and for post-exposure prophylaxis.

3.2. *IL-6 inhibitors*

Similar to the previous coronavirus, the systemic organ damage seen in COVID-19 is due to a “cytokine storm”, release of proinflammatory cytokines including IL-6 [15,34,35]. Tocilizumab, a monoclonal antibody that blocks the IL-6 receptor, is FDA approved for the treatment of cytokine release syndrome (CRS) [36,37]. An early retrospective report on 21 patients with severe or critical COVID-19 showed significant improvement in CRS symptoms, including resolution of fever and decreased oxygen requirements after treatment with tocilizumab [38]. Although case series were promising, recommendations included the need for RCTs.

On April 27, 2020, a press release regarding the CORIMUNO-TOCI trial (NCT04331808), a multicenter, open-label RCT, noted significant improvement among patients with moderate or severe COVID-19 randomized to receive tocilizumab versus standard of care [39]. Sarilumab, another monoclonal antibody that blocks the IL-6 receptor, is currently being studied in a phase 2/3 adaptive, double-blind, placebo-controlled RCT (NCT04315298). After recommendations by an independent DSMB, a press release on April 27, 2020 announced that the study will only enroll patients with critical disease due to negative outcomes in other groups [40]. Results of both trials are still pending peer review. Additional clinical trials are under way for multiple immunomodulators in the treatment of COVID-19 and are not recommended outside of a clinical trial.

4. Discussion

The recent epidemics of SARS-CoV-1, MERS-CoV, and Ebola highlight the importance of carrying out RCTs during a public health emergency. In those outbreaks, treatment decisions were made on the basis of observational reports and limited RCTs [41]. An immediate consequence of this approach is an incorrect assumption that investigative treatment is more likely to benefit than cause harm [42]. In the long term, lack of RCTs leads to insufficient answers regarding safe and effective treatment and risks, degrading public trust in health agencies [42,43]. The unprecedented speed with which numerous clinical trials have been initiated during the COVID-19 pandemic underscore the ability of the scientific community to provide this essential research.

Conflicts of interest: The authors have nothing to disclose.

Appendix A. Supplementary data

Supplementary material related to this article can be found, in the online version, at doi:https://doi.org/10.1016/j.euf.2020.05.019.

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