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Use of novel antithrombotic agents for COVID-19: Systematic summary of ongoing randomized controlled trials

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Abstract

Background: Coronavirus disease 2019 (COVID-19) is associated with macro- and micro-thromboses, which are triggered by endothelial cell activation, coagulopathy, and uncontrolled inflammatory response. Conventional antithrombotic agents are under assessment in dozens of randomized controlled trials (RCTs) in patients with COVID-19, with preliminary results not demonstrating benefit in several studies.
INTRODUCTION

Coronavirus disease 2019 (COVID-19) is associated with venous and arterial thrombosis.\textsuperscript{1–3} Dozens of randomized controlled trials (RCTs) are evaluating the utility of conventional antithrombotic agents in COVID-19.\textsuperscript{4} Results from the available RCTs of the conventional antithrombotic agents have not yet led to definitive answers. In patients admitted to the intensive care unit (ICU), intermediate-dose or full-dose prophylactic anticoagulation did not lead to improvement in clinical outcomes.\textsuperscript{5–8} Among patients hospitalized in medical wards, the results for heparin-based regimens are promising, although some details are yet to be clarified. Escalated-dose prophylaxis with rivaroxaban was not associated with improvement in outcomes.\textsuperscript{9} It is in this setting that there has been interest in novel agents with antithrombotic effects (with coexisting anti-inflammatory and/or antiviral properties) in patients with COVID-19. We summarized the ongoing RCTs of novel antithrombotic agents being tested in COVID-19 and their potential mechanisms of action.

METHODS

We searched clinicaltrials.gov and the World Health Organization International Clinical Trials Registry Platform to identify RCTs of novel antithrombotic agents in patients with COVID-19.

RESULTS

We identified 998 records, of which 27 RCTs met the eligibility criteria (Figure 1). We did not identify registered RCTs for danaparoid, soluble thrombomodulin, or activated protein C.
The presumed mechanism of action relevant to COVID-19 of novel agents with antithrombotic properties is illustrated in Figure 2. Some of these agents have anticoagulant properties, some have profibrinolytic functions, and others may impact thromboinflammation by reduction in the formation of neutrophil extracellular traps (NETs).

Table 1 summarizes the ongoing RCTs of 10 novel agents and comparator arms in each RCT, and their respective clinical trial registration number. A summary of ongoing or completed trials are described in Figure 3. These completed or ongoing RCTs have focused only on hospitalized patients with COVID-19, except one trial of quercetin, which includes outpatients. Although there may be some overlap in the putative mechanisms of action, for simplicity, these agents are grouped as those drugs affecting the coagulation cascade, drugs affecting endothelial activation, and agents with mixed mechanisms of action.4,10 A brief discussion of these agents and their trials is provided in the following sections.

3.1 | Drugs affecting the coagulation cascade

The hypercoagulopathy in COVID-19 is associated with increased levels of tissue factor (TF), thrombin, von Willebrand factor (VWF), and type-1 plasminogen activator inhibitor (PAI-1), as well as reduced levels of plasminogen activators and antithrombin.4 Drugs affecting the coagulation cascade in this review can be divided into three groups: tissue factor pathway inhibitors (recombinant nematode anticoagulant protein c2 [rNAPc2] and quercetin), serine protease inhibitors (antithrombin, nafamostat, and ulinastatin), and those that augment fibrinolysis (defibrotide). Due to multiple properties of defibrotide, it will be described in a distinct section, subsequently.

3.1.1 | Tissue factor inhibitors: rNAPc2 and quercetin

rNAPc2 inhibits TF/factor VIIa complex and may decrease the interleukin-10 response and dampen the cytokine storm.11
rNAPc2 is being studied in ASPEN-COVID-19 (Assessing Safety, Hospitalization and Efficacy of rNAPc2 in COVID-19) among 160 patients with COVID-19 to determine its effect on the time to recovery, change of D-dimer level, and bleeding events as co-primary outcomes.

Quercetin and isoquercetin have anti-inflammatory and antithrombotic properties. Quercetin derivatives are the protein disulfide isomerase inhibitors, which suppresses TF, inhibit glycoprotein IIb/IIIa activation and platelet aggregation, and decrease thrombin generation and D-dimer level. These agents decrease reactive oxygen species (ROS) levels and pro-inflammatory cytokines. By decreasing ROS levels, quercetin can inhibit nod-like receptor family pyrin domain containing 3 (NLRP3) inflammasome activation. In addition, quercetin can suppress NLRP3 inflammasome directly.

Quercetin and its derivatives are being evaluated in five RCTs, including four in hospitalized patients. The primary outcome of three ongoing RCTs, conducted in a total of 600 hospitalized non-ICU patients, is disease progression [Study of Isoquercetin Plus Standard of Care Versus Standard of Care Only for the Treatment of COVID-19 [NCT04536090], Masitinib Combined With Isoquercetin and Best Supportive Care in Hospitalized Patients With Moderate and Severe COVID-19 [NCT04622865], and Study to Investigate the Clinical Efficacy of Isoquercetin in Patients With COVID-19 [NCT04733651]]. The assessment of positivity of the nasopharyngeal polymerase chain reaction swab is the primary outcome of one RCT of isoquercetin in 60 hospitalized (non-ICU and ICU) patients (IRCT20200419047128N2).

Trial to Study the Adjuvant Benefits of Quercetin Phytosome in Patients With COVID-19 (NCT04578158) is assessing the effect of quercetin on hospitalization rates in 152 outpatients with COVID-19.
## Table 1. Review of RCTs Categorized Based on the Mechanism of Action

| Trial Code/Name | Blinding Status | Patient recruitment duration | Actual (Daily Dose (daily)) | Major Inclusion Criteria | Secondary | Major Exclusion Criteria | Primary Endpoint Follow-up Duration (days) | Other | Efficacy Outcomes | Inflammatory or other surrogate markers |
|----------------|----------------|----------------------------|-----------------------------|--------------------------|-----------|--------------------------|---------------------------------------------|-------|------------------|----------------------------------------|
| TALASAZ ET AL. |                |                            |                             |                          |           |                          |                                             |       |                  |                                        |

### Drugs Affecting Coagulation Cascade

#### Tissue Factor Inhibitors
- **rNAPc2**
  - **ASPEN-COVID-13** (NCT046555901)
    - Higher dose: 7.5 µg/kg SC on Day 1, 3, and 5
    - Lower dose: 5 µg/kg SC on Day 1, 3, and 5
    - Adult PCR confirmed COVID-19 with evidence of systemic inflammation
    - History of APS, High bleeding risk, CHD, Liver disease
    - e-D-dimer, Level, bleeding

- **Quercetin derivatives**
  - **ASCOT-ADAPT** (NCT04536090)
    - High dose: 700 mg BID on day 1, then 500 mg BID for 27 days
    - Adult confirmed COVID-19
    - High bleeding risk, Antecedent intensified Heparin derivatives or DAPT, CHD
    - - Clinical status improvement
  - **ASPEN-COVID-19** (NCT04574958)
    - 400 mg PO daily for 30 days
    - Adult RT-PCR confirmed COVID-19
    - Hypersensitivity reaction to quercetin
    - - Clinical status improvement
  - **AS201200001672** (NCT04622865)
    - High dose: 700 mg BID on day 1, then 500 mg BID for 30 days
    - Adult confirmed COVID-19
    - Hypersensitivity reaction to quercetin
    - - Clinical status improvement
  - **ASPEN-COVID-19** (NCT04673385)
    - 1 g PO daily for 28 days
    - Adult PWRT-PCR confirmed COVID-19
    - High bleeding risk, Antecedent antithrombotic, Strong CYP3A4 inducer, CHD, Liver disease
    - - Clinical status improvement

#### Serine Protease Inhibitors
- **Antithrombin**
  - **ANTITROMBINA** (NCT79474442)
    - 50 U/Kg IV BID for 3 days
    - Adult confirmed COVID-19 with evidence of systemic inflammation
    - High bleeding risk, Immunosuppression by cancer or transplant
    - - -
  - **ASCOT-ADAPT** (NCT04443393)
    - 0.2mg/kg BID for 4 days or until DC
    - Adult PCR/RT-PCR confirmed COVID-19
    - High bleeding risk, Disseminated IFI, Currently receiving acute respiratory support, CHD, Liver disease
    - - -
  - **DEFINE** (NCT79447353)
    - 0.2mg/kg BID for 4 days or until DC
    - Adult confirmed COVID-19
    - Decompensated HF, Antecedent AC or Antithrombotic, X-sparking diabetes, CHD, Liver disease
    - - Adverse events
  - **RACONIA** (NCT794452400)
    - Not provided
    - Adult confirmed COVID-19
    - High bleeding risk, Requiring ECMO, Chronic ILD, Long QTc, Requiring high dose of loop diuretic or immunosuppressive therapy, CHD, Liver disease
    - - Clinical status improvement
  - **CRTR202006102020** (NCT0491200626)
    - 0.1mg/kg/hour IV for 10 days or until DC
    - Adult confirmed COVID-19
    - High bleeding risk, Requiring ECMO or IV, Chronic ILD, Long QTc, Requiring high dose of loop diuretic or immunosuppressive therapy, Decompensated HF, CHD, Liver disease
    - - Clinical status improvement
  - **NCT04419120**
    - 0.1-0.2 mg/kg/hour IV for 10 - 21 days
    - Age 18-65 years, confirmed COVID-19
    - History of or CHD, Liver disease
    - - -
  - **NCT04423221**
    - 0.1mg/kg/hour IV for 10 days or until DC
    - Adult confirmed COVID-19 (104)
    - High bleeding risk, History of long QTc, Ventricular arrhythmia, CHD, Liver disease
    - - -
  - **NCT04624143**
    - Not provided
    - Adult confirmed COVID-19
    - High bleeding risk, History of or CHD, Liver disease
    - - -

- **Chiluzatin**
  - **Chiluzatin** (NCT04333307)
    - 200,000 U IV infusion every 8 hours for 5 days or until DC
    - Age 16-75 years, confirmed COVID-19
    - - -
  - **Chiluzatin** (NCT04300032105)
    - 300,000 U IV infusion every 12 hours for mild cases and 1 or 1.6 MU for severe or critical cases
    - Age 16-75 years, confirmed COVID-19
    - - -
  - **Chiluzatin** (NCT04393331)
    - 200,000 U IV infusion every 8 hours for 7 days
    - Age 18-65 years, confirmed COVID-19
    - - -
  - **Chiluzatin** (NCT04393302)
    - 200,000 U IV infusion every 8 hours for 5 days or until DC
    - Adult confirmed COVID-19
    - Using antibody immunotherapy, CHD, Liver disease
    - - -

(Continues)
3.1.2 | Serine protease inhibitors: antithrombin, nafamostat, and ulinostatin

Antithrombin inactivates clotting enzymes, particularly factor II (FII) and factor X (FX).a Disruption of the endothelial cell glycocalyx with COVID-19 may lead to loss of heparan sulfate and hypercoagulability.4 ANTITROMBINA (Pilot Study of Antithrombin as Prophylaxis of Acute Respiratory Distress Syndrome in Patients With COVID-19) is evaluating the effect of antithrombin in 48 patients with COVID-19 for a primary composite outcome of all-cause mortality or need for mechanical ventilation.

As a synthetic serine protease inhibitor, nafamostat inhibits thrombin, FXa, and FXIIa. Moreover, it has anti-inflammatory and antiviral effects by blocking protease serine 2 activity and viral entry.14 Nafamostat is being studied in nine RCTs. Out of these nine, in five RCTs including a total of 2887 hospitalized non-ICU patients, the impact of nafamostat on death, need for mechanical ventilation, vasopressor therapy, clinical improvement or viral load is being assessed (ASCOT-ADAPT [Australasian COVID-19 Trial Adaptive Platform Trial], SEN-CoV-Fadj [Efficacy and Safety Evaluation of Treatment Regimens in Adult COVID-19 Patients in Senegal], A Study to Evaluate the Efficacy and Safety of Nafamostat Mesilate in Treatment of Coronavirus Infection [CTRI/2020/06/026220], Combination Therapy of Favipiravir and Nafamostat Mesilate in Patients with COVID-19 Pneumonia [JRCTs031200026], and A Study Evaluating the Efficacy and
### Safety of CKD-314 in Hospitalized Adult Patients Diagnosed With COVID-19 Pneumonia [NCT04628143]. ASCOT-ADAPT, as the trial with the largest number of participants in this group, is evaluating nafamostat in an adaptive platform trial with 2400 participants for a primary composite outcome of all-cause mortality or need for invasive or non-invasive ventilation or vasopressor or inotropic support. This drug is being assessed in another four RCTs with a total of 504 hospitalized patients (DEFINE [Rapid Experimental Medicine for COVID-19], RACONA [Efficacy of Nafamostat in Covid-19 Patients], Clinical Efficacy of Nafamostat Mesylate for COVID-19 Pneumonia [NCT04418128], and A Study Evaluating the Efficacy and Safety of CKD-314 [Nafabelltan] in Hospitalized Adult Patients Diagnosed With COVID-19 Pneumonia [NCT04623021]). The most common primary efficacy outcome (6/9) is time to clinical improvement. Severe acute respiratory syndrome coronavirus 2 (SARS-CoV-2) viral load level and safety of nafamostat are the primary outcomes in SEN-CoV-Fadj and DEFINE trials, respectively.

### Ulinastatin inhibits elastase and thrombin, factor IX (FIX)a, FXa, FXIa, and interleukin-6, but upregulates angiotensin-converting enzyme 2.15 Ulinastatin may attenuate lung injury by inhibiting transforming growth factor-β1, tumor necrosis factor-α (TNF-α), and nuclear factor-κB.16 Ulinastatin is being investigated in four RCTs (A Clinical Trial for Ulinastatin Injection in the Treatment of Patients with Severe Novel Coronavirus Pneumonia (COVID-19) [ChiCTR2000030779], Efficacy and Safety of Ulinastatin in the Treatment of Novel Coronavirus Pneumonia [COVID-19] [ChiCTR2000032135], Ulinastatin for COVID-19 in Patients with Breathlessness [CTRI/2020/06/025704], and Ulinastatin for the Treatment of COVID-19 in Hospitalized Patients [NCT04393311]) among a total of 430 participants. The primary outcomes are change from baseline PaO₂/FiO₂ ratios in two RCTs and time to recovery in NCT04393311 trial. Blood gas and the Sequential Organ Failure Assessment (SOFA) score are being assessed as the co-primary outcome in the ChiCTR2000030779 trial.

### Investigational Agents - Management of COVID-19

| Investigational Agents | Outpatient | Floor | ICU |
|------------------------|------------|-------|-----|
| Dociparstat            | X          | ✓     | X   |
| rNAPc2                 | X          | ✓     | X   |
| Crizanlizumab          | X          | ✓     | X   |
| C5 inhibitors          | X          | ✓     | X   |
| Nafamostat             | X          | ✓     | ✓   |
| Defibrotide            | X          | ✓     | X   |
| Ulinastatin            | X          | ✓     | X   |
| Antithrombin           | X          | ✓     | X   |
| Quercetin              | ✓          | ✓     | ✓   |

There are a total of 27 trials. 11 trials enroll from floor and ICU. All these agents are being investigated only in the setting of hospitalized patients, except for one RCT of quercetin. For more details please review Table 1. COVID-19, coronavirus disease 2019; ICU, Intensive Care Unit; rNAPc2: recombinant nematode anticoagulant protein c2.
3.2 | Drugs affecting endothelial activation

COVID-19 may lead to endothelial activation\(^7,18\) and drugs affecting endothelial activation can be divided into two groups: P-selectin inhibitors and complement inhibitors.

Soluble P-selectin levels are elevated in patients with COVID-19 and increased P-selectin expression on endothelial cells can tether tissue factor expressing monocytes or microparticles to the vessel wall, which may contribute to thromboinflammation.\(^19\) Crizanlizumab and defibrotide are the agents acting against P-selectin that block leukocyte tethering. Another drug, dociparstat, is a heparin derivative with modest anticoagulant activity but with the capacity to block P-selectin-mediated cell adhesion. Activation of complement system during SARS-CoV-2 infection is associated with increasing the pro-inflammatory complement such as C5, C5a, and C5b, which may exacerbate endothelial damage. An increase in activated C5a is associated with viral mediated acute lung injury. Reduced C5a generation may prevent lung damage during SARS-CoV-2 infection. Eculizumab and ravulizumab are human monoclonal antibodies with immunoregulatory effects by blocking complement C5 and cleavage into C5a and C5b. In addition, C5 inhibitors including eculizumab and ravulizumab can prevent the activation of endothelial cells by inhibition of C5b formation, production of ROS, and the initiation of cytokine storm. Preventing membrane attack complex formation on the vascular endothelial cells due to inhibition of C5b may protect endothelial cells from further damage leading to thrombotic microangiopathy (TMA).\(^20–22\)

3.2.1 | P-selectin inhibitors: crizanlizumab and dociparstat

Crizanlizumab is a monoclonal antibody that blocks the adhesion of leukocytes and platelets to the vessel wall.\(^19\) The CRITICAL (Crizanlizumab for Treating COVID-19 Vasculopathy) trial is evaluating its effect on P-selectin levels in 50 hospitalized non-ICU patients with COVID-19.

Dociparstat may reduce the release of pro-inflammatory cytokines and decrease neutrophil NET formation by inhibiting high mobility group box protein 1 and platelet factor 4.\(^4\) NETs can enhance the activity of fibrinogen, VWF, and other protein components involved in thrombosis, and may also trap red blood cells, promote platelet aggregation, and finally induce thrombus formation. Dociparstat is being studied in NCT04389840 (Dociparstat for the Treatment of Severe COVID-19 in Adults at High Risk of Respiratory Failure), a pilot RCT of three patients hospitalized with COVID-19.

3.2.2 | Complement component 5 inhibitors: eculizumab and ravulizumab

Use of eculizumab in patients with severe COVID-19 is associated with reduced D-dimer level and inflammatory markers.\(^23\) Therefore, some investigators hypothesize that it may improve hypoxia and patient outcomes such as survival. The CORIMUNO19-ECU (Trial Evaluating Efficacy and Safety of Eculizumab [Soliris] in Patients With COVID-19 Infection, Nested in the CORIMUNO-19 Cohort) trial is evaluating the impact of eculizumab on survival without the need for intubation as the primary outcome in 120 hospitalized patients with COVID-19.

Ravulizumab has a longer half-life compared to eculizumab with the advantage of a single-dose administration. This drug is being studied in three ongoing RCTs with a total of 1469 hospitalized patients (TACTIC-R [Multi-Arm Therapeutic Study in Pre-ICU Patients Admitted With Covid-19—Repurposed Drugs], Efficacy and Safety Study of IV Ravulizumab in Patients With COVID-19 Severe Pneumonia [NCT04369469], and Ravulizumab and COVID-19 [NCT04570397]). A composite of mortality, and improvement in SARS-CoV-2-induced acute kidney injury, are the main outcomes in these RCTs.

3.3 | Mixed-acting agents: defibrotide

Defibrotide is a polydispersed oligonucleotide synthesized by depolymerization of DNA extracted from porcine intestinal mucosa. It has a complex mechanism of action with antiviral activity, antithrombotic properties, and anti-inflammatory effects via reducing TNF-\(\alpha\) and IL-6, and vascular endothelial growth factor levels. Defibrotide upregulates tissue plasminogen activator expression, decreases PAI-1 levels, and enhances plasmin activity.\(^24,25\) Defibrotide can inhibit viral attachment by suppression of syndecan-1 directly and indirectly via inhibiting heparanase. Also, defibrotide can diminish viral dissemination by heparanase. Furthermore, it can inhibit endothelial cell activation through a number of mechanisms including enhancing endothelium-derived nitric oxide/nitric oxide synthase activity, diminishing the generation of the macrophage-derived ROS, and downregulating P-selection.\(^26,27\) The DEFACOVID trial (Defibrotide as Prevention and Treatment of Respiratory Distress and Cytokine Release Syndrome of Covid 19) is evaluating whether defibrotide results in clinical improvement in 150 hospitalized patients with COVID-19.

4 | CONCLUSIONS

Multiple novel therapies possessing antithrombotic properties are under investigation in RCTs of patients with COVID-19. Several of these agents have pleiotropic anti-inflammatory and antiviral effects, which may help reduce the viral load or fibrosis, and improve oxygenation. Results from these trials will improve our understanding of the disease pathophysiology and may help expand therapeutic options in COVID-19.

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