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Abstract:
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Invited Editorial Focus

Anticoagulant treatment of COVID-19 as early as possible – Sulodexide and perspectives

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The coronavirus disease (COVID-19), caused by the severe acute respiratory syndrome coronavirus-2 (SARS-CoV-2), infects endothelium, lung, heart, vascular system, gastrointestinal tube, kidney, and other organs via interaction of virus' spike S protein with angiotensin-converting enzyme 2 receptor on cell surfaces. [1] The infection mechanism includes pro-inflammatory changes in the arterial and venous walls resulting in endotheliitis followed by acute venous and arterial thrombosis contributing to up to 20% of COVID-19-related mortality. [2] However, patients may remain asymptomatic following infection or develop symptoms suspicious for COVID-19 about 5 days after infection with SARS-CoV-2.[3] Upon deterioration of symptoms patients are hospitalized and anticoagulation with low-molecular weight heparin (LMWH) is now regarded as cornerstone therapy for admitted patients with COVID-19.[4, 5]

For asymptomatic patients with laboratory-confirmed COVID-19 it is uncertain whether hydroxychloroquine reduces hospitalization. [6] The National Institutes of Health treatment guidelines express uncertainty regarding the use of anti-SARS-CoV-2 monoclonal antibodies, bamlanivimab and casavirimab, in this population. [7] Fluvoxamine, otherwise used for compulsive obsessive disorder, exerts σ-1 receptor agonism with reduction of sepsis-related in-

flammatory response and was in a small randomized controlled trial (RCT) in non-hospitalized patients with COVID-19 associated with reduced clinical deterioration. [8] Convalescent plasma with high titers of SARS-CoV-2 antibodies reduced deterioration of respiratory symptoms in older outpatients with mild COVID-19 symptoms in a small RCT, [9] although a meta-analysis of 4 RCTs failed to demonstrate any benefit. [10]

Heparins and other glycosaminoglycans act on the thromboinflammatory process by their anticoagulant and non-anticoagulant effects. [11] Taking these potential new mechanisms of anticoagulants in consideration the benefit of any glycosaminoglycan or anticoagulant of other origin may offer an attractive therapy for persons with mild or moderate symptoms of SARS-CoV-2 to prevent hospitalization.

Serval studies are in progress to investigate the benefit of an anticoagulant given as early as possible for patients suffering from mild to moderate severity of COVID-19 using low-molecular weight heparin (LMWH), sulodexide, the direct oral anticoagulants (DOACs) apixaban and edoxaban, and the antiplatelet drug acetylsalicylic acid (ASA) at various doses. Some studies add colchicine to ensure an anti-inflammatory action of DOACs or ASA (**->Table 1**). [12, 13, 14, 15, 16, 17,18, 19] The unmet clinical need is speeding up planning of studies and therefore, some of the planned or ongoing trials may be missing in this listing.

The first trial is now published by Gonzales et al evaluating sulodexide for individuals with early stages of COVID-19 to reduce the proportion of hospitalized patients and their length of hospital stays, the proportion of patients requiring oxygen support and the number of days on such support.[15, 20] They took advantage of the lack of an approved anticoagulant therapy to design a trial with the orally available glycosaminoglycan sulodexide versus placebo with blinding of study personal and participants. The low risk of bleeding during treatment with sulodexide may have increased the confidence in this treatment. A recent meta-analysis has shown, that sulodexide was associated with reduced odds of all-cause mortality, cardiovascular mortality, myocardial infarction, and deep vein thrombosis, without a significant increase in bleeding compared with placebo or no treatment. [21]

Gonzalez Ochoa et al followed the standard procedures with permuted block randomization at a 1:1 ratio of capsules containing 500 LRU sulodexide or placebo given twice daily for 21 days. They included patients aged > 40 years with suspicion of COVID-19 and with at least 3 days with two of the symptoms: cough, fever or headache, plus one of runny nose, diarrhea, dyspnea, loss of taste or smell, conjunctivitis and body or muscle ache. A polymerase

chain reaction (PCR) test for SARS-CoV-2 had to be presented by participants within 3 days of randomization and if negative, medication was stopped and patients were observed until end of study for intention to treat (ITT) analysis. Follow-up of participants was done virtually or in person for 21 days and further until an outcome had occurred or until the end of the trial. The primary endpoint of hospitalization occurred statistically significant less frequently in participants on sulodexide (17.4%) versus placebo (29.4%) (p=0.031). Secondary endpoints showed significantly less frequent and shorter requirement of oxygen support at home plus in-hospital for participants on sulodexide compared to placebo. Length of hospital stay, mortality or hemorrhage were not different between the groups. All results were confirmed by the ITT analysis.

The concentration of D-dimer and C-reactive protein (CRP) were normal and not different between participants treated with sulodexide and placebo at baseline. At day 14 D-dimer and CRP were higher in both groups compared to baseline but were significantly higher during administration of placebo compared to sulodexide. This finding is of particular interest for the pathophysiology of COVID-19 and the anticoagulant and anti-inflammatory properties of sulodexide and potential usefulness for identification of patients who may suffer from a progression of COVID-19 when treated at home.

Strengths and limitations of the study were considered by the authors and some may be worth to be added.

- Strengths of the study include, that authors decided
    - not to wait for the results of the PCR result for SARS-CoV-2 to start the study drug,
    - to use the higher of the available doses of sulodexide for the participants,
    - to determine D-dimer and CRP at start and after 14 days to generate information on the potential benefit of the anticoagulant and anti-inflammatory actions of sulodexide for home treatment.
- Limitations may be added such as,
    - The relatively small sample size and that 12% could not be analyzed due to lack of data
    - The lack of dose adjustment or change to LMWH or a DOAC in participants with increase of D-dimer at day 14

- The lack of analysis according to elevation of D-dimer and / or CRP at day 14 per group.

Other anticoagulant options

The studies available through ClinicalTrials.gov as of 15th March 2021 include *LMWH* enoxaparin, the DOACs *apixaban* and *edoxaban* and *ASA* in comparison to placebo or colchicine for treatment of mild to moderate COVID-19 infection, verified by a positive PCR test for SARS-CoV-2. Endpoints and some other details are listed in **->Table 1**.

Advantages of LMWHs are the simultaneous anticoagulant and anti-inflammatory properties which, however, differ in the dose response effect regarding the two actions. DOACs may act through inhibition of factor Xa and thrombin via the thrombin receptor on inflammatory diseases. Some of the direct factor Xa inhibitors are approved for prevention of VTE in patients with malignant disease which is thought to be mediated by non-anticoagulant effects DOACs. [22]

Chronic anticoagulant therapy

It has been hypothesized that chronic oral anticoagulation with vitamin-K antagonists (VKA) or direct oral anticoagulants (DOACs) may mitigate the course of mildly or moderately symptomatic SARS-CoV-2 positive tested persons to more severe COVID-19 disease stages.[23] This hypothesis is currently investigated in the retrospective, observational, single-center CORONA study on the clinical evolution (in terms of survival and thromboembolic complications) of patients on chronic treatment with anticoagulants or antiplatelet agents that are hospitalized for COVID-19 compared with patients who do not receive these agents. [24] However, it needs to be acknowledged that 2 studies reported failure of long-term anticoagulation to reduce hospitalization and mortality in COVID-19 patients. [25, 26]

Perspectives

1) Inhalation of drugs is an attractive therapeutic option for COVID-19 with pulmonary manifestation. The local anti-inflammatory and anticoagulant effect of inhaled heparin may act through its negative charges on the positively charged local toxic proteins in COVID-19 for potential use in mild to moderate COVID-19. [27, 28] Heparin or LMWH are absorbed after inhalation [29], and systemic heparin may require laboratory dose

adjustment. Nebulized interferon [30] may be effective in severe courses of COVID-19 on top of LMWH.

2) Upon COVID-19 symptoms in conjunction with a positive PCR-SARS-Cov-2 test in SARS-CoV-2 vaccinated persons, bamlanivimab and casavirimab [7] may be considered worthwhile to be combined with sulodexide at home or with LMWH in hospital.
3) New oral antiviral antibiotics are developed for treatment of COVID-19. [31] Anticoagulation will also be required in these patients.
4) Upon admission to hospital patients who were treated at home with VKA or DOACs require immediate switch to LMWH. Rapid and accurate beside monitoring methods are prothrombin time / international normalized ratio for VKA [32] and DOAC Dipstick™ or other point of care methods for DOACs [33] to avoid excessive anticoagulation by presence of two types of anticoagulants (**Fig ->1**).
5) SARS-CoV-2 is already mutating into more transmissible and virulent variants. Whether results of studies with the agents discussed about apply to these variants remains to be seen.

Conflict of Interest

None declared.

Figure 1: Overview of antithrombotic agents for treatment of stages of COVID-19 at home, in hospital and after hospital discharge

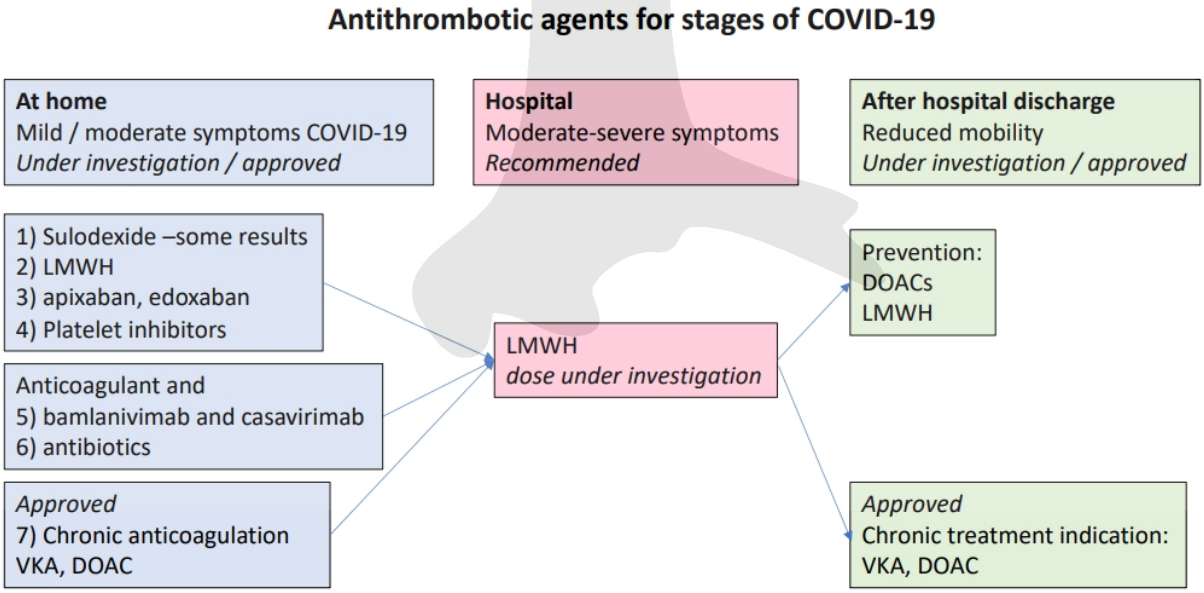

Table: Clinical studies on treatment of COVID-19 at home. Search results in https://clinicaltrials.gov with keywords: COVID-19, anticoagulation, as of 18 Mar 2021:

Citation (ref)	anticoagulant control	Dose duration	Primary outcome	Participants N=	Design	Estimated study end-date
NCT04400799 ([12])	Enoxaparin control	40 mg od No study drugs 14 days	hospitalization all-cause mortality day 14	1000	Prospective Open label, randomized multicentric	April 2021
NCT04508439 ([13])	Enoxaparin enoxaparin	40 mg od and 1 mg/kg bw bid sc 15 days crossover 30 days total	hospital care admission, days in hospital care, days supplemental oxygen day 30	130	Prospective Randomized open label, Crossover assignment monocentric	Dec 2020
NCT04483830 ([15])	Sulodexide placebo	500 LRU bid placebo pills 21 days	hospital care admission, days in hospital care, days supplemental oxygen day 21 D-dimer and CRP Days 0 vs 14	243	prospective, randomized, placebo- controlled multicentric	Sept 2020
NCT04746339 ([16])	Apixaban placebo	2.5 mg bid Placebo pills	days alive and out of hospital day 30	1000	Prospective Randomized Quadruple blind multicentric	Dec 2021
NCT04498273 ([17])	Apixaban Aspirin placebo	2.5 mg bid 5 mg bid 81 mg od No treatment 30 days	composite endpoint: hospitalization for cardiovascular/ pulmonary events, symptomatic VTE, arterial thromboembolism, myocardial infarction, ischemic stroke, all-cause mortality day 45	7000	Prospective Randomized Quadruple blind multicentric	Sept 2021

Table 1 continued

Citation (ref)	anticoagulant control	Dose duration	Primary outcome	Participants N=	Design	Estimated study end-date
NCT04516941 ([18])	Edoxaban Colchicine control	60 mg od 30 mg od if CrCl ≤ 50 ml/min or BW ≤ 60 kg 25 ± 3 days 0.5 mg bid, 3 days 0.5 mg od day 4 to 14 ± 3 or 25 ± 3 No active treatment	Edoxaban versus control: asymptomatic proximal DVT, symptomatic PE and DVT, myocardial infarction, ischemic stroke, non-CNS systemic embolism mortality day 25 ± 3 Colchicine versus control: SARS-CoV-2 clearance rates determined by PCR or freedom from death or hospitalisation day 14 ± 3	420	Prospective Randomized Open label 2x2 factorial design bicentric	Dec 2021
NCT04324463 ([19])	Colchicine Aspirin Control Rivaroxaban Interferon-Beta	0.6 mg bid 3 days 0.6 mg od day 4 to 25 75 to 100 mg od Usual care 25 days 2.5 mg bid, Inpatients only Inpatients only	Colchicine – Aspirin: composite of hospitalization or death day 45	4000	Prospective Open-label, parallel group, 2x2 factorial design, randomized, multicentric	June 2021
NCT04518735 ([24])	chronic therapy warfarin acenocumarol dabigatran, apixaban edoxaban, rivaroxaban, aspirin, clopidogrel, prasugrel, ticagrelor, cangrelor, dipyridamole no anticoagulant therapy	According approved treatment regimens any indication	VKA and antiplatelet therapy and control: Comparison of clinical outcomes depending on previous antithrombotic therapy per group: Mortality Transfer to the Intensive Care Unit day 28	1707	Retrospective Case control monocentric	Jun 2020

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