An exploratory study of the effect of tranexamic acid treatment on the progression of COVID-19 in outpatients

Study Protocol and Statistical Analysis Plan

NCT04338074

Date 05/03/2021

Timothy J. Ness, MD, PhD Principal Investigator
University of Alabama at Birmingham
Birmingham, AL 35294

Protocol Summary - in nontechnical, lay language

a. Summarize the purpose and objectives of this protocol in one short paragraph. **The current proposal seeks to determine the effect of a 5 day treatment with oral tranexamic acid (TXA) on the outcomes of outpatients who are newly identified (within 72 hours of test result and within 7 days of onset of symptoms) as test positive for the SARS-CoV-2 virus. Subjects receiving COVID-19 testing within the UAB system will be identified and contacted by telephone, informed of the study with its potential risks/benefits. If they agree to proceed, they will be consented, randomized to TXA or placebo treatment. Because of concerns related to hypercoagulability in COVID-19 patients and with TXA treatment, all subjects will also be treated with prophylactic anticoagulation using the anticoagulant, apixaban 5 mg p.o. BID**

b. Describe how outcomes will be measured for this protocol. **The primary outcome of this study is the need for admission to a hospital due to COVID-19. Secondary outcomes include symptom progression and any other available medical information such as visible bruising.**

Background - in nontechnical, lay language

A recent report in Physiological Reviews (attached) proposed that the endogenous protease plasmin acts on SARS-CoV-2 by cleaving a newly inserted furin site in the S protein portion of the virus resulting in increased infectivity and virulence. Patients with hypertension, diabetes, coronary artery disease, cerebrovascular illness, COPD and kidney dysfunction commonly have elevated levels of plasmin/plasminogen and it was proposed that this may be the mechanism for poorer outcomes in patients with these co-morbidities. A logical treatment that might blunt this process would be the inhibition of the conversion of plasminogen to plasmin. Fortunately, there is an inexpensive, commonly used drug, tranexamic acid, TXA, which suppresses this conversion and could be re-purposed for the treatment of COVID-19.

TXA is a synthetic analog of the amino acid lysine which reversibly binds four to five lysine receptor sites on plasminogen. This reduces conversion of plasminogen to plasmin, and is normally used to prevent fibrin degradation. TXA is FDA approved for outpatient use as a treatment of heavy menstrual bleeding (typical dose 1300 mg p.o. TID x 5 days) and off-label use for many other indications. TXA is used perioperatively as a standard-of-care at UAB for orthopedic and cardiac bypass surgeries and so used regularly in the most fragile, elderly patients with multiple co-morbidities where it has been found safe. At UAB, it is commonly employed in hemorrhaging trauma patients and currently is being studied for perioperative use in Cesarean section surgeries. It has also been utilized for spinal surgery, neurosurgery, ENT surgeries, orthognathic surgeries and even long term for the treatment of cosmetic dermatological disorders with a long track record of safety.

Given the potential benefit and limited toxicity of TXA it would appear warranted to perform rapid randomized, double-blind placebo controlled exploratory trials at UAB in the treatment of the early phases of COVID-19 to determine whether it reduces infectivity and virulence of the SARS-CoV-2 virus as hypothesized. Involvement of each patient is only for 7 days before primary endpoints and then intermittent contact until resolution of symptoms out to 30 days.

It is hypothesized that administration of TXA will reduce the incidence of hospitalization of diagnosed COVID-19 outpatients Potential benefits would be immediate for the patient. Given expected patient numbers in community, 7 days to final assessment and limited "pilot" numbers, it should be rapidly performed.

Participants (Screening and Selection)

a. How many participants are to be enrolled at UAB (if other sites relying on UAB IRB, list the number for each site)? **100**

If multi-site study, total number at all sites/institutions: **n/a**

b. Describe the characteristics of anticipated or planned participants (if multiple groups, repeat list for each group).

Sex: **Both sexes**

Race/Ethnicity: **All**

Age: **Adults, 19 years of age or older. Younger individuals appear to be at low risk of COVID-19**

Health status: **COVID-19 positive**

c. From what population(s) will the participants be derived? **UAB-associated testing sites including the UAB Hospitals, UAB Employee Health, Kirklin Clinic and satellites.**

Describe your ability to obtain access to the proposed population that will allow recruitment of the necessary number of participants: **A Co-PI of this project, Dr. Sonya Heath, is a faculty of the Infectious Disease Division of the Department of Medicine. She currently is responsible for Employee Health testing and is a member of her divisional task force related to COVID-19 studies at UAB. Identification of patients would be a cooperative effort with the members of the Infectious Disease Division.**

d. Describe the inclusion/exclusion criteria:

Inclusion: a recent positive test (within 96 hours of testing; within 7 days of onset of symptoms) for COVID-19; currently an outpatient with no expected immediate hospitalization; English speaking and with phone/internet capability adequate for daily communication. At present, only RNA detecting COVID-19 tests are considered valid and will be the only ones accepted.

Exclusion: an immediate need for hospitalization; history of seizures; history of significant renal disease; history of hypercoagulation-related disorders including pulmonary thromboembolisms, deep venous thromboses, vision/ocular changes; recent or ongoing anticoagulation treatments; cardiac or other vascular stents; active bleeding; history of GI bleed; history of intracranial hemorrhage; pregnancy; use of estrogen-containing oral contraceptives; active malignancy

e. If participants will comprise more than one group or stratification, describe each group (e.g., treatment/intervention, placebo, controls, sham treatment) **and** provide the number of participants anticipated in each group. **Subjects will be randomized into a TXA treatment group (n=50) and a Placebo group (n=50). There will be a *post hoc* analysis that uses stratification according to high vs. low risk for progression of COVID-19 based on age/comorbidities. Notably, 45% of adult Alabamians qualify for the high risk group: elderly, obesity, hypertension, diabetes, COPD, CAD.**

f. Indicate which, if any, of the special populations listed below will be involved in the protocol. Include the Special Populations Review Form (SPRF) if indicated.

☒ Employees or students at institution where research conducted

For each box checked, describe why the group is included **and** the additional protections provided to protect the rights and welfare of these participants who are vulnerable to coercion: **Some of the recruited patients will have been tested through UAB Employee Health. As part of the consent process, they will be informed that involvement or nonparticipation will have no impact upon their jobs and/or academic standing. To exclude this population would be to deprive them of an opportunity to participate.**

g. List any persons other than those directly involved in the protocol who will be at risk. If none, enter "None": **None**

h. Describe the recruitment process (e.g., medical record review, referrals, letter of invitation, existing patients) that will be used to seek potential participants (e.g., individuals, records, specimens)..

All patients undergoing COVID-19 testing at UAB-associated testing sites (e.g. UAB Hospitals, UAB Employee Health, Kirklin Clinic and satellites) or referred from them to UAB-associated treatment sites (e.g. UAB COVID-19 Clinic) will be given a packet of information (attached) at the time of testing or first contact which they will keep (none returned to study). The packet describes the study, provides contact information for the PI/study personnel. Only patients who contact the study personnel will be recruited.

If a patient has tested positive for COVID-19, they will be informed of the test result by a treating physician.

Working remotely, the study will be described by the PI/study personnel and if the patient agrees to participate in the study, they will be consented using remote methods.

i. Describe the screening process/procedures for potential participants. **All newly identified COVID-19 positive patients will be screened for inclusion/exclusion criteria by telephone following informed consent. Demographics, recent/ongoing symptoms and history related to co-morbidities and other health status will be determined.**

Protocol Procedures, Methods, and Duration - in nontechnical, lay language

a. Describe the procedures for all aspects of your protocol. Tell us what you are doing.

This study involves the following:

1) Subjects will be randomized into two groups:

(a) tranexamic acid (TXA) 1300 mg by mouth three times per day x 5 days

(b) placebo tablets by mouth three times per day x 5 days.

The clearance half-life of TXA is approximately 3 hours so drug will have washed out by the day following the final treatment.

2) Due to the possible risk of hypercoagulability being greater in the COVID-19 population, all subjects (both TXA and placebo groups) will also be asked to self-administer apixaban (5 mg p.o. BID), in an unblinded fashion as anticoagulation during the 5 day study period.

A minimal exposure "drive-by" interaction will occur in which there is a transfer of treatment materials (drugs and instructions) while the patient remains isolated in their vehicle. This is currently planned for a small component of the off-street parking area immediately adjacent to the 1917 Clinic located at 908 20th St. This interaction will consist of conversation with either one of the investigators or one of the research nurses named in the IRB Personnel Form. As in all physical interactions with COVID-19 patients, study personnel would don appropriate personal protective equipment. Communication will either occur via cell phone or by talking loudly so it can be heard through the window. They will also have 24/7 access to research personnel by phone/internet to ask additional information.

Notably, this "drive-by" interaction has several advantages over the alternative (mailing medications/instructions to patients) in that it assures delivery and initiation of the treatments, it reduces the potential exposure of postal personnel to a known COVID-19 patient.

Contact after the "drive-by" interaction would be exclusively by telephone or via the internet.

All subjects will be contacted by telephone or internet daily and ongoing symptoms will be assessed for 7 days. In subjects with symptoms, additional contact(s) will be made at 3 day intervals for up to 30 days until resolution of any symptoms.

The primary endpoint for the study is hospital admission for COVID-19 within 7 days of enrollment.

b. What is the probable length of time required for the entire protocol (i.e., recruitment through data analysis to study closure)? **6 months**

c. What is the total amount of time each participant will be involved? **To primary endpoint – daily for 7 days after that, intermittently until resolution of symptoms – for up to a maximum of 30 days.**

d. List the procedures, the length of time the procedure takes, the total # of times the procedure is performed, and indicate whether each is performed solely for research or would already be performed for treatment or diagnostic purposes (routine care) for the population.
-Insert additional table rows as needed.
-If procedure is sometimes research and sometimes routine care, include on separate lines with number of times as each.

Procedure	Length of Time Required of Participants	Total # of Times the Procedure is Performed	Research (Res) –OR- Routine Care
Consent	**1 hour**	**1**	☒Res ☐Routine
"Drive-by" interaction to pick up study drugs/placebo	**30 min**	**1**	☒Res ☐Routine
Daily Phone or email Contact	**20-30 min each contact**	**7 times until primary endpoint, then follow-up at 3 day intervals until symptoms resolve up to 30 days**	☒Res ☐Routine

f. Will participants be compensated? ☒Yes ☐No

If Yes, complete i-v.

i. Type: (e.g., cash, check, gift card, merchandise): **Gift card**

ii. Amount or Value: **$50**

iii. Method (e.g., mail, at visit): **Received at time of "drive-by" interaction**

iv. Timing of Payments: (e.g., every visit, each month): **once**

v. Maximum Amount of Compensation per Participant: **$50**

Benefits

Describe the potential benefits of the research.

The participant may benefit directly from participation in this study. Clearly benefits to the patient and society if it is demonstrated that TXA reduces the severity of COVID-19. This pilot study is unlikely to demonstrate definitive results as it is not powered sufficiently for that endpoint (would require 200 patients per group for 50% reduction). It will, however, provide the necessary preliminary data needed for a larger multicenter trial of the same intervention. Its primary purpose is an assessment of safety and the generation of efficacy estimates for TXA.

Risks - in nontechnical, lay language

a. List the known risks for participants as a result of participation in the research. This should not include the minimal risk of loss of confidentiality. However, it should include any physical, psychological, social,

economic, and/or legal risks. If there is a greater than minimal risk of loss of confidentiality describe why this is so. Do not list risks associated with the standard-of-care procedures.

NOTE: Risks included here should be included in the consent form or information sheet, as applicable.

The drug tranexamic acid (TXA) is commonly employed at UAB as its administration is a standard-of-care in association with orthopedic and cardiac bypass surgeries. There is an extensive clinical literature associated with its use and it is FDA-approved for the treatment of heavy menstrual bleeding using the same dose as is utilized in the present study. It is available Over-The-Counter in the UK. That said, it is not without risks as its primary indication is as an inhibitor of plasmin activation. Plasmin is a protease that breaks down the fibrin in clots and so there is an increased risk of clot formation when TXA is utilized. For that reason, use is typically excluded in people with a history of forming clots such as in Deep Venous Thrombosis (DVT) or Pulmonary Thromboembolus (PTE). Patients will be instructed that if they demonstrate signs/symptoms of DVT or PTE (i.e. swollen limbs, distended veins, sudden onset of shortness of breath) at the time of enrollment or during the study (they are asked these questions during the regular telephone contacts), they are to immediately inform the research nurse and will be instructed to go to an Emergency Room for evaluation/treatment. They will also immediately stop any study medications. There has also been reports of seizures in individuals who receive high doses of TXA intravenously. Although these are not expected, patients will be instructed to let family members know that they should call the research nurses and/or immediately go to an Emergency Room if there is any alteration in mental status or uncontrolled muscle contractions.

Because there are concerns that TXA as well as COVID-19 might increase risks of forming blood clots, subjects will all be treated with a an oral anticoagulant, apixaban at a dose demonstrated to be effective prophylaxis in clinical conditions commonly treated at UAB (5 mg p.o. BID). All blood thinners have risks, in particular risks of increased bleeding and subjects will be excluded if they have a medical history suggesting increased risk from anticoagulants (e.g. history of GI bleed).

b. Estimate the frequency, severity, and reversibility of each risk listed.

SIDE EFFECTS REPORTED IN THE FDA APPROVAL STUDIES FOR TXA

Table 2: Adverse Events Reported by ≥ 5% of Subjects Treated with TXA	3900 mg/day n (%) (N=232)	Placebo n (%) (N=139)
Total Number of Adverse Events	1500	923
Number of Subjects with at Least One Adverse Event	208 (89.7%)	122 (87.8%)
HEADACHE[a]	117 (50.4%)	65 (46.8%)
NASAL & SINUS SYMPTOMS[b]	59 (25.4%)	24 (17.3%)
BACK PAIN	48 (20.7%)	21 (15.1%)
ABDOMINAL PAIN[c]	46 (19.8%)	25 (18.0%)
MUSCULOSKELETAL PAIN[d]	26 (11.2%)	4 (2.9%)
ARTHRALGIA[e]	16 (6.9%)	7 (5.0%)
MUSCLE CRAMPS & SPASMS	15 (6.5%)	8 (5.8%)
MIGRAINE	14 (6.0%)	8 (5.8%)
ANEMIA	13 (5.6%)	5 (3.6%)
FATIGUE	12 (5.2%)	6 (4.3%)

[a] Includes headache and tension headache

[b] Nasal and sinus symptoms include nasal, respiratory tract and sinus congestion, sinusitis, acute sinusitis, sinus headache, allergic sinusitis and sinus pain, and multiple allergies and seasonal allergies

[c] Abdominal pain includes abdominal tenderness and discomfort

[d] Musculoskeletal pain includes musculoskeletal discomfort and myalgia

[e] Arthralgia includes joint stiffness and swelling

The following adverse reactions have been identified from post-marketing experience with TXA. Because these reactions are reported voluntarily from a population of uncertain size, it is not always possible to reliably estimate their frequency or establish a causal relationship to drug exposure.

Based on worldwide post-marketing reports, the following have been reported in patients receiving TXA for various indications:

- **Nausea, vomiting, and diarrhea**
- **Allergic skin reactions**
- **Anaphylactic shock and anaphylactoid reactions**
- **Thromboembolic events (e.g., deep vein thrombosis, pulmonary embolism, cerebral thrombosis, acute renal cortical**
- **necrosis, and central retinal artery and vein obstruction)**
- **Impaired color vision and other visual disturbances**
- **Dizziness**

Risks of TXA & seizures reported in cardiac surgeries – at doses of 24-50 mg/kg IV (versus the bioequivalent dose of <10 mg/kg given in this study) the incidence was 1.4%. No seizures were reported in the FDA studies of oral dosing. There are three case reports of seizures in non-cardiac cases all using IV administration of TXA.

RISKS OF APIXABAN. Hemorrhagic clinical events reported to be related to long-term (>6 mo) apixaban therapy occurred at an incidence of approximately 1.5%. Non-hemorrhagic clinical events were <1%. Use of a 5 day course would have less risk and the effects of apixaban can be readily and immediately reversed.

Informed Consent

a. How will consent be obtained?

Patients interested in participating will be emailed a copy of the consent form The PI/study personnel will verbally present the study by going over the consent form. The PI/study personnel will arrange a video (Zoom) conference with the subject and a witness (who may be someone already in the subject's household). The call will include the following: (1) Identification of who is on the call. (2) Review of the consent form by the PI/study personnel and answering any questions the subject may have, (3) Confirmation by the witness that the subject's questions have been answered, (4) Confirmation by the PI/study personnel that the subject is willing to participate in the study and sign the consent form while the witness is listening on the phone, (5) Verbal confirmation by the subject that they would like to participate in the study and that they have signed and dated the consent form.

The signed consent form then be scanned/photographed and emailed back to the PI/study personnel. A copy of the consent form signed by the investigator and witness will be placed in the study record. Following FDA guidelines, a hard copy of the consent form signed by the subject will not be retained (e.g., due to potential contamination of the document by infectious material).

Statistical Plan

Update (5/2/2021) The statistical plan for this study was to compare categorical data for the primary endpoint which was hospital admission during the 7 day treatment period. A simple Chi Square comparison was planned. Any secondary data were to be described qualitatively and not analyzed statistically.

In this truncated study, no subjects met the primary endpoint and there were insufficient data to perform any meaningful analysis.