

# BMJ Open Efficacy and tolerance of early administration of tranexamic acid in patients with cirrhosis presenting with acute upper gastrointestinal bleeding: a study protocol for a multicentre, randomised, double-blind, placebo-controlled trial (the EXARHOSE study)

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## ABSTRACT

**Introduction** The management of acute upper gastrointestinal bleeding (UGIB) is challenging in patients with cirrhosis, as it is responsible for severe complications and high mortality rates. Tranexamic acid (TXA) may help control the bleeding by counterbalancing cirrhosis-related hyperfibrinolysis. Still, there is a lack of unbiased data to conclude on its efficacy. The aim of this study is to evaluate the efficacy of TXA in the early treatment of acute UGIB in patients with cirrhosis.

**Methods and analysis** This study is a multicentre, randomised, double-blind, placebo-controlled trial, for adult patients with cirrhosis presenting with an acute UGIB and allocated to one of two arms: TXA or placebo (saline). Physicians from emergency mobile services, emergency departments (EDs) or intensive care units (ICUs) can include patients. Besides study intervention, standard care for UGIB will be performed as recommended. Intervention will consist an intravenous infusion of 10 mL of TXA (1 g) or saline, immediately followed by three identical intravenous infusions over 8 hours each (total dose of 4 g of TXA or 40 mL of placebo over 24 hours). Main analyses will be conducted in intention to treat on every patient included, then in modified intention to treat on patients with underlying lesion of portal hypertension visualised by endoscopy. The main objective is to show efficacy of TXA until day 5 on a composite criterion (bleeding control, rebleeding episodes and mortality). Secondary objectives aim at showing the efficacy of TXA on each individual component of the main outcome measure and others at 6 weeks and later (transjugular intrahepatic portosystemic shunt procedure, cirrhosis-specific complications, length of stay in ICU and in hospital, safety and tolerance of TXA, liver transplantation). Included patients will be followed up to 1 year after inclusion. 500 patients will be necessary to show a reduction in the prevalence of the primary outcome

## Strengths and limitations of this study

- Tranexamic acid (TXA) may be beneficial in acute upper gastrointestinal bleeding (UGIB). Yet, it has never been evaluated in patients with cirrhosis, who often present with haemostatic imbalance at the early phase of acute UGIB and suffer from high mortality rates.
- This study is the first randomised, multicentre, double-blind, placebo-controlled trial in patients with cirrhosis suffering from acute UGIB. It aims at analysing the efficacy of TXA on a composite criterion at day 5 after enrolment (bleeding control, early recurrence, death).
- This therapeutic protocol is easy to implement and adapted to the multiple settings implied in the urgent care of patients with cirrhosis suffering from acute UGIB (emergency mobile services, emergency departments and intensive care units).
- Due to poorly described in vivo haemostatic imbalance after UGIB onset in this population, patients will be eligible for 24 hours after the first haematemesis. Regarding the most recent data in non-cirrhotic patients (ie, severe trauma), for whom a time from onset to TXA administration >3 hours showed no clinical benefit in bleeding control, the conclusions of this study might be limited by delayed TXA administration.

from 30% to 18% with a bilateral alpha risk of 5% and a power of 80%.

**Ethics and dissemination** Ethical approval has been obtained from the Comité de Protection des Personnes Ile-de-France 1 (CPP-IDF1). Results will be disseminated via publications in peer-review medical journals and scientific forums.

**Protocol version** This protocol is based on the latest version, as established on 11 October 2017 and validated by the IRB CPP Ile-de-France 1.

**Trial registration number** NCT03023189.

## INTRODUCTION

### Upper gastrointestinal bleeding in patients with cirrhosis

Upper gastrointestinal bleeding (UGIB) is frequent, with an estimated incidence of 150/100 000 in France.<sup>1</sup> Despite improvement in preventive and therapeutic measures over the last two decades, acute UGIB is still associated with high mortality rates in patients with cirrhosis, rising up to 30% at 6 weeks, especially in the most severe patients (Child score B or C and/or high odel for End-stage Liver Disease score (MELD), and high portal hypertension). Moreover, acute UGIB is directly responsible for 50% of deaths in these patients, either because it is uncontrolled during the acute phase (until day 5), or because of rebleeding episodes (within 6 weeks).<sup>2,3</sup> Acute UGIB is the most frequent cause of cirrhosis decompensation and also has an impact on long-term prognosis: the risk of recurrence reaches 60% in the year following the first episode and the survival rate after 3 years is only 30%. Acute UGIB is also responsible for several complications in patients with cirrhosis, which are associated with high mortality rates, either specific to cirrhosis (acute on chronic liver failure, hepatorenal syndrome, ascites liquid infection and hepatic encephalopathy) or non-specific (sepsis).<sup>4,5</sup> The management of acute UGIB is therefore of major importance in patients with cirrhosis.

The Baveno-VI guidelines, (and in France, the national authority for health (HAS), recommend standardised, early, aggressive therapeutic strategies for acute UGIB in patients with cirrhosis.<sup>3,6,7</sup> Proton pump inhibitors (PPIs), splanchnic vasopressors (somatostatin, terlipressin) and antibiotics are to be introduced as soon as possible: according to the HAS, vasopressors should be given on-scene (or en route to the hospital) by emergency mobile services (EMSs). Above all, vasopressors and PPIs should be introduced before interventional measures (gastric endoscopy, transjugular intrahepatic portosystemic shunt (TIPS)). These interventional procedures are also recommended within precise time frames and indications.

Patients with cirrhosis often present with haemostatic abnormalities at baseline state, including spontaneous hyperfibrinolysis. Still, apart from situations of cirrhotic decompensation, the haemostasis of these patients remains globally preserved, as a result of the balance between pro and anticoagulative alterations.<sup>8</sup> It seems that the baseline coagulopathy is not directly responsible for acute UGIB but could be a surrogate marker of the evolution and severity of portal hypertension. Nevertheless, every cause of cirrhotic decompensation, including acute UGIB, can increase haemostatic disorders and lead to either hypercoagulation or hyperfibrinolysis. To this day, the direction of the haemostatic imbalance during cirrhotic decompensation remains quite unknown and

unpredictable, but clinical data suggest that it is often set to hyperfibrinolysis and haemorrhage. Hyperfibrinolysis could disrupt the pharmacological control of acute UGIB, but biological evaluation of the haemostasis in patients with cirrhosis is difficult in a routine practice. Standard tests are poorly correlated to the real haemostasis level, as they imperfectly estimate the intricate mechanisms of fibrinolysis and coagulation.

For these reasons, the management of primary or secondary haemostasis imbalance is not clearly specified nor recommended in the Baveno-VI consensus, due to a lack of data. In case of haemorrhagic shock, blood transfusion should aim at obtaining an haemoglobin (Hb)  $\geq 8$  g/dL; there is insufficient data to recommend and specify the use of other haemostatic products, potentially harmful due to the role of blood volume increase on bleeding (fresh frozen plasma, fibrinogen, platelets, activated factor VII etc).<sup>3,9</sup> Therefore, few novel therapeutic measures are available to the clinicians in charge of these patients during the acute phase, including EMS, emergency department (ED) and intensive care units (ICU's) paramedics or physicians.

### Antifibrinolytics

Early administration of antifibrinolytic agents such as tranexamic acid (TXA) could efficiently help control acute UGIB in patients with cirrhosis. Despite a promising theoretical interest, four meta-analyses conducted in 2012, 2014 and 2015 by the Cochrane Collaboration concluded on the necessity of unbiased, prospective, randomised, double-blinded studies to evaluate the role of TXA in acute UGIB.<sup>10-13</sup>

These meta-analyses stated that TXA has showed a probable benefit in acute UGIB from all cause, either on mortality or bleeding control and transfusion. Yet, the population of all-cause UGIB may be very different from the cirrhotic subgroup: the overall main aetiologies of UGIB are peptic ulcers (36%) and oesophagitis (24%) whereas variceal bleeding (from all cause) represent only 11%.<sup>14</sup> In acutely bleeding patients, only 9% present with an underlying cirrhosis. In peptic ulcer disease, in-hospital mortality is around 9%; in variceal bleeding (from any cause), it is 15% and in specifically patients with cirrhosis, it reaches up to 30%. Hence, patients with cirrhosis represent a small subgroup of patients suffering from acute UGIB, more fragile than others and with higher mortality rates (related to various physiological impairments as described earlier, of which haemostatic imbalance appears to be one of the most important). Patients with cirrhosis often present with haemostatic imbalance, which may be more severe than in non-cirrhotic ones.

Therefore, the evaluation of TXA in this subgroup appears to be of particular interest, as it may be more beneficial in these patients at high risk of coagulation abnormalities, complications, lack of bleeding control, rebleeding episodes and mortality.

TXA is easy of use and showed clinical benefits on haemorrhage and/or mortality in several other indications

(surgical, obstetrical and traumatic) with no significant increase in the risk of side effects. It is now routinely used in different settings (either in or out of hospital). The efficient dose in adults is undefined and depends on the clinical situation, but it seems that an intravenous bolus of 10 mg/kg followed by an infusion of 1 mg/kg/hour is sufficient to provide bleeding control and to reduce the needs for blood transfusion.<sup>15 16</sup> In the Clinical Randomisation of an Antifibrinolytic in Significant Haemorrhage (CRASH)-2 trial, adult patients with trauma received 2 g of TXA (an intravenous bolus of 1 g, followed by an infusion of 1 g over 8 hours). In the Haemorrhage Alleviation with Tranexamic acid - Intestinal system (HALT-IT) study, currently recruiting adults suffering from acute digestive bleeding of all cause, the dose of TXA is 4 g over 24 hours (1 g intravenous bolus, followed by an infusion of 3 g over 24 hours).<sup>17</sup> These doses seem reasonable facing existing data, as superior ones are believed to lead to increased thromboembolic events or seizures.

To this day, TXA has not been evaluated in acute UGIB of patients with cirrhosis, despite encouraging in vitro and clinical results in a surgical setting.<sup>18 19</sup> Indeed, when administered during a liver transplantation surgery—of which cirrhosis is the main aetiology<sup>19 20</sup>—TXA has showed benefits on blood transfusion needs and on the occurrence of haemorrhagic complications. To date, neither TXA nor any other antifibrinolytic drug is recommended for the treatment of acute UGIB, in either cirrhotic or non-cirrhotic patients.

### Study objectives

We hypothesise that, when administered early and coupled with routine treatment in patients with cirrhosis presenting with acute UGIB of all causes, TXA could be beneficial for controlling the acute haemorrhage, avoiding rebleeding episodes and reducing mortality within 5 days after its administration.

## METHODS AND ANALYSIS

### Study design and settings

The EXARHOSE study will be a pragmatic, multi-centre, randomised, double-blind, placebo-controlled trial conducted in 48 departments of 20 community and university hospitals in France (list available in the complete protocol or on demand to the corresponding author). It will involve EMS, EDs and ICUs.

### Patients

#### Eligibility criteria

Eligibility criteria are synthesised in [table 1](#).

Because cirrhosis may be undiagnosed and UGIB may be difficult to assess at the time of enrolment, patients may be included based on the uncertainty principle. This attitude seems reasonable, regarding the performance of clinical examination for signs of liver failure and/or portal hypertension (also see ‘Data collection’): medical history (chronic alcoholic consumption, known cirrhosis and

**Table 1** Eligibility criteria of the EXARHOSE protocol

Inclusion criteria	Non-inclusion criteria
Age ≥18	TXA already administered for the current UGIB episode, and before screening for eligibility
Patient in charge of an <ul style="list-style-type: none"> <li>▶ EMS and/or</li> <li>▶ ED and/or</li> <li>▶ ICU physician</li> </ul>	Gastric endoscopy already performed for the current UGIB episode, and before screening for eligibility
Acute UGIB (haematemesis) <ul style="list-style-type: none"> <li>▶ &lt;24 hours from onset</li> <li>▶ As described by the patient or a bystander, or witnessed by the investigator or any caregiver</li> <li>▶ Isolated or associated with LGIB</li> </ul>	TXA contraindication <ul style="list-style-type: none"> <li>▶ Known allergy</li> <li>▶ DIC</li> <li>▶ Thromboembolic event</li> <li>▶ Documented creatinine serum level &gt;500 µmol/L or clearance &lt;30 mL/min</li> <li>▶ Seizures when in charge of investigator</li> </ul>
Cirrhosis <ul style="list-style-type: none"> <li>▶ Known</li> <li>▶ Or suspected on clinical, biological, radiological data or the patient’s history</li> </ul>	Cardiac arrest even if a ROSC is achieved  Linguistic barriers to the understanding of the study
Social insurance coverage	Ongoing pregnancy
Written consent <ul style="list-style-type: none"> <li>▶ Patient</li> <li>▶ Relative</li> <li>▶ Or inclusion on emergency procedure</li> </ul>	Patient already included in <ul style="list-style-type: none"> <li>▶ EXARHOSE (new UGIB episode)</li> <li>▶ another therapeutic protocol</li> </ul>
Guardianship	

DIC, disseminated intravascular coagulation; ED, emergency department; EMS, emergency mobile service; EXARHOSE, multicentre, randomised, double-blind, placebo-controlled trial; ICU, intensive care unit; LGIB, lower gastrointestinal bleeding; ROSC, return of spontaneous circulation; TXA, tranexamic acid; UGIB, upper gastrointestinal bleeding.

related complications, ongoing treatment, former therapeutic interventions, radiology and echography elements, biological results etc); liver failure (jaundice, encephalopathy, stellate angiomas, palmar erythrode, digital clubbing, gynaecomastia, encephalopathy); portal hypertension (collateral venous circulation, jugular turgor, ascites).

In addition, if the patient is unable to express proper consent, he may be included on emergency procedures, allowing the investigators to perform the initial intervention before looking to obtain the consent, either from the patient himself or a representative.

Study centres and investigators will be eligible to perform the interventions if they routinely participate in the management of adult patients presenting with acute UGIB, whether cirrhotic or not.

### Recruitment

Patients with cirrhosis presenting with acute UGIB can be referred to multiple types and places of hospitalisation

(hepatology, gastroenterology, ICU, ED, EMS). As they are at high risk of severe complications, and because urgent fibroscopy is not always available in France if not in ICU, we chose to focus on ICUs with a fibroscopy team available 24 hours a day, assuming that the majority of cirrhotic patients with acute UGIB would transit via one of those ICUs. Then, in order to shorten delays to TXA administration, we chose to recruit patients at every possible stage of their care pathway, from UGIB onset to ICU (EMS, ED).

In any case, patients recruited in a facility that does not grant access to urgent endoscopy will be transferred to another participating centre capable to proceed to the rest of the interventions within recommended time frames.

### Allocation

After screening for eligibility, the patient or his representative will receive loyal, complete, understandable information about the study protocol, objectives, constraints, potential side effects and safety measures, and about their right to withdraw consent and participation at any time. This information will be available in paper form, which will have to be filled by both the investigator and the patient or representative (identification, date and signature) (see online supplementary files 1–4). Because of the emergency to provide care in case of acute UGIB, if the patient is unable to give proper consent and no representative is present, the investigator can include and randomise the patient in accordance with emergency procedures. This legal procedure, based on the Article L.1122-1-2 of the French Public Health Code and the agreement of the Comity for the Protection of Patients, allows randomisation in situations where the intervention treatment may be beneficial to the patient.

In any case, consent will be necessary to continue the treatment and collect data. Similarly to the initial consent, the patient will be asked to sign it, if he agrees to pursue his participation, as soon as he is able to. In case the representative arrives before the patient is able to give his consent, he will be informed and asked to sign pursuit consent for the participation of his relative.

If a curatorship is discovered after inclusion, the curator will be informed as soon as possible. Patients under guardianship will not be enrolled. If the guardianship is discovered after inclusion, the participation of the patient will be stopped.

If the patient whose consent has not been given dies after inclusion, and if his representative expresses no withdrawal, collected data will be usable.

Randomisation will be 1:1 with stratification by centre (ie, every participating department) and will be based on computer-generated secured lists. Because of the sample size of each participating centre (estimated at 10–15 per year), stratifying on another factor (such as previous variceal bleeding) may be source of suboptimal statistical relevance, even though clinically important. Nevertheless, due to the randomisation and the sample size, one

can expect that other factors will be equally distributed over the two arms.

The pharmacy of the Creteil University Hospital will ensure that every treatment unit, containing four identical and blind medicine bottles, is identified by a single number corresponding to one of the randomisation blocks. ICU and ED clinicians will use the treatment unit with the lowest number, while EMS clinicians will use the unit located in their ambulance. After utilisation of a unit in the prehospital setting, EMS vehicles will be reloaded with the treatment unit with the lowest number. Randomisation lists will be under the responsibility of the pharmacy of the Creteil Hospital and will have to be transmitted in case of need of unblinding.

After inclusion, entry form data will be faxed to the trial coordinating centre of the Creteil University Hospital (see online supplementary file 5).

Randomisation lists will be in possession of the pharmacist and the trial coordinating centre of the Creteil University Hospital, the promoter of the study (DRCI, Délégation à la Recherche Clinique et à l'Innovation) and the antipoison centre.

### Interventions

After inclusion, intervention will consist in a 10 mL intravenous infusion of TXA (1 g) or saline over 10 min, immediately followed by three identical intravenous infusions over 8 hours each (total dose of 4 g of TXA or 40 mL of placebo over 24 hours).

Intervention will be associated to routine practice, as recommended, that is,: conditioning (intravenous access, tracheal intubation or other airways management technique if needed); medical interventions (immediate splanchnic vasopressors: terlipressin or somatostatin and derivatives before endoscopy (up to 5 days), PPIs in case of suspicion of associated peptic ulcer, antibiotics (fluoroquinolones or third generation cephalosporins, during 5 days)); haemodynamic stabilisation (fluid infusion, systemic vasopressors as noradrenalin or adrenalin); blood transfusion\*; technical interventions (endoscopy as soon as possible, within 12 hours, associated to haemostatic measures after infusion of erythromycin, early TIPS within 72 hours (Child C or B with active bleeding at endoscopy)).

Afterwards, patients will receive further procedures as recommended, including secondary prophylaxis (from day 6 after onset): beta blockers, variceal ligation, N-butyl-cyanoacrylate, TIPS etc. As these procedures are routinely processed by the centres participating in EXARHOSE, and because the study is pragmatic, no protocol will be mandatory for the secondary prophylaxis.

\*Blood transfusion procedures: in patients with cirrhosis, despite the lack of clear recommendations, Hb should reasonably be maintained above 8 g/dL. Blood transfusion should then aim at reaching this minimum. There is no sufficient data on the benefit of fibrinogen, fresh frozen plasma or platelet transfusion in patients with cirrhosis. Therefore, no recommendations will be

made in the study protocol and investigators will be free to prescribe non-red cells packs according to local habits.

Study intervention may be interrupted in case of major side effects (ie, death, seizures, severe acute kidney injury as previously defined, discovery of pregnancy during TXA infusion, anaphylaxis and others), patient initiative (withdrawal of consent, request) or physician initiative for any relevant situation, or promoter initiative.

Main investigators in each participating centre will perform oral presentations and staffs, give printed and electronic documents (synthesised protocol, pharmaceuticals procedures, posters etc) and reminders (newsletter with frequently asked questions, news and protocol modifications etc) to ensure good compliance of the caregiving staff to the protocol.

### Blinding

As the EXARHOSE study is double blind, patient/representative, investigator and involved caregivers (physicians, nurses, others) will be blind as to the allocated treatment. Data managers of the trial coordinating centre and data managers of the electronic study file will also be blind.

The unblinding, if estimated necessary by the investigator, will be made by telephone contact with the promoter (DRCI, during daytime) or the antipoison centre (weekends and night-time).

### Outcomes

The main objective is to show efficacy of TXA on the bleeding control at day 5 after enrolment, including (1) immediate control (2) absence of early bleeding recurrence (until day 5) and (3) absence of death (until day 5). The composite criterion is defined by every following criterion:

- ▶ Immediate bleeding control after initiation of specific medical treatment (splanchnic vasopressors and/or PPI), including fluid infusion, blood transfusion and/or systemic vasopressors, and defined by the presence of every following criterion:
  - Transfusion target (Hb  $\geq 7$ g/dL) reached within 24 hours after initial contact.
  - No introduction or no increase of systemic vasopressors (adrenalin, noradrenalin). Splanchnic vasopressors (terlipressin, somatostatin and derivatives) are not concerned.
  - Absence of need for transfusion of two or more blood pack units within 24 hours to maintain transfusion target (Hb  $\geq 7$ g/dL).
  - Absence of persistent haemorrhagic shock or absence of installation of haemorrhagic shock after initial contact (Systolic blood pressure (SBP)  $< 100$  mm Hg or Mean Blood Pressure (MBP)  $< 60$  mm Hg and/or Heart Rate (HR)  $> 100$  b/min).
- ▶ Absence of rebleeding episodes, as assessed by the caregiving team and based on clinical, biological and/or endoscopic elements.
- ▶ Absence of death.

Secondary objectives are to show efficacy of TXA on each individual component of the main outcome measure (at day 28, day 42, 6 and 12 months after enrolment) and others (TIPS procedure, cirrhosis-related specific complications, length of stay in ICU and in hospital, safety and tolerance of TXA, liver transplantation).

The safety and tolerance of TXA will be assessed on declarations and follow-up of adverse effects during intervention, whether documented (seizures, thromboembolic events, acute kidney injury, anaphylaxis etc) or only suspected.

The choice for a composite criterion was justified by the following rationale: (1) because patients with cirrhosis are more fragile than other bleeding populations, they present with high morbimortality rates after onset of cirrhosis-related specific complication, including within 5 days (encephalopathy, sepsis, hepatorenal syndrome etc). (2) The benefit of early interventions in patients with cirrhosis may be global and not limited to death within 5 days: TXA could reduce the duration of bleeding episode, hence lower the length of stay in ICU, the occurrence of other complications (sepsis, encephalopathy, hepatorenal syndrome). (3) This composite outcome has already been used in several studies in acute UGIB.<sup>21-23</sup>

Thus, death should not be the only criterion for evaluating early interventions in patients with cirrhosis suffering from acute UGIB.

### Participant timeline

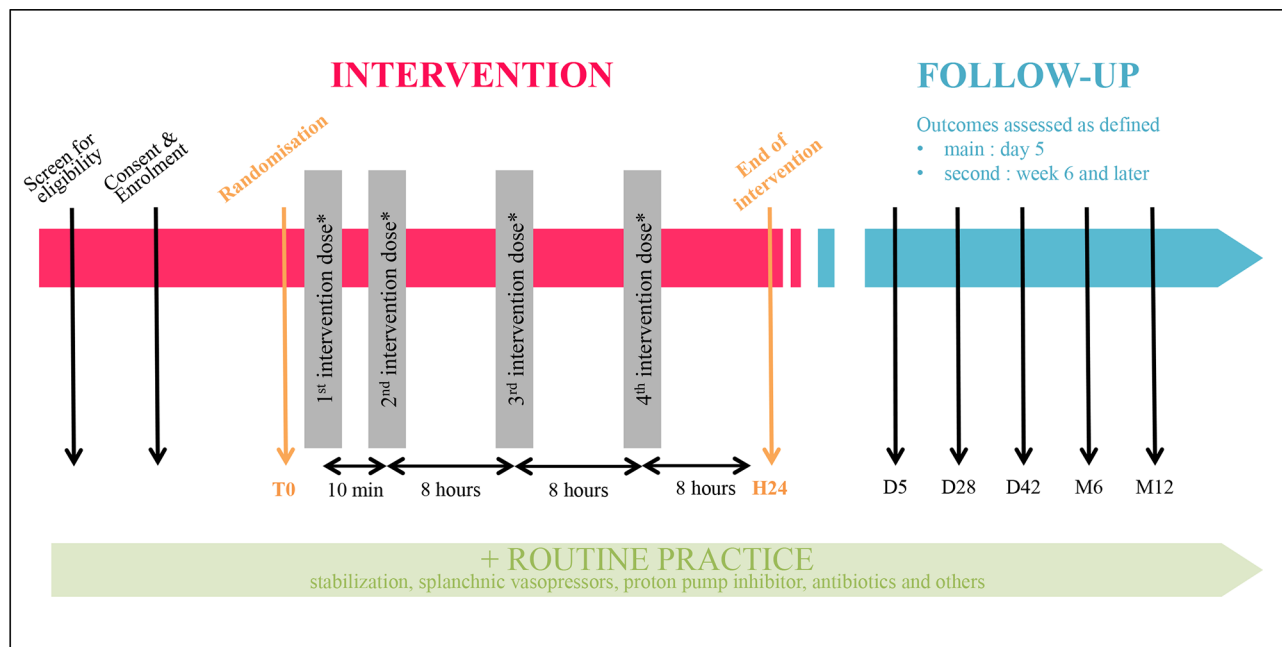
Period of enrolment will last 2 years after enrolment of the first patient. Patients will be followed up to 1 year after inclusion. Total duration of the study will be 3 years after the first inclusion (figure 1).

Follow-up visits will be at day 5, day 28, day 42, 3 months, 6 months and 1 year after inclusion and will be conducted by the physician in charge during hospitalisation, then by a clinical research technician under responsibility of the latter. It will consist in both clinical and biological evaluation, depending on the date and hospitalisation status. When out of hospital, vital status patient will be assessed by telephone. After three unsuccessful tries with no answer, the patient will be classified as lost to follow-up.

### Sample size

We estimate that the prevalence of the composite criterion, as previously described and based on existing data, will be 30% in the control group. Considering a bilateral alpha risk of 5%, a power of 80% and a prevalence of patients lost to follow-up or incorrectly included of 15%, 250 patients per group will be necessary to show an absolute reduction of risk of 12% in the intervention group (30%–18%) in both intention-to-treat (ITT) and modified ITT populations (15% of patients included by error expected).

This sample size calculation differs from the CRASH-2, World MATernal ANtifibrinolytic (WOMAN) and HALT-IT studies because (1) the target population is not the same



**Figure 1** Intervention and follow-up timeline of the EXARHOSE study. \*Intravenous TXA (1g) or placebo (saline, 10 mL). Follow-up during hospitalisation: clinical and biological outcomes; follow-up after discharge: telephone interrogation (patient and physician). EXARHOSE, multicentre, randomised, double-blind, placebo-controlled trial; TXA, tranexamic acid.

and is more fragile at baseline than others, (2) the main judgement criterion is composite (not only death) and its prevalence should be higher in the EXARHOSE control group than others studies and (3) the efficacy of TXA might be superior in patients with cirrhosis due to possibly deeper and longer haemostatic imbalance.

### Data collection

Each investigator of each study centre will collect data. Methods of collection will vary on the place of inclusion: EMS and ED investigators will use a paper file that will have to be filled in duplicates and then transmitted to the receiving ICU, and entered in an electronic case report form (eCRF) by clinical research technicians. ICU investigators will use the eCRF. Every data concerning outcomes and side effects will be collected. In case of incomplete collection, clinical trials technicians will go to the study centres to retrieve missing data and collect them in the eCRF.

Collected data will include (not limitative): (1) medical history (general condition, existing digestive pathologies, other than cirrhosis: peptic ulcer, gastropathy, angiodysplasia, known cirrhosis (time of diagnosis, aetiology time of last endoscopy, time and type of complications such as gastrointestinal bleeding, hepatorenal syndrome, ascites infection or hepatic encephalopathy), (2) clinical examination (ascites, collateral venous circulation, type and severity of varices, jaundice, encephalopathy, stellate angiomas, palmar erythroze, digital clubbing, gynaecomastia, Child-Pugh and MELD scores, haemodynamic and respiratory statuses), (3) biological tests and values (Hb, serum electrolytes, blood gas, liver enzymes), (4) therapeutic interventions and secondary prophylaxis

(fluid infusion (type and volume), splanchnic vasopressor (type and posology), systemic vasopressors (type and posology), respiratory support, blood transfusion (type and volume), time of endoscopy, oesophageal and/or gastric lesions, time of TIPS) and (5) outcomes.

In ICU, data will be collected daily on routine practice, including prognostic and severity scores, cirrhosis scores and more. Mandatory follow-up dates are H24, day 5, day 28, day 42, 6 months and 1 year after inclusion.

The collected data are under the responsibility of the trial promoter (DRCI, Assistance Publique - Hôpitaux de Paris (AP-HP)), the coordinating investigator, the trial coordinating centre (Unité de Recherche Clinique (URC) Henri Mondor) and every investigator of the study.

### Data management

Final collection will be made through the data reported in the eCRF, which is under the responsibility of the online information system for clinical trials management (CleanWeb, Telemedecine Technologies SAS, France). Data managers of the trial coordinating centre (Unit of Clinical Research, Creteil University Hospital) built the interface of the eCRF, and are responsible for its updates and modifications under the supervision of the coordinating investigator.

### Statistical methods

#### Analysis

Descriptive statistical analysis will be conducted to evaluate the randomisation groups in terms of demographic, clinical and biological characteristics. Quantitative variables will be presented as mean±SD deviation

or medians+IQR range on normality of the distributions, and categorical variables in numbers and percentages.

The analysis of the main composite outcome (control of the bleeding until day 5) and binary secondary outcomes (until week 6: control of the bleeding, rebleeding episodes, mortality, complications, specific therapies) will rely on comparative tests ( $\chi^2$  or Fisher's exact tests) depending on conditions of application. Longitudinal analysis will be conducted using general estimating equations logistic regression models to account for the stratification by centre. Intergroup comparisons of quantitative variables when measured at a given time (clinical scores, time of hospitalisation) will be conducted using Student's t-test or Mann-Whitney U tests depending on conditions of application. Longitudinal analysis aiming to evaluate the differential evolution of intergroup parameters will be conducted using mixed-effects linear models counting for the correlation of variables repeated in time.

The analysis of time to death within the year after inclusion will rely on censored data techniques (Kaplan-Meier curbs, univariate log-rank tests, proportional risks Cox regression model, Fine and Gray competitive risks models for the analysis of the bleeding-related specific mortality).

Statistical analysis will be conducted on the ITT principle for the main primary endpoint analysis. ITT population will consist of the included and randomised patients (agreement given or included on urgent measures, no retraction expressed and consent to continue treatment). Modified ITT analysis will also be conducted on patients with signs of portal hypertension visualised during gastric fibroscopy and after excluding those patients included by error, as well as complementary per-protocol (PP) analyses (with no major deviation from the protocol). Modified ITT and PP will be performed as supportive analyses to describe the population excluded from the modified ITT/PP, evaluate the impact on the main ITT analysis and the robustness of obtained results.

No intermediary analyses will be conducted. All missing or invalid data will be systematically checked and searched for in patients' medical records. The main ITT analysis will be conducted after imputing missing data for the primary outcome under the worst-case hypothesis (considering a success in the control group and a failure in the experimental group), and after applying multiple imputation by chained equations (MICE) to check for the stability of the results.

Every analysis will be conducted using Stata V.14.1 in the department of Public Health of the University Hospital Henri Mondor, Créteil, France.

#### Missing data

Every missing or invalid data will be verified in the patient's medical file. Sensitivity analyses will be conducted on several techniques of data replacement, including the last observation carry forward method, worse scenario hypothesis and MICE.

#### Data monitoring

AP-PH classifies from A to D every biomedical research protocol based on the estimated risk for participating patients. The promoter must guarantee safety and respect to the latter, and set a quality insurance system aiming to monitor ongoing researches. For that purpose, the promoter mandates clinical research associates (CRAs) for opening, monitoring and closing visits in participating centres. The verifications aim at assessing:

- ▶ The respect of the right, safety and protection of participating patients.
- ▶ The accuracy, validity and exhaustiveness of collected data.
- ▶ The accordance with a valid protocol, good practice recommendations and legal dispositions of the research.

The risk associated with the EXARHOSE study has been classified C. Regarding the complexity, impact and budget of the study, and in agreement with the coordinating investigator, the monitoring level has been set to intermediary.

The promoter has ultimate authority on data monitoring.

#### Quality control

A CRA will be sent by the promoter to verify elements as follows:

- ▶ Written consent.
- ▶ Respect of the protocol and related procedures.
- ▶ Quality of the collected data (accuracy, missing data, consistency with source documents, appointments, original laboratory results etc).
- ▶ Management of used treatment units.

#### Harms

The use of TXA in acute UGIB of patients with cirrhosis must be associated with the evaluation of its tolerance and safety, despite encouraging data in other settings and a well-documented safety profile. In fact, TXA is probably associated with an increased risk of seizures,<sup>24-26</sup> and the risk of thromboembolic events remains uncertain.<sup>27</sup> Seizures seem to occur at much higher doses than the one used in the EXARHOSE study (more than four times higher).

Harm data will be collected from randomisation until ICU discharge. It will consider side effects and major side effects, defined as follows:

- ▶ Side effects: every harmful manifestation occurring during a research protocol, whether this manifestation is due to the research intervention or not.
- ▶ Major side effects: every harmful manifestation leading to death, life-threatening condition, hospitalisation or prolongation of hospitalisation, handicap or incapacity, congenital malformation.
- ▶ Unexpected side effects: every harmful manifestation which nature, severity or evolution is not concordant with the summary of product characteristics.

Investigators should notify major side effects to the promoter, as soon as they become aware of it, except effects that can be expected regarding the underlying condition of the patient and/or routine healthcare interventions.

The treatment administration will be withdrawn in case of discovery, after treatment initiation, of a contraindication to TXA, appearance of a major side effect or after decision of the promoter.

An independent survey committee, composed of five physicians (one emergency physician, one ICU physician, one hepatogastroenterology physician, one pharmacologist, one methodologist/statistician), will evaluate the prevalence and occurrence of side effects, in order to decide of protocol modifications or withdrawal.

### Auditing

Investigators agree to accept audits for quality insurance as carried out by the promoter, as well as inspections conducted by competent authorities. Every data, documents and reports may lead to audits and inspections for which the medical secret cannot be opposable. Independent agents can carry out audits at any time if mandated by the promoter. People leading and surveying the research accept to follow the will of the promoter and/or competent authorities regarding audits and inspections.

### Pilot committee

A pilot committee, composed of the coordinating investigator (MH), the scientific coordinators (RA and LJ), JM, CC-X, the coordinators of the trial coordinating centre (URC Henri Mondor: AR and DS) and the CRA (VNdB), will periodically meet to insure good follow-up and coordination of the trial. It will be responsible for the creation and diffusion of every communication support, the contact with participating centres and investigators, and every decision related to the trial coordination.

### Patient and public involvement

The development of the research question, outcome measures and burden of intervention did not involve the patients eligible for the EXARHOSE study. Nevertheless, patients' representatives were involved in the evaluation and validation of every version of the study protocol: they participated in each meeting of the ethic committee (three to date) and required substantial modifications in the title, eligibility criteria, main objective composite criterion, outcomes measures, information and consent notes of the study.

The final results of the study will be communicated by mail to every patient when published.

### Standard Protocol Items: Recommendations for Interventional Trials checklist

This article followed the Standard Protocol Items: Recommendations for Interventional Trials (SPIRIT) 2013 statement on the writing of a study protocol for a

clinical trial. The filled SPIRIT checklist can be found in online supplementary file 6.

### Ethics and dissemination

The National Agency for Medicine Security (ANSM) gave final approbation.

### Protocol amendments

In case of necessity, the trial coordinating centre and the coordinating investigator will send protocol amendments to the ethics committee and the ANSM, with the help of the representative for the trial promoter (DRCI, AP-HP), which has ultimate authority. After acceptance, the amendment will be transmitted to every investigator.

### Confidentiality

People involved in the quality control of a biomedical research must insure confidentiality about the study protocol and the participating patients, especially about their identity and outcomes. Everyone is submitted to professional secret as defined by the articles 226–13 and 226–14 of the penal code. During the study, collected data are anonymised. Identity data (name, date of birth, address) must never clearly appear anywhere.

Data treatment is regulated by article 54 paragraph 5 of the modified law no.78–17 from 6 January 1978 (2008). The promoter signed a conformity commitment to the Referent Methodology MR-001 of the national commission of informatics and freedom. The promoter is the data owner and neither use nor transmission to anybody can be made without his consent.

Research documents will be archived by each investigator centre for 15 years after the end of the study.

### Access to data

Access to data will be restricted to the trial coordinating centre (for analysis or screening for side effects), the independent committee or the promoter. Identity data will be stored by the trial coordinating centre for follow-up. Investigators and participating caregivers will not be permitted to access any data. Access to final anonymous dataset will be possible under appropriate request to the promoter.

Full protocol access will be granted via supplemental data in published journal articles.

### Ancillary and post-trial care

No ancillary study or post-trial care is planned to date.

### Dissemination policy

The EXARHOSE protocol and results will be published in peer-reviewed journals, based on the Consolidated Standards of Reporting Trials statement. Results will be disseminated via journal articles and congress presentations. The publication rules will be adjusted on the level of participation of every investigating team.

### DISCUSSION

We propose the first, multicentre, randomised, double-blind, placebo-controlled study evaluating the efficacy



of TXA in acute UGIB of patients with cirrhosis. Despite recent preventive and therapeutic clinical improvements, these patients continue to suffer from high rates of UGIB. Moreover, as they often present with haemostatic abnormalities at baseline, possibly worsened by acute episodes of UGIB, haemorrhage is directly responsible for half of the deaths until week 6. To date, the use of TXA in patients with cirrhosis presenting with acute UGIB is not supported by any recommendations, due to a lack of high-quality evidence. Recent meta-analyses suggested a potential benefit of TXA in UGIB with no significant increase of adverse effects. Yet, imperfect methodology and insufficient patient sample size make it impossible to conclude. An international study named HALT-IT, conducted by the CRASH-2 trial collaborators, is currently recruiting patients suffering from GIB from any cause and aim to show efficacy of TXA on mortality at day 28.<sup>17</sup> A total of 8000 adult patients are to be included, regardless from their medical history and time from GIB onset.

As we believe patients with cirrhosis to account for the majority of deaths and severe complications in the population presenting with GIB, and as TXA has shown efficacy in several haemorrhagic states depending on the delay of administration,<sup>28-29</sup> we hypothesise that, when administered as soon as possible and within the first 24 hours after onset, it could help reduce mortality and cirrhosis-related specific complications in the early phase of acute UGIB as defined by the Baveno guidelines (until week 6). We chose to only include patients with cirrhosis with acute UGIB because of the imprecise timing of haemorrhage onset in case of isolated melena. Despite discussed evidence of potential harm of TXA when administered after 3 hours from haemorrhage onset in patients with trauma and delivering women, and because of real-life practice where patients with cirrhosis access urgent healthcare with significant delay, we decided to extend the inclusion period to 24 hours after UGIB onset. This attitude is only supported by poor evidence and knowledge of haemostatic imbalance in patients with cirrhosis. We, therefore, aim to conduct sensitivity analyses on efficacy of TXA depending on its delay of administration.

Patients suffering from acute UGIB may be encountered within different urgent healthcare facilities, including EMS, ED and ICU. As to minimise the number of missed eligible patients and to insure real-life practice, any participating physician related to one of those settings will be able to enrol and include patients.

TXA efficacy has been evaluated in liver transplantation and has shown no increase in risk of side effects, especially thromboembolic events.<sup>20</sup> Yet, because of imperfect methodology, evidence is of poor significance and needs to be reinforced by specific, randomised, controlled studies. We, therefore, aim to analyse it, with the help of an independent survey committee.

Patient recruitment began on 3 April 2017 and is currently ongoing in most participating centres.

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**Contributors** MH, coordinating investigator, is an emergency physician at the EMS of Creteil University Hospital (SAMU 94). He submitted and endorsed the EXARHOSE study project. RA (ICU physician in Bondy University Hospital) and LJ (emergency physician at Melun General Hospital) are the scientific experts. They helped establish the study protocol and coordination. EA is the methodologist and works in the Public Health Service of Creteil University Hospital. He participated in the early submission of the protocol and established the statistical methods. DS and AR are project leaders of the trial coordinating center. They are responsible for the printing and management of every document, and communications with the promoter and other state agencies, data managers, CRA and others. OA and VNdB are CRA. They proceeded to documents editing, centers openings, correspondence with investigators and monitoring visits. FP is data manager. He built the eCRF and managed the investigators list and their electronic authorisations. OT is pharmacist at the Creteil Hospital. He is responsible for treatment conditioning, randomisation lists and treatment units' replenishment. JM (anaesthesiologist in Creteil University Hospital) and CC-X (emergency physician in SAMU 94) are members of the pilot committee.

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**Patient consent** Obtained.

**Ethics approval** The ethics committee CPP no.1 (Hôtel Dieu University Hospital, Paris) has approved the EXARHOSE study protocol.

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