Impact of Doxycycline on Covid-19 Patients With Risk Factors of Disease Degradation: Dynamic, A Randomised Controlled Double-blind Trial

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Study protocol

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Abstract

Background: The DYNAMIC study is based on three properties of tetracyclines. (1) Tetracyclines are known to chelate zinc from metalloproteases (MMPs). It is possible that their chelating activity may help to inhibit COVID-19 infection by limiting its ability to replicate in the host. (2) As seen with dengue virus, tetracyclines may also be able to inhibit the replication of positive polarity single-stranded RNA viruses, such as COVID-19. (3) In addition, tetracyclines are modulators of innate immunity (anti-inflammatory activity), a property that has been used to treat inflammatory skin diseases for many years. They could therefore participate in limiting the cytokine storm induced by COVID-19. The lipophilic nature of tetracyclines and their strong pulmonary penetration could allow them to inhibit viral replication at this level. Among tetracyclines, the advantages of doxycycline are triple: its long history of safety (infrequent side effects with no notable risks), the short duration of treatment and its low cost.

Methods: By estimating the rate of patients presenting pulmonary signs requiring hospitalisation in at-risk patients infected with COVID-19 at 25%, we hypothesise that on doxycycline, this rate would decrease to 12%. The main objective involves 2 embedded hypotheses tested successively in case of rejection of the previous one: (i) Decrease the rate of patients requiring hospitalisation, (ii) Decrease the use of mechanical ventilatory assistance.

Discussion: This study could have an impact on the management of COVID-19 risk factor patientsupstream of hospitals by general practitioners. These patients,if kept at home under experimental treatment, would participate in reducing the risk of dissemination of SAR-CoV-2in the population.Thus, this treatment would contribute to supporting the deconfinement strategy through blocking the viral infection early and reducing the contagious period.

Trial Registration: On ClinicalTrials.gov, registration number NCT04371952, first published on 30 April 2020.

Background

In Wuhan, China, in the last quarter of 2019, a new coronavirus, the third documented passage from animals to humans, emerged [1]. Known as SARS-CoV-2 (severe acute respiratory syndrome coronavirus 2) [2], it spread rapidly in China and many other countries [3,4]. On 11 February 2020, the World Health Organization (WHO) announced the name of the epidemic disease caused by SARS-CoV-2: COVID-19(https://www.who.int/dg/speeches/detail/who-director-general-s-remarks-at-the-media-briefing-on-2019-ncov-on-11-february-2020).

The latest Chinese meta-analysis performed on 43 studies involving 3,600 patients provides an overview of the clinical characteristics, laboratory results, chest imaging results, disease severity and case fatality rate of COVID-19 patients [5].The dominant clinical features of COVID-19 are, in mixed association, fever, cough,asthaenia, rhinorrhea, headache, dysgeusia, dysosmia, diarrhaea[6,7]. The most frequently reported

laboratory abnormalities are a decreased lymphocyte count, elevated C-reactive protein (CRP), D-dimers and elevated lactate dehydrogenase [7].

The great majority of patients with COVID-19 have a good prognosis, but there are critical situations and even deaths [8]. Most of these critically ill and deceased patients did not develop severe clinical manifestations in the early stages of the disease. Some of the patients only had mild fever, cough or muscle pain. Their condition suddenly deteriorated in the latter stages of the disease. Acute Respiratory Distress Syndrome (ARDS) and multi-organ failure occur rapidly, resulting in death within a short time [9].

The pandemic has shown that some patients may have risk factor(s) for adverse outcomes: 70 years of age and older, Body Mass Index (BMI) greater than 30 (obesity[10–13]), cardiovascular history, chronic respiratory disease that may decompensate with viral infection, respiratory failure, poorly controlled and/or complicated diabetes, patients with chronic renal failure on dialysis and cancer patients under treatment[14].

The massive release of cytokines,known as a cytokine storm, is considered as one of the major causes of ARDS and multi-organ failure [15]. It plays an important role in the process of worsening the disease [16]. Therefore, effective suppression of the cytokine storm is an important tool in preventing the deterioration of health and saving the lives of patients with SARS-CoV-2 infection.Controlling the cytokine storm in its early stages, by using treatment such as immunomodulators and anti-cytokines, as well as reducing infiltration of lung inflammatory cells, is one of the keys to reducing the mortality rate of patients with COVID-19[17].

Different therapeutics are currently being evaluated in clinical trials. No therapy has proven its effectiveness to date. Based on previous experience in the fight against the SARS-CoV and MERS-CoV epidemics, we can draw some lessons for certain treatment strategies against coronaviruses.Inter alia, while anti-inflammatory activity is required during this cytokine storm, early treatment of SARS patients with corticosteroids increases the plasma viral load in non-hospitalised intensive care patients, resulting in the worsening of the disease. Trials are underway to determine whether or not anti-inflammatory therapies are beneficial in the second phase of the disease, after the intensive viral replication phase [18].Neuraminidase inhibitors (oseltamivir, peramivir, zanamivir, etc.), ganciclovir, acyclovir and ribavirin, used for the treatment of influenza virus, are not indicated for COVID-19[19].

Chloroquine and hydroxychloroquine are anti-malarial agents with anti-inflammatory properties and immunomodulatory activities. The *in vitro* antiviral activity of chloroquine was identified in the late 1960s [20,21] and the growth of many different viruses can be inhibited in cell culture by chloroquine and hydroxychloroquine, including the SARS coronavirus [22].Recently, Wang *et al*. tested chloroquine *in vitro* on a clinical isolate of SARS-CoV-2; one of their conclusions was that "chloroquine (is) very effective in controlling 2019-nCoV (first name ofSARS-CoV-2) infection *in vitro*" [23]. Gautret*et al*. were the first to report *in vivo* data on hydroxychloroquine in a non-randomised, uncontrolled clinical trial [24].However, the results of these initial clinical studies do not make it possible to reach a conclusion on the efficacy of this drug in patients with COVID-19 due to major methodological weaknesses. French and European

clinical trials are currently testing this therapy in randomised controlled trials at different stages of the disease, without major respiratory manifestations at inclusion (HYCOVID NCT04325893, OUTCOV NCT04365582) or with respiratory complications (CORIMMUNO-VIRO NCT04341870, DISCOVERY NCT04315948).

Interferons alpha and beta (IFN-αβ) inhibit viral replication by inducing an IFN-stimulated gene. However, IFN-αβ exacerbates disease by improving the recruitment and function of mononuclear macrophages and other innate immune cells. Although an early response to interferon has a protective effect on mice infected with SARS-CoV, late IFN-αβ signalling causes an imbalance in anti -SARS-CoV immune responses in humans. Therefore, IFN-αβ inhibitors or antagonists could be administered in the advanced stages of severe disease to prevent excessive inflammatory responses [25].

Tocilizumab is an interleukin-6 (IL-6) antagonist that suppresses immune system function. Currently, tocilizumab is mainly applied in autoimmune diseases such as rheumatoid arthritis [26]. Tocilizumab itself has a therapeutic effect on the cytokine storm induced by the infection [27].Moreover, serum IL-6 levels are significantly increased in critically ill patients with COVID-19. Tocilizumab is thus an interesting therapeutic approach for the cytokine storm for hospitalised patients and currently, 13 clinical trials are testing tocilizumab as a therapy in this pandemic.

Other clinical studies, using molecules that are active against other viruses - hepatitis C virus (HCV), human immunodeficiency virus (HIV), H1N1 virus, cytomegalovirus (CMV)and Ebola virus - are trying to find a treatment for SARS-CoV-2 such as the combination oflopinavirand ritonavir. Lopinavir is an anti-protease,which is active on HIV-1 administered in fixed-dose combination with another anti-protease, whereas ritonavir is a potent CYP3A4 inhibitor that "boosts" lopinavir concentrations. Lopinavir appears to block the major protease of SARS-CoV, thereby inhibiting viral replication [28].

Remdesivir, developed by Gilead Sciences to fight Ebola and related viruses, lowers viral replication by inhibiting a key viral enzyme, RNA polymerase. This molecule did not help Ebola patients in a clinical trial carried outduring the 2019 epidemic in the Democratic Republic of Congo. But in 2017, researchers showed in *in vitro* and animal studies that the drug can inhibit the SARS-CoV and MERS-CoV viruses[29]. However, no drug has yet demonstrated efficacy in the treatment of COVID-19, based on preliminary data presented by the European Medicines Agency (EMA)[30].(

Doxycycline is a second generation semi-synthetic tetracycline that is chemically derived from first generation tetracyclines, originally found in soil bacteria, actinomycetes[31].Doxycycline was approved by the Food and Drug Administration (FDA) as an antibiotic in 1967 and to this day remains in the antibiotic arsenal of most clinicians [31]. Following recent advances in the knowledge of the anti-inflammatory cutaneous effects of doxycycline, its use has been extended in dermatology by using this anti-inflammatory capacity more than its antimicrobial capacity. In addition to rosacea, acne and hidradenitis suppuritiva, doxycycline is used for other dermatological diseases, including bullous dermatoses, cutaneous sarcoidosis, Kaposi's sarcoma and neutrophil dermatoses (neutrophil chemotaxis) [32].

Based on these three properties of tetracyclines, we believe, like Sodhit and Etminan[33] or Sargiacomo*et al*[34] and Farouk and Salman [35], that doxycycline could be an effective treatment for COVID-19. The coronavirus family is known to bind to host metalloproteases (MMPs), particularly for viral survival. Tetracyclines are known to chelate zinc from MMPs [36]. It is possible that their chelating activity may help inhibit SARS-CoV-2 infection by limiting its ability to replicate in the host [37].Tetracyclines may also be able to inhibit the replication of positive polarity single-stranded RNA viruses, such as SARS-CoV-2. Indeed, the antiviral activity of doxycycline had already been reported against retroviruses 20 years ago, and a significant reduction in retrovirus titer was observed after incubation of doxycycline-infected cells [38]. Other studies have shown that doxycycline inhibits the formation of dengue virus plaques by disrupting the conformational changes in the viral envelope that are necessary for virus entry [39]. They also showed that at normal human body temperature and fever conditions, doxycycline significantly inhibited the serine protease of the virus and a concentration-dependent decrease in viral replication was observed [40].

Most recently, on 14 April 2020, Bruno Pradines' team showed *in vitro* the antiviral activity of doxycycline on SARS-CoV-2 [41]. In addition, tetracyclines are modulators of innate immunity (anti-inflammatory activity), a property that has been used in the treatment of inflammatory skin diseases for many years. These modulatory effects manifest on several targets of innate immunity. They can decrease the expression of NFB, the release of inflammatory cytokines such as TNF-α, IL-1β and IL-6, inhibit the formation of inflammatory granulomas and the release of free radicals, independently of their antibiotic mechanism [32].Furthermore, a recent publication has shown that coronaviruses, species-independent, induce mast cell proliferation in the respiratory submucosa, which in turn produces inflammatory agents such as histamine and protease, in addition to inflammatory cytokines such as IL-1 and IL-33 [42].

Two other studies have shown that chemically modified tetracyclines can induce mast cell apoptosis and activation of protein kinase C, thereby lowering the levels of inflammatory agents [43]. These teams have suggested that tetracyclines can be used to treat inflammatory disorders, including those induced by coronaviruses [42,43]. It should also be noted that, because of their anti-inflammatory capabilities, tetracyclines have also been documented to have *in vi*tro activity on other viral infections such as HIV, West Nile virus and viral encephalitis [44]. Doxycycline may therefore be involved in limiting the cytokine storm induced by SARS-CoV-2. Finally, the lipophilic nature of tetracyclines and their strong pulmonary penetration could enable them to inhibit viral replication directly at the inflammatory site.

The interest of doxycycline also lies in its long history of safety (infrequent side effects with no notable risks), its short treatment duration, which will be 14 days in our study (corresponding to the period during which SARS-CoV-2 can induce serious signs in the patient) and its low cost.

As already mentioned, it is often elderly patients with co-morbidities who worsen during the second week of the disease and who then have to be hospitalised for respiratory degradation or even put on mechanical ventilation. Our hypothesis is to propose this treatment as soon as a risk factor patient is confirmed COVID-19 + by PCR with only a few symptoms, without any serious signs and before the

appearance of oxygen dependence in order to reduce or even abolish the cytokine storm, and thus the evolution towards a serious form of the disease, which will in turn avoid hospitalisation.

Our study will be a multi-centre, randomised, placebo-controlled study to determine the efficacy of doxycycline in this context, by measuring the decrease in the number of patients hospitalised compared to the control arm.

Methods/design

Study design

This is a prospective, phase III, randomised, double-blind, placebo-controlled, multi-centre, national study to evaluate the use of doxycycline on patients with at less one risk of worsening COVID-19 disease.

As the study is double-blind, the study treatment and its placebo, will be managed by the pharmacist of the coordinating centre, CHU Nantes. The oral dose of 200 mg of doxycycline,anti-inflammatory dose, or the matching placebo, will be taken once a day, in the evening one hour beforegoing to bed, for14 days.Dispensation will be made at the inclusion/randomisation visit. No dose adjustment is required. The treatment will end if the patient is hospitalised between D0 and D14.

Six French University Hospital CHU Nantes, AP-HP [HôpitalAvicennes], CHU Bordeaux,CHU Caen, CHU Dijon and CHU Grenoble,) will include 330 patients to provide at least 280 analysable patients. The inclusion period may be 3 to 6 months depending on the recruitment rate post-deconfinement.. The treatment time is 14 days per patient and the last patient visit will be 28 days (+/- 2 days) from the start of treatment.

Patients cannot be included in any other interventional research; unless they are hospitalised, provided that there is no drug interaction with any other experimental treatment. Patients included in the study who will receive an investigational treatment (e.g. IL inhibitor or anti-IL6) during hospitalisation will be kept in the study. Their data will be analysed for the primary endpoint assessment only. Their data will not be analysed for the evaluation of secondary endpoints, except for the safety endpoint.

Study population

Male or female patients over 45 years of age suspected of COVID-19 by their treating physician or by a physician from a COVID-19 unit at a participating centre are the study population. After a positive SARS-CoV-2 PCR performed at the hospital, they may be included in the study. We chose 45 years of age as the minimum age in this study because this is the low end of the range for COVID-19+ patients likely to be admitted to intensive care units[45]. These patients have also one or more risk factor(s) for aggravating the disease as described by the French High Council of Public Health[14]: 70 years of age or older, cardiovascular history (stroke, coronary artery disease, complicated hypertension, cardiac surgery, NYHA

III or IV heart failure), insulin-dependent diabetes which is unbalanced or secondary complicated; respiratory disease likely to decompensate for viral infection, patients with chronic renal failure on dialysis, cancer patients under treatment. We have added BMI (BMI>30) as a risk criterion, based on the recent data from the literature [10–13]. Exclusion criteria arevulnerable populations and the contraindication of the use of doxycycline. Box 1 presents all the inclusion/exclusion criteria.

Study schedule

The plan for the study described in this section is presented in Figure 1 and the flowchart in Figure 2. The screening is performed either by a possible network of general practitioners (GPs) associated with a participating centre; or by COVID-19 emergencies or the COVID-19 unit of the investigating centre.

A patient suspected of COVID-19,with one or more characteristic clinical signsand having one or more risk factors for aggravation of the disease are sent to the Hospital for PCR SARS-Cov2 sampling.If the PCR is positive, the investigator explains the DYNAMIC study, checks the eligibility criteria and obtains signed informed consent from the patient. The Supplementary Material file contains the French informed consent form that patients sign prior to inclusion in the trial (then updated protocol is at version 1.2on 11May 2020). Furthermore, blood samples for serology and immunological markers will be collected, stored and kept if the patient signed the biocollection informed consent. In this informed consent form, it is noted that the samples may be used for scientific research. This biocollection and its consent procedure has been registered to French Ethic Committee: CPP Ouest IV under number DC-2011-1399.After a clinical examination, patients will be randomised either in the Doxycycline arm or in the placebo arm. The patients, the investigators and their teams will be blind and will not know the treatment assigned. As Karanicolas*et al.* pointed out in their article, the biostatisticianswill also be masked until analyses to reduce the study bias are performed[46].

At 3 and 14 days, a telephone call will be made bythe hospital doctor or his/her team. A clinical assessment of the patientwill be carried outaccording to the questionnaire shown in figure 3. If necessary, a face-to-face consultation,to accurately assess the extent of the worsening of the disease, will be conducted immediately after this call.

At 7 days, a face-to-face follow-up visit will be performed. After a clinical examination, a SARS-CoV-2 qualitative PCR will be carried out. At 28 days, the end-of-study visit will be performed, also face-to-face. A blood sample will be kept for serology and other immunological markers. The patient will return any unused therapeutic units and the empty blister packs.

A premature end-of-study visit corresponds to the end-of-study visit (D28 visit), with the exception of serology if the premature exit occurs before 14 days. For included patients who are hospitalised before 28 days, the experimental treatment is stopped as soon as they are hospitalised and they are considered as a failure. Clinical data related to hospitalisation will be reported in the CRF. For patients hospitalised after 28 days and until 90 days post-treatment, follow-up will be carried out until discharge. This follow-up will

allow the collection of vigilance data, some hospitalisation data (date of end of hospitalisation, length of hospitalisation in intensive care unit, duration of mechanical respiratory assistance, possible death).

During the trial, any drug judged to be necessary for the well-being of the patient, which should not interfere with the evaluation of the test drug, may be administered at the discretion of the investigator. Absorption of doxycycline is impaired by antacids containing aluminium, calcium, as well as magnesium, bismuth subsalicylate and iron-zinc-containing preparations. The study drug should be taken at a different time to antacids. Other prohibited treatments are those prohibited by the SCP of doxycyclineand are listed in exclusion criteria (see Box1).However, in the absence of a change in the therapeutic management of a patient arriving at hospital according to the treatment arm, it is not necessary to include a blinding procedure in this protocol.Treatment will be stopped if hospitalisation.

Objectives and statistics

Objectives

The main objective is to evaluate the decrease in the percentageof patients with respiratory aggravation (oxygen saturation rate ≤ 93% in room air) after at least 48 hours of experimental treatment or requiring hospitalisation for COVID-19. The 48-hour delay allows a more objective attribution of the clinical course to advanced treatment. The embedded second main objective is to evaluate the decrease in the percentage of patients requiring mechanical ventilator support.

The secondary objectives are to evaluate:

- the decrease in the percentage of patients with SARS-CoV-2 positive PCR at 7 days after the start of experimental treatment,

- the decrease of the total length of hospital stay,

- the decrease of the length of hospitalisation in the intensive care unit,

- the decrease of the duration of mechanical ventilatory assistance,

- the decrease of the rate of deaths related to SARS-CoV-2 infection,

- an assessment of the safety of doxycycline.

Outcomes

The main criterion is an efficacy criterion corresponding to the percentage of patients with clinical respiratory aggravation (SaO2 ≤ 93%) after at least 48 hours of treatment and the percentage of patients hospitalised for COVID-19 after at least 48 hours of experimental treatment. The criterion corresponding

to the embedded second main objective corresponds to the percentage of patients requiring mechanical ventilator assistance. These three criteria aremonitored in the 2 arms from 48hoursof treatment to 28 days corresponding to the end-of-study visit.

For the secondary outcomes:

Efficacy: These outcomes correspond to the report of the:

- Number of positive SARS-CoV-2 PCR tests at the inclusion visit and D7,

- Total length of hospital stay,

- Total length of hospital stay in the intensive care unit,

- Duration of mechanical ventilator assistance,

- Number of deaths related to SARS-CoV-2 infection.

Safety: Report of the number of Adverse Events (AE) and Serious Adverse Events (SAE) over 28 days

Apart from the first and the last secondary criterion, the other criteria will be noted at 28 days. If the patient is hospitalised during the duration of the study,this data will be noted 3 months after the beginning of the treatment. For all these secondary outcomes, percentages will be calculated.

Statistical methods

The DYNAMIC study is a superiority study of doxycycline efficacy. Theembedded testing strategy will be used to successively test:

- the decrease in the percentage of patients presenting, after at least 48 hours of treatment, a respiratory aggravation (SaO_2 93%) or requiring hospitalisation related to the SARS-CoV-2 infection,

- a decrease in the percentage of patients requiring mechanical ventilator assistance if the first null hypothesis is rejected.

An intermediate futility analysis will be carried out, after 100 patients have been evaluated, with the objective of being able to stop the clinical trial if there is no probability that the null hypothesis will be rejected at the end of the full study. The one and only response to this analysis is whether or not to stop the trial because of lack of efficacy. The Peto method will be used with an alpha risk at the intermediate analysis of 1 per thousand and at the final analysis of 5% [47].As already quoted, the biostatistician will be part of the masked team. He will give the results of this intermediate analysis to the Data and Safety Monitoring Committee (DMSC), which may unblind or not depending on the results.

The analysis will be stratified by centre and number of severity factors (1 versus ≥2). The severity factors are ≥ 70 years, BMI > 30, cardiovascular history (stroke, coronary artery disease, complicated hypertension, cardiac surgery, NYHA III or IV heart failure), insulin-dependent diabetic patients who are unbalanced or have complications secondary to their disease, respiratory disease likely to decompensate for viral infection, patients with chronic renal failure on dialysis, cancer patients on treatment at the time of inclusion. Randomisation will be carried out for each centre in order to balance the treatment arms.

A Modified Intent to Treat analysis will be applied. It will include all eligible randomised patients who have signed the consent for the trial. It will exclude patients who withdrew their consent prior to the assessment of the first primary endpoint, randomised patients who were inappropriately included (inclusion or exclusion criteria not met) and patients who did not receive any dose of treatment.

A per-protocol analysis will also be implemented, including all patients evaluated in their treatment group and having received more than 75% of the total treatment dose.

For the main criteria (percentage of patients), we will use a Mantel-Haenszel test to compare stratified percentages across centres and the number of risk factors. For the quantitative secondary criteria, a mixed linear model will be used to take into account the risk factors and the centre effect (random factor). The statistical software used will be R, version 3.8 or later. The significance thresholds will be set at 5%.

Sample size

It is estimated,among eligible patients in the study, that 25% of patients will present pulmonary signs with SaO_2£93% and/or will require hospitalisation. It is hypothesised that with doxycycline, this rate would increase to 12%. Indeed, the article concerning the effect of doxycycline on dengue patients: "Dengue Patients Treated With Doxycycline Showed Lower Mortality Associated with a Reduction in IL-6 and TNF Levels" [48], shows that the group on doxycycline has a lower mortality than those in the untreated group (11.2% [13/116] vs 20.9% [24/115], respectively, p=0.05). In addition, doxycycline administration resulted in a significant drop in IL6 and TNF. These results therefore confirm our hypothesis of a 12% reduction

For the second embedded hypothesis, it is estimated that 23% (source: https://www.data.gouv.fr/fr/datasets/donnees-hospitalieres-relatives-a-lepidemie-de-covid-19/) of the hospitalisedpatients are admitted to intensive care units. With the recruitment we have, we will have a power of 80% to show a decrease of 23 to 10%.

Under these hypotheses, with a 5% alpha risk in a bilateral situation and a power of 80%, we would have to evaluate 280 patients in total in both arms. If the first hypothesis is rejected, the power of the test of the second hypothesis would then be 83.5%. Three hundred and thirty (330) patients will be included to compensate for study exits and non-assessable patients.

Randomisation

Randomisation will be stratified by centre and by severity factors (1 versus ≥2). It will be performed according to a 1:1 ratio and balanced by blocks. The random numbers will be generated by computer. Subjects are randomised into blocks as the allocation progresses, a block being a sub-group of predetermined size within which there is a random allocation of patients. The software used for the randomisation is SAS version 9.4. The randomisation key is known only to the biostatistician and the data managers, to make it impossible for the investigator to assign a particular treatment. It should be noted that the biostatistician who carries out the randomisation is different to the biostatistician who will carry out the statistical analysis.

Adverse event management

For doxycycline, the main adverse events (AEs) expected are skin disorders (photosensitivity reaction, rash), immune system disorders (urticaria, rash, pruritus, angioedema, anaphylactic reaction) or digestive disorders (nausea, epigastralgia, diarrhaea, anorexia, glossitis, enterocolitis, anal or genital candidiasis). There have been no reports of overdosage. Those reported for other tetracyclines, following renal impairment (hepatic toxicity, hyperazotemia, hyperphosphataemia, acidosis), are unlikely to occur with doxycycline, due to the lack of a change in blood levels in relation to the functional value of the kidney. Concerning the placebo, the main expected effects are digestive disorders (excess gas, feeling of abdominal bloating, abdominal cramps and pain, diarrhaea). As regards the pathology, patients with an uncomplicated viral infection of the upper respiratory tract may have non-specific symptoms such as fever, fatigue, cough (with or without discharge), anorexia, malaise, muscle aches, sore throat, dyspnea, nasal congestion or headache. Rarely, patients may also experience diarrhaea, nausea and vomiting [7,49], and loss of taste or smell [50].The disease can worsen to pneumonia, acute respiratory distress syndrome [51], sepsis and septic shock [52].

All serious adverse events (SAEs), whether expected or unexpected, require the completion of a SAE report. The investigator must ensure that the information entered in this report is accurate and clear. The SAE should be reported immediately (within 24 hours of being highlighted by the investigator) to the sponsor. After receiving an unexpected SAE report, the sponsor notifies the authorities. Furthermore, a Data and Safety Monitoring Committee (DSMC) has been set up. It is a consultative committee responsible for reviewing the safety of a study on behalf of the sponsor and the coordinator/principal investigator of the study. Members of the Committee who are competent in the field of clinical trials (pathology methodology and pharmacovigilance) are not involved in the study.

The DSMC is a referral point for pharmacovigilance if a SUSAR or an SAE poses particular analytical difficulty or if a doubt arises about the risk/benefit of the study. Moreover, it will make a decision on the outcome of the futility analysis. In the event of early termination of the study by decision of the DSMC or the Study Sponsor, the regulatory authorities and the Ethical Review Board will be informed by post within a maximum of 15 days. In any event, written confirmation will be sent to the coordinating investigator of

the study (specifying the reasons for early termination) and to the principal investigator of each centre, if applicable. All patients in the study will be informed and will be required to attend their early discharge visit.

Ethical, regulatory and dissemination aspects

The clinical study will be conducted in accordance with the relevant versions of the French Public Health Code, national and international good clinical practice (GCP) guidelines, and the Declaration of Helsinki, each in the applicable version.

In accordance with French law, the study protocol was submitted to the French regulatory authority (ANSM).This clinical study was submitted to and approved by the Ethical Review Board of Boulogne-Billancourt(Comité de Protection des Personnes – CPP Ile de France VIII) on 13 May 2020. Requests for substantial modifications should be addressed by the sponsor for approval or notification to the ANSM and/or the Ethical Review Board concerned in compliance with Law 2004-806 of 9 August, 2004 and its implementing decrees.The amended protocol should be a dated and updated version. If necessary, the information form and consent form should be amended.The updated protocol is version 1.2 on 11 May 2020. The trial is not yet recruiting and the anticipated date of enrolment of the first participant is expected on 1 June 2020. The anticipated study completion is anticipated to be on 1 January 2021.

All the submissions/declarations were made by the Sponsor Department at CHU Nantes, which of course, manages the quality of the data collected. The data collected during the study will be processed electronically in accordance with the requirements of the CNIL, the French Data Protection Authority (in compliance with the French Reference Methodology MR001).The data-sharing will be only between the investigators. However, the datasets analysed during the current study will be available from the corresponding author on reasonable request.

An electronic Case Report Form (eCRF) shall be drawn up for each included patient. The identification of the subject will be performed using the first letter of the family name, the first letter of the first name, the centre number and the inclusion number. This code should be the only information featuring on the eCRF enabling a retrospective link to the patient. The investigator, or their team, shall also encode the patient data on any documents that may be in their possession (imaging, biology test reports, etc.) attached to the eCRF. At the end of the study, database reconciliation is carried out between the CRF database and the safety database. This reconciliation is performed before database locking. Similarly, an annual reconciliation is carried out when updating the Annual Safety Report (ASR).

As required, the sponsor has provided an insurance policy to cover the financial consequences of its civil liability in accordance with the regulations. This protocol was created thanks to a Scientific Committee. The Scientific Committee is coordinated by Prof. B Dréno and its membership comprises external and internal experts in COVID-19 pathology,a general practitioner, experts in clinical trials and a methodologist. An inspection or audit may take place as part of this study, performed by the Sponsor

and/or by the regulatory authorities. Inspectors will check the documents, logistics, records and any other resources that the authorities consider to be associated with the clinical trial and that may be located at the trial site itself.

The trial results will be published in international, medical and scientific journals and presented at national and international conferences. The investigators will follow the rules and guidelines of the International Committee for Medical Journal Editors (ICMJE)[53]. In practice, the Scientific Committee will be among the authors of the publication, as will the investigators who included the patients in the trial.

Discussion

The COVID-19pandemic is affecting all continents. Saturation of the hospital care system is feared in many countries. On 11 May 2020, there were 4,238,140 cases and 286,078 deaths (https://www.worldometers.info/coronavirus/). The confinement of the French population and practically the whole world was decided to try to avoid hospital overcrowding.However, in France, according to figures provided by the Ministry of Health on 16 March 2020, 97 hospitals out of the 650 - public or private - that have an emergency structure had, by 13 March 2020, activated the "hospital under stress" plan, highlighting the saturation of the emergency services.

Researchers are looking for a life-saving drug. So far, 1,410 clinical studies have been published in https://clinicaltrials.gov/since the beginning of the pandemic. Of these studies, 830 are intervention research. However, there are only38 studies dealing with outpatient clinical research. The great strength of our study is to test doxycycline on at-risk patients, on an outpatient basis, before the cytokine wave. Thus, our target is the early onset of the viral infection and it involves very close work with general practitioners. As the French National Academy of Medicine communicates, the mobilisation of general practitioners, during the first months of 2020, prevented hospital emergency units from being overwhelmed by requests for first recourse, thus confirming the complementarity of private and public sector resources[54].

Now, acontainment release strategy is in place and its effectiveness will be mainly supportedby general practitioners. They are the key players in the strategy for detecting new cases of COVID-19 and thus play a crucial role in our study.

In its "Clinical management of severe acute respiratory infection (SARI) when COVID-19 disease is suspected" the WHO proposes that elderly patients and those with co-morbidities such as cardiovascular disease and type II diabetes should be hospitalised even if they do not show signs of severity.The French High Council of Public Health (HCSP) has determined patients with risk factors[14] who have become the target population of our study in France.We have added obesity as a risk factor since it seems to be present in the literature for COVID-19+ patients in intensive care units[55].The impact of our treatment could, by avoiding hospitalisations, be to relieve congestion by allowing healthcare personnel to focus on serious cases and freeing up resuscitation places.

This experimental treatment could support the deconfinement strategy by early blocking of the viral infection in case of contamination, byreducing the period of contagiousness,by the possibility of home care in the event of contaminationwith a treatment whose tolerance has been proven for nearly sixty years, even in elderly patients.

The medico-economic interest is also very important. The treatment is inexpensive, around 3 euros per 15 tablets, and we hope to avoid the transfer of patients to other intensive care units, which are very expensive for the community.

Very recently, in Italy, Bonzano*et al*. noted the benefit of doxycycline for patients with COVID-19 [56]. Their retrospective study, even on only 6 patients,suggests promising results that our randomised clinical trial will be able to strengthen by removing the bias of a retrospective study on few cases. If the results are as positive as we hope, this treatment could be given to the entire population, possibly in prevention of the disease.

Trial status

The updated protocol is version 1.2 on 11 May 2020.

The first patient inclusion is expected by1 June 2020. With an inclusion period of 6 months, the last patient may be included on 1 December 2020 and the study will be ended after their follow-up visits 1 month later.

List Of Abbreviations

AE	Adverse Event
ANSM	Agence Nationale de Sécurité du Médicament et des produits de santé
ARS	Agence régionale de Santé
BMI	Body Mass Index
CNIL	Commission Nationale de l'Informatique et des Libertés
CRF	Case Report Form
CRP	C Reactive protein
eCRF	Electronic Case Report Form
FDA	Food and Drug Administration
HCSP	Haut Conseil de la Santé Publique

MMP	Metalloproteases
SAE	Serious Adverse Event
Sa O_2	Oxygen Saturation
SARS-CoV2	Severe Acute Respiratory Syndrome Coronavirus
WHO	World Health Organisation

Declaration

Ethics Approval and Consent to Participate

All patients participating in the study will be given oral and written information about this trial and will sign the informed consent form.

An independent ethical review board, the Comité de Protection des PersonnesBoulogne-Billancourt,CPP Ile de France VIII, issued a favourable opinion for this clinical trial and gave its informed consent on 1.2.

Consent for publication

Not applicable

Availability of data and materials

Data-sharing is not applicable to this paper as no datasets were generated or analysed during the current study.

The data from the completed trial will not be shared and will only be transmitted to the sponsor. Data collected during the test may be processed electronically, in accordance with the requirements of the CNIL (compliance with reference methodology MR001).

DECLARATION OF Competing interests

The authors declare that they have no competing interests.

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by the University Hospital of Nantes (CHU Nantes)It should be noted that the pharmaceutical company has no relevance to the data collected or to the protocol and its amendments.

Authors' contribution

AP; FV; AK; BD and JMN wrote the manuscript, DB; FB; CR; GG; AD; MTL; LP¨; EM; PG; AJ; SB; JC and LF, assisted with the drafting of the manuscript. BD, DB; FB; GG; AP, AK; FV and JMN designed the trial. BD; AP; AK; FV; DB; CR; SB; LF and AJ wrote the protocol and/or the file for the experimental drug and assisted with the drafting of the manuscript. SB coordinated the submission of the protocol and the follow-up of (1) the Etic Committee and (2) the regulatory authorities and coordinated the trial. JMN wrote the methodological/statistical analyses in the protocol. BD; DB; FB; MTL; LP; EM and JC participated in patient enrolment and follow-up. AJ assisted with pharmacovigilance for the trial. LF wrote the file for experimental drug and coordinates the provision of treatment in the centres.

All authors read and approved the final manuscript.

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In March 2020,Pierre Gandon submitted an opinion to the Nouvelle-Aquitaine French regional public health authority (AgenceRégionale de Santé - ARS) regarding the potential interest of doxycycline in COVID-19, having noticed that acne sufferers on doxycycline escaped seasonal viral infections.

Laboratoires Pierre Fabre and Bailleul and the University Hospital of Nantes (CHU Nantes) are supporting this clinical trial financially.

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Figures

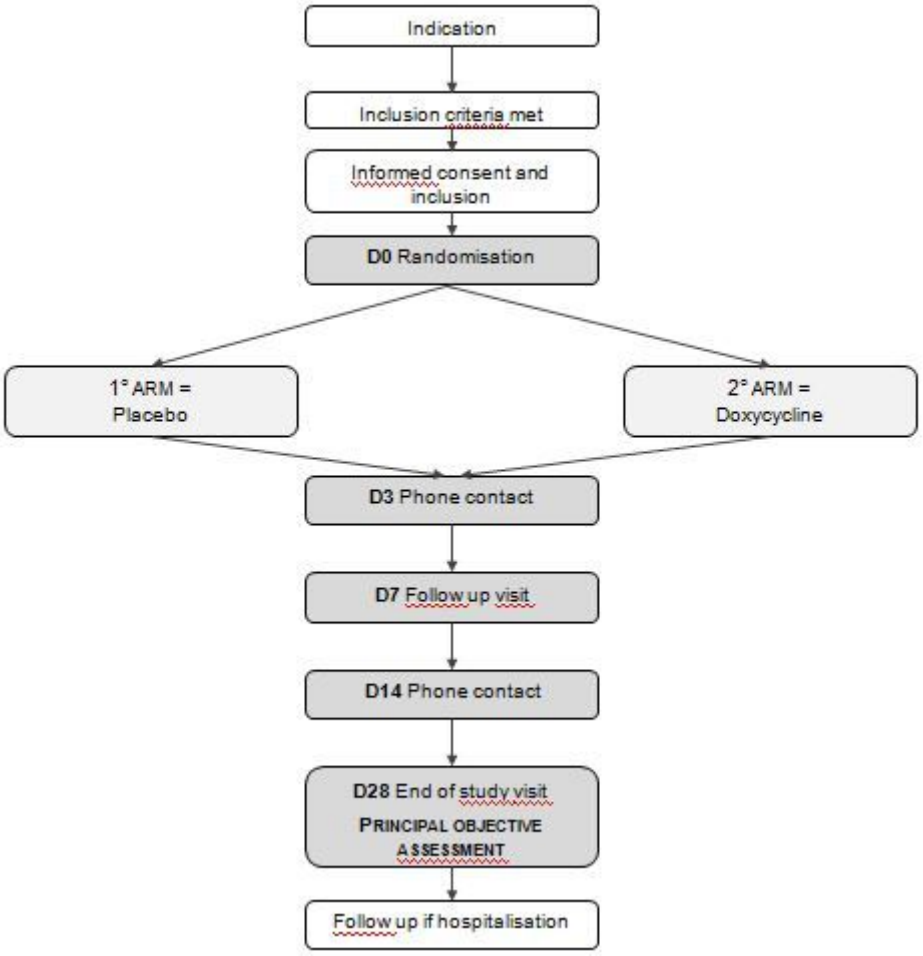

Figure 1

Study Schedule

STUDY PROCEDURE	SCREENING	INCLUSION VISIT	1ST PHONE CONTACT	FOLLOW UP VISIT	2ND PHONE CONTACT	END OF STUDY VISIT
VISIT DAYS	D-2 to D-1	D0	D3 (± 1 day)	D7 (± 2 days)	D14 (± 1 day)	D28 (± 2 days)
Patient information	x	x				
Informed consent		x				
Randomisation		x				
Medical history	x					
Physical examination	x	x		x		x
Clinical status assessment			x		x	
SARS-CoV-2 qualitative PCR	x			x		
SARS-CoV-2 serology		x				x
Pregnancy test		x				
Treatment dispensation		x				
Compliance request						x
Adverse events			x	x	x	x if hospitalisation, follow-up until end of hospitalisation

Figure 2

Flowchart study

QUESTION			CONSULTATION REQUIRED AS SOON AS POSSIBLE ?	
	YES	NO	YES	NO
1. Worsening signs				
2. Fever				
3. Headaches				
4. Cough/sputum				
5. Nasal discharge				
6. Sore throat				
7. Breathlessness at rest/ during activities				
8. Thoracic pain				
9. Vomitting				
10. Diarrhea				
11. Drowsiness				
12. Regular feeding/hydration				

Figure 3

Telephone questionnaire for clinical assessment

Supplementary Files

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