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Deferasirox on COVID-19: safety and efficacy of iron-chelating therapy. A multicentric, randomized, triple blinded study

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Abstract:

Background and Rationale: *SARS-CoV-2, the virus that causes COVID-19, can cause a multitude of health effects. One of the registered effects of COVID-19 is hyperferritinemia due to an excess of necrotic cells and mitochondrial load spread, generating high levels of iron and ferritin. Deferasirox (Exjade®), an iron-chelating agent, has been proposed to treat COVID-19 patients with hyperferritinemia. The objective of this investigation is to submit estimations with high levels of fidelity about the effect of the treatment and the severity of the patients administered the drug blindly in a cohort of hospitals in the city of Santiago, Dominican Republic.*

Methods: *Multicentric study, randomized, triple-blind of parallel groups to evaluate the effects of Deferasirox and standard therapy in patients hospitalized for COVID-19 and hyperferritinemia versus therapy standard for COVID-19. A sample of 94 participants (47 in each group) is necessary to detect the effects of the treatment measured as progressing and becoming severe while being hospitalized.*

Discussion: *Clinical evidence has shown the efficacy and safety of Deferasirox and its use in admitted patients with COVID-19 and hyperferritinemia. Based on this, by executing a retrospective analysis, the authors of this protocol Performed a successful security analysis in Deferasirox patients, noticing that their mortality was not greater, avoiding severity and also suggesting an improvement in the biomarkers.*

Keywords: *Deferasirox, COVID-19, Hyperferritinemia*

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Abbreviations:

COVID-19: Coronavirus disease 19

D.R.: Dominican Republic

UGT: Uridine diphosphate glucuronyltransferase

SARS CoV-2 RT PCR: Polymerase-transcriptase

BACKGROUND AND RATIONALE

Deferasirox or Exjade® is an iron chelator derived from benzoic acid bis-hydroxyphenyl-triazole. This compound is synthesized from salicylic acid condensation and mediated by thionyl chloride (Sedgwick et al., 2021). Deferasirox binds with a high affinity to iron in the ferric state in a 2:1 ratio (tridentate agent), although showing a slight affinity for other metals like copper and zinc. It mobilizes iron selectively from the liver and heart, facilitating its urinary excretion (Gerhardsson & Kazantzis, 2015). Its effectiveness orally is 4-5 higher than parenteral deferoxamine (Cada et al., 2006), some of its applications are in hyperferritinemic syndromes, reducing the elevated iron concentration (Agarwal, 2010). COVID-19 is considered hyperferritinemic, mainly due to the fact that SARS-CoV-2 requires ferritin to guarantee its division and survival, based on the inflammatory impact of disease evolution, where the excess of necrotic cells and mitochondrial load spread in the body causes an increase in iron and ferritin levels, therefore considering deferasirox for the treatment of SARS-CoV-2 disease (Vlahakos et al., 2021).

The SARS-CoV-2 pandemic has caused a change in lifestyle worldwide. Currently, the Dominican Republic (D.R.) protocol for diagnosing and treating patients with COVID-19 relies on antivirals, immunomodulatory drugs, antibiotics, statins, antithrombotic, and anticoagulation prophylaxis (República Dominicana, 2021). Recently, the use of iron chelators such as Deferasirox has been implemented based on the observation of elevated levels of ferritin in COVID-19 patients. Likewise, a high level of this biomarker, regardless of the cause, is associated with a worse prognosis in COVID-19 (Deng & Jiang, 2019).

The need to find an effective therapy to decrease COVID-19 mortality and severity is a global priority. Currently, there is a set of drugs established as standard guidelines, which will evolve according to patient's needs and new findings in research. However, with the increased serum ferritin levels in COVID-19 patients, a drug should be implemented towards reducing this. Although literature exists regarding this question, little research demonstrates the efficacy and role in severity due to the use or not of iron chelators such as deferasirox in hospitalized patients with COVID-19 who are presenting hyperferritinemia (Vlahakos et al., 2021). In consequence, we hypothesize that the treatment with deferasirox is superior to standard therapy in COVID-19 patients presenting hyperferritinemia in avoiding severity. Therefore, our team wants to estimate the study treatment effect on lowering the severity after randomization over the use or not of Exjade® in patients admitted for COVID-19 using a group of hospitals in the city of Santiago, Dominican Republic.

MATERIALS AND METHODS

Trial Design & Study Settings

We propose a multicenter, randomized, triple-blind (participant, investigator and data analyst), parallel-group study to evaluate the effect of deferasirox (Exjade®) and standard therapy for COVID-19 in hospitalized patients with COVID-19 and hyperferritinemic syndrome versus standard therapy for COVID-19 + placebo. Patients will be allocated in a 1:1 ratio between the two treatment arms. The study will be conducted in two third-level centers with COVID-19 units, located in the urban area of the city of Santiago de los Caballeros, Dominican Republic.

Eligibility Criteria

Participants must meet all of the following criteria:

- Male or female ≥18 years with COVID-19 diagnosis (clinical symptoms of less than 10 days of appearance or confirmation with laboratory tests).

- Hospitalization in one of the centers included in the study.
- Serum ferritin > 400 ng/mL in men and > 300 ng/mL in women.
- Transferrin saturation ≥45%.
- ALT ≤200 U / L without clinical evidence nor suspicion of liver cirrhosis.
- Provides written voluntary informed consent.

Participants with one or more of the following criteria will be excluded:

- Previous allergic reaction to Deferasirox.
- Blood transfusions six months before entering the trial and/or chelation therapy 1 month before entering the trial.
- Current infection with Hepatitis B, Hepatitis C or HIV.
- Serum creatinine values twice the age-appropriate upper limit or creatinine clearance <40 mL/min.
- Significant proteinuria (urine protein concentration/urine creatinine concentration > 1.0).
- Platelet count <50 x 109/L.
- History of ocular or auditory toxicity due to chelation therapy.
- Theophylline treatment.
- Pregnancy or breastfeeding.
- Refusing to continue being part of the study.
- Patients with hemochromatosis or elevated levels of ferritin due to a different medical condition.
- Patients that are currently admitted in the ICU ward.

Interventions

Randomization of eligible participants in equitable proportions between Deferasirox + standard therapy for COVID-19 or standard therapy for COVID-19 + placebo, will receive a dose based on their weight calculations in kg (20 mg/kg/day) and approximated to available Exjade® tablets presentation (500 mg per tablet). The placebo would be made in the same shape, color, smell and taste as the study drug. Both drugs will be placed in 0.9% saline or water to create a suspension (administered orally at the same time of day for the duration of the study).

Before starting therapy and at the end of the hospital stay, biochemical values (serum ferritin, C-reactive protein (CRP), erythrocyte sedimentation rate (ESR), D-dimer, serum creatinine, creatinine clearance, serum transaminases, and bilirubin) and eye and hearing examinations should be obtained of each patient regardless of their therapy group. However, if the patient remains hospitalized >6 days, another biochemical evaluation of the previously mentioned components must be included on this date.

Modification/discontinuation

The study drug shall be discontinued if any of the following occurs:

- Allergic reactions: Any reaction to the drug's components (lactose monohydrate, crospovidone, povidone, sodium lauryl sulfate, microcrystalline cellulose, silicon dioxide).
- Ophthalmological reactions: Ophthalmological deterioration or damage evidenced by physical examination.
- Auditory reactions: Hearing impairment or damage evidenced by the patient's referral.
- Pregnancy: Becoming pregnant during the study time.
- Renal failure: If creatinine clearance is between 40-60 mL/min, the initial dose should be reduced to 50%. If the patient is hospitalized for more than six days and creatinine clearance values decrease to <40 mL/min, therapy will be discontinued. If there is an increase in serum creatinine (>33% compared to the start of treatment) dose should be reduced to 50%.

- Hepatic failure: If the patient is in Child-Pugh B, the dose should be reduced to 50% before patient's consent to continue in the study, while if the patient is in Child-Pugh C, therapy should be discontinued.
- Ferritin levels: If ferritin levels on the sixth day are less than 300 ng/L, patients should continue to be observed, and therapy with Deferasirox should be discontinued.
- Drug interactions: Concomitant use of uridine diphosphate glucuronyltransferase (UGT) inducers (phenytoin, phenobarbital, ritonavir, rifampicin) or bile acid sequestrants (cholestyramine, colesevelam, colestipol) may decrease Exjade® exposure. If the use of any of these drugs cannot be stopped, consider increasing the dose of Exjade® by 50%. If a patient is on repaglinide therapy, decreasing repaglinide should be considered while on Deferasirox therapy.

Outcomes

Primary outcomes

To provide reliable estimates of the effect of study treatment on progression in the severity within hospitalization after randomization of the use or *not of Exjade®.*

Secondary outcomes

- Safety: Reported adverse effects that vary from baseline systemic manifestations of hyperferritinemia observed during the hospital stay will be reported before the implementation of the drug to avoid any confusion with adverse effects of Exjade®.
- Efficacy: Days of hospital stay will be evaluated between both study arms to evaluate the efficacy of the therapy with Deferasirox and the outcome of the disease.
- Mortality: death of patient during the hospital stay and active participation in the study protocol.

Sample Size

Calculations are based on the primary objective, seeking the effect proportion of the Deferasirox over severity in COVID-19 patients with hyperferritinemic syndrome. Investigators made inferences based on literature related to the topic, along with the opinion of several specialized experts and lastly taking into account the data collected from a pilot study that took place in a hospital located in the city of Santiago de los Caballeros, in Dominican Republic. A normal distribution of continuous variables was assumed, arriving at the following:

To have 80% power, alpha of 0.05, allowing a confidence level of 97.5% and basing severity of the disease as the admittance of the patient to the ICU ward once it was already admitted in the hospital and following the data gathered during the pilot study related to the main objective, showing in approximately 30% of patients with COVID-19 and hyperferritinemic syndrome, the need for admittance to the ICU, we would require a sample of 81 patients. Allowing a 15% loss to follow up, we would need a total of 94 participants (47 per group). STATA (Version 17) will be used for statistical analysis.

Recruitment

Research team will contact the health care centers involved in the study, in which 1-2 treating clinicians will carry out initial scrutiny of each patient to evaluate their ability to enter the study. After its identification, the patient or family (in case of limitation of will) will receive the study and the informed consent explanation.

Randomization and Allocation

All participants who consent to participate and meet eligibility criteria will be enrolled when authorized personnel enter the subject's assessment information into the program. They will be assigned at a 1:1 ratio through a previously generated random list linked to one of the two treatment groups employing simple type randomization via STATA. Remaining anonymous to maintain blinding.

Allocation concealment

A representative from each private hospital will be assigned to participate, who will be in charge of the database with randomized patients, allowing researchers and patients to be unaware of their allocation, thus protecting the data collected. This representative will be known as the pharmacist assistant since his main role would be the allocation concealment of the intervention and the placebo.

Table 1. Timeline (Schedule and Procedures)

Activities	Month of completion from acceptance of the protocol					
	2	4	6	8	10	12
Informed consent	x	x	x	x	x	
Data collection in hospital centers	x	x	x	x	x	
Data collection supervision	x	x	x	x	x	
Statistical data audit	x	x	x	x	x	x
Formatting data for data analysis						x
Data analysis						x
Drafting and review of the final report						x

Blinding

Given the nature of the intervention, participants and investigators shall be masked to treatment allocation to perform a triple-blinded study (participant, investigator and data analyst).

By using TeamScope™ software, which is responsible for securely encrypting the information of the participants, assigning a code per patient, and ensuring randomization; the masking process is certified by denoting the treatment groups with the letter A or B (by standard therapy + placebo or standard therapy + Deferasirox respectively). To avoid unintentionally unmasking the patients when they are being administered the study drug, the placebo would be made in the same shape, color, smell and taste of the study drug. All participants would receive advice on their allocation at the time the research report is published.

To maintain the data analyst blinding, we will rely on a contract with an external statistician to analyze the data blinded directly from the software. The research team would be notified of the allocation from the TeamScope team at the moment of receiving the final results from the independent statistician.

Emergency Unblinding

Maintaining the quality and legitimacy of the study is imperative; patient's treatment allocation will be known only in extreme cases that warrant breaking confidentiality and masking process. Including a severe adverse effect coupled with the use of investigational treatment; these shall be reported to relevant authorities without exceeding 15 days and documented this event in detail. Researchers must ensure that the masking code will only be broken under the established protocol.

Investigators will provide a 24-hour emergency phone number to obtain information on the patient's cohort.

Data collection methods

Primary Outcome

The primary outcome objective is to provide reliable estimates of the effect of Exjade® on severity progression within hospitalization after initiation of treatment. COVID-19 patients will undergo various methods to diagnosis confirmation, including reverse polymerase-transcriptase chain reaction (SARS CoV-2 RT PCR) considered the gold standard, antigen tests (AG. SARS-CoV-2), antibody test, tomographic findings (CO-RADS classification) and biochemical values (previously mentioned), which will be carried out at the time of the entry of the patient to the emergency room, upon admission to the isolation room, or transfer to ICU (Intensive Care Unit) COVID-19.

The severity of the disease will be assessed as non-severe or severe according to the need for mechanical ventilation or the ICU ward requirement. Also, there will be a multivariable analysis consisting on logistic regression to assess the role of other independent variables as possible confounders.

Secondary Outcomes

- Safety of treatment will stay documented by reports of adverse effects provided by participants, carried out through routine evaluations and rounds.
- Efficacy will be evaluated through control laboratory tests carried out during each patient's hospital stay (serum creatinine, creatinine clearance, serum transaminases, and bilirubin) to evaluate kidney and liver function, thus ruling out some of the most common adverse effects of Exjade®.
- Mortality will be looked into as in-hospital passing of the patient that was enrolled in the study protocol.

Retention

For patients who discontinue the drug after having obtained clinical and chemical data before or after the control test, the following criteria will be taken into account for statistical analysis:

- Serum ferritin.
- Hepatic transaminases.
- CRP.
- ESR
- D-dimer
- Serum creatinine.
- Creatinine clearance.
- Bilirubin.
- Hearing and ophthalmological evaluation.

Once the patient is enrolled, physicians will make every effort to follow the patient throughout the study period; likewise, the research team will be in charge of surveillance after being discharged from the hospital. Similarly, the hospital staff assigned by the research team at the center is responsible for developing and implementing local standard procedures to achieve this level of monitoring.

Participants can withdraw from the study for any reason at any time. The investigator may also withdraw study participants to protect their safety or if they are unwilling or unable to comply with the required study procedures after consulting with the research team. Participants may be withdrawn if the study sponsor, government, or regulatory authorities terminate the study before the planned completion date.

Data Management

The data coordination center (CCD) located at the leading site will be used. TeamScope ™ system will be used for the creation of the form. All participant's data will be entered electronically and kept on file at the medical center to, later on, be compiled in the main center and stored in numerical order, in a safe and accessible place. These will remain in storage for 10 years after the end of the study, which is the responsibility of the coordinator of the clinical trial.

To comply with data integrity, reference data rules, range, and consistency checks will be supported against data already stored in the database. These verifications will apply at data entry in a specific field or before it is written to the final database. Modifications to the data written in the database will be documented through the data change system or in a query system. Any changes an individual user can make will stay documented by the user identification code to the database. Using the archived data for any unauthorized purpose in any other research is strictly prohibited.

Data security and backup

Access to study data will be restricted. Medical centers will only have access to the data of their center.

Investigators will use a password system, which will change periodically. All forms prepared for participant data entry will remain undisclosed to maintain anonymity.

Investigators will execute a full backup of each medical center's primary database twice a month. Likewise, they will carry out incremental data backups daily to ensure the integrity of the database in the event of any loss of study data during the active period of investigation.

Statistical methods

For all indicators, a comparison will be made between the control group vs. Deferasirox regardless of whether they have received the assigned treatment (Analysis by intention to treat) through STATA IC 17.

Description of all variables will be through an univariate descriptive statistics: relative and absolute frequency for categorical variables, the mean and standard deviation for continuous normal variables, and median and interquartile range for continuous non-normal variables. To determine normality, Shapiro-Wilk test and histogram graphical comparison will be used. Statistical significance will be assumed when obtaining a p-value less than 0.05. The authors reserve the right to perform multivariate statistical analysis of linear or logistic regression type as estimated by the dependent variable in a post-hoc exploratory manner to establish associations between the sociodemographic and clinical profile with the results (primary or secondary).

Primary:

To estimate in-hospital progression to severity in hospitalized patients, relative risk will be calculated binary, reporting as odds ratio of the event with its confidence intervals and p-value.

Secondary:

- Safety, measured by the adverse effects profile, will be carried out through univariate descriptive statistics in both groups., and the incidence of each report comparison through Chi-Square test. In the event of a non-significant value but high suspicion of an unfavorable intervention profile, a panel of expert clinicians outside the protocol will submit a second evaluation.
- Bivariate inferential statistics will evaluate hospital stay through an unpaired t-student test (one-sided) in case of verifying normality of the data and with Wilcoxon otherwise.

Subgroups: performance of all primary and secondary analyzes according to the following subgroups:

- The severity of the disease (severe vs non-severe depending on the need for ICU).
- Time since onset of symptoms (generated from a cut-off point that balances both groups in numbers).
- Age groups (taking 65 years as cut-off point according to increased mortality patterns).

Missing data

If missing data represents less than 30%, there'll be data substitution by multiple imputations. This will only be taken as valid if subsequent sensitivity analysis proves it valid. If it isn't validated by the sensitivity analysis, it will go to a modality where only the cases with all the necessary data of the leading clinical and laboratory indicators will be analyzed. If the data absence rate is greater than 30%, the data will only be described due to lack of rigor for its complete analysis.

Data monitoring

For intermediate evaluation of information, there is an evaluation and audit committee of results within the research team. Declaring total independence from conflict of interests with the sponsoring element of the study, entailing to inhibit all members who cannot detach themselves from potential influences. The data will be gathered jointly by a blinded member of the research team in each center and the pharmacist assistant of each center, which will be in charge of specifying the allocation of the treatment on the document to be evaluated.

While the study is running, it's in charge of generating reports of incidence of adverse effects in a

univariate descriptive way. Reports are generated every 15 days, except for a systemic severe adverse effect, in which all information will be referred to an external expert clinical evaluator committee to determine the follow-up or not of the study. During this process, the recruitment process is stopped, but not the follow-up of patients already recruited.

Upon reaching 50% of the expected sample, an interim analysis according to the original data analysis plan but with a p-value adjusted to 0.01 to accept statistical significance. In case of being optimistic for the primary clinical result, the adverse event profile is generated, with their respective statistical comparisons. The protocol would be evaluated as complete regardless of secondary objectives.

All the results included in the preliminary interim analysis will be included in the final report to evaluate efficacy by the incidence of infection.

Harms

Collection of data referring to adverse effects presented by participants will be gathered from the moment of the consent signing until the patient ceases to be part of the study due to death or discharge from the hospital, will be recorded and communicated to the relevant health security authorities and the national bioethics committee (CONABIOS) in the period stated before.

If any adverse event occurs in the participant after the participant has discontinued the study intervention, it should not be reported unless the study team confirms the signs and symptoms as an event associated with the study drug or some protocol procedure; taking into account the patient's previous medical history and concomitant medication used.

Any of the unspecific adverse events plus the clinical suspicion of being caused by the drug will be reported as an official adverse event. The recognized adverse effects of Exjade® are the following (Gerhardsson et al., 2015) (Tanaka et al., 2014) (Vlahakos et al., 2021):

Mild

- Diarrhea
- Gastrointestinal discomfort
- Increased liver transaminases
- Sickness
- Vomiting
- Earache

Intermediate

- Hair loss
- Difficulty sleeping
- Common cold
- Proteinuria
- Fever

Severe

- Creatinine increase >30%
- Erythema multiforme
- Fanconi syndrome
- Cytopenia
- Hearing loss
- Increased ocular pressure
- Cataracts exacerbation
- Angioedema
- Liver failure
- IgA vasculitis
- Sudden blindness
- Stomach or intestinal ulcer

DISCUSSION

Ferritin is a molecule that binds and stores iron for biological processes in the cell, such as viral replication, generation of ATP, and DNA synthesis. SARS-CoV-2 requires ferritin to guarantee its division and survival, which is why the rationale for

using a ferritin chelator as part of management derives from this premise. Likewise, iron has an ambiguous effect on the regulation of the immune response (Perricone et al., 2020).

This form of iron (labile plasma iron) is not bound to transferrin, contributes to the formation of reactive oxygen species, which promotes inflammation, tissue damage, and fibrosis (Perricone et al., 2020).

Since COVID-19 management is currently in the experimental phase, deferasirox (Exjade®) already operates in the context of compassionate use in patients admitted and with hyperferritinemia (Birlutiu et al., 2021). Therefore, we propose to conduct a study evaluating progression to severity after treatment for COVI-19 using standard therapy and deferasirox vs patients using only standard therapy and placebo.

COVID-19 came to test our health systems and research response capabilities. With impressive infection kinetics and multi-organic damage, clinicians shall use all our resources to avoid the escalation of damage. This protocol represents an answer to a group of high ferritin patients, explaining part of this viral infection pathophysiology and available safe treatment. Several solutions like this one would complement personalized medicine for these patients. Also, negative results would clarify how the high levels of iron-mediators are a half step in the inflammatory process and possibly discard it as a cause of damage.

Conflict of interest

The authors declare no conflict of interest.

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Furthermore, the same hyperinflammatory state can increase transferrin levels in the body. If the ability of iron to bind to transferrin exceeds, iron levels increase in blood.

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