FUTILITY STUDY OF DEFEROXAMINE MESYLATE IN INTRACEREBRAL HEMORRHAGE
REVISED PROTOCOL
VERSION IV/I
DATE: 05/15/2014

SUMMARY AND RATIONALE FOR PROTOCOL CHANGES

BACKGROUND:

Prompted by a large body of pre-clinical evidence suggesting that the iron chelator, deferoxamine mesylate, confers substantial neuroprotective effects after intracerebral hemorrhage (ICH) in various animal models and species, clinical investigations of the use of deferoxamine in ICH patients began in 2009 when the NINDS funded a prospective, phase I, multi-center, pilot, open-label, dose-finding study using the continuous reassessment method to determine the safety, feasibility, tolerability, and maximum tolerated dose of deferoxamine in ICH patients (R01 NS 057127). Twenty subjects were treated with deferoxamine in 5 dose-tiers varying from 7 mg/kg/day to 62 mg/kg/day given by intravenous infusion for 3 consecutive days after ICH onset. Repeated daily infusions of DFO at doses up to 62 mg/kg/day (up to a maximum of 6000 mg/day) in patients with acute spontaneous ICH for 3 consecutive days after ICH onset were found to be feasible, well tolerated, and did not increase serious adverse events or mortality. In September 2012, the NINDS funded a larger multi-center, phase II, futility design, clinical trial: "Futility Study of Deferoxamine Mesylate in ICH" (U01 NS074425), which was entitled as "HIgh dose DEFeroxamine (HI-DEF) Trial". Enrollment began in March 2013 and eligible subjects were randomized to either deferoxamine at 62 mg/kg/day (the maximum tolerated dose identified in phase I study), or saline placebo, given by continuous IV infusion for 5 consecutive days. The duration of infusion was increased from 3 days in phase I to 5 days in phase II based on emerging animal data suggesting that longer treatment is more effective and the recommendation of peer review. The main objectives were: 1- To assess whether it is futile to move deferoxamine forward as a therapeutic intervention for ICH into Phase III evaluation, by comparing the outcome of DFO-treated subjects to placebo-treated subjects with respect to good outcome (defined as mRS of 0-2 at 90 days), in a futility analysis; and 2- To assess the safety of deferoxamine infusions (at a dose of 62 mg/kg/day, up to a maximum daily dose of 6000 mg/day), given for 5 consecutive days, in a large cohort of ICH patients. We specifically wished to collect more data on treatment-related adverse events in order to ascertain that patients with ICH can complete this dose given over the extended 5-day duration of infusion without experiencing unreasonable neurological complications, mortality, or other serious adverse events related to DFO use.

Enrollment into this trial was placed on hold in October 2013 to investigate a potential safety concern. Five cases of adult respiratory distress syndrome (ARDS), three of which were fatal with two of the three deaths being directly attributed to ARDS, were reported after enrollment of 42 subjects. Although ARDS is a known complication of ICH, it has been also reported as a side effect of prolonged high-dose IV infusions of deferoxamine in the package insert of the product. This led to extensive review of all reported cases of ARDS, respiratory failure, and pulmonary edema by an expert in ARDS, blinded to treatment assignment. This review identified three more cases of undiagnosed ARDS; two cases of pulmonary edema in HI-DEF and one case of respiratory failure due to aspiration in phase I were thought to be probable/possible ARDS. In February 2014, the DSMB decided to terminate enrollment on

account of safety concerns, and unblinded the investigators to the treatment assignments; 6 of the 7 cases of ARDS in HI-DEF occurred in the deferoxamine-treated group. The expert review concluded that a plausible cause for ARDS, other than the study drug or ICH itself, was identified in 4 cases, while no other explanation for the remaining 3 cases (other than ICH or the drug) was apparent. No other safety concerns emerged. The NINDS-appointed DSMB concluded that: "although the ARDS cases in the treatment group were in the ballpark frequency of at least one paper in the literature on ARDS in patients with ICH, the imbalance in the frequency of ARDS cases between the treatment and placebo groups suggests that pulmonary toxicity of the drug is highly likely."

The investigators subsequently modified the protocol to minimize the pulmonary toxicity of deferoxamine and to enhance safety of future participants, in order to continue further investigation of this promising therapy for a devastating condition like ICH. The outline of the proposed modifications to the prior protocol was included in a letter to the DSMB on March 22, 2014 (a copy of the letter is included for reference). The DSMB provided additional feedback and accepted our proposed modifications in May 2014i. The current version IV of the protocol incorporates all of these modifications.

Below is a summary of the main changes to the initial protocol and the rationale for each change (when applicable).

SUMMARY OF MAIN CHANGES:

1- In the study synopsis and section 4.2, we revised the exclusion criteria to exclude patients at high risk for developing ARDS from participating in the study. We have added the following new exclusion criteria:
    1. Patients with confirmed aspiration, pneumonia, or evident bilateral pulmonary infiltrates on chest x-ray or CT scan prior to enrollment
    2. Patients with significant respiratory disease such as chronic obstructive pulmonary disease, pulmonary fibrosis, or any use (chronic or intermittent) of inhaled O_2 at home
    3. FiO_2 >0.35 (>4 L/min) prior to enrollment
    4. Sepsis (present source of infection ± lactic acidosis), Systemic Inflammatory Response Syndrome (Temp >100.4F or <96.8F; Heart rate >90; Respiratory rate >20 or $PaCo_2$ <32 mmHg; WBC >12, <4, or bands >10%), or shock (SBP <90 mmHg) at presentation
    5. The presence of 4 or more of the following risk modifiers for ARDS prior to enrollment:
        i. Tachypnea (respiratory rate >30)
        ii. SpO_2 <95%
        iii. Obesity (BMI >30)
        iv. Acidosis (pH <7.35)
        v. Hypoalbuminemia (albumin <3.5 g/dL)
        vi. Concurrent use of chemotherapy

2- We require that a chest x-ray be performed before subjects' enrollment in order to exclude the presence of pulmonary edema or bilateral infiltrates (see above). We revised sections 4.3.1, 4.3.2, 6.1.2, and table 6.2 to reflect this new requirement.

3- We decreased the daily dose from 62 mg/kg/day to 32 mg/kg/day, and shortened the duration of treatment from 5 days to 3 days to minimize the potential for pulmonary toxicity of deferoxamine. We revised the relevant sections (study synopsis, and sections 1.1 and 3.1) to reflect this change; and provided justification for the choice of the new dose and duration of treatment in the revised protocol (section 3.3).

4- We now require that the investigators must follow ARDSNet recommendations for management of intubated patients to minimize ventilator-induced injury and ARDS. We updated sections 5.2 on safety monitoring and 7.3 on prevention and management of adverse events; and added appendix VI to detail ARDSNet recommendations.

5- We also require that all investigators must use the currently established Berlin criteria to define ARDS and its severity to ensure standardized and accurate reporting of ARDS in future participants. We updated section 5.2 with this requirement and added appendix VII to detail the Berlin criteria.

6- We made the following changes in order to facilitate timely and accurate detection of ARDS cases:

   a. We now require that the following data are recorded at least once daily in intubated patients with changes in respiratory status requiring changes in ventilator settings and increased oxygen requirement, and entered into the trial's electronic database on WebDCU™: PaO_2/FiO_2 ratio; plateau & peak pressures; and chest x-ray results. We also require that a chest x-ray is performed in any subject whenever the PaO_2/FiO_2 ratio is <300. Sections 5.2, 6.1.1, and 6.1.2 have been updated to include these requirements.

   b. We added a new adverse event "respiratory compromise of any cause" to our existing list of Adverse Events of Special Interest, and will require that the investigators complete a dedicated case report form for this adverse event on WebDCU™ within 24 hours of onset to trigger immediate review by the medical safety monitors. We updated sections 5.2, 7.5, 7.6 , 9.2 , 9.3 to reflect these changes.

   c. We require that a chest x-ray be performed whenever the PaO_2/FiO_2 ratio is <300. We revised sections 6.1.1 and table 6.2 to reflect this new requirement.

7- We revised the criteria for premature discontinuation of the study drug infusion to include the development of ARDS (using the Berlin definition) as a common sense approach to minimize harm to future participants. We updated sections 7.3 and 7.4 accordingly.

8- We added a new section (7.7) to describe a stopping rule allowing for early detection of a signal for pulmonary toxicity in the deferoxamine-treated group, which may warrant termination of the revised protocol by the NINDS-appointed DSMB. We updated section 10.4 to refer to the stopping rule.

9- We made the following modifications to simplify the study protocol and to facilitate long-

term outcome assessment based on our experience to date:

a. We eliminated the 90-day CT scan. This was originally intended to assess for the potential effects of treatment with deferoxamine on brain atrophy and residual cavity size. However, this has proven to be challenging especially for patients residing at long-term care facilities or nursing homes. We revised our exploratory aims and the sections 6.1.1 and 6.1.2 , table 6.2 accordingly.
b. We eliminated testing for serum iron studies and added albumin to the labs required before enrollment into the trial. We have treated a total of 41 subjects with deferoxamine to date (20 in phase I and 21 in phase II). None developed clinically significant iron deficiency or anemia requiring treatment. Therefore, we elected to eliminate serum iron studies to avoid the potential for any conceived unblinding for treatment assignment, which could confound reporting of adverse events and assessment of relationship to the study intervention. Low albumin has been associated with increased risk for ARDS and serum albumin level <3.5 g/dL could lead to exclusion from the study (see point #1 above). We revised section 6.1.2 and table 6.2 to reflect these changes.
c. We added a follow-up phone call at 6 months (180 days) to assess modified Rankin Scale score (mRS), given emerging data that ICH patients require longer time to recover, and ordinal analysis of mRS as a secondary outcome measure. We updated our secondary objectives, and sections 1.2, 3.1 , 3.2 , 3.3 , 6.1.1 , and table 6.2 to reflect these changes.
d. We also modified the randomization algorithm to take into account baseline ICH volume and ICH severity (based on NIHSS score) because preliminary review of the data from the 42 subjects who were enrolled earlier revealed significant imbalances in ICH volume and severity of neurological deficits between the two groups. We revised sections 4.3.6 and 8.1 accordingly.

10- We revised section 8.4 point out that the sample size will be decreased from 324 in the initial protocol to 294 in the current version. We decreased the anticipated drop-out rate due to loss-to-follow-up, withdrawal of consent, as well as randomized subjects in whom the study drug is not initiated to 5% based on our experience to date. This sample size still provides 80% power for the main futility analysis using a one-sided alpha level of 0.10.

SUMMARY OF OTHER CHANGES:

1. Since we are no longer using high dose deferoxamine, the short title of the study has been changed from High Dose Defroxamine in ICH (HI-DEF Trial) to Intracerebral Hemorrhage Deferoxamine (iDEF) Trial. In addition, this version of the protocol has been numbered a IV/I to reflect that it is an extension of prior versions of the protocol while indicating that this new phase of the study is separate from the earlier phase in which further enrollment which was terminated.

2. We revised the section on Study Administrative Organization to update the composition of the study's Executive Committee to delete personnel who are no longer involved in the study and to add the names of new members; to point out that the DSMB now includes an ad hoc expert in pulmonary diseases and critical care medicine; and to highlight the change

in the existing safety monitoring structure to provide closer and more experienced oversight of the respiratory complications during the study. We have replaced the current medical safety monitor with a neurointensivist, and a pulmonary critical care specialist with expertise in ARDS to assist with detailed review of future cases of respiratory failure and pulmonary edema. Both monitors will adjudicate each case to ascertain the diagnosis and to determine the presence vs. absence of plausible explanations, other than the study drug, for ARDS occurrence.

3. We updated section 2.1.3.2 on deferoxamine's safety consideration to include the recent data on ARDS occurrence. Similarly, we added a new section (2.2.3) to summarize the safety data from the 42 subjects who were enrolled in the early part of this study. We also updated section 7.2 on the potential complications of the study intervention to provide the new safety data.

4. We revised section 10.4 on the Data and Safety monitoring plan to indicate that confirmed ARDS cases will be reported to the DSMB on an ongoing basis; refer to the stopping rule; and point out that the first overall interim safety analysis will be performed after the first 40 subjects complete their in-hospital assessments.