Ciprofloxacin Versus Levofloxacin in Stem Cell Transplant

NCT03850379

Study protocol March 14, 2018

4. **SIGNIFICANCE:** State concisely the importance of this project by relating the purpose to broader, long-range objectives. **This selective intervention will establish a unique setting to asess the efficacy of the use of levofloxacin vs ciprofloxacin prophylaxis in patients undergoing SCT**

5. **SUBJECTS IN THE PROJECT:**
   a. State the inclusion and exclusion criteria for enrollment of subjects.**Eligibility Criteria: Patients 18-75 years of age with a diagnosis of a hematological malignancy. Meet the BMT program criteria to undergo hematopoietic stem cell transplantation.**
   b. Describe the control population (if utilized) and justify its selection.**NA**
   c. Support the likelihood of recruiting the number of subjects required to complete the project. Relate this to other projects recruiting similar subjects.**In our growing program we have been doing almost 100 SCT per year and all need prophylaxis antibiotics to prevent infection**

6. **PROJECT DESIGN AND PROTOCOL:**
   a. Describe the experimental design/methodology.**This is a prospective study comparing consecutive patients who will be be receiving ciprofloxacin prophylaxis vs. levofloxacin prophylaxis for SCT till engraftment defined as ANC >1000,**
   b. Outline the protocol, corresponding it to the specific aims; identify the data or endpoints to be analyzed to reach the specific aims. **Primary Objective: to assess incidence of bloodstream bacterial infections in the ciprofloxacin group compared to levofloxacin group up today 60 after SCT. Secondary objectives: To assess time to engraftment, incidence of Clostridium difficile infection, rate of febrile neutropenia, Incidence of Gram positive and gram negative bacterial breakthrough infections, inpatient mortality, rate of hypotension ,ICU admissions , fungal infections. In allo SCT patients assess rate of acute graft versus host disease (GVHD) by day60. Blood stream infections will be documented along with type of pathogen and drug resistence . Also C diff infection will be documented. Time of engraftment will be documented. secondary objectives like GVHD, PFS, OS will be assessed using this regimen. PFS and OS were estimated from day0 according to the Kaplan-Meier method. Estimates of treatment related mortality, acute GVHD and chronic GVHD rates will be based upon cumulative incidence estimates, treating relapse as a competing risk. Engraftment rates (and corresponding 95% confidence intervals) will be estimated by the proportion of patients who engraft. Neutrophil recovery is defined as a sustained absolute neutrophil count (ANC) > 0.5 x 109/L for 3 consecutive days. Engraftment date is the first day of three (3) consecutive days that the ANC exceeds 0.5 x109/L. Delayed engraftment is defined as the evidence of engraftment beyond day 28 post SC infusion achieved after the administration of therapeutic (high dose) hematopoietic growth factors. Primary Graft failure is defined as failure to achieve an ANC > 0.5 x 109/L for 3 consecutive days by day 28 post SC infusion, with no evidence of donor derived cells by bone marrow chimerism studies and no evidence of persistent or relapsing disease. Secondary graft failure is defined as a sustained declined of ANC <0.5 x 109/L for 3 consecutive days after initial documented engraftment with no evidence of disease progression. Autologous reconstitution is defined by the presence of ANC > 0.5 x 109/L without evidence of donor-derive cells by bone marrow chimerism studies. This can occur at initial engraftment or later after initial engraftment has been documented. Complete remission (CR) is defined according to disease specific criteria as per the CIBMTR. Relapse defined according to disease specific criteria will be recorded by the day of detection.**
   c. Discuss potential limitations and difficulties in the protocol.**Uncontrolled multi-variables and their contribution to patient's disease course may attenuate the results. Sorting and stratifying each variable may create multiple small groups of patients which may not possess the power to reflect and determine differences among those small groups**
   d. Provide a tentative schedule for conducting and completing this project and, if applicable, the multicenter study.**we do around 100 SCT per year , so we will need 3 years to recruit the patients and 4 years to finalize the data**
   e. Data collection: **Submit a copy of the data collection tool or list the data fields to be collected (review IRB policy, *Access to Medical Records for Research*).attached**

7. **DATA ANALYSIS:** Describe the analysis of the data and relate this to the specific aims in detail. Case reports and medical record reviews also require a description of the planned data analysis (ie. descriptive, observational). The Committee recommends free consultation with the Division of Biostatistics and Research Epidemiology *before* IRB submission. **Number of pts needed: to prove 10% improvement in overall bacterial infections control (Decrease from 20% to 10%), need 308 pts; 154 in each group To achieve 70% power . Data will be collected and analyzed. We will prospectively follow patients who will get**

HSCT . Objectives are to explore the impact of cipro vs levo on incidence of bacteremia and incidence of resistant and non-resistant gram-positive strains bacteremia. Also impact of Levo vs Cipro incidence of Clostridium difficile and GVHD Demographics, disease-related and transplant-related variables mentioned above will be collected. A two sample test of proportion equality will be used as the test for the primary aim. PFS is defined as the time from HSCT to the time of progression, death or last contact whichever occurred first. OS is defined as the time from HSCT to the time of death or last contact. OS and PFS will be estimated using the Kaplan-Meier method.

8. **JUSTIFICATION FOR NUMBER OF SUBJECTS OR DATA:**

a. State the number of subjects or data points to be analyzed in the project at this institution and the total number for multicenter studies. The Committee recommends consultation with the Division of Biostatistics and Research Epidemiology (313) 874-6360. **2. The target sample size is 308 patients. Accrual Period: 3 years.**

b. *Describe the statistical justification for this number of subjects or data points.* ***after discussion with biostat to calculate Number of pts needed: to prove 10% improvement in overall bacterial infections control (Decrease from 20% to 10%), need 308 pts; 154 in each group To achieve 70% power .***

FORM A
HENRY FORD HEALTH SYSTEM (IRB) DRUG/SUBSTANCE INFORMATION

(This form must be completed for each individual drug or substance -*investigational or marketed*- that is being administered as part of this research study)

1. Generic/Chemical Name: **Ciprofloxacin**	2. Trade Name: **Cipro**
3. Manufacturer: **Bayer**	4. Mode of Administration: **P.O.** other: **IV**
5. How Supplied (dose form & strength): **500 mg**	6. Who will be administer the drug/substance? **P2 Nurse**
7. Dosage and Schedule Proposed:**500 mg BID**	
8. Will you be utilizing research pharmacy for storage or dispensing of any medication? (if this is an inpatient study, you are required to use research pharmacy). ☐ Yes ☒ No	
9. Describe the primary actions of the drug/substance:**Prevnet infections in neutrpenic patients by Inhibiting DNA-gyrase in susceptible organisms**	
10. Describe the therapeutic benefit anticipated from the use of this drug/substance: **Prevent infections in neutrpenic patients after the conditioning regimen for SCT**	
11. List the known side effects (these should also be listed in the consent form in this manner): ✓ Likely: **none** ✓ Less likely:**headache** ✓ **Skin rash (1%)** ✓ **Diarrhea (2%), vomiting (1%), abdominal pain (<1%), nausea (3%)** ✓ **Increased liver enzymes AST (1%)** ✓ **Fever (<1%** ✓ Rare, but serious: <1% : severe allergic reaction with low blood pressure and difficulty breathing, Clostridium difficile-associated diarrhea, confusion, convulsions, decreased visual acuity, depression, liver failure, peripheral neuropathy (may be irreversible), abnormal heart conduction on ECG, rupture of tendon, inflammation in pancreas , low counts	
12. Describe the precautions used to insure that the risks associated with the administration of this drug/substance is minimized: **toxicities will be monitored and dosage will be modified per BMT protocol**	

☐ Yes ☒ No	13. Are there special storage safety or handling conditions required? If yes, please describe:
☐ Yes ☒ No	14. Is there an IND #? If 'yes', is this an (check which one applies): ☐ investigational drug/substance ☐ approved drug being investigated to provide data to the FDA in support of a new indication or to change the labeling
☒ Yes ☐ No	15. Have restrictions been placed on the use of this drug/substance by the FDA? If yes, describe them: **Fluoroquinolones have been associated with disabling and potentially irreversible serious adverse reactions that have occurred together, including: tendinitis and tendon rupture, peripheral neuropathy, and CNS effects. Discontinue ciprofloxacin immediately and avoid the use of fluoroquinolones in patients who experience any of these serious adverse reactions.**
☒ Yes ☐ No	16. Are other drugs/substances known to interact in important ways with the investigational agent being tested in this protocol? If yes, list the drugs/substances (and/or their categories) and describe the precautions for avoiding adverse events resulting from such interactions: **Fluoroquinolones may prolong QTc interval sane as antifungal azoles but we assess ECG and QT interval in all out SCT pts and use alternatives when QT is prolongued**
☐ Yes ☒ No	17. Is the drug/substance to be used in children? If yes, has it been approved for use in these subjects?
☐ Yes ☒ No	18. Is the drug/substance to be used in pregnant women? If yes, has it been approved for use in these subjects?
☒ Yes ☐ No	19. Will the dosage/schedule be modified within the protocol in response to efficacy or side effects? If yes, what end points will drive the dosage alterations? **drug will be discontinued and alternative prophyalxis will be used in the event of unacceptable toxicity per our ID transplant protocol Azithromycin 250 mg PO QD**
☒ Yes ☐ No	20. Is compliance with dosage schedule monitored? If yes, how? **P2 nurse giving the medicationa and documenting in MAR**
☐ Yes ☒ No	21. Is this a blinded study? If yes, describe the provisions that have been made for breaking the code in the event of a significant adverse event?
☒ Yes ☐ No	22. Have provisions been made for "after hours" or holiday availability of the PI or Co-PI for consultation? If yes, describe them: **the PI and co -investigators will be on call on a continual basis while patients are treatedon this stud**

FORM B
HENRY FORD HEALTH SYSTEM IRB MEDICAL DEVICE INFORMATION

(This form must be completed for each individual device -investigational or marketed- which is being used as part of this research study)

1. Name of Device:
2. Manufacturer:
3. Marketed? ☐ Yes ☐ No (If 510K received, include FDA documentation)
4. Investigational? ☐ Yes ☐ No If yes, IDE#: (include FDA IND letter)
5. What is the sponsor's or FDA's risk determination for this study? ☐ Significant Risk Device Study ☐ Nonsignificant Risk Device Study

FORM A

HENRY FORD HEALTH SYSTEM (IRB) DRUG/SUBSTANCE INFORMATION

(This form must be completed for each individual drug or substance -*investigational or marketed*- that is being administered as part of this research study)

1. Generic/Chemical Name: **Levofloxacin**	2. Trade Name: **Levaquin**
3. Manufacturer: **Janssen**	4. Mode of Administration: **P.O.** other:
5. How Supplied (dose form & strength): **tablet 500 mg**	6. Who will be administer the drug/substance?
7. Dosage and Schedule Proposed:**500 mg once daily**	
8. Will you be utilizing research pharmacy for storage or dispensing of any medication? (if this is an inpatient study, you are required to use research pharmacy). ☐ Yes ☒ No	
9. Describe the primary actions of the drug/substance:**inhibits DNA-gyrase in susceptible organisms thereby inhibits relaxation of supercoiled DNA and promotes breakage of DNA strands to help prevent infections**	
10. Describe the therapeutic benefit anticipated from the use of this drug/substance:	
11. List the known side effects (these should also be listed in the consent form in this manner): ✓ Likely: **none** ✓ Less likely:**Chest pain (1%), edema (1%)** ✓ **Headache (6%), insomnia (4%), dizziness (3%)** ✓ **Skin rash (2%), itching (1%)** ✓ **Nausea (7%), diarrhea (5%), constipation (3%), abdominal pain (2%), vomiting (2%)** ✓ **Vaginal itching (1%)** ✓ **Infectionwith candida (1%)** ✓ **Difficulty breathing (1%)** ✓ Rare, but serious: <1% : severe allergic reaction with low blood pressure and difficulty breathing, Clostridium difficile-associated diarrhea, confusion, convulsions, decreased visual acuity, depression, liver failure, peripheral neuropathy (may be irreversible), abnormal heart conduction on ECG, rupture of tendon, inflammation in pancreas , low counts	
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☒ Yes ☐ No	15. Have restrictions been placed on the use of this drug/substance by the FDA? If yes, describe them: **Fluoroquinolones are associated with disabling and potentially irreversible serious adverse reactions that may occur together, including tendinitis and tendon rupture, peripheral neuropathy, and CNS effects. Discontinue levofloxacin immediately and avoid use of fluoroquinolones in patients who experience any of these serious adverse reactions.**
☒ Yes ☐ No	16. Are other drugs/substances known to interact in important ways with the investigational

	agent being tested in this protocol? If yes, list the drugs/substances (and/or their categories) and describe the precautions for avoiding adverse events resulting from such interactions: **Fluoroquinolones may prolong QTc interval sane as antifungal azoles but we assess ECG and QT interval in all out SCT pts and use alternatives when QT is prolongued**
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DO NOT SUBMIT THIS FORM IF YOU ARE NOT USING A DRUG/SUBSTANCE IN THIS STUDY