An Open Label Randomized Controlled Trial To Prevent the Progression of Respiratory Syncytial Virus Upper Respiratory Tract Infection to Lower Respiratory Tract Infection in patients after Hematopoietic Stem Cell Transplant.

Short Title: Use of oral ribavirin for the treatment of RSV upper respiratory tract infection in patients after HSCT

Protocol Body

1.0 Objectives

Primary Objectives:

1) To determine whether oral ribavirin given for therapy of Respiratory Syncytial Virus (RSV) upper respiratory tract infection (URI) can prevent its progression to Lower respiratory tract Infection (LRI)-pneumonia, when compared to aerosolized ribavirin – modified regimen in HSCT recipients at moderate or high risk for progression.

Secondary Objectives:

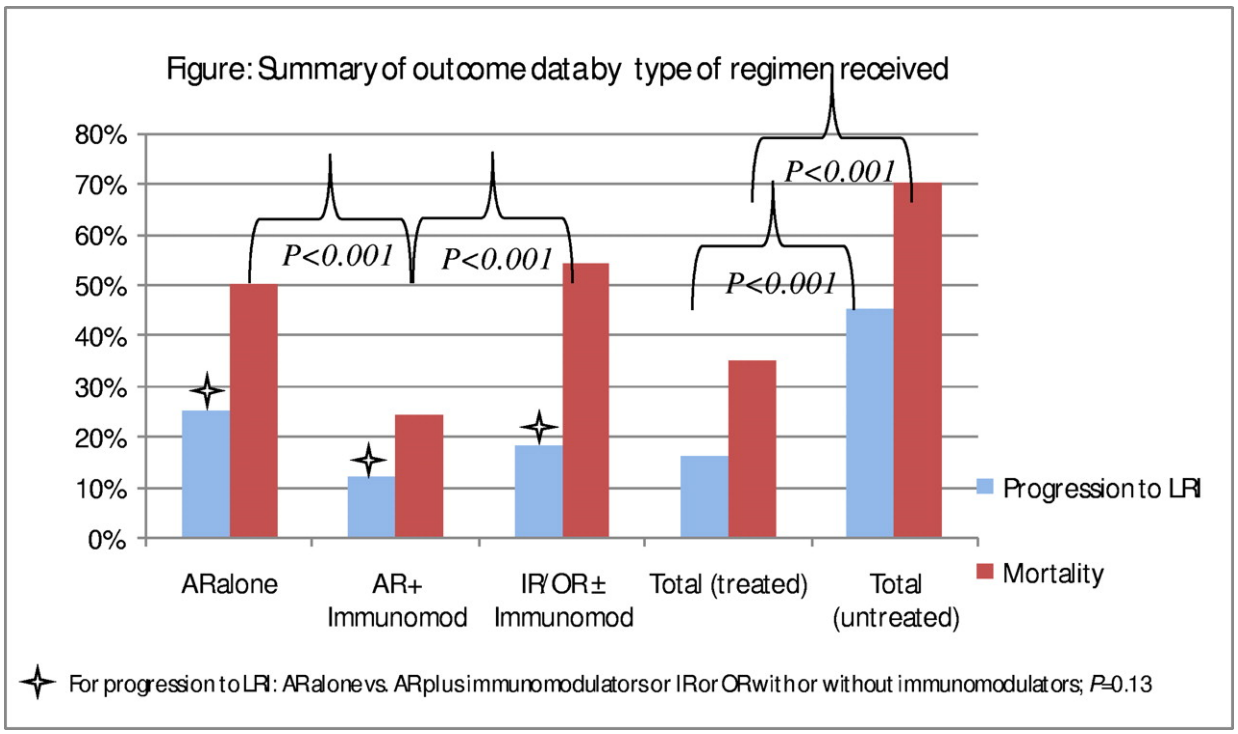
1) To determine the safety of oral ribavirin therapy when compared to aerosolized ribavirin.

2) To calculate the cost effectiveness of using oral ribavirin when compared to aerosolized ribavirin.

3) To compare RSV viral loads in nasal washes and/or other respiratory specimens and RSV neutralizing antibodies in serum between patients on both arms of the study and a observational arm where low risk patients for progression are not receiving either regimen of ribavirin.

2.0 Background

Over the past 2 decades, it has become apparent that community respiratory viruses (e.g. RSV, influenza, parainfluenza, picornavirus) can cause serious infections in patients with cancer, particularly in patients with acute leukemia and after hematopoietic stem cell transplantation (HSCT) recipients, resulting in substantial morbidity and mortality. They are also associated with bacterial or fungal co-infections leading to the development of respiratory super-infections. Though studies have shown that many RSV infections may resolve uneventfully without therapy, some patients do progress to LRI, increasing the morbidity and the mortality of such patients. In fact, a recent study concluded that cancer patients with RSV LRI, and with severe immunodeficiency and pre-engraftment are at high risk for RSV-attributed mortality. The use of ribavirin based regimens has been shown to halt this progression and reduce the morbidity and mortality in mainly case series from single institutions with no data from randomized or nonrandomised trials. Furthermore, in a recent systematic review on the use of ribavirin either orally, intravenously or in its aerosolized form, we determined that such therapy may halt progression of RSV from the upper to the lower respiratory tract with better survival in patients after HSCT transplantation (*Figure, Shah J and Chemaly RF, Blood, March 2011*).



Abbreviations: AR= Aerosolized ribavirin; IR= Intravenous ribavirin; OR= Oral ribavirin

Aerosolized ribavirin is the recommended therapy for RSV LRI and became the standard of care in many cancer centers. It has been used for treatment of LRI in leukemic and HSCT patients, usually in combination with IVIG. Because of the substantial morbidity and risk of fatality from LRI, ribavirin is also given pre-emptively to high-risk cancer patients with RSV URI to prevent progression to LRI. Despite its potential benefits, the drug is not routinely recommended due to inconvenience of administration, cost, and questionable efficacy because of lack of randomised controlled trials. The cost of a 10 day course of aerosolized ribavirin alone could be between $50,000 and $80,000, based on estimates from our financial department. While RSV infection involving only the URT may resolve uneventfully in some immunosuppressed patients, the infection can progress to the LRT with a substantial increase in mortality rate in many other patients. Hence, many of these patients who present with RSV URI are treated with aerosolized ribavirin to prevent progression. In the above mentioned systematic review, we concluded that "prompt diagnosis of RSV infection should be coupled with an aggressive approach to management in HSCT patients who have at least one identifiable risk factor for progression to LRI, such as absolute lymphocyte count (ALC) less than 300/μL or GVHD, with early initiation of ribavirin therapy in either aerosolized or oral form before development of RSV LRI. The oral form of this drug should be explored further, as it is less expensive and probably has fewer and milder side effects than the aerosolized formulation". It is common practice in many institutions (in the United States and Europe) to initiate oral ribavirin therapy for RSV infections in HSCT recipients instead of the aerosolized form because of all the above mentioned limitations of the latter.

We also validated a scoring system on a cohort of 284 allogeneic HSCT recipients and determined the risk of progressing to LRI and mortality based on the score assigned. Briefly, a weighted index accounting for the number and intensity of immunodeficiency markers was

developed and validated in this cohort. Adjusted relative risks calculated from Cox proportional hazards regression modeling were assigned as weights to these immunodeficiency markers; absolute neutrophil count (ANC), ALC; myeloablative chemotherapy; corticosteroids in past 30 days; GvHD; HSCT within 30 days or pre-engraftment or both; and age were utilized to generate an immunodeficiency score (ISS) (range: 0–12) for each patient. ISS scores were discretized to classify patients into low-risk (0-2), moderate-risk (3-6), and high-risk (7-12) groups. Each increased level of the ISS was accompanied by stepwise increases in the cumulative morbidity (LRI) and mortality attributable to immunodeficiency. There were significant differences in the progression to LRI and mortality (p<0.0001) based on the scoring classification groups. RSV-targeted antiviral therapy given at the URI stage was a significant predictor of LRI and mortality. The ISS predicted the risk of these outcomes more proficiently, when the system was stratified by treatment (Table). This new ISS provides an easy, practical, and clinically applicable method of predicting the risk of progression to RSV LRI and death in allo-HSCT recipients who have or have not received antiviral therapy (*Abstract in the Proceedings of the 51th ICAAC meeting in Chicago, IL, 9/2011*). Based on these results, only patients with ISS of at least 3 (moderate to high risk) will be offered therapy for RSV URI.

		Therapy at URI Stage			No Therapy at URI Stage			Total		
		%	n	N	%	n	N	%	n	N
Progression to LRI	Low	6	4	70	38	18	48	19	22	118
	Moderate	14	12	85	51	27	53	28	39	138
	High	33	5	15	100	13	13	64	18	28
	Total	**12**	**21**	**170**	**51**	**58**	**114**	**28**	**79**	**284**
Mortality	Low	2	2	70	3	1	48	3	3	118
	Moderate	4	3	85	11	6	53	7	9	138
	High	20	3	15	62	8	13	39	11	28
	Total	**5**	**8**	**170**	**13**	**15**	**114**	**8**	**23**	**284**

The recommended method for ribavirin administration at our institution is a daily dose of 6g delivered at a concentration of 20 milligrams/milliliter for 18 hours daily (standard regimen) aerosolization by a small-particle aerosol generator unit (SPAG-2) via a face mask inside a scavenging tent for 5 to 10 days. A modified regimen with dose of 60 milligrams/milliliter (or 2 grams) given over 3 hours period every 8 hours for 5 to 10 days has also been used. A recent randomized trial completed at our institution showed that the probability of progression to pneumonia while on the modified regimen is less than the rate of pneumonia on the standard regimen (probability of 0.889; unpublished data; *Oral presentation at the 49th Interscience*

Conference on Antimicrobial Agents and Chemotherapy, 2009). Although this dosage schedule has been used, either one can be inconvenient for patients, and makes routine patient care more difficult.

Alternatively, many patients have been treated with oral ribavirin with particularly encouraging results (*Figure above*). This drug has been approved by the Food and Drug Administration (FDA) in combination with interferon alfa-2b for the treatment of Hepatitis C and it is commercially available in generic form. Although oral ribavirin was adopted as part of the armamentarium for therapy of RSV infection in immunocompromised patients in many centers in the US and Europe, further trials are necessary to demonstrate its efficacy and safety. A recent study done in Basel, Switzerland reported a total of 19 HSCT patients treated with oral ribavirin, of these 11 patients had URI, while 8 had LRI. A decrease in RSV viral loads of 2 $\log_{10}$ copies/mL within 7 days after treatment initiation was seen in 11 patients and none progressed to LRI or died. Another 6 patients reported a mean decrease in RSV load of 2 $\log_{10}$ copies/mL within 14 days of diagnosis, LRI occurred in 2 patients and 1 died. The authors also found that the rate of disease progression and mortality rate to be comparable to studies evaluating aerosolized ribavirin *(Khanna et al, CID 2008:46 407).* They further concluded that prospective, multicenter studies are needed to identify effective antiviral treatment for RSV infection among immunocompromised patient groups, where systemic ribavirin could be an option.

A systematic evaluation of oral ribavirin as an alternative therapeutic regimen for RSV infection needs to be explored. A double blind randomized comparative trial is not feasible due to the relatively small number of HSCT patients with this infection every year on the national level. We would like to conduct this phase II randomized trial to evaluate the efficacy and safety of oral ribavirin for prevention of RSV LRI when compared to aerosolized regimen ("modified regimen"). If oral use of ribavirin is as effective as the aerosolized regimen, this would be immensely beneficial to the patients as it would make the administration of ribavirin easier and more convenient and may prevent hospitalization in a good proportion of patients with tremendous impact on cost savings. Furthermore, it may increase its use and also encourage its early use in the therapy of RSV URI, which may have a favorable impact on overall morbidity and mortality in our immunocompromised patients.

3.0 Background Drug Information and Dosage

Ribavirin in its oral or aerosolized form is commercially available. Drug information is provided in the attached package insert (Appendix D).

Oral ribavirin has been used at varying doses for treatment of RSV based on bioavailability and a large volume of distribution. A loading dose of 10 mg/kg orally has been used as bioavailability can range from 30-74% due to first pass metabolism (Khanna N, et al. *Clin Infect Dis*. 2008;46(3):402-412). Due to the short duration of therapy, 5 to 10 days, this will help to increase ribavirin concentration more quickly. After the loading dose, a total daily dose of 20 mg/kg/day divided into three doses given with food (max dose of 1800 mg per day). This dosing strategy falls within a previous efficacy and toxicity trial where doses between 15-45 mg/kg/day were employed (*Chakrabarti S, et al. Bone Marrow Transplant*. *2001;28(8):759-763*). Efficacy and decreased toxicity were found in the lower dose cohorts 15-30 mg/kg/day.

4.0 Patient Eligibility

Inclusion criteria:

4.1 HSCT patients with either moderate risk or high risk immunodeficiency based on immunodeficiency scoring system would be eligible for entry on study if a nasopharyngeal wash or throat swab specimen is positive by rapid RSV antigen testing and/or on culture within 72 hours (therapeutic arms). (Please see Appendix E for definitions and Immunodeficiency Scoring)

4.2 HSCT patients with low risk immunodeficiency based on immunodeficiency scoring system would be eligible for entry on study if a nasopharyngeal wash or throat swab specimen is positive by rapid RSV antigen testing and/or on culture within 72 hours but will not be randomized to therapeutic arms and will be followed as per standard of care (observational arm).

4.3 Patients must be at least 18 years of age and able to swallow pills.

4.4 Patients with RSV infection limited to the URT as documented by negative Chest radiographic findings within the last 48 hours of enrollement and pulse oxygenation of more than 90 mm of Hg on room air.

4.5 Women of child bearing potential with a negative urine or blood pregnancy test within a month of enrollment (only for patients who are going to be randomised to either therapeutic arms).

4.6 Patients with Hemoglobin levels more than or equal to 8 g/dl would be eligible for the study even if they are currently receiving blood products.

4.7 Patients may receive up to 2 doses of aerosolized ribavirin on the modified regimen before enrollment into the study.

Exclusion criteria:

4.1 Patients with previous history of hypersensitivity to ribavirin or its components

4.2 Women who are pregnant or plan a pregnancy within 8 weeks after completion of treatment (only for patients who are going to be randomised to either therapeutic arms).

4.3 Patients with evidence of RSV LRI as documented by a positive rapid RSV antigen testing and/or culture on nasal washes **AND** new or progressive infiltrates on chest radiographic studies suggestive of viral etiology and/or pulse oxygen less than 90 mm of Hg on room air.

4.4 Patients with positive RSV by rapid antigen testing and/or culture in bronchoalveolar lavage regardless of the chest radiographic findings at study entry.

4.5 Patients who are considered to be moderately or severely anemic as per the NCI classification will not be included in the study, i.e patients with hemoglobin level less than 8 g/dl.

4.6 Patients with Total Bilirubin, Aspartate Aminotransferase (AST) and/or Alanine Aminotransferase (ALT) three times the upper limit of normal.

4.7 Male partners of women who are pregnant (only for patients who are going to be randomised to either therapeutic arms).

4.8 Patients with known history of autoimmune hepatitis, Hepatitic C or those with hemoglobinopathies (eg, thalassemia major, sickle cell anemia).

4.9 Patients with creatinine clearance less than or equal to 50 ml/min.

5.0 Patients taking didanozine, azthioprine, or nucleoside reverese transciptase inhibitors.

Patients who will be enrolled on the observational arm have to meet inclusion criteria #4.2, 4.3, and 4.4 and exclusion criteria #4.3 and 4.4 only as these patients will not receive theray for RSV.

5.0 Treatment Plan

This is an open label randomised trial. All eligible patients will be randomized to receive ribavirin therapy either at the modified schedule of 60 mg/ml of the drug for a 3-hour period 3 times/day for at least 5 days by aerosolization via a SPAG-2 generator via a face mask **OR** patients will receive a one time loading dose of 10 mg/kg oral dose then 20 mg/kg orally (rounded to the nearest 200 mg dose) divided into three doses per day at a maximum of total dose of 1800 mg/day (therapeutic arms). The duration of either regimen is recommended to be up to 10 days but could be extended for more than 10 days at the discretion of the treating physician.

In addition, patients will receive inhalational bronchodilator therapy consistent of Xopenex 0.63 mg HHN every 6-8 hours as needed and as per standard of care. Patients may receive albuterol (2.5 mg per 3ml for adults) nebulization, if Xopenex is not tolerated. Patients will not be given IVIG or palivizumab for treatment of the RSV URI. Patients who develop evidence of LRI at any time will be considered reaching the primary endpoint and will be managed at the discretion of the treating physician as per standard of care (for example, patients can be treated by the standard or the modified aerosolized regimen with or without IVIG or palivizumab).

Patients with mild immundeficiency who are at low risk (scoring of 0-2 on ISS) for progression and when treatment is not indicated for RSV URI as per standard of care (observational arm) will be followed prospectively once a week up to 4 weeks from the diagnosis of RSV.

For schedule of events tables see PDOL appendix I.

6.0 Pretreatment evaluation

6.1 Patients will be identified based on eligibility criteria. After a patient is identified and expresses interest, the study will be explained by the study team and the informed consent form will be given to the patient to be signed.

6.2 All patients should have an initial nasopharyngeal wash positive for RSV by rapid testing and/or culture at onset of therapy unless a positive result was obtained from a specimen during the preceding 72 hours.

6.3 Routine blood tests will be obtained as per the standard of care within 48 hours of study entry as follows:

A. Hemoglobin, Hematocrit, WBC with differential if available, platelets count, pregnancy test from urine or blood for women of child-bearing potential.

B. Chemistry profile – BUN, Creatinine, Total bilirubin, Aspartate Aminotransferase (AST) and/or Alanine Aminotransferase (ALT), and alkaline phosphatase.

C. Nasal washes and blood at the time of enrollement will be taken and saved for testing for RSV viral loads and titers and neutralizing antibodies in serum at a later date (see section 7.1).

6.4 An initial history and physical examination.

6.5 A chest radiographic study (i.e. chest radiographs and/or CT scan of chest) will be obtained if not done within preceding 48 hours as per standard of care.

7.0 Evaluation During Study

7.1 Nasal washes for the therapeutic arm will be repeated on day 3 ±1 day, day 7 (± 1 days), day 14 (± 1 days), and by day 14 ± 1 days after end of therapy; and will be stored at 6-8 degrees Celsius until it can be taken to Dr. Piedra's laboratory for analysis. Blood specimens for the therapeutic arm will be drawn at enrollment and 14 +/- 1 days after end of therapy. These specimens will be shipped for batch analysis to Dr. Pedro Piedra laboratory at Baylor College of Medicine (One Baylor Plaza, Room 248E, Houston, Texas) for viral loads, titers and for neutralizing antibodies testing (Please see references 7-9 for methods). For patients on the observational arm, nasal washes for RSV viral loads will be done once a week for 4 weeks and blood specimens will be taken at enrollment and the 4th week on study for neutralizing antibodies testing and for RSV viral load. Leftover of blood and nasal washes will be saved at Dr Piedra's laboratory for future testing.

7.2 Routine blood tests as in 6.3 will be repeated at least once weekly until study is completed as part of the standard of care for patients who are on the therapeutic arms. Patients on observational arm will have routine blood tests done at enrollment and the 4th week on study.

7.3 Patients will be monitored for signs and symptoms of URI and LRI (Please see Appendix G and H for Clinical Assessment Tool). Patients who are hospitalized will be seen 2 times a week from the time of enrollment until discontinuation of ribavirin therapy. Patients who are not hospitalized will be monitored twice a week until the discontinuation of therapy or once a week for 4 weeks for patients on the observational arm. Any possible evidence of pulmonary infection should be confirmed by a repeat chest radiographic study and/or oxygen saturation level. All patients on the therapeutic arms will have a final visit 14 days $\pm$ 1 days after end of therapy.

7.4 Follow-up after end of therapy or discontinuation of therapy: Patients will be seen 14 days $\pm$ 1 days after discontinuation of therapy for the final determination of response, unless there is progression to pneumonia. In the latter scenario or if study drug is discontinued for Serious Adverse Events (SAEs), patients will be followed for up to 14 days from the time of occurance of the event or until resolution of the SAE whichever occurs last or up to 30 days from the last dose of the study drug.

7.5 Physical Exams for the therapeutic arm will be done at day 3 ±1 day, day 7 (± 1 days), day 14 ($\pm$ 1 days), and then 14 days ($\pm$ 1 days) after end of therapy. Concomitant medications that are used to treat LRI will be recorded day (3 ±1 day), day 7 (± 1 days), and then at 14 days ($\pm$ 1 days) after end of therapy. Physical exams for observational arm will be done once a week for 4 weeks.

7.6 As standard of care, patients will have pulmonary function tests scheduled bewteen 6-10 weeks after completing therapy for RSV.

8.0 Criteria for Response

The principal investigator or his delegates will make the initial or preliminary determination of response at 14 $\pm$ 1 days after end of therapy. Patients will be considered as a success if there are no signs (clinical and/or radiologic) or symptoms of progression to pneumonia at the end of study, that is 14 $\pm$ 1 days after discontinuation of therapy or at week 4 of follow-up for patients on the observational arm. At the end of each winter season and without knowledge of the determination of response of the PI or delegates, an independent internal panel (1 expert in HSCT and 1 in Infectious Diseases to be determined) will review each case and determine failure (pneumonia) or success (no evidence of pneumonia) rate on each arm of the study. The panel will have the final determination of response.

9.0 Criteria for Removal from the Study

9.1 Patients will be considered to have failed therapy if they develop evidence of pulmonary infection secondary to RSV (documented by chest radiographic study and/or Oxygen saturation level less than 90 mm Hg on room air). Therapy could be stopped or could be changed to either the standard or the modified regimen of aerosolized ribavirin if the patient is on the oral schedule and changed to the standard or continued on the modified regimen of aerosolized ribavirin if the patient is on the aerosolized regimen; all at the discretion of the primary care service. IVIG 500mg/kg every other day for 4 doses or Synagis (palivizumab) 15mg/kg as a single dose can be used in combination with aerosolized ribavirin.

9.2 Adverse events to ribavirin requiring discontinuation of therapy are: deterioration of respiratory function, abnormal liver function tests (>5 x the upper normal limits), frequent bronchospasms not responding to bronchodilators, hypotension and cardiac arrest.

9.3 Anemia may occur due to ribavirin and therapy would be discontinued if there is evidence of severe hemolysis and/or the patient develops severe anemia as per the NCI classification i.e. Hemoglobin below 8 g/dl for more than 48 hours and does not respond to blood and/or blood products transfusion.

10.0 Cost Analysis

All patients who receive aerosolized ribavirin have to be hospitalized for the entire duration of the therapy, or even more depending on the patient condition. Patients who will be treated with oral ribavirin may be hospitalized at the discretion of the primary service. An average per day cost of keeping patients in hospital for ribavirin administration will be obtained from the financial department and institutional records and will be used to calculate the total cost of treating patients with ribavirin using the following formula:

Total cost of treating the patients with ribavirin (aerosolized or oral) = cost of keeping the patient in-hospital per day for RSV × total number of days the patient is kept in hospital + cost of the drug (aerosolized and oral ribavirin) and its administration (for aerosolized ribavirin).

This will be compared to the total cost of administering oral ribavirin on an outpatient basis by adding the total cost of the drug and the follow up visits. In either arm of the study, if a patient progresses to pneumonia, the total cost of treating the patient with aerosolized ribavirin (if applicable) will be calculated using the above formula and added to the total cost.

11.0 Statistical Considerations

This is a randomized phase II non-inferiority screening trial following the principles described by Rubinstein et al. (2005). Our primary outcome for this trial is progression to lower respiratory tract infection (i.e., pneumonia) by day 14 after the completion of therapy. Patients who are found to have pneumonia by day 14 after completion of therapy will be considered treatment failures. Patients who have not developed pneumonia by day 14 after completion of therapy will be considered treatment successes.

Randomization

Patients will be randomized to either aerosolized ribavirin (standard therapy) or oral ribavirin (experimental therapy) using the CORe patient registration system. Block randomization will be utilized and stratified by risk of progression (moderate versus high).

Sample Size

We expect that 20% of patients randomized to aerosolized ribavirin will be considered treatment failures, and we expect that 15% of patients randomized to oral ribavirin will be considered treatment failures. With a non-inferiority margin of 10%, a sample size of 38 patients per

treatment arm will yield 80% power to reject the following null hypothesis with a 1-sided significance level of 0.20:

$$H0: \pi_{oral} - \pi_{aerosol} \geq 0.10$$

$$H1: \pi_{oral} - \pi_{aerosol} < 0.10$$

where $\pi_{aerosol}$ is the treatment failure rate for aerosolized ribavirin and π_{oral} is the treatment failure rate for oral ribavirin. We expect to enroll these patients over 2 winter seasons.

This sample size calculation includes an interim analysis for futility using the methods of Lan and DeMets (1983) with an O'Brien-Fleming (1979) stopping boundary. The futility analysis will be conducted once 38 patients have been evaluated for treatment failure. We expect the timing of this futility analysis to be after the first winter season of the study. The nominal significance level for this futility analysis is 0.6040, and the nominal significance level at the end of the study is 0.2116.

This sample size calculation was performed using East 5.2 (Copyright © 2008, Cytel Inc., Cambridge, MA).

For the observational arm, up to 20 patients will be enrolled for a total of 96 patients for the whole trial.

Analysis

We will use descriptive statistics to summarize the demographic and clinical characteristics of patients in each treatment arm and the observational arm.

We will use the Cochran-Mantel-Haenszel test stratified by risk groupto test the null hypothesis stated above. We will also estimate the treatment failure rates with exact 95% binomial confidence intervals for each treatment arm.

We will tabulate adverse events for each treatment arm by severity and relationship to study therapy.

We will use descriptive statistics to summarize the costs associated with each treatment arm. Costs for each patient will be calculated as described in section 10.0 above.

We will use descriptive statistics to summarize the RSV viral loads and neutralizing antibodies for each treatment arm and the observational arm.

12.0 Reporting Requirements & Drug Accountability

A case report form will be required for each patient entered on study (please see appendix G and H). An interim safety analysis of the data focusing on SAEs will be done after each winter season.

We will maintain the study drug records of aerosolized ribavirin including documentation of the amount received and duration as per respiratory therapy protocol. For oral ribavirin, subjects should bring their medication bottles back at each visit even if they are empty so site personnel can assess study drug compliance.

13.0 References:

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