Use of oral ribavirin in place of inhaled formulation for the treatment of RSV

Over the past few years, the cost of inhaled ribavirin has increased dramatically to $23.5K per dose. In addition to the cost of the medication, it also poses many logistical problems given then need for a small particle aerosol generator and the health risks related to exposure to healthcare workers and the surrounding environment. Additionally, inhaled ribavirin can lead to many adverse effects for the patient including bronchoconstriction and/or respiratory distress.

Several studies have been published looking at the safety and efficacy of using oral ribavirin for the treatment of RSV in immunocompromised patients who are able to take oral medications.

Literature Review

Fourth European Conference on Infections in Leukaemia: Guidelines for Diagnosis and Treatment of HSV, PIV, hMPV, Rhinovirus, and Coronavirus

- AlloSCT patients with RSB URTI and risk factors for progression to LRTI should be treated with aerosolized or systemic ribavirin (BII)
- For treatment of RSV, systemic ribavirin can be administered orally (BIII)
- Patients being treated with systemic ribavirin should be monitored for adverse events including anemia, abnormal liver function, and declining renal function (BIII)

Marcelin et. al. (2014) – Oral ribavirin therapy for respiratory syncytial virus infections in moderately to severely immunocompromised patients

- n = 34 (25-hematologic malignancy, 3-lung transplant, 11-receipt of cytotoxic chemotherapy)
- Retrospective review of moderately to severely immunosuppressed patients with PCR documented RSV
- Adverse effects were noted in 2 patients (1 hemolytic anemia and lactic acidosis, 1 altered mental status)
- No patients died from RSV infection (3 died from underlying conditions, all others clinically improved)
- Dosing used: (<75kg – 600mg BID; ≥75kg – 800mg BID)

Lehners et. al. (2013) – Risk factors and containment of respiratory syncytial virus outbreak in a hematology and transplant unit

- n = 56 (53 RSA-A, 3 RSV-B)
- Multivariate analysis of nosocomial RSV infections in a hematology and SCT unit
- While ribavirin therapy was associated with prolonged viral shedding [OR 8.94] it was also associated with lower fatal outcomes [OR 0.14]
- Utilized weight adapted dosing [total daily dose administered in two divided doses]
    - <65 kg – 800 mg
    - 65-80 kg – 1000 mg
    - >80 kg – 1200 mg

Casey et. al. (2013) – Oral ribavirin for treatment of respiratory syncytial virus and parainfluenza 3 virus infections post allogeneic haematopoietic stem cell transplantation

- n = 15 (13-RSV, 2-PIV3)
- Retrospective review of all patients treated with oral ribavirin for RSV and PIV3 since Jan 2009 with a positive nasopharyngeal swab
- At the time of diagnosis, 7 patients had URTI and 8 patients had LRTI
    - Ribavirin at 10mg/kg/day dosing did not appear to prevent the progression from URTI to LRTI but response was seen in 6/7 cases after dose escalation
    - Response from therapy was noted in 6/8 cases of LRTI
    - Recommended that 20mg/kg/day dosing should be used as initiation
    - Doses up to 55mg/kg/day were well tolerated
- No therapy required cessation due side effects or intolerance

Chakrabarti et. al. (2001) – Pre-emptive oral ribavirin therapy of paramyxovirus infections after haematopoietic stem cell transplantation

- n = 10 (5-RSV, 5-PIV3)
- All 5 episodes of RSV improved with oral ribavirin while only 2 of the PIV cases had a similar response
- Very well tolerated at a dose up to 45mg/kg/day
    - 2 patients noted moderate nausea at a dose of 45mg/kg/day and 60mg/kg/day respectively
    - Reversible anemia was seen in all patients with treatment durations longer than 2 weeks but 2 cases were very early after transplantation

Li et. al. (2012) - Oral versus inhaled ribavirin therapy for respiratory syncytial virus infection after lung transplantation

- n = 21 (6-oral, 15-inhaled)
- A retrospective study looking at 6-month outcomes in lung transplant patients with RSV.
    - Included single lung, double lung, and lung-heart
- No statistically significant difference was noted between patients receiving oral or inhaled ribavirin

Pelaez et. al. (2008) – Efficacy of oral ribavirin in lung transplant patients with respiratory syncytial virus lower respiratory tract infections

- n = 5
- Prospective study followed lung transplant patients up to 565 days after RSV diagnosis via positive nasopharyngeal swab (NPS) with confirmatory bronchoscopy with BAL
- No post-RSV bronchiolitis obliterans syndrome (BOS) was documented up to 1.5 years after treatment
- Mean time to negative repeat NPS was 7-10 days

Sparrelid et. al. (1997) – Ribavirin therapy in bone marrow transplant recipients with viral respiratory tract infections

- n = 13 (12-alloSCT, 1-autoSCT)
- Retrospective study looking at 13 patients with proven viral respiratory tract infections (Influenza B, RSV, and Parainfluenza (2/3))
- No serious adverse effects were noted with systemic ribavirin
    - Two patients had reversible signs of hemolysis with only one requiring more erythrocyte transfusions that expected after BMT

Burrows et. al. (2015) – Oral ribavirin for respiratory syncytial virus infection after lung transplantation: Efficacy and cost-efficiency

- n = 52
- Retrospective study looking at 52 lung transplant patients with 56 episodes of symptomatic RSV infection as diagnosed via positive nasopharyngeal swab
- The only adverse effect noted for the oral ribavirin was worsening of pre-existing anemia (23/33 cases) and development of new anemia (5/21 cases) which did not require cessation of treatment. One patient did require a blood transfusion.
- No patients died during the treatment phase

Other institutional use of oral ribavirin

Oral ribavirin only

- Moffitt
- Vanderbilt
- NY Presbyterian Hospital
- Yale-New Haven Hospital
- Virginia Commonwealth

Oral ribavirin preferred with inhaled criteria

- MD Anderson
- University of Virginia
- Cleveland Clinic
- Mayo Clinic

Recommendation

- Empiric use of ribavirin is not recommended; only patients who meet all three of the criteria listed below should be considered for ribavirin therapy:
    - Symptoms of upper or lower respiratory tract infection (as described above)
    - Positive molecular test for RSV
    - High risk for RSV disease progression (meets at least one of the criteria listed in Table 1)

Table 1: High Risk Patients

- **Allogeneic or autologous hematopoietic stem cell transplant within the previous 30 days**
- **Allogeneic or autologous HSCT AND absolute lymphocyte count less than 300 cells/mm^3**
- **Allogeneic HSCT with active graft versus host disease (GVHD) on immunosuppressants ***
- **Leukemia or HSCT patients with absolute neutrophil count less than 500 cells/mm^3**

**corticosteroids included*

- All cases where it is decided that treatment is required, should utilize oral ribavirin.
    - Dosing regimen:
        - <75 kg – 600mg q12h
        - ≥75 kg – 800mg q12h
    - Should be taken with food to maximize bioavailability
- Reserve the use of inhaled ribavirin for the most severe cases in patients that are unable to take oral formulations as well.
- Restrictions:
    - Inhaled ribavirin: restricted to ID order only
    - Oral ribavirin: ID consult within 24 hours of initiation