REVIEW

Ribavirin in the treatment of severe acute respiratory syndrome (SARS)

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INTRODUCTION

Severe acute respiratory syndrome (SARS) has recently been recognised as a newly emerging infectious disease with significant morbidity and mortality. It has been suggested that (early) antiviral treatment with ribavirin and high-dose glucocorticosteroids may be beneficial. We have summarised the available data on ribavirin to facilitate decision-making when confronted with (suspected) SARS.

RIBAVIRIN: MECHANISM OF ACTION, CLINICAL EXPERIENCE (OTHER THAN WITH SARS) AND TOXICITY

Ribavirin is a purine nucleoside analogue that was discovered by ICN Pharmaceuticals in 1970. It prevents the replication of a large number of RNA and DNA viruses *in vitro*, including myxo-, paramyxo-, arena-, bunya-, herpes-, adeno-, pox- and retroviruses. Although the antiviral mechanism of action is not fully defined, ribavirin competitively inhibits the enzyme inosine monophosphate dehydrogenase, which is required for the synthesis of guanosine, and thereby interferes with nucleic acid synthesis resulting in 'lethal mutagenesis' of the RNA genome.[1-3]
The active metabolite of the drug, ribavirin triphosphate, concentrates in erythrocytes and erythrocyte levels gradually decrease with an apparent $T_{1/2}$ of 40 days. Ribavirin is primarily eliminated by renal excretion and dose reduction is required in patients with renal insufficiency. Ribavirin can be given orally (with a bioavailability of 40 to 50%), intravenously or as an aerosol.[4]
Aerolised ribavirin is approved in the Netherlands and the United States for treatment of respiratory syncytial virus (RSV) bronchiolitis and pneumonia in hospitalised children, but its use is limited by concerns regarding efficacy, risk of occupational exposure and cost. Ribavirin has a variable effect on shortening the duration of virus shedding and improves certain clinical measures relative to that of placebo in infants hospitalised with RSV pneumonia, including high-risk infants with bronchopulmonary dysplasia or congenital heart disease.[5] In infants receiving mechanical ventilation for RSV-related respiratory failure, no consistent benefits on duration of ventilatory support or mortality have been documented.[6,7] In a Cochrane meta-analysis a trend was found towards a reduction in the length of stay and days of ventilation dependence.[8] Despite these discouraging data, the American Academy of Paediatrics still advises that ribavirin is considered in severe cases of bronchiolitis, as well as in ventilated infants and infants with underlying diseases.[9]
In patients with Lassa fever, intravenous or oral ribavirin significantly reduces mortality, especially when therapy is initiated during the first six days of illness.[10] In adults with chronic hepatitis C, long-term oral ribavirin reversibly reduces serum transaminase elevations, hepatic inflammation on biopsy and fatigue without significantly affecting serum HCV-RNA concentrations.[11,12] This suggests the existence of immunomodulatory properties that may in part account for the antiviral activities *in vivo*.[3]
Combination therapy with interferon-alpha-2b significantly increases the frequency of biochemical and virological response during and after cessation of therapy.[13-15]
Systemic ribavirin causes dose-related anaemia due to extravascular haemolysis and, at higher doses, suppression of bone marrow release of erythroid elements. Reversible

increases in serum bilirubin, iron and uric acid can occur, and hypocalcaemia, hypomagnesaemia, hyperammonaemia and pancreatitis have also been described. In HIV patients receiving other nucleoside analogues as part of highly active antiretroviral therapy, elevated concentrations of lactate and pyruvate have been reported. Bolus intravenous injections may cause rigors. Other side effects include pruritus, rash, nausea, depression and cough. Adverse haematological effects have not been associated with aerolised ribavirin, but this may cause mild conjunctivitis, rash, bronchospasm and reversible deterioration in pulmonary function.[1,2]

Ribavirin may affect the embryo because of its interference with DNA and RNA replication. Teratogenic effects have been found in rodent studies with relatively low doses (1-10 mg/kg), but the true risk for teratogenic effects in humans is unknown.[1,16]

RIBAVIRIN AND (SARS-ASSOCIATED) CORONAVIRUS

Animal studies and *in vitro* susceptibility testing

Ribavirin is effective for the treatment of mouse coronavirus hepatitis. Although its inhibitory activity against the mouse coronavirus is weak, it can decrease the release of proinflammatory cytokines from the macrophages of mice and also switches the Th-2 response to a Th-1 response.[17] Ribavirin may therefore serve as an immunomodulator, irrespective of its antiviral role.

In vitro susceptibility testing of ribavirin against the SARS-related coronavirus has been carried out at two institutions. Both Health Canada's National Microbiology Laboratory and the US Army Medical Research Institute of Infectious Diseases report that these tests have failed to demonstrate direct antiviral activity (inhibition of replication or cell to cell spread) of ribavirin against two isolates of the SARS-related coronavirus, at nontoxic concentrations that were effective for Lassa fever virus and other haemorrhagic fever viruses.[18,19]

Clinical reports

Reports of the use of ribavirin in cases with (suspected) SARS are limited to retrospective case series with conflicting results and numerous methodological issues.[20-26]

In a first report of 50 patients with SARS in Hong Kong, of which 49 received ribavirin, Peiris *et al.* state that a delay in starting ribavirin and corticosteroids was a risk factor for severe complicated disease.[20] In a following publication, the same authors report that they followed 75 SARS patients for three weeks who were treated with intravenous amoxicillin-clavulanate and oral azitromycin.[21] As soon as the diagnosis of SARS was established, treatment was started with 8 mg/kg intravenous ribavirin every 8 hours for 14 days and a tailing regimen of hydrocortisone (starting 200 mg iv every 8 hours) over 10 days, followed by oral prednisolone for 11 days. If patients worsened, pulses of methylprednisolone were given. In addition, patients with chronic hepatitis B were given 100 mg of oral lamivudine daily while taking corticosteroids. Fever and pneumonia initially improved but 85% of the patients developed recurrent fever after a mean of 9 days. Nine patients (12%) developed spontaneous pneumomediastinum and 20% of the patients developed acute respiratory distress syndrome (ARDS) in week 3. During the study period five patients died: two due to acute myocardial infarction, one of sepsis and two of sepsis and ARDS. Age and chronic hepatitis B infection were independent risk factors for progression to ARDS. The viral load, measured by quantitative RT-PCR, peaked at day 10. The authors concluded that the clinical progression with the inverted V viral-load profile suggested that the symptoms were initially related to the effect of viral replication and cytolysis but that the worsening in week 2 was probably related to immunopathological damage as a result of an overexuberant host-response. Because all patients in this series received ribavirin, the effect of this regimen could not be compared with standard treatment without antivirals.

In another series, 31 patients with probable SARS in Hong Kong were treated according to a treatment protocol consisting of antibacterials as first-line therapy.[22] Ribavirin and methylprednisolone were added in case of severe or prolonged illness. Of these 31 patients, one recovered on antibacterial treatment alone, 17 showed a rapid response after the addition of ribavirin and the standard corticosteroid regimen, and 13 achieved improvement only after higher dosages of corticosteroids were given. High-dose corticosteroids did not give rise to severe complications, although prophylactic antibiotics were given to patients with fever and elevated white cell counts. No side effects of ribavirin were encountered, especially no haemolysis or arrhythmia. No patients required mechanical ventilation and there was no mortality in this group.

More data that characterise the major outbreak of SARS in Hong Kong have been supplied by two other reports: first, ten cases that were treated empirically with ribavirin, eight of which were thought to have benefited from it, and, second, 138 cases with suspected SARS that received a combination therapy of ribavirin and corticosteroids if certain criteria were met.[23,24] Again, as these studies are case series, they do not address the question whether ribavirin is useful or not.

In a description of ten cases in Canada, two of three patients who did not receive ribavirin died, whereas only one of seven patients who received ribavirin died.[25]

In contrast to these reports, a larger retrospective case series involving 144 patients in Canada with suspected or probable SARS found that poor outcome was more common in those treated with ribavirin (RR 1.9, 95% CI: 0.45-8.0, p=0.36, univariate analysis).[26] This was not statistically significant. The majority of patients in this case series (126/144, 88%) received ribavirin, of them 91% received it within the first 48 hours of hospitalisation. As it is not clear why the other patients did not receive ribavirin, this raises the suspicion of selection bias. Forty percent of patients received corticosteroids, in dosages varying between approximately 20 to 50 mg hydrocortisone for ten days. One patient received pulse corticosteroid therapy. In this case series significant toxicity of ribavirin is described: 49% of patients had a decrease in haemoglobin level of at least 2g/dl, 40% had an elevation of transaminases of at least 1.5 fold rise and 14% had bradycardia. These toxicities led to the premature discontinuation of ribavirin in 18% of patients.

ROLE OF CORTICOSTEROIDS IN THE TREATMENT OF SARS

Analogous to the treatment of severe RSV infection, corticosteroids have been advocated in the treatment of SARS. In a recent meta-analysis, a statistically significant improvement in clinical symptoms, length of stay, and duration of symptoms is suggested with the use of systemic corticosteroids for RSV bronchiolitis.[27] However, a reduction of less than half a day in the length of stay is of questionable clinical relevance. Since this meta-analysis, three additional studies have been published using systemic prednisolone or nebulised budesonide. Two of these studies did not show any beneficial effect at all.[28-30] It can be concluded that treatment with corticosteroids is not generally indicated for the treatment of RSV bronchiolitis, but that the most severely ill patients, treated with mechanical ventilation, might benefit from it.[9]

In SARS, pathological findings have shown diffuse alveolar damage. In addition, computed tomographic findings of the chest did reveal bilateral peripheral changes with ground-glass consolidation that were suggested to be similar to what is seen in bronchiolitis obliterans with organising pneumonia (BOOP), an inflammatory reaction that usually responds to corticosteroids.[24,31] In addition, avoidance of a 'cytokine storm' has been used as an argument in favour of corticosteroids.[24,32] In contrast, Oba *et al.* believe that the pathogenesis of SARS is diffuse alveolar damage with ARDS.[33] As the use of corticosteroids in ARDS is controversial[34-36] and effective antiviral agents for SARS are lacking, they believe that systemic corticosteroids should not be used.

In a recent 'perspective' in the *New England Journal of Medicine* the use of corticosteroids 'in this time of uncertainty' is only advised for 'the more ill patients' and it seems to us that this is a rational advice given today's circumstances.[37]

CONCLUSION

In vitro tests have failed to demonstrate a direct antiviral activity of ribavirin against two isolates of the SARS-related coronavirus. There are no solid clinical data to show that ribavirin is effective for the treatment of patients with SARS. Reports on side effects of ribavirin vary from no side effects to important toxicities which led to the discontinuation of ribavirin therapy in many cases. Taking this into account, Health Canada has recently stated that it will no longer provide access to ribavirin for the treatment of SARS. Similarly, we feel that the presently available data do not support the use of ribavirin in the treatment of patients with SARS. Although highly controversial, treatment with corticosteroids may be considered in severely ill patients, based upon data from RSV bronchiolitis, BOOP and preliminary reports on SARS. Whether or not corticosteroids are indeed beneficial in the treatment of SARS remains to be established.

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