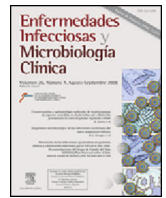




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Review article

Use of ribavirin in viruses other than hepatitis C. A review of the evidence[☆]

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ABSTRACT

Ribavirin is a molecule with antiviral activity against different viruses. In clinical practice, it has made its niche almost exclusively for the treatment of the hepatitis C virus. However, there are other diseases in which it could be of benefit and it has the advantage of being suitable for oral, intravenous and inhaled administration. We conducted a review of the indications of the main drug agencies (Spanish, European and American) and other possible indications, mainly haemorrhagic fevers and coronavirus.

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Uso de ribavirina en virus distintos de la hepatitis C. Una revisión de la evidencia

RESUMEN

La ribavirina es una molécula con actividad antiviral sobre diferentes virus. Ha encontrado su hueco en la práctica clínica de forma casi exclusiva para el tratamiento del virus de la hepatitis C, pero existen otras enfermedades que podrían beneficiarse de su empleo. Su disponibilidad para administración por vía oral, por vía intravenosa e inhalada es una característica beneficiosa. En este trabajo se realiza una revisión de las indicaciones en las principales agencias del medicamento (española, europea y americana), así como de otras posibles indicaciones, principalmente sobre fiebres hemorrágicas y coronavirus.

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Palabras clave:

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1- β -D-Ribofuranosil-1,2,4-triazol-3-carboxamida

Introduction

Ribavirin is a molecule which was synthesised for the first time in 1972. It is also known by the name of Virazole or 1- β -D-ribofuranosyl-1,2,4-triazole-3-carboxamide. It is a pyrimidine nucleoside which was designed as an in vitro broad-spectrum agent, and the first description was published in the journal *Science*.¹ The action on both DNA (herpes virus 1 and 2, murine cytomegalovirus, vaccine virus, adenovirus type 3) and RNA viruses

(rabies-related viruses, virus responsible for myxoma, parainfluenza virus types 1 and 3, influenza A and B, rhinovirus 1A, 13 and 56, Coxsackie B, poliovirus type 2, vesicular stomatitis virus and Semliki Forest virus) were detailed in this work. Subsequently, its activity on other viral diseases was determined, and it found its place in clinical practice almost exclusively for the treatment of hepatitis C virus (HCV).

In this paper, a review of the references in the PubMed database (up to 31 December 2017) was carried out, crossing (in English) the keyword “ribavirin” with those corresponding to the following viruses or diseases: adenovirus, hantavirus, syncytial respiratory virus, Lassa fever, Crimean-Congo haemorrhagic fever, Argentinian haemorrhagic fever and coronavirus. Articles written in English and in Spanish were reviewed, preferentially selecting the meta-analyses for each disease; in the event that they did not exist, phase I, II, III and IV clinical trials were reviewed. Finally, if they were not found in the previous searches, a review of the cases or case series

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published was performed. In some cases, references to other works were obtained from the articles reviewed.

Mechanism of action

Different mechanisms of action have been proposed for this molecule, and the most likely scenario is that it works in different ways in different viruses.² The first mechanism that has been suggested is the interference in the *de novo* synthesis of the guanosine derivatives (in particular guanosine triphosphate [GTP]). Inosine monophosphate dehydrogenase catalyses the formation of xanthine monophosphate from inosine monophosphate to subsequently continue the synthesis pathway of the guanosine derivatives. Ribavirin monophosphate is capable of competitively and potentially inhibiting this enzyme, reducing the reserves of these nucleotides (or nucleosides) to half in the treated cells. Antiviral activity parallel to the depletion of GTP reserves has been demonstrated in studies with the yellow fever virus and paramyxovirus, such as the respiratory syncytial virus (RSV). Secondly, an immunomodulatory activity has been suggested, indicating that ribavirin may increase the activity of T lymphocytes, and, in particular, Th lymphocytes. This hypothesis was based on the observation that during the treatment with ribavirin in patients infected with HCV, it could reduce cytolysis without modifying the circulating viral load. Therefore, it would not have an exclusively antiviral effect. The observation that the *L*-enantiomer of ribavirin (levovirin) does not present direct antiviral activity, being capable of also producing an induction of the Th1 response in the murine model, supported this hypothesis. However, it has not been possible to recognise the immunomodulatory effect *in vivo*, and, even in mathematical models designed for this, it is concluded that the effect is based on direct antiviral activity. Another mechanism that has been proposed is that of direct inhibition of the polymerase. The main intracellular metabolite of ribavirin is ribavirin triphosphate (RTP). In this way, it could be a competitive inhibitor of other similar nitrogenous bases, such as adenosine triphosphate (ATP) or GTP. This effect has been observed in studies conducted with the influenza virus, reovirus and vesicular stomatitis virus. Some RNA viruses contain a structure with 7-methylguanosine, which is essential for the stability of RNA and which is synthesised in three different catalytic processes. In other viruses, the translation process is measured by a molecule known as eukaryotic translation initiation factor 4E (eIF4E). The ribavirin molecule could interact with the enzymes responsible for *capping* (RNA cap synthesis) or bind to eIF4E, preventing the start of translation. This mechanism could be responsible for the antiviral activity observed in some viruses (Lassa fever, SARS). Lastly, a mechanism of mutagenesis has been proposed. Given the structural similarity, the incorporation of ribavirin in the RNA chain would be possible and would produce mutant viruses during replication. However, this would not only alter the “original” chain, replacing GTP with RTP, but also the binding to the complementary bases cytidine and thymidine (or uracil) has the same efficacy. This is due to the spatial arrangement and the flexibility in the rotation of a carboxamide group. The mutagenic effect of ribavirin has been demonstrated in studies with poliovirus, hand-foot-and-mouth disease, West Nile virus and hantavirus.

Indications in the summary of product characteristics

As we have mentioned previously, the clinical use of ribavirin is almost exclusively limited to the treatment of HCV infection. However, when a review is performed of the indications in the main medicines agencies (Spanish Agency of Medicines and Medical Devices, European Medicines Agency and U.S. Food and Drug

Administration [FDA]), other less well-known approved indications can be found.

- The drug Virazole, in the form of vials for respiratory inhalation, can be found on the website of the Spanish Agency of Medicines and Medical Devices.³ There is no mention of the specific indication, stating that the drug is not currently marketed in Spain and that there are supply problems. It was used in aerosols in children with severe lower respiratory tract infection caused by RSV. Treatment consisted of nebulisation for 12–18 h for a period of three to seven days.
- On the European Medicines Agency's website,⁴ two applications of ribavirin which have been investigated, apart from the indication for HCV, are also found. These are for adenovirus infections and hantavirus infections. In both cases, it was decided to withdraw its consideration in these indications.
- Finally, the approval of Virazole for nebulisation is indicated on the FDA's website,⁵ although the conditions are not specified.

We will now review the clinical evidence of the effectiveness of ribavirin for treating infections caused by RSV, adenovirus and hantavirus.

Respiratory syncytial virus

There is a meta-analysis carried out by the Cochrane Database of Systematic Reviews⁶ in relation to the use of ribavirin in lower respiratory tract infections in children and adolescents, with two subsequent updates and one withdrawn in 2010. The latest review is therefore the one published in 2007. In this review, after analysing 12 clinical trials, the conclusion is reached that ribavirin is not effective at reducing mortality or in the development of respiratory deterioration; however, a reduction in the hospital stay and in the number of days of mechanical ventilation (approximately two days in both cases) is observed.

Another different aspect of the use of ribavirin in transplant recipients was the treatment of respiratory infections caused by RSV. Shah and Chemaly⁷ carried out a review of the literature regarding the works performed on adult transplant recipients with RSV infection and published between 1980 and 2010. They evaluated 26 studies, both prospective and retrospective (randomised and observational clinical trials), in which the main variable was mortality attributed to RSV or disease progression. The use of ribavirin in any form (aerosolised, oral or intravenous) appeared in these works. The overall conclusion is that the use of ribavirin (whether or not it was associated with immunoglobulins) reduced progression to disease of the lower respiratory tracts and reduced mortality. Inhaled ribavirin was useful, but it was especially more effective when associated with immunoglobulin, although its diffusion in the consolidated parenchyma could be reduced. The cost was the main drawback of this therapy (approximately \$50,000 per patient).

Adenovirus

Firstly, it must be pointed out that, when the published literature was reviewed (109 articles in PubMed), there were no meta-analyses or clinical trials. The scientific evidence is available from case series and isolated cases. There are seven published case series^{8–14} and 21 isolated cases,^{15–35} which accounts in total for published experience on less than 150 cases (Tables 1 and 2). As can be observed, there is heterogeneity both regarding the virus treated (serotypes) and in the characteristics of the patients (age, gender, risk factors) and in the syndromes produced (pneumonia, cystitis, digestive disease, focal/disseminated disease), disease progression time, combination with other drugs, etc. Therefore, a

Table 1
Notifications of isolated cases of disease due to adenovirus treated with ribavirin.

Age/gender	Risk factor	Disease	Serotype	Interval to RBV	Treatment	Clinical course	Follow-up	Reference
39/M	Immunocompetent	Pneumonia	NA	>2 days	Oral RBV	NA	Recovery	15
32/F	Kidney transplant recipient	Cystitis	NA	NA	IV RBV + IG	Blood (10 days) and urine (21) clearance	Recovery	16
26/M	Kidney transplant recipient	Cystitis	NA	7 days	RBV + IG	Clearance 20 days	Recovery	17
46/F	Kidney transplant recipient	Viraemia/viruria	NA	NA	Oral RBV	NA	Recovery	18
41/M	Haematopoietic transplant	Cystitis	11	94 days	Oral RBV (2 cycles)	Clearance 250 days	Recovery	19
46/F	Kidney and pancreas transplant	Cystitis/nephropathy	NA	12 days	IV RBV + IG	NA	Recovery	20
13 months/F	Liver transplant	Hepatitis	5	18 days	IV RBV	Clearance 30 days	Recovery	21
10 months/M	Liver transplant	Pneumonia	1	NA	IV RBV	NA	Recovery	22
44/M	Haematopoietic transplant	Disseminated disease	2	36 h	IV RBV	No clearance	Death	23
43/M	Haematopoietic transplant	Disseminated disease	NA	29 days	IV RBV	Clearance 17 days	Recovery	24
37/F	Haematopoietic transplant	Haemorrhagic cystitis	NA	25 days	IV RBV	No clearance	Death	25
38/M	AIDS	Pneumonia	NA	NS	IV + oral RBV	NA	Recovery	26
Neonate	NS	Disseminated infection	NA	48 h	IV RBV	NA	Recovery	27
67/F	Cryoglobulinaemia. Immunosuppressants	Pneumonitis	NA	>48 h	IV RBV + IG	11 days	Recovery	28
3/M	Haematopoietic transplant	GI infection	NA	34 days	IV RBV + IG	5 days	Recovery	29
27/M	Haematopoietic transplant	Haemorrhagic cystitis	11	69 days	IV RBV ± ganciclovir	22 days	Recovery	30
NA	Severe combined immunodeficiency	Pneumonia	NA	NA	IV RBV	NA	Recovery	31
9/M	Haematopoietic transplant	Haemorrhagic cystitis	NA	NA	IV RBV	5 days	Recovery	32
8/M	Haematopoietic transplant	Haemorrhagic cystitis	NA	NA	IV RBV	30 days	Recovery	33
NA	Haematopoietic transplant	Nephritis	11	NA	IV RBV	NA	Recovery	34
NA	Haematopoietic transplant	NA	NA	NA	IV RBV	NA	Failure	35

GI: gastrointestinal; IG: immunoglobulin; IV: intravenous; F: female; M: male; NA: not available; NS: not specified; RBV: ribavirin.

conclusion cannot be obtained and, for this reason, its use has not been approved to date.

Hantavirus

Regarding the use of ribavirin, in diseases caused by hantavirus, there is a meta-analysis published in 2014 by Moreli et al.³⁶ which is worthy of an in-depth review. It is a systematic review in which 518 studies are identified; after applying the exclusion criteria, only seven studies can be analysed, which accounts for a total of 506 patients.

Two groups (haemorrhagic fever with renal syndrome and hantavirus pulmonary syndrome), in addition to two subgroups (studies conducted in animals [4] or in humans [3]) are distinguished. Overall mortality was 35%. In the hantavirus pulmonary syndrome group, a randomised study and three prospective cohorts were identified. In the animal studies, a reduction in mortality was observed in the treatment group versus placebo, but not in the studies in humans, with a mortality rate in both groups of 40%. In the haemorrhagic fever with renal syndrome group, three studies were included. A reduction in mortality was observed when ribavirin was used compared to placebo (2.5% versus 8.5% mortality) with a relative risk (RR) of 0.56 (0.42–0.76) in both the animal and human subgroups.

With the existing data in this meta-analysis, it could be suggested that Old World hantavirus infections (haemorrhagic fever with renal syndrome) could benefit from the use of ribavirin, whereas it would not be useful in hantavirus pulmonary syndrome. The authors state that they have not been able to consider the time from diagnosis to the administration of ribavirin: hantavirus pulmonary syndrome has a mortality rate of 50% and may indicate a more rapid progression of the disease than in haemorrhagic fever with renal syndrome, which has a mortality rate of 15%. This would be a key factor, indicating the greater need to start therapy at an early stage.

Another bias may have been the restriction of works selected according to language: only works published in English, Spanish or Portuguese were selected. Given that China has the most cases of hantavirus with haemorrhagic fever (in the period from 1950 to 2007, a total of 1,557,622 cases of haemorrhagic fever with renal syndrome were reported, with a clear tendency to reduce the incidence), it is possible that a priori information published in Chinese has been eliminated which would modify the results obtained.

Lastly, it must be taken into account that the list of hantaviruses is extensive (23, including the Hantaan, Seoul, Puumala and Dobrava viruses for haemorrhagic fever with renal syndrome and the Sin Nombre and Andes viruses in hantavirus pulmonary syndrome). The heterogeneity between viruses (not only between syndromes) may determine the results. This is what may be indicated by a recent study conducted to evaluate the efficacy and safety of ribavirin in the treatment of haemorrhagic fever with renal syndrome caused by the Puumala virus, which does not benefit from the use of ribavirin.³⁷ It was an open, randomised study, on 73 patients, of whom 36 received standard support therapy and 37 the same therapy in addition to intravenous ribavirin. The study was not able to demonstrate efficacy in clinical aspects or in viral kinetics in the treatment, with important side effects (mainly anaemia, hyperbilirubinaemia, sinus bradycardia and skin rash).

Other indications (aside from the summary of product characteristics)

Lassa fever

When a review is performed of the treatment of Lassa fever with ribavirin, 108 publications are obtained. However, when the clinical trials and meta-analyses are evaluated, only one reference in relation to the effectiveness of the treatment is found.³⁸ It is a study conducted in Sierra Leone in 1986 by the Ministry of Health in collaboration with the Centers for Disease Control and Prevention

Table 2

Case series of disease due to adenovirus treated with ribavirin.

Cases	Age/gender	Risk factor	Disease	Serotype	Interval to RBV	Treatment	Clinical course	Follow-up	Reference
5	<18/2 M and 3 F	Heart transplant (2) bone marrow transplant (1), neonates (2)	3 cases of pneumonia. 2 cases of haemorrhagic cystitis	2 and 34. Unknown 3	6–21 days	IV RBV (1 with cidofovir)	Clearance ^a in 3–6 weeks	2 recoveries	8
9	Median 17/5 M and 4 F	Haematological diseases (leukaemias/ lymphomas), all bone marrow transplant recipients	Haemorrhagic cystitis	NS	>4 weeks	IV RBV (2 patients receive 2 cycles) 3 previously oral vidarabine	Clearance ^a in 47 days	3 recoveries, 6 deaths (5 partial responses)	9
15	Median 30/11 M and 4 F	Immunocompetent	Pneumonia (ARDS)	55 (73.3%)	NS	4 cases with RBV + oseltamivir; IG in 10 cases	NS	11 recoveries and 4 deaths	10
18	Median 28/16 M and 2 F	Immunocompetent	Pneumonia (ARDS)	3, 7, 11, and 14	NS	IV RBV in 2 cases	NS	NS	11
17	14 adults and 3 children	Haematological diseases (leukaemias/ lymphomas), all bone marrow transplant recipients	Viraemia. 6 with disseminated disease	NS	NS	2 cases with IV RBV, 11 with cidofovir	NS	3 deaths (adults)	12
32	Median 41/28 M and 10 F	Haematological diseases (leukaemias/ lymphomas), all bone marrow transplant recipients	8 respiratory infection. 16 GI. 8 respiratory + GI	NS	Median 5 days (1–30)	IV RBV ± cidofovir (5 cases)	Clearance in 10 cases in 19 days (respiratory) and 19 cases (GI)	6 recoveries (respiratory) and 9 (GI)	13
35	25 patients > 18/21 males and 14 F	34 haematological malignancies	Enteritis, cystitis, encephalitis, hepatitis, pneumonia, asymptomatic	1, 2, 3, 5, 8, A31	Median 80 days (19–193)	18 IV RBV 5 combined. 4 other antivirals. 13 not treated	Median clearance 11 days (7–35)	3 recoveries in those treated (cidofovir shows efficacy). 11 recoveries in those not treated	14

GI: gastrointestinal; IG: immunoglobulin; IV: intravenous; F: female; M: male; NS: not specified; RBV: ribavirin.
 Case series of disease due to adenovirus treated with ribavirin.

Table 3
Cases of disease due to MERS-CoV treated with ribavirin.

Age (years)/gender	Risk factor	Time to RBV	Treatment	Clinical course	Country	Reference
68/male	HTN, DL	NA	RBV regimen A on days 8–16 + 2 days with IFN- α	Recovery	South Korea	51
43/male	NA	NA	RBV (regimen not specified) on days 1–12 + IFN- α 1st day	Recovery ^a	China	52
32/female	Pregnant	7 days	RBV regimen B + pegylated IFN- α	Death	United Arab Emirates	53
64/male	HTN, DM ^b	15 days	RBV regimen C + LP/r + pegylated IFN α -2a	Recovery	Republic of Korea	54
69/male	None	13 days	RBV regimen C + LP/r + pegylated IFN	Death ^c	Saudi Arabia	55

DL: dyslipidaemia; DM: diabetes mellitus; HTN: hypertension; IFN: interferon; LP/r: lopinavir/ritonavir; NA: not available or unknown; RBV: ribavirin.

^a The patient recovered, but the test continued to be positive. Gamma globulin was administered.

^b He also had other comorbidities, such as splenectomy and pancreatectomy, and *Mycobacterium avium-intracellulare* infection.

^c Death due to colon adenocarcinoma.

Cases of disease due to MERS-CoV treated with interferon and ribavirin.

Regimen A. 2000 mg as loading dose, 600 mg/8 h 3 days, and 400 mg/8 h for 4 days.

Regimen B. Loading dose (400 mg 0–600 mg) and subsequently 1200 mg/12 h.

The doses of lopinavir/ritonavir were 400/100 mg/12 h, administered orally.

Regimen C. Loading dose 2000 mg and then 1200 mg/8 h orally.

(CDC), which started in 1977, and in which the administration of convalescent plasma, oral ribavirin and intravenous ribavirin was evaluated. The study is rather complex. However, despite this fact, it can be concluded that treatment with intravenous or oral ribavirin is recommended at any time of the disease (with it being more effective in the first six days of the disease). Initially, a phase I case-control study of the clinical and diagnostic aspects of Lassa fever in untreated patients was designed (30 clinical and laboratory variables were collected which were analysed subsequently), and, once these variables were collected, a randomised trial was conducted with 70 patients (39 with oral ribavirin and 31 with plasma; pregnant women were included without being randomised in the latter group), without knowing at this time the results of the analysis of the variables collected. In all cases, treatment was started in the first 24 h. Subsequently, elevation of transaminases and viraemia greater than 1000 copies/ml were identified as poor prognosis variables.

At a later stage, after the variables indicating poor prognosis had been determined, a phase II study was developed, selecting the patients with one of the poor prognosis variables (elevation of transaminases upon diagnosis; viraemia was not available). Two groups of patients (29 patients in the intravenous ribavirin group and 33 in the intravenous ribavirin plus plasma group) were randomised. Pregnant women received only two plasma units. Overall, treatment with ribavirin reduced mortality. This included the analysis of the patients included both in the phase I study and in the phase II study. In patients with viraemia >1000 copies/ml and treated with ribavirin, mortality was lower than in those who were not receiving treatment (mortality with intravenous ribavirin of 32% versus 76% without therapy ($p=0.00015$); mortality with oral ribavirin of 30% versus 76% without therapy ($p=0.008$). The same occurred if the viraemia was <1000 copies/ml (mortality with intravenous ribavirin of 9% versus 28% without therapy ($p=0.02$); mortality with oral ribavirin of 7% versus 28% without therapy ($p=0.01$).

There is a second study, conducted by Fisher-Hoch et al.,³⁹ which appears in PubMed as a clinical trial regarding the use of ribavirin in Lassa fever. Although it is true that it refers to its use in a clinical trial, what it describes is the onset of an adverse effect which is associated with recovery (“shivering/chills”) and what seems to be related to the speed of administration of the drug (<1 min). These side effects disappeared after correcting the speed of infusion. Some studies have been conducted to evaluate ribavirin as post-exposure prophylaxis, but they have not provided conclusive results.^{40,41}

Crimean-Congo haemorrhagic fever

There is only one randomised clinical trial which evaluates the use of ribavirin for Crimean-Congo haemorrhagic fever, conducted

between 2004 and 2007 with 136 patients.⁴² In a baseline form, there were no differences in gender, age, incubation period (around five days), clinical or analytical characteristics. The administration of ribavirin was done before confirming the diagnosis, meaning that the time to administration of it was around four days. No differences were found in terms of mortality, analytical recovery or length of hospital stay. Subsequently, two meta-analyses evaluated the usefulness of ribavirin for Crimean-Congo haemorrhagic fever. The first is from 2010⁴³ and reviews 21 works. The conclusion that the authors draw is that ribavirin in the clinical trial was not superior to not using ribavirin, but in the joint evaluation of all the results, mortality was reduced (RR: 0.56; 95% CI: 0.35–0.90; 955 participants). What was not found was a difference in duration of the hospital admission. The second meta-analysis is from 2011,⁴⁴ and also includes the only randomised clinical trial, but only seven more works, which are observational with control group, are introduced. No benefit of ribavirin with the aggregated data is found either. Both meta-analyses underline the risk of bias in all the works, whether it be selection, external validity or attrition bias.

South American haemorrhagic fevers

Ribavirin has not managed to demonstrate its usefulness in the reduction of mortality due to the Junin virus (Argentine haemorrhagic fever) in two very small clinical trials.^{45,46} Nevertheless, in the first study, blocked viral replication and a delay in the time to death was observed, compared with historical controls. Clearance of viraemia was even obtained in patients who died (in this phase of the disease the virus is detected in up to 80% of cases). Given that there is a treatment which has proven to be effective if administered in the first seven days of the disease (convalescent serum), studies which used ribavirin were conducted in advanced stages of the disease, which would justify the poor outcomes. It is probably not possible to conduct new studies in this regard, since there is also a vaccine which has proven to be effective at reducing the incidence of the disease.⁴⁷

There are practically no reported cases of the Machupo virus treated with ribavirin (Bolivian haemorrhagic fever): only two isolated cases in which intravenous ribavirin was administered and they recovered.⁴⁸ The same applies to cases of Sabia virus. In 1995, one case of Sabia virus was treated with intravenous ribavirin, managing to cure the patient.⁴⁹

Respiratory viruses: coronavirus

One retrospective study was conducted in 44 patients with coronavirus⁵⁰ to compare the combination of interferon and ribavirin versus placebo, observing an improvement in survival at 14 (70% vs 29%) and 28 days (30% vs 17%) in favour of the combination

Table 4

Case series of disease due to MERS-CoV treated with ribavirin (+ IFN).

n	Gender and age characteristics ^a	Risk factor	Time ^a to RBV	Treatment	Mortality	Reference
14	54 (23–79). 9 M/5 F	28.6% medical; 42% with kidney disease	6 days (1–13)	Combination in 11 cases, but not specified	64% ^b	56
32	65 (25–88). 14 M/18 F	15.6% medical; 18.75% on haemodialysis	1 day	Regimen A	69% ^c	57
6	58.8 (17–84). 5 M/1 F	50% Heart disease	8.5 days (1–19)	Regimen B	50%	58
2	52 M/42 F	No identified risk factors	0 and 1 day	Regimen C	0%	59
5	57.6 (24–81). 3 M/2 F	100% Kidney disease	19 days (10–22)	Regimen D	100%	60

F: female; M: male.

Regimen A. Ribavirin (2000 mg loading dose, followed by 600 mg/12 h) + IFN alpha-2a (180 µg/week for 2 weeks) or IFN beta-1a (44 mg 3 times/week).

Regimen B. Ribavirin (2000 mg loading dose, then 1200 mg/8 h for 4 days), followed by 600 mg/8 h for 4–6 days (adjusted to kidney function) + IFN alpha-2b (180 µg/week for 2 weeks).

Regimen C. Ribavirin (2000 mg loading dose, then 1200 mg/8 h for 4 days) + pegylated IFN alpha-2b 180 µg/week for 2 weeks).

Regimen D. Ribavirin (2000 mg loading dose, then 800 mg/8 h through nasogastric tube) + IFN alpha-2b 100 mg/week for 2 weeks.

^a Given the heterogeneity of the articles, the mean or the median and the range is sometimes reported.^b All survivors took the RBV + IFN combination.^c No differences in the type of IFN alpha or beta.

All the series are from Saudi Arabia.

of drugs, although the difference at 28 days was not statistically significant (probably due to the small sample size). The mean treatment initiation time with ribavirin was three days. In addition, isolated cases^{51–55} and case series,^{56–60} which reflect variable degrees of therapeutic success (Tables 3 and 4), have been reported.

Studies on ribavirin

New applications of ribavirin are currently being investigated. Four studies to investigate its usefulness in influenza, three on arbovirus, three on hepatitis B, three on hantavirus, two on paramyxovirus, two on Coxsackie virus and one on coronavirus are registered.

Conclusion

Ribavirin is a broad-spectrum antiviral that is currently looking for a new role in the treatment of various infections. Its availability for administration via the oral, intravenous or inhaled route is a beneficial characteristic. There is evidence of benefit in RSV infection and Lassa fever, with its use being proposed in certain situations of disease due to hantavirus, Crimean-Congo haemorrhagic fever and coronavirus, such as Middle East respiratory syndrome coronavirus (MERS-CoV). The availability of ribavirin in oral formulation currently exists in Spain, while the inhaled and intravenous forms must be requested through the Spanish Agency of Medicines and Medical Devices.

References

- Sidwell RW, Huffman JH, Khare GP, Allen LB, Witkowski JT, Robins RK. Broad-spectrum antiviral activity of Virazole: 1-beta-D-ribofuranosyl-1,2,4-triazole-3-carboxamide. *Science*. 1972;177:705–6.
- Graci JD, Cameron CE. Mechanisms of action of ribavirin against distinct viruses. *Rev Med Virol*. 2006;16:37–48.
- Agencia Española de Medicamentos y Productos Sanitarios, AEMPS. Available from: <https://www.aemps.gob.es/> [accessed 26.11.17].
- European Medicines Agency. Available from: <http://www.ema.europa.eu/ema/> [accessed 26.11.17].
- U S Food and Drug Administration Home Page. Available from: <https://www.fda.gov/> [accessed 26.11.17].
- Ventre K, Randolph A. Ribavirin for respiratory syncytial virus infection of the lower respiratory tract in infants and young children. *Cochrane Database Syst Rev*. 2004;12.
- Shah JN, Chemaly RF. Management of RSV infections in recipients of hematopoietic stem cell transplantation. *Blood*. 2015;117:2755–64.
- Gavin PJ, Katz BZ. Intravenous ribavirin treatment for severe adenovirus disease in immunocompromised children. *Pediatrics*. 2002;110 Pt 1:e9.
- Miyamura K, Hamaguchi M, Taji H, Kanie T, Kohno A, Tanimoto M, et al. Successful ribavirin therapy for severe adenovirus hemorrhagic cystitis after allogeneic marrow transplant from close HLA donors rather than distant donors. *Bone Marrow Transplant*. 2000;25:545–8.
- Tan D, Zhu H, Fu Y, Tong F, Yao D, Walline J, et al. Severe community-acquired pneumonia caused by human adenovirus in immunocompetent adults: a multicenter case series. *PLOS ONE*. 2016;11:e0151199.
- Gu L, Liu Z, Li X, Qu J, Guan W, Liu Y, et al. Severe community-acquired pneumonia caused by adenovirus type 11 in immunocompetent adults in Beijing. *J Clin Virol*. 2012;54:295–301.
- Omar H, Yun Z, Lewensohn-Fuchs I, Pérez-Bercoff L, Örvell C, Engström L, et al. Poor outcome of adenovirus infections in adult hematopoietic stem cell transplant patients with sustained adenovirus viremia. *Transpl Infect Dis*. 2010;12:465–9.
- Schleuning M, Buxbaum-Conradi H, Jäger G, Kolb H-J. Intravenous ribavirin for eradication of respiratory syncytial virus (RSV) and adenovirus isolates from the respiratory and/or gastrointestinal tract in recipients of allogeneic hematopoietic stem cell transplants. *Hematol J*. 2004;5:135–44.
- Bordigoni P, Carret AS, Venard V, Witz F, le Faou A. Treatment of adenovirus infections in patients undergoing allogeneic hematopoietic stem cell transplantation. *Clin Infect Dis*. 2001;32:1290–7.
- Yoon BW, Song YG, Lee SH. Severe community-acquired adenovirus pneumonia treated with oral ribavirin: a case report. *BMC Res Notes*. 2017;10:47.
- Park UJ, Hyun SK, Kim HT, Cho WH, Han SY. Successful treatment of disseminated adenovirus infection with ribavirin and intravenous immunoglobulin in an adult renal transplant recipient: a case report. *Transplant Proc*. 2015;47:791–3.
- Ramírez J, Bostock IC, Martin-Onraet A, Calleja S, Sanchez-Cedillo A, Navarro-Vargas LA, et al. Fever, haematuria, and acute graft dysfunction in renal transplant recipients secondary to adenovirus infection: two case reports. *Case Rep Nephrol*. 2013;2013:195753.
- Ulrych EE, Dzieciatkowski T, Przybylski M, Zduńczyk D, Boguradzki P, Torosian T, et al. Disseminated adenovirus disease in immunocompromised patient successfully treated with oral ribavirin: a case report. *Arch Immunol Ther Exp (Warsz)*. 2011;59:473–7.
- Abe S, Miyamura K, Oba T, Terakura S, Kasai M, Kitaori K, et al. Oral ribavirin for severe adenovirus infection after allogeneic marrow transplantation. *Bone Marrow Transplant*. 2003;32:1107–8.
- Emovon OE, Lin A, Howell DN, Afzal F, Baillie M, Rogers J, et al. Refractory adenovirus infection after simultaneous kidney-pancreas transplantation: Successful treatment with intravenous ribavirin and pooled human intravenous immunoglobulin. *Nephrol Dial Transplant*. 2003;18:2436–8.
- Arav-Boger R, Echavarría M, Forman M, Charache P, Persaud D. Clearance of adenoviral hepatitis with ribavirin therapy in a pediatric liver transplant recipient. *Pediatr Infect Dis J*. 2000;19:1097–100.
- Shetty AK, Gans HA, So S, Millan MT, Arvin AM, Gutierrez KM. Intravenous ribavirin therapy for adenovirus pneumonia. *Pediatr Pulmonol*. 2000;29:69–73.
- Chakrabarti S, Collingham KE, Fegan CD, Milligan DW. Fulminant adenovirus hepatitis following unrelated bone marrow transplantation: failure of intravenous ribavirin therapy. *Bone Marrow Transplant*. 1999;23:1209–11.
- Jurado Chacón M, Hernández Mohedo F, Navarro Marí JM, Ferrer Chaves C, Escobar Vedia JL, de Pablos Gallego JM. Adenovirus pneumonitis successfully treated with intravenous ribavirin. *Haematologica*. 1998;83:1128–9.
- Mann D, Moreb J, Smith S, Gian V. Failure of intravenous ribavirin in the treatment of invasive adenovirus infection following allogeneic bone marrow transplantation: a case report. *J Infect*. 1998;36:227–8.
- Maslo C, Girard PM, Urban T, Guessant S, Rozenbaum W. Ribavirin therapy for adenovirus pneumonia in an AIDS patient. *Am J Respir Crit Care Med*. 1997;156 Pt 1:1263–4.
- Aebi C, Headrick CL, McCracken GH, Lindsay CA. Intravenous ribavirin therapy in a neonate with disseminated adenovirus infection undergoing extracorporeal membrane oxygenation: pharmacokinetics and clearance by hemofiltration. *J Pediatr*. 1997;130:612–5.
- Sabroe I, McHale J, Tait DR, Lynn WA, Ward KN, Shaunak S. Treatment of adenoviral pneumonitis with intravenous ribavirin and immunoglobulin. *Thorax*. 1995;50:1219–20.

29. Kapelushnik J, Or R, Delukina M, Nagler A, Livni N, Engelhard D. Intravenous ribavirin therapy for adenovirus gastroenteritis after bone marrow transplantation. *J Pediatr Gastroenterol Nutr.* 1995;21:110–2.
30. Jurado M, Navarro JM, Hernández J, Molina MA, DePablos JM. Adenovirus-associated haemorrhagic cystitis after bone marrow transplantation successfully treated with intravenous ribavirin. *Bone Marrow Transplant.* 1995;15:651–2.
31. Wulffraat NM, Geelen SP, van Dijken PJ, de Graeff-Meeder B, Kuis W, Boven K. Recovery from adenovirus pneumonia in a severe combined immunodeficiency patient treated with intravenous ribavirin. *Transplantation.* 1995;59:927.
32. Cassano WF. Intravenous ribavirin therapy for adenovirus cystitis after allogeneic bone marrow transplantation. *Bone Marrow Transplant.* 1991;7:247–8.
33. Murphy GF, Wood DP, McRoberts JW, Henslee-Downey PJ. Adenovirus-associated hemorrhagic cystitis treated with intravenous ribavirin. *J Urol.* 1993;149:565–6.
34. Liles WC, Cushing H, Holt S, Bryan C, Hackman RC. Severe adenoviral nephritis following bone marrow transplantation: successful treatment with intravenous ribavirin. *Bone Marrow Transplant.* 1993;12:409–12.
35. Hromas R, Clark C, Blanke C, Tricot G, Cornetta K, Hedderman A, et al. Failure of ribavirin to clear adenovirus infections in T cell-depleted allogeneic bone marrow transplantation. *Bone Marrow Transplant.* 1994;14:663–4.
36. Moreli ML, Marques-Silva AC, Pimentel VA, da Costa VG. Effectiveness of the ribavirin in treatment of hantavirus infections in the Americas and Eurasia: a meta-analysis. *Virusdisease.* 2014;25:385–9.
37. Malinin OV, Platonov AE. Insufficient efficacy and safety of intravenous ribavirin in treatment of haemorrhagic fever with renal syndrome caused by Puumala virus. *Infect Dis (Auckl).* 2017;49:514–20.
38. McCormick JB, King IJ, Webb PA, Scribner CL, Craven RB, Johnson KM, et al. Lassa fever effective therapy with ribavirin. *N Engl J Med.* 1986;314:20–6.
39. Fisher-Hoch SP, Gborie S, Parker L, Huggins J. Unexpected adverse reactions during a clinical trial in rural West Africa. *Antiviral Res.* 1992;19:139–47.
40. Hadi CM, Goba A, Khan SH, Bangura J, Sankoh M, Koroma S, et al. Ribavirin for Lassa Fever postexposure prophylaxis. *Emerg Infect Dis.* 2010;16:2009–11.
41. Isa SE, Okwute A, Iraoyah KO, Nathan SY, Simji GS, Okolo MO, et al. Postexposure prophylaxis for Lassa fever: experience from a recent outbreak in Nigeria. *Niger Med J.* 2016;57:246–50.
42. Koksai I, Yilmaz G, Aksoy F, Aydin H, Yavuz I, Iskender S, et al. The efficacy of ribavirin in the treatment of Crimean-Congo hemorrhagic fever in Eastern Black Sea region in Turkey. *J Clin Virol.* 2010;47:65–8.
43. Soares-Weiser K, Thomas S, Thomson G, Garner P. Ribavirin for Crimean-Congo hemorrhagic fever: systematic review and meta-analysis. *BMC Infect Dis.* 2010;10:207.
44. Ascioglu S, Leblebicioglu H, Vahaboglu H, Chan KA. Ribavirin for patients with Crimean-Congo haemorrhagic fever: a systematic review and meta-analysis. *J Antimicrob Chemother.* 2011;66:1215–22.
45. Enria DA, Briggiler AM, Levis S, Vallejos D, Maiztegui JI, Canonico PG. Tolerance and antiviral effect of ribavirin in patients with Argentine hemorrhagic fever. *Antiviral Res.* 1987;7:353–9.
46. Enria DA, Maiztegui JI. Antiviral treatment of Argentine hemorrhagic fever. *Antiviral Res.* 1994;23:23–31.
47. Enria DA, Briggiler AM, Sánchez Z. Treatment of Argentine hemorrhagic fever. *Antiviral Res.* 2008;78:132–9.
48. Kilgore PE, Ksiazek TG, Rollin PE, Mills JN, Villagra MR, Montenegro MJ, et al. Treatment of Bolivian hemorrhagic fever with intravenous ribavirin. *Clin Infect Dis.* 1997;24:718–22.
49. Barry M, Russi M, Armstrong L, Geller D, Tesh R, Dembry L, et al. Brief report: treatment of a laboratory-acquired Sabiá virus infection. *N Engl J Med.* 1995;333:294–6.
50. Omrani AS, Saad MM, Baig K, Bahloul A, Abdul-Matin M, Alaidaroos AY, et al. Ribavirin and interferon alfa-2a for severe Middle East respiratory syndrome coronavirus infection: a retrospective cohort study. *Lancet Infect Dis.* 2014;14:1090–5.
51. Lee JY, Kim Y-J, Chung EH, Kim D-W, Jeong I, Kim Y, et al. The clinical and virological features of the first imported case causing MERS-CoV outbreak in South Korea, 2015. *BMC Infect Dis.* 2017;17:498.
52. Luo Y, Ou R, Ling Y, Qin T. The therapeutic effect of high flow nasal cannula oxygen therapy for the first imported case of Middle East respiratory syndrome to China. *Zhonghua Wei Zhong Bing Ji Jiu Yi Xue.* 2015;27:841–4.
53. Malik A, el Masry KM, Ravi M, Sayed F. Middle East respiratory syndrome coronavirus during pregnancy, Abu Dhabi United Arab Emirates, 2013. *Emerg Infect Dis.* 2016;22:515–7.
54. Kim UJ, Won E-J, Kee S-J, Jung S-I, Jang H-C. Combination therapy with lopinavir/ritonavir, ribavirin and interferon- α for Middle East respiratory syndrome. *Antivir Ther.* 2016;21:455–9.
55. Spanakis N, Tsiodras S, Haagmans BL, Raj VS, Pontikis K, Koutsoukou A, et al. Virological and serological analysis of a recent Middle East respiratory syndrome coronavirus infection case on a triple combination antiviral regimen. *Int J Antimicrob Agents.* 2014;44:528–32.
56. Khalid I, Alraddadi BM, Dairi Y, Khalid TJ, Kadri M, Alshukairi AN, et al. Acute management and long-term survival among subjects with severe Middle East respiratory syndrome coronavirus pneumonia and ARDS. *Respir Care.* 2016;61:340–8.
57. Shalhoub S, Farahat F, al-Jiffri A, Simhairi R, Shamma O, Siddiqi N, et al. IFN- α 2a or IFN- β 1a in combination with ribavirin to treat Middle East respiratory syndrome coronavirus pneumonia: a retrospective study. *J Antimicrob Chemother.* 2015;70:2129–32.
58. Khalid M, Khan B, al Rabiah F, Alismaili R, Saleemi S, Rehan-Khalid AM, et al. Middle Eastern Respiratory Syndrome Corona Virus (MERS CoV): case reports from a tertiary care hospital in Saudi Arabia. *Ann Saudi Med.* 2014;34:396–400.
59. Khalid M, al Rabiah F, Khan B, al Mobeireek A, Butt TS, al Mutairy E. Ribavirin and interferon- α 2b as primary and preventive treatment for Middle East respiratory syndrome coronavirus: a preliminary report of two cases. *Antivir Ther.* 2015;20:87–91.
60. Al-Tawfiq J, Momattin a, Dib H, Memish JZ. Ribavirin and interferon therapy in patients infected with the Middle East respiratory syndrome coronavirus: an observational study. *Int J Infect Dis.* 2014;20:42–6.