

Ribavirin Analogs

William W. Shields, DO^{a,*}, Paul J. Pockros, MD^b

KEYWORDS

- Hepatitis C virus • Ribavirin • Anemia • Taribavirin
- Pegylated interferon

Hepatitis C virus (HCV) is the most common bloodborne pathogen in the United States, with 3.2 million persons chronically infected. Approximately 20% of individuals infected will develop cirrhosis during a period of 20 to 30 years, with the potential complications of portal hypertension and its sequelae and hepatocellular carcinoma. Chronic hepatitis C accounts for an estimated 8000 to 10,000 deaths in the United States annually, and this number is expected to more than double by 2010.¹

Interferon alpha has been the backbone of chronic hepatitis C therapy for the last 20 years.² Monotherapy with interferon yields sustained virologic response (SVR) rates of 8% to 17%.^{3,4} The use of ribavirin has been investigated as monotherapy in patients with chronic hepatitis C, and it was demonstrated to have improvement in serum aminotransferase levels and histology but had no impact on HCV RNA levels; therefore ribavirin is ineffective when used as a single agent.⁵ Subsequent studies showed that ribavirin, in combination with interferon alpha, improved SVR rates up to 36% to 38% compared with standard interferon alone.^{6,7} The highest SVR rates are achieved with once-weekly dosing of subcutaneous pegylated interferon combined with daily oral ribavirin, and this is the present standard of care in the United States, European Union, and Japan.² Weight-based dosing of ribavirin (1000 mg/d based on weight <75 kg or 1200 mg/d based on weight >75 kg) has been shown to significantly improve SVR rates compared with lower, fixed dosing of ribavirin at 800 mg/d in genotype 1 infection.⁸ However, higher dosing of ribavirin is limited by the development of hemolytic anemia, which usually occurs in at least 25% of treated patients.⁹ The development of significant anemia often leads to ribavirin dose reductions, which can negatively impact SVR rates.¹⁰

RIBAVIRIN PHARMACOLOGY

Ribavirin (1- β -D-ribofuranosyl-1H-1,2,4-triazole-3-carboxamide) was first discovered in 1972.¹¹ Structurally, ribavirin is a purine ribonucleoside analog with broad-spectrum activity against both RNA and DNA viruses (**Fig. 1**).¹² The drug is approved by the US

^a Department of Gastroenterology and Hepatology, Naval Medical Center San Diego, 34800 Bob Wilson Drive, San Diego, CA 92134, USA

^b Division of Gastroenterology and Hepatology, Scripps Clinic, The Scripps Research Institute, 10666 North Torrey Pines Road, La Jolla, CA 92037, USA

* Corresponding author.

E-mail address: william.shields@med.navy.mil (W.W. Shields).

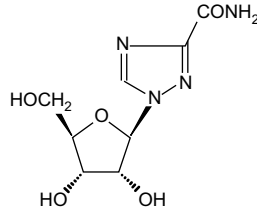


Fig. 1. Chemical structure of ribavirin. (From Copegus [ribavirin, USP] [package insert]. Roche Laboratories Inc, Nutley, New Jersey, 2004.)

Food and Drug Administration for the treatment of pediatric respiratory syncytial virus infection and for combination therapy with interferon or pegylated interferon for chronic hepatitis C.¹³

The mechanism of action of ribavirin in chronic hepatitis C is not completely understood. Four mechanisms, indirect and direct, have been proposed (**Fig. 2**).¹⁴ First, ribavirin may be considered a prodrug that enters the cell and is converted to the active metabolites ribavirin-5'-monophosphate (RMP), ribavirin-5'-diphosphate, and ribavirin-5'-triphosphate (RTP) through the sequential action of 3 cellular kinases.¹⁵ RMP mimics inosine-5'-monophosphate and is a competitive inhibitor of host inosine monophosphate dehydrogenase (IMPDH). IMPDH is a required enzyme for the synthesis of guanosine triphosphate (GTP), and GTP is an important substrate for viral

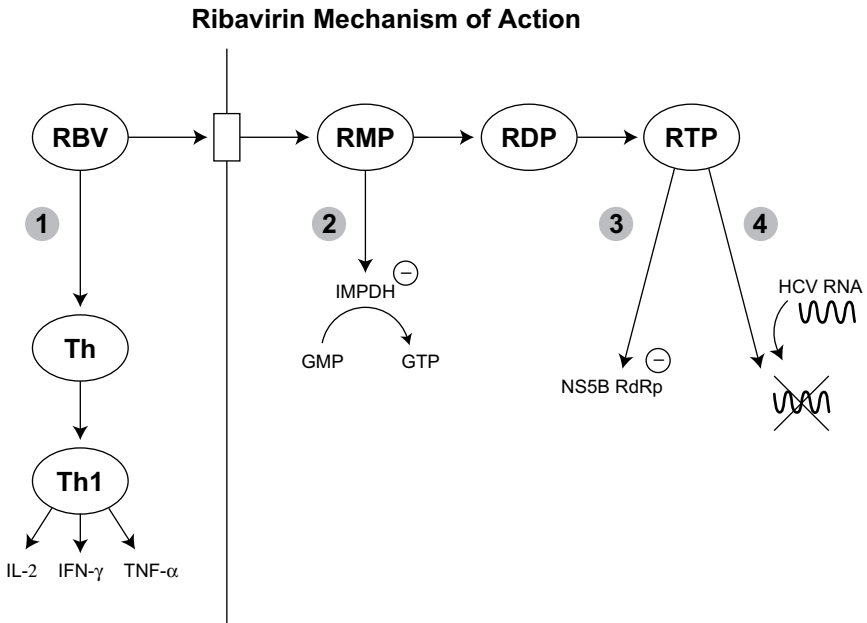


Fig. 2. Proposed mechanisms of action of ribavirin. Ribavirin may act as an immune enhancer by modulating the T-helper cell balance toward Th1 and type 1 cytokines (1). RMP inhibits the host enzyme IMPDH decreasing intracellular levels of GTP (2). RTP may be a direct inhibitor of viral NS5B RdRp (3). RTP may be incorporated into the viral RNA and act as an RNA mutagen (4). (Data from Lau JY, Tam RC, Liang TJ, et al. Mechanism of action of ribavirin in the combination treatment of chronic HCV infection. *Hepatology* 2002;35(5):1002–9).

RNA synthesis. Therefore, inhibition of IMPDH decreases intracellular levels of GTP and may lead to suppression of replication of viral genomes. Second, ribavirin may act to enhance immune clearance of HCV by modulating the T-helper (Th) cell balance toward Th1.¹⁶ Ribavirin augments type 1 cytokines interleukin (IL)-2, interferon- γ , and tumor necrosis factor- α and suppresses type 2 cytokines IL-4 and IL-5.¹⁷ A dominant type 2 cytokine response is associated with the development of chronicity in HCV.¹⁴ Third, ribavirin may have direct antiviral mechanisms through the inhibition of the NS5B RNA dependent RNA polymerase (RdRp). RTP has been shown to have activity against RdRp of bovine viral diarrheal virus, which is closely related to HCV.¹⁴ Lastly, ribavirin may act as an RNA mutagen, as has been shown in a poliovirus model. RTP may be used by the viral RdRp and misincorporated into the viral RNA. RTP can base pair with cytidine and uridine, promoting transitions of A to G and G to A, thus leading to viral "error catastrophe."¹⁸

The most significant adverse effect of ribavirin is a reversible hemolytic anemia. This effect of ribavirin significantly affects patient quality of life and negatively affects SVR rates. Ribavirin is actively transported into erythrocytes, where it is then converted to its phosphate metabolites. These phosphorylated metabolites cannot diffuse outside of cells, and they progressively accumulate intracellularly during treatment. Increased intracellular ribavirin concentration as phosphorylated metabolites can predict the occurrence of anemia (Fig. 3).¹⁹ The increase in phosphorylated metabolites is associated with a marked decrease in cellular ATP levels, leading to a decrease in sodium-potassium pump activity contributing to oxidative damage to the erythrocyte membrane and thus leading to erythrophagocytic extravascular destruction.²⁰

RIBAVIRIN ANALOGS

Recent studies of direct antiviral agents have demonstrated that there will continue to be a need for combination of direct antiviral plus pegylated interferon and ribavirin and that deletion of ribavirin from the combination regimen resulted in lowered efficacy.^{21,22} Several of these agents promote anemia on their own or worsen ribavirin-associated anemia.^{23,24} Therefore, the search for ribavirin analogs, which would have equivalent

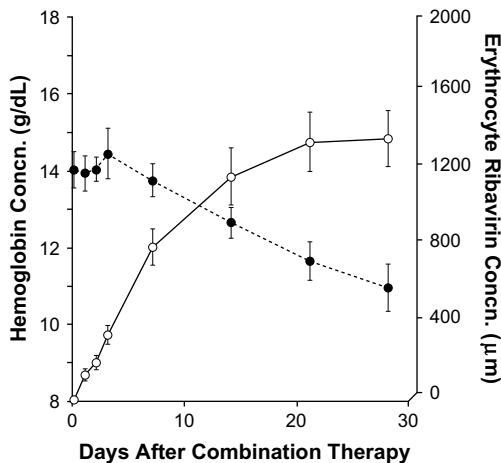


Fig. 3. Intracellular ribavirin concentration predicts the occurrence of anemia. (From Homma M, Matsuzaki Y, Inoue Y, et al. Marked elevation of erythrocyte ribavirin levels in interferon and ribavirin-induced anemia. Clin Gastroenterol Hepatol 2004;2:338; with permission).

efficacy, but diminished toxicity, remains an important milestone to HCV treatment. Several compounds have been investigated, as outlined in the following sections.

Taribavirin (Viramidine)

Taribavirin is a 3-carboxamide derivative of ribavirin. It is a prodrug, which is activated and converted to ribavirin by the enzyme adenosine deaminase (Fig. 4).¹³ The major site of conversion is in the hepatocyte; therefore this prodrug is able to deliver more ribavirin to the liver and less to other cells, including red blood cells. In turn, this decreases the accumulation of phosphorylated metabolites and subsequent hemolytic anemia. The liver-targeting property of taribavirin has yielded an improved safety profile over ribavirin in animal and human studies.²⁵ In addition to being a prodrug to ribavirin, taribavirin has been shown to act as a direct inhibitor of nucleoside phosphorylase that slows the degradation of the newly formed active phosphorylated metabolites of ribavirin, which can improve drug efficacy.²⁶

The first human studies of taribavirin were reported in 2004. This initial study demonstrated that taribavirin was well tolerated, was rapidly converted to ribavirin, and was renally excreted.²⁷ A phase 2, open-label study followed, which included 180 patients with chronic hepatitis C. Patients were randomized to receive pegylated interferon alpha-2a 180 µg/wk plus taribavirin (800 mg/d, 1200 mg/d, or 1600 mg/d) or ribavirin (1000 mg/d or 1200 mg/d). The results of this study showed SVR rates of 23%, 37%, and 29% for the 3 arms of taribavirin versus 44% for ribavirin. Significantly fewer patients in the taribavirin arms developed severe anemia, defined as hemoglobin less than 10 g/dL, than in those receiving ribavirin, 4% versus 27%.²⁸

The results of this phase 2 study led to 2 large phase 3 clinical trials: viramidine safety and efficacy versus ribavirin (VISER) 1 and VISER 2. VISER 1 compared taribavirin 600 mg twice a day plus pegylated interferon alpha-2b with ribavirin plus pegylated interferon alpha-2b. About 970 patients with chronic hepatitis C, all genotypes, who were treatment-naïve, were enrolled. Overall, SVR rates were lower in those receiving taribavirin (38%) than in those receiving ribavirin (52%). Taribavirin did not meet the criteria for noninferiority to ribavirin efficacy endpoint on an intent-to-treat basis. Taribavirin did demonstrate a superior safety profile, with anemia rates (Hb < 10 g/dL) being significantly lesser than ribavirin (5% vs 24%).²⁹ VISER 2 compared taribavirin 600 mg twice a day plus pegylated interferon alpha-2a with ribavirin plus pegylated interferon alpha-2a. About 962 patients with chronic hepatitis C of all genotypes, who were treatment-naïve, were enrolled. VISER 2 produced similar results as VISER 1, with SVR rates being lesser in taribavirin-treated patients (40%) than in ribavirin treated patients (55%). Again, anemia rates were significantly lesser with taribavirin than with ribavirin (6% vs 22%).³⁰

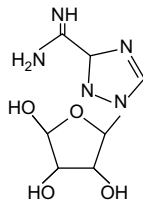


Fig. 4. Chemical structure of taribavirin. (From Wu JZ, Larson G, Walker H, et al. Phosphorylation of ribavirin and viramidine by adenosine kinase and cytosolic 5'-nucleotidase II: implications for ribavirin metabolism in erythrocytes. *Antimicrob Agents Chemother* 2005;49(6):2164–71.)

A post hoc subgroup analysis suggested improved SVR rates with higher weight-based dosing of taribavirin.³¹ Therefore, a phase 2b study was initiated in 275 patients with chronic hepatitis C, genotype 1, who were treatment-naïve, that compared taribavirin at doses of 20, 25, or 30 mg/kg/d with weight-based dosing of ribavirin.³² All patients received pegylated interferon alpha-2b. Interim analysis results at treatment week 24 were presented at the 59th annual meeting of the American Association for the Study of Liver Diseases in 2008. Rapid virologic response rates for the 3 arms of taribavirin were 16.4%, 14.3%, and 16.2% versus 11.4% for ribavirin. The percentage of patients who had undetectable HCV RNA at 12 weeks was 41.8%, 41.4%, and 25% for the 3 arms of taribavirin versus 31.4% for ribavirin. Rates of anemia, defined as hemoglobin less than 10 g/dL, were significantly lower in the taribavirin arms (13.4%, 11.4%, and 19.1%) than for ribavirin (30%). The most common adverse effects were fatigue, headache, nausea, and diarrhea and were similar across all study arms with the exception of diarrhea, which occurs more frequently with taribavirin. This study is ongoing, and further interim results, including end-of-treatment data, have been released by Valeant Pharmaceuticals International, California, USA. The rates of undetectable HCV RNA at 48 weeks (end-of-treatment response) were reported as 43.4%, 32.9%, and 29.4% for the 3 arms of taribavirin versus 32.9% for ribavirin. Rates of anemia at end of treatment were 13.4%, 15.7%, and 27.9% for taribavirin and 32.9% for ribavirin.³³

Levovirin (ICN 17,621)

Levovirin (1- β -L-ribofuranosyl-1,2,4-triazole-3-carboxamide) is an L-isomer of ribavirin (Fig. 5). Similar to ribavirin, levovirin has been shown to enhance Th1 host immune response, which is important in the clearance of HCV infection. Levovirin is not recognized by host kinases, therefore, phosphorylated metabolites do not accumulate. Inhibition of IMPDH has not been demonstrated, and the compound does not accumulate in erythrocytes. Therefore, hemolytic anemia does not occur in normal or HCV-infected persons given this compound. Levovirin has been shown to decrease serum alanine transaminase levels in a murine hepatitis model.^{34,35} One large randomized, double-blind, phase 2 clinical trial involving levovirin has been presented;³⁶ however, the data have not been published in manuscript form. The study showed that although there was a marked reduction in anemia, there was no added benefit in achieving a complete early virologic response when levovirin was combined with pegylated interferon and compared with pegylated interferon monotherapy, and thus the drug was not carried into further trials.

OTHER IMPDH INHIBITORS

VX-497 (Merimepodib)

VX-497 is a phenyloxazole derivative with the chemical name (S)-N-3-[3-(3-methoxy-4-oxazol-5-yl-phenyl)-ureido]-benzyl-carbamic acid tetrahydroguran-3-yl-ester (Fig. 6).

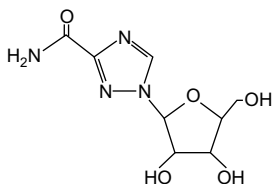


Fig. 5. Chemical structure of levovirin.

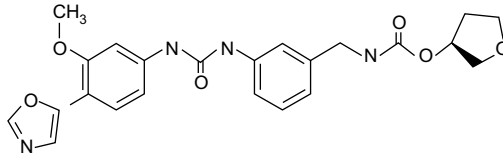


Fig. 6. Chemical structure of VX-497.

VX-497 is a selective, potent, reversible, uncompetitive inhibitor of IMPDH. Early preclinical studies showed that VX-497 demonstrated activity against a variety of viruses and was 10- to 100-fold more potent than ribavirin against hepatitis B virus, human cytomegalovirus, respiratory syncytial virus, herpes simplex virus -1, encephalomyocarditis virus, parainfluenza 3 virus, and Venezuelan equine encephalomyelitis virus. There was an additive antiviral effect when combined with interferon alpha.³⁷ A dose escalation and tolerability study of 55 patients with chronic hepatitis C, who were genotype 1 and treatment-naïve, demonstrated that VX-497 was well tolerated and effective against HCV. In this trial, patients were randomized to standard interferon 3 million IU subcutaneously 3 times a week in combination with VX-497 100 mg or 300 mg every 8 hours for 4 weeks or standard interferon alone. A per protocol analysis showed that standard interferon plus VX-497 100 mg significantly decreased HCV RNA levels compared with standard interferon alone (-1.768 log versus -0.86 log).³⁸ A second phase 2 study investigated the addition of VX-497 to pegylated interferon alpha-2b and ribavirin in patients with chronic hepatitis C who were nonresponders to previous therapy. In this study, all patients received pegylated interferon alpha-2b and ribavirin, but they were randomized to placebo or VX-497 at 25 mg every 12 hours or 50 mg every 12 hours. At week 24, 8 of 11 patients in the 50-mg group had undetectable HCV RNA, 2 of 10 in the 25-mg group, and 3 of 10 in the placebo group. In general, VX-497 was well tolerated.³⁹ The final results of this phase 2 trial are pending publication. Further drug development is unlikely in view of recent evidence that ribavirin's antiviral activity is not related to IMPDH inhibition.⁴⁰

Mycophenolate Mofetil

Mycophenolate mofetil (MMF, CellCept) is a potent IMPDH inhibitor. This well-known immunosuppressant compound is used for management after organ transplantation. Because of its IMPDH inhibition, MMF has been studied in combination with interferon alpha. It has been shown to inhibit HCV replication; however, it has been ineffective in improving virologic response rates.^{41,42} Because of its immunosuppressive effects, MMF may play a role in the treatment of HCV-related autoimmune diseases.⁴³

SUMMARY

Ribavirin is ineffective as monotherapy against HCV; however, it has been shown to be critical in attaining early virologic response and SVR when combined with interferon and/or pegylated interferon. The recent addition of direct antiviral agents to combination therapy will not change this paradigm. Ribavirin has dose-limiting toxicities (primarily hemolytic anemia), which often lead to discontinuation or dose reduction, negatively impacting SVR rates. The mechanism by which ribavirin exerts its antiviral activity remains unknown, but it is likely due to the induction of viral mutagenesis. The ribavirin analog taribavirin is a liver-targeted prodrug, which has less accumulation of phosphorylated metabolites within red blood cells, thereby reducing the incidence of hemolytic anemia. Early studies, which demonstrated equal efficacy with lesser

anemia, were encouraging; however, 2 large phase 3 studies were disappointing, because they demonstrated inferiority to ribavirin. A subsequent ongoing phase 2 study, using higher, weight-based dosing of taribavirin, has thus far yielded encouraging results and maintained a significantly less rate of anemia. Taribavirin may be a promising alternative to ribavirin in the future. Other ribavirin analogs and IMPDH inhibitors have yielded less promising results and are not in advanced clinical development.

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