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Ribavirin: Broad Spectrum Dreams, Narrowing Reality

Ribavirin (1-β-D-ribofuranosyl-1, 2, 4-traizole-3-carboxamide) is a broad spectrum virustatic agent with *in vitro* activity against both DNA and RNA viruses that was first developed by ICN Pharmaceuticals[1]. It is a ribonucleoside pro-drug that when metabolized is structurally similar to host purine RNA nucleotides and is best known as an anti-viral drug used to treat hepatitis C viral (HCV) infection, yet first was used to treat severe respiratory syncytial virus (RSV)[2].

From ICN Pharmaceuticals to Valeant Pharmaceuticals International

Founded in 1960 by Yugoslavian defector Milan Paníc in a Southern California garage, ICN Pharmaceuticals quickly found success in drug development. In the early 1960's researchers were able to isolate the nucleoside antibiotic pyrazofuranin from the bacteria *Steptomyces* showdoensis, it possessed modest antiviral activity. This sparked efforts at ICN Pharmaceutical's Nucleic Acid Research Institute to synthesize new nucleosides using pyrazofuranin as a starting point leading to a collection of nucleoside analogs with increased potency, spectrum of activity and reduced toxicity. In 1970 they discovered ribavirin. In 1991 ICN acquired 75 percent interest in Galenika Pharmaceutical, the major drug distributor in Yugoslavia, renaming it Galenika ICN expanding the company's sales making it one of the first Western companies to reach out with investments in Eastern Europe following the fall of communism. Expansion into Western Europe followed and ultimately Africa, Asia and Australia. In 1992 Paníc returned to Yugoslavia to serve as Prime Minister and eventually lost a presidential bid against Slobodan Milosevic. After being ousted as Prime Minister Paníc's problems continued. The SEC intervened when he started claiming that ribavirin was an AIDS cure and encouraged further controversy when as profits began to decline was continuing to

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receive a large salary and bonuses in addition to a string of sexual harassment charges from employees. In 2002 agitated shareholders after voicing their continual discontent with Paníc at the helm of ICN successfully removed him as ICN's chairman and CEO. Shortly after new management took over in 2003, ICN changed its name to Valeant Pharmaceuticals International and presently continues expanding its franchise licensing their products around the world[1].

The Equal Opportunity Anti-Viral

The chemistry behind ribavirin is quite interesting, it is structurally similar to sugar D-ribose, and during its synthesis is actually prepared from natural D-ribose. The carboxide group that is generated during the synthesis causes the drug to resemble adenosine or guanosine; it is this similarity that allows it to be incorporated into RNA[3,4].

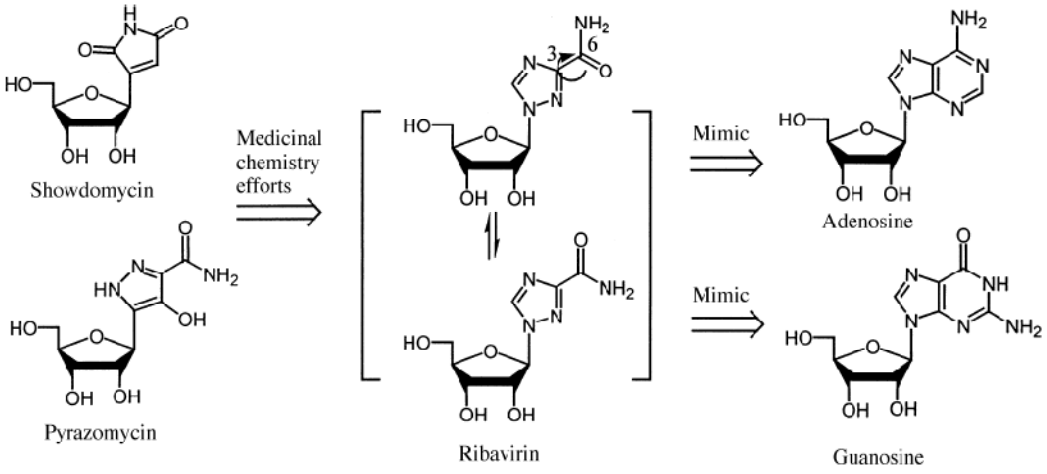

Figure 1: Ribavirin was conceived from the two natural ribonucleosides, showdomycin and pyrazomycin, both of which shows significant broad-spectrum antiviral activity[9].

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Once ribavirin is integrated it can pair with either uracil or cytosine inducing mutations during RNA-dependent replication in RNA viruses leading to hypermutation and non-infectious virion production. The mechanism of action toward DNA viruses isn't quite as clear, although ribavirin 5'- monophosphate can inhibit cellular inosine monophosphate dehydrogenase, which is thought to deplete cellular pools of GTP and affect DNA viral replication[5]. Lastly ribavirin is known to be able to enhance host T-cell mediated immunity by switching T-cell phenotype from type 2 to type 1, with type 1 responses generating the interferon needed to halt viral infections and replication[6].

Ribavirin is absorbed in the GI tract with an absolute oral bioavailability of about 65%, the level of which can be increased by also taking a fatty meal or decreased with the co-administration antacids[7]. The drug is widely distributed in all tissues, including the central nervous system and is eliminated via the urine[5]. "The pharmacokinetics of ribavirin is dominated by trapping of the drug by kinase mediated phophorylation within cells.[8]" This is especially the case within erythrocytes as they lack the phosphatases to remove that phosphate group allowing concentrations of the drugs to reach very high levels. The effectiveness of this drug is compounded by the fact that the enzyme that traps ribavirin inside of cells, adenine kinase, has increased activity within virally infected cells[10]. The mean half life for this drug is about 12 days, yet the long-term kinetics are influenced by that of the RBCs that sequester the drug. These cells store the drug for its entire life span, up to 120 days.

Table 1 exhibits ribavirin's anti-viral activity by family demonstrated within *in vitro* cell culture systems and *in vivo* studies within 10 years after its initial synthesis.

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Virus Type	*In vitro* Activity	*In vivo* Activity
RNA	influenza, paramyxovirus, picornaviruses, reoviruses, togaviruses, rhabdoviruses	arenaviridae, coronaviridae, bunyaviridae, paramyxoviridae, picornaviridae, retroviridae, reoviridae
DNA	adenovirus, herpesvirus, pox virus, rabies virus, myxoma virus,	adenovirus, herpesviridae, parvoviridae, poxviridae,

*From *Ribavirin: A Broad Spectrum Antiviral Agent* [3]

Not For Everyone and Not Without Warning

Ribavirin is contraindicated in women who are pregnant or may become pregnant. Significant teratogenic effects have been observed in all non-primate animal studies, and while failed to produce birth defects in baboons, should remain within Category X on the FDA's assessment of the risk of fetal injury[11]. Teratogenicity was evident even after a single dose with major malformations in bones of the skull and gastrointestinal tract. Ribavirin remains a potential reproductive hazard for the entire length of time it remains in the body, which mentioned earlier can be up to 6 months due to the adverse trapping within erythrocytes.

The primary toxicity associated with ribavirin is a hemolytic anemia[11]. This outcome is directly related to the dose dependent buildup of the drug within erythrocytes. Oxidative damage to red blood cell membranes is usually prevented by the reducing agent, glutathione. Accumulated ribavirin phosphate results in reduced ATP levels, these lower ATP levels impair

glutathione levels within the cells with an associated increased sensitivity of the erythrocyte to oxidative damage and lysis[10]. This side effect usually occurs within the first two weeks once therapy is initiated in about 13% of patients on ribavirin[7]. Lastly this induced anemia may exacerbate existing cardiac conditions with fatal and nonfatal myocardial infarctions reported.

Getting Through the Red Tape

Ribavirin, operating under the trade names Copegus®, Rebetol®, Ribasphere®, Vilona ®, and Virazole® is currently indicated by the FDA for severe RSV infection (alone as monotherapy) and HCV infection (in combination with pegylated interferon). Internationally, outside of the auspices of the FDA ribavirin is used to treat a wider variety of viral infections. Those indications include the treatment of influenza, enterovirus 71 (hand, foot and mouth disease), rabies, and a variety of viral hemorrhagic fevers such as Lassa fever, Hantavirus, and Crimean-Congo hemorrhagic fever[11].

Virazole®, the form of ribavirin used to treat RSV in children is prepared as an aerosol is rarely used today. While the patient population requiring this medication is quite low it nevertheless provided one of the few, if only, therapeutic options for severe respiratory infections in children in the early 1980's when it first gained approval[2]. 9 years later the cause of "Non-A, Non-B hepatitis" was identified and nearly a decade after that oral ribavirin was approved to treat HCV infection, its most well known indication of use. Interestingly, ribavirin monotherapy had little therapeutic effect against HCV, and an important clinical observation that the combination of ribavirin with interferon had a synergistic effect and improved efficacy[12]. This important breakthrough again allowed ribavirin to fill a void in the treatment of a disease

that had few alternatives, except in the case of HCV, for a disease that afflicts 270-300 million people worldwide.

The time passed from first synthesis of ribavirin to approval for RSV infection was roughly 10 years, as was the time from the discovery of HCV to the approval of ribavirin for the treatment of hepatitis. It is understood that the FDA functions to "protect the public health by assuring the safety, efficacy, and security of human drugs," and as a result of this responsibility drug developers must submit their compounds to intense scrutiny that even out major roadblocks takes time. A more interesting story for ribavirin is its failed attempt at a specific indication of use and its pursuit of approval[13]. It was previously mentioned that Milan Paníc, founder of ICN received some grief from the United States Securities and Exchange Committee when he started touting ribavirin as an AIDS cure, his cries were not completely unfounded[1]. When HIV/AIDS was first noticed clinically in the early 1980's with scores of gay men began showing up in hospitals with a rare but not unheard of type of tumor, Kaposi's Sarcoma the eye brows of the oncologists and infectious disease docs in the city perked up. This "serious but not a big deal tumor" as described by Paul Volberding was only the beginning as others began appearing with the same constellation of malignancies and infections, the HIV epidemic has gotten headway[14]. In those early days the etiological agent that was responsible for this "syndrome" was unknown although most were certain it was an infection of some sort and as people started dying the race to identify this cause intensified. In 1984 when the HIV virus was identified (either by Gallo or Montagnier) a target was now in the crosshairs of physicians and pharmaceutical companies.

Pharmaceutical companies began testing existing antivirals within the development pipeline against HIV in-vitro and physicians conducted clinical trials with hopeful candidates.

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This was a frustratingly slow process and people continued to die at alarming numbers. Some patients began looking outside of the United States for answers. Without other options, HIV patients in California began traveling south for antiviral medication. Two medications offered HIV patients some hope and relief; ribavirin and isoprinosine[15,16]. At this point in time, ICN's ribavirin was marketed in Mexico for treatment of influenza[13,15]. Patients reported that while on both ribavirin and isoprinosine, they experienced decreased weight loss, resolution of fevers and sweats, and increased energy[13]. Members in the HIV community formed "AIDS Buyers Clubs" that would go to Mexico to buy ribarivin and Isoprinosine in bulk and at a discount, thereby expanding the number of patients that had access to this medication, including patients too sick to make the trip[15].

The flow of patients to Mexico for medications started to attract attention by the media, including the New York Times, the Oakland Tribune, which ran a lead article entitled "AIDS victims pin Hopes on Drug Smugglers". This complicated the management of HIV patients by clinicians because they were taking care of patients on a drug that was at that point in time not approved for use in the United States and they had limited understanding of the use, benefits, side effects, and adverse events associated with the drugs. Secondly, it confounded the studies of compounds that were going through the proper channels as patients in the trials would be secretly taking ribavirin and Isoprinosine[15].

Patients approached the FDA to ask for access to ribavirin in the United States, but the FDA felt bullied by the HIV community to approve a drug without the proper screening. The FDA was doubtful of "cures from Mexico" and "fraudulent" studies[15]. The HIV community felt that the FDA was leaving them with no viable options, other than going to Mexico or waiting, as

they developed their own drug. At this time, the FDA was in the process of approving a government developed antiviral from the National Cancer Institute, named compound S, later known as AZT or zidovudine, a reverse transcriptase inhibitor[13-15]. As the number of patients taking ribavirin in conjunction with Isoprinosine increased, a grassroots effort from an organization called Project Inform, began collecting clinical data from these patients. They presented their data to the FDA, but the FDA was hesitant to approve a drug based on retrospective studies, let alone one that examined two untested drugs simultaneously. The FDA required a prospective study of the drugs individually[15]. During this time, an aerosolized form of ribavirin became approved for treatment of RSV in newborns. This was frustrating for the HIV community as it prevented the off-label use of ribavirin in the United States, as physicians could not achieve therapeutic ranges with the aerosolized form.

Researchers began to study the efficacy of ribavirin and isoprinosine according to the FDA's guidelines, using a treatment IND. A 60-day trial at San Francisco General Hospital of isoprinosine showed no improvement in symptoms and was therefore stopped. At Cornell researchers claimed that the therapeutic effect was limited by significant pancytopenia. Both studies were limited in scope and caused further delay of ribavirin approval, as AZT was approved by the FDA in 1987[13]. Members of the HIV community were frustrated because they knew from experience that both drugs were only effective in combination

Subsequent ribavirin studies in the early 1990s in Europe found that the drug produced a 48% reduction in progression to AIDS diagnosis[16]. Initially seen by the HIV community as a huge success, the FDA claimed that the studies was flawed in terms of design, conduct, analysis, and should not have been published. About one study in particular, the FDA stated "the flaws of

the study include abnormally high rates of progression to AIDS of patients who were not treated, the uneven randomization of subjects to the different treatments, the inclusion of a large number of patients in the study who had symptoms that should have made them ineligible for the study, the unlikelihood that the levels of the drug in the body that were achieved could be effected to inhibit the virus, and the lack of effect on virally infected cells or cells of the immune system as demonstrated by lack of change in these cells in laboratory tests[16]." Without efficacy studies to satisfy the FDA, the development of ribavirin was paused.

Ironically, in 1998 ribavirin was approved for treatment of HCV only in combination with interferon, even though the FDA had refused to consider testing ribavirin in combination with other drugs, including isoprinosine[10].

Ribavirin in the 21st Century

For the past thirteen years, the combination of ribavirin and interferon, marketed as Copegus®, Rebetol®, or Ribasphere®, has been one of the few viable treatment options for HCV. That market share is rapidly diminishing, as within the past month two new drugs have been approved for treatment of HCV, telaprevir (Incivek®) and boceprevir (Victrelis®). These drugs inhibit the action of the viral protease enzyme reducing the infectivity of progeny virions from infected cells. Not only have these drugs demonstrated efficacy across HCV genotypes, they provide hope to patients that have failed prior treatment. These drugs are the first among twenty in development that have greater potency and efficacy that ribavirin.

Just as ribavirin was derived from a naturally occurring nucleoside, researchers have tried to derive ribivirin like compounds in the attempts to increase specificity and limit toxicity. If

successful, these compounds may find a niche in the future, but they have yet to be widely adopted in the presence of "safer" alternatives[9].

Ribavirin continues to receive Emergency Investigational New Drug (EIND) applications which grant permission for use by the FDA on a case by case basis for the treatment of serious viral infections, such as adenovirus, parainfluenza and most notably severe acute respiratory syndrome (SARS) caused by a coronavirus, for which no other treatment may be available. This granted compassionate use may extend the usefulness of ribavirin in situations where its benefit as an antiviral outweighs its toxicity[18]. However, when it is given as an EIND, it is administered intravenously which greatly increases its toxicity, in particular anemia. This broadly acting antiviral can remain a weapon in the arsenal against emerging viral infections until more specific treatments are developed.

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