

a series of fact sheets written
by experts in the field of liver
disease

HCV Treatment: Interferon and Ribavirin

Alan Franciscus, Editor-in-Chief

Interferon (in one form or another) has been used to treat hepatitis C since 1991 and ribavirin has been used in combination with an interferon product since 1998. We are now on the brink of a new treatment regime that will include direct HCV antivirals (protease and polymerase inhibitors). These new medications, when combined with pegylated interferon and ribavirin, are expected to increase HCV response rates.

The new treatment regimes are expected to be approved in 2011-2012, and pegylated interferon and ribavirin is expected to be part of HCV therapy for another 10 years or maybe even longer. Therapies that do not include interferon and/or ribavirin are in early stages of development and do hold much promise; but right now there are too many unknowns to make any type of intelligent guess. Given that we will have to live with interferon and ribavirin for the foreseeable future, this fact sheet will discuss the current combination of interferon and ribavirin with regard to what we know and don't know about these medications.

There are two types of Interferons that are naturally produced by the body. Type II interferon is mainly involved with controlling the immune functions of the body. There is only one form of Type II interferon – gamma interferon.

Type I interferon is known as alpha or beta and is made up of proteins produced by the body in response to a viral infection. For instance, when someone becomes infected with the flu virus the immune system immediately produces and releases various types of interferon to protect cells from the invading virus. The symptoms people experience from the flu, such as muscle pain, fever and headaches, are due to the body's natural production of interferon.

In more detail, interferon works by binding to cell surface receptors and triggering the production of intracellular second messengers, including 2'5' oligo-adenylate synthetase, protein kinases, cell surface proteins, and nuclear proteins.

Interferon also works in other ways by increasing the body's immune response against viruses and infected cells:

- **Antiviral action** – Interferon helps to prevent the entry of a virus into a cell, which limits the replication of new viruses and the amount of new cells that the virus infects. Within the liver cell interferon inhibits the replication of viruses by preventing the virus from uncoating and by interfering with viral protein synthesis.
- **Immunomodulatory effect** – Interferon stimulates the production of cytokines (chemical messengers) that activate macrophages, natural killer (NK) cells, and cytotoxic T-lymphocytes (CTLs, or killer T-cells) which then surround and kill the infected cell and the virus within the cell.
- **Antitumor effects** – Interferon reduces the production of both normal and malignant (cancerous) cells and inhibits oncogene expression. Interferon also enhances direct T-cell-mediated cytotoxicity against tumor cells. This kills cancer and tumor cells.
- **Enhanced cell surface expression of MHC** – Interferon enhances the expression of class 1 major histocompatibility (MHC) antigens on the surface of infected cells. Expression of these proteins on the cell

surface allows virus-infected cells to be targeted and destroyed by CTLs.

Sometimes the body does not make enough natural interferon to effectively fight an infection – the addition of genetically re-engineered interferon helps the body to fight off a viral infection such as hepatitis C.

Standard Interferon

Standard interferons (also called conventional interferon) are administered by subcutaneous injection (right underneath the skin) three times a week. Standard interferon’s half life (the time required by the body to metabolize or inactivate half the amount of the substance) is two to five hours. Because of standard interferon’s short half-life it is unable to constantly suppress the hepatitis C virus. Standard interferon is a pre-mixed solution. The first standard interferon, Intron A brand, was approved in 1991.

The most common FDA approved standard interferons used to treat hepatitis C include Genentech’s Roferon-A, Merck’s Intron A, and Three Rivers Pharmaceutical’s Infergen.

Pegylated Interferon

Pegylated interferon is a long-acting formulation of interferon that can be injected less often – once a week. Pegylation is

a process in which polyethylene glycol (the PEG molecule) is attached to a protein. This creates a shield around the interferon which helps to protect it and also delays the breakdown and clearance of interferon from the body. Since the PEG module allows interferon to stay in the body longer there is greater suppression of the hepatitis C virus.

There are currently **two** FDA approved pegylated interferons – Merck’s Peg-Intron was approved in August 2001; and Roche’s Pegasys was approved in October 2002.

Ribavirin

Ribavirin (Rebetol, produced by Merck; Copegus, produced by Genentech; or Ribasphere, produced by Three Rivers Pharmaceuticals) is a nucleoside analog (also called a nucleoside reverse transcriptase inhibitor, or NRTI) antiviral drug. It is taken orally (by mouth) twice a day. The exact way ribavirin works is unknown. However, it is believed that when ribavirin enters a cell it is phosphorylated; it then acts as an inhibitor of inosine 5'-monophosphate dehydrogenase (IMPDH). IMPDH inhibitors such as ribavirin reduce the intracellular synthesis and storage of guanine, a nucleotide “building block” necessary for DNA and RNA production, thus inhibiting viral replication. IMPDH inhibitors also interfere with the reproduction of rapidly proliferating cells and cells with a high rate of protein turnover; because of this, IMPDH inhibitors can cause side effects such as nausea and immunosuppression.

Treatment with ribavirin monotherapy has little effect on HCV RNA levels, but is associated with a decline in serum ALT. This suggests that ribavirin may not be acting as an antiviral agent, but rather as a modulator of immune system function. Ribavirin monotherapy for HCV is ineffective, and the drug is only approved for use in combination with interferon.

Today’s Standard of Care:

The current standard of care is the combination of pegylated interferon plus ribavirin. The standard duration of treatment is 48 weeks for genotype 1 and 24 weeks for genotypes 2 and 3. Ribavirin is taken twice a day (with food) and is dosed by body weight for indi-

Drug	Brand Name	Manufacturer
Standard interferon		
Interferon-alpha-2a	Roferon-A	Roche
Interferon-alpha-2b	Intron-A	Merck
Interferon alfacon 1 (consensus interferon)	Infergen	Valeant
Pegylated interferon:		
Pegylated-alpha-2a	Pegasys	Roche
Pegylated-alpha-2b	Peg-Intron	Merck
Ribavirin:		
	Rebetol	Merck
	Copegus	Roche
	Ribasphere	Three Rivers Pharmaceuticals, LLC
Generic ribavirin:		
	Ribavirin	Warrick Pharmaceuticals
	Ribavirin	Teva Pharmaceutical Industries

viduals with HCV genotype 1 (800 to 1,400 mg a day) and in people with HCV genotype 2 and 3 it is given at a flat or fixed daily dose of 800 mg.

Peg-Intron (peginterferon alpha 2b) plus ribavirin

Peg-Intron is a lyophilized powder that must be reconstituted before use. It is dosed by body weight. The sustained virological response rate (SVR) for Peg-Intron monotherapy is 14% for genotype 1 and 47% for genotypes 2 and 3. The SVR for Peg-Intron plus ribavirin combination therapy is 41% for genotype 1 and 75% for genotypes 2 through 6.

Pegasys (peginterferon alfa 2a) plus ribavirin

Pegasys comes in a ready-made solution that does not require reconstitution. The standard dose is 180 µg for all patients. The SVR for Pegasys monotherapy is 28% for genotype 1 and 56% for genotypes 2 and 3. Pegasys monotherapy is also indicated for treatment of chronic hepatitis B and for people with compensated cirrhosis. The SVR for Pegasys plus ribavirin combination therapy is 44-51% for genotype 1 and 70-82% for genotypes 2 through 6. Pegasys plus ribavirin combination therapy is also indicated for treating hepatitis C in people with HIV.

Newer types of interferons:

Albumin, interferon brand name **ZALBIN**, is a long-acting type of interferon that is fused with the blood protein albumin needs to be injected only once every two weeks. In Phase III studies it was found that ZALBIN met the primary end-point of the study – that is, that the treatment results were found to be non-inferior to Pegasys. Human Genome Sciences and their co-development partner, Novartis, have sent the clinical trial data to the FDA for consideration for marketing approval. If approved by the FDA the most likely timeframe for release would be late 2010-2011.

There are many other types of interferon that are being developed and tested to treat hepatitis C. **IL-29** (type III interferon), **Belerofon** (an oral medication), and **Locteron** look promising, but the push for HCV therapies that do not include interferon and/or ribavirin calls into question an aggressive push to develop these and other interferons, at least with regard to a treatment for hepatitis C.

For the latest information on interferons and other drugs in development, please see “Hepatitis C Treatments in Current

Clinical Development,” <http://www.hcvadvocate.org/hepatitis/hepC/HCVDrugs.html>, on the HCV Advocate website

Interferon and ribavirin reference guide:

There are currently four FDA-approved HCV treatment regimens:

1. interferon-alpha monotherapy
2. interferon-alpha plus ribavirin
3. pegylated interferon monotherapy
4. pegylated interferon plus ribavirin

Patient Assistance Programs

Roche – Pegasys – Pegassist

www.pegassist.com

Phone: 1-877-PEGASYS (1-877-734-2797)

Schering – Be in Charge

www.beincharge.com

Phone: 1-888-437-2608

Three Rivers Pharmaceuticals

- Ribacare:

www.3riverspharma.com/pat_riba.htm

1-866-650-RIBA

- Aspire (Infergen):

www.infergen.com/7-Resources/1-Aspire.html

For more information about hepatitis C, hepatitis B and HCV coinfections, please visit www.hcvadvocate.org.

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A publication of the Hepatitis C Support Project

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The information in this fact sheet is designed to help you understand and manage HCV and is not intended as medical advice. All persons with HCV should consult a medical practitioner for diagnosis and treatment of HCV.

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