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HCV Treatment: Interferon and Ribavirin

Alan Franciscus, Editor-in-Chief

THERE ARE TWO TYPES OF INTERFERONS that are naturally produced by the body. Type II interferon is 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 an individual becomes infected with the flu virus, the immune system immediately produces various interferons to protect other 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 prevents the entry of a virus into a cell, which limits the amount of new cells that become infected. Interferon also inhibits the replication of viruses by preventing the virus from uncoating within the cell and preventing the viral replication process within the cell by interfering with the 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 kill the virus and the infected 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 and 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 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 most common FDA approved standard interferons used to treat hepatitis C are Roche's Roferon-A, Schering'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 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.

The are currently **two** FDA approved pegylated interferons – Schering-Plough's Peg-Intron was approved in August 2001; and Roche's Pegasys was approved in October 2002.

Ribavirin

Ribavirin (brand name Rebetol, produced by Schering-Plough; Copegus, produced by Roche Pharmaceuticals; or brand name 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 individuals 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.

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

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 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 and as a treatment for hepatitis B.

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

HCV Treatment – Side Effect Management

http://www.hcvadvocate.org/hepatitis/factsheets.asp

- *A Guide to Hepatitis C: Treatment Side Effect Management*
- *Managing Side Effects of HCV Treatment*
- *Side Effect Management: Anxiety, Mania, and Depression*
- *Side Effect Management: Dental Hygiene*
- *Side Effect Management: Depression*
- *Side Effect Management: Depression—For Family and Friends*
- *Side Effect Management: Diarrhea*
- *Side Effect Management: Hair Loss*
- *Side Effect Management: Headaches*
- *Side Effect Management: Hemolytic Anemia*
- *Side Effect Management: Injection Site Reactions*
- *Side Effect Management: Maintaining a Positive Attitude*
- *Side Effect Management: Mouth Sores*
- *Side Effect Management: Nausea*
- *Side Effect Management: Neutropenia*
- *Side Effect Management: Rashes*
- *Side Effect Management: Taste Changes*
- *Side Effect Management: Water*
- *Side Effect Management: Weight Loss*

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

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Executive Director
Editor-in-Chief, HCSP Publications
Alan Franciscus

Design
Paula Fener

Production
C.D. Mazoff, PhD

Contact information:
Hepatitis C Support Project
PO Box 427037
San Francisco, CA 94142-7037

alanfranciscus@hcvadvocate.org

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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